DOKUMEN KORESPODENSI

Nama Jurnal : **Journal of Pharmaceutical Innovation**
Judul : **Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms**
Publisher : Springer Nature
Volume/Issue : 17(4)
Tahun : 2022
DOI : https://doi.org/10.1007/s12247-021-09591-0
Index : SJR(2022) 0.357
Penulis Pertama : Wuryanto Hadinugroho
Penulis Korespodensi : Wuryanto Hadinugroho
Tahapan & Lampiran :

No.	Tahapan	Waktu
1.	**Submission to Journal of Pharmaceutical Innovation** Manuscript draft	**24-07-2021**
2.	**First revision request** Email first revision request Manuscript draft of first revision request	**30-08-2021**
3.	**Submission of first revision to Journal of Pharmaceutical Innovation** Email received the first revision manuscript Manuscript draft of first revision	**05-09-2021**
4.	**Second revision request** Email second revision request	**11-09-2021**
5.	**Submission of second revision to Journal of Pharmaceutical Innovation** Email respon of second revision request from Authors Manuscript draft of second revision	**11-09-2021**
6.	**Respon of email second revision** Email respon from JEO Assistant	**13-09-2021**
7.	**Respon of Submission of second revision to Journal of Pharmaceutical Innovation** Email received the second revision manuscript	**28-09-2021**
7.	**Paper accepted for publication** Email of accepted paper	**03-10-2021**
8.	**Paper publish** Email of online publish paper	**12-10-2021**

-

Journal of Pharmaceutical Innovation

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

--Manuscript Draft--

Manuscript Number:	JOPI-D-21-00339
Full Title:	Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms
Article Type:	Original Article
Keywords:	CA-LBG; citric acid; locust bean gum; disintegrating agent; direct compression
Order of Authors:	Wuryanto Hadinugroho, Dr
	Suwaldi Martodihardjo, Prof
	Achmad Fudholi
	Sugeng Riyanto, Prof
Corresponding Author:	Wuryanto Hadinugroho, Dr Widya Mandala Catholic University: Universitas Katolik Widya Mandala Surabaya Surabaya, Jawa Timur INDONESIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Widya Mandala Catholic University: Universitas Katolik Widya Mandala Surabaya
Corresponding Author's Secondary Institution:	
First Author:	Wuryanto Hadinugroho, Dr
First Author Secondary Information:	
Order of Authors Secondary Information:	
Funding Information:	kementerian pendidikan dan kebudayaan (0299 / E3 / 2016) — Dr Wuryanto Hadinugroho
Abstract:	Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The purpose of this study was to analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG. The aim of the tablet formulation was to determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets. The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, degree of esterification, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. The method of making tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg. Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.
Suggested Reviewers:	Oliver Germershaus, Prof. University of Applied Sciences and Arts Northwestern Switzerland: Fachhochschule Nordwestschweiz FHNW oliver.germershaus@fhnw.ch Experienced in macromolecular modification and pharmaceutical technology
	Chen Jian, Prof.

	Fudan University - Handan Campus: Fudan University jiangchen@shmu.edu.cn Experienced in formulations and technology of pharmaceutical
	Jianping Zhou, Prof. China Pharmaceutical University School of Pharmacy zhoujianp60@163.com Experienced in formulations and technology of pharmaceutical
	Xiaochen Gu, Prof. University of Manitoba Xiaochen.Gu@umanitoba.ca Experienced in formulations and technology of pharmaceutical
	Artik Angkawijaya, Ph.D National Taiwan University of Science and Technology artikelisa@mail.ntust.edu.tw Experienced in the synthesis of modified natural polymers

Surabaya, July 24th, 2021

Prof. Stephen Scypinski
Editors-in-Chief
Journal of Pharmaceutical Innovation

Please find enclosed our original research manuscript entitled "Preparation of citric acid-locust bean gum (CA-LBG) for the disintegrating agent of tablet dosage forms" We hope for this work which has never been published in other journals to be considered for publication in the Journal of Pharmaceutical Innovation. We believe that the Journal of Pharmaceutical Innovation is of high quality for publication related to modification synthesis of natural polymers, characterization and potential studies of materials, formulation of tablet dosage forms. The novelty of this study, the synthesis of CA-LBG uses a concentration of HCl 0.24 M as the catalyst and UV irradiation time (100 minutes) as an energy source that creates the chemical bond. The CA-LBG was further investigated as a disintegration agent in tablet dosage forms. The CA-LBG was characterized by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, degree of esterification, solubility, and viscosity. The tablet formulation used CA-LBG as disintegrating agent with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. The method of making tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg. In addition, the dissolution of the tablet was evaluated using diclofenac sodium as the active ingredient model. The experiment was conducted to determine the potential for the disintegration of CA-LBG in tablet formulations as an alternative choice of disintegrating agent to be developed in the future.

Regardless of the decision that will publish/reject this manuscript. We are very grateful and expect suggestions and corrections from reviewers and editors to improve this manuscript.

Also, for the purpose of reviewing our paper, we would like to propose several names:

1. Prof. Oliver Germershaus, *Department of* pharmaceutical technology of macromolecular substances, *Faculty of* Pharmatechnology and Chemical-Bioprocesstechnology, University of Applied Sciences and Arts Northwestern Switzerland, Email: oliver.germershaus@fhnw.ch
2. *Prof. Chen Jian*, Department of Pharmaceutics, School of Pharmacy, Fudan University, Shanghai, China, Email: jiangchen@shmu.edu.cn
3. Prof. Jianping Zhou, Department of Pharmaceutics, China Pharmaceutical University, Email: zhoujianp60@163.com
4. Prof. Xiaochen Gu, Department of Pharmaceutics, College of Pharmacy, University of Manitoba, Canada, Email: Xiaochen.Gu@umanitoba.ca
5. Artik Elisa Angkawijaya, Ph.D., National Taiwan University of Science and Technology, Email: artikelisa@mail.ntust.edu.tw

Thank you for your attention and cooperation.
Yours sincerely,

Wuryanto Hadinugroho
Department of Pharmacy Science and Industrial
Faculty of Pharmacy
Widya Mandala Surabaya Catholic University
Kalisari Selatan no. 1, Pakuwon City, Surabaya 60112, Indonesia
Email: wuryanto.hadinugroho@ymail.com
Tel. +62 31 3891264 Fax. + 62 31 3891267

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

Wuryanto Hadinugroho[1,2*], Suwaldi Martodihardjo[2], Achmad Fudholi[2], Sugeng Riyanto[2]

1 Department of Pharmaceutical, Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, Indonesia

2 Department of Pharmaceutical, Faculty of Pharmacy, Gadjah Mada University, Sekip Utara, Yogyakarta, Indonesia

*Corresponding authors: e-mail address: wuryanto.hadinugroho@ymail.com; Tel.: +62 81 330 904 484, Fax: +62 31 990 052 88

Abstract

Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The purpose of this study was to analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG. The aim of the tablet formulation was to determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets. The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, degree of esterification, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. The method of making tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg. Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Keyword: CA-LBG, citric acid, locust bean gum, disintegrating agent, direct compression

1. Introduction

Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations (Dionísio and Grenha 2012; Dey et al. 2013; Das et al. 2015; Sheskey, J. P., Cook, G. W., and Cable 2017). Locust bean gum is a natural polymer that has the potential to be modified to produce new materials as excipients in tablet formulations.

Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). The O atoms (C-6) of mannose and galactose at LBG bind to the positive C atom of the carbonyl groups at CA. Positive C atoms are created from the protonation of carbonyl groups under acidic conditions (Chudzikowski 1971; Samavati et al. 2007; Tamaki et al. 2010; Dey et al. 2013; Hadinugroho et al. 2017, 2019).

The HCl is a strong acid that is effective for creating acidic conditions (Colas 2005; Bhattacharya et al. 2008). Variation of HCl concentration in the synthetic effect on the character of CA-LBG. The concentration of HCl affects the rate of protonation of the carbonyl group of CA to form a positive C atom. Increasing the concentration of HCl causes an increase in the creation of positive C atoms. This condition increases CA binding to LBG. The characteristics of CA-LBG are influenced by the concentration of CA bound to LBG (Hadinugroho et al. 2019).

The low wavelengths of UV irradiation (200-400 nm) are a source of energy strong enough to form chemical bonds (Tjandraatmadja et al. 1999; Santiago, E. V., Lopez, S. H. and Romero 2006; Yeh et al. 2011). The UV irradiation for a certain duration determines the formation of positive C atoms from the carbonyl group in CA with the O atoms (C-6) of mannose and galactose at LBG. The results of previous studies reported that this esterification produced a carbonyl ester group on CA-LBG which was not owned by LBG. In addition, the study reported that CA-LBG has a viscosity of 7-11 cP (Hadinugroho et al. 2019).

The CA-LBG utilization as material synthesis products need to be studied further. Pharmaceutical formulation is one area where CA-LBG can be used as an alternative to pharmaceutical excipients. Previous studies have reported that CA-LBG has the potential as a disintegrating agent for tablet dosage formulations (Hadinugroho et al. 2019).

The purpose of this study was to analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG. The aim of the tablet formulation was to determine the effect of the application of CA-LBG as a disintegration agent on the physical quality of tablets. The novelty of this study, the synthesis of CA-LBG uses a concentration of HCl 0.24 M as the catalyst and UV irradiation time (100 minutes) as an energy source that creates the chemical bond. HCl concentrations of 0.18 M and 0.30 M were experimental control concentrations to determine the success of the synthesis and characterization of CA-LBG. The CA-LBG experiment as a disintegrating agent was further studied with various concentrations. Sodium starch glycolate (SSG) and croscarmellose sodium (CS) were comparable disintegrating agents to study the disintegration activity of CA-LBG. SSG and CS are tablet disintegrating agents that are often used in tablet formulations because both able to swell in the disintegrating medium in a fast time. The rounded shape with the smooth surface of the SSG and the shape of the root with the corrugated surface of the CS can affect the tablet quality (Markl and Zeitler 2017; Sheskey, J. P., Cook, G. W., and Cable 2017). The experiment was

conducted to determine the potential for the disintegration of CA-LBG in tablet formulations as an alternative choice of disintegrating agent to be developed in the future.

2. Material and methods

2.1. Raw materials and chemicals

Materials needed in this study were locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Merck KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich, GmbH, USA), acetone (Cawan Anugerah Chemika, Indonesia), sodium starch glycolate (JRS Pharma, India), croscarmellose sodium (FMC Biopolymer, USA), spray dried lactose (Foremost Farms, USA), diclofenac sodium (Dwilab Mandiri, Indonesia), sterilized water for injection (Otsuka, Indonesia), and distilled water (Brataco Chemical, Indonesia).

2.2. Preparation of CA-LBG

The swollen LBG in a glass bowl (7.10 10^{-6} Molar LBG / 50 mL distilled water 55-60 ^{o}C) added CA (0.42 Molar) and HCl (0.18; 0.24; 0.30 Molar) (Table 1). The mixture was stirred for 10 minutes. The mixture was irradiated with UV 254 nm (100 minutes) (8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet CA-LBG was precipitated with acetone and washed with acetone-distilled water (1:1). The solid CA-LBG is dried at ambient temperature (Hadinugroho et al. 2017).

Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG performed was fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR), scanning electron microscope (SEM), degree of esterification, solubility, and viscosity.

2.3. Fourier transform infrared spectroscopy

The structure and the functional group of CA-LBG were analyzed by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.) in the wavenumber range of 4000-450 cm^{-1} spectra were recorded.

2.4. Nuclear magnetic resonance

The ^{1}H and ^{13}C NMR of CA-LBG was analyzed by liquid state NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan). The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra were recorded.

2.5. Scanning electron microscope

The surface morphology of CA-LBG was analyzed using SEM (JSM-6510LA, JEOL, Japan). The CA-LBG was mounted on a holder, coated by platinum, and observed (distance 10 mm and voltage10 kV).

2.6. Degree of esterification

The determination of the degree of esterification follows the experimental equation that has been done previously (Hadinugroho et al. 2019). Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group

compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar). The degree of esterification is determined by comparing the carboxylate group in the reacting CA (Molar) and the carboxylate group at the initial CA (Molar) and calculated according to Equation 3 (Hadinugroho et al. 2019).

Dissolved CA (mEq).

$$dissolved\ CA\ [mEq] = dissolved\ acid[mEq] - dissolved\ HCl[meq] \quad \textbf{Equation 1}$$

Weight CA reacting (gram)

$$W\ CA\ reacting\ = W\ initial\ CA - W\ dissolved\ CA \quad \textbf{Equation 2}$$

Degree of esterification

$$Degree\ of esterification\ [\%] = \frac{carboxylic\ group\ on\ the\ CA\ reacting\ [Molar]}{carboxylic\ group\ on\ the\ CA\ initial\ [Molar]}\ x\ 100\ \% \quad \textbf{Equation 3}$$

2.7. Solubility study

Solubility was determined by 0.5 g CA-LBG added 50 mL distilled water and allowed to stand for 24 h (Wd). Then, the filtrate was separated from the swollen sample. The filtrate was dried on a water bath at 70 ° C and reweighed (Wds) on a microbalance (Mettler Toledo AL204, Switzerland). The solubility of the CA-LBG was analyzed according to Equation 4:

Solubility (%) = Wds/Wd x 100 **Equation 4**

where Wds and Wd are soluble weight and initial weight (dry weight respectively) (Gulrez et al. 2011).

2.8. Viscosity

The CA-LBG viscosity test using a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG (3% w/v) was swelled in 300 mL of warm distilled

water and left at ambient temperature. Spindle no. S61 was installed on Brookfield. Viscosity was recorded when Brookfield was rotated at 100 rpm.

2.9. Preparation of tablets

Preparation of tablets begins with weighing the ingredients according to the formula (Table 1). Preparation of tablets by direct compress was prepared by mixing homogeneous SDL and CA-LBG / SSG / CS using a cubic mixer (2 minutes, 100 rpm) (Erweka). The physical quality of tablet mass was evaluated for flowability and compressibility. The mass of the tablets was compressed with a weight of 200 mg per tablet using a single punch machine (Jenn Chian Machinery, Taiwan). The physical quality of the tablets was evaluated for thickness, weight, break force, tensile strength, friability, and disintegration time.

2.10. Flowability

Tablet mass (100 g) was placed in a funnel hole on a flowability tester (Erweka, Germany). When the funnel valve is opened, tablet mass flows. Flow time can be observed on the flowability tester monitor.

2.11. Compressibility

Tablet mass was poured into a measuring tube (100 mL, angle ± 40^{o}) whose weight was known. The filled measuring tube is weighed, placed on a tapped density volumeter apparatus (Erweka, Germany), and tapped (500 taps). Weight and volume of tablet mass (before and after tapped) were recorded to determine the bulk density and the tapped density. Tablet mass versus volume before tapped is bulk density. Granule weight/tablet mass versus volume after tapped is the tapped density. The compressibility index is the difference between

tapped density and bulk density versus tapped density (Equation 5) (Michael E. Aulton and Kevin M. G. Taylor 2017).

$$compressibility\ index\ (\%) = \frac{tapped\ density - bulk\ density}{tapped\ density}\ x\ 100\% \quad \textbf{Equation 5}$$

2.12. Weight and thickness

Tablet weight and thickness were determined using 20 randomly selected tablets. Each tablet was weighed using an analytical weighing scale (Mettler Toledo, Switzerland) and thickness was accurately measured using a thickness gauge (Mitutoyo 7301, Japan).

2.13. Break force and tensile strength

Tablet break force (BF) was determined using 6 randomly selected tablets (The United States Pharmacopeial Convention 2018). The tablet is placed on the break force tester plate (Schleuniger, Netherlands). The metal block moves towards the tablet and presses until the tablet cracks/breaks. The tablet break force value is determined from the start of cracks/breaks, indicated on the monitor.

The strength of the tablet against mechanical stress is determined specifically using the tensile strength parameter according to the shape of the convex tablet. Tensile strength (σt) is calculated following Equation 6 (Pitt et al. 1989; Shang et al. 2013).

$$\sigma t = \frac{10F}{\pi D^2 (2.84\left(\frac{t}{D}\right) - 0.126\left(\frac{t}{W}\right) + 3.15\left(\frac{W}{D}\right) + 0.001)} \quad \textbf{Equation 6}$$

F is the break force, D is the diameter of the tablet, t is the total thickness of the tablet, and W is the thickness of the center of the tablet without convex.

2.14. Friability

Tablet friability was determined using a randomly selected number of tablets with a total tablet weight equal to 6500 mg (The United States Pharmacopeial Convention 2018). Each tablet was dust-free and the total weight of all tablets was determined (W0). All tablets were put into a drum friability tester (Erweka, Germany) and rotated for 4 minutes (25 rpm). After being removed from the drum, each tablet was dust-free and weighed again (W1). The friability of the tablet is the difference in the total weight of the tablet before and after rotated compared to the weight before rotated (Equation 7).

$$friability\ (\%) = \frac{W0-W1}{W0}\ 100\% \qquad \textbf{Equation 7}$$

2.15. Disintegration time

Tablet disintegration time was determined using 6 tablets randomly selected from 18 previously randomly selected tablets (The United States Pharmacopeial Convention 2018). Each tablet was inserted into each tube in the chamber disintegration tester apparatus (Erweka Z3, Germany). The chamber is up-down in a distilled water bath (37^{o} C; 900 mL). The disintegration time was determined from the longest time required for the tube net to be free of tablet fragments.

2.16. Dissolution

The experiment was prepared using a tablet mass added with diclofenac sodium as a model active ingredient. Each tablet contains 50 mg of diclofenac sodium to be compressed to a weight of 250 mg (Uday Kumar and Babu 2014; Hammami et al. 2020). Dissolution using phosphate buffer medium pH 6.8 (900 mL; 37 ± 0.5 ^{o} C; 50 rpm) for 60 minutes using the paddle method (Electrolab TDT-08L, India) (Zupančič Bozič et al. 1997; Bertocchi et al. 2005). The release of ketoprofen was sampled and observed at 5, 15, 30, 45, and 60 minutes. Analysis

of dissolved diclofenac sodium concentration using a UV-vis spectrophotometer (Hitachi U-1900, Japan) at a wavelength of 276 nm (Ghasemi et al. 2005; Gouda et al. 2013).

3. Result and discussion

3.1. Mechanism of the CA-LBG synthesis reaction

In the synthesis of CA-LBG, the acidity of HCl could be induced protonation of O atoms from the carbonyl group of citric acid and created positive C atoms. The hydroxyl (OH) group of C-6 at mannose and galactose atoms reacts with the protonated citric acid carbonyl group to create a tetrahedral cation. Protonated OH ($^{+}OH_2$) oxygen groups with H_2O loss to form CA-LBG. UV irradiation is the energy source to create bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose (Hadinugroho et al. 2017, 2019). The schematic and details of the synthesis are shown in Figure 1 and Table 1.

3.2. Fourier transform infrared spectroscopy

The results of the CA-LBG and LBG infrared analysis are shown in Figure 2 and Table 1. The stretch peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose. Sharp peaks appear at 2920.60 cm^{-1}; 2923.35 cm^{-1}, 2923.56 cm^{-1}; and 2923.35 cm^{-1} are related to C-H bonds of CA and LBG. In CA-LBG, the sharp peak comes from C-H symmetrically of CA (Coates 2006). The sharp peak of CA-LBG appeared at 1739.22 cm^{-1}; 1736.39 cm^{-1}; and 1735.85 cm^{-1} are related to the carbonyl ester group that was produced from the synthesis reaction. The carbonyl ester group is created by the bond between the positive C atom of the protonated carbonyl group in CA and the O atom of C-6 at mannose and galactose in LBG. In a previous study, the OH group appeared around 3300 cm^{-1}. C-H appears around 2900 cm^{-1}, and C=O appears

around 1750-1735 cm^{-1}(Hadinugroho et al. 2019). This shows the success of the synthesis and continued by NMR confirmation.

3.3. Nuclear magnetic resonance

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies (Hadinugroho et al. 2017, 2019).

The results of the CA-LBG NMR analysis are shown in Figure 3. In the ^{1}H NMR spectrum of CA, a pair of twin peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 (e) in CA. Sharp peaks of 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that a pair of CA twin peaks appear around δ = 2.7-3.0 ppm. Sharp peaks from mannose and galactose appear around 4.5-3.0 ppm (Hadinugroho et al. 2017, 2019).

In the ^{13}C NMR spectrum of CA-LBG, peaks at δ = 176.790 ppm and δ = 173.459 ppm are related to C = O (b,c) resulting from the synthesis reaction. The peak at δ = 73.325 ppm is related to the central C atom of CA (a). The peak at δ = 43.349 ppm is related to C-H_2 (d) of CA. The peaks at δ = 100.192 ppm, δ = 100.000 ppm, δ = 75.072 ppm and δ = 71.453 ppm are related to C-H and C-H_2 at mannose. The peaks at δ = 69,985 ppm, δ = 61.260 ppm, δ = 61.010 ppm, δ = 60.559 ppm are related to C-H and C-H_2 at mannose and galactose. Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H_2 appeared at δ = 44-43 ppm (Jans and Kinne 1991; Doll et al. 2006; Zhang et al. 2016; Hadinugroho et al. 2019). The peak absorption of mannose and galactose appears at δ = 105-60 ppm (Parvathy et al. 2005; Azero and Andrade 2006; Bhatia et al. 2013; Gillet et al. 2014; Hadinugroho et al. 2019). This shows the success of the synthesis.

3.4. Scanning electron microscopy

The SEM images of CA-LBG (Batch B) are shown in Figure 4. In magnification100x, particles of CA-LBG appear in an irregular shape. In magnification 3500x, particles CA-LBG have the surface morphology of CA-LBG appear coral-corrugated. Based on previous experiments, LBG has a corrugated morphology and CA creates coral morphology (Hadinugroho et al. 2019). The LBG particles have a shape coral- corrugated indicates available interaction with CA with LBG and successful synthesis.

3.5. Degree of esterification

The degree of esterification of CA-LBG for all batches is shown in Table 1. The high concentration of HCl under synthesis conditions increases the degree of esterification due to the high amount of CA bound to LBG. The HCl increases the acidity of the synthesis conditions to protonate the O atom from the carbonyl group and creates a positive C atom, thereby causing CA to bind to LBG. The CA-LBG batch A to batch C shows the higher the degree of esterification in proportion to the increase in the concentration of HCl because the protonation of the O atom from the carbonyl group and the formation of a positive C atom is faster. This condition accelerates creates bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose.

3.6. Solubility

The solubility of CA-LBG for each synthesis condition is shown in Table 1. The CA-LBG of batch A to batch B presents the solubility decreasing in proportion to the increasing degree of esterification. The more CA molecules bound to the LBG produce CA-LBG with stable ester bonds. Bonds of positive C atoms from carboxylic groups and O atoms of C-6 at

mannose and galactose decrease the ability of CA-LBG to interact with distilled water. In this condition, CA-LBG particles are difficult to wet so inhibit solubility in distilled water.

3.7. Viscosity

The viscosity of CA-LBG for each batch is shown in Table 1. LBG has a high viscosity, but the presence of excess CA can reduce the viscosity. The viscosity of CA-LBG from batch A to batch B decreased in proportion to the increasing degree of esterification. The carbonyl ester groups formed from the bonding of positive C atoms from carboxylate groups with O atoms of C-6 in mannose and galactose reduce the ability of CA-LBG to trap distilled water so viscosity decreases.

3.8. Flowability

The results of the flowability study on all tablet mass formulas containing CA-LBG showed that an increase in the concentration of CA-LBG increased the flow time of tablet mass (Table 2) because influenced by the irregular shape of particles and the surface like coral inhibit the flow of mass tablet (Figure 5). The CL-1 formula has the fastest flow time due to the influence of the spherical shape of the SDL granules to dominate the flowability although CA-LBG is present in the tablet mass (Sheskey, J. P., Cook, G. W., and Cable 2017). The formula containing SSG and CS showed an increase in concentration cause increased flow time tablet mass. SSG particles are rounded and have a smooth surface, should be able to rate up the flow time but SSG particles are also hygroscopic, thus inhibiting the flow time of tablet mass (Sheskey, J. P., Cook, G. W., and Cable 2017). The CS particles are rod-shaped with a corrugated surface, which at high concentrations can inhibit the flow of tablets mass (Sheskey, J. P., Cook, G. W., and Cable 2017). According to the flow time requirements, all tablet mass

formulas containing a variety of disintegrating agents meet the requirements is 100 g tablet mass can flow in less than 10 seconds (Szumilo et al. 2017).

The effect of the presence of various disintegrating agents on the tablet mass is shown in Figure 5, which is a plot between the concentration of the disintegrating agent and the flow rate [g s^{-1}]. In general, the tablet profile containing CA-LBG the most slope of flow rate although the CA-LBG concentration was increasing. In addition, the decrease in flow rate of tablet mass with a high concentration of CA-LBG is proportional to the flow rate of tablet mass containing high concentrations of SSG and CS. This case is because the particle surface of CA-LBG like coral can fill each other with a porosity of SDL surface (Sheskey, J. P., Cook, G. W., and Cable 2017). The sharp decrease in the profile of tablet mass containing CS at low concentrations (CS-1) indicates that the flow rate is more influenced by the spherical shape of the SDL granules so accelerate the flow, while at higher concentrations (CS-2) the root shape and corrugated surfaces of the CS particles begin to inhibit the flow. The flow rate profile of tablet mass containing SSG at low concentrations (SSG-1) is more slope than the tablet mass containing CS at the same concentration (CS-1) because the hygroscopicity of SSG particles inhibits the flow of tablet mass. The hygroscopic effect of SSG particles at higher concentrations (SSG-2 to SSG-6) can be overcome by the rounded shape and smooth surface of the SSG particles so that the decrease flow rate is more slope.

3.9. Compressibility

The tablet mass density evaluation results on all tablet mass formulas containing CA-LBG or SSG showed that increasing the concentration of the disintegrating agent increased the value of ρ_{tapped}-ρ_{bulk} (Table 2), due to the influence of the shape and surface of the disintegrating agent particles. The initial composition of the tablet mass was SDL granules arranged randomly, the porosity between the SDL granules was filled with disintegrating agent particles.

The CA-LBG particles which have an irregular shape and a coral-like surface are randomly arranged on the porosity between the SDL granules according to the shape and area of the porosity between the initial particles. The volume decrease during the tapping was caused by the movement of SDL granules and CA-LBG particles. The CA-LBG particle corners fill each other surface porosity between particles and SDL granule surface porosity. In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density arrangement between SDL granules and the area of porosity that could accommodate all CA-LBG particles. The volume decrease in the tapping of the formula with the higher CA-LBG concentration causes the porosity between the SDL granules to be wider because the CA-LBG particles surround the SDL granules tightly.

The rounded shape and smooth surface of the SSG particles give a tablet mass arrangement with more regular porosity than the CA-LBG particles. The smooth surface of SSG particles causes movement of SDL granules / SSG particles and decreases in volume during tapping so that the porosity narrows and SSG particles fill the porosity of the SDL granule surface. Formulas containing CS have a different value of ρ_{tapped}-ρ_{bulk} from formulas containing other disintegrating agents, namely the increasing the concentration of CS, the lowering the value of ρ_{tapped}-ρ_{bulk}. The rod-shape and corrugated surface of the CS particles envelop according to the SDL granule shape in layers and has a narrow porosity. The surface of the CS particles decreases the ability of the particles to move and the volume decreases on tapping because the surface corrugated of the CS particles will interlock with other CS particles.

The results of the density evaluation are further confirmed by the compressibility profile shown in Figure 6, where increasing the concentration of the disintegrating agent increases the mass compressibility of tablets containing CA-LBG / SSG and decreases the mass compressibility of tablets containing CS. The mass compressibility of tablets containing CA-

LBG was slightly lower than the mass of tablets containing SSG because the angles of CA-LBG particles fill each other surface porosity between particles and SDL granule surface porosity.

3.10. Weight and thickness

All tablet masses contain a variety of disintegrating agents and their concentration is compressed into tablets and according to weight is around 200 mg (Table 2), which shows that all tablet masses are able to flow freely from the hopper and fill the dies space in the tablet compressing machine. This condition is in accordance with the results of the evaluation of flowability and compressibility.

The variation in tablet thickness from the mass of tablets containing various disintegrating agents is influenced by the arrangement, shape, and surface of the SDL granule or the disintegrating agent particle so that when compression is applied produced deformation of the granule/particle, bond interlocking, and narrowing the porosity between deformations. The irregular shape and coral-like surface of the CA-LBG particles provide an opportunity for the particle corners to fill each other with the SDL particle/granule surface porosity so the tablet mass is compressed to produce a low-porosity tablet. The rounded shape and smooth surface of the SSG particles produce tablets with a regular form of porosity. The root shape and corrugated surface of the CS particles provide an opportunity to interlock between the particles and the corrugated surface so the tablet mass is compressed to produce a low-porosity tablet.

The CL-1 tablet is thicker even though the number of CA-LBG particles is less than the CL-2 tablet because the CA-LBG particles tend to fill the porosity of the SDL granules surface. In the CL-2 tablet, CA-LBG particles fill the surface porosity of SDL granules and porosity between SDL granules. The number of SDL granules of CL-2 tablet mass reduces so that produces a thinner tablet. The CL-3 and CL-4 tablets are thicker than the other CL tablets

because the CA-LBG particles surround the SDL granules so that the volume is high and when the tablet mass is compressed into thick tablets. The CL-4 tablet is thicker than the CL-3 tablet due to the increasing number of CA-LBG particles resulting in a wider area surrounding the SDL granules. The number of CA-LBG particles in the CL-5 and CL-6 formula tablets is increasing so the area of the CA-LBG particles surrounding the SDL granules is wider, but the porosity between the CA-LBG particles is narrow so that the mass of the tablets is compressed to produce a thinner tablet. The CL-6 tablet is thicker than the CL-5 tablet because the CA-LBG particle area surrounding the SDL granules is wider.

The SSG-1 tablet is thicker than other SSG tablets because SSG particles fill the porosity of the SDL granules surface so, with the highest number of granules, the tablet mass is compressed to produce thick tablets. Tablet mass of SSG-2 and SSG-3 show the number of SSG particles is increasing and the number of SDL granules is decreasing. The SSG particles in the SSG-2 tablet mass filled the surface porosity of the SDL granules and the dense porosity of the SDL granules. The SSG-3 tablet mass shows the number of SDL granules was reduced so the mass of the tablets was compressed to produce a thinner tablet. The tablet mass of SSG-4 to SSG-6 contains more SSG particles and surrounds the decreasing SDL granules. The SSG-5 tablet is thicker than the SSG-4 tablet because the SSG deformation area surrounding the SDL deformation is wider. The SSG-6 tablet contained more SSG surrounding the SDL deformation with the area is wider. The SSG-6 tablet thickness is similar to SSG-5 because the number of SDL deformation in the tablet mass is reduced.

The thickness of the CS-1 tablet was dominated by the effect filling of CS particles on porosity SDL granules surface so when compressed the tablet mass experienced deformation with porosity varying of shapes and areas. The tablet of CS-2 to CS-4 contain more CS particles and fewer SDL granules. The increasing number of CS particles formed the interlocking deformation between the particles and enveloped the SDL granules so that produce thicker

tablets with narrow porosity but in large numbers. The greater the number of CS particles, the wider the enveloping and interlocking area of the CS particles, resulting in a thicker tablet. The thickness of the CS-5 and CS-6 formula tablets was dominated by the increase in the number of CS particles. CS particles in the CS-5 tablet mass forming long interlocking on surrounding SDL granules. The tablet mass contains limited SDL granules so produce thin tablets when compressed. The CS-6 tablet is thicker than the CS-5 tablet because the interlocking area enveloping the SDL granule is wider.

3.11. Break force and tensile strength

Evaluation of tablet resistance to mechanical stress is measured by the BF value and shown in Table 2. The resistance of the CL-1 tablet is influenced by the dominance of SDL granules interlocking bonds when compressed to result in deformation with a wide porosity so that the tablets have a low resistance to mechanical stress. The BF value of the CL-2 tablet is higher than CL-1tablet because the number of CA-LBG particles is more and fills the dense porosity between SDL granules so when compressed the interlocking bonds are stronger and the porosity is narrower. The CL-3 tablet shows the highest BF value than other CL tablets because the deformation of CA-LBG particles around the SDL granule when compressed is able to form interlocking bonds with narrow porosity so that the thick tablet and resistant to mechanical stress. In addition, the corners of the CA-LBG particles fill the surface porosity between the CA-LBG particles and the SDL granule surface porosity so strengthening the interlocking bond. The CL-4 to CL-6 tablets have a similar mechanism as the CL-3 formula tablets, but the number of CA-LBG particles is increasing and SDL granules are decreasing so that when compressed, produce tablets with a lot of narrow porosity and a decrease in tablet resistance to mechanical stress. The tablet of CL-5 and CL-6 show similar BF values due to

the CL-6 tablet, although the interlocking bonds between particles are more dominant with the number of narrow porosity increases.

The SSG particles in the SSG-1tablet mass fill the surface porosity of the SDL granules so inducing the granules to be slightly moist and the interlocking bonds between the SDL deformation are weaker. In addition, SDL granules after being compressed produce wide porosity deformation. The resistance of the SSG-2 tablet is higher than the SSG-1 tablet because the narrow porosity between the SDL granules is filled with SSG particles so that the mass of the granules is compressed resulting in a narrower porosity deformation. The SSG-3 tablet shows the strongest resistance than other tablets because SSG particles surround SDL granules when compressed able to form deformation interlocking bonds with narrow and regular porosity so tablets are resistant to mechanical stress. SSG-4 to SSG-6 tablets have a similar mechanism to SSG-3 tablets, but the number of SSG particles is increasing and SDL granules are decreasing so the mass of SSG-5 and SSG 6 when compressed produces tablets with more narrow porosity and decrease in the resistance of the tablet to mechanical stress. In addition, the slightly hygroscopic character of SSG particles decreased the resistance of tablets shown in the SSG-4 tablet because the deformation interlocking bonds of SSG particles around the SDL granules were weak.

The little number of CS particles in the CS-1 tablet tends to fill the porosity of the SDL granules. When compressed, the interlocking bond is dominated by SDL deformation with wide porosity so the resistance of the tablets to mechanical stress is weak. The CS-2 tablet has a similar mechanism to the CS-1 tablet but the porosity between the SDL granules is filled with CS particles so produces a tablet with narrower porosity and is more resistant to mechanical pressure. The CS-3 tablet has a similar mechanism to the CS-2 tablet but the number of CS particles is more so the CS particles form interlocking between particles and envelop the SDL granules. When compressed, the enveloping CS particles form an interlocking bond

deformation with a narrow and large porosity so the tablet surface resistance is weak. In the CS-4 tablet, the interlocking CS particles to envelope the SDL granules and a wider area so produce tablets with interlocking narrow porosity and strong surface to withstand mechanical stress. The CS-5 and CS-6 tablets have a similar mechanism to the CS-4 tablets but the number of CS particles is increasing and the SDL granules are decreasing. In CS-5 tablet, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface. In CS-6 tablet, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.

The BF value was further confirmed by the tensile strength parameter to determine the comparison between tablets contain disintegrating agent variation according to the concentration in the experiment (Figure 7). The tensile strength profile of CA-LBG tablets is similar to that of SSG tablets due to the influence of the particle shape of CA-LBG and SSG. The irregular shape and coral surface of the CA-LBG particles produce tablets with strong deformation interlocking bonds. The tensile strength intensity of CA-LBG tablets is similar to that of SSG tablets showing a deformation interlocking bond that can adjust the concentration used in the tablets. In the experiment, the peak tensile strength of CA-LBG tablets and SSG tablets was a concentration of 2% while CS tablets was a concentration of 4%. This concentration is the optimum condition for forming tablets with the most stable interlocking deformation bonds against mechanical stress.

3.12. Friability

Evaluation of tablet resistance to mechanical movement is measured by friability parameters and is shown in Table 2. The friability of the CL-1 tablet is influenced by the low BF value due to the interlocking bond of SDL deformation with wide porosity so that SDL

deformation on the tablet surface releases particles when subjected to mechanical movement. In addition, the CA-LBG particles on the tablet surface were also released. The CL-2 tablet is more friable than the CL-1 tablet although the BF value is higher because the number of CA-LBG particles on the surface of the tablet is more so more particles are released when subject to mechanical movement. The CL-3 to CL-6 tablets showed a tendency to decrease in friability although the BF value was lower because of a strong interlocking bond on the deformation of granules and particles, so reducing the release of tablet surface particles when subjected to mechanical movement. The CL-6 tablet is more friable than the CL-5 tablet because the number of SDL deformation decreases so that the foundation to withstand mechanical movements is reduced.

The SSG-1 tablet is the most friable than SSG other tablets because of the low BF value due to SDL deformation interlocking bonds with wide porosity so that the tablet surface releases lactose and SSG particles when subjected to mechanical movement. The decrease in the friability of the SSG-2 and SSG-3 tablets proportional to the higher BF value indicates a strong interlocking bond from the deformation of granules and particles so resistant to mechanical movement. The friability of the SSG-4 to SSG-6 tablets tends to decrease because the strength of the interlocking bonding of SSG deformation is able to withstand mechanical movements. The SSG-6 tablet is more friable than the SSG-5 tablet because the number of SDL deformation is reduced so the foundation to withstand mechanical movements is reduced.

The CS-1 tablet is the most friable than the other CS tablets because the SDL deformation interlocking bond dominates with a wide porosity so the lactose and CS particles on the surface are released when subject to mechanical movement. The friability of the CS-2 and CS-3 tablets increased proportionally to the BF values of the two tablet formulas decreased. The more SSG deformation interlocking bonds, the stronger the tablet withstands mechanical movements. The friability of the CS-4 to CS-6 tablets proportional to the BF value and tends

to decrease. The CS deformation on the tablet surface has a strong interlocking bond to withstand mechanical movements. The CS-6 tablet is more friable than the CS-5 tablet because of the reduced deformation of SDL as a foundation to resist mechanical movements.

The comparison of the effect of the presence of the disintegrating agent in each tablet formula to friability according to the concentration in the experiment is shown in Figure 8. The friability profile of the three CA-LBG tablets is similar but different at the peak of each disintegrating agent (CA-LBG 1%; CS 2%; SSG 4%). These peaks indicate that the tablet surface has bonds weakly of interlocking deformation and less stable to mechanical movements. The friability value before the peak concentration was also influenced by the release of particles from the SDL deformation, while after the peak concentration was influenced by the quality of the interlocking bond of deformation particles on the tablet surface so resistant to mechanical motion. CA-LBG tablets are more friable than other tablets due to the influence of the coral surface on the particles which tend to be friable when the porosity is not filled with other particles. The high friability profile of CA-LBG tablets appears at low concentrations because the surface porosity of the CA-LBG particles is not filled due to the limited number of CA-LBG particles. In addition, the irregularly shaped CA-LBG particles causing the porosity of tablets were number and wide.

3.13. Disintegration time

The evaluation of tablet disintegration rates for all formulas with various disintegrating agents and concentrations is shown in Table 2. The disintegration of tablets containing CA-LBG showed a fast disintegration time proportional to the increasing concentration of CA-LBG. The value of BF and friability do not affect the function of the CA-LBG to disintegrate the tablet. The irregular particle shape and the corrugated surface of the CA-LBG particles resulted in a tablet with porosity for penetration of the disintegrating medium (Figure 4). The

deformation porosity of CA-LBG formed on the tablet is proportional to the CA-LBG concentration in the tablet formula. The porosity of a large number on the tablet cause increases the channel for penetration of the disintegrating medium so that the tablet is disintegrating. The CA-LBG is an ester excipient that has low viscosity and low solubility in water (Table 1). This characteristic causes a repulsive force between deformations of CA-LBG on tablets when wet by disintegration medium. The repulsion force increases in proportion to the CA-LBG concentration in the tablet formula. The repulsive force between the CA-LBG deformations causes the tablets to disintegrate.

Tablets containing SSG showed that SSG concentration, BF value, and friability were influenced the disintegration time. The speed of tablet disintegration time is proportional to the increasing SSG concentration shown in the SSG-1 to SSG-4 tablets. Deformation of SSG in tablets attracts disintegration medium so SSG deformation swells and pushes deformation of other granules and particles to move away from each other so that the tablet is disintegrating. SSG-5 and SSG-6 tablets show the resistance of the tablets to pressure and mechanical movements affect the speed of disintegration. Increased BF value and low tablet friability caused long tablet disintegration time due to the strong interlocking bond between the deformation of granule or particle, thus inhibiting tablet disintegration.

Tablets containing CS showed an increase in CS concentration causing the disintegration time to rapidly. The resistance of tablets indicated by BF value and friability did not affect the function of CS as a tablet disintegrating agent. Tablets containing CS attracts the disintegrating medium for penetration into the tablet so that the CS deformation swell and push deformation around. The more the CS deformation swell, the faster the tablet integrates.

The comparison of the ability of the disintegrating agent in each tablet formula according to the concentration in the experiment is shown in Figure 9. The time profile for the disintegration of CA-LBG tablets is similar to that of CS tablets because the two disintegrating

agents perform their function not influenced by the quality of other tablets so that the increase in concentration is proportional to the increase in disintegration speed. tablet. In contrast to SSG tablets, the disintegration time is also influenced by the hardness and friability of the tablets, thus inhibiting the disintegration process in tablets with SSG concentrations of 8% and 12%. The disintegration time profile of CA-LBG tablets is longer than CS tablets because low solubility of CA-LBG so that the wetting time of CA-LBG tablets is longer and inhibits integration.

3.14. Dissolution

Experiments to study drug release from the dosage form were carried out using tablets of 1%, 2%, and 4% concentrations of each disintegrating agent. The effect of the disintegrating agent on the release of diclofenac sodium from the tablet is presented in Figure 10. The dissolution profile of the tablets containing CA-LBG showed that the release of diclofenac sodium from the tablets appeared to be different at 5 and 15 minutes. The higher the CA-LBG concentration on the cause tablet more rapidly disintegrates and releases more diclofenac sodium. All tablets with each concentration of CA-LBG meet the requirements for releasing diclofenac sodium (Directorate General of Medicine and Food 1995).

Comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11). Tablets containing CA-LBG showed a slower release of diclofenac sodium than tablets containing SSG and CS because of the gradual release at 5 and 15 minutes. The low solubility of CA-LBG inhibits the wetting of the tablets for disintegration thus inhibiting the solubility of diclofenac sodium in the dissolution medium.

4. Conclusion

Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. Increasing the concentration of HCl in the synthesis causes a decrease in the viscosity of CA-LBG due to an increase in CA molecules bound to LBG. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In addition, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased the compressibility. The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Acknowledgement

The authors thank the research, technology, and higher education department, Indonesia for support of this work by providing research grants (0299/E3/2016). The author also thanks PT. Makmur Food (Indonesia) for supporting locust bean gum (viscogum); LPPT Gadjah Mada University (Indonesia) for the SEM, DSC, NMR instrument support; Faculty of Pharmacy, Gadjah Mada University (Indonesia) for support of pharmaceutical technology facilities; Faculty of Pharmacy, Widya Mandala Catholic University Surabaya (Indonesia) for pharmaceutical technology facilities and instruments.

Declarations

Author contribution statement

Wuryanto Hadinugroho: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Suwaldi Martodihardjo, Achmad Fudholi, Sugeng Riyanto: Conceived and designed the experiments; Analyzed and interpreted the data.

Declarations of interest

The authors declare no conflict of interest.

References

Azero EG, Andrade CT (2006) Characterisation of Prosopis juliflora seed gum and the effect of its addition to κ-carrageenan systems. J Braz Chem Soc 17:844–850. https://doi.org/10.1590/S0103-50532006000500005

Bertocchi P, Antoniella E, Valvo L, et al (2005) Diclofenac sodium multisource prolonged release tablets - A comparative study on the dissolution profiles. J Pharm Biomed Anal 37:679–685. https://doi.org/10.1016/j.jpba.2004.11.041

Bhatia H, Gupta PK, Soni PL, Division C (2013) Extraction , Purification and Characterization of a Galactomannan From Prosopis Juliflora (Sw .) Dc . Seed. Int J Sci Enviroment Technol 2:708–724

Bhattacharya A, Rawlins JW, Ray P (2008) Polymer Grafting and Crosslinking. A John Wiley & Sons, Inc, Publication, Canada

Chudzikowski RJ (1971) Guar gum and its applications. J Soc Cosmet Chem 22:43–60

Coates J (2006) Interpretation of Infrared Spectra, A Practical Approach. Encycl Anal Chem

10815–10837. https://doi.org/10.1002/9780470027318.a5606

Colas A (2005) Cow Corning Silicones : Preparation Properties and Performance. Midland

Das N, Triparthi N, Basu S, et al (2015) Progress in the development of gelling agents for improved culturability of microorganisms. Front Microbiol 6:1–7. https://doi.org/10.3389/fmicb.2015.00698

Dey P, Maiti S, Sa B (2013) Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide. J Biomater Sci Polym Ed 24:663–683. https://doi.org/10.1080/09205063.2012.703950

Dionísio M, Grenha A (2012) Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci 4:175–185. https://doi.org/10.4103/0975-7406.99013

Directorate General of Medicine and Food (1995) Indonesian Pharmacopoeia 4th edition. Ministry of Health Republic of Indonesia, Jakarta

Doll KM, Shogren RL, Willett JL, Swift G (2006) Solvent-free polymerization of citric acid and D-sorbitol. J Polym Sci Part A Polym Chem 44:4259–4267. https://doi.org/10.1002/pola.21535

Ghasemi J, Niazi A, Ghobadi S (2005) Simultaneous spectrophotometric determination of benzyl alcohol and diclofenac in pharmaceutical formulations by chemometrics method. J Chinese Chem Soc 52:1049–1054. https://doi.org/10.1002/jccs.200500148

Gillet S, Aguedo M, Blecker C, et al (2014) Use of 13C-NMR in structural elucidation of polysaccharides: case of locust bean gum. Liège

Gouda AA, Kotb El-Sayed MI, Amin AS, El Sheikh R (2013) Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: A review. Arab J Chem 6:145–163. https://doi.org/10.1016/j.arabjc.2010.12.006

Gulrez SKH, Al-Assaf S, Phillips GO (2011) Hydrogels: Methods of Preparation, Characterisation and Applications. In: Progress in Molecular and Environmental

Bioengineering - From Analysis and Modeling to Technology Applications

Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S (2019) Esterification of citric acid with locust bean gum. Heliyon 5:e02337. https://doi.org/10.1016/j.heliyon.2019.e02337

Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S (2017) Study of a catalyst of citric acid crosslinking on locust bean gum. J Chem Technol Metall 52:1086–1091

Hammami MM, Hussein RF, Alswayeh R, Alvi SN (2020) Eight enteric-coated 50 mg diclofenac sodium tablet formulations marketed in Saudi Arabia: In vitro quality evaluation. BMC Res Notes 13:1–6. https://doi.org/10.1186/s13104-020-05270-4

Jans AWH, Kinne RKH (1991) 13C NMR spectroscopy as a tool to investigate renal metabolism. Kidney Int 39:430–437. https://doi.org/10.1038/ki.1991.54

Markl D, Zeitler JA (2017) A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res 34:890–917. https://doi.org/10.1007/s11095-017-2129-z

Michael E. Aulton, Kevin M. G. Taylor (2017) Aulton's Pharmaceutics The Design and Manufacture of Medicines. Churchill Livingstone Elsevier, New York

Parvathy KS, Susheelamma NS, Tharanathan RN, Gaonkar AK (2005) A simple non-aqueous method for carboxymethylation of galactomannans. Carbohydr Polym 62:137–141. https://doi.org/10.1016/j.carbpol.2005.07.014

Pitt KG, Newton JM, Richardson R, Stanley P (1989) The Material Tensile Strength of Convex- faced Aspirin Tablets. J Pharm Pharmacol 41:289–292. https://doi.org/10.1111/j.2042-7158.1989.tb06458.x

Samavati V, Razavi SH, Rezaei KA, Aminifar M (2007) Intrinsic viscosity of locust bean gum and sweeteners mixture in dilute solutions. Electron J Environ Agric Food Chem 6:1879–1889

Santiago, E. V., Lopez, S. H. A, Romero AR (2006) Photochemical cross-linking study of polymers containing diacetylene groups in their main chain and azobenzene compounds

as pendant groups. Superf y vacío 19:1–7

Shang C, Sinka IC, Jayaraman B, Pan J (2013) Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. Int J Pharm 442:57–64. https://doi.org/10.1016/j.ijpharm.2012.09.005

Sheskey, J. P., Cook, G. W., and Cable GC (2017) Handbook of Pharmaceutical Excipients 8th by Sheskey, Paul J Cook, Walter G Cable, Colin G. Pharmaceutical Press and American Pharmacists Association, London-Washington DC

Szumilo M, Belniak P, Swiader K, et al (2017) Assessment of physical properties of granules with paracetamol and caffeine. Saudi Pharm J 25:900–905. https://doi.org/10.1016/j.jsps.2017.02.009

Tamaki Y, Teruya T, Tako M (2010) The chemical structure of galactomannan isolated from seeds of Delonix regia. Biosci Biotechnol Biochem 74:1110–1112. https://doi.org/10.1271/bbb.90935

The United States Pharmacopeial Convention (2018) Pharmacopeia 41-National Formulary 36, 41st edn. Twinbrook Parkway, Rockville

Tjandraatmadja GF, Burn LS, Jollands MJ (1999) The effects of ultraviolet radiation on polycarbonate glazing. Proc 8th Int Conf Durab Build Constr Mater Vancouver, Canada 30:884–898

Uday Kumar M, Babu K (2014) Design and evaluation of fast dissolving tablets containing diclofenac sodium using fenugreek gum as a natural superdisintegrant. Asian Pac J Trop Biomed 4:S329–S334. https://doi.org/10.12980/APJTB.4.2014B672

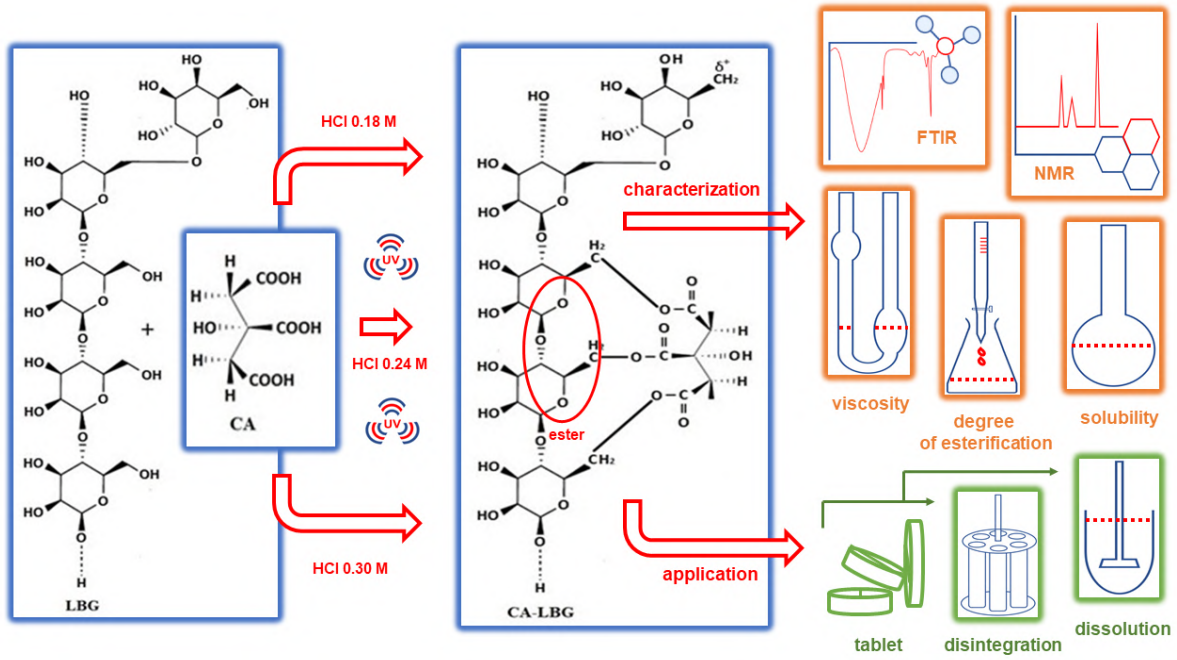
Yeh CC, Chen CN, Li YT, et al (2011) The effect of polymer molecular weight and UV radiation on physical properties and bioactivities of PCL films. Cell Polym 30:261–276. https://doi.org/10.1177/026248931103000503

Zhang Y ling, Zhao C xia, Liu X dong, et al (2016) Application of poly(aspartic acid-citric

acid) copolymer compound inhibitor as an effective and environmental agent against calcium phosphate in cooling water systems. J Appl Res Technol 14:425–433. https://doi.org/10.1016/j.jart.2016.08.006

Zupančič Bozič D, Vrečer F, Kozjek F (1997) Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur J Pharm Sci 5:163–169. https://doi.org/10.1016/S0928-0987(97)00273-X

Graphical Abstract



Figure

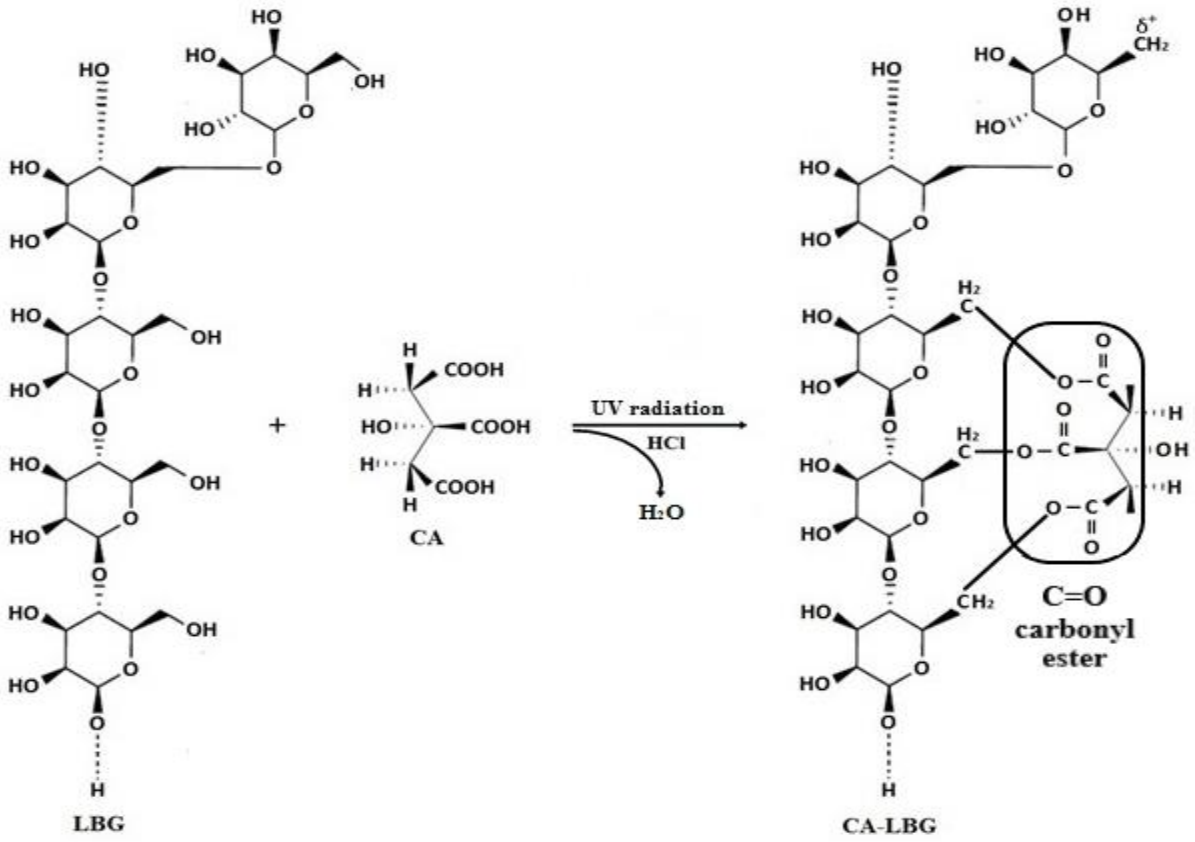


Figure 1. CA-LBG production mechanism. Synthesis of CA-LBG was carried out by adding 0.42 M CA to 7.10 x 10-6 M LBG which had swollen. The mixture was added with HCl (0.18-0.42 M) and UV irradiated (100 minutes).

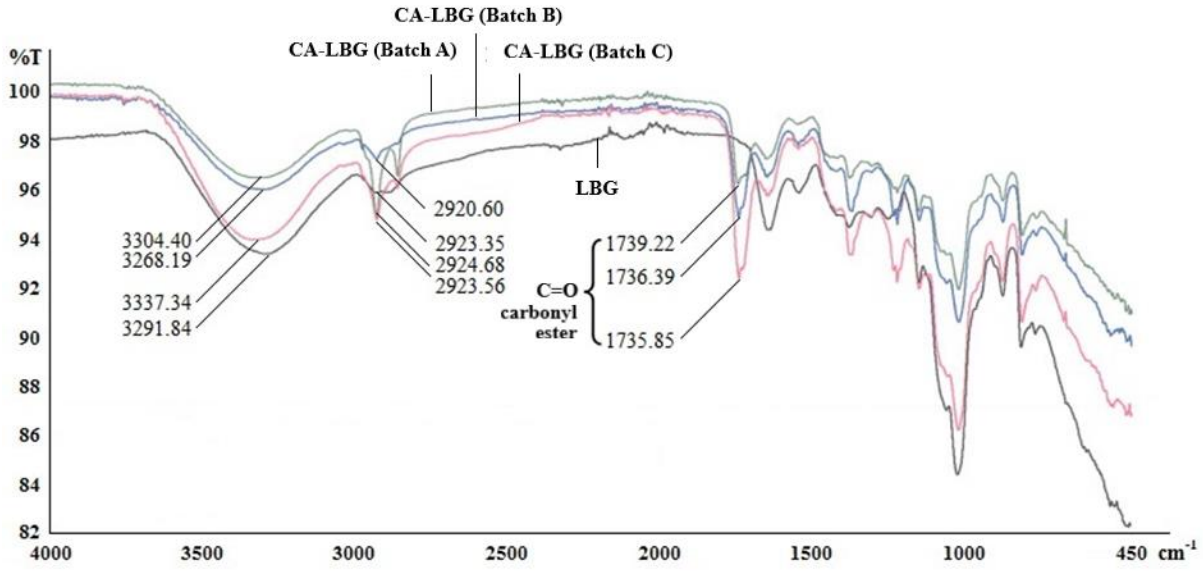


Figure 2. FTIR spectrum of LBG and CA-LBG. LBG as a comparison is shown in black spectra. CA-LBG was synthesized using a 0.18 M HCl catalyst (Batch A) shown in green spectra. CA-LBG was synthesized using a 0.24 M HCl catalyst (Batch B) shown in blue spectra. CA-LBG was synthesized using 0.30 M HCl catalyst (Batch C) shown in red spectra. The carbonyl ester group (C=O) is a specific group that presents at CA-LBG and absent at LBG.

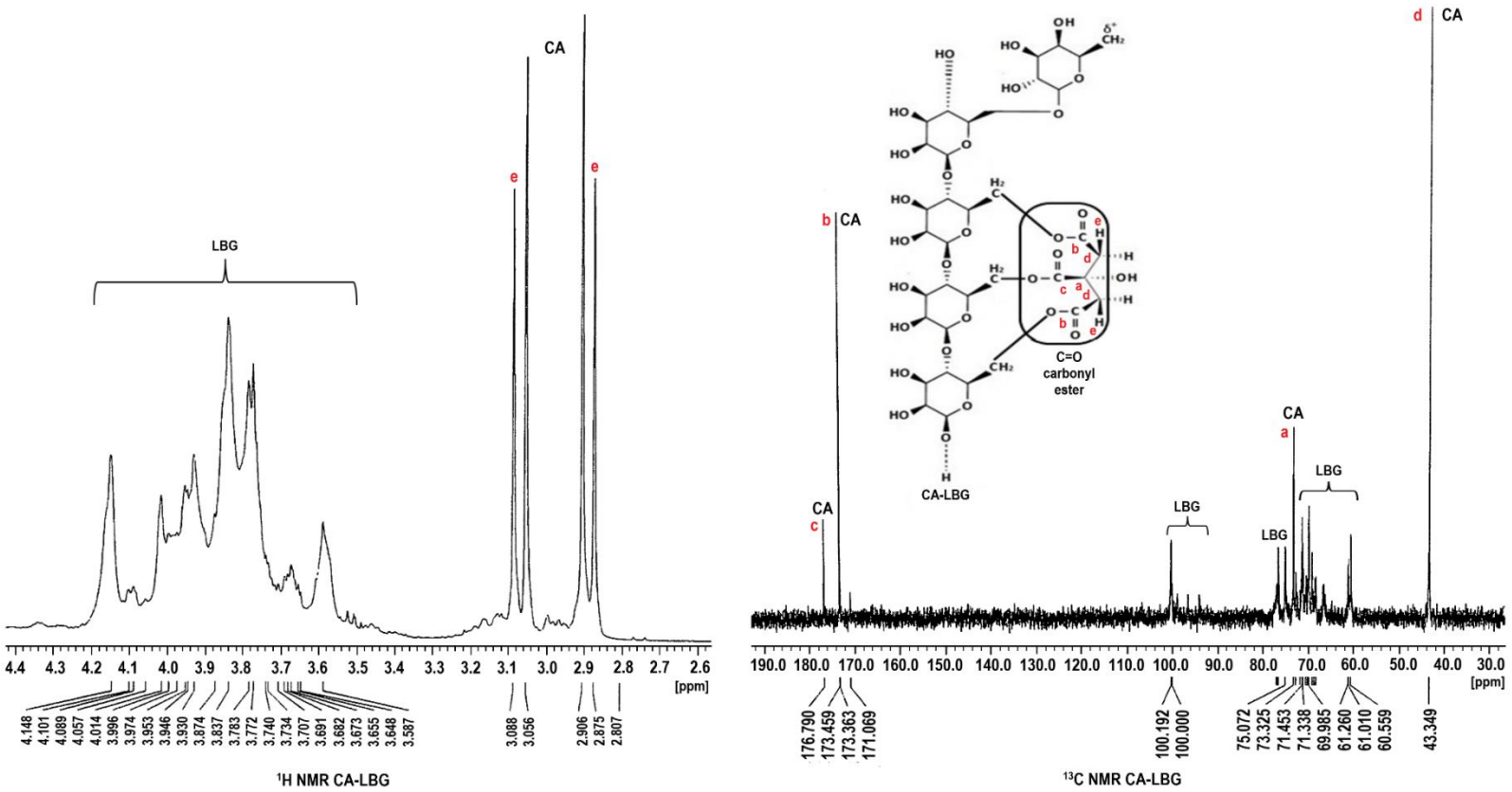
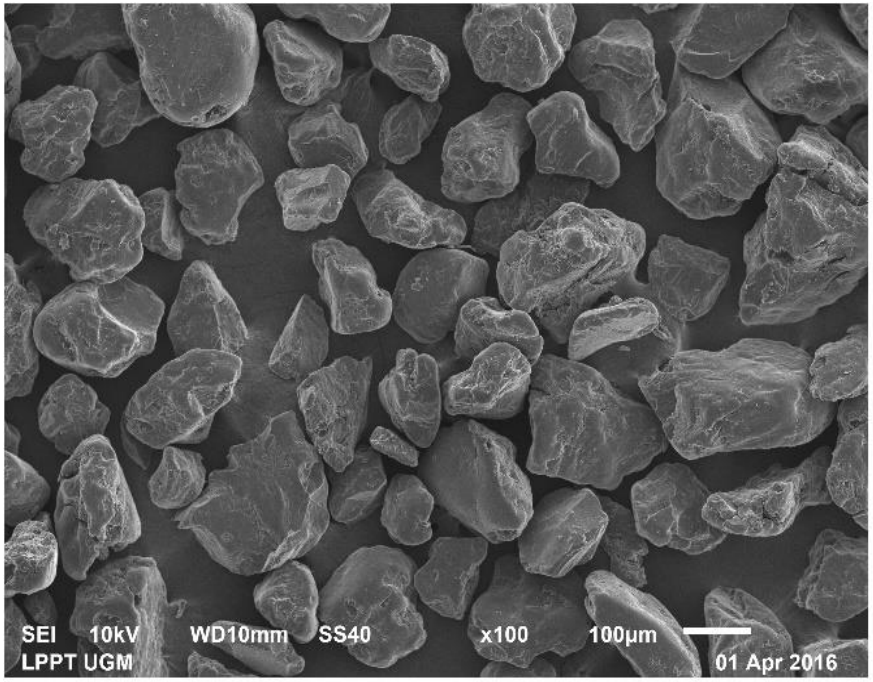
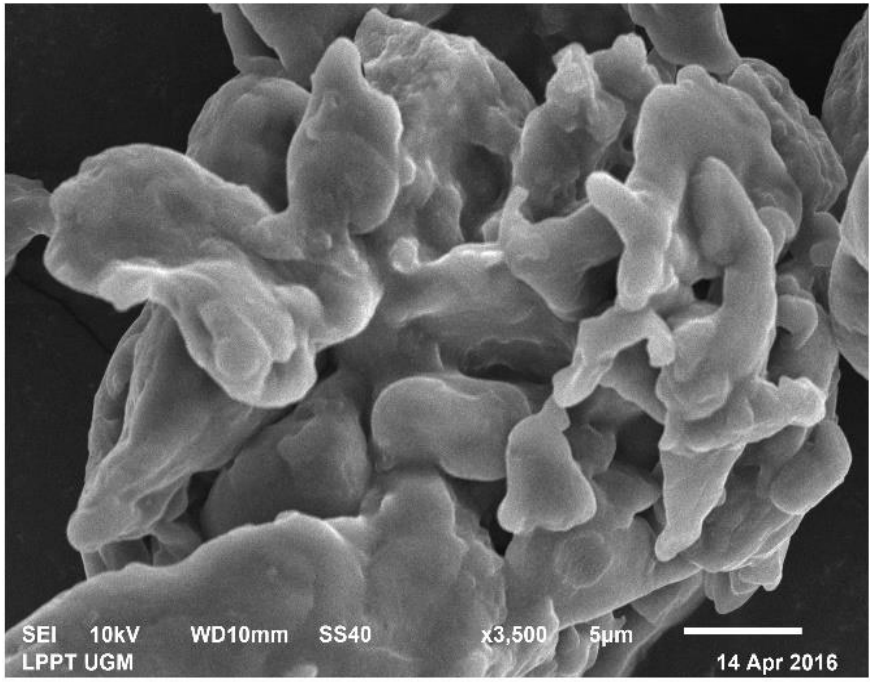


Figure 3. ^{1}H NMR and ^{13}C NMR spectrum of CA-LBG representative (Batch B). CA-LBG was synthesized using catalyst 0.24 M HCl. The presence of CA at CA-LBG was shown in the peaks of a, b, c, d, and e.



CA-LBG [magnification 100x]



CA-LBG [magnification 3500x]

Figure 4. SEM images of CA-LBG representative, synthesized using catalyst 0.24 M HCl (Batch B)

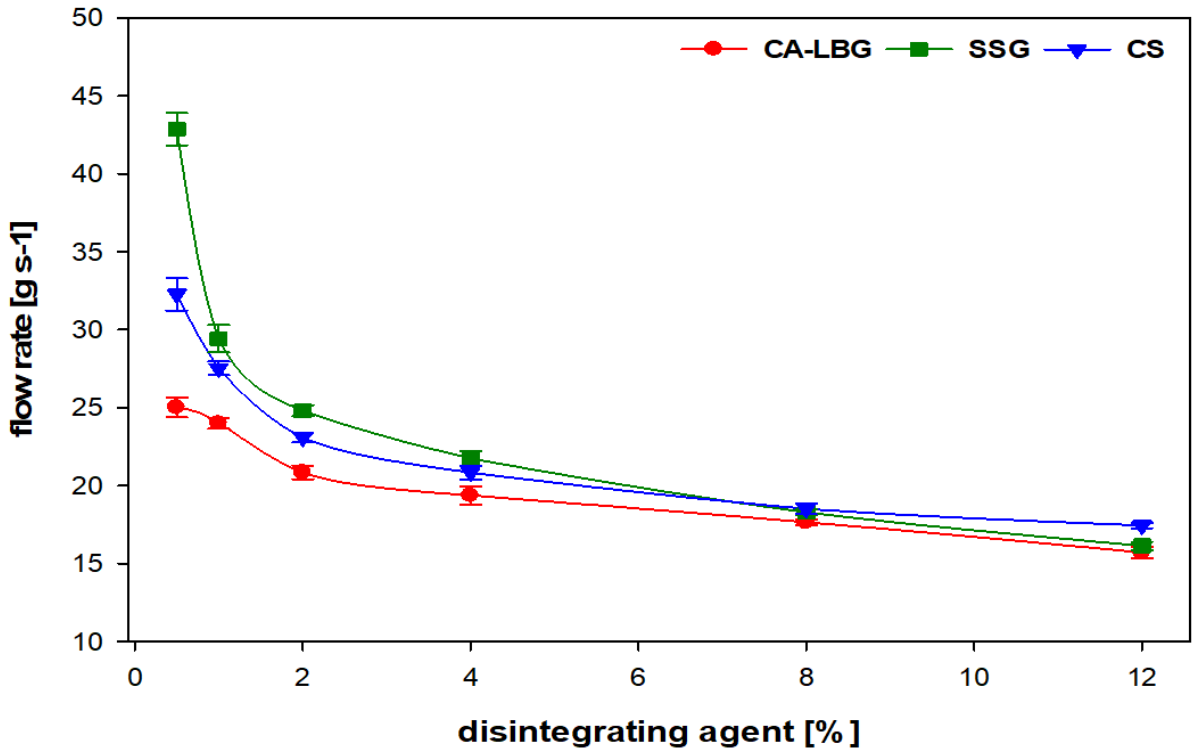


Figure 5. The flow rate profile of the mass of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

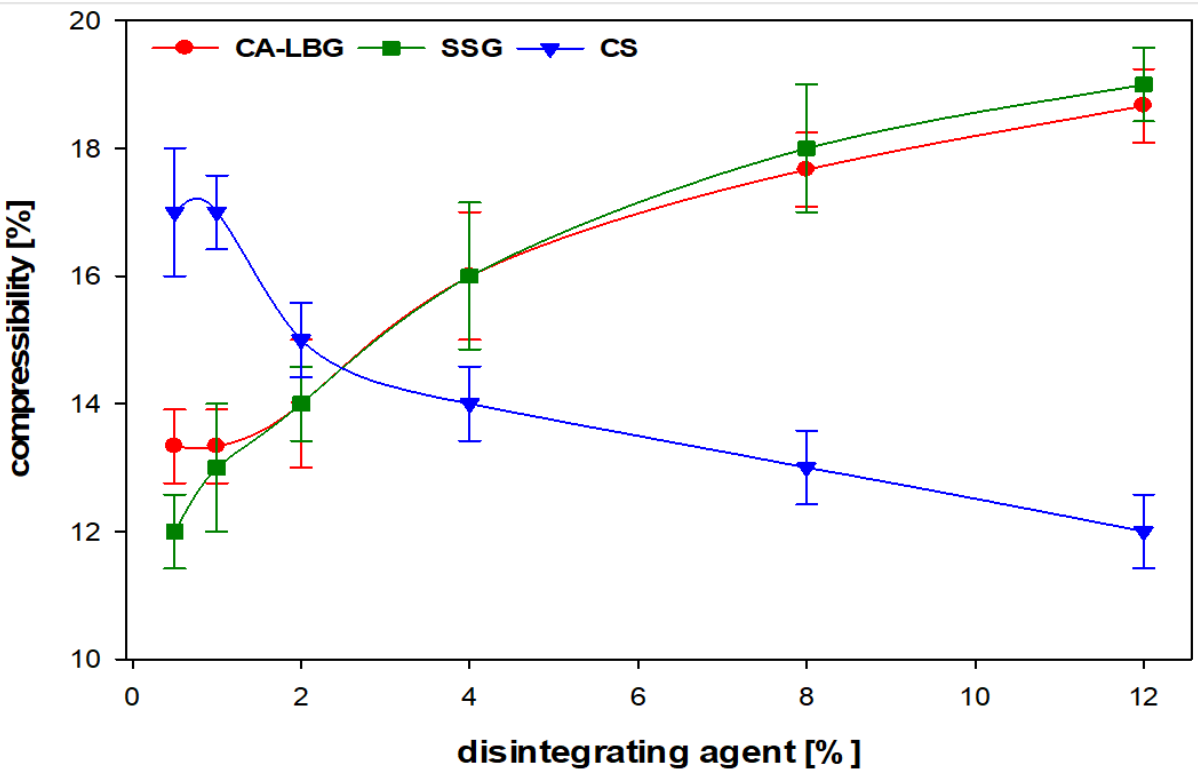


Figure 6. The compressibility profile of the tablet mass contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

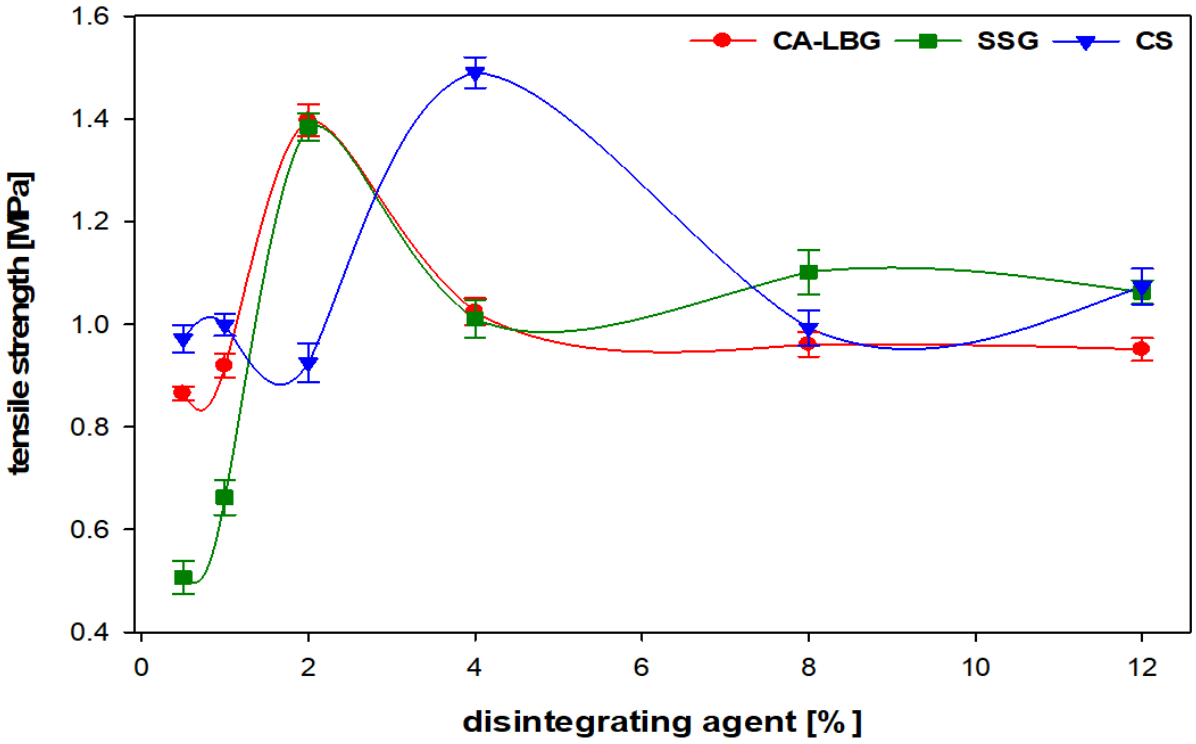


Figure 7. The tensile strength profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

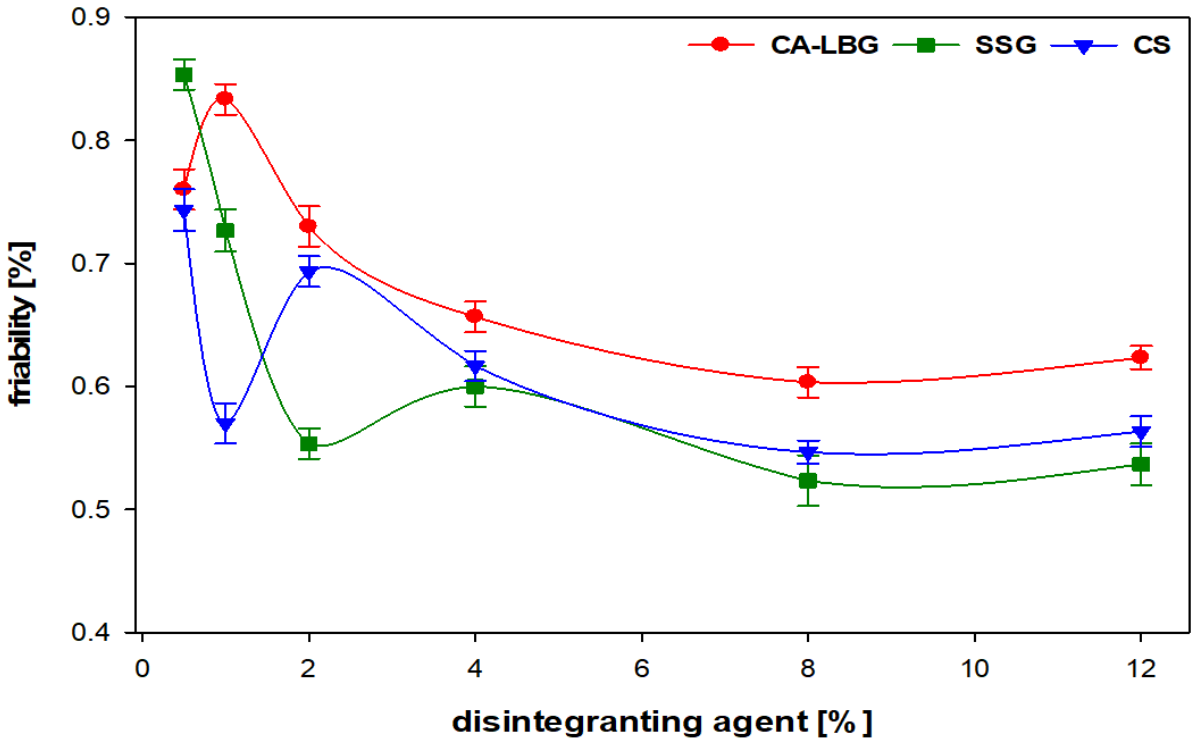


Figure 8. The friability profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

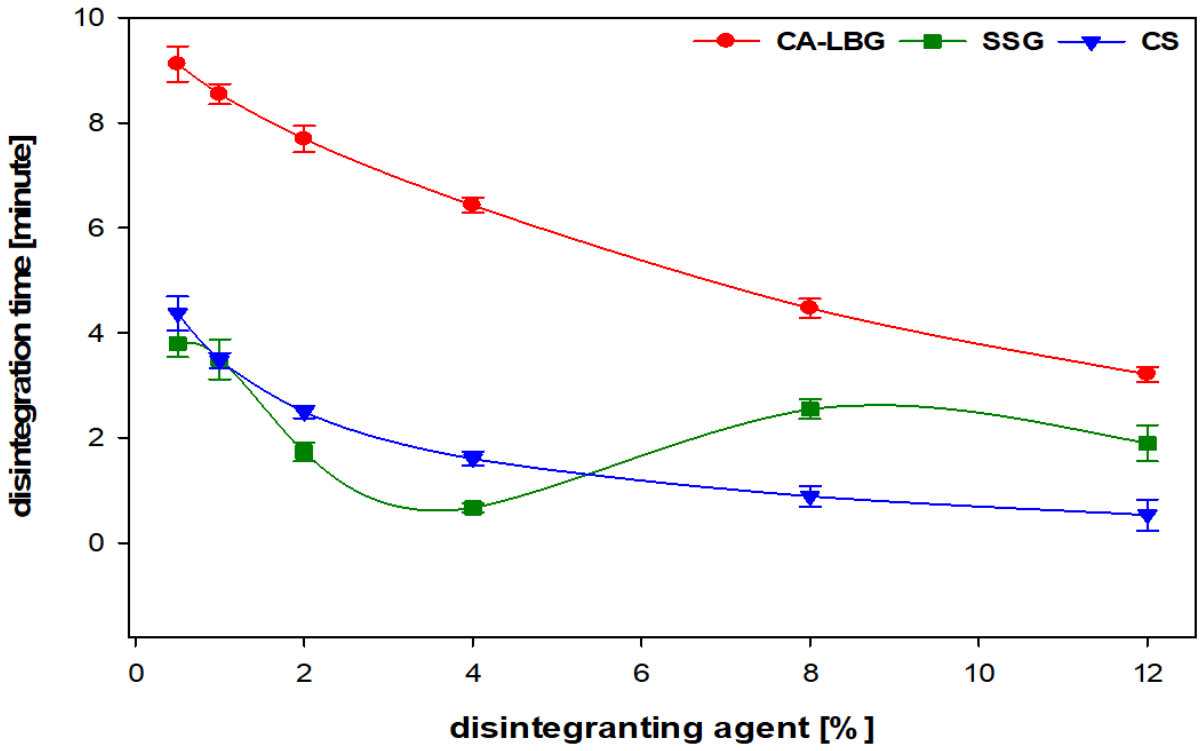


Figure 9. The disintegration time profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

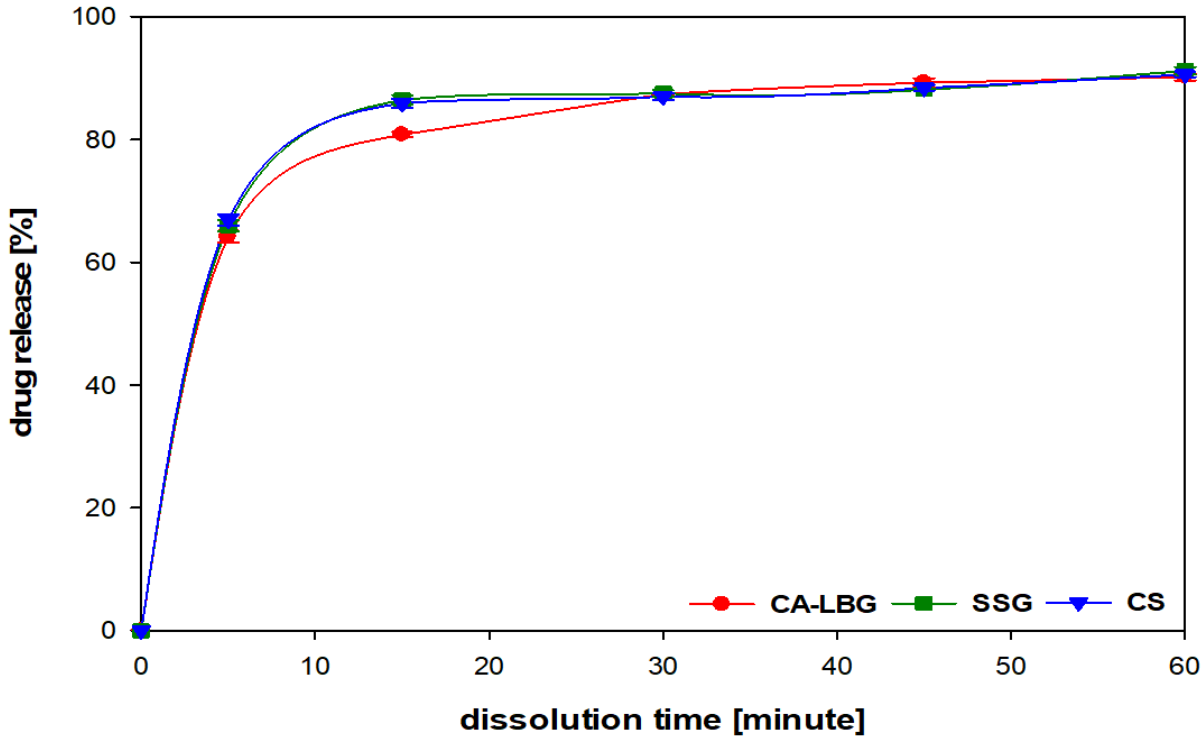
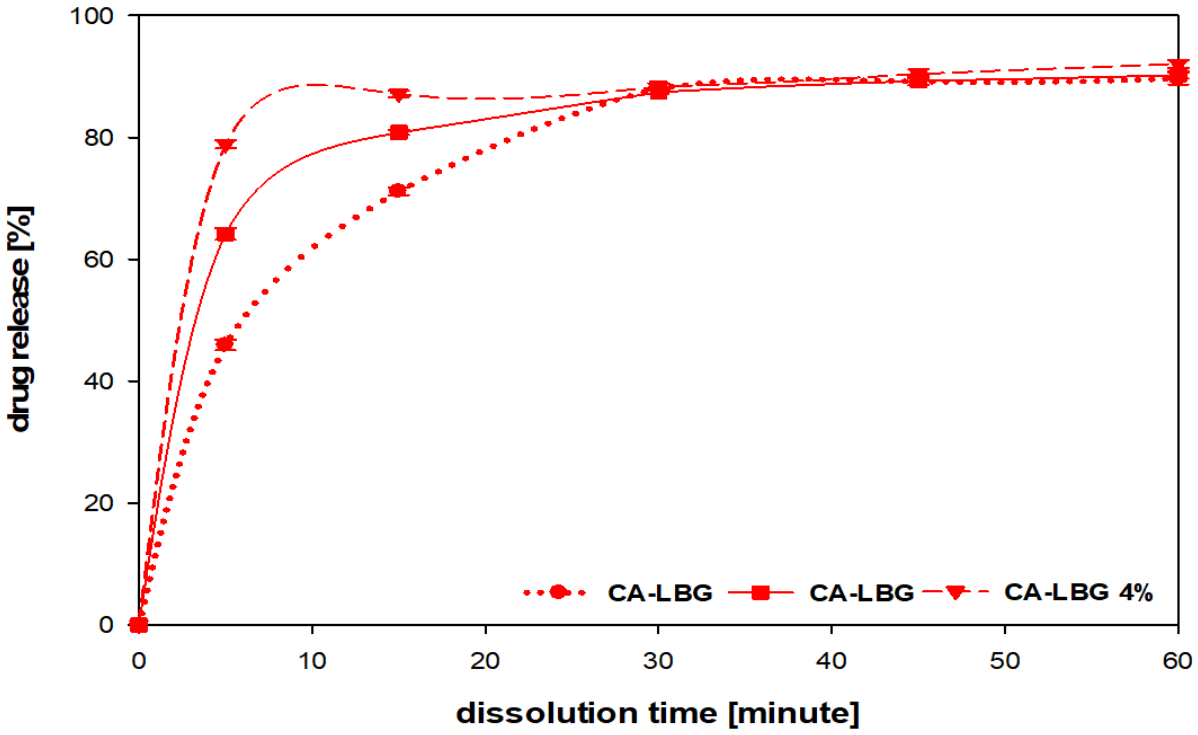


Figure 10. The dissolution profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 2%.



106

107 **Figure 11.** The dissolution profile of the tablet contains CA-LBG 1%; 2% and 4%.

Table 1. Detail synthesis of CA-LBG using the concentration of HCl and irradiated with UV (254 nm,100 minutes). Value physical parameters of CA-LBG: the degree of esterification, carbonyl ester wavelength, solubility, and viscosity.

Batch Code	LBG 10^{-6} [Molar]	CA [Molar]	HCl [Molar]	Carbonyl Ester [cm^{-1}]	Degree of Esterification [%]	Solubility [%]	Viscosity [cP]
A	7.10	0.42	0.18	1739.22	8.27 ± 0.19	36.63 ± 1.14	11.20 ± 0.10
B	7.10	0.42	0.24	1736.39	9.13 ± 0.13	29.30 ± 1.16	9.48 ± 0.06
C	7.10	0.42	0.30	1735.85	9.69 ± 0.23	22.64 ± 1.15	7.76 ± 0.07

Table 2. Details of tablet formulations using disintegrating agents. Evaluate the physical quality of the tablet mass and the tablet.

formula code	disintegrating agent			flow time	ρ_{tapped}-ρ_{bulk}	actual weight	thickness	break force	friability	disintegration time
	CA-LBG	SSG	CS							
	[%]	[%]	[%]	[sec.]	[g.mL^{-1}]	[mg]	[mm]	[kp]	[%]	[min.]
CL-1	0.5	-	-	4.0 ± 0.10	0.041 ± 0.00	201.0 ± 0.25	4.39 ± 0.01	4.0 ± 0.06	0.76 ± 0.02	9.12 ± 0.34
CL-2	1	-	-	4.2 ± 0.06	0.041 ± 0.00	201.2 ± 0.47	4.38 ± 0.01	4.2 ± 0.10	0.83 ± 0.01	8.54 ± 0.19
CL-3	2	-	-	4.8 ± 0.10	0.044 ± 0.01	201.2 ± 0.12	4.40 ± 0.01	6.4 ± 0.15	0.73 ± 0.02	7.69 ± 0.25
CL-4	4	-	-	5.2 ± 0.15	0.053 ± 0.01	201.1 ± 0.21	4.41 ± 0.01	4.7 ± 0.12	0.66 ± 0.01	6.43 ± 0.14
CL-5	8	-	-	5.7 ± 0.06	0.059 ± 0.01	200.9 ± 0.26	4.38 ± 0.01	4.4 ± 0.10	0.60 ± 0.01	4.47 ± 0.18
CL-6	12	-	-	6.4 ± 0.15	0.061 ± 0.00	201.1 ± 0.36	4.39 ± 0.01	4.4 ± 0.12	0.62 ± 0.01	3.21 ± 0.14
SSG-1	-	0.5	-	2.3 ± 0.06	0.036 ± 0.00	200.8 ± 0.06	4.40 ± 0.01	2.3 ± 0.15	0.85 ± 0.01	3.79 ± 0.25
SSG-2	-	1	-	3.4 ± 0.10	0.042 ± 0.00	201.1 ± 0.44	4.38 ± 0.01	3.0 ± 0.15	0.73 ± 0.02	3.49 ± 0.38
SSG-3	-	2	-	4.0 ± 0.06	0.047 ± 0.01	201.0 ± 0.51	4.35 ± 0.01	6.3 ± 0.12	0.55 ± 0.01	1.73 ± 0.18
SSG-4	-	4	-	4.6 ± 0.10	0.051 ± 0.00	200.7 ± 0.21	4.37 ± 0.01	4.6 ± 0.17	0.60 ± 0.02	0.67 ± 0.09
SSG-5	-	8	-	5.5 ± 0.06	0.057 ± 0.00	201.1 ± 0.32	4.38 ± 0.01	5.0 ± 0.21	0.52 ± 0.02	2.55 ± 0.19
SSG-6	-	12	-	6.2 ± 0.10	0.063 ± 0.00	200.7 ± 0.15	4.38 ± 0.01	4.9 ± 0.12	0.54 ± 0.02	1.90 ± 0.35
CS-1	-	-	0.5	3.1 ± 0.10	0.056 ± 0.00	200.8 ± 0.60	4.43 ± 0.01	4.5 ± 0.12	0.74 ± 0.02	4.37 ± 0.33
CS-2	-	-	1	3.6 ± 0.06	0.052 ± 0.00	200.8 ± 0.35	4.46 ± 0.01	4.7 ± 0.10	0.57 ± 0.02	3.47 ± 0.15
CS-3	-	-	2	4.3 ± 0.06	0.050 ± 0.00	201.0 ± 0.31	4.42 ± 0.01	4.3 ± 0.17	0.69 ± 0.01	2.49 ± 0.12
CS-4	-	-	4	4.8 ± 0.10	0.045 ± 0.00	201.1 ± 0.60	4.40 ± 0.01	6.9 ± 0.12	0.62 ± 0.01	1.60 ± 0.13
CS-5	-	-	8	5.4 ± 0.10	0.038 ± 0.00	201.2 ± 0.35	4.34 ± 0.01	4.5 ± 0.15	0.55 ± 0.01	0.89 ± 0.20
CS-6	-	-	12	5.7 ± 0.06	0.038 ± 0.01	200.9 ± 0.15	4.45 ± 0.01	5.0 ± 0.15	0.56 ± 0.01	0.53 ± 0.30

Decision on your manuscript #JOPI-D-21-00339

Dari: Journal of Pharmaceutical Innovation (em@editorialmanager.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Senin, 30 Agustus 2021 pukul 08.48 GMT+7

Dear Dr Hadinugroho:

We have received the reports from our advisors on your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms", which you submitted to Journal of Pharmaceutical Innovation.

Based on the advice received, your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions.
When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments.
Your list of responses should be uploaded as a file in addition to your revised manuscript.

In order to submit your revised manuscript electronically, please access the following web site:

https://www.editorialmanager.com/jopi/

Your username is: wuryanto.hadinugroho@ymail.com
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.

Please click "Author Login" to submit your revision.

We look forward to receiving your revised manuscript.

Sincerely yours,

Robert A Lodder

Journal of Pharmaceutical Innovation

COMMENTS FOR THE AUTHOR:

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.
https://www.editorialmanager.com/jopi/l.asp?i=48098&l=2FGZ8OZG

Reviewer #2: I have already included the necessary changes that needs to be done in the document file. Please follow and compleate the requiriments and correct the paper accordingly. Thank you for your efforts!

Reviewer #3: I have provided my decision to the editor.

Reviewer #4: The following paper by the author should probably be cited in this manuscript due to similarities in the coverage:
Hadinugroho, W., Martodihardjo, S., Fudholi, A., & Riyanto, S. (2019). Esterification of citric acid with locust bean gum. Heliyon, 5(8), e02337.

Correct the spelling of disintegrating agent on the x-axis in Figure 8, 9.

Some editing would improve the readability of the manuscript.For example, the meaning of this sentence is not clear (p. 2, line 45):
"Variation of HCl concentration in the synthetic effect on the character of CA-LBG."

CIC Pharmaceutical Sciences might be a better journal for this work.

Please note that this journal is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted.

Authors may need to take specific actions to achieve compliance with funder and institutional open access mandates. If your research is supported by a funder that requires immediate open access (e.g. according to Plan S principles) then you should select the gold OA route, and we will direct you to the compliant route where possible. For authors selecting the subscription publication route our standard licensing terms will need to be accepted, including our self-archiving policies. Those standard licensing terms will supersede any other terms that the author or any third party may assert apply to any version of the manuscript.

 Find out more about compliance

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Journal of Pharmaceutical Innovation

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

--Manuscript Draft--

Manuscript Number:	JOPI-D-21-00339
Full Title:	Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms
Article Type:	Original Article
Keywords:	CA-LBG; citric acid; locust bean gum; disintegrating agent; direct compression
Abstract:	Purpose Analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets. Methods Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, ~~degree of esterification,~~ solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg. Results Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility. Conclusion The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Abstract

Purpose Analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

Methods Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, degree of esterification, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.

Results Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.

Conclusion The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Keyword: CA-LBG, citric acid, locust bean gum, disintegrating agent, direct compression

1. Introduction

Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations (Dionísio and Grenha 2012; Dey et al. 2013; Das et al. 2015; Sheskey, J. P., Cook, G. W., and Cable 2017). Locust bean gum is a natural polymer that has the potential to be modified to produce new materials as excipients in tablet formulations.

Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). The O atoms (C-6) of mannose and galactose at LBG bind to the positive C atom of the carbonyl groups at CA. Positive C atoms are created from the protonation of carbonyl groups under acidic conditions (Chudzikowski 1971; Samavati et al. 2007; Tamaki et al. 2010; Dey et al. 2013; Hadinugroho et al. 2017, 2019).

The HCl is a strong acid that is effective for creating acidic conditions (Colas 2005; Bhattacharya et al. 2008). Variation of HCl concentration in the synthetic effect on the character of CA-LBG. The concentration of HCl affects the rate of protonation of the carbonyl group of CA to form a positive C atom. Increasing the concentration of HCl causes an increase in the creation of positive C atoms. This condition increases CA binding to LBG. The characteristics of CA-LBG are influenced by the concentration of CA bound to LBG (Hadinugroho et al. 2019).

The low wavelengths of UV irradiation (200-400 nm) are a source of energy strong enough to form chemical bonds (Tjandraatmadja et al. 1999; Santiago, E. V., Lopez, S. H. and Romero 2006; Yeh et al. 2011). The UV irradiation for a certain duration determines the formation of positive C atoms from the carbonyl group in CA with the O atoms (C-6) of mannose and galactose at LBG. The results of previous studies reported that this esterification produced a carbonyl ester group on CA-LBG which was not owned by LBG. In addition, the study reported that CA-LBG has a viscosity of 7-11 cP (Hadinugroho et al. 2019).

The CA-LBG utilization as material synthesis products need to be studied further. Pharmaceutical formulation is one area where CA-LBG can be used as an alternative to pharmaceutical excipients. Previous studies have reported that CA-LBG has the potential as a disintegrating agent for tablet dosage formulations (Hadinugroho et al. 2019).

The purpose of this study was to analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG. The aim of the tablet formulation was to determine the effect of the application of CA-LBG as a disintegration agent on the physical quality of tablets. The novelty of this study, the synthesis of CA-LBG uses a concentration of HCl 0.24 M as the catalyst and UV irradiation time (100 minutes) as an energy source that creates the chemical bond. HCl concentrations of 0.18 M and 0.30 M were experimental control concentrations to determine the success of the synthesis and characterization of CA-LBG. The CA-LBG experiment as a disintegrating agent was further studied with various concentrations. Sodium starch glycolate (SSG) and croscarmellose sodium (CS) were comparable disintegrating agents to study the disintegration activity of CA-LBG. SSG and CS are tablet disintegrating agents that are often used in tablet formulations because both able to swell in the disintegrating medium in a fast time. The rounded shape with the smooth surface of the SSG and the shape of the root with the corrugated surface of the CS can affect the tablet quality (Markl and Zeitler 2017; Sheskey, J. P., Cook, G. W., and Cable 2017). The experiment was

conducted to determine the potential for the disintegration of CA-LBG in tablet formulations as an alternative choice of disintegrating agent to be developed in the future.

2. Material and methods

2.1. Raw materials and chemicals

Materials needed in this study were locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Merck KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich, GmbH, USA), acetone (Cawan Anugerah Chemika, Indonesia), sodium starch glycolate (JRS Pharma, India), croscarmellose sodium (FMC Biopolymer, USA), spray dried lactose (Foremost Farms, USA), diclofenac sodium (Dwilab Mandiri, Indonesia), sterilized water for injection (Otsuka, Indonesia), and distilled water (Brataco Chemical, Indonesia).

2.2. Preparation of CA-LBG

The swollen LBG in a glass bowl (7.10 10^{-6} Molar LBG / 50 mL distilled water 55-60 ^{o}C) added CA (0.42 Molar) and HCl (0.18; 0.24; 0.30 Molar) (Table 1). The mixture was stirred for 10 minutes. The mixture was irradiated with UV 254 nm (100 minutes) (8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet CA-LBG was precipitated with acetone and washed with acetone-distilled water (1:1). The solid CA-LBG is dried at ambient temperature (Hadinugroho et al. 2017).

Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG performed was fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR), scanning electron microscope (SEM), degree of esterification, solubility, and viscosity.

2.3. Fourier transform infrared spectroscopy

The structure and the functional group of CA-LBG were analyzed by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.) in the wavenumber range of 4000-450 cm^{-1} spectra were recorded.

2.4. Nuclear magnetic resonance

The ^{1}H and ^{13}C NMR of CA-LBG was analyzed by liquid state NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan). The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra were recorded.

2.5. Scanning electron microscope

The surface morphology of CA-LBG was analyzed using SEM (JSM-6510LA, JEOL, Japan). The CA-LBG was mounted on a holder, coated by platinum, and observed (distance 10 mm and voltage10 kV).

2.6. Degree of esterification

The determination of the degree of esterification follows the experimental equation that has been done previously (Hadinugroho et al. 2019). Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group

compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar). The degree of esterification is determined by comparing the carboxylate group in the reacting CA (Molar) and the carboxylate group at the initial CA (Molar) and calculated according to Equation 3 (Hadinugroho et al. 2019).

Dissolved CA (mEq).

$$dissolved\ CA\ [mEq] = dissolved\ acid[mEq] - dissolved\ HCl[meq] \quad \textbf{Equation 1}$$

Weight CA reacting (gram)

$$W\ CA\ reacting\ = W\ initial\ CA - W\ dissolved\ CA \quad \textbf{Equation 2}$$

Degree of esterification

$$Degree\ of esterification\ [\%] = \frac{carboxylic\ group\ on\ the\ CA\ reacting\ [Molar]}{carboxylic\ group\ on\ the\ CA\ initial\ [Molar]}\ x\ 100\ \% \quad \textbf{Equation 3}$$

2.7. Solubility study

Solubility was determined by 0.5 g CA-LBG added 50 mL distilled water and allowed to stand for 24 h (Wd). Then, the filtrate was separated from the swollen sample. The filtrate was dried on a water bath at 70 ° C and reweighed (Wds) on a microbalance (Mettler Toledo AL204, Switzerland). The solubility of the CA-LBG was analyzed according to Equation 4:

Solubility (%) = Wds/Wd x 100 **Equation 4**

where Wds and Wd are soluble weight and initial weight (dry weight respectively) (Gulrez et al. 2011).

2.8. Viscosity

The CA-LBG viscosity test using a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG (3% w/v) was swelled in 300 mL of warm distilled

water and left at ambient temperature. Spindle no. S61 was installed on Brookfield. Viscosity was recorded when Brookfield was rotated at 100 rpm.

2.9. Preparation of tablets

Preparation of tablets begins with weighing the ingredients according to the formula (Table 1). Preparation of tablets by direct compress was prepared by mixing homogeneous SDL and CA-LBG / SSG / CS using a cubic mixer (2 minutes, 100 rpm) (Erweka). The physical quality of tablet mass was evaluated for flowability and compressibility. The mass of the tablets was compressed with a weight of 200 mg per tablet using a single punch machine (Jenn Chian Machinery, Taiwan). The physical quality of the tablets was evaluated for thickness, weight, break force, tensile strength, friability, and disintegration time.

2.10. Flowability

Tablet mass (100 g) was placed in a funnel hole on a flowability tester (Erweka, Germany). When the funnel valve is opened, tablet mass flows. Flow time can be observed on the flowability tester monitor.

2.11. Compressibility

Tablet mass was poured into a measuring tube (100 mL, angle ± 40^{o}) whose weight was known. The filled measuring tube is weighed, placed on a tapped density volumeter apparatus (Erweka, Germany), and tapped (500 taps). Weight and volume of tablet mass (before and after tapped) were recorded to determine the bulk density and the tapped density. Tablet mass versus volume before tapped is bulk density. Granule weight/tablet mass versus volume after tapped is the tapped density. The compressibility index is the difference between

tapped density and bulk density versus tapped density (Equation 5) (Michael E. Aulton and Kevin M. G. Taylor 2017).

$$compressibility\ index\ (\%) = \frac{tapped\ density - bulk\ density}{tapped\ density}\ x\ 100\% \quad \textbf{Equation 5}$$

2.12. Weight and thickness

Tablet weight and thickness were determined using 20 randomly selected tablets. Each tablet was weighed using an analytical weighing scale (Mettler Toledo, Switzerland) and thickness was accurately measured using a thickness gauge (Mitutoyo 7301, Japan).

2.13. Break force and tensile strength

Tablet break force (BF) was determined using 6 randomly selected tablets (The United States Pharmacopeial Convention 2018). The tablet is placed on the break force tester plate (Schleuniger, Netherlands). The metal block moves towards the tablet and presses until the tablet cracks/breaks. The tablet break force value is determined from the start of cracks/breaks, indicated on the monitor.

The strength of the tablet against mechanical stress is determined specifically using the tensile strength parameter according to the shape of the convex tablet. Tensile strength (σt) is calculated following Equation 6 (Pitt et al. 1989; Shang et al. 2013).

$$\sigma t = \frac{10F}{\pi D^2 (2.84\left(\frac{t}{D}\right) - 0.126\left(\frac{t}{W}\right) + 3.15\left(\frac{W}{D}\right) + 0.001)} \quad \textbf{Equation 6}$$

F is the break force, D is the diameter of the tablet, t is the total thickness of the tablet, and W is the thickness of the center of the tablet without convex.

2.14. Friability

Tablet friability was determined using a randomly selected number of tablets with a total tablet weight equal to 6500 mg (The United States Pharmacopeial Convention 2018). Each tablet was dust-free and the total weight of all tablets was determined (W0). All tablets were put into a drum friability tester (Erweka, Germany) and rotated for 4 minutes (25 rpm). After being removed from the drum, each tablet was dust-free and weighed again (W1). The friability of the tablet is the difference in the total weight of the tablet before and after rotated compared to the weight before rotated (Equation 7).

$$friability\ (\%) = \frac{W0-W1}{W0}\ 100\% \qquad \textbf{Equation 7}$$

2.15. Disintegration time

Tablet disintegration time was determined using 6 tablets randomly selected from 18 previously randomly selected tablets (The United States Pharmacopeial Convention 2018). Each tablet was inserted into each tube in the chamber disintegration tester apparatus (Erweka Z3, Germany). The chamber is up-down in a distilled water bath (37^{o} C; 900 mL). The disintegration time was determined from the longest time required for the tube net to be free of tablet fragments.

2.16. Dissolution

The experiment was prepared using a tablet mass added with diclofenac sodium as a model active ingredient. Each tablet contains 50 mg of diclofenac sodium to be compressed to a weight of 250 mg (Uday Kumar and Babu 2014; Hammami et al. 2020). Dissolution using phosphate buffer medium pH 6.8 (900 mL; 37 ± 0.5 ^{o} C; 50 rpm) for 60 minutes using the paddle method (Electrolab TDT-08L, India) (Zupančič Bozič et al. 1997; Bertocchi et al. 2005). The release of ketoprofen was sampled and observed at 5, 15, 30, 45, and 60 minutes. Analysis

of dissolved diclofenac sodium concentration using a UV-vis spectrophotometer (Hitachi U-1900, Japan) at a wavelength of 276 nm (Ghasemi et al. 2005; Gouda et al. 2013).

3. Result and discussion

3.1. Mechanism of the CA-LBG synthesis reaction

In the synthesis of CA-LBG, the acidity of HCl could be induced protonation of O atoms from the carbonyl group of citric acid and created positive C atoms. The hydroxyl (OH) group of C-6 at mannose and galactose atoms reacts with the protonated citric acid carbonyl group to create a tetrahedral cation. Protonated OH ($^{+}OH_2$) oxygen groups with H_2O loss to form CA-LBG. UV irradiation is the energy source to create bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose (Hadinugroho et al. 2017, 2019). The schematic and details of the synthesis are shown in Figure 1 and Table 1.

3.2. Fourier transform infrared spectroscopy

The results of the CA-LBG and LBG infrared analysis are shown in Figure 2 and Table 1. The stretch peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose. Sharp peaks appear at 2920.60 cm^{-1}; 2923.35 cm^{-1}, 2923.56 cm^{-1}; and 2923.35 cm^{-1} are related to C-H bonds of CA and LBG. In CA-LBG, the sharp peak comes from C-H symmetrically of CA (Coates 2006). The sharp peak of CA-LBG appeared at 1739.22 cm^{-1}; 1736.39 cm^{-1}; and 1735.85 cm^{-1} are related to the carbonyl ester group that was produced from the synthesis reaction. The carbonyl ester group is created by the bond between the positive C atom of the protonated carbonyl group in CA and the O atom of C-6 at mannose and galactose in LBG. In a previous study, the OH group appeared around 3300 cm^{-1}. C-H appears around 2900 cm^{-1}, and C=O appears

around 1750-1735 cm^{-1}(Hadinugroho et al. 2019). This shows the success of the synthesis and continued by NMR confirmation.

3.3. Nuclear magnetic resonance

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies (Hadinugroho et al. 2017, 2019).

The results of the CA-LBG NMR analysis are shown in Figure 3. In the ^{1}H NMR spectrum of CA, a pair of twin peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 (e) in CA. Sharp peaks of 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that a pair of CA twin peaks appear around δ = 2.7-3.0 ppm. Sharp peaks from mannose and galactose appear around 4.5-3.0 ppm (Hadinugroho et al. 2017, 2019).

In the ^{13}C NMR spectrum of CA-LBG, peaks at δ = 176.790 ppm and δ = 173.459 ppm are related to C = O (b,c) resulting from the synthesis reaction. The peak at δ = 73.325 ppm is related to the central C atom of CA (a). The peak at δ = 43.349 ppm is related to C-H_2 (d) of CA. The peaks at δ = 100.192 ppm, δ = 100.000 ppm, δ = 75.072 ppm and δ = 71.453 ppm are related to C-H and C-H_2 at mannose. The peaks at δ = 69,985 ppm, δ = 61.260 ppm, δ = 61.010 ppm, δ = 60.559 ppm are related to C-H and C-H_2 at mannose and galactose. Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H_2 appeared at δ = 44-43 ppm (Jans and Kinne 1991; Doll et al. 2006; Zhang et al. 2016; Hadinugroho et al. 2019). The peak absorption of mannose and galactose appears at δ = 105-60 ppm (Parvathy et al. 2005; Azero and Andrade 2006; Bhatia et al. 2013; Gillet et al. 2014; Hadinugroho et al. 2019). This shows the success of the synthesis.

3.4. Scanning electron microscopy

The SEM images of CA-LBG (Batch B) are shown in Figure 4. In magnification100x, particles of CA-LBG appear in an irregular shape. In magnification 3500x, particles CA-LBG have the surface morphology of CA-LBG appear coral-corrugated. Based on previous experiments, LBG has a corrugated morphology and CA creates coral morphology (Hadinugroho et al. 2019). The LBG particles have a shape coral- corrugated indicates available interaction with CA with LBG and successful synthesis.

3.5. Degree of esterification

The degree of esterification of CA-LBG for all batches is shown in Table 1. The high concentration of HCl under synthesis conditions increases the degree of esterification due to the high amount of CA bound to LBG. The HCl increases the acidity of the synthesis conditions to protonate the O atom from the carbonyl group and creates a positive C atom, thereby causing CA to bind to LBG. The CA-LBG batch A to batch C shows the higher the degree of esterification in proportion to the increase in the concentration of HCl because the protonation of the O atom from the carbonyl group and the formation of a positive C atom is faster. This condition accelerates creates bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose.

3.6. Solubility

The solubility of CA-LBG for each synthesis condition is shown in Table 1. The CA-LBG of batch A to batch B presents the solubility decreasing in proportion to the increasing degree of esterification. The more CA molecules bound to the LBG produce CA-LBG with stable ester bonds. Bonds of positive C atoms from carboxylic groups and O atoms of C-6 at

mannose and galactose decrease the ability of CA-LBG to interact with distilled water. In this condition, CA-LBG particles are difficult to wet so inhibit solubility in distilled water.

3.7. Viscosity

The viscosity of CA-LBG for each batch is shown in Table 1. LBG has a high viscosity, but the presence of excess CA can reduce the viscosity. The viscosity of CA-LBG from batch A to batch B decreased in proportion to the increasing degree of esterification. The carbonyl ester groups formed from the bonding of positive C atoms from carboxylate groups with O atoms of C-6 in mannose and galactose reduce the ability of CA-LBG to trap distilled water so viscosity decreases.

3.8. Flowability

The results of the flowability study on all tablet mass formulas containing CA-LBG showed that an increase in the concentration of CA-LBG increased the flow time of tablet mass (Table 2) because influenced by the irregular shape of particles and the surface like coral inhibit the flow of mass tablet (Figure 5). The CL-1 formula has the fastest flow time due to the influence of the spherical shape of the SDL granules to dominate the flowability although CA-LBG is present in the tablet mass (Sheskey, J. P., Cook, G. W., and Cable 2017). The formula containing SSG and CS showed an increase in concentration cause increased flow time tablet mass. SSG particles are rounded and have a smooth surface, should be able to rate up the flow time but SSG particles are also hygroscopic, thus inhibiting the flow time of tablet mass (Sheskey, J. P., Cook, G. W., and Cable 2017). The CS particles are rod-shaped with a corrugated surface, which at high concentrations can inhibit the flow of tablets mass (Sheskey, J. P., Cook, G. W., and Cable 2017). According to the flow time requirements, all tablet mass

formulas containing a variety of disintegrating agents meet the requirements is 100 g tablet mass can flow in less than 10 seconds (Szumilo et al. 2017).

The effect of the presence of various disintegrating agents on the tablet mass is shown in Figure 5, which is a plot between the concentration of the disintegrating agent and the flow rate [g s^{-1}]. In general, the tablet profile containing CA-LBG the most slope of flow rate although the CA-LBG concentration was increasing. In addition, the decrease in flow rate of tablet mass with a high concentration of CA-LBG is proportional to the flow rate of tablet mass containing high concentrations of SSG and CS. This case is because the particle surface of CA-LBG like coral can fill each other with a porosity of SDL surface (Sheskey, J. P., Cook, G. W., and Cable 2017). The sharp decrease in the profile of tablet mass containing CS at low concentrations (CS-1) indicates that the flow rate is more influenced by the spherical shape of the SDL granules so accelerate the flow, while at higher concentrations (CS-2) the root shape and corrugated surfaces of the CS particles begin to inhibit the flow. The flow rate profile of tablet mass containing SSG at low concentrations (SSG-1) is more slope than the tablet mass containing CS at the same concentration (CS-1) because the hygroscopicity of SSG particles inhibits the flow of tablet mass. The hygroscopic effect of SSG particles at higher concentrations (SSG-2 to SSG-6) can be overcome by the rounded shape and smooth surface of the SSG particles so that the decrease flow rate is more slope.

3.9. Compressibility

The tablet mass density evaluation results on all tablet mass formulas containing CA-LBG or SSG showed that increasing the concentration of the disintegrating agent increased the value of ρ_{tapped}-ρ_{bulk} (Table 2), due to the influence of the shape and surface of the disintegrating agent particles. The initial composition of the tablet mass was SDL granules arranged randomly, the porosity between the SDL granules was filled with disintegrating agent particles.

The CA-LBG particles which have an irregular shape and a coral-like surface are randomly arranged on the porosity between the SDL granules according to the shape and area of the porosity between the initial particles. The volume decrease during the tapping was caused by the movement of SDL granules and CA-LBG particles. The CA-LBG particle corners fill each other surface porosity between particles and SDL granule surface porosity. In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density arrangement between SDL granules and the area of porosity that could accommodate all CA-LBG particles. The volume decrease in the tapping of the formula with the higher CA-LBG concentration causes the porosity between the SDL granules to be wider because the CA-LBG particles surround the SDL granules tightly.

The rounded shape and smooth surface of the SSG particles give a tablet mass arrangement with more regular porosity than the CA-LBG particles. The smooth surface of SSG particles causes movement of SDL granules / SSG particles and decreases in volume during tapping so that the porosity narrows and SSG particles fill the porosity of the SDL granule surface. Formulas containing CS have a different value of ρ_{tapped}-ρ_{bulk} from formulas containing other disintegrating agents, namely the increasing the concentration of CS, the lowering the value of ρ_{tapped}-ρ_{bulk}. The rod-shape and corrugated surface of the CS particles envelop according to the SDL granule shape in layers and has a narrow porosity. The surface of the CS particles decreases the ability of the particles to move and the volume decreases on tapping because the surface corrugated of the CS particles will interlock with other CS particles.

The results of the density evaluation are further confirmed by the compressibility profile shown in Figure 6, where increasing the concentration of the disintegrating agent increases the mass compressibility of tablets containing CA-LBG / SSG and decreases the mass compressibility of tablets containing CS. The mass compressibility of tablets containing CA-

LBG was slightly lower than the mass of tablets containing SSG because the angles of CA-LBG particles fill each other surface porosity between particles and SDL granule surface porosity.

3.10. Weight and thickness

All tablet masses contain a variety of disintegrating agents and their concentration is compressed into tablets and according to weight is around 200 mg (Table 2), which shows that all tablet masses are able to flow freely from the hopper and fill the dies space in the tablet compressing machine. This condition is in accordance with the results of the evaluation of flowability and compressibility.

The variation in tablet thickness from the mass of tablets containing various disintegrating agents is influenced by the arrangement, shape, and surface of the SDL granule or the disintegrating agent particle so that when compression is applied produced deformation of the granule/particle, bond interlocking, and narrowing the porosity between deformations. The irregular shape and coral-like surface of the CA-LBG particles provide an opportunity for the particle corners to fill each other with the SDL particle/granule surface porosity so the tablet mass is compressed to produce a low-porosity tablet. The rounded shape and smooth surface of the SSG particles produce tablets with a regular form of porosity. The root shape and corrugated surface of the CS particles provide an opportunity to interlock between the particles and the corrugated surface so the tablet mass is compressed to produce a low-porosity tablet.

The CL-1 tablet is thicker even though the number of CA-LBG particles is less than the CL-2 tablet because the CA-LBG particles tend to fill the porosity of the SDL granules surface. In the CL-2 tablet, CA-LBG particles fill the surface porosity of SDL granules and porosity between SDL granules. The number of SDL granules of CL-2 tablet mass reduces so that produces a thinner tablet. The CL-3 and CL-4 tablets are thicker than the other CL tablets

because the CA-LBG particles surround the SDL granules so that the volume is high and when the tablet mass is compressed into thick tablets. The CL-4 tablet is thicker than the CL-3 tablet due to the increasing number of CA-LBG particles resulting in a wider area surrounding the SDL granules. The number of CA-LBG particles in the CL-5 and CL-6 formula tablets is increasing so the area of the CA-LBG particles surrounding the SDL granules is wider, but the porosity between the CA-LBG particles is narrow so that the mass of the tablets is compressed to produce a thinner tablet. The CL-6 tablet is thicker than the CL-5 tablet because the CA-LBG particle area surrounding the SDL granules is wider.

The SSG-1 tablet is thicker than other SSG tablets because SSG particles fill the porosity of the SDL granules surface so, with the highest number of granules, the tablet mass is compressed to produce thick tablets. Tablet mass of SSG-2 and SSG-3 show the number of SSG particles is increasing and the number of SDL granules is decreasing. The SSG particles in the SSG-2 tablet mass filled the surface porosity of the SDL granules and the dense porosity of the SDL granules. The SSG-3 tablet mass shows the number of SDL granules was reduced so the mass of the tablets was compressed to produce a thinner tablet. The tablet mass of SSG-4 to SSG-6 contains more SSG particles and surrounds the decreasing SDL granules. The SSG-5 tablet is thicker than the SSG-4 tablet because the SSG deformation area surrounding the SDL deformation is wider. The SSG-6 tablet contained more SSG surrounding the SDL deformation with the area is wider. The SSG-6 tablet thickness is similar to SSG-5 because the number of SDL deformation in the tablet mass is reduced.

The thickness of the CS-1 tablet was dominated by the effect filling of CS particles on porosity SDL granules surface so when compressed the tablet mass experienced deformation with porosity varying of shapes and areas. The tablet of CS-2 to CS-4 contain more CS particles and fewer SDL granules. The increasing number of CS particles formed the interlocking deformation between the particles and enveloped the SDL granules so that produce thicker

tablets with narrow porosity but in large numbers. The greater the number of CS particles, the wider the enveloping and interlocking area of the CS particles, resulting in a thicker tablet. The thickness of the CS-5 and CS-6 formula tablets was dominated by the increase in the number of CS particles. CS particles in the CS-5 tablet mass forming long interlocking on surrounding SDL granules. The tablet mass contains limited SDL granules so produce thin tablets when compressed. The CS-6 tablet is thicker than the CS-5 tablet because the interlocking area enveloping the SDL granule is wider.

3.11. Break force and tensile strength

Evaluation of tablet resistance to mechanical stress is measured by the BF value and shown in Table 2. The resistance of the CL-1 tablet is influenced by the dominance of SDL granules interlocking bonds when compressed to result in deformation with a wide porosity so that the tablets have a low resistance to mechanical stress. The BF value of the CL-2 tablet is higher than CL-1tablet because the number of CA-LBG particles is more and fills the dense porosity between SDL granules so when compressed the interlocking bonds are stronger and the porosity is narrower. The CL-3 tablet shows the highest BF value than other CL tablets because the deformation of CA-LBG particles around the SDL granule when compressed is able to form interlocking bonds with narrow porosity so that the thick tablet and resistant to mechanical stress. In addition, the corners of the CA-LBG particles fill the surface porosity between the CA-LBG particles and the SDL granule surface porosity so strengthening the interlocking bond. The CL-4 to CL-6 tablets have a similar mechanism as the CL-3 formula tablets, but the number of CA-LBG particles is increasing and SDL granules are decreasing so that when compressed, produce tablets with a lot of narrow porosity and a decrease in tablet resistance to mechanical stress. The tablet of CL-5 and CL-6 show similar BF values due to

the CL-6 tablet, although the interlocking bonds between particles are more dominant with the number of narrow porosity increases.

The SSG particles in the SSG-1tablet mass fill the surface porosity of the SDL granules so inducing the granules to be slightly moist and the interlocking bonds between the SDL deformation are weaker. In addition, SDL granules after being compressed produce wide porosity deformation. The resistance of the SSG-2 tablet is higher than the SSG-1 tablet because the narrow porosity between the SDL granules is filled with SSG particles so that the mass of the granules is compressed resulting in a narrower porosity deformation. The SSG-3 tablet shows the strongest resistance than other tablets because SSG particles surround SDL granules when compressed able to form deformation interlocking bonds with narrow and regular porosity so tablets are resistant to mechanical stress. SSG-4 to SSG-6 tablets have a similar mechanism to SSG-3 tablets, but the number of SSG particles is increasing and SDL granules are decreasing so the mass of SSG-5 and SSG 6 when compressed produces tablets with more narrow porosity and decrease in the resistance of the tablet to mechanical stress. In addition, the slightly hygroscopic character of SSG particles decreased the resistance of tablets shown in the SSG-4 tablet because the deformation interlocking bonds of SSG particles around the SDL granules were weak.

The little number of CS particles in the CS-1 tablet tends to fill the porosity of the SDL granules. When compressed, the interlocking bond is dominated by SDL deformation with wide porosity so the resistance of the tablets to mechanical stress is weak. The CS-2 tablet has a similar mechanism to the CS-1 tablet but the porosity between the SDL granules is filled with CS particles so produces a tablet with narrower porosity and is more resistant to mechanical pressure. The CS-3 tablet has a similar mechanism to the CS-2 tablet but the number of CS particles is more so the CS particles form interlocking between particles and envelop the SDL granules. When compressed, the enveloping CS particles form an interlocking bond

deformation with a narrow and large porosity so the tablet surface resistance is weak. In the CS-4 tablet, the interlocking CS particles to envelope the SDL granules and a wider area so produce tablets with interlocking narrow porosity and strong surface to withstand mechanical stress. The CS-5 and CS-6 tablets have a similar mechanism to the CS-4 tablets but the number of CS particles is increasing and the SDL granules are decreasing. In CS-5 tablet, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface. In CS-6 tablet, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.

The BF value was further confirmed by the tensile strength parameter to determine the comparison between tablets contain disintegrating agent variation according to the concentration in the experiment (Figure 7). The tensile strength profile of CA-LBG tablets is similar to that of SSG tablets due to the influence of the particle shape of CA-LBG and SSG. The irregular shape and coral surface of the CA-LBG particles produce tablets with strong deformation interlocking bonds. The tensile strength intensity of CA-LBG tablets is similar to that of SSG tablets showing a deformation interlocking bond that can adjust the concentration used in the tablets. In the experiment, the peak tensile strength of CA-LBG tablets and SSG tablets was a concentration of 2% while CS tablets was a concentration of 4%. This concentration is the optimum condition for forming tablets with the most stable interlocking deformation bonds against mechanical stress.

3.12. Friability

Evaluation of tablet resistance to mechanical movement is measured by friability parameters and is shown in Table 2. The friability of the CL-1 tablet is influenced by the low BF value due to the interlocking bond of SDL deformation with wide porosity so that SDL

deformation on the tablet surface releases particles when subjected to mechanical movement. In addition, the CA-LBG particles on the tablet surface were also released. The CL-2 tablet is more friable than the CL-1 tablet although the BF value is higher because the number of CA-LBG particles on the surface of the tablet is more so more particles are released when subject to mechanical movement. The CL-3 to CL-6 tablets showed a tendency to decrease in friability although the BF value was lower because of a strong interlocking bond on the deformation of granules and particles, so reducing the release of tablet surface particles when subjected to mechanical movement. The CL-6 tablet is more friable than the CL-5 tablet because the number of SDL deformation decreases so that the foundation to withstand mechanical movements is reduced.

The SSG-1 tablet is the most friable than SSG other tablets because of the low BF value due to SDL deformation interlocking bonds with wide porosity so that the tablet surface releases lactose and SSG particles when subjected to mechanical movement. The decrease in the friability of the SSG-2 and SSG-3 tablets proportional to the higher BF value indicates a strong interlocking bond from the deformation of granules and particles so resistant to mechanical movement. The friability of the SSG-4 to SSG-6 tablets tends to decrease because the strength of the interlocking bonding of SSG deformation is able to withstand mechanical movements. The SSG-6 tablet is more friable than the SSG-5 tablet because the number of SDL deformation is reduced so the foundation to withstand mechanical movements is reduced.

The CS-1 tablet is the most friable than the other CS tablets because the SDL deformation interlocking bond dominates with a wide porosity so the lactose and CS particles on the surface are released when subject to mechanical movement. The friability of the CS-2 and CS-3 tablets increased proportionally to the BF values of the two tablet formulas decreased. The more SSG deformation interlocking bonds, the stronger the tablet withstands mechanical movements. The friability of the CS-4 to CS-6 tablets proportional to the BF value and tends

to decrease. The CS deformation on the tablet surface has a strong interlocking bond to withstand mechanical movements. The CS-6 tablet is more friable than the CS-5 tablet because of the reduced deformation of SDL as a foundation to resist mechanical movements.

The comparison of the effect of the presence of the disintegrating agent in each tablet formula to friability according to the concentration in the experiment is shown in Figure 8. The friability profile of the three CA-LBG tablets is similar but different at the peak of each disintegrating agent (CA-LBG 1%; CS 2%; SSG 4%). These peaks indicate that the tablet surface has bonds weakly of interlocking deformation and less stable to mechanical movements. The friability value before the peak concentration was also influenced by the release of particles from the SDL deformation, while after the peak concentration was influenced by the quality of the interlocking bond of deformation particles on the tablet surface so resistant to mechanical motion. CA-LBG tablets are more friable than other tablets due to the influence of the coral surface on the particles which tend to be friable when the porosity is not filled with other particles. The high friability profile of CA-LBG tablets appears at low concentrations because the surface porosity of the CA-LBG particles is not filled due to the limited number of CA-LBG particles. In addition, the irregularly shaped CA-LBG particles causing the porosity of tablets were number and wide.

3.13. Disintegration time

The evaluation of tablet disintegration rates for all formulas with various disintegrating agents and concentrations is shown in Table 2. The disintegration of tablets containing CA-LBG showed a fast disintegration time proportional to the increasing concentration of CA-LBG. The value of BF and friability do not affect the function of the CA-LBG to disintegrate the tablet. The irregular particle shape and the corrugated surface of the CA-LBG particles resulted in a tablet with porosity for penetration of the disintegrating medium (Figure 4). The

deformation porosity of CA-LBG formed on the tablet is proportional to the CA-LBG concentration in the tablet formula. The porosity of a large number on the tablet cause increases the channel for penetration of the disintegrating medium so that the tablet is disintegrating. The CA-LBG is an ester excipient that has low viscosity and low solubility in water (Table 1). This characteristic causes a repulsive force between deformations of CA-LBG on tablets when wet by disintegration medium. The repulsion force increases in proportion to the CA-LBG concentration in the tablet formula. The repulsive force between the CA-LBG deformations causes the tablets to disintegrate.

Tablets containing SSG showed that SSG concentration, BF value, and friability were influenced the disintegration time. The speed of tablet disintegration time is proportional to the increasing SSG concentration shown in the SSG-1 to SSG-4 tablets. Deformation of SSG in tablets attracts disintegration medium so SSG deformation swells and pushes deformation of other granules and particles to move away from each other so that the tablet is disintegrating. SSG-5 and SSG-6 tablets show the resistance of the tablets to pressure and mechanical movements affect the speed of disintegration. Increased BF value and low tablet friability caused long tablet disintegration time due to the strong interlocking bond between the deformation of granule or particle, thus inhibiting tablet disintegration.

Tablets containing CS showed an increase in CS concentration causing the disintegration time to rapidly. The resistance of tablets indicated by BF value and friability did not affect the function of CS as a tablet disintegrating agent. Tablets containing CS attracts the disintegrating medium for penetration into the tablet so that the CS deformation swell and push deformation around. The more the CS deformation swell, the faster the tablet integrates.

The comparison of the ability of the disintegrating agent in each tablet formula according to the concentration in the experiment is shown in Figure 9. The time profile for the disintegration of CA-LBG tablets is similar to that of CS tablets because the two disintegrating

agents perform their function not influenced by the quality of other tablets so that the increase in concentration is proportional to the increase in disintegration speed. tablet. In contrast to SSG tablets, the disintegration time is also influenced by the hardness and friability of the tablets, thus inhibiting the disintegration process in tablets with SSG concentrations of 8% and 12%. The disintegration time profile of CA-LBG tablets is longer than CS tablets because low solubility of CA-LBG so that the wetting time of CA-LBG tablets is longer and inhibits integration.

3.14. Dissolution

Experiments to study drug release from the dosage form were carried out using tablets of 1%, 2%, and 4% concentrations of each disintegrating agent. The effect of the disintegrating agent on the release of diclofenac sodium from the tablet is presented in Figure 10. The dissolution profile of the tablets containing CA-LBG showed that the release of diclofenac sodium from the tablets appeared to be different at 5 and 15 minutes. The higher the CA-LBG concentration on the cause tablet more rapidly disintegrates and releases more diclofenac sodium. All tablets with each concentration of CA-LBG meet the requirements for releasing diclofenac sodium (Directorate General of Medicine and Food 1995).

Comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11). Tablets containing CA-LBG showed a slower release of diclofenac sodium than tablets containing SSG and CS because of the gradual release at 5 and 15 minutes. The low solubility of CA-LBG inhibits the wetting of the tablets for disintegration thus inhibiting the solubility of diclofenac sodium in the dissolution medium.

4. Conclusion

Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. Increasing the concentration of HCl in the synthesis causes a decrease in the viscosity of CA-LBG due to an increase in CA molecules bound to LBG. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility. The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

References

Azero EG, Andrade CT (2006) Characterisation of Prosopis juliflora seed gum and the effect of its addition to κ-carrageenan systems. J Braz Chem Soc 17:844–850. https://doi.org/10.1590/S0103-50532006000500005

Bertocchi P, Antoniella E, Valvo L, et al (2005) Diclofenac sodium multisource prolonged release tablets - A comparative study on the dissolution profiles. J Pharm Biomed Anal 37:679–685. https://doi.org/10.1016/j.jpba.2004.11.041

Bhatia H, Gupta PK, Soni PL, Division C (2013) Extraction , Purification and Characterization of a Galactomannan From Prosopis Juliflora (Sw .) Dc . Seed. Int J Sci Enviroment Technol 2:708–724

Bhattacharya A, Rawlins JW, Ray P (2008) Polymer Grafting and Crosslinking. A John Wiley & Sons, Inc, Publication, Canada

Chudzikowski RJ (1971) Guar gum and its applications. J Soc Cosmet Chem 22:43–60

Coates J (2006) Interpretation of Infrared Spectra, A Practical Approach. Encycl Anal Chem 10815–10837. https://doi.org/10.1002/9780470027318.a5606

Colas A (2005) Cow Corning Silicones : Preparation Properties and Performance. Midland

Das N, Triparthi N, Basu S, et al (2015) Progress in the development of gelling agents for improved culturability of microorganisms. Front Microbiol 6:1–7. https://doi.org/10.3389/fmicb.2015.00698

Dey P, Maiti S, Sa B (2013) Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide. J Biomater Sci Polym Ed 24:663–683. https://doi.org/10.1080/09205063.2012.703950

Dionísio M, Grenha A (2012) Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci 4:175–185. https://doi.org/10.4103/0975-7406.99013

Directorate General of Medicine and Food (1995) Indonesian Pharmacopoeia 4th edition. Ministry of Health Republic of Indonesia, Jakarta

Doll KM, Shogren RL, Willett JL, Swift G (2006) Solvent-free polymerization of citric acid and D-sorbitol. J Polym Sci Part A Polym Chem 44:4259–4267. https://doi.org/10.1002/pola.21535

Ghasemi J, Niazi A, Ghobadi S (2005) Simultaneous spectrophotometric determination of benzyl alcohol and diclofenac in pharmaceutical formulations by chemometrics method. J Chinese Chem Soc 52:1049–1054. https://doi.org/10.1002/jccs.200500148

Gillet S, Aguedo M, Blecker C, et al (2014) Use of 13C-NMR in structural elucidation of polysaccharides: case of locust bean gum. Liège

Gouda AA, Kotb El-Sayed MI, Amin AS, El Sheikh R (2013) Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: A review. Arab J Chem 6:145–163. https://doi.org/10.1016/j.arabjc.2010.12.006

Gulrez SKH, Al-Assaf S, Phillips GO (2011) Hydrogels: Methods of Preparation, Characterisation and Applications. In: Progress in Molecular and Environmental Bioengineering - From Analysis and Modeling to Technology Applications

Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S (2019) Esterification of citric acid with locust bean gum. Heliyon 5:e02337. https://doi.org/10.1016/j.heliyon.2019.e02337

Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S (2017) Study of a catalyst of citric acid crosslinking on locust bean gum. J Chem Technol Metall 52:1086–1091

Hammami MM, Hussein RF, Alswayeh R, Alvi SN (2020) Eight enteric-coated 50 mg diclofenac sodium tablet formulations marketed in Saudi Arabia: In vitro quality evaluation. BMC Res Notes 13:1–6. https://doi.org/10.1186/s13104-020-05270-4

Jans AWH, Kinne RKH (1991) 13C NMR spectroscopy as a tool to investigate renal metabolism. Kidney Int 39:430–437. https://doi.org/10.1038/ki.1991.54

Markl D, Zeitler JA (2017) A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res 34:890–917. https://doi.org/10.1007/s11095-017-2129-z

Michael E. Aulton, Kevin M. G. Taylor (2017) Aulton's Pharmaceutics The Design and Manufacture of Medicines. Churchill Livingstone Elsevier, New York

Parvathy KS, Susheelamma NS, Tharanathan RN, Gaonkar AK (2005) A simple non-aqueous method for carboxymethylation of galactomannans. Carbohydr Polym 62:137–141. https://doi.org/10.1016/j.carbpol.2005.07.014

Pitt KG, Newton JM, Richardson R, Stanley P (1989) The Material Tensile Strength of Convex- faced Aspirin Tablets. J Pharm Pharmacol 41:289–292. https://doi.org/10.1111/j.2042-7158.1989.tb06458.x

Samavati V, Razavi SH, Rezaei KA, Aminifar M (2007) Intrinsic viscosity of locust bean gum and sweeteners mixture in dilute solutions. Electron J Environ Agric Food Chem 6:1879–1889

Santiago, E. V., Lopez, S. H. A, Romero AR (2006) Photochemical cross-linking study of polymers containing diacetylene groups in their main chain and azobenzene compounds as pendant groups. Superf y vacío 19:1–7

Shang C, Sinka IC, Jayaraman B, Pan J (2013) Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. Int J Pharm 442:57–64. https://doi.org/10.1016/j.ijpharm.2012.09.005

Sheskey, J. P., Cook, G. W., and Cable GC (2017) Handbook of Pharmaceutical Excipients 8th by Sheskey, Paul J Cook, Walter G Cable, Colin G. Pharmaceutical Press and American Pharmacists Association, London-Washington DC

Szumilo M, Belniak P, Swiader K, et al (2017) Assessment of physical properties of granules with paracetamol and caffeine. Saudi Pharm J 25:900–905. https://doi.org/10.1016/j.jsps.2017.02.009

Tamaki Y, Teruya T, Tako M (2010) The chemical structure of galactomannan isolated from seeds of Delonix regia. Biosci Biotechnol Biochem 74:1110–1112. https://doi.org/10.1271/bbb.90935

The United States Pharmacopeial Convention (2018) Pharmacopeia 41-National Formulary 36, 41st edn. Twinbrook Parkway, Rockville

Tjandraatmadja GF, Burn LS, Jollands MJ (1999) The effects of ultraviolet radiation on polycarbonate glazing. Proc 8th Int Conf Durab Build Constr Mater Vancouver, Canada 30:884–898

Uday Kumar M, Babu K (2014) Design and evaluation of fast dissolving tablets containing diclofenac sodium using fenugreek gum as a natural superdisintegrant. Asian Pac J Trop Biomed 4:S329–S334. https://doi.org/10.12980/APJTB.4.2014B672

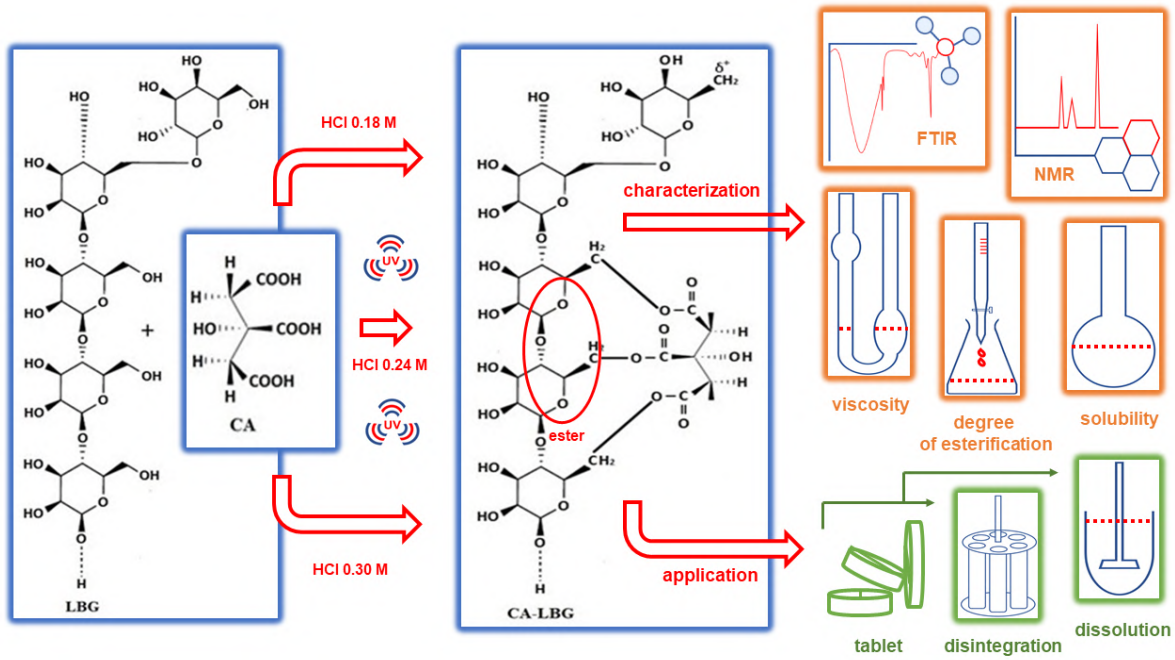
Yeh CC, Chen CN, Li YT, et al (2011) The effect of polymer molecular weight and UV radiation on physical properties and bioactivities of PCL films. Cell Polym 30:261–276.

https://doi.org/10.1177/026248931103000503

Zhang Y ling, Zhao C xia, Liu X dong, et al (2016) Application of poly(aspartic acid-citric acid) copolymer compound inhibitor as an effective and environmental agent against calcium phosphate in cooling water systems. J Appl Res Technol 14:425–433. https://doi.org/10.1016/j.jart.2016.08.006

Zupančič Božič D, Vrečer F, Kozjek F (1997) Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur J Pharm Sci 5:163–169. https://doi.org/10.1016/S0928-0987(97)00273-X

Graphical Abstract



Figure

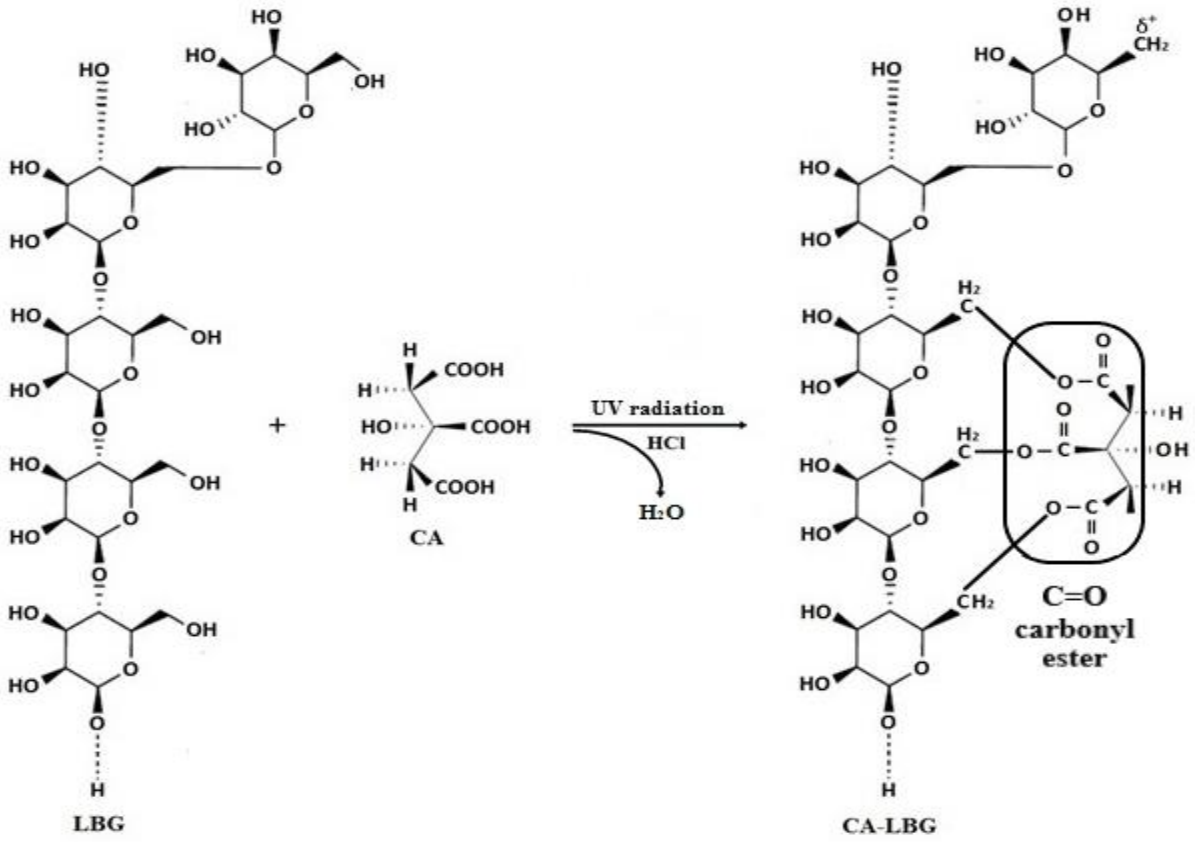


Figure 1. CA-LBG production mechanism. Synthesis of CA-LBG was carried out by adding 0.42 M CA to 7.10 x 10-6 M LBG which had swollen. The mixture was added with HCl (0.18-0.42 M) and UV irradiated (100 minutes).

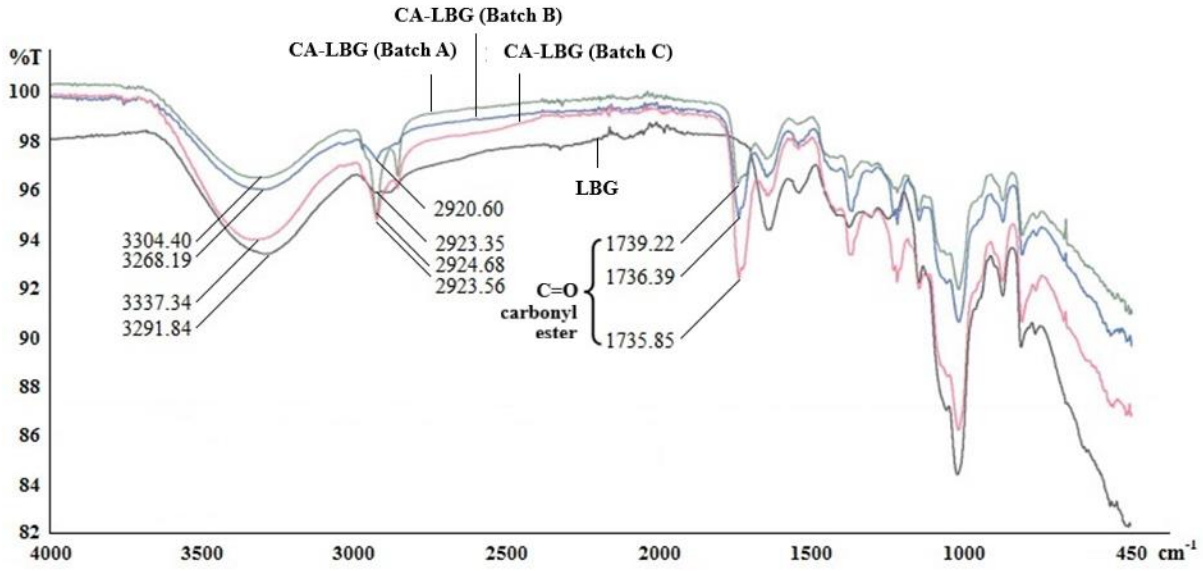


Figure 2. FTIR spectrum of LBG and CA-LBG. LBG as a comparison is shown in black spectra. CA-LBG was synthesized using a 0.18 M HCl catalyst (Batch A) shown in green spectra. CA-LBG was synthesized using a 0.24 M HCl catalyst (Batch B) shown in blue spectra. CA-LBG was synthesized using 0.30 M HCl catalyst (Batch C) shown in red spectra. The carbonyl ester group (C=O) is a specific group that presents at CA-LBG and absent at LBG.

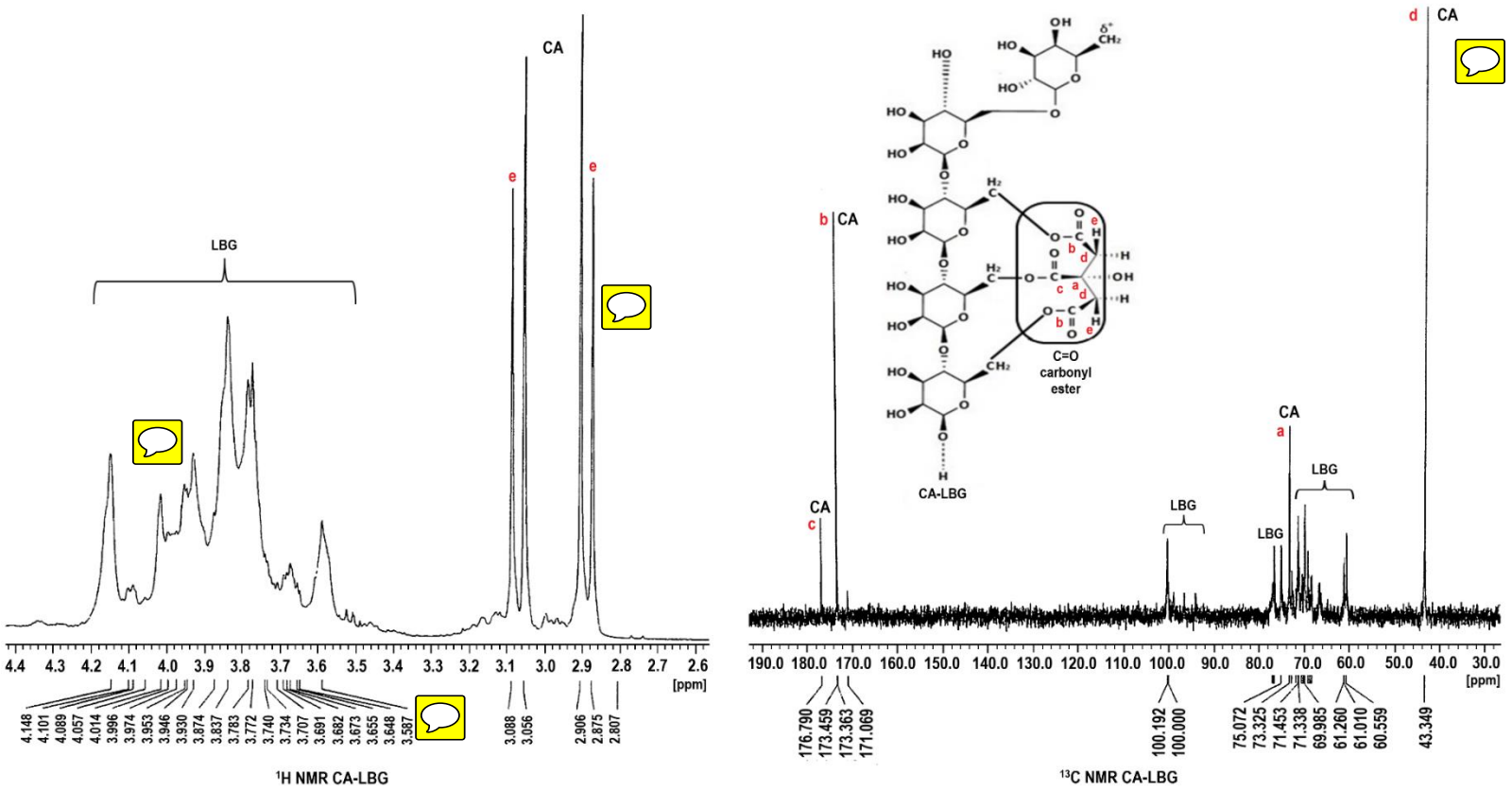
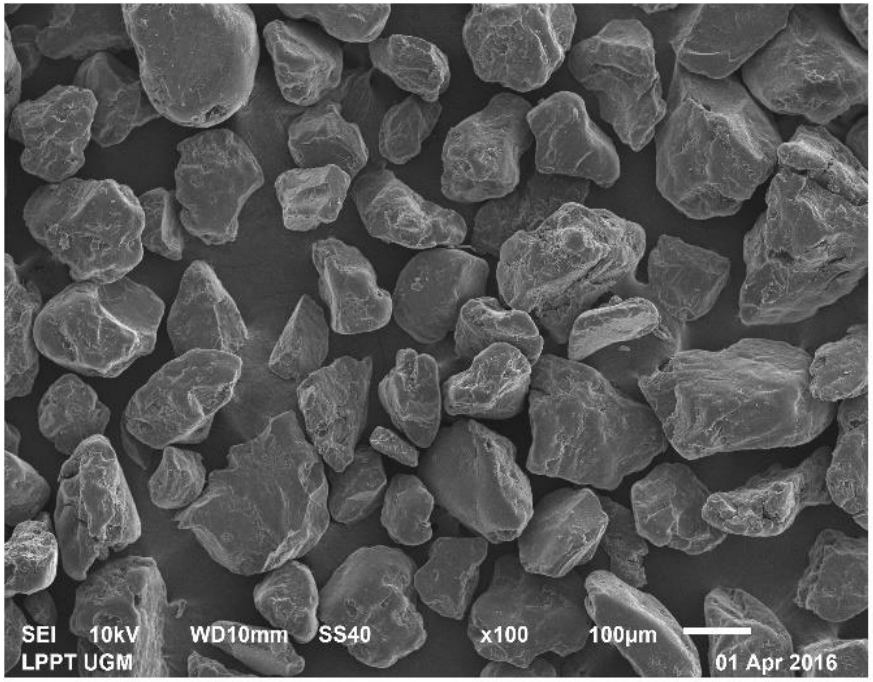
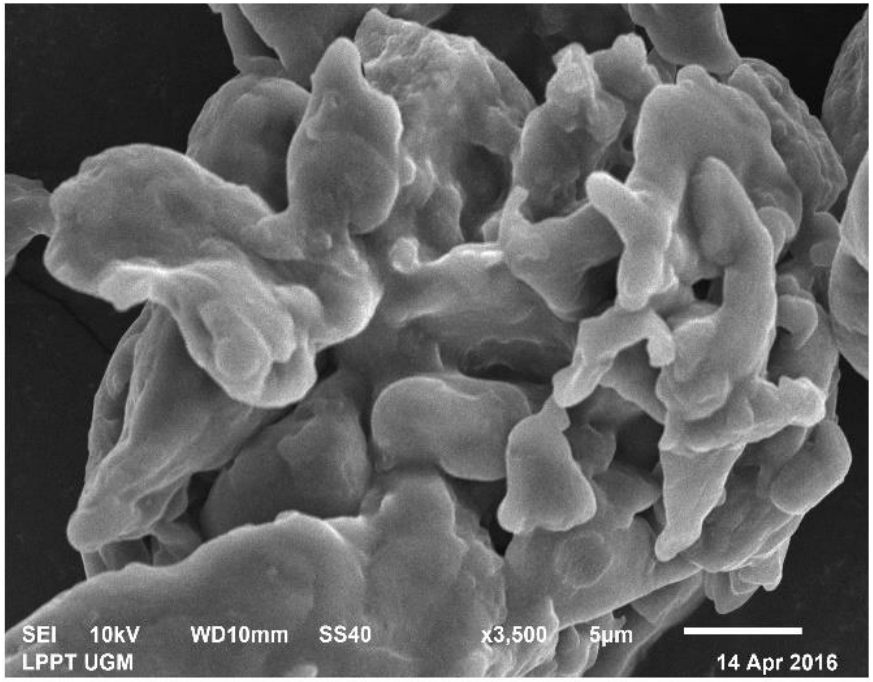


Figure 3. ^{1}H NMR and ^{13}C NMR spectrum of CA-LBG representative (Batch B). CA-LBG was synthesized using catalyst 0.24 M HCl. The presence of CA at CA-LBG was shown in the peaks of a, b, c, d, and e.



CA-LBG [magnification 100x]



CA-LBG [magnification 3500x]

Figure 4. SEM images of CA-LBG representative, synthesized using catalyst 0.24 M HCl (Batch B)

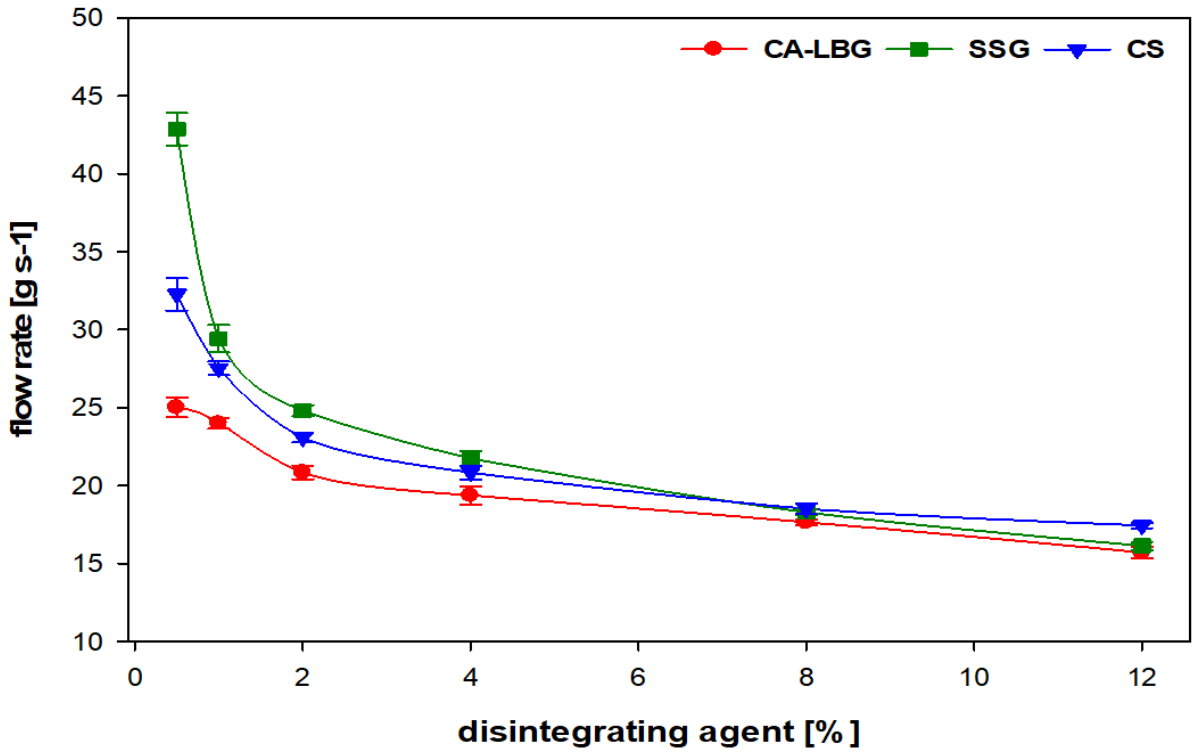


Figure 5. The flow rate profile of the mass of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

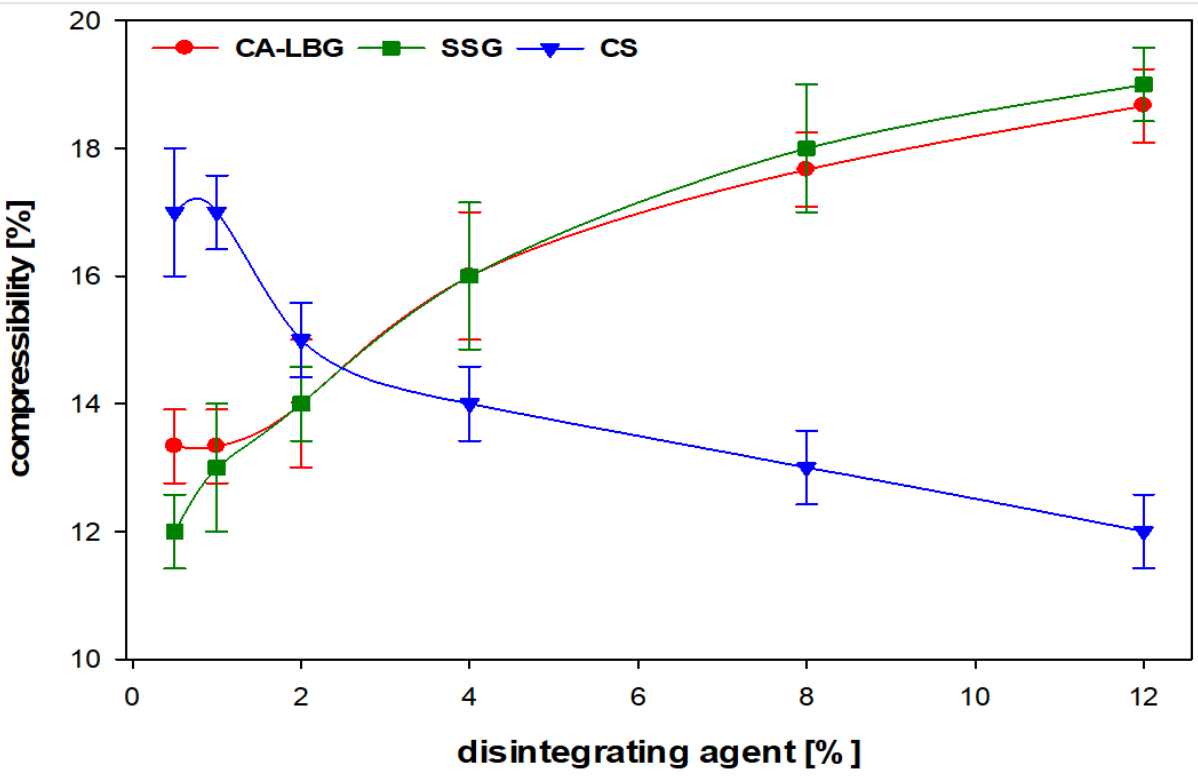


Figure 6. The compressibility profile of the tablet mass contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

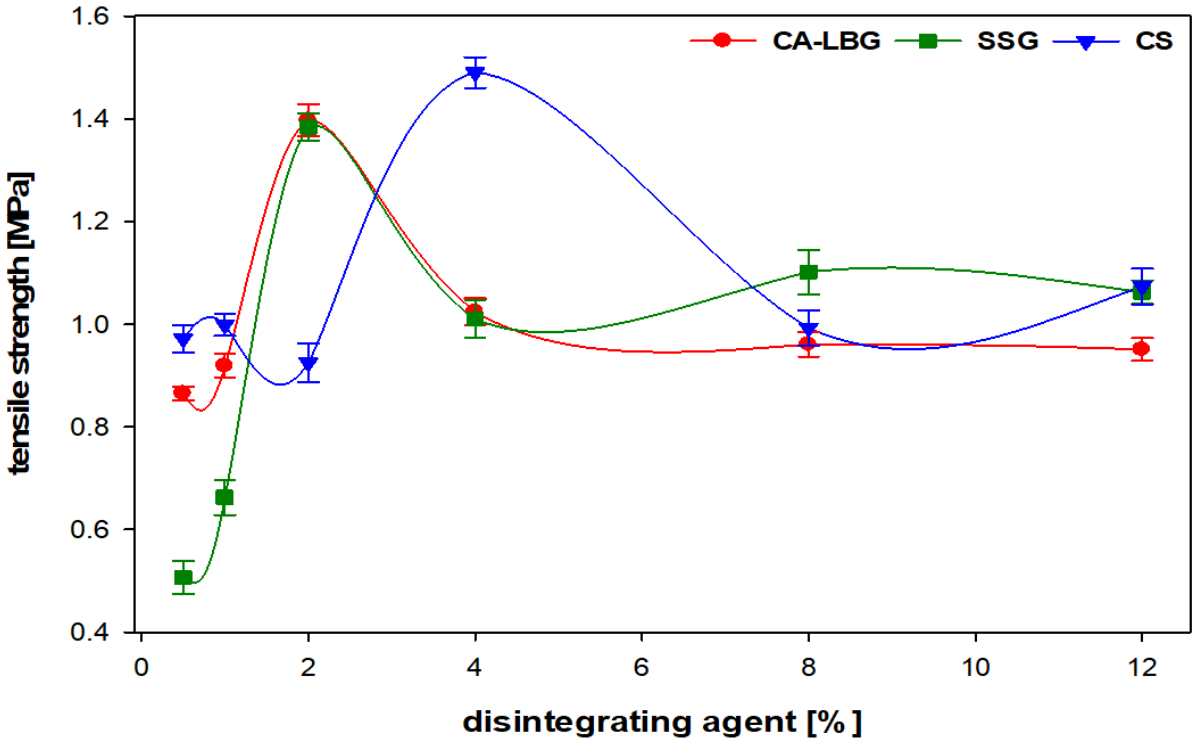


Figure 7. The tensile strength profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

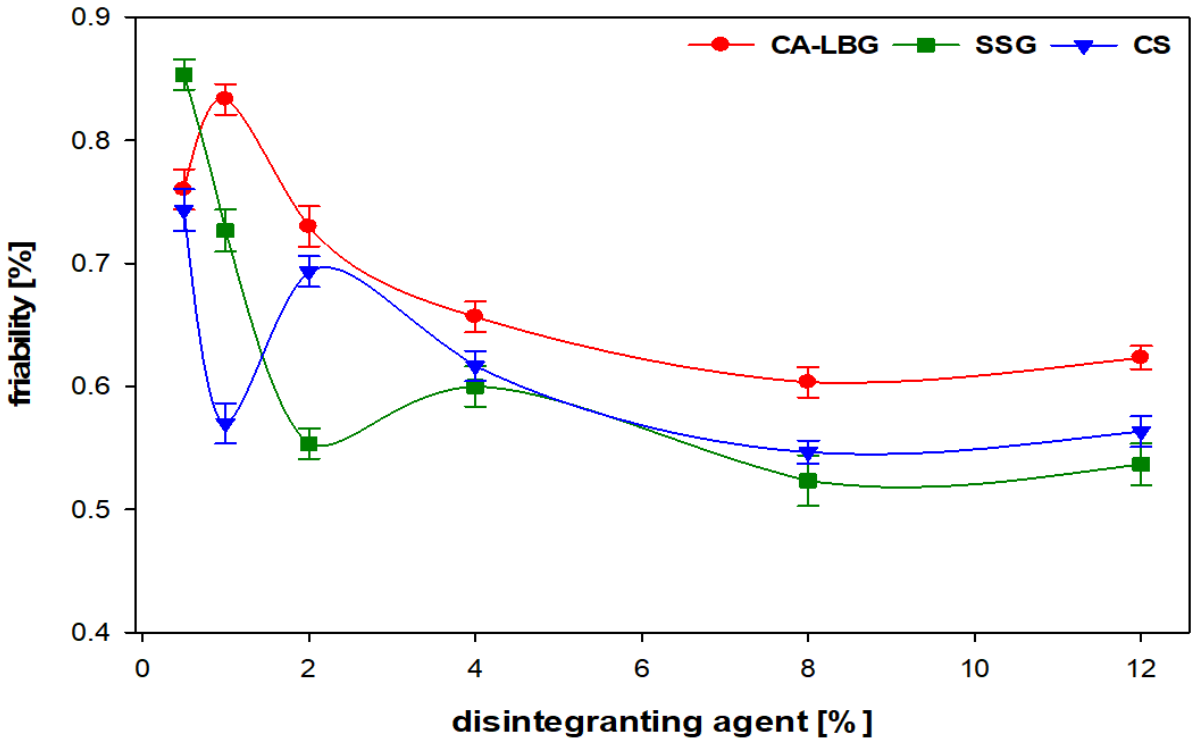


Figure 8. The friability profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

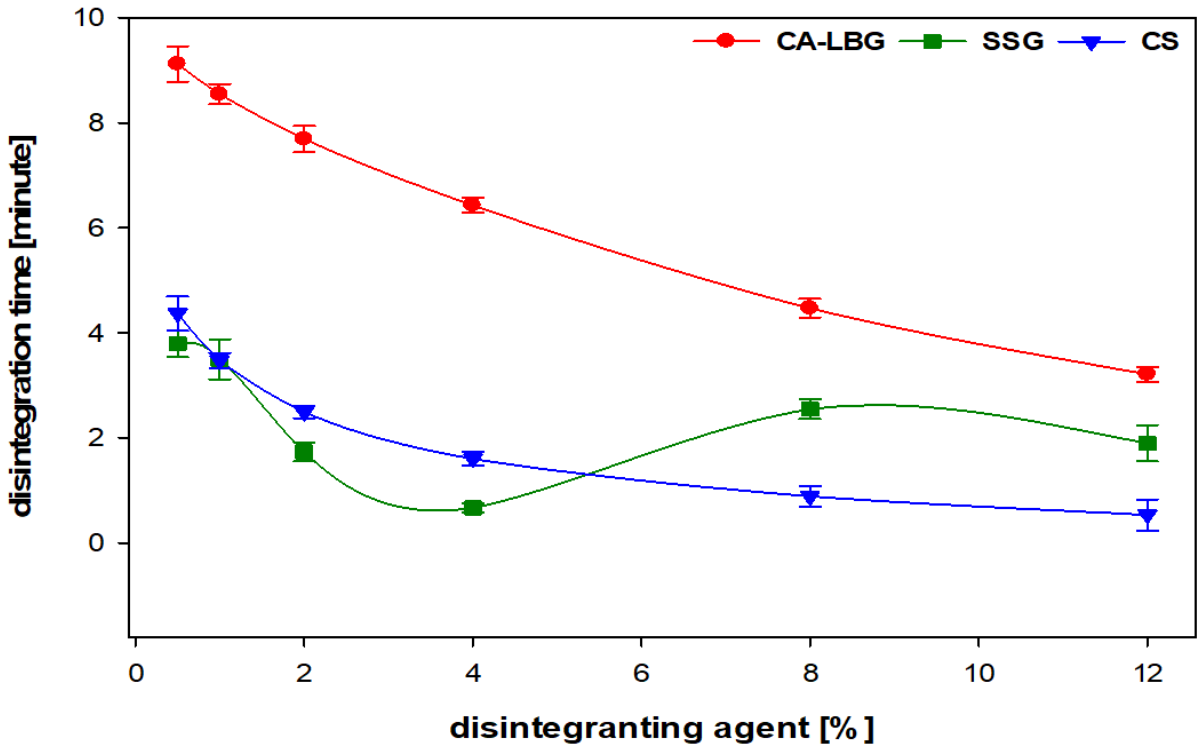


Figure 9. The disintegration time profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

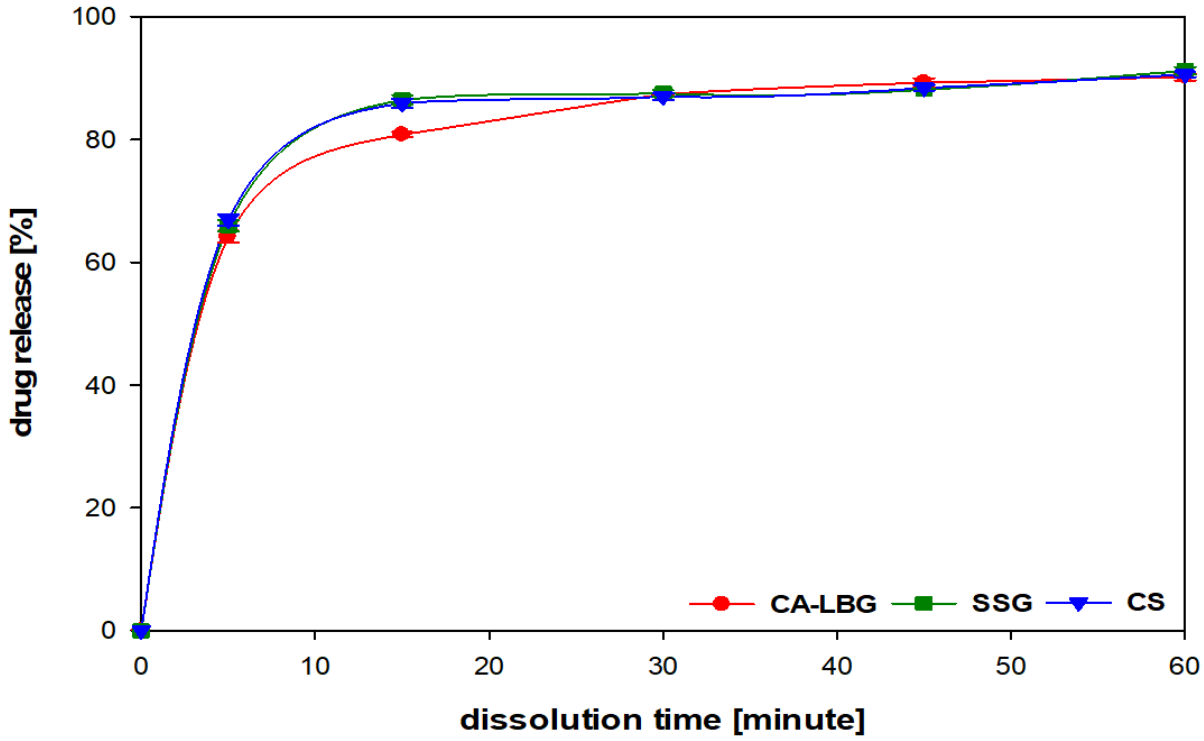
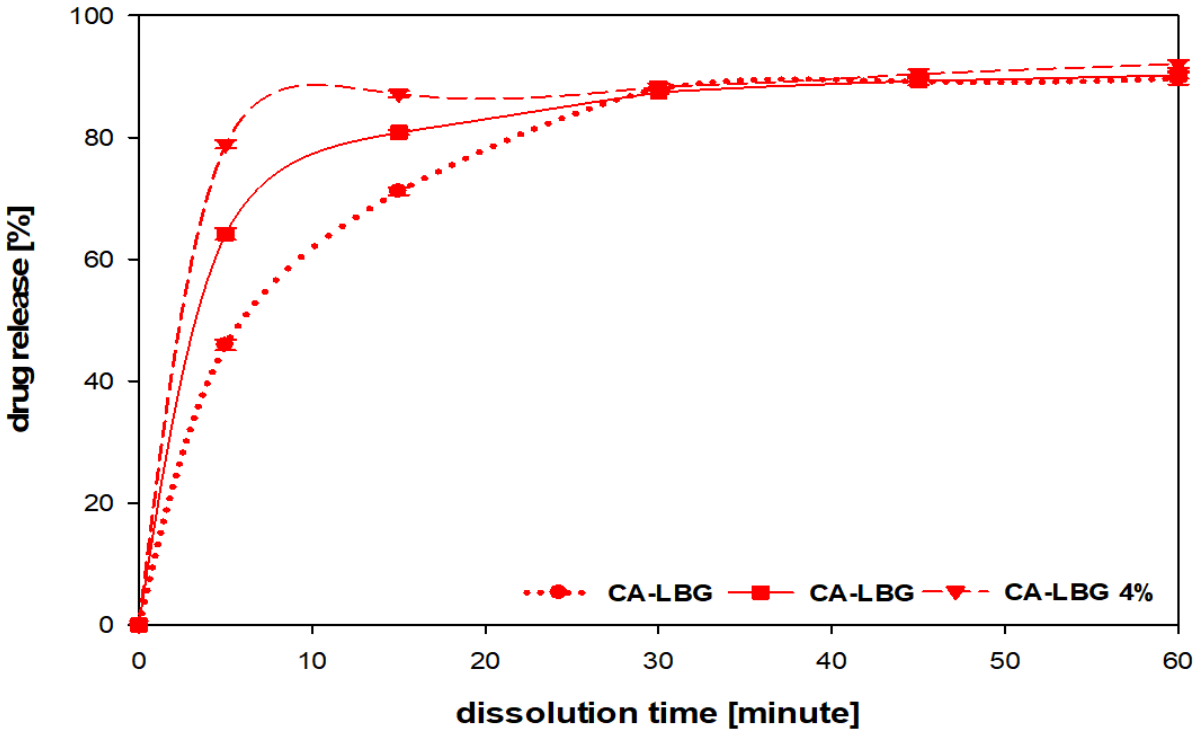


Figure 10. The dissolution profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 2%.



106

107 **Figure 11.** The dissolution profile of the tablet contains CA-LBG 1%; 2% and 4%.

Table 1. Detail synthesis of CA-LBG using the concentration of HCl and irradiated with UV (254 nm,100 minutes). Value physical parameters of CA-LBG: the degree of esterification, carbonyl ester wavelength, solubility, and viscosity.

Batch Code	LBG 10^{-6} [Molar]	CA [Molar]	HCl [Molar]	Carbonyl Ester [cm^{-1}]	Degree of Esterification [%]	Solubility [%]	Viscosity [cP]
A	7.10	0.42	0.18	1739.22	8.27 ± 0.19	36.63 ± 1.14	11.20 ± 0.10
B	7.10	0.42	0.24	1736.39	9.13 ± 0.13	29.30 ± 1.16	9.48 ± 0.06
C	7.10	0.42	0.30	1735.85	9.69 ± 0.23	22.64 ± 1.15	7.76 ± 0.07

Table 2. Details of tablet formulations using disintegrating agents. Evaluate the physical quality of the tablet mass and the tablet.

formula code	disintegrating agent			flow time	ρ_{tapped}-ρ_{bulk}	actual weight	thickness	break force	friability	disintegration time
	CA-LBG [%]	SSG [%]	CS [%]	[sec.]	[g.mL^{-1}]	[mg]	[mm]	[kp]	[%]	[min.]
CL-1	0.5	-	-	4.0 ± 0.10	0.041 ± 0.00	201.0 ± 0.25	4.39 ± 0.01	4.0 ± 0.06	0.76 ± 0.02	9.12 ± 0.34
CL-2	1	-	-	4.2 ± 0.06	0.041 ± 0.00	201.2 ± 0.47	4.38 ± 0.01	4.2 ± 0.10	0.83 ± 0.01	8.54 ± 0.19
CL-3	2	-	-	4.8 ± 0.10	0.044 ± 0.01	201.2 ± 0.12	4.40 ± 0.01	6.4 ± 0.15	0.73 ± 0.02	7.69 ± 0.25
CL-4	4	-	-	5.2 ± 0.15	0.053 ± 0.01	201.1 ± 0.21	4.41 ± 0.01	4.7 ± 0.12	0.66 ± 0.01	6.43 ± 0.14
CL-5	8	-	-	5.7 ± 0.06	0.059 ± 0.01	200.9 ± 0.26	4.38 ± 0.01	4.4 ± 0.10	0.60 ± 0.01	4.47 ± 0.18
CL-6	12	-	-	6.4 ± 0.15	0.061 ± 0.00	201.1 ± 0.36	4.39 ± 0.01	4.4 ± 0.12	0.62 ± 0.01	3.21 ± 0.14
SSG-1	-	0.5	-	2.3 ± 0.06	0.036 ± 0.00	200.8 ± 0.06	4.40 ± 0.01	2.3 ± 0.15	0.85 ± 0.01	3.79 ± 0.25
SSG-2	-	1	-	3.4 ± 0.10	0.042 ± 0.00	201.1 ± 0.44	4.38 ± 0.01	3.0 ± 0.15	0.73 ± 0.02	3.49 ± 0.38
SSG-3	-	2	-	4.0 ± 0.06	0.047 ± 0.01	201.0 ± 0.51	4.35 ± 0.01	6.3 ± 0.12	0.55 ± 0.01	1.73 ± 0.18
SSG-4	-	4	-	4.6 ± 0.10	0.051 ± 0.00	200.7 ± 0.21	4.37 ± 0.01	4.6 ± 0.17	0.60 ± 0.02	0.67 ± 0.09
SSG-5	-	8	-	5.5 ± 0.06	0.057 ± 0.00	201.1 ± 0.32	4.38 ± 0.01	5.0 ± 0.21	0.52 ± 0.02	2.55 ± 0.19
SSG-6	-	12	-	6.2 ± 0.10	0.063 ± 0.00	200.7 ± 0.15	4.38 ± 0.01	4.9 ± 0.12	0.54 ± 0.02	1.90 ± 0.35
CS-1	-	-	0.5	3.1 ± 0.10	0.056 ± 0.00	200.8 ± 0.60	4.43 ± 0.01	4.5 ± 0.12	0.74 ± 0.02	4.37 ± 0.33
CS-2	-	-	1	3.6 ± 0.06	0.052 ± 0.00	200.8 ± 0.35	4.46 ± 0.01	4.7 ± 0.10	0.57 ± 0.02	3.47 ± 0.15
CS-3	-	-	2	4.3 ± 0.06	0.050 ± 0.00	201.0 ± 0.31	4.42 ± 0.01	4.3 ± 0.17	0.69 ± 0.01	2.49 ± 0.12
CS-4	-	-	4	4.8 ± 0.10	0.045 ± 0.00	201.1 ± 0.60	4.40 ± 0.01	6.9 ± 0.12	0.62 ± 0.01	1.60 ± 0.13
CS-5	-	-	8	5.4 ± 0.10	0.038 ± 0.00	201.2 ± 0.35	4.34 ± 0.01	4.5 ± 0.15	0.55 ± 0.01	0.89 ± 0.20
CS-6	-	-	12	5.7 ± 0.06	0.038 ± 0.01	200.9 ± 0.15	4.45 ± 0.01	5.0 ± 0.15	0.56 ± 0.01	0.53 ± 0.30

Acknowledgement of Receipt of #JOPI-D-21-00339R1

Dari: Journal of Pharmaceutical Innovation (em@editorialmanager.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Minggu, 5 September 2021 pukul 09.30 GMT+7

Dear Dr Hadinugroho:

We acknowledge, with thanks, receipt of the revised version of your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms", submitted to Journal of Pharmaceutical Innovation. The manuscript number is JOPI-D-21-00339R1.
You may check the status of your manuscript at any time by accessing the following web site:

https://www.editorialmanager.com/jopi/

Your username is: wuryanto.hadinugroho@ymail.com
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.

We will inform you of the Editor's decision as soon as possible.

Best regards,

The Editorial Office
Journal of Pharmaceutical Innovation

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Journal of Pharmaceutical Innovation

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

--Manuscript Draft--

Manuscript Number:	JOPI-D-21-00339R1
Full Title:	Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms
Article Type:	Original Article
Keywords:	CA-LBG; citric acid; locust bean gum; disintegrating agent; direct compression
Order of Authors:	Wuryanto Hadinugroho, Dr
	Suwaldi Martodihardjo, Prof
	Achmad Fudholi
	Sugeng Riyanto, Prof
Corresponding Author:	Wuryanto Hadinugroho, Dr Widya Mandala Catholic University: Universitas Katolik Widya Mandala Surabaya Surabaya, Jawa Timur INDONESIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Widya Mandala Catholic University: Universitas Katolik Widya Mandala Surabaya
Corresponding Author's Secondary Institution:	
First Author:	Wuryanto Hadinugroho, Dr
First Author Secondary Information:	
Order of Authors Secondary Information:	
Funding Information:	kementerian pendidikan dan kebudayaan (0299 / E3 / 2016) — Dr Wuryanto Hadinugroho
Abstract:	Purpose: Analyze the effect of HC l concentration 0.24 mol as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets. Methods: Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), esterification efficiency, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg. Results: Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility. Conclusion: The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Response to reviewer comments

Comment of reviewer 2

I have already included the necessary changes that needs to be done in the document file. Please follow and compleate the requiriments and correct the paper accordingly. Thank you for your efforts!

Comments of attached document:

1. **The reviewer suggested "put :" in each abstract chapter and removed the word excess of "degree of esterification"**

   Response:

   Thank you for the suggestions. We have added a ":" sign in each abstract chapter. We have also removed the excess of the word "degree of esterification" and replaced it with the word "esterification efficiency". Substitution of the term to meet the reviewer's suggestion on page 5, line 115.

   Original manuscript (page 1)

   Purpose Analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

   Methods Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, degree of esterification, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.

   Results Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.

   Conclusion The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

   Revised manuscript (page 1)

   Purpose: Analyze the effect of HC l concentration 0.24 mol as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

   Methods: Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR),

nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), esterification efficiency, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.
Results: Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.
Conclusion: The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

2. **Comment: "This sentence is a repeat of the previous one, please delete here" (page 2, line 32).**
   Response:
   Thank you for the suggestions. We have removed the sentence.

   Original manuscript (page 2, line 32).
   Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations (Dionísio and Grenha 2012; Dey et al. 2013; Das et al. 2015; Sheskey, J. P., Cook, G. W., and Cable 2017). Locust bean gum is a natural polymer that has the potential to be modified to produce new materials as excipients in tablet formulations.

   Revised manuscript (page 2, line 31)
   Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations [1–4].

3. **Comment: "Do consider removing this paragraph, as the ester synthesis mechanism is a well known chemical reaction" (page 2, line 39).**
   Response:
   Thank you for the suggestions. We have removed the sentence.

   Original manuscript (page 2, line 39)
   Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). The O atoms (C-6) of mannose and

galactose at LBG bind to the positive C atom of the carbonyl groups at CA. Positive C atoms are created from the protonation of carbonyl groups under acidic conditions (Chudzikowski 1971; Samavati et al. 2007; Tamaki et al. 2010; Dey et al. 2013; Hadinugroho et al. 2017, 2019).

Revised manuscript (page 2, line 35)
Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). [2,5–9].

4. **Comment: correct as 'synthesis' (page 2, line 44).**
   Response:
   Thank you for the suggestions. We have corrected the word.

   Original manuscript (page 2, line 44)
   Variation of HCl concentration in the synthetic effect on the character of CA-LBG.

   Revised manuscript (page 2, line 37)
   Variation of HCl concentration in the synthesis effect on the character of CA-LBG.

5. **Comment (page 4, line 88):**
   Please correct the paragraph accordingly;
   'The swollen LBG was placed in a glass bowl (7,10X10(-6) mol/50 ml concentration at a temperature rate of 55-60 C) and CA (0.42 mol) was added with different concentrations of HCl (0.18, 0.24 and 0.30 mol). The mixture was stirred for 10 mins and irradiated with UV light for 100 mins (254 nm, 8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet solid was precipitated with acetone and washed with acetone-distilled water (1:1, v/v). The solid CA-LBG was dried at ambient temperature (Hadinugroho et al. 2017).
   Response:
   Thank you for the suggestions. We have corrected the paragraph accordingly following the suggestions.

   Original manuscript (page 4, line 88)
   The swollen LBG in a glass bowl (7.10 10^{-6} Molar LBG / 50 mL distilled water 55-60 °C) added CA (0.42 Molar) and HCl (0.18; 0.24; 0.30 Molar) (Table 1). The mixture was stirred for 10 minutes. The mixture was irradiated with UV 254 nm (100 minutes) (8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet CA-LBG was precipitated with acetone and washed with acetone-distilled water (1:1). The solid CA-LBG is dried at ambient temperature (Hadinugroho et al. 2017).

   Revised manuscript (page 4, line 79)
   The swollen LBG was placed in a glass bowl (7.10 x10^{-6} mol/50 mL concentration at a temperature rate of 55-60 °C) and CA (0.42 mol) was added with different concentrations of HCl (0.18; 0.24; and 0.30 mol). The mixture was stirred for 10 minutes and irradiated with UV light for 100 minutes (254 nm, 8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The

wet solid was precipitated with acetone and washed with acetone-distilled water (1:1, v/v). The solid CA-LBG was dried at ambient temperature [7].

6. **Comment (page 4, line 94):**
   Please correct the paragraph accordingly;
   'The characterization of CA-LBG was performed by using FTIR (fourier transform infrared) and NMR (nyuclear magnetic resonance) spectroscopic techniques. SEM (scanning electron microscope), degree of esterification, solubility and viscosity tests were also carried out in order to elucidate the structure.
   Response:
   Thank you for the suggestions. We have corrected the paragraph accordingly following the suggestions.

   Original manuscript (page 4, line 94)
   Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG performed was fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR), scanning electron microscope (SEM), degree of esterification, solubility, and viscosity.

   Revised manuscript (page 4, line 85)
   Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG was performed by using FTIR (fourier transform infrared) and NMR (nuclear magnetic resonance) spectroscopic techniques. SEM (scanning electron microscope), esterification efficiency, solubility, and viscosity tests were also carried out in order to elucidate the structure.

7. **Comment: correct as 'was' (page 5, line 108).**
   Response:
   Thank you for the suggestions. We have corrected the word.

   Original manuscript (page 5, line 108)
   The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra were recorded.

   Revised manuscript (page 4, line 99)
   The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra was recorded.

8. **Comment (page 5, line 115):**
   “just a small suggestion, you can also give the synthetic yield of the compound, this is also scientific and more easy in terms of experiemental procedure. But these calculations are also fine”

Response:
Thank you for the suggestions. We have added a description of the percentage of synthesis results in the paragraph on page 5, line 116. In addition, we have also added values of the percentage of yield in Table 1.

Original manuscript (page 5, line 115)
Degree of esterification
The determination of the degree of esterification follows the experimental equation that has been done previously (Hadinugroho et al. 2019). Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar).

Revised manuscript (page 5, line 105)
Esterification efficiency
The efficiency of the synthesis was evaluated through the yield percentage of CA-LBG to the total raw material. The evaluation of esterified CA was determined by the degree of esterification. The determination of the degree of esterification follows the experimental equation that has been done previously [6]. Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar).

Table 1. Detail synthesis of CA-LBG using the concentration of HCl and irradiated with UV (254 nm,100 minutes). Value physical parameters of CA-LBG: yield, the degree of esterification, carbonyl ester wavelength, solubility, and viscosity.

Batch Code	LBG 10^{-6} [mol]	CA [mol]	HCl [mol]	Carbonyl Ester [cm^{-1}]	Yield [%]	Degree of Esterification [%]	Solubility [%]	Viscosity [cP]
A	7.10	0.42	0.18	1739.22	26.62 ± 0.05	8.27 ± 0.19	36.63 ± 1.14	11.20 ± 0.10
B	7.10	0.42	0.24	1736.39	27.13 ± 0.09	9.13 ± 0.13	29.30 ± 1.16	9.48 ± 0.06
C	7.10	0.42	0.30	1735.85	27.66 ± 0.06	9.69 ± 0.23	22.64 ± 1.15	7.76 ± 0.07

9. Comment: correct as 'stretching' (page 10, line 238).

Response:

Thank you for the suggestions. We have corrected the word.

Original manuscript (page 10, line 238)

The stretch peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

Revised manuscript (page 09, line 221)

The stretching peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

10. Comment (page 11, line 250):

"have you used any solvent? If so, please specify"

Response:

Thank you for the suggestions. We have added a description of the solvent used for the preparation of the NMR assay.

Original manuscript (page 11, line 250)

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies (Hadinugroho et al. 2017, 2019).

Revised manuscript (page 10, line 230)

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies [6,7]. NMR examination using CA-LBG dissolved in deuterium (D_2O) (H2O).

11. Comment (page 11, line 256):

"please add the integration and splitting of the peaks. Are you certain all are twin? if so, their names must be dublet. The peak shapes are named as singlet, dublet, tripleti quartet and multiplet. Please give the related details."

Response:

Thank you for the suggestions. We have added a description of peak integration and splitting.

Original manuscript (page 11, line 256)

The results of the CA-LBG NMR analysis are shown in Figure 3. In the ^1H NMR spectrum of CA, a pair of twin peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 (e) in CA. Sharp peaks of 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that a pair of CA twin peaks appear around δ = 2.7-3.0 ppm. Sharp peaks from mannose and galactose appear around 4.5-3.0 ppm (Hadinugroho et al. 2017, 2019).

Revised manuscript (page 10, line 246)
The results of the CA-LBG NMR analysis are shown in Figure 3. The ^{1}H NMR spectrum of CA showed two doublet peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 in CA. The two doublet peaks are protons from symmetric C on CA reacting on LBG. The position of one adjacent proton due to bond rotation and causes the signal to split so that the peak appears splitting. Multiplet peaks at δ = 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that two doublet peaks of CA around δ = 2.7-3.0 ppm. Multiplet peaks from mannose and galactose appear around 4.5-3.0 ppm [6,7].

12. **Comment (page 11, line 262):**
"We have corrected the paragraph by sharing only the number of peaks, ranging from high to low energy fields. We also do not ascertain every carbon peak."
Response:
Thank you for the suggestions. We have corrected the paragraph by sharing only the number of peaks, ranging from high to low energy fields. We also do not ascertain every carbon peak.

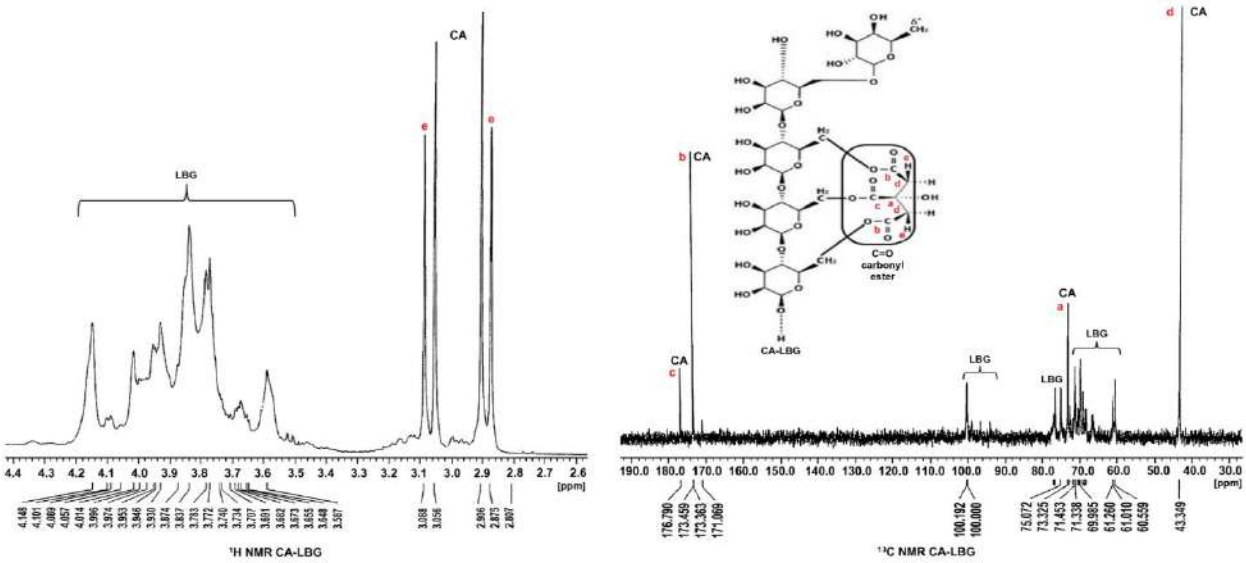
Original manuscript (page 11, line 262)
In the ^{13}C NMR spectrum of CA-LBG, peaks at δ = 176.790 ppm and δ = 173.459 ppm are related to C = O (b,c) resulting from the synthesis reaction. The peak at δ = 73.325 ppm is related to the central C atom of CA (a). The peak at δ = 43.349 ppm is related to C-H_2 (d) of CA. The peaks at δ = 100.192 ppm, δ = 100.000 ppm, δ = 75.072 ppm and δ = 71.453 ppm are related to C-H and C-H_2 at mannose. The peaks at δ = 69,985 ppm, δ = 61.260 ppm, δ = 61.010 ppm, δ = 60.559 ppm are related to C-H and C-H_2 at mannose and galactose. Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H_2 appeared at δ = 44-43 ppm (Jans and Kinne 1991; Doll et al. 2006; Zhang et al. 2016; Hadinugroho et al. 2019). The peak absorption of mannose and galactose appears at δ = 105-60 ppm (Parvathy et al. 2005; Azero and Andrade 2006; Bhatia et al. 2013; Gillet et al. 2014; Hadinugroho et al. 2019). This shows the success of the synthesis.

Revised manuscript (page 10, line 246)
The peaks of the CA-LBG ^{13}C NMR spectra from the high to low energy field were at δ = 176.790 ppm; δ = 173.459 ppm; 173.363 ppm; 171.069 ppm; δ = 100.192 ppm; δ = 100.000 ppm; δ = 75.072 ppm; δ = 73.325 ppm; δ = 71.453 ppm; 71.338 ppm; δ = 69.985 ppm; δ = 61.260 ppm, δ = 61.010 ppm, and δ = 60.559; and δ = 43.349. Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H2 appeared at δ = 44-43 ppm. [6,28–30]. The peak absorption of mannose and galactose appears at δ = 105-60 ppm [6,31–34]. This shows the success of the synthesis.

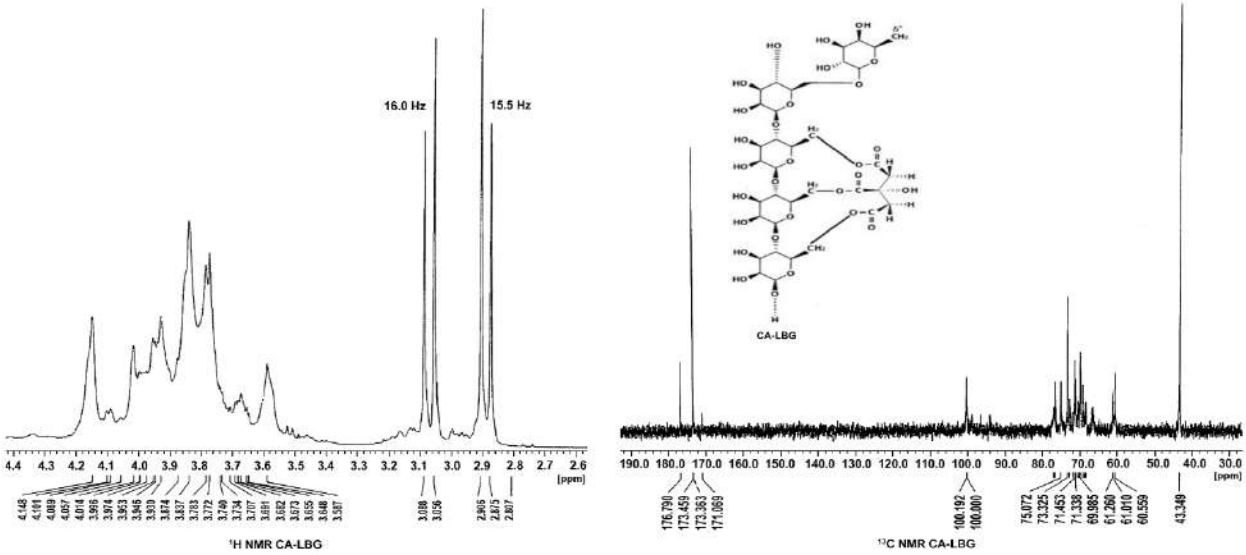
13. **Comment (page 33, Figure 3):**
"I wouldnt suggest you write the carbons as certain like here. Untill you perform a 2D NMR analysis, it is better not to specify the peaks."
"here the peak shape is double dublet, please share the J values."

Response:
Thank you for the suggestions. We have corrected Figure 3 and did not specify the peak. In addition, we have also added the value of J and only shared the number of peaks of the multiplet without specifying the peak.

Original (Figure 3) (page 33, Figure 3)



Revised (Figure 3) (page 32, Figure 3)



Comment of reviewer 3:
"I have provided my decision to the editor."
Response:
Thank you for the suggestions. Thanks for the comments. We really appreciate.

Comment of reviewer 4:

1. **Comment: "The following paper by the author should probably be cited in this manuscript due to similarities in the coverage:**
   Hadinugroho, W., Martodihardjo, S., Fudholi, A., & Riyanto, S. (2019). Esterification of citric acid with locust bean gum. Heliyon, 5(8), e02337."
   Response:
   Thank you for the suggestions. We have included citations in this manuscript for the article: Hadinugroho, W., Martodihardjo, S., Fudholi, A., & Riyanto, S. (2019). Esterification of citric acid with locust bean sap. Heliyon, 5(8), e02337. In addition, we have also been listed on the reference (number 6).

   (Page 2, paragraph 2, line 35)
   Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). [2,5–9]

   (Page 2, paragraph 3, line 42)
   The HCl is a strong acid that is effective for creating acidic conditions [10,11]. Variation of HCl concentration in the synthesis effect on the character of CA-LBG. The concentration of HCl affects the rate of protonation of the carbonyl group of CA to form a positive C atom. Increasing the concentration of HCl causes an increase in the creation of positive C atoms. This condition increases CA binding to LBG. The characteristics of CA-LBG are influenced by the concentration of CA bound to LBG [6].

   (Page 2, paragraph 4, line 47)
   The low wavelengths of UV irradiation (200-400 nm) are a source of energy strong enough to form chemical bonds [12–14]. The UV irradiation for a certain duration determines the formation of positive C atoms from the carbonyl group in CA with the O atoms (C-6) of mannose and galactose at LBG. The results of previous studies reported that this esterification produced a carbonyl ester group on CA-LBG which was not owned by LBG. In addition, the study reported that CA-LBG has a viscosity of 7-11 cP [6]

   (Page 3, paragraph 5, line 51)
   The CA-LBG utilization as material synthesis products needs to be studied further. Pharmaceutical formulation is one area where CA-LBG can be used as an alternative to pharmaceutical excipients. Previous studies have reported that CA-LBG has the potential as a disintegrating agent for tablet dosage formulations [6].

   (Page 5, line 120)
   The degree of esterification is determined by comparing the carboxylate group in the reacting CA (Molar) and the carboxylate group at the initial CA (Molar) and calculated according to Equation 3 [6].

(Page 9, line 216)
In the synthesis of CA-LBG, the acidity of HCl could be induced protonation of O atoms from the carbonyl group of citric acid and created positive C atoms. The hydroxyl (OH) group of C-6 at mannose and galactose atoms reacts with the protonated citric acid carbonyl group to create a tetrahedral cation. Protonated OH ($^{+}OH_2$) oxygen groups with H_2O loss to form CA-LBG. UV irradiation is the energy source to create bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose [6,7].

(Page 10, line 230)
The sharp peak of CA-LBG appeared at 1739.22 cm^{-1}; 1736.39 cm^{-1}; and 1735.85 cm^{-1} are related to the carbonyl ester group that was produced from the synthesis reaction. The carbonyl ester group is created by the bond between the positive C atom of the protonated carbonyl group in CA and the O atom of C-6 at mannose and galactose in LBG. In a previous study, the OH group appeared around 3300 cm^{-1}. C-H appears around 2900 cm^{-1}, and C=O appears around 1750-1735 cm^{-1}[6]

(Page 10, line 237)
NMR examination of the two other conditions has been confirmed in previous studies [6,7].

(Page 10, line 245)
Multiplet peaks at δ = 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that two doublet peaks of CA around δ = 2.7-3.0 ppm. Multiplet peaks from mannose and galactose appear around 4.5-3.0 ppm [6,7].

(Page 11, line 251 & 252)
Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H2 appeared at δ = 44-43 ppm. [6,28–30]. The peak absorption of mannose and galactose appears at δ = 105-60 ppm [6,31–34]. This shows the success of the synthesis.

(Page 11, line 258)
Based on previous experiments, LBG has a corrugated morphology and CA creates coral morphology [6].

References

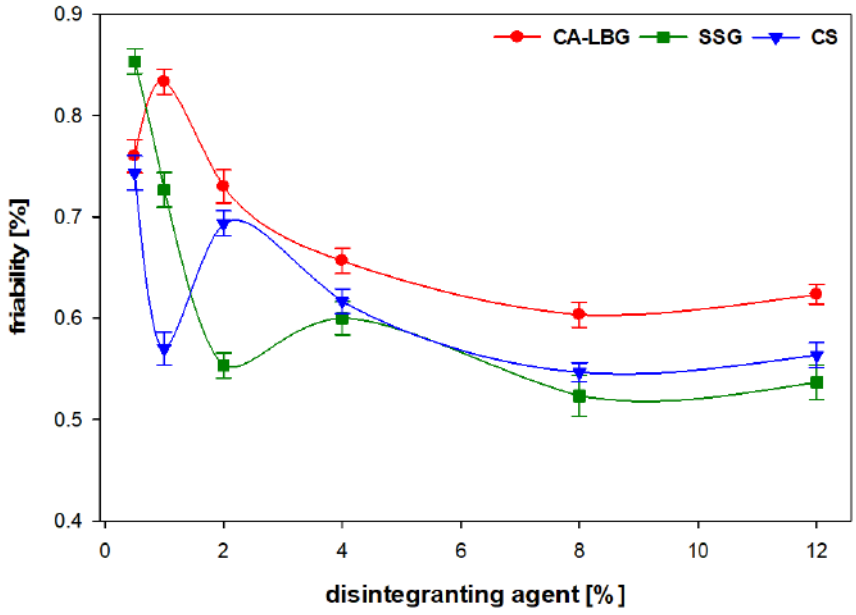
1. Das N, Triparthi N, Basu S, Bose C, Maitra S, Khurana S. Progress in the development of gelling agents for improved culturability of microorganisms. Front Microbiol. 2015;6:1–7.
2. Dey P, Maiti S, Sa B. Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide. J Biomater Sci Polym Ed. 2013;24:663–83.
3. Dionísio M, Grenha A. Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci. 2012;4:175–85.
4. Sheskey, Paul J Cook, Walter G Cable, Colin G. Handbook of Pharmaceutical Excipients 8th. London-Washington DC: Pharmaceutical Press and American Pharmacists Association; 2017.
5. Chudzikowski RJ. Guar gum and its applications. J Soc Cosmet Chem. 1971;22:43–60.
6. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Esterification of citric acid with

locust bean gum. Heliyon. Elsevier Ltd; 2019; 5: e02337. https://doi.org/10.1016/j.heliyon.2019.e02337

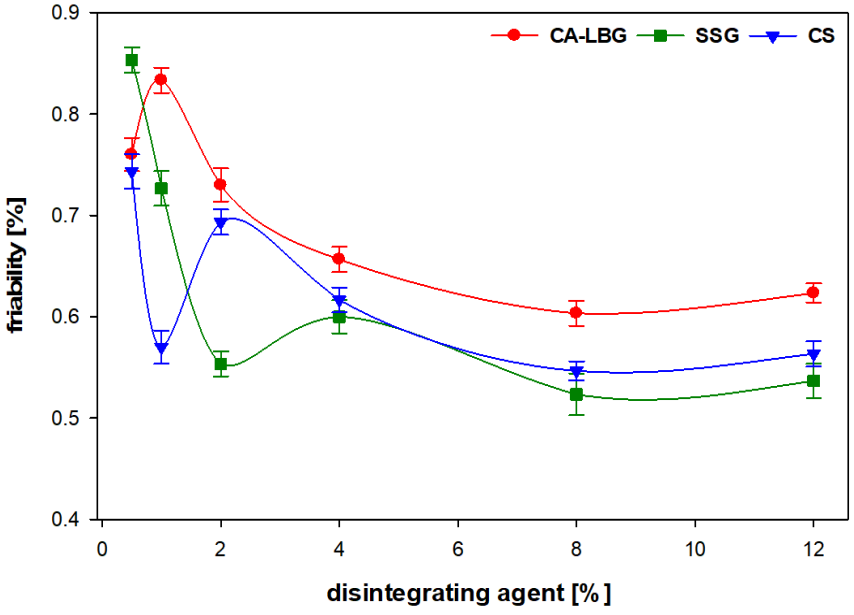
7. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Study of a catalyst of citric acid crosslinking on locust bean gum. J Chem Technol Metall. 2017;52:1086–91.

2. **Comment: "Correct the spelling of disintegrating agent on the x-axis in Figure 8, 9."**
   Response:
   Thank you for the suggestions. We have correct the spelling of disintegrating agent on the x-axis in Figure 8, 9.

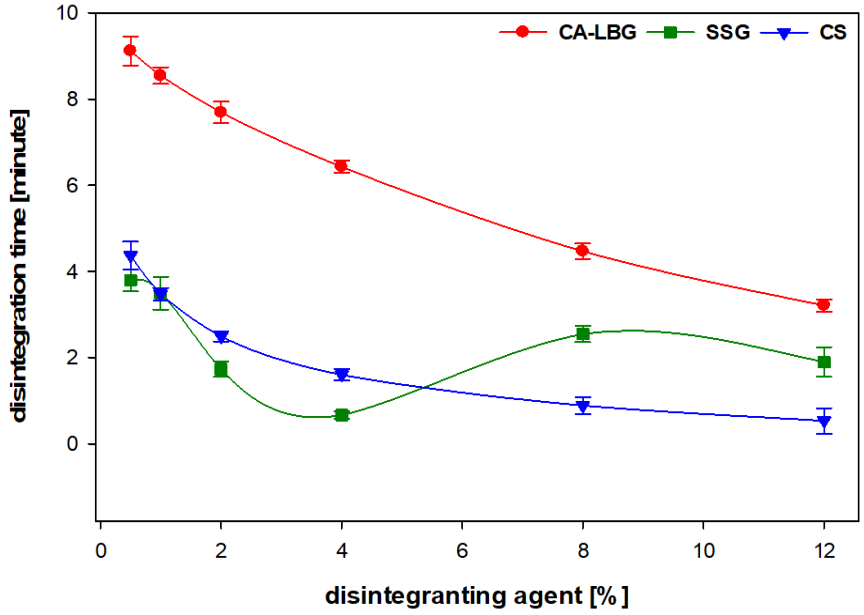
Original (Figure 8) (page 38)



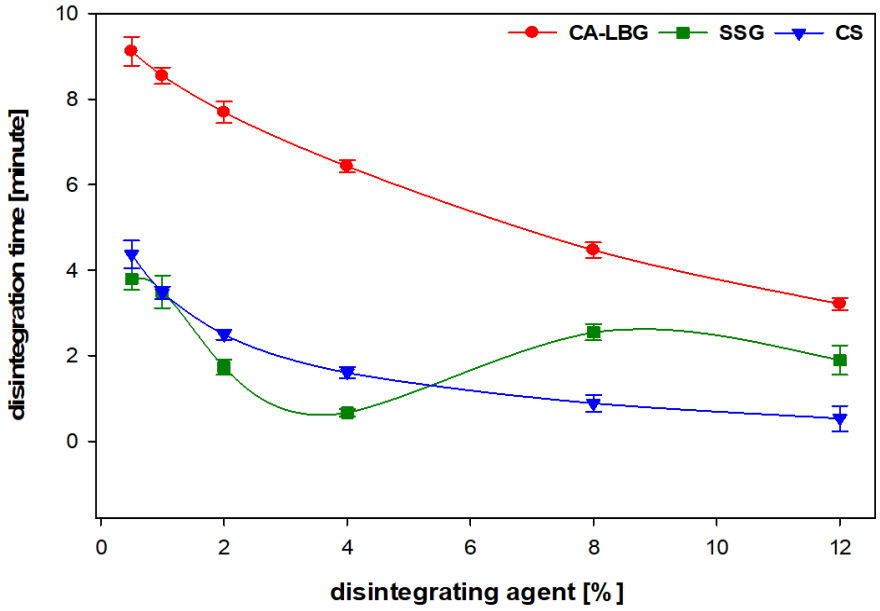
Revised (Figure 8) (page 37)



Original (Figure 9) (page 39)



Revised (Figure 9) (page 38)



3. **Comment:**

"Some editing would improve the readability of the manuscript.For example, the meaning of this sentence is not clear (p. 2, line 45): "Variation of HCl concentration in the synthetic effect on the character of CA-LBG."

Response:

Thank you for the suggestions. We have tried to check and correct the words/sentences in this manuscript electronically and discuss it with linguists. We look forward to suggestions if something is still wrong or missed.

Original manuscript (Page 2, line 44)

Variation of HCl concentration in the synthetic effect on the character of CA-LBG.

Revised manuscript (Page 2, line 37)

Variation of HCl concentration in the synthesis effect on the character of CA-LBG.

Original manuscript (Page 3, line 57)

The CA-LBG utilization as material synthesis products need to be studied further.

Revised manuscript (Page 2, line 48)

The CA-LBG utilization as material synthesis products needs to be studied further.

Original manuscript (Page 5, line 108)

The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra were recorded.

Revised manuscript (Page 4, line 98)

The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra was recorded.

Original manuscript (Page 10, line 238)

The stretch peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

Revised manuscript (Page 9, line 221)

The stretching peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

Original manuscript (Page 11, line 247)

This shows the success of the synthesis and continued by NMR confirmation.

Revised manuscript (Page 10, line 237)

This indicates the success of the synthesis and CA-LBG was further confirmed by NMR.

Original manuscript (Page 12, line 277)

The LBG particles have a shape coral- corrugated indicates available interaction with CA with LBG and successful synthesis.

Revised manuscript (Page 11, line 259)

The LBG particles have a shape coral-corrugated indicates the available interaction of CA with LBG and shows successful synthesis.

Original manuscript (Page 14, line 324)
In general, the tablet profile containing CA-LBG the most slope of flow rate although the CA-LBG concentration was increasing.
Revised manuscript (Page 13, line 307)
In general, the tablet profile containing CA-LBG had the most slope of the flow rate although the CA-LBG concentration was increasing.

Original manuscript (Page 15, line 351)
In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density arrangement between SDL granules and the area of porosity that could accommodate all CA-LBG particles.
Revised manuscript (Page 14, line 334)
In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density and the area of porosity arrangement between SDL granules for could accommodate all CA-LBG particles.

Original manuscript (Page 15, line 361)
The rod-shape and corrugated surface of the CS particles envelop according to the SDL granule shape in layers and has a narrow porosity.
Revised manuscript (Page 14, line 344)
The rod-shaped and corrugated surface of the CS particles is enveloping according to the SDL granule shape in layers and has a narrow porosity.

Original manuscript (Page 20, line 473)
In CS-5 tablet, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface.
Revised manuscript (Page 19, line 456)
In CS-5 tablets, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface.

Original manuscript (Page 20, line 475)
In CS-6 tablet, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.
Revised manuscript (Page 19, line 458)
In CS-6 tablets, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.

Original manuscript (Page 20, line 486)
In the experiment, the peak tensile strength of CA-LBG tablets and SSG tablets was a concentration of 2% while CS tablets was a concentration of 4%.
Revised manuscript (Page 19, line 469)
In the experiment, the peak of tensile strength of CA-LBG tablets and SSG tablets was at a concentration of 2%, while the peak of tensile strength CS tablets was at a concentration of 4%.

Original manuscript (Page 21, line 518)
The friability of the CS-4 to CS-6 tablets proportional to the BF value and tends to decrease.
Revised manuscript (Page 21, line 501)
The friability of the CS-4 to CS-6 tablets is proportional to the BF value and tends to decrease.

Original manuscript (Page 24, line 586)
Comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11).
Revised manuscript (Page 23, line 569)
A comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11).

4. **Comment: "CIC Pharmaceutical Sciences might be a better journal for this work."**
   Response:
   Thank you for the suggestions.

Surabaya, September 4th, 2021

Dear Prof. Robert A Lodder
Editor
Journal of Pharmaceutical Innovation

Please find enclosed our revised manuscript entitled "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms". This manuscript was revised based on the suggestions of reviewers. We inform you that changes to the manuscript based on suggestions from reviewers are written in blue ink. We also attach a list of responses to the suggestions of reviewers.

Regardless of the decision that will publish/reject this manuscript. We are very grateful and expect suggestions and corrections from reviewers and editors to improve this manuscript.

We thank you for your attention and cooperation.

Yours sincerely,
Dr. Wuryanto Hadinugroho
Department of Pharmacy Science and Industrial
Widya Mandala Surabaya Catholic University
Kalisari Selatan 1, Pakuwon City, Surabaya 60112, Indonesia
Email: wuryanto.hadinugroho@ymail.com
Tel. +62 31 3891264
Fax. + 62 31 3891267

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

Wuryanto Hadinugroho[1,2*], Suwaldi Martodihardjo[2], Achmad Fudholi[2], Sugeng Riyanto[2]

1 Department of Pharmaceutical, Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, Indonesia

2 Department of Pharmaceutical, Faculty of Pharmacy, Gadjah Mada University, Sekip Utara, Yogyakarta, Indonesia

*Corresponding authors: e-mail address: wuryanto.hadinugroho@ymail.com; Tel.: +62 81 330 904 484, Fax: +62 31 990 052 88

Declarations

Author contribution statement

Wuryanto Hadinugroho: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Suwaldi Martodihardjo, Achmad Fudholi, Sugeng Riyanto: Conceived and designed the experiments; Analyzed and interpreted the data.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgement

The authors thank the research, technology, and higher education department, Indonesia for support of this work by providing research grants (0299/E3/2016). The author also thanks PT. Makmur Food (Indonesia) for supporting locust bean gum (viscogum); LPPT Gadjah Mada University (Indonesia) for the SEM, DSC, NMR instrument support; Faculty of Pharmacy, Gadjah Mada University (Indonesia) for support of pharmaceutical technology facilities; Faculty of Pharmacy, Widya Mandala Catholic University Surabaya (Indonesia) for pharmaceutical technology facilities and instruments.

Abstract

Purpose: Analyze the effect of HC l concentration 0.24 mol as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

Methods: Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), esterification efficiency, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.

Results: Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.

Conclusion: The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Keyword: CA-LBG, citric acid, locust bean gum, disintegrating agent, direct compression

Introduction

Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations [1–4].

Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). [2,5–9].

The HCl is a strong acid that is effective for creating acidic conditions [10,11]. Variation of HCl concentration in the synthesis effect on the character of CA-LBG. The concentration of HCl affects the rate of protonation of the carbonyl group of CA to form a positive C atom. Increasing the concentration of HCl causes an increase in the creation of positive C atoms. This condition increases CA binding to LBG. The characteristics of CA-LBG are influenced by the concentration of CA bound to LBG [6].

The low wavelengths of UV irradiation (200-400 nm) are a source of energy strong enough to form chemical bonds [12–14]. The UV irradiation for a certain duration determines the formation of positive C atoms from the carbonyl group in CA with the O atoms (C-6) of mannose and galactose at LBG. The results of previous studies reported that this esterification produced a carbonyl ester group on CA-LBG which was not owned by LBG. In addition, the study reported that CA-LBG has a viscosity of 7-11 cP [6].

The CA-LBG utilization as material synthesis products needs to be studied further. Pharmaceutical formulation is one area where CA-LBG can be used as an alternative to

pharmaceutical excipients. Previous studies have reported that CA-LBG has the potential as a disintegrating agent for tablet dosage formulations [6].

The purpose of this study was to analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG. The aim of the tablet formulation was to determine the effect of the application of CA-LBG as a disintegration agent on the physical quality of tablets. The novelty of this study, the synthesis of CA-LBG uses a concentration of HCl 0.24 mol as the catalyst and UV irradiation time (100 minutes) as an energy source that creates the chemical bond. HCl concentrations of 0.18 mol and 0.30 mol were experimental control concentrations to determine the success of the synthesis and characterization of CA-LBG. The CA-LBG experiment as a disintegrating agent was further studied with various concentrations. Sodium starch glycolate (SSG) and croscarmellose sodium (CS) were comparable disintegrating agents to study the disintegration activity of CA-LBG. SSG and CS are tablet disintegrating agents that are often used in tablet formulations because both able to swell in the disintegrating medium in a fast time. The rounded shape with the smooth surface of the SSG and the shape of the root with the corrugated surface of the CS can affect the tablet quality [4,15]. The experiment was conducted to determine the potential for the disintegration of CA-LBG in tablet formulations as an alternative choice of disintegrating agent to be developed in the future.

Material and methods

Raw materials and chemicals

Materials needed in this study were locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Merck KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich, GmbH, USA), acetone (Cawan Anugerah Chemika, Indonesia), sodium starch glycolate (JRS Pharma, India), croscarmellose sodium (FMC Biopolymer, USA), spray dried lactose

(Foremost Farms, USA), diclofenac sodium (Dwilab Mandiri, Indonesia), sterilized water for injection (Otsuka, Indonesia), and distilled water (Brataco Chemical, Indonesia).

Preparation of CA-LBG

The swollen LBG was placed in a glass bowl (7.10 x10^{-6} mol/50 mL concentration at a temperature rate of 55-60 °C) and CA (0.42 mol) was added with different concentrations of HCl (0.18; 0.24; and 0.30 mol). The mixture was stirred for 10 minutes and irradiated with UV light for 100 minutes (254 nm, 8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet solid was precipitated with acetone and washed with acetone-distilled water (1:1, v/v). The solid CA-LBG was dried at ambient temperature [7].

Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG was performed by using FTIR (fourier transform infrared) and NMR (nuclear magnetic resonance) spectroscopic techniques. SEM (scanning electron microscope), esterification efficiency, solubility, and viscosity tests were also carried out in order to elucidate the structure.

Fourier transform infrared spectroscopy

The structure and the functional group of CA-LBG were analyzed by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.) in the wavenumber range of 4000-450 cm^{-1} spectra were recorded.

Nuclear magnetic resonance

The ^{1}H and ^{13}C NMR of CA-LBG was analyzed by liquid state NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan). The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra was recorded.

Scanning electron microscope

The surface morphology of CA-LBG was analyzed using SEM (JSM-6510LA, JEOL, Japan). The CA-LBG was mounted on a holder, coated by platinum, and observed (distance 10 mm and voltage10 kV).

Esterification efficiency

The efficiency of the synthesis was evaluated through the yield percentage of CA-LBG to the total raw material. The evaluation of esterified CA was determined by the degree of esterification. The determination of the degree of esterification follows the experimental equation that has been done previously [6]. Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar). The degree of esterification is determined by comparing the carboxylate group in the reacting CA (Molar) and the carboxylate group at the initial CA (Molar) and calculated according to Equation 3 [6].

Dissolved CA (mEq).

$$dissolved\ CA\ [mEq] = dissolved\ acid [mEq] - dissolved\ HCl [meq] \quad \textbf{Equation 1}$$

Weight CA reacting (gram)

$$W\ CA\ reacting\ = W\ initial\ CA - W\ dissolved\ CA \quad \textbf{Equation 2}$$

Degree of esterification

$$Degree\ of esterification\ [\%] = \frac{carboxylic\ group\ on\ the\ CA\ reacting\ [Molar]}{carboxylic\ group\ on\ the\ CA\ initial\ [Molar]}\ x\ 100\ \%$$ **Equation 3**

Solubility

Solubility was determined by 0.5 g CA-LBG added 50 mL distilled water and allowed to stand for 24 h (Wd). Then, the filtrate was separated from the swollen sample. The filtrate was dried on a water bath at 70 ° C and reweighed (Wds) on a microbalance (Mettler Toledo AL204, Switzerland). The solubility of the CA-LBG was analyzed according to Equation 4:

Solubility (%) = Wds/Wd x 100 **Equation 4**

where Wds and Wd are soluble weight and initial weight (dry weight respectively) [16].

Viscosity

The CA-LBG viscosity test using a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG (3% w/v) was swelled in 300 mL of warm distilled water and left at ambient temperature. Spindle no. S61 was installed on Brookfield. Viscosity was recorded when Brookfield was rotated at 100 rpm.

Preparation of tablets

Preparation of tablets begins with weighing the ingredients according to the formula (Table 1). Preparation of tablets by direct compress was prepared by mixing homogeneous SDL and CA-LBG / SSG / CS using a cubic mixer (2 minutes, 100 rpm) (Erweka). The physical quality of tablet mass was evaluated for flowability and compressibility. The mass of the tablets was compressed with a weight of 200 mg per tablet using a single punch machine (Jenn Chian Machinery, Taiwan). The physical quality of the tablets was evaluated for thickness, weight, break force, tensile strength, friability, and disintegration time.

Flowability

Tablet mass (100 g) was placed in a funnel hole on a flowability tester (Erweka, Germany). When the funnel valve is opened, tablet mass flows. Flow time can be observed on the flowability tester monitor.

Compressibility

Tablet mass was poured into a measuring tube (100 mL, angle ± 40^{o}) whose weight was known. The filled measuring tube is weighed, placed on a tapped density volumeter apparatus (Erweka, Germany), and tapped (500 taps). Weight and volume of tablet mass (before and after tapped) were recorded to determine the bulk density and the tapped density. Tablet mass versus volume before tapped is bulk density. Granule weight/tablet mass versus volume after tapped is the tapped density. The compressibility index is the difference between tapped density and bulk density versus tapped density (Equation 5) [17].

$$compressibility\ index\ (\%) = \frac{tapped\ density - bulk\ density}{tapped\ density}\ x\ 100\% \qquad \textbf{Equation 5}$$

Weight and thickness

Tablet weight and thickness were determined using 20 randomly selected tablets. Each tablet was weighed using an analytical weighing scale (Mettler Toledo, Switzerland) and thickness was accurately measured using a thickness gauge (Mitutoyo 7301, Japan).

Break force and tensile strength

Tablet break force (BF) was determined using 6 randomly selected tablets [18]. The tablet is placed on the break force tester plate (Schleuniger, Netherlands). The metal block moves towards the tablet and presses until the tablet cracks/breaks. The tablet break force value is determined from the start of cracks/breaks, indicated on the monitor.

The strength of the tablet against mechanical stress is determined specifically using the tensile strength parameter according to the shape of the convex tablet. Tensile strength (σt) is calculated following Equation 6 [19,20].

$$\sigma t = \frac{10F}{\pi D^2(2.84(\frac{t}{D})-0.126(\frac{t}{W})+3.15(\frac{W}{D})+0.001)} \quad \textbf{Equation 6}$$

F is the break force, D is the diameter of the tablet, t is the total thickness of the tablet, and W is the thickness of the center of the tablet without convex.

Friability

Tablet friability was determined using a randomly selected number of tablets with a total tablet weight equal to 6500 mg [18]. Each tablet was dust-free and the total weight of all tablets was determined (W0). All tablets were put into a drum friability tester (Erweka, Germany) and rotated for 4 minutes (25 rpm). After being removed from the drum, each tablet was dust-free and weighed again (W1). The friability of the tablet is the difference in the total weight of the tablet before and after rotated compared to the weight before rotated (Equation 7).

$$friability\ (\%) = \frac{W0-W1}{W0}\ 100\% \quad \textbf{Equation 7}$$

Disintegration time

Tablet disintegration time was determined using 6 tablets randomly selected from 18 previously randomly selected tablets [18]. Each tablet was inserted into each tube in the chamber disintegration tester apparatus (Erweka Z3, Germany). The chamber is up-down in a distilled water bath (37° C; 900 mL). The disintegration time was determined from the longest time required for the tube net to be free of tablet fragments.

Dissolution

The experiment was prepared using a tablet mass added with diclofenac sodium as a model active ingredient. Each tablet contains 50 mg of diclofenac sodium to be compressed to a weight of 250 mg [21,22]. Dissolution using phosphate buffer medium pH 6.8 (900 mL; 37 ± 0.5 ° C; 50 rpm) for 60 minutes using the paddle method (Electrolab TDT-08L, India) [23,24]. The release of ketoprofen was sampled and observed at 5, 15, 30, 45, and 60 minutes. Analysis of dissolved diclofenac sodium concentration using a UV-vis spectrophotometer (Hitachi U-1900, Japan) at a wavelength of 276 nm [25,26].

Result and discussion

Mechanism of the CA-LBG synthesis reaction

In the synthesis of CA-LBG, the acidity of HCl could be induced protonation of O atoms from the carbonyl group of citric acid and created positive C atoms. The hydroxyl (OH) group of C-6 at mannose and galactose atoms reacts with the protonated citric acid carbonyl group to create a tetrahedral cation. Protonated OH ($^{+}OH_2$) oxygen groups with H_2O loss to form CA-LBG. UV irradiation is the energy source to create bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose [6,7]. The schematic and details of the synthesis are shown in Figure 1 and Table 1.

Fourier transform infrared spectroscopy

The results of the CA-LBG and LBG infrared analysis are shown in Figure 2 and Table 1. The stretching peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose. Sharp peaks appear at 2920.60 cm^{-1}; 2923.35 cm^{-1}, 2923.56 cm^{-1}; and 2923.35 cm^{-1} are related to C-H bonds of CA and LBG. In CA-LBG, the sharp peak comes from C-H symmetrically of CA [27]. The

sharp peak of CA-LBG appeared at 1739.22 cm^{-1}; 1736.39 cm^{-1}; and 1735.85 cm^{-1} are related to the carbonyl ester group that was produced from the synthesis reaction. The carbonyl ester group is created by the bond between the positive C atom of the protonated carbonyl group in CA and the O atom of C-6 at mannose and galactose in LBG. In a previous study, the OH group appeared around 3300 cm^{-1}. C-H appears around 2900 cm^{-1}, and C=O appears around 1750-1735 cm^{-1}[6]. This indicates the success of the synthesis and CA-LBG was further confirmed by NMR.

Nuclear magnetic resonance

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies [6,7]. NMR examination using CA-LBG dissolved in deuterium (D_2O) (H2O).

The results of the CA-LBG NMR analysis are shown in Figure 3. The ^{1}H NMR spectrum of CA showed two doublet peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 in CA. The two doublet peaks are protons from symmetric C on CA reacting on LBG. The position of one adjacent proton due to bond rotation and causes the signal to split so that the peak appears splitting. Multiplet peaks at δ = 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that two doublet peaks of CA around δ = 2.7-3.0 ppm. Multiplet peaks from mannose and galactose appear around 4.5-3.0 ppm [6,7].

The peaks of the CA-LBG ^{13}C NMR spectra from the high to low energy field were at δ = 176.790 ppm; δ = 173.459 ppm; 173.363 ppm; 171.069 ppm; δ = 100.192 ppm; δ = 100.000 ppm; δ = 75.072 ppm; δ = 73.325 ppm; δ = 71.453 ppm; 71.338 ppm; δ = 69.985 ppm; δ = 61.260 ppm, δ = 61.010 ppm, and δ = 60.559; and δ = 43.349. Previous studies reported that

the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H2 appeared at δ = 44-43 ppm. [6,28–30]. The peak absorption of mannose and galactose appears at δ = 105-60 ppm [6,31–34]. This shows the success of the synthesis.

1.2. Scanning electron microscopy

The SEM images of CA-LBG (Batch B) are shown in Figure 4. In magnification100x, particles of CA-LBG appear in an irregular shape. In magnification 3500x, particles CA-LBG have the surface morphology of CA-LBG appear coral-corrugated. Based on previous experiments, LBG has a corrugated morphology and CA creates coral morphology [6]. The LBG particles have a shape coral-corrugated indicates the available interaction of CA with LBG and shows successful synthesis.

Esterification efficiency

The yield percentage and degree of esterification of CA-LBG for all batches are shown in Table 1. The high concentration of HCl under synthesis conditions increases yield percentage and degree of esterification due to the high amount of CA bound to LBG. The HCl increases the acidity of the synthesis conditions to protonate the O atom from the carbonyl group and creates a positive C atom, thereby causing CA to bind to LBG. The CA-LBG batch A to batch C shows the higher the degree of esterification in proportion to the increase in the concentration of HCl because the protonation of the O atom from the carbonyl group and the formation of a positive C atom is faster. This condition accelerates creates bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose.

Solubility

The solubility of CA-LBG for each synthesis condition is shown in Table 1. The CA-LBG of batch A to batch B presents the solubility decreasing in proportion to the increasing degree of esterification. The more CA molecules bound to the LBG produce CA-LBG with stable ester bonds. Bonds of positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose decrease the ability of CA-LBG to interact with distilled water. In this condition, CA-LBG particles are difficult to wet so inhibit solubility in distilled water.

Viscosity

The viscosity of CA-LBG for each batch is shown in Table 1. LBG has a high viscosity, but the presence of excess CA can reduce the viscosity. The viscosity of CA-LBG from batch A to batch C decreased in proportion to the increasing degree of esterification. The carbonyl ester groups formed from the bonding of positive C atoms from carboxylate groups with O atoms of C-6 in mannose and galactose reduce the ability of CA-LBG to trap distilled water so viscosity decreases.

Flowability

The results of the flowability study on all tablet mass formulas containing CA-LBG showed that an increase in the concentration of CA-LBG increased the flow time of tablet mass (Table 2) because influenced by the irregular shape of particles and the surface like coral inhibit the flow of mass tablet (Figure 5). The CL-1 formula has the fastest flow time due to the influence of the spherical shape of the SDL granules to dominate the flowability although CA-LBG is present in the tablet mass [4]. The formula containing SSG and CS showed an increase in concentration cause increased flow time tablet mass. SSG particles are rounded and have a smooth surface, should be able to rate up the flow time but SSG particles are also hygroscopic,

thus inhibiting the flow time of tablet mass [4]. The CS particles are rod-shaped with a corrugated surface, which at high concentrations can inhibit the flow of tablets mass [4]. According to the flow time requirements, all tablet mass formulas containing a variety of disintegrating agents meet the requirements is 100 g tablet mass can flow in less than 10 seconds [35].

The effect of the presence of various disintegrating agents on the tablet mass is shown in Figure 5, which is a plot between the concentration of the disintegrating agent and the flow rate [g s^{-1}]. In general, the tablet profile containing CA-LBG had the most slope of the flow rate although the CA-LBG concentration was increasing. In addition, the decrease in flow rate of tablet mass with a high concentration of CA-LBG is proportional to the flow rate of tablet mass containing high concentrations of SSG and CS. This case is because the particle surface of CA-LBG like coral can fill each other with a porosity of SDL surface [4]. The sharp decrease in the profile of tablet mass containing CS at low concentrations (CS-1) indicates that the flow rate is more influenced by the spherical shape of the SDL granules so accelerate the flow, while at higher concentrations (CS-2) the root shape and corrugated surfaces of the CS particles begin to inhibit the flow. The flow rate profile of tablet mass containing SSG at low concentrations (SSG-1) is more slope than the tablet mass containing CS at the same concentration (CS-1) because the hygroscopicity of SSG particles inhibits the flow of tablet mass. The hygroscopic effect of SSG particles at higher concentrations (SSG-2 to SSG-6) can be overcome by the rounded shape and smooth surface of the SSG particles so that the decrease flow rate is more slope.

Compressibility

The tablet mass density evaluation results on all tablet mass formulas containing CA-LBG or SSG showed that increasing the concentration of the disintegrating agent increased the

value of ρ_{tapped}-ρ_{bulk} (Table 2), due to the influence of the shape and surface of the disintegrating agent particles. The initial composition of the tablet mass was SDL granules arranged randomly, the porosity between the SDL granules was filled with disintegrating agent particles.

The CA-LBG particles which have an irregular shape and a coral-like surface are randomly arranged on the porosity between the SDL granules according to the shape and area of the porosity between the initial particles. The volume decrease during the tapping was caused by the movement of SDL granules and CA-LBG particles. The CA-LBG particle corners fill each other surface porosity between particles and SDL granule surface porosity. In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density and the area of porosity arrangement between SDL granules for could accommodate all CA-LBG particles. The volume decrease in the tapping of the formula with the higher CA-LBG concentration causes the porosity between the SDL granules to be wider because the CA-LBG particles surround the SDL granules tightly.

The rounded shape and smooth surface of the SSG particles give a tablet mass arrangement with more regular porosity than the CA-LBG particles. The smooth surface of SSG particles causes movement of SDL granules / SSG particles and decreases in volume during tapping so that the porosity narrows and SSG particles fill the porosity of the SDL granule surface. Formulas containing CS have a different value of ρ_{tapped}-ρ_{bulk} from formulas containing other disintegrating agents, namely the increasing the concentration of CS, the lowering the value of ρ_{tapped}-ρ_{bulk}. The rod-shaped and corrugated surface of the CS particles is enveloping according to the SDL granule shape in layers and has a narrow porosity. The surface of the CS particles decreases the ability of the particles to move and the volume decreases on tapping because the surface corrugated of the CS particles will interlock with other CS particles.

The results of the density evaluation are further confirmed by the compressibility profile shown in Figure 6, where increasing the concentration of the disintegrating agent increases the mass compressibility of tablets containing CA-LBG / SSG and decreases the mass compressibility of tablets containing CS. The mass compressibility of tablets containing CA-LBG was slightly lower than the mass of tablets containing SSG because the angles of CA-LBG particles fill each other surface porosity between particles and SDL granule surface porosity.

Weight and thickness

All tablet masses contain a variety of disintegrating agents and their concentration is compressed into tablets and according to weight is around 200 mg (Table 2), which shows that all tablet masses are able to flow freely from the hopper and fill the dies space in the tablet compressing machine. This condition is in accordance with the results of the evaluation of flowability and compressibility.

The variation in tablet thickness from the mass of tablets containing various disintegrating agents is influenced by the arrangement, shape, and surface of the SDL granule or the disintegrating agent particle so that when compression is applied produced deformation of the granule/particle, bond interlocking, and narrowing the porosity between deformations. The irregular shape and coral-like surface of the CA-LBG particles provide an opportunity for the particle corners to fill each other with the SDL particle/granule surface porosity so the tablet mass is compressed to produce a low-porosity tablet. The rounded shape and smooth surface of the SSG particles produce tablets with a regular form of porosity. The root shape and corrugated surface of the CS particles provide an opportunity to interlock between the particles and the corrugated surface so the tablet mass is compressed to produce a low-porosity tablet.

The CL-1 tablet is thicker even though the number of CA-LBG particles is less than the CL-2 tablet because the CA-LBG particles tend to fill the porosity of the SDL granules surface. In the CL-2 tablet, CA-LBG particles fill the surface porosity of SDL granules and porosity between SDL granules. The number of SDL granules of CL-2 tablet mass reduces so that produces a thinner tablet. The CL-3 and CL-4 tablets are thicker than the other CL tablets because the CA-LBG particles surround the SDL granules so that the volume is high and when the tablet mass is compressed into thick tablets. The CL-4 tablet is thicker than the CL-3 tablet due to the increasing number of CA-LBG particles resulting in a wider area surrounding the SDL granules. The number of CA-LBG particles in the CL-5 and CL-6 formula tablets is increasing so the area of the CA-LBG particles surrounding the SDL granules is wider, but the porosity between the CA-LBG particles is narrow so that the mass of the tablets is compressed to produce a thinner tablet. The CL-6 tablet is thicker than the CL-5 tablet because the CA-LBG particle area surrounding the SDL granules is wider.

The SSG-1 tablet is thicker than other SSG tablets because SSG particles fill the porosity of the SDL granules surface so, with the highest number of granules, the tablet mass is compressed to produce thick tablets. Tablet mass of SSG-2 and SSG-3 show the number of SSG particles is increasing and the number of SDL granules is decreasing. The SSG particles in the SSG-2 tablet mass filled the surface porosity of the SDL granules and the dense porosity of the SDL granules. The SSG-3 tablet mass shows the number of SDL granules was reduced so the mass of the tablets was compressed to produce a thinner tablet. The tablet mass of SSG-4 to SSG-6 contains more SSG particles and surrounds the decreasing SDL granules. The SSG-5 tablet is thicker than the SSG-4 tablet because the SSG deformation area surrounding the SDL deformation is wider. The SSG-6 tablet contained more SSG surrounding the SDL deformation with the area is wider. The SSG-6 tablet thickness is similar to SSG-5 because the number of SDL deformation in the tablet mass is reduced.

The thickness of the CS-1 tablet was dominated by the effect filling of CS particles on porosity SDL granules surface so when compressed the tablet mass experienced deformation with porosity varying of shapes and areas. The tablet of CS-2 to CS-4 contain more CS particles and fewer SDL granules. The increasing number of CS particles formed the interlocking deformation between the particles and enveloped the SDL granules so that produce thicker tablets with narrow porosity but in large numbers. The greater the number of CS particles, the wider the enveloping and interlocking area of the CS particles, resulting in a thicker tablet. The thickness of the CS-5 and CS-6 formula tablets was dominated by the increase in the number of CS particles. CS particles in the CS-5 tablet mass forming long interlocking on surrounding SDL granules. The tablet mass contains limited SDL granules so produce thin tablets when compressed. The CS-6 tablet is thicker than the CS-5 tablet because the interlocking area enveloping the SDL granule is wider.

Break force and tensile strength

Evaluation of tablet resistance to mechanical stress is measured by the BF value and shown in Table 2. The resistance of the CL-1 tablet is influenced by the dominance of SDL granules interlocking bonds when compressed to result in deformation with a wide porosity so that the tablets have a low resistance to mechanical stress. The BF value of the CL-2 tablet is higher than CL-1tablet because the number of CA-LBG particles is more and fills the dense porosity between SDL granules so when compressed the interlocking bonds are stronger and the porosity is narrower. The CL-3 tablet shows the highest BF value than other CL tablets because the deformation of CA-LBG particles around the SDL granule when compressed is able to form interlocking bonds with narrow porosity so that the thick tablet and resistant to mechanical stress. In addition, the corners of the CA-LBG particles fill the surface porosity between the CA-LBG particles and the SDL granule surface porosity so strengthening the

interlocking bond. The CL-4 to CL-6 tablets have a similar mechanism as the CL-3 formula tablets, but the number of CA-LBG particles is increasing and SDL granules are decreasing so that when compressed, produce tablets with a lot of narrow porosity and a decrease in tablet resistance to mechanical stress. The tablet of CL-5 and CL-6 show similar BF values due to the CL-6 tablet, although the interlocking bonds between particles are more dominant with the number of narrow porosity increases.

The SSG particles in the SSG-1 tablet mass fill the surface porosity of the SDL granules so inducing the granules to be slightly moist and the interlocking bonds between the SDL deformation are weaker. In addition, SDL granules after being compressed produce wide porosity deformation. The resistance of the SSG-2 tablet is higher than the SSG-1 tablet because the narrow porosity between the SDL granules is filled with SSG particles so that the mass of the granules is compressed resulting in a narrower porosity deformation. The SSG-3 tablet shows the strongest resistance than other tablets because SSG particles surround SDL granules when compressed able to form deformation interlocking bonds with narrow and regular porosity so tablets are resistant to mechanical stress. SSG-4 to SSG-6 tablets have a similar mechanism to SSG-3 tablets, but the number of SSG particles is increasing and SDL granules are decreasing so the mass of SSG-5 and SSG 6 when compressed produces tablets with more narrow porosity and decrease in the resistance of the tablet to mechanical stress. In addition, the slightly hygroscopic character of SSG particles decreased the resistance of tablets shown in the SSG-4 tablet because the deformation interlocking bonds of SSG particles around the SDL granules were weak.

The little number of CS particles in the CS-1 tablet tends to fill the porosity of the SDL granules. When compressed, the interlocking bond is dominated by SDL deformation with wide porosity so the resistance of the tablets to mechanical stress is weak. The CS-2 tablet has a similar mechanism to the CS-1 tablet but the porosity between the SDL granules is filled with

CS particles so produces a tablet with narrower porosity and is more resistant to mechanical pressure. The CS-3 tablet has a similar mechanism to the CS-2 tablet but the number of CS particles is more so the CS particles form interlocking between particles and envelop the SDL granules. When compressed, the enveloping CS particles form an interlocking bond deformation with a narrow and large porosity so the tablet surface resistance is weak. In the CS-4 tablet, the interlocking CS particles to envelope the SDL granules and a wider area so produce tablets with interlocking narrow porosity and strong surface to withstand mechanical stress. The CS-5 and CS-6 tablets have a similar mechanism to the CS-4 tablets but the number of CS particles is increasing and the SDL granules are decreasing. In CS-5 tablets, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface. In CS-6 tablets, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.

The BF value was further confirmed by the tensile strength parameter to determine the comparison between tablets contain disintegrating agent variation according to the concentration in the experiment (Figure 7). The tensile strength profile of CA-LBG tablets is similar to that of SSG tablets due to the influence of the particle shape of CA-LBG and SSG. The irregular shape and coral surface of the CA-LBG particles produce tablets with strong deformation interlocking bonds. The tensile strength intensity of CA-LBG tablets is similar to that of SSG tablets showing a deformation interlocking bond that can adjust the concentration used in the tablets. In the experiment, the peak of tensile strength of CA-LBG tablets and SSG tablets was at a concentration of 2%, while the peak of tensile strength CS tablets was at a concentration of 4%. This concentration is the optimum condition for forming tablets with the most stable interlocking deformation bonds against mechanical stress.

Friability

Evaluation of tablet resistance to mechanical movement is measured by friability parameters and is shown in Table 2. The friability of the CL-1 tablet is influenced by the low BF value due to the interlocking bond of SDL deformation with wide porosity so that SDL deformation on the tablet surface releases particles when subjected to mechanical movement. In addition, the CA-LBG particles on the tablet surface were also released. The CL-2 tablet is more friable than the CL-1 tablet although the BF value is higher because the number of CA-LBG particles on the surface of the tablet is more so more particles are released when subject to mechanical movement. The CL-3 to CL-6 tablets showed a tendency to decrease in friability although the BF value was lower because of a strong interlocking bond on the deformation of granules and particles, so reducing the release of tablet surface particles when subjected to mechanical movement. The CL-6 tablet is more friable than the CL-5 tablet because the number of SDL deformation decreases so that the foundation to withstand mechanical movements is reduced.

The SSG-1 tablet is the most friable than SSG other tablets because of the low BF value due to SDL deformation interlocking bonds with wide porosity so that the tablet surface releases lactose and SSG particles when subjected to mechanical movement. The decrease in the friability of the SSG-2 and SSG-3 tablets proportional to the higher BF value indicates a strong interlocking bond from the deformation of granules and particles so resistant to mechanical movement. The friability of the SSG-4 to SSG-6 tablets tends to decrease because the strength of the interlocking bonding of SSG deformation is able to withstand mechanical movements. The SSG-6 tablet is more friable than the SSG-5 tablet because the number of SDL deformation is reduced so the foundation to withstand mechanical movements is reduced.

The CS-1 tablet is the most friable than the other CS tablets because the SDL deformation interlocking bond dominates with a wide porosity so the lactose and CS particles

on the surface are released when subject to mechanical movement. The friability of the CS-2 and CS-3 tablets increased proportionally to the BF values of the two tablet formulas decreased. The more SSG deformation interlocking bonds, the stronger the tablet withstands mechanical movements. The friability of the CS-4 to CS-6 tablets is proportional to the BF value and tends to decrease. The CS deformation on the tablet surface has a strong interlocking bond to withstand mechanical movements. The CS-6 tablet is more friable than the CS-5 tablet because of the reduced deformation of SDL as a foundation to resist mechanical movements.

The comparison of the effect of the presence of the disintegrating agent in each tablet formula to friability according to the concentration in the experiment is shown in Figure 8. The friability profile of the three CA-LBG tablets is similar but different at the peak of each disintegrating agent (CA-LBG 1%; CS 2%; SSG 4%). These peaks indicate that the tablet surface has bonds weakly of interlocking deformation and less stable to mechanical movements. The friability value before the peak concentration was also influenced by the release of particles from the SDL deformation, while after the peak concentration was influenced by the quality of the interlocking bond of deformation particles on the tablet surface so resistant to mechanical motion. CA-LBG tablets are more friable than other tablets due to the influence of the coral surface on the particles which tend to be friable when the porosity is not filled with other particles. The high friability profile of CA-LBG tablets appears at low concentrations because the surface porosity of the CA-LBG particles is not filled due to the limited number of CA-LBG particles. In addition, the irregularly shaped CA-LBG particles causing the porosity of tablets were number and wide.

Disintegration time

The evaluation of tablet disintegration rates for all formulas with various disintegrating agents and concentrations is shown in Table 2. The disintegration of tablets containing CA-

LBG showed a fast disintegration time proportional to the increasing concentration of CA-LBG. The value of BF and friability do not affect the function of the CA-LBG to disintegrate the tablet. The irregular particle shape and the corrugated surface of the CA-LBG particles resulted in a tablet with porosity for penetration of the disintegrating medium (Figure 4). The deformation porosity of CA-LBG formed on the tablet is proportional to the CA-LBG concentration in the tablet formula. The porosity of a large number on the tablet cause increases the channel for penetration of the disintegrating medium so that the tablet is disintegrating. The CA-LBG is an ester excipient that has low viscosity and low solubility in water (Table 1). This characteristic causes a repulsive force between deformations of CA-LBG on tablets when wet by disintegration medium. The repulsion force increases in proportion to the CA-LBG concentration in the tablet formula. The repulsive force between the CA-LBG deformations causes the tablets to disintegrate.

Tablets containing SSG showed that SSG concentration, BF value, and friability were influenced the disintegration time. The speed of tablet disintegration time is proportional to the increasing SSG concentration shown in the SSG-1 to SSG-4 tablets. Deformation of SSG in tablets attracts disintegration medium so SSG deformation swells and pushes deformation of other granules and particles to move away from each other so that the tablet is disintegrating. SSG-5 and SSG-6 tablets show the resistance of the tablets to pressure and mechanical movements affect the speed of disintegration. Increased BF value and low tablet friability caused long tablet disintegration time due to the strong interlocking bond between the deformation of granule or particle, thus inhibiting tablet disintegration.

Tablets containing CS showed an increase in CS concentration causing the disintegration time to rapidly. The resistance of tablets indicated by BF value and friability did not affect the function of CS as a tablet disintegrating agent. Tablets containing CS attracts the

disintegrating medium for penetration into the tablet so that the CS deformation swell and push deformation around. The more the CS deformation swell, the faster the tablet integrates.

The comparison of the ability of the disintegrating agent in each tablet formula according to the concentration in the experiment is shown in Figure 9. The time profile for the disintegration of CA-LBG tablets is similar to that of CS tablets because the two disintegrating agents perform their function not influenced by the quality of other tablets so that the increase in concentration is proportional to the increase in disintegration speed. tablet. In contrast to SSG tablets, the disintegration time is also influenced by the hardness and friability of the tablets, thus inhibiting the disintegration process in tablets with SSG concentrations of 8% and 12%. The disintegration time profile of CA-LBG tablets is longer than CS tablets because low solubility of CA-LBG so that the wetting time of CA-LBG tablets is longer and inhibits integration.

Dissolution

Experiments to study drug release from the dosage form were carried out using tablets of 1%, 2%, and 4% concentrations of each disintegrating agent. The effect of the disintegrating agent on the release of diclofenac sodium from the tablet is presented in Figure 10. The dissolution profile of the tablets containing CA-LBG showed that the release of diclofenac sodium from the tablets appeared to be different at 5 and 15 minutes. The higher the CA-LBG concentration on the cause tablet more rapidly disintegrates and releases more diclofenac sodium. All tablets with each concentration of CA-LBG meet the requirements for releasing diclofenac sodium [36].

A comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11). Tablets containing CA-LBG showed a slower release of diclofenac sodium than tablets containing SSG and CS

because of the gradual release at 5 and 15 minutes. The low solubility of CA-LBG inhibits the wetting of the tablets for disintegration thus inhibiting the solubility of diclofenac sodium in the dissolution medium.

Conclusion

Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. Increasing the concentration of HCl in the synthesis causes a decrease in the viscosity of CA-LBG due to an increase in CA molecules bound to LBG. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility. The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

References

1. Das N, Triparthi N, Basu S, Bose C, Maitra S, Khurana S. Progress in the development of gelling agents for improved culturability of microorganisms. Front Microbiol. 2015;6:1–7.

2. Dey P, Maiti S, Sa B. Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide. J Biomater Sci Polym Ed. 2013;24:663–83.

3. Dionísio M, Grenha A. Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci. 2012;4:175–85.

4. Sheskey, Paul J Cook, Walter G Cable, Colin G. Handbook of Pharmaceutical Excipients

8th. London-Washington DC: Pharmaceutical Press and American Pharmacists Association; 2017.

5. Chudzikowski RJ. Guar gum and its applications. J Soc Cosmet Chem. 1971;22:43–60.

6. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Esterification of citric acid with locust bean gum. Heliyon. Elsevier Ltd; 2019; 5: e02337. https://doi.org/10.1016/j.heliyon.2019.e02337

7. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Study of a catalyst of citric acid crosslinking on locust bean gum. J Chem Technol Metall. 2017;52:1086–91.

8. Samavati V, Razavi SH, Rezaei KA, Aminifar M. Intrinsic viscosity of locust bean gum and sweeteners mixture in dilute solutions. Electron J Environ Agric Food Chem. 2007;6:1879–89.

9. Tamaki Y, Teruya T, Tako M. The chemical structure of galactomannan isolated from seeds of Delonix regia. Biosci Biotechnol Biochem. 2010;74:1110–2.

10. Bhattacharya A, Rawlins JW, Ray P. Polymer Grafting and Crosslinking. Polym. Grafting Crosslink. Canada: A John Wiley & Sons, Inc, Publication; 2008.

11. Colas A. Cow Corning Silicones : Preparation Properties and Performance. Materials. Midland; 2005.

12. Santiago, E. V., Lopez, S. H. A, Romero AR. Photochemical cross-linking study of polymers containing diacetylene groups in their main chain and azobenzene compounds as pendant groups. Superf y vacío. 2006;19:1–7.

13. Tjandraatmadja GF, Burn LS, Jollands MJ. The effects of ultraviolet radiation on polycarbonate glazing. Proc 8th Int Conf Durab Build Constr Mater Vancouver, Canada. 1999;30:884–98.

14. Yeh CC, Chen CN, Li YT, Chang CW, Cheng MY, Chang HI. The effect of polymer molecular weight and UV radiation on physical properties and bioactivities of PCL films.

Cell Polym. 2011;30:261–76.

15. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res. Pharmaceutical Research; 2017;34:890–917.

16. Gulrez SKH, Al-Assaf S, Phillips GO. Hydrogels: Methods of Preparation, Characterisation and Applications. Prog Mol Environ Bioeng - From Anal Model to Technol Appl. 2011.

17. Michael E. Aulton, Kevin M. G. Taylor. Aulton's Pharmaceutics The Design and Manufacture of Medicines. BMC Public Health. New York: Churchill Livingstone Elsevier; 2017.

18. The United States Pharmacopeial Convention. Pharmacopeia 41-National Formulary 36. 41st ed. Rockville: Twinbrook Parkway; 2018.

19. Shang C, Sinka IC, Jayaraman B, Pan J. Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. Int J Pharm. Elsevier B.V.; 2013;442:57–64. http://dx.doi.org/10.1016/j.ijpharm.2012.09.005

20. Pitt KG, Newton JM, Richardson R, Stanley P. The Material Tensile Strength of Convex-faced Aspirin Tablets. J Pharm Pharmacol. 1989;41:289–92.

21. Uday Kumar M, Babu K. Design and evaluation of fast dissolving tablets containing diclofenac sodium using fenugreek gum as a natural superdisintegrant. Asian Pac J Trop Biomed. Hainan Medical University; 2014;4:S329–34. http://dx.doi.org/10.12980/APJTB.4.2014B672

22. Hammami MM, Hussein RF, Alswayeh R, Alvi SN. Eight enteric-coated 50 mg diclofenac sodium tablet formulations marketed in Saudi Arabia: In vitro quality evaluation. BMC Res Notes. BioMed Central; 2020;13:1–6. https://doi.org/10.1186/s13104-020-05270-4

23. Bertocchi P, Antoniella E, Valvo L, Alimonti S, Memoli A. Diclofenac sodium multisource prolonged release tablets - A comparative study on the dissolution profiles. J Pharm

Biomed Anal. 2005;37:679–85.

24. Zupančič Bozič D, Vrečer F, Kozjek F. Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur J Pharm Sci. 1997;5:163–9.

25. Ghasemi J, Niazi A, Ghobadi S. Simultaneous spectrophotometric determination of benzyl alcohol and diclofenac in pharmaceutical formulations by chemometrics method. J Chinese Chem Soc. 2005;52:1049–54.

26. Gouda AA, Kotb El-Sayed MI, Amin AS, El Sheikh R. Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: A review. Arab J Chem. 2013;6:145–63. http://dx.doi.org/10.1016/j.arabjc.2010.12.006

27. Coates J. Interpretation of Infrared Spectra, A Practical Approach. Encycl Anal Chem. 2006;10815–37.

28. Doll KM, Shogren RL, Willett JL, Swift G. Solvent-free polymerization of citric acid and D-sorbitol. J Polym Sci Part A Polym Chem. 2006;44:4259–67.

29. Jans AWH, Kinne RKH. 13C NMR spectroscopy as a tool to investigate renal metabolism. Kidney Int. 1991;39:430–7.

30. Zhang Y ling, Zhao C xia, Liu X dong, Li W, Wang J long, Hu Z guang. Application of poly(aspartic acid-citric acid) copolymer compound inhibitor as an effective and environmental agent against calcium phosphate in cooling water systems. J Appl Res Technol. 2016;14:425–33.

31. Azero EG, Andrade CT. Characterisation of Prosopis juliflora seed gum and the effect of its addition to κ-carrageenan systems. J Braz Chem Soc. 2006;17:844–50.

32. Bhatia H, Gupta PK, Soni PL, Division C. Extraction , Purification and Characterization of a Galactomannan From Prosopis Juliflora (Sw .) Dc . Seed. Int J Sci Enviroment Technol.

2013;2:708–24.

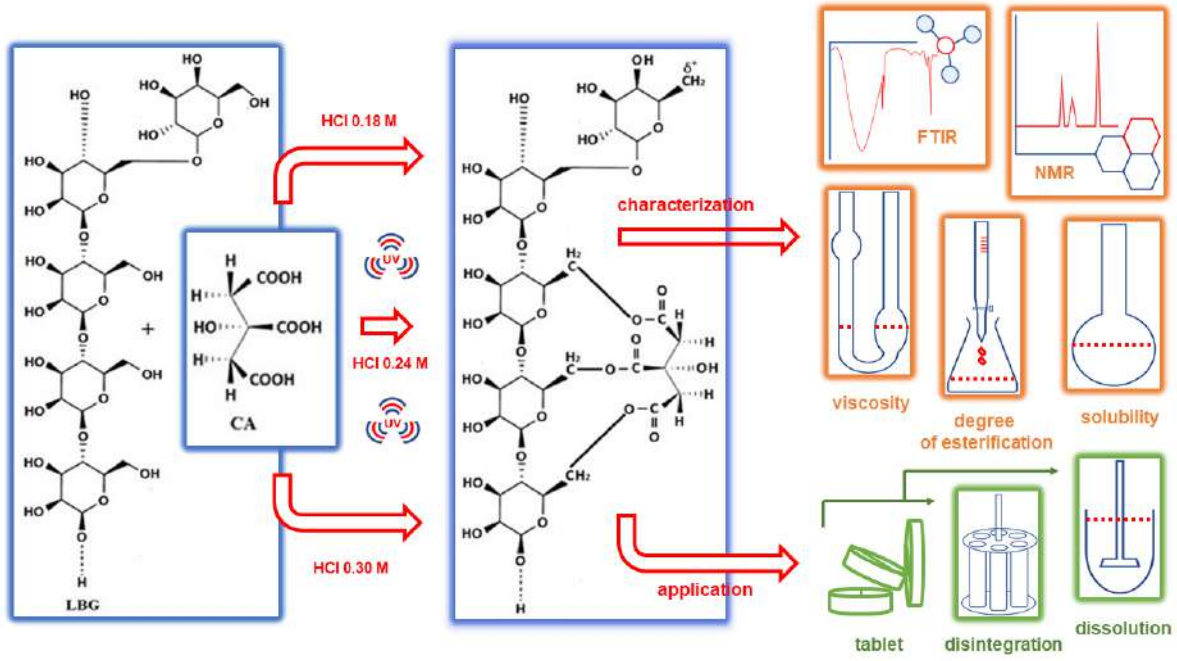
33. Gillet S, Aguedo M, Blecker C, Jacquet N, Richel A. Use of 13C-NMR in structural elucidation of polysaccharides: case of locust bean gum. Young Belgium Magn. Reson. Sci. Liege: University of Liege; 2014.

34. Parvathy KS, Susheelamma NS, Tharanathan RN, Gaonkar AK. A simple non-aqueous method for carboxymethylation of galactomannans. Carbohydr Polym. 2005;62:137–41.

35. Szumilo M, Belniak P, Swiader K, Holody E, Poleszak E. Assessment of physical properties of granules with paracetamol and caffeine. Saudi Pharm J. King Saud University; 2017;25:900–5. http://dx.doi.org/10.1016/j.jsps.2017.02.009

36. Directorate General of Medicine and Food. Indonesian Pharmacopoeia 4th edition. Jakarta: Ministry of Health Republic of Indonesia; 1995.

Graphical Abstract



Figure

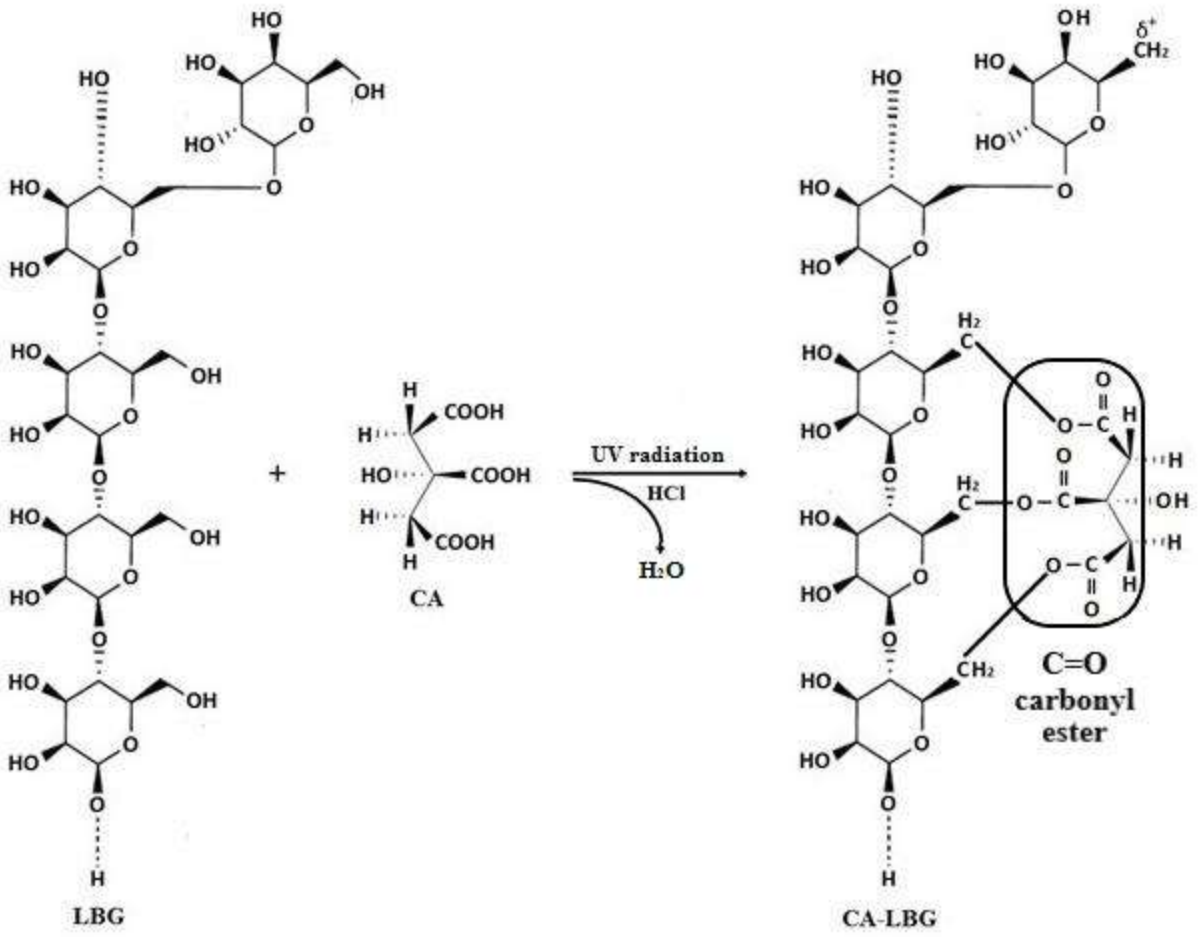


Figure 1. CA-LBG production mechanism. Synthesis of CA-LBG was carried out by adding 0.42 M CA to 7.10 x 10-6 M LBG which had swollen. The mixture was added with HCl (0.18-0.42 M) and UV irradiated (100 minutes).

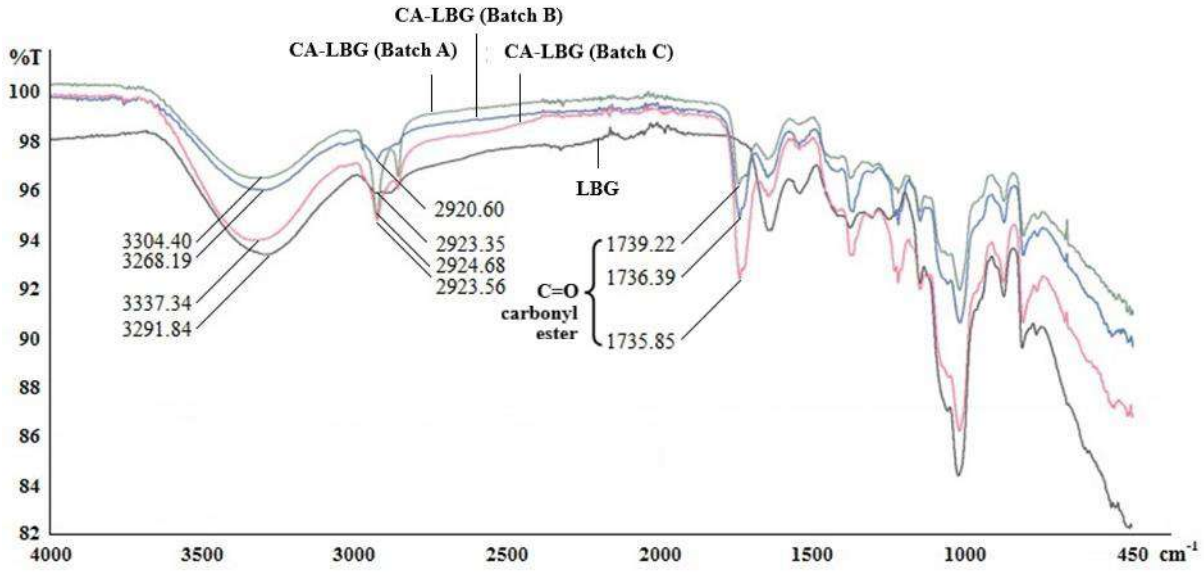


Figure 2. FTIR spectrum of LBG and CA-LBG. LBG as a comparison is shown in black spectra. CA-LBG was synthesized using a 0.18 M HCl catalyst (Batch A) shown in green spectra. CA-LBG was synthesized using a 0.24 M HCl catalyst (Batch B) shown in blue spectra. CA-LBG was synthesized using 0.30 M HCl catalyst (Batch C) shown in red spectra. The carbonyl ester group (C=O) is a specific group that presents at CA-LBG and absent at LBG.

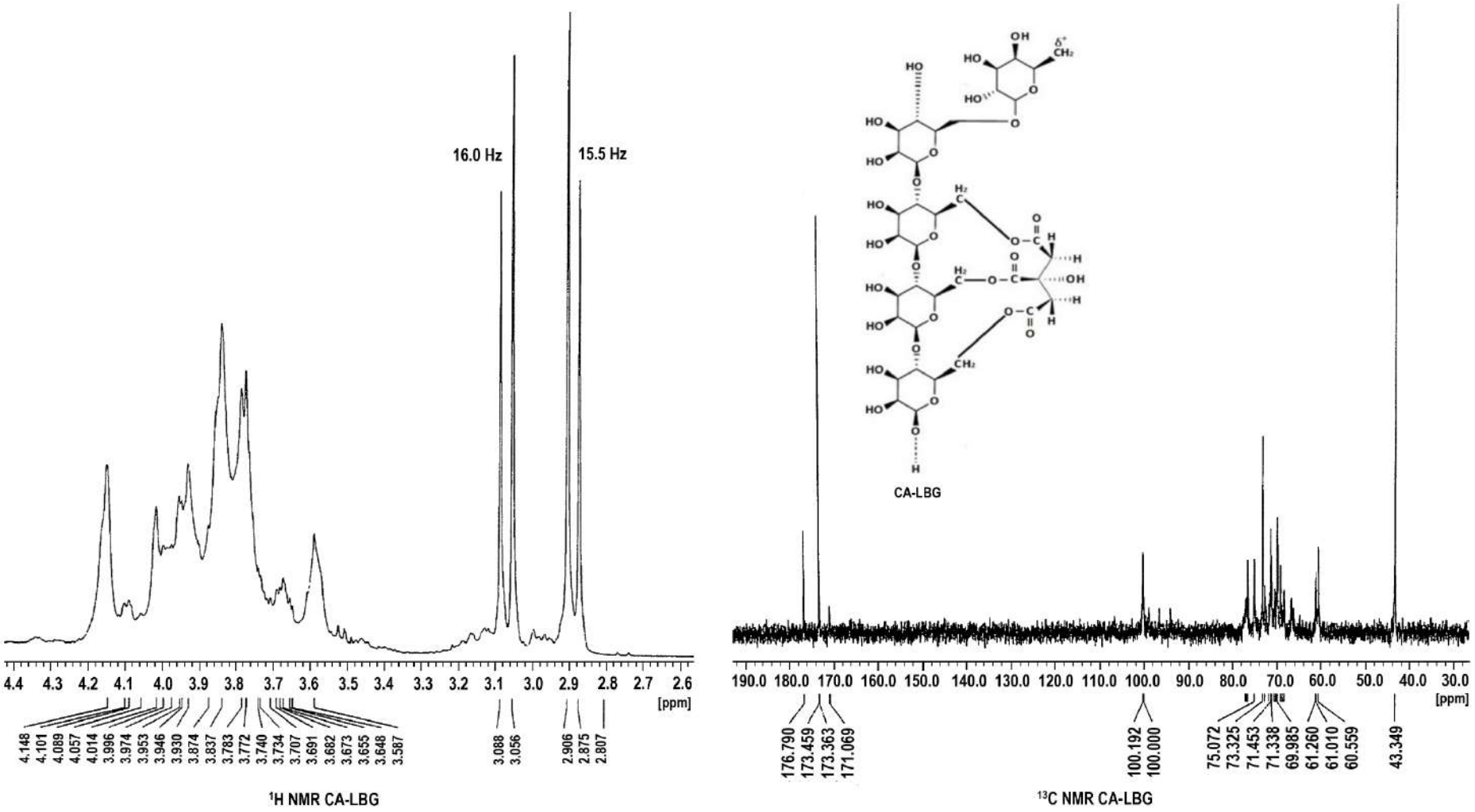
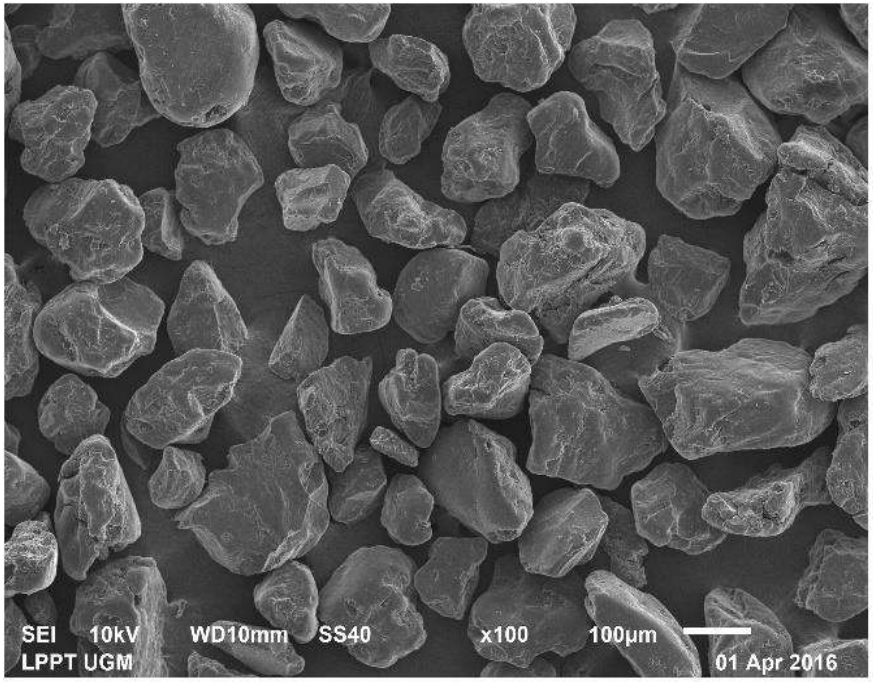
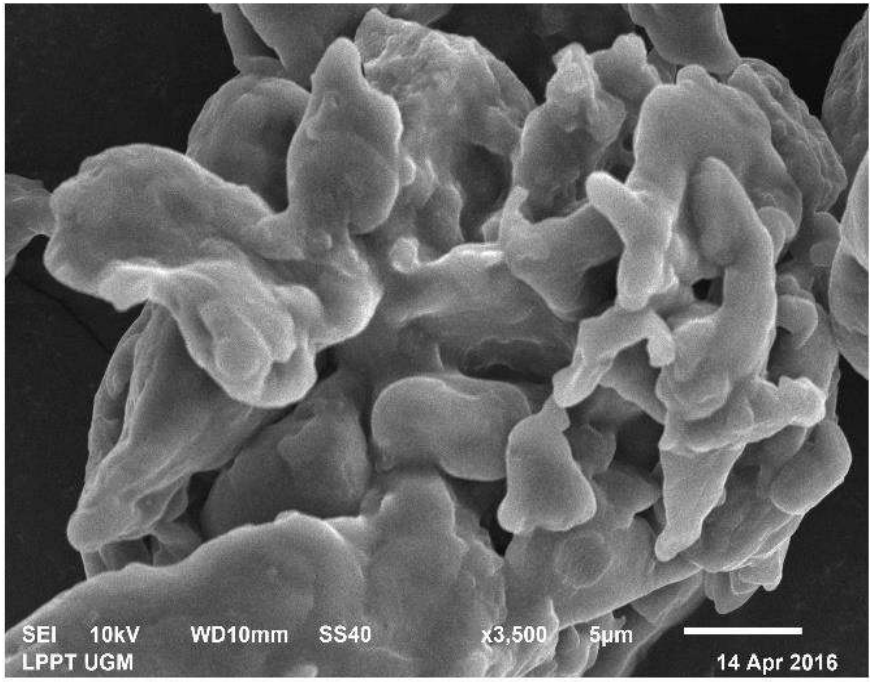


Figure 3. ^{1}H NMR and ^{13}C NMR spectrum of CA-LBG representative (Batch B). CA-LBG was synthesized using catalyst 0.24 M HCl. The presence of CA at CA-LBG was shown in the peaks of a, b, c, d, and e.



CA-LBG [magnification 100x]



CA-LBG [magnification 3500x]

Figure 4. SEM images of CA-LBG representative, synthesized using catalyst 0.24 M HCl (Batch B)

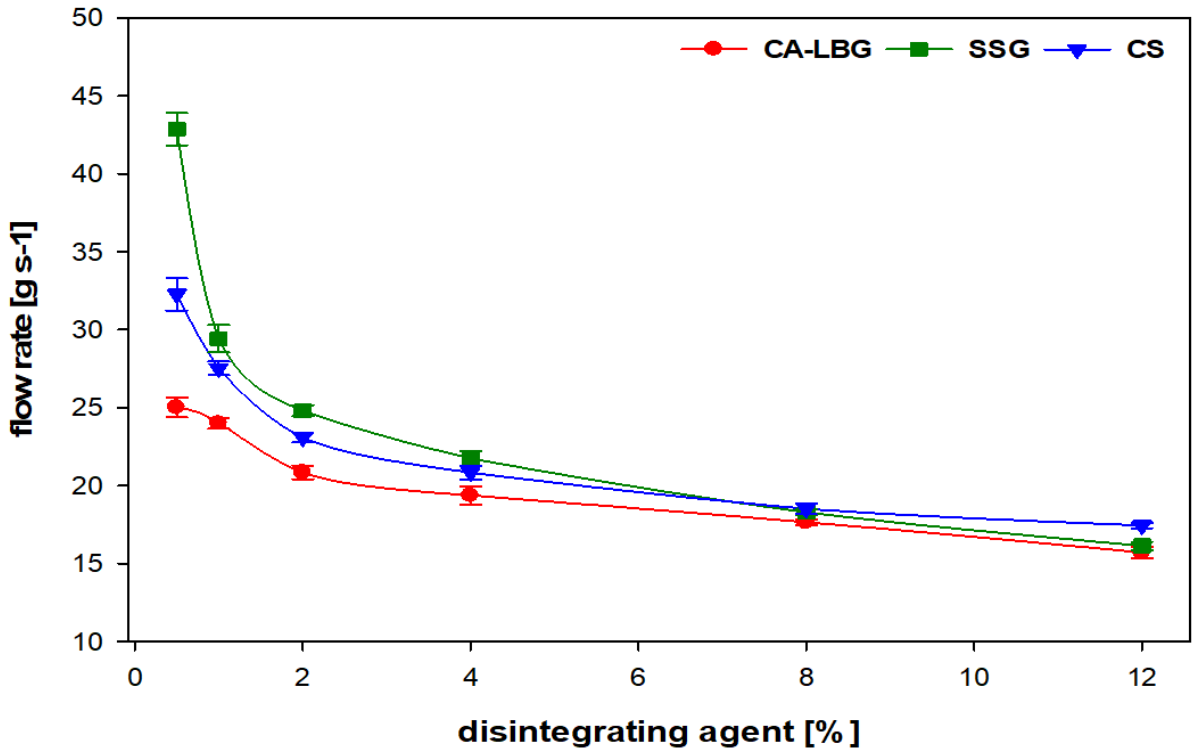


Figure 5. The flow rate profile of the mass of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

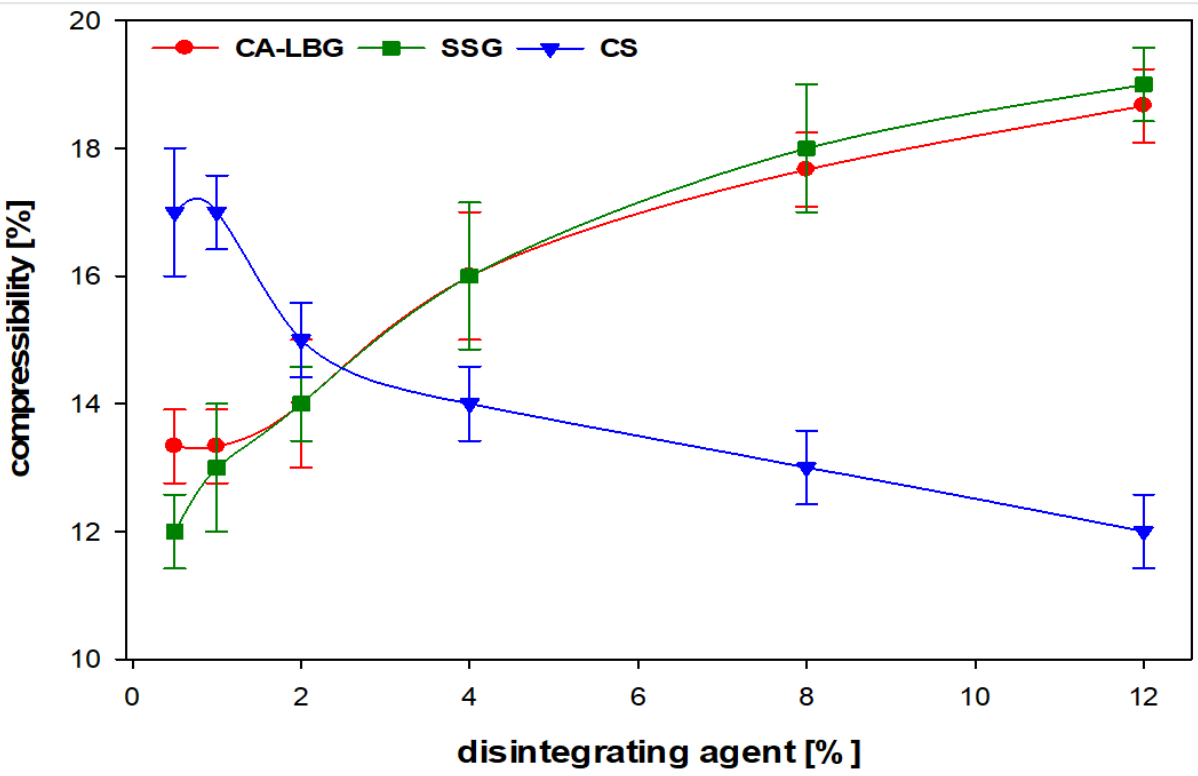


Figure 6. The compressibility profile of the tablet mass contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

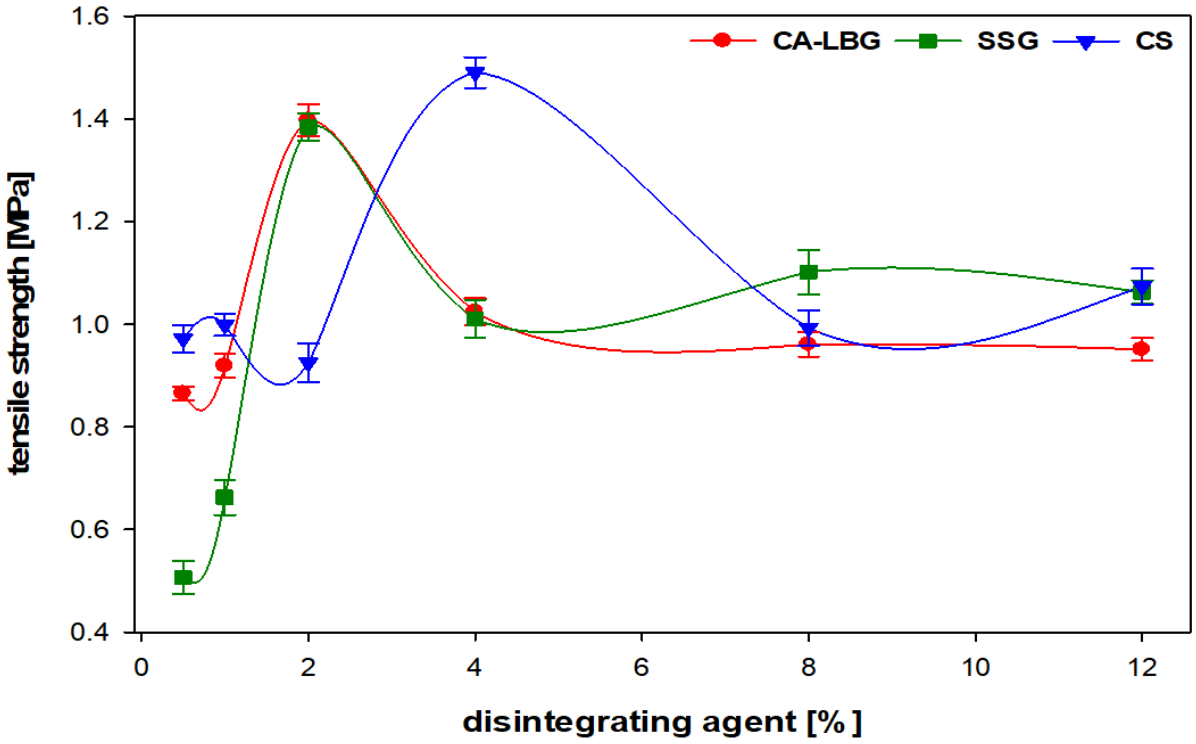


Figure 7. The tensile strength profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

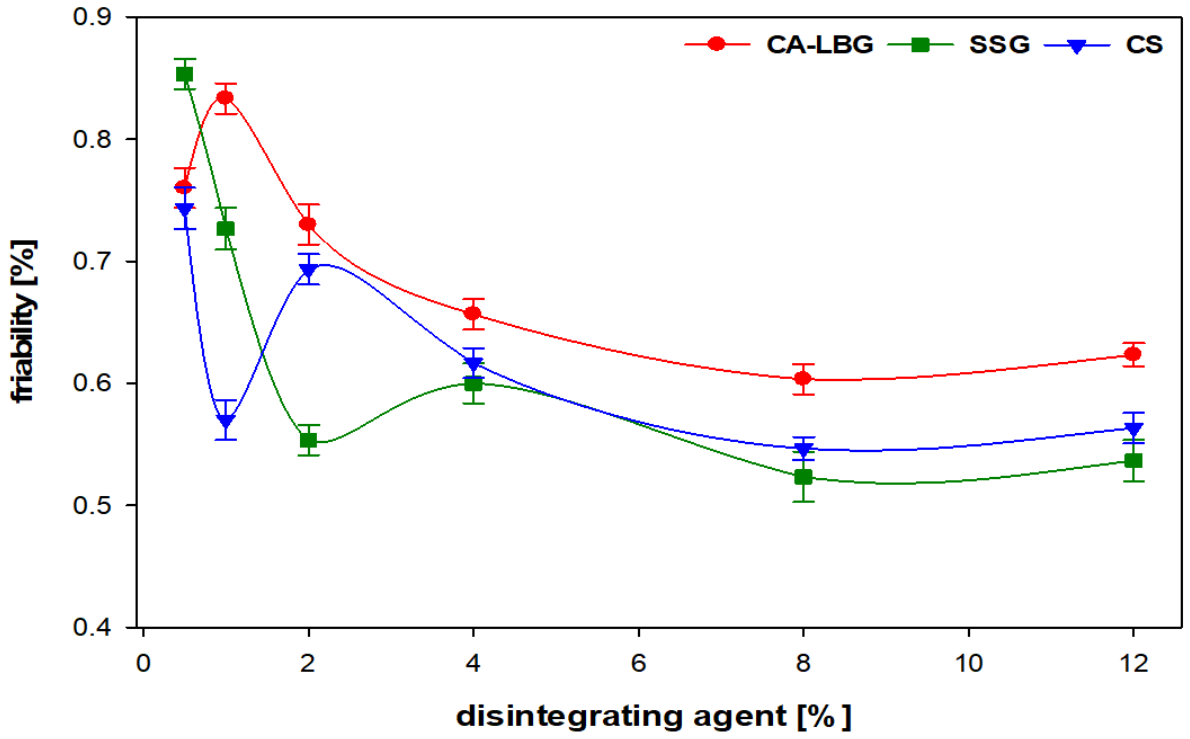


Figure 8. The friability profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

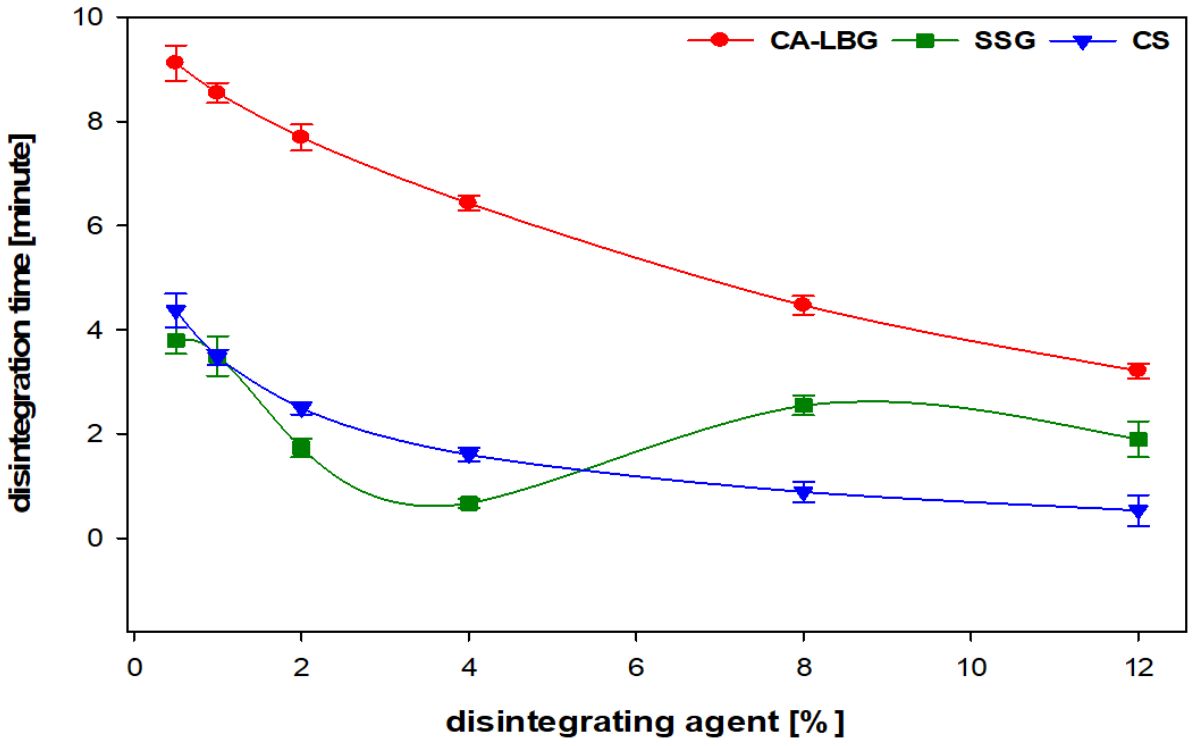


Figure 9. The disintegration time profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

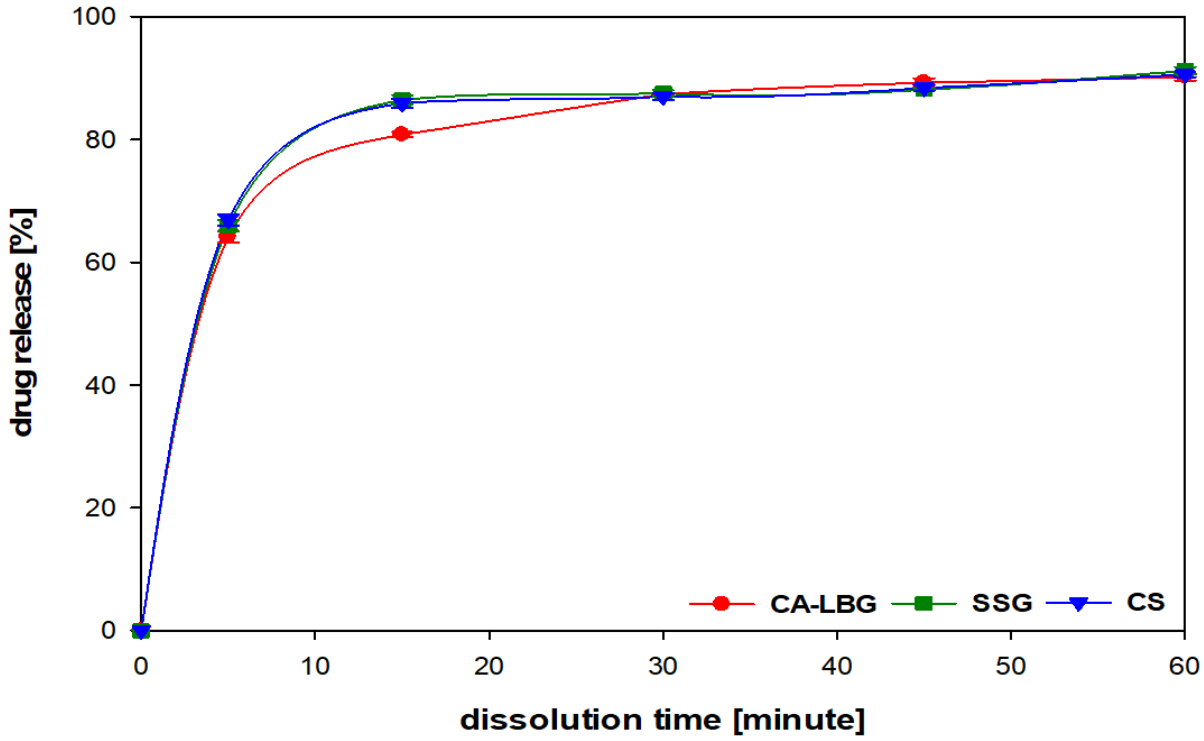
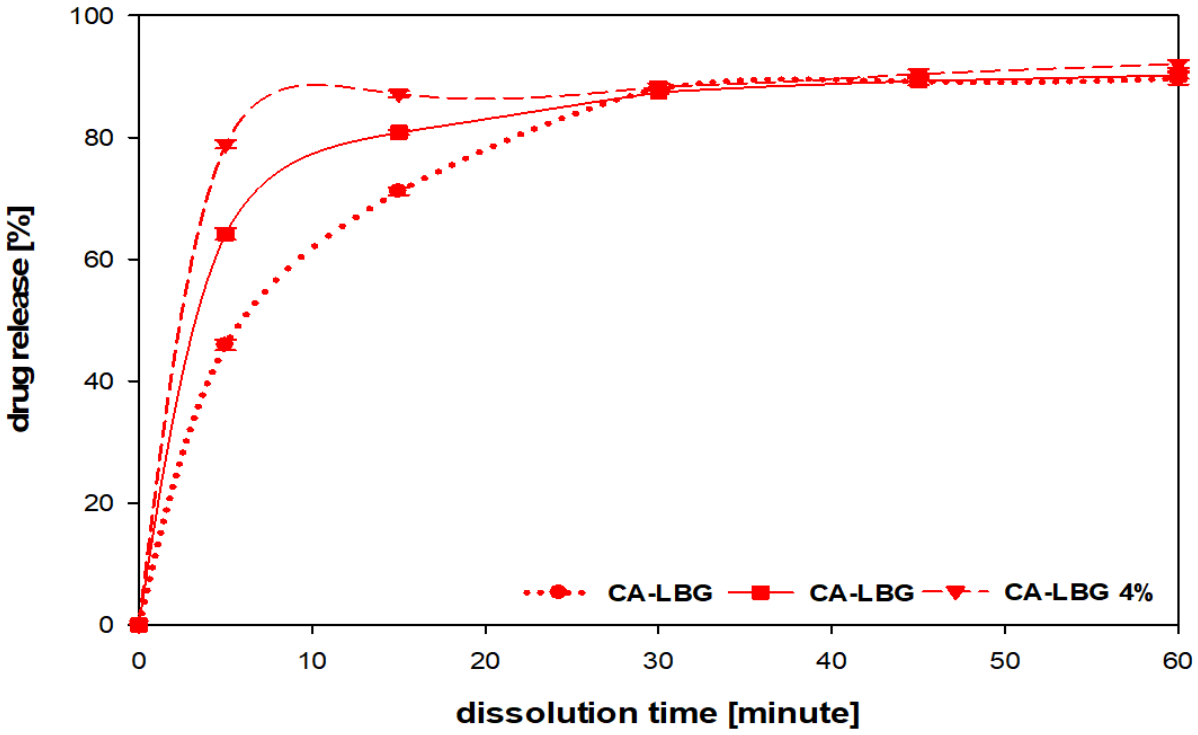


Figure 10. The dissolution profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 2%.



106

107 **Figure 11.** The dissolution profile of the tablet contains CA-LBG 1%; 2% and 4%.

Table

Table 1. Detail synthesis of CA-LBG using the concentration of HCl and irradiated with UV (254 nm,100 minutes). Value physical parameters of CA-LBG: yield, the degree of esterification, carbonyl ester wavelength, solubility, and viscosity.

Batch Code	LBG 10^{-6} [mol]	CA [mol]	HCl [mol]	Carbonyl Ester [cm^{-1}]	Yield [%]	Degree of Esterification [%]	Solubility [%]	Viscosity [cP]
A	7.10	0.42	0.18	1739.22	26.62 ± 0.05	8.27 ± 0.19	36.63 ± 1.14	11.20 ± 0.10
B	7.10	0.42	0.24	1736.39	27.13 ± 0.09	9.13 ± 0.13	29.30 ± 1.16	9.48 ± 0.06
C	7.10	0.42	0.30	1735.85	27.66 ± 0.06	9.69 ± 0.23	22.64 ± 1.15	7.76 ± 0.07

Table 2. Details of tablet formulations using disintegrating agents. Evaluate the physical quality of the tablet mass and the tablet.

formula code	disintegrating agent			flow time	ρ_{tapped}-ρ_{bulk}	actual weight	thickness	break force	friability	disintegration time
	CA-LBG	SSG	CS							
	[%]	[%]	[%]	[sec.]	[g.mL^{-1}]	[mg]	[mm]	[kp]	[%]	[min.]
CL-1	0.5	-	-	4.0 ± 0.10	0.041 ± 0.00	201.0 ± 0.25	4.39 ± 0.01	4.0 ± 0.06	0.76 ± 0.02	9.12 ± 0.34
CL-2	1	-	-	4.2 ± 0.06	0.041 ± 0.00	201.2 ± 0.47	4.38 ± 0.01	4.2 ± 0.10	0.83 ± 0.01	8.54 ± 0.19
CL-3	2	-	-	4.8 ± 0.10	0.044 ± 0.01	201.2 ± 0.12	4.40 ± 0.01	6.4 ± 0.15	0.73 ± 0.02	7.69 ± 0.25
CL-4	4	-	-	5.2 ± 0.15	0.053 ± 0.01	201.1 ± 0.21	4.41 ± 0.01	4.7 ± 0.12	0.66 ± 0.01	6.43 ± 0.14
CL-5	8	-	-	5.7 ± 0.06	0.059 ± 0.01	200.9 ± 0.26	4.38 ± 0.01	4.4 ± 0.10	0.60 ± 0.01	4.47 ± 0.18
CL-6	12	-	-	6.4 ± 0.15	0.061 ± 0.00	201.1 ± 0.36	4.39 ± 0.01	4.4 ± 0.12	0.62 ± 0.01	3.21 ± 0.14
SSG-1	-	0.5	-	2.3 ± 0.06	0.036 ± 0.00	200.8 ± 0.06	4.40 ± 0.01	2.3 ± 0.15	0.85 ± 0.01	3.79 ± 0.25
SSG-2	-	1	-	3.4 ± 0.10	0.042 ± 0.00	201.1 ± 0.44	4.38 ± 0.01	3.0 ± 0.15	0.73 ± 0.02	3.49 ± 0.38
SSG-3	-	2	-	4.0 ± 0.06	0.047 ± 0.01	201.0 ± 0.51	4.35 ± 0.01	6.3 ± 0.12	0.55 ± 0.01	1.73 ± 0.18
SSG-4	-	4	-	4.6 ± 0.10	0.051 ± 0.00	200.7 ± 0.21	4.37 ± 0.01	4.6 ± 0.17	0.60 ± 0.02	0.67 ± 0.09
SSG-5	-	8	-	5.5 ± 0.06	0.057 ± 0.00	201.1 ± 0.32	4.38 ± 0.01	5.0 ± 0.21	0.52 ± 0.02	2.55 ± 0.19
SSG-6	-	12	-	6.2 ± 0.10	0.063 ± 0.00	200.7 ± 0.15	4.38 ± 0.01	4.9 ± 0.12	0.54 ± 0.02	1.90 ± 0.35
CS-1	-	-	0.5	3.1 ± 0.10	0.056 ± 0.00	200.8 ± 0.60	4.43 ± 0.01	4.5 ± 0.12	0.74 ± 0.02	4.37 ± 0.33
CS-2	-	-	1	3.6 ± 0.06	0.052 ± 0.00	200.8 ± 0.35	4.46 ± 0.01	4.7 ± 0.10	0.57 ± 0.02	3.47 ± 0.15
CS-3	-	-	2	4.3 ± 0.06	0.050 ± 0.00	201.0 ± 0.31	4.42 ± 0.01	4.3 ± 0.17	0.69 ± 0.01	2.49 ± 0.12
CS-4	-	-	4	4.8 ± 0.10	0.045 ± 0.00	201.1 ± 0.60	4.40 ± 0.01	6.9 ± 0.12	0.62 ± 0.01	1.60 ± 0.13
CS-5	-	-	8	5.4 ± 0.10	0.038 ± 0.00	201.2 ± 0.35	4.34 ± 0.01	4.5 ± 0.15	0.55 ± 0.01	0.89 ± 0.20
CS-6	-	-	12	5.7 ± 0.06	0.038 ± 0.01	200.9 ± 0.15	4.45 ± 0.01	5.0 ± 0.15	0.56 ± 0.01	0.53 ± 0.30

Decision on your manuscript #JOPI-D-21-00339R1

Dari: Journal of Pharmaceutical Innovation (em@editorialmanager.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Sabtu, 11 September 2021 pukul 02.01 GMT+7

Dear Dr Hadinugroho:

We have received the reports from our advisors on your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms", which you submitted to Journal of Pharmaceutical Innovation.

Based on the advice received, your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions.
When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments.
Your list of responses should be uploaded as a file in addition to your revised manuscript.

In order to submit your revised manuscript electronically, please access the following web site:

https://www.editorialmanager.com/jopi/

Your username is: wuryanto.hadinugroho@ymail.com
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.

Please click "Author Login" to submit your revision.

We look forward to receiving your revised manuscript.

Sincerely yours,

Stephen Scypinski

Journal of Pharmaceutical Innovation

COMMENTS FOR THE AUTHOR:

Please note that this journal is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-

processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted.

Authors may need to take specific actions to achieve compliance with funder and institutional open access mandates. If your research is supported by a funder that requires immediate open access (e.g. according to Plan S principles) then you should select the gold OA route, and we will direct you to the compliant route where possible. For authors selecting the subscription publication route our standard licensing terms will need to be accepted, including our self-archiving policies. Those standard licensing terms will supersede any other terms that the author or any third party may assert apply to any version of the manuscript.

 Find out more about compliance

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Re: Decision on your manuscript #JOPI-D-21-00339R1

Dari: Wuryanto Hadinugroho (wuryanto.hadinugroho@ymail.com)

Kepada: jedjoseph.adel@springernature.com

Tanggal: Sabtu, 11 September 2021 pukul 10.56 GMT+7

Dear
Prof. Stephen Scypinski
Editor-in-Chief
Journal of Pharmaceutical Innovation

Thank you for your email. Regarding the manuscript revision process that my team will do, I ask for information. Where can I find new comments from reviewers? In the comments column in the email, I did not find any comments. I also didn't find any new documents attached to the View Attachments column https://www.editorialmanager.com/jopi/l.asp?i=48098&l=2FGZ8OZG

On August 30th, 2021, I have received the manuscript decision by email from Prof. Robert A Lodder by attaching reviewer comments and documents in the View Attachments column. I have submitted a revised manuscript on September 5th, 2021, as directed by the editorial manager.

I ask for information if the revised manuscript that I have sent has shortcomings and does not comply with the procedure. My team will gladly revise if there are still corrections and suggestions from reviewers or editors.

Thank you for your attention and cooperation.

Yours sincerely,
Wuryanto Hadinugroho

> Pada Sabtu, 11 September 2021 02.01.28 WIB, Journal of Pharmaceutical Innovation <em@editorialmanager.com> menulis:
>
> Dear Dr Hadinugroho:
>
> We have received the reports from our advisors on your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms", which you submitted to Journal of Pharmaceutical Innovation.
>
> Based on the advice received, your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions.
> When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments.
> Your list of responses should be uploaded as a file in addition to your revised manuscript.
>
> In order to submit your revised manuscript electronically, please access the following web site:
>
> https://www.editorialmanager.com/jopi/
>
> Your username is: wuryanto.hadinugroho@ymail.com
> If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.
>
> Please click "Author Login" to submit your revision.

We look forward to receiving your revised manuscript.

Sincerely yours,

Stephen Scypinski

Journal of Pharmaceutical Innovation

COMMENTS FOR THE AUTHOR:

Please note that this journal is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted.

Authors may need to take specific actions to achieve compliance with funder and institutional open access mandates. If your research is supported by a funder that requires immediate open access (e.g. according to Plan S principles) then you should select the gold OA route, and we will direct you to the compliant route where possible. For authors selecting the subscription publication route our standard licensing terms will need to be accepted, including our self-archiving policies. Those standard licensing terms will supersede any other terms that the author or any third party may assert apply to any version of the manuscript.

 Find out more about compliance

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Journal of Pharmaceutical Innovation

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

--Manuscript Draft--

Manuscript Number:	JOPI-D-21-00339R2
Full Title:	Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms
Article Type:	Original Article
Keywords:	CA-LBG; citric acid; locust bean gum; disintegrating agent; direct compression
Order of Authors:	Wuryanto Hadinugroho, Dr
	Suwaldi Martodihardjo, Prof
	Achmad Fudholi
	Sugeng Riyanto, Prof
Corresponding Author:	Wuryanto Hadinugroho, Dr Widya Mandala Catholic University: Universitas Katolik Widya Mandala Surabaya Surabaya, Jawa Timur INDONESIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Widya Mandala Catholic University: Universitas Katolik Widya Mandala Surabaya
Corresponding Author's Secondary Institution:	
First Author:	Wuryanto Hadinugroho, Dr
First Author Secondary Information:	
Order of Authors Secondary Information:	
Funding Information:	kementerian pendidikan dan kebudayaan (0299 / E3 / 2016) — Dr Wuryanto Hadinugroho
Abstract:	Purpose: Analyze the effect of HC l concentration 0.24 mol as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets. Methods: Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), esterification efficiency, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg. Results: Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility. Conclusion: The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Response to reviewer comments

Comment of reviewer 2

I have already included the necessary changes that needs to be done in the document file. Please follow and compleate the requiriments and correct the paper accordingly. Thank you for your efforts!

Comments of attached document:

1. **The reviewer suggested "put :" in each abstract chapter and removed the word excess of "degree of esterification"**

   Response:

   Thank you for the suggestions. We have added a ":" sign in each abstract chapter. We have also removed the excess of the word "degree of esterification" and replaced it with the word "esterification efficiency". Substitution of the term to meet the reviewer's suggestion on page 5, line 115.

   Original manuscript (page 1)

   Purpose Analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

   Methods Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), degree of esterification, degree of esterification, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.

   Results Synthesis conditions using 0.24 M HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.

   Conclusion The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

   Revised manuscript (page 1)

   Purpose: Analyze the effect of HC l concentration 0.24 mol as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

   Methods: Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR),

nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), esterification efficiency, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.
Results: Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.
Conclusion: The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

2. **Comment: "This sentence is a repeat of the previous one, please delete here" (page 2, line 32).**
   Response:
   Thank you for the suggestions. We have removed the sentence.

   Original manuscript (page 2, line 32).
   Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations (Dionísio and Grenha 2012; Dey et al. 2013; Das et al. 2015; Sheskey, J. P., Cook, G. W., and Cable 2017). Locust bean gum is a natural polymer that has the potential to be modified to produce new materials as excipients in tablet formulations.

   Revised manuscript (page 2, line 31)
   Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations [1–4].

3. **Comment: "Do consider removing this paragraph, as the ester synthesis mechanism is a well known chemical reaction" (page 2, line 39).**
   Response:
   Thank you for the suggestions. We have removed the sentence.

   Original manuscript (page 2, line 39)
   Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). The O atoms (C-6) of mannose and

galactose at LBG bind to the positive C atom of the carbonyl groups at CA. Positive C atoms are created from the protonation of carbonyl groups under acidic conditions (Chudzikowski 1971; Samavati et al. 2007; Tamaki et al. 2010; Dey et al. 2013; Hadinugroho et al. 2017, 2019).

Revised manuscript (page 2, line 35)
Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). [2,5–9].

4. **Comment: correct as 'synthesis' (page 2, line 44).**
   Response:
   Thank you for the suggestions. We have corrected the word.

   Original manuscript (page 2, line 44)
   Variation of HCl concentration in the synthetic effect on the character of CA-LBG.

   Revised manuscript (page 2, line 37)
   Variation of HCl concentration in the synthesis effect on the character of CA-LBG.

5. **Comment (page 4, line 88):**
   Please correct the paragraph accordingly;
   'The swollen LBG was placed in a glass bowl (7,10X10(-6) mol/50 ml concentration at a temperature rate of 55-60 C) and CA (0.42 mol) was added with different concentrations of HCl (0.18, 0.24 and 0.30 mol). The mixture was stirred for 10 mins and irradiated with UV light for 100 mins (254 nm, 8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet solid was precipitated with acetone and washed with acetone-distilled water (1:1, v/v). The solid CA-LBG was dried at ambient temperature (Hadinugroho et al. 2017).
   Response:
   Thank you for the suggestions. We have corrected the paragraph accordingly following the suggestions.

   Original manuscript (page 4, line 88)
   The swollen LBG in a glass bowl (7.10 10^{-6} Molar LBG / 50 mL distilled water 55-60 °C) added CA (0.42 Molar) and HCl (0.18; 0.24; 0.30 Molar) (Table 1). The mixture was stirred for 10 minutes. The mixture was irradiated with UV 254 nm (100 minutes) (8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet CA-LBG was precipitated with acetone and washed with acetone-distilled water (1:1). The solid CA-LBG is dried at ambient temperature (Hadinugroho et al. 2017).

   Revised manuscript (page 4, line 79)
   The swollen LBG was placed in a glass bowl (7.10 x10^{-6} mol/50 mL concentration at a temperature rate of 55-60 °C) and CA (0.42 mol) was added with different concentrations of HCl (0.18; 0.24; and 0.30 mol). The mixture was stirred for 10 minutes and irradiated with UV light for 100 minutes (254 nm, 8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The

wet solid was precipitated with acetone and washed with acetone-distilled water (1:1, v/v). The solid CA-LBG was dried at ambient temperature [7].

6. **Comment (page 4, line 94):**
   Please correct the paragraph accordingly;
   'The characterization of CA-LBG was performed by using FTIR (fourier transform infrared) and NMR (nyuclear magnetic resonance) spectroscopic techniques. SEM (scanning electron microscope), degree of esterification, solubility and viscosity tests were also carried out in order to elucidate the structure.
   Response:
   Thank you for the suggestions. We have corrected the paragraph accordingly following the suggestions.

   Original manuscript (page 4, line 94)
   Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG performed was fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR), scanning electron microscope (SEM), degree of esterification, solubility, and viscosity.

   Revised manuscript (page 4, line 85)
   Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG was performed by using FTIR (fourier transform infrared) and NMR (nuclear magnetic resonance) spectroscopic techniques. SEM (scanning electron microscope), esterification efficiency, solubility, and viscosity tests were also carried out in order to elucidate the structure.

7. **Comment: correct as 'was' (page 5, line 108).**
   Response:
   Thank you for the suggestions. We have corrected the word.

   Original manuscript (page 5, line 108)
   The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra were recorded.

   Revised manuscript (page 4, line 99)
   The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra was recorded.

8. **Comment (page 5, line 115):**
   “just a small suggestion, you can also give the synthetic yield of the compound, this is also scientific and more easy in terms of experiemental procedure. But these calculations are also fine”

Response:
Thank you for the suggestions. We have added a description of the percentage of synthesis results in the paragraph on page 5, line 116. In addition, we have also added values of the percentage of yield in Table 1.

Original manuscript (page 5, line 115)
Degree of esterification
The determination of the degree of esterification follows the experimental equation that has been done previously (Hadinugroho et al. 2019). Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar).

Revised manuscript (page 5, line 105)
Esterification efficiency
The efficiency of the synthesis was evaluated through the yield percentage of CA-LBG to the total raw material. The evaluation of esterified CA was determined by the degree of esterification. The determination of the degree of esterification follows the experimental equation that has been done previously [6]. Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar).

Table 1. Detail synthesis of CA-LBG using the concentration of HCl and irradiated with UV (254 nm,100 minutes). Value physical parameters of CA-LBG: yield, the degree of esterification, carbonyl ester wavelength, solubility, and viscosity.

Batch Code	LBG 10^{-6} [mol]	CA [mol]	HCl [mol]	Carbonyl Ester [cm^{-1}]	Yield [%]	Degree of Esterification [%]	Solubility [%]	Viscosity [cP]
A	7.10	0.42	0.18	1739.22	26.62 ± 0.05	8.27 ± 0.19	36.63 ± 1.14	11.20 ± 0.10
B	7.10	0.42	0.24	1736.39	27.13 ± 0.09	9.13 ± 0.13	29.30 ± 1.16	9.48 ± 0.06
C	7.10	0.42	0.30	1735.85	27.66 ± 0.06	9.69 ± 0.23	22.64 ± 1.15	7.76 ± 0.07

9. Comment: correct as 'stretching' (page 10, line 238).

Response:

Thank you for the suggestions. We have corrected the word.

Original manuscript (page 10, line 238)

The stretch peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

Revised manuscript (page 09, line 221)

The stretching peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

10. Comment (page 11, line 250):

"have you used any solvent? If so, please specify"

Response:

Thank you for the suggestions. We have added a description of the solvent used for the preparation of the NMR assay.

Original manuscript (page 11, line 250)

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies (Hadinugroho et al. 2017, 2019).

Revised manuscript (page 10, line 230)

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies [6,7]. NMR examination using CA-LBG dissolved in deuterium (D_2O) (H2O).

11. Comment (page 11, line 256):

"please add the integration and splitting of the peaks. Are you certain all are twin? if so, their names must be dublet. The peak shapes are named as singlet, dublet, tripleti quartet and multiplet. Please give the related details."

Response:

Thank you for the suggestions. We have added a description of peak integration and splitting.

Original manuscript (page 11, line 256)

The results of the CA-LBG NMR analysis are shown in Figure 3. In the ^1H NMR spectrum of CA, a pair of twin peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 (e) in CA. Sharp peaks of 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that a pair of CA twin peaks appear around δ = 2.7-3.0 ppm. Sharp peaks from mannose and galactose appear around 4.5-3.0 ppm (Hadinugroho et al. 2017, 2019).

Revised manuscript (page 10, line 246)
The results of the CA-LBG NMR analysis are shown in Figure 3. The ^{1}H NMR spectrum of CA showed two doublet peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 in CA. The two doublet peaks are protons from symmetric C on CA reacting on LBG. The position of one adjacent proton due to bond rotation and causes the signal to split so that the peak appears splitting. Multiplet peaks at δ = 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that two doublet peaks of CA around δ = 2.7-3.0 ppm. Multiplet peaks from mannose and galactose appear around 4.5-3.0 ppm [6,7].

12. **Comment (page 11, line 262):**
"We have corrected the paragraph by sharing only the number of peaks, ranging from high to low energy fields. We also do not ascertain every carbon peak."
Response:
Thank you for the suggestions. We have corrected the paragraph by sharing only the number of peaks, ranging from high to low energy fields. We also do not ascertain every carbon peak.

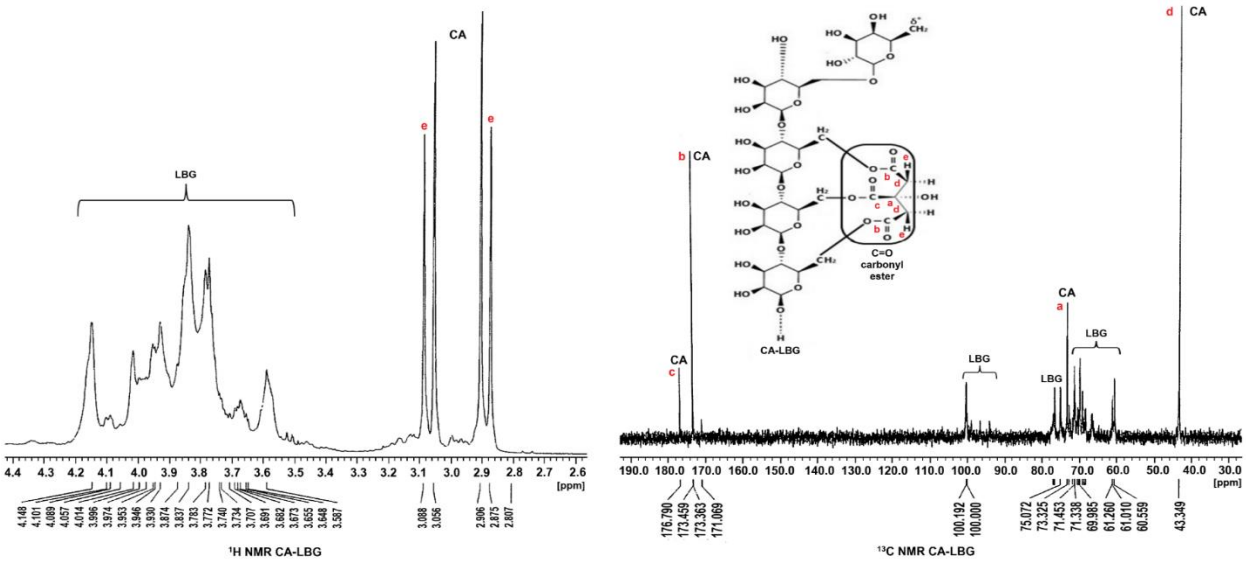
Original manuscript (page 11, line 262)
In the ^{13}C NMR spectrum of CA-LBG, peaks at δ = 176.790 ppm and δ = 173.459 ppm are related to C = O (b,c) resulting from the synthesis reaction. The peak at δ = 73.325 ppm is related to the central C atom of CA (a). The peak at δ = 43.349 ppm is related to C-H_2 (d) of CA. The peaks at δ = 100.192 ppm, δ = 100.000 ppm, δ = 75.072 ppm and δ = 71.453 ppm are related to C-H and C-H_2 at mannose. The peaks at δ = 69,985 ppm, δ = 61.260 ppm, δ = 61.010 ppm, δ = 60.559 ppm are related to C-H and C-H_2 at mannose and galactose. Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H_2 appeared at δ = 44-43 ppm (Jans and Kinne 1991; Doll et al. 2006; Zhang et al. 2016; Hadinugroho et al. 2019). The peak absorption of mannose and galactose appears at δ = 105-60 ppm (Parvathy et al. 2005; Azero and Andrade 2006; Bhatia et al. 2013; Gillet et al. 2014; Hadinugroho et al. 2019). This shows the success of the synthesis.

Revised manuscript (page 10, line 246)
The peaks of the CA-LBG ^{13}C NMR spectra from the high to low energy field were at δ = 176.790 ppm; δ = 173.459 ppm; 173.363 ppm; 171.069 ppm; δ = 100.192 ppm; δ = 100.000 ppm; δ = 75.072 ppm; δ = 73.325 ppm; δ = 71.453 ppm; 71.338 ppm; δ = 69.985 ppm; δ = 61.260 ppm, δ = 61.010 ppm, and δ = 60.559; and δ = 43.349. Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H2 appeared at δ = 44-43 ppm. [6,28–30]. The peak absorption of mannose and galactose appears at δ = 105-60 ppm [6,31–34]. This shows the success of the synthesis.

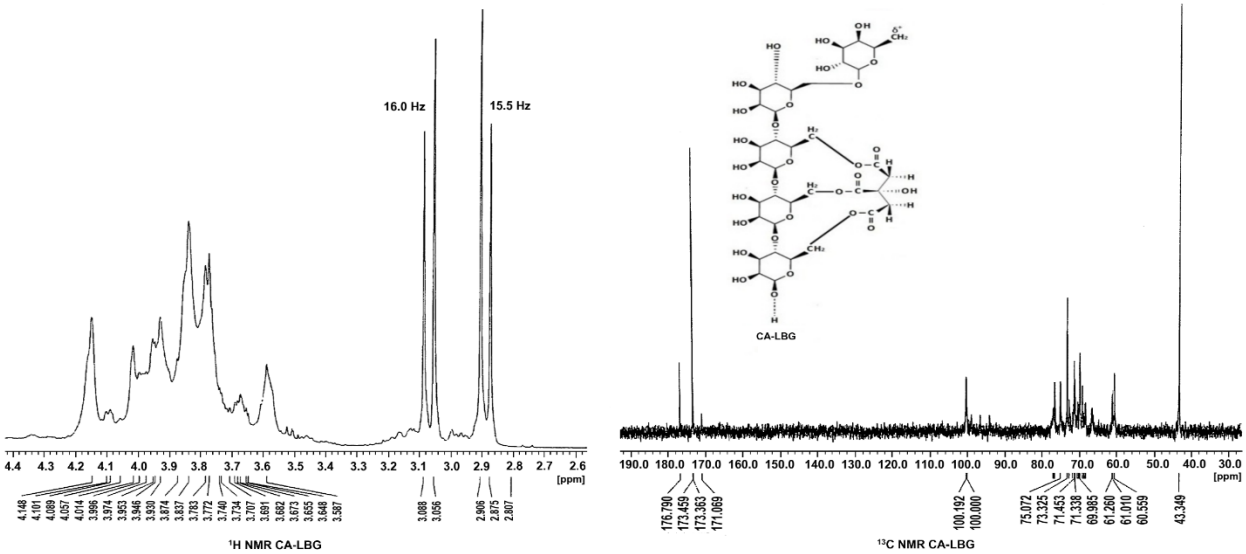
13. **Comment (page 33, Figure 3):**
"I wouldnt suggest you write the carbons as certain like here. Untill you perform a 2D NMR analysis, it is better not to specify the peaks."
"here the peak shape is double dublet, please share the J values."

Response:
Thank you for the suggestions. We have corrected Figure 3 and did not specify the peak. In addition, we have also added the value of J and only shared the number of peaks of the multiplet without specifying the peak.

Original (Figure 3) (page 33, Figure 3)



Revised (Figure 3) (page 32, Figure 3)



Comment of reviewer 3:
"I have provided my decision to the editor."
Response:
Thank you for the suggestions. Thanks for the comments. We really appreciate.

Comment of reviewer 4:

1. **Comment: "The following paper by the author should probably be cited in this manuscript due to similarities in the coverage:**
   Hadinugroho, W., Martodihardjo, S., Fudholi, A., & Riyanto, S. (2019). Esterification of citric acid with locust bean gum. Heliyon, 5(8), e02337."
   Response:
   Thank you for the suggestions. We have included citations in this manuscript for the article: Hadinugroho, W., Martodihardjo, S., Fudholi, A., & Riyanto, S. (2019). Esterification of citric acid with locust bean sap. Heliyon, 5(8), e02337. In addition, we have also been listed on the reference (number 6).

   (Page 2, paragraph 2, line 35)
   Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). [2,5–9]

   (Page 2, paragraph 3, line 42)
   The HCl is a strong acid that is effective for creating acidic conditions [10,11]. Variation of HCl concentration in the synthesis effect on the character of CA-LBG. The concentration of HCl affects the rate of protonation of the carbonyl group of CA to form a positive C atom. Increasing the concentration of HCl causes an increase in the creation of positive C atoms. This condition increases CA binding to LBG. The characteristics of CA-LBG are influenced by the concentration of CA bound to LBG [6].

   (Page 2, paragraph 4, line 47)
   The low wavelengths of UV irradiation (200-400 nm) are a source of energy strong enough to form chemical bonds [12–14]. The UV irradiation for a certain duration determines the formation of positive C atoms from the carbonyl group in CA with the O atoms (C-6) of mannose and galactose at LBG. The results of previous studies reported that this esterification produced a carbonyl ester group on CA-LBG which was not owned by LBG. In addition, the study reported that CA-LBG has a viscosity of 7-11 cP [6]

   (Page 3, paragraph 5, line 51)
   The CA-LBG utilization as material synthesis products needs to be studied further. Pharmaceutical formulation is one area where CA-LBG can be used as an alternative to pharmaceutical excipients. Previous studies have reported that CA-LBG has the potential as a disintegrating agent for tablet dosage formulations [6].

   (Page 5, line 120)
   The degree of esterification is determined by comparing the carboxylate group in the reacting CA (Molar) and the carboxylate group at the initial CA (Molar) and calculated according to Equation 3 [6].

(Page 9, line 216)
In the synthesis of CA-LBG, the acidity of HCl could be induced protonation of O atoms from the carbonyl group of citric acid and created positive C atoms. The hydroxyl (OH) group of C-6 at mannose and galactose atoms reacts with the protonated citric acid carbonyl group to create a tetrahedral cation. Protonated OH ($^{+}OH_2$) oxygen groups with H_2O loss to form CA-LBG. UV irradiation is the energy source to create bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose [6,7].

(Page 10, line 230)
The sharp peak of CA-LBG appeared at 1739.22 cm^{-1}; 1736.39 cm^{-1}; and 1735.85 cm^{-1} are related to the carbonyl ester group that was produced from the synthesis reaction. The carbonyl ester group is created by the bond between the positive C atom of the protonated carbonyl group in CA and the O atom of C-6 at mannose and galactose in LBG. In a previous study, the OH group appeared around 3300 cm^{-1}. C-H appears around 2900 cm^{-1}, and C=O appears around 1750-1735 cm^{-1}[6]

(Page 10, line 237)
NMR examination of the two other conditions has been confirmed in previous studies [6,7].

(Page 10, line 245)
Multiplet peaks at δ = 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that two doublet peaks of CA around δ = 2.7-3.0 ppm. Multiplet peaks from mannose and galactose appear around 4.5-3.0 ppm [6,7].

(Page 11, line 251 & 252)
Previous studies reported that the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H2 appeared at δ = 44-43 ppm. [6,28–30]. The peak absorption of mannose and galactose appears at δ = 105-60 ppm [6,31–34]. This shows the success of the synthesis.

(Page 11, line 258)
Based on previous experiments, LBG has a corrugated morphology and CA creates coral morphology [6].

References

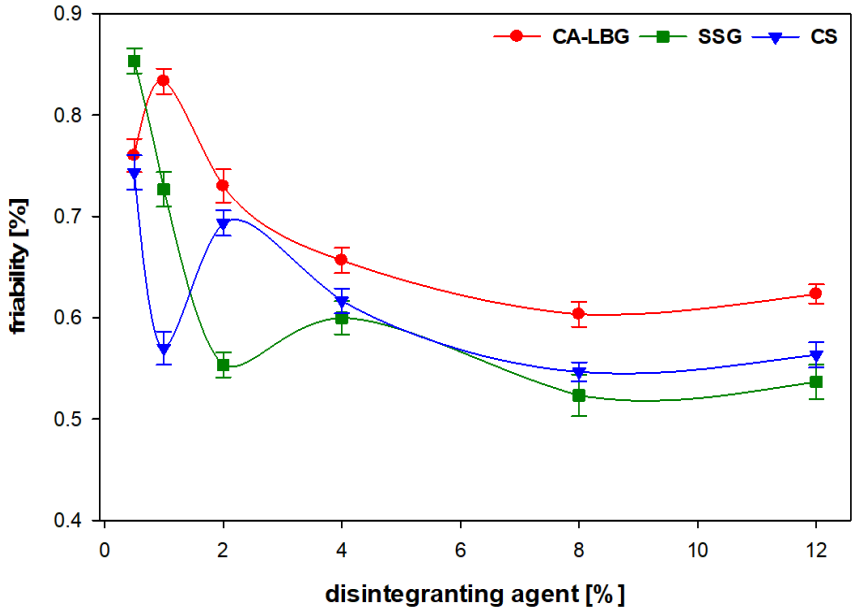
1. Das N, Triparthi N, Basu S, Bose C, Maitra S, Khurana S. Progress in the development of gelling agents for improved culturability of microorganisms. Front Microbiol. 2015;6:1–7.
2. Dey P, Maiti S, Sa B. Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide. J Biomater Sci Polym Ed. 2013;24:663–83.
3. Dionísio M, Grenha A. Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci. 2012;4:175–85.
4. Sheskey, Paul J Cook, Walter G Cable, Colin G. Handbook of Pharmaceutical Excipients 8th. London-Washington DC: Pharmaceutical Press and American Pharmacists Association; 2017.
5. Chudzikowski RJ. Guar gum and its applications. J Soc Cosmet Chem. 1971;22:43–60.
6. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Esterification of citric acid with

locust bean gum. Heliyon. Elsevier Ltd; 2019; 5: e02337. https://doi.org/10.1016/j.heliyon.2019.e02337

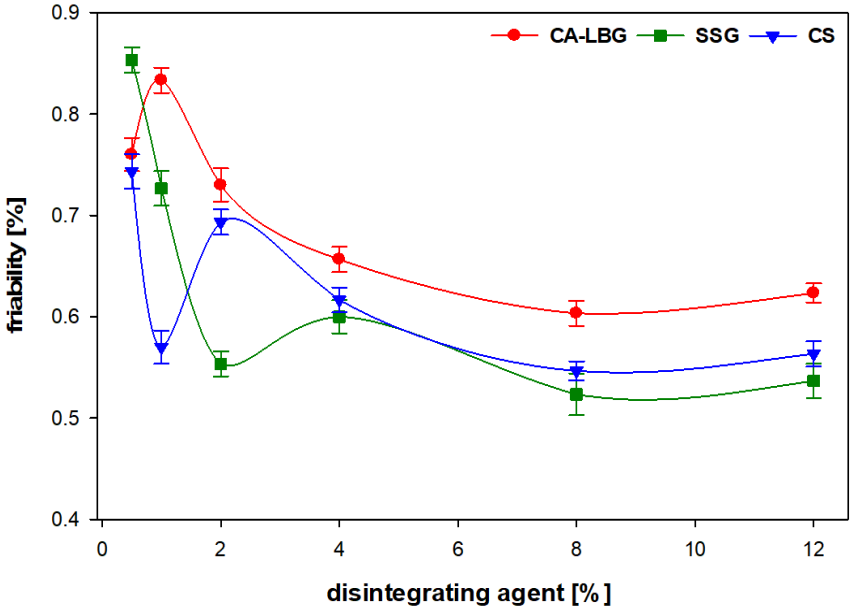
7. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Study of a catalyst of citric acid crosslinking on locust bean gum. J Chem Technol Metall. 2017;52:1086–91.

2. **Comment: "Correct the spelling of disintegrating agent on the x-axis in Figure 8, 9."**
   Response:
   Thank you for the suggestions. We have correct the spelling of disintegrating agent on the x-axis in Figure 8, 9.

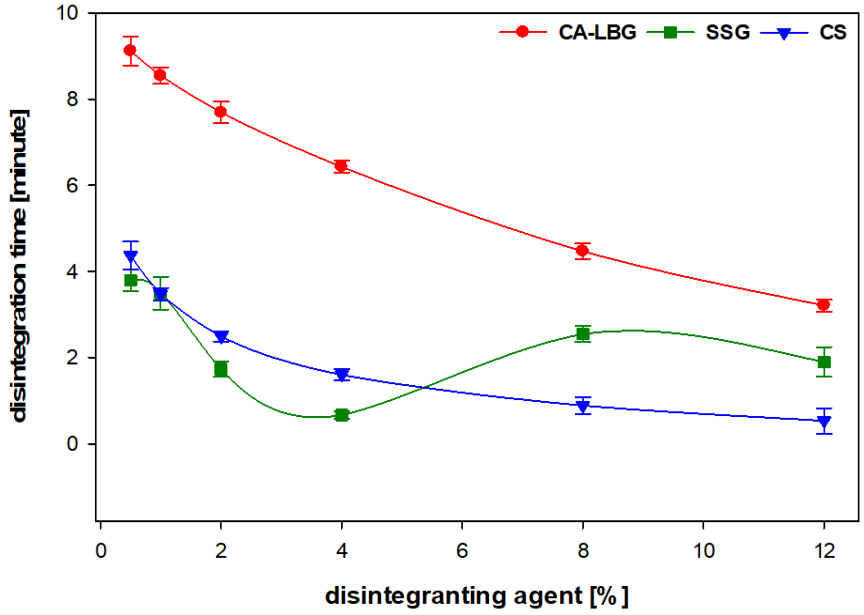
Original (Figure 8) (page 38)



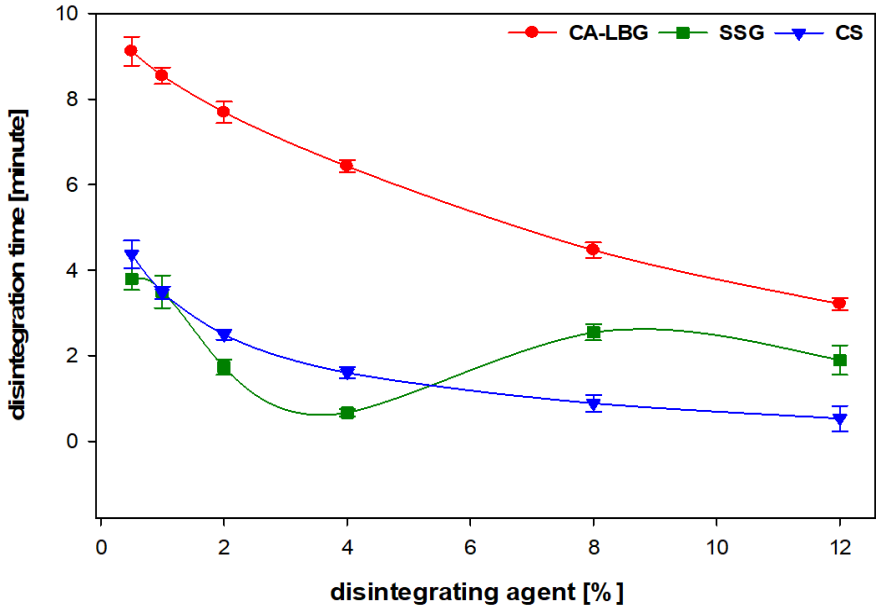
Revised (Figure 8) (page 37)



Original (Figure 9) (page 39)



Revised (Figure 9) (page 38)



3. **Comment:**

"Some editing would improve the readability of the manuscript.For example, the meaning of this sentence is not clear (p. 2, line 45): "Variation of HCl concentration in the synthetic effect on the character of CA-LBG."

Response:

Thank you for the suggestions. We have tried to check and correct the words/sentences in this manuscript electronically and discuss it with linguists. We look forward to suggestions if something is still wrong or missed.

Original manuscript (Page 2, line 44)

Variation of HCl concentration in the synthetic effect on the character of CA-LBG.

Revised manuscript (Page 2, line 37)

Variation of HCl concentration in the synthesis effect on the character of CA-LBG.

Original manuscript (Page 3, line 57)

The CA-LBG utilization as material synthesis products need to be studied further.

Revised manuscript (Page 2, line 48)

The CA-LBG utilization as material synthesis products needs to be studied further.

Original manuscript (Page 5, line 108)

The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra were recorded.

Revised manuscript (Page 4, line 98)

The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra was recorded.

Original manuscript (Page 10, line 238)

The stretch peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

Revised manuscript (Page 9, line 221)

The stretching peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose.

Original manuscript (Page 11, line 247)

This shows the success of the synthesis and continued by NMR confirmation.

Revised manuscript (Page 10, line 237)

This indicates the success of the synthesis and CA-LBG was further confirmed by NMR.

Original manuscript (Page 12, line 277)

The LBG particles have a shape coral- corrugated indicates available interaction with CA with LBG and successful synthesis.

Revised manuscript (Page 11, line 259)

The LBG particles have a shape coral-corrugated indicates the available interaction of CA with LBG and shows successful synthesis.

Original manuscript (Page 14, line 324)
In general, the tablet profile containing CA-LBG the most slope of flow rate although the CA-LBG concentration was increasing.
Revised manuscript (Page 13, line 307)
In general, the tablet profile containing CA-LBG had the most slope of the flow rate although the CA-LBG concentration was increasing.

Original manuscript (Page 15, line 351)
In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density arrangement between SDL granules and the area of porosity that could accommodate all CA-LBG particles.
Revised manuscript (Page 14, line 334)
In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density and the area of porosity arrangement between SDL granules for could accommodate all CA-LBG particles.

Original manuscript (Page 15, line 361)
The rod-shape and corrugated surface of the CS particles envelop according to the SDL granule shape in layers and has a narrow porosity.
Revised manuscript (Page 14, line 344)
The rod-shaped and corrugated surface of the CS particles is enveloping according to the SDL granule shape in layers and has a narrow porosity.

Original manuscript (Page 20, line 473)
In CS-5 tablet, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface.
Revised manuscript (Page 19, line 456)
In CS-5 tablets, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface.

Original manuscript (Page 20, line 475)
In CS-6 tablet, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.
Revised manuscript (Page 19, line 458)
In CS-6 tablets, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.

Original manuscript (Page 20, line 486)
In the experiment, the peak tensile strength of CA-LBG tablets and SSG tablets was a concentration of 2% while CS tablets was a concentration of 4%.
Revised manuscript (Page 19, line 469)
In the experiment, the peak of tensile strength of CA-LBG tablets and SSG tablets was at a concentration of 2%, while the peak of tensile strength CS tablets was at a concentration of 4%.

Original manuscript (Page 21, line 518)
The friability of the CS-4 to CS-6 tablets proportional to the BF value and tends to decrease.
Revised manuscript (Page 21, line 501)
The friability of the CS-4 to CS-6 tablets is proportional to the BF value and tends to decrease.

Original manuscript (Page 24, line 586)
Comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11).
Revised manuscript (Page 23, line 569)
A comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11).

4. **Comment: "CIC Pharmaceutical Sciences might be a better journal for this work."**
   Response:
   Thank you for the suggestions.

Surabaya, September 28th, 2021

Dear Prof. Stephen Scypinski
Editor
Journal of Pharmaceutical Innovation

Please find enclosed our revised manuscript entitled “Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms”. This manuscript was revised based on the suggestions of reviewers. We inform you that changes to the manuscript based on suggestions from reviewers are written in blue ink. We also attach a list of responses to the suggestions of reviewers.

We would also like to inform you that on August 30th, 2021, we have received the text of the decision via email from Prof. Robert A Lodder by attaching comments from reviewers 2, 3, and 4. In addition, we also accept documents in the View Attachments column. We submitted a revised manuscript and review response by September 4th, 2021, as directed by the editor-in-chief.

Comments from reviewer 2 in the View Attachments column informed by Prof. Stephen Scypinski (September 11th, 2021) are the same as reviewer's comment 2 (View Attachments) which was revised and responded to earlier with submissions September 4th, 2021.

We are currently resubmitting revised manuscripts and review responses from reviewers 2, 3, and 4. If something goes wrong, we will gladly revise it.

Regardless of the decision that will publish/reject this manuscript. We are very grateful and expect suggestions and corrections from reviewers and editors to improve this manuscript.

We thank you for your attention and cooperation.

Yours sincerely,
Dr. Wuryanto Hadinugroho
Department of Pharmacy Science and Industrial
Widya Mandala Surabaya Catholic University
Kalisari Selatan 1, Pakuwon City, Surabaya 60112, Indonesia
Email: wuryanto.hadinugroho@ymail.com
Tel. +62 31 3891264
Fax. + 62 31 3891267

Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms

Wuryanto Hadinugroho[1,2*], Suwaldi Martodihardjo[2], Achmad Fudholi[2], Sugeng Riyanto[2]

1 Department of Pharmaceutical, Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, Indonesia

2 Department of Pharmaceutical, Faculty of Pharmacy, Gadjah Mada University, Sekip Utara, Yogyakarta, Indonesia

*Corresponding authors: e-mail address: wuryanto.hadinugroho@ymail.com; Tel.: +62 81 330 904 484, Fax: +62 31 990 052 88

Declarations

Author contribution statement

Wuryanto Hadinugroho: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Suwaldi Martodihardjo, Achmad Fudholi, Sugeng Riyanto: Conceived and designed the experiments; Analyzed and interpreted the data.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgement

The authors thank the research, technology, and higher education department, Indonesia for support of this work by providing research grants (0299/E3/2016). The author also thanks PT. Makmur Food (Indonesia) for supporting locust bean gum (viscogum); LPPT Gadjah Mada University (Indonesia) for the SEM, DSC, NMR instrument support; Faculty of Pharmacy, Gadjah Mada University (Indonesia) for support of pharmaceutical technology facilities; Faculty of Pharmacy, Widya Mandala Catholic University Surabaya (Indonesia) for pharmaceutical technology facilities and instruments.

Abstract

Purpose: Analyze the effect of HC l concentration 0.24 mol as a synthesis catalyst on the viscosity of CA-LBG and determine the effect of the application of CA-LBG as a disintegrating agent on the physical quality of tablets.

Methods: Citric acid-locust bean gum (CA-LBG) was synthesized from citric acid (CA) and locust bean gum (LBG) using hydrochloric acid (HCl) and UV irradiation (254 nm, 100 minutes). The CA-LBG was analyzed by fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), scanning electron microscopy (SEM), esterification efficiency, solubility, and viscosity. The tablet formulation used CA-LBG with a concentration variation of 0.5%; 1%; 2%; 4%; 8%; and 12%. Preparation of tablets by direct compression uses a spray dray lactose (SDL) as a filler with a tablet weight of 200 mg.

Results: Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility.

Conclusion: The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

Keyword: CA-LBG, citric acid, locust bean gum, disintegrating agent, direct compression

Introduction

Natural polymers are a resource that can be used and developed as pharmaceutical excipients. One of the natural polymers in pharmaceutical excipients is locust bean gum (LBG) which functions as the matrix, binder, disintegrating agent, thickening agent, suspending agent, gelling agent, etc. The LBG is a polymer that has the potential to be modified to produce new materials as excipients in tablet formulations [1–4].

Citric Acid-Locust Bean Gum (CA-LBG) is a modified polymer synthesized from citric acid (CA) and locust bean gum (LBG). The synthesis was carried out using hydrochloric acid (HCl) as a catalyst and ultraviolet (UV) irradiation as an energy source to form ester bonds. LBG consists of mannose and galactose monomer chains (4:1). [2,5–9].

The HCl is a strong acid that is effective for creating acidic conditions [10,11]. Variation of HCl concentration in the synthesis effect on the character of CA-LBG. The concentration of HCl affects the rate of protonation of the carbonyl group of CA to form a positive C atom. Increasing the concentration of HCl causes an increase in the creation of positive C atoms. This condition increases CA binding to LBG. The characteristics of CA-LBG are influenced by the concentration of CA bound to LBG [6].

The low wavelengths of UV irradiation (200-400 nm) are a source of energy strong enough to form chemical bonds [12–14]. The UV irradiation for a certain duration determines the formation of positive C atoms from the carbonyl group in CA with the O atoms (C-6) of mannose and galactose at LBG. The results of previous studies reported that this esterification produced a carbonyl ester group on CA-LBG which was not owned by LBG. In addition, the study reported that CA-LBG has a viscosity of 7-11 cP [6].

The CA-LBG utilization as material synthesis products needs to be studied further. Pharmaceutical formulation is one area where CA-LBG can be used as an alternative to

pharmaceutical excipients. Previous studies have reported that CA-LBG has the potential as a disintegrating agent for tablet dosage formulations [6].

The purpose of this study was to analyze the effect of HCl concentration 0.24 M as a synthesis catalyst on the viscosity of CA-LBG. The aim of the tablet formulation was to determine the effect of the application of CA-LBG as a disintegration agent on the physical quality of tablets. The novelty of this study, the synthesis of CA-LBG uses a concentration of HCl 0.24 mol as the catalyst and UV irradiation time (100 minutes) as an energy source that creates the chemical bond. HCl concentrations of 0.18 mol and 0.30 mol were experimental control concentrations to determine the success of the synthesis and characterization of CA-LBG. The CA-LBG experiment as a disintegrating agent was further studied with various concentrations. Sodium starch glycolate (SSG) and croscarmellose sodium (CS) were comparable disintegrating agents to study the disintegration activity of CA-LBG. SSG and CS are tablet disintegrating agents that are often used in tablet formulations because both able to swell in the disintegrating medium in a fast time. The rounded shape with the smooth surface of the SSG and the shape of the root with the corrugated surface of the CS can affect the tablet quality [4,15]. The experiment was conducted to determine the potential for the disintegration of CA-LBG in tablet formulations as an alternative choice of disintegrating agent to be developed in the future.

Material and methods

Raw materials and chemicals

Materials needed in this study were locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Merck KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich, GmbH, USA), acetone (Cawan Anugerah Chemika, Indonesia), sodium starch glycolate (JRS Pharma, India), croscarmellose sodium (FMC Biopolymer, USA), spray dried lactose

(Foremost Farms, USA), diclofenac sodium (Dwilab Mandiri, Indonesia), sterilized water for injection (Otsuka, Indonesia), and distilled water (Brataco Chemical, Indonesia).

Preparation of CA-LBG

The swollen LBG was placed in a glass bowl (7.10 x10^{-6} mol/50 mL concentration at a temperature rate of 55-60 °C) and CA (0.42 mol) was added with different concentrations of HCl (0.18; 0.24; and 0.30 mol). The mixture was stirred for 10 minutes and irradiated with UV light for 100 minutes (254 nm, 8-watt shortwave CH-4132 Muttenz, Camag, Switzerland). The wet solid was precipitated with acetone and washed with acetone-distilled water (1:1, v/v). The solid CA-LBG was dried at ambient temperature [7].

Chemical characterization was carried out to confirm the success of esterification. The characterization of CA-LBG was performed by using FTIR (fourier transform infrared) and NMR (nuclear magnetic resonance) spectroscopic techniques. SEM (scanning electron microscope), esterification efficiency, solubility, and viscosity tests were also carried out in order to elucidate the structure.

Fourier transform infrared spectroscopy

The structure and the functional group of CA-LBG were analyzed by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.) in the wavenumber range of 4000-450 cm^{-1} spectra were recorded.

Nuclear magnetic resonance

The ^{1}H and ^{13}C NMR of CA-LBG was analyzed by liquid state NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan). The CA-LBG (5-15 mg) was stirred for 45 minutes. The filtrate was placed in the glass tube and spectra was recorded.

Scanning electron microscope

The surface morphology of CA-LBG was analyzed using SEM (JSM-6510LA, JEOL, Japan). The CA-LBG was mounted on a holder, coated by platinum, and observed (distance 10 mm and voltage10 kV).

Esterification efficiency

The efficiency of the synthesis was evaluated through the yield percentage of CA-LBG to the total raw material. The evaluation of esterified CA was determined by the degree of esterification. The determination of the degree of esterification follows the experimental equation that has been done previously [6]. Acetone solution and acetone-distilled water to precipitate and wash the acidic CA-LBG mass comes from unreacted HCl and CA. The concentrations of both were analyzed potentiometrically with NaOH (0.2 N) as the titrant which had been standardized using oxalic acid. The dissolved acid concentration (mEq) was analyzed by means of the titrant volume needed to reach the endpoint of neutralization and was determined according to Equation 1. The dissolved CA (mEq) is converted (gram) (W CA dissolved)] and the reacting CA is determined according to Equation 2. The carboxylate group weight of the reacting CA (gram) is determined by the mass relative of the carboxylate group compared to the mass relative of CA multiplied by the weight of the CA reacting. The carboxylic group weight in reacting CA (gram) is converted to (Molar). The degree of esterification is determined by comparing the carboxylate group in the reacting CA (Molar) and the carboxylate group at the initial CA (Molar) and calculated according to Equation 3 [6].

Dissolved CA (mEq).

$$dissolved\ CA\ [mEq] = dissolved\ acid [mEq] - dissolved\ HCl [meq] \quad \textbf{Equation 1}$$

Weight CA reacting (gram)

$$W\ CA\ reacting\ = W\ initial\ CA - W\ dissolved\ CA \quad \textbf{Equation 2}$$

Degree of esterification

$$Degree\ of esterification\ [\%] = \frac{carboxylic\ group\ on\ the\ CA\ reacting\ [Molar]}{carboxylic\ group\ on\ the\ CA\ initial\ [Molar]}\ x\ 100\ \%$$ **Equation 3**

Solubility

Solubility was determined by 0.5 g CA-LBG added 50 mL distilled water and allowed to stand for 24 h (Wd). Then, the filtrate was separated from the swollen sample. The filtrate was dried on a water bath at 70 ° C and reweighed (Wds) on a microbalance (Mettler Toledo AL204, Switzerland). The solubility of the CA-LBG was analyzed according to Equation 4:

Solubility (%) = Wds/Wd x 100 **Equation 4**

where Wds and Wd are soluble weight and initial weight (dry weight respectively) [16].

Viscosity

The CA-LBG viscosity test using a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG (3% w/v) was swelled in 300 mL of warm distilled water and left at ambient temperature. Spindle no. S61 was installed on Brookfield. Viscosity was recorded when Brookfield was rotated at 100 rpm.

Preparation of tablets

Preparation of tablets begins with weighing the ingredients according to the formula (Table 1). Preparation of tablets by direct compress was prepared by mixing homogeneous SDL and CA-LBG / SSG / CS using a cubic mixer (2 minutes, 100 rpm) (Erweka). The physical quality of tablet mass was evaluated for flowability and compressibility. The mass of the tablets was compressed with a weight of 200 mg per tablet using a single punch machine (Jenn Chian Machinery, Taiwan). The physical quality of the tablets was evaluated for thickness, weight, break force, tensile strength, friability, and disintegration time.

Flowability

Tablet mass (100 g) was placed in a funnel hole on a flowability tester (Erweka, Germany). When the funnel valve is opened, tablet mass flows. Flow time can be observed on the flowability tester monitor.

Compressibility

Tablet mass was poured into a measuring tube (100 mL, angle ± 40^{o}) whose weight was known. The filled measuring tube is weighed, placed on a tapped density volumeter apparatus (Erweka, Germany), and tapped (500 taps). Weight and volume of tablet mass (before and after tapped) were recorded to determine the bulk density and the tapped density. Tablet mass versus volume before tapped is bulk density. Granule weight/tablet mass versus volume after tapped is the tapped density. The compressibility index is the difference between tapped density and bulk density versus tapped density (Equation 5) [17].

$$compressibility\ index\ (\%) = \frac{tapped\ density - bulk\ density}{tapped\ density}\ x\ 100\% \qquad \textbf{Equation 5}$$

Weight and thickness

Tablet weight and thickness were determined using 20 randomly selected tablets. Each tablet was weighed using an analytical weighing scale (Mettler Toledo, Switzerland) and thickness was accurately measured using a thickness gauge (Mitutoyo 7301, Japan).

Break force and tensile strength

Tablet break force (BF) was determined using 6 randomly selected tablets [18]. The tablet is placed on the break force tester plate (Schleuniger, Netherlands). The metal block moves towards the tablet and presses until the tablet cracks/breaks. The tablet break force value is determined from the start of cracks/breaks, indicated on the monitor.

The strength of the tablet against mechanical stress is determined specifically using the tensile strength parameter according to the shape of the convex tablet. Tensile strength (σt) is calculated following Equation 6 [19,20].

$$\sigma t = \frac{10F}{\pi D^2(2.84(\frac{t}{D})-0.126(\frac{t}{W})+3.15(\frac{W}{D})+0.001)} \quad \textbf{Equation 6}$$

F is the break force, D is the diameter of the tablet, t is the total thickness of the tablet, and W is the thickness of the center of the tablet without convex.

Friability

Tablet friability was determined using a randomly selected number of tablets with a total tablet weight equal to 6500 mg [18]. Each tablet was dust-free and the total weight of all tablets was determined (W0). All tablets were put into a drum friability tester (Erweka, Germany) and rotated for 4 minutes (25 rpm). After being removed from the drum, each tablet was dust-free and weighed again (W1). The friability of the tablet is the difference in the total weight of the tablet before and after rotated compared to the weight before rotated (Equation 7).

$$friability\ (\%) = \frac{W0-W1}{W0}\ 100\% \quad \textbf{Equation 7}$$

Disintegration time

Tablet disintegration time was determined using 6 tablets randomly selected from 18 previously randomly selected tablets [18]. Each tablet was inserted into each tube in the chamber disintegration tester apparatus (Erweka Z3, Germany). The chamber is up-down in a distilled water bath (37° C; 900 mL). The disintegration time was determined from the longest time required for the tube net to be free of tablet fragments.

Dissolution

The experiment was prepared using a tablet mass added with diclofenac sodium as a model active ingredient. Each tablet contains 50 mg of diclofenac sodium to be compressed to a weight of 250 mg [21,22]. Dissolution using phosphate buffer medium pH 6.8 (900 mL; 37 ± 0.5 ° C; 50 rpm) for 60 minutes using the paddle method (Electrolab TDT-08L, India) [23,24]. The release of ketoprofen was sampled and observed at 5, 15, 30, 45, and 60 minutes. Analysis of dissolved diclofenac sodium concentration using a UV-vis spectrophotometer (Hitachi U-1900, Japan) at a wavelength of 276 nm [25,26].

Result and discussion

Mechanism of the CA-LBG synthesis reaction

In the synthesis of CA-LBG, the acidity of HCl could be induced protonation of O atoms from the carbonyl group of citric acid and created positive C atoms. The hydroxyl (OH) group of C-6 at mannose and galactose atoms reacts with the protonated citric acid carbonyl group to create a tetrahedral cation. Protonated OH ($^{+}OH_2$) oxygen groups with H_2O loss to form CA-LBG. UV irradiation is the energy source to create bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose [6,7]. The schematic and details of the synthesis are shown in Figure 1 and Table 1.

Fourier transform infrared spectroscopy

The results of the CA-LBG and LBG infrared analysis are shown in Figure 2 and Table 1. The stretching peaks appear at 3268.19 cm^{-1}; 3291.84 cm^{-1}: 3304.40 cm^{-1}; and 3337.34 cm^{-1} are related to the hydroxyl (OH) groups of C atoms at mannose and galactose. Sharp peaks appear at 2920.60 cm^{-1}; 2923.35 cm^{-1}, 2923.56 cm^{-1}; and 2923.35 cm^{-1} are related to C-H bonds of CA and LBG. In CA-LBG, the sharp peak comes from C-H symmetrically of CA [27]. The

sharp peak of CA-LBG appeared at 1739.22 cm^{-1}; 1736.39 cm^{-1}; and 1735.85 cm^{-1} are related to the carbonyl ester group that was produced from the synthesis reaction. The carbonyl ester group is created by the bond between the positive C atom of the protonated carbonyl group in CA and the O atom of C-6 at mannose and galactose in LBG. In a previous study, the OH group appeared around 3300 cm^{-1}. C-H appears around 2900 cm^{-1}, and C=O appears around 1750-1735 cm^{-1}[6]. This indicates the success of the synthesis and CA-LBG was further confirmed by NMR.

Nuclear magnetic resonance

The NMR examination was carried out only in one of the experimental conditions (batch B) due to the resulting CA-LBG will be used as a disintegrating agent in the tablet dosage forms. NMR examination of the two other conditions has been confirmed in previous studies [6,7]. NMR examination using CA-LBG dissolved in deuterium (D_2O) (H2O).

The results of the CA-LBG NMR analysis are shown in Figure 3. The ^{1}H NMR spectrum of CA showed two doublet peaks at δ = 3.088 ppm and δ = 3.056 ppm, δ = 2.906 and ppm, δ = 2.875 ppm shows the presence of CA at LBG. The peak is from C-H_2 in CA. The two doublet peaks are protons from symmetric C on CA reacting on LBG. The position of one adjacent proton due to bond rotation and causes the signal to split so that the peak appears splitting. Multiplet peaks at δ = 4.148-3.587 ppm from mannose and galactose in LBG. Previous studies reported that two doublet peaks of CA around δ = 2.7-3.0 ppm. Multiplet peaks from mannose and galactose appear around 4.5-3.0 ppm [6,7].

The peaks of the CA-LBG ^{13}C NMR spectra from the high to low energy field were at δ = 176.790 ppm; δ = 173.459 ppm; 173.363 ppm; 171.069 ppm; δ = 100.192 ppm; δ = 100.000 ppm; δ = 75.072 ppm; δ = 73.325 ppm; δ = 71.453 ppm; 71.338 ppm; δ = 69.985 ppm; δ = 61.260 ppm, δ = 61.010 ppm, and δ = 60.559; and δ = 43.349. Previous studies reported that

the C=O group appeared at δ = 180-170 ppm, the central C atom appeared at δ = 80-70 ppm, C-H and C-H2 appeared at δ = 44-43 ppm. [6,28–30]. The peak absorption of mannose and galactose appears at δ = 105-60 ppm [6,31–34]. This shows the success of the synthesis.

1.2. Scanning electron microscopy

The SEM images of CA-LBG (Batch B) are shown in Figure 4. In magnification100x, particles of CA-LBG appear in an irregular shape. In magnification 3500x, particles CA-LBG have the surface morphology of CA-LBG appear coral-corrugated. Based on previous experiments, LBG has a corrugated morphology and CA creates coral morphology [6]. The LBG particles have a shape coral-corrugated indicates the available interaction of CA with LBG and shows successful synthesis.

Esterification efficiency

The yield percentage and degree of esterification of CA-LBG for all batches are shown in Table 1. The high concentration of HCl under synthesis conditions increases yield percentage and degree of esterification due to the high amount of CA bound to LBG. The HCl increases the acidity of the synthesis conditions to protonate the O atom from the carbonyl group and creates a positive C atom, thereby causing CA to bind to LBG. The CA-LBG batch A to batch C shows the higher the degree of esterification in proportion to the increase in the concentration of HCl because the protonation of the O atom from the carbonyl group and the formation of a positive C atom is faster. This condition accelerates creates bonds between positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose.

Solubility

The solubility of CA-LBG for each synthesis condition is shown in Table 1. The CA-LBG of batch A to batch B presents the solubility decreasing in proportion to the increasing degree of esterification. The more CA molecules bound to the LBG produce CA-LBG with stable ester bonds. Bonds of positive C atoms from carboxylic groups and O atoms of C-6 at mannose and galactose decrease the ability of CA-LBG to interact with distilled water. In this condition, CA-LBG particles are difficult to wet so inhibit solubility in distilled water.

Viscosity

The viscosity of CA-LBG for each batch is shown in Table 1. LBG has a high viscosity, but the presence of excess CA can reduce the viscosity. The viscosity of CA-LBG from batch A to batch C decreased in proportion to the increasing degree of esterification. The carbonyl ester groups formed from the bonding of positive C atoms from carboxylate groups with O atoms of C-6 in mannose and galactose reduce the ability of CA-LBG to trap distilled water so viscosity decreases.

Flowability

The results of the flowability study on all tablet mass formulas containing CA-LBG showed that an increase in the concentration of CA-LBG increased the flow time of tablet mass (Table 2) because influenced by the irregular shape of particles and the surface like coral inhibit the flow of mass tablet (Figure 5). The CL-1 formula has the fastest flow time due to the influence of the spherical shape of the SDL granules to dominate the flowability although CA-LBG is present in the tablet mass [4]. The formula containing SSG and CS showed an increase in concentration cause increased flow time tablet mass. SSG particles are rounded and have a smooth surface, should be able to rate up the flow time but SSG particles are also hygroscopic,

thus inhibiting the flow time of tablet mass [4]. The CS particles are rod-shaped with a corrugated surface, which at high concentrations can inhibit the flow of tablets mass [4]. According to the flow time requirements, all tablet mass formulas containing a variety of disintegrating agents meet the requirements is 100 g tablet mass can flow in less than 10 seconds [35].

The effect of the presence of various disintegrating agents on the tablet mass is shown in Figure 5, which is a plot between the concentration of the disintegrating agent and the flow rate [g s^{-1}]. In general, the tablet profile containing CA-LBG had the most slope of the flow rate although the CA-LBG concentration was increasing. In addition, the decrease in flow rate of tablet mass with a high concentration of CA-LBG is proportional to the flow rate of tablet mass containing high concentrations of SSG and CS. This case is because the particle surface of CA-LBG like coral can fill each other with a porosity of SDL surface [4]. The sharp decrease in the profile of tablet mass containing CS at low concentrations (CS-1) indicates that the flow rate is more influenced by the spherical shape of the SDL granules so accelerate the flow, while at higher concentrations (CS-2) the root shape and corrugated surfaces of the CS particles begin to inhibit the flow. The flow rate profile of tablet mass containing SSG at low concentrations (SSG-1) is more slope than the tablet mass containing CS at the same concentration (CS-1) because the hygroscopicity of SSG particles inhibits the flow of tablet mass. The hygroscopic effect of SSG particles at higher concentrations (SSG-2 to SSG-6) can be overcome by the rounded shape and smooth surface of the SSG particles so that the decrease flow rate is more slope.

Compressibility

The tablet mass density evaluation results on all tablet mass formulas containing CA-LBG or SSG showed that increasing the concentration of the disintegrating agent increased the

value of ρ_{tapped}-ρ_{bulk} (Table 2), due to the influence of the shape and surface of the disintegrating agent particles. The initial composition of the tablet mass was SDL granules arranged randomly, the porosity between the SDL granules was filled with disintegrating agent particles.

The CA-LBG particles which have an irregular shape and a coral-like surface are randomly arranged on the porosity between the SDL granules according to the shape and area of the porosity between the initial particles. The volume decrease during the tapping was caused by the movement of SDL granules and CA-LBG particles. The CA-LBG particle corners fill each other surface porosity between particles and SDL granule surface porosity. In the CL-1 and CL-2 formulas, the porosity of the mass arrangement of tablets was dominated by the effect of the density and the area of porosity arrangement between SDL granules for could accommodate all CA-LBG particles. The volume decrease in the tapping of the formula with the higher CA-LBG concentration causes the porosity between the SDL granules to be wider because the CA-LBG particles surround the SDL granules tightly.

The rounded shape and smooth surface of the SSG particles give a tablet mass arrangement with more regular porosity than the CA-LBG particles. The smooth surface of SSG particles causes movement of SDL granules / SSG particles and decreases in volume during tapping so that the porosity narrows and SSG particles fill the porosity of the SDL granule surface. Formulas containing CS have a different value of ρ_{tapped}-ρ_{bulk} from formulas containing other disintegrating agents, namely the increasing the concentration of CS, the lowering the value of ρ_{tapped}-ρ_{bulk}. The rod-shaped and corrugated surface of the CS particles is enveloping according to the SDL granule shape in layers and has a narrow porosity. The surface of the CS particles decreases the ability of the particles to move and the volume decreases on tapping because the surface corrugated of the CS particles will interlock with other CS particles.

The results of the density evaluation are further confirmed by the compressibility profile shown in Figure 6, where increasing the concentration of the disintegrating agent increases the mass compressibility of tablets containing CA-LBG / SSG and decreases the mass compressibility of tablets containing CS. The mass compressibility of tablets containing CA-LBG was slightly lower than the mass of tablets containing SSG because the angles of CA-LBG particles fill each other surface porosity between particles and SDL granule surface porosity.

Weight and thickness

All tablet masses contain a variety of disintegrating agents and their concentration is compressed into tablets and according to weight is around 200 mg (Table 2), which shows that all tablet masses are able to flow freely from the hopper and fill the dies space in the tablet compressing machine. This condition is in accordance with the results of the evaluation of flowability and compressibility.

The variation in tablet thickness from the mass of tablets containing various disintegrating agents is influenced by the arrangement, shape, and surface of the SDL granule or the disintegrating agent particle so that when compression is applied produced deformation of the granule/particle, bond interlocking, and narrowing the porosity between deformations. The irregular shape and coral-like surface of the CA-LBG particles provide an opportunity for the particle corners to fill each other with the SDL particle/granule surface porosity so the tablet mass is compressed to produce a low-porosity tablet. The rounded shape and smooth surface of the SSG particles produce tablets with a regular form of porosity. The root shape and corrugated surface of the CS particles provide an opportunity to interlock between the particles and the corrugated surface so the tablet mass is compressed to produce a low-porosity tablet.

The CL-1 tablet is thicker even though the number of CA-LBG particles is less than the CL-2 tablet because the CA-LBG particles tend to fill the porosity of the SDL granules surface. In the CL-2 tablet, CA-LBG particles fill the surface porosity of SDL granules and porosity between SDL granules. The number of SDL granules of CL-2 tablet mass reduces so that produces a thinner tablet. The CL-3 and CL-4 tablets are thicker than the other CL tablets because the CA-LBG particles surround the SDL granules so that the volume is high and when the tablet mass is compressed into thick tablets. The CL-4 tablet is thicker than the CL-3 tablet due to the increasing number of CA-LBG particles resulting in a wider area surrounding the SDL granules. The number of CA-LBG particles in the CL-5 and CL-6 formula tablets is increasing so the area of the CA-LBG particles surrounding the SDL granules is wider, but the porosity between the CA-LBG particles is narrow so that the mass of the tablets is compressed to produce a thinner tablet. The CL-6 tablet is thicker than the CL-5 tablet because the CA-LBG particle area surrounding the SDL granules is wider.

The SSG-1 tablet is thicker than other SSG tablets because SSG particles fill the porosity of the SDL granules surface so, with the highest number of granules, the tablet mass is compressed to produce thick tablets. Tablet mass of SSG-2 and SSG-3 show the number of SSG particles is increasing and the number of SDL granules is decreasing. The SSG particles in the SSG-2 tablet mass filled the surface porosity of the SDL granules and the dense porosity of the SDL granules. The SSG-3 tablet mass shows the number of SDL granules was reduced so the mass of the tablets was compressed to produce a thinner tablet. The tablet mass of SSG-4 to SSG-6 contains more SSG particles and surrounds the decreasing SDL granules. The SSG-5 tablet is thicker than the SSG-4 tablet because the SSG deformation area surrounding the SDL deformation is wider. The SSG-6 tablet contained more SSG surrounding the SDL deformation with the area is wider. The SSG-6 tablet thickness is similar to SSG-5 because the number of SDL deformation in the tablet mass is reduced.

The thickness of the CS-1 tablet was dominated by the effect filling of CS particles on porosity SDL granules surface so when compressed the tablet mass experienced deformation with porosity varying of shapes and areas. The tablet of CS-2 to CS-4 contain more CS particles and fewer SDL granules. The increasing number of CS particles formed the interlocking deformation between the particles and enveloped the SDL granules so that produce thicker tablets with narrow porosity but in large numbers. The greater the number of CS particles, the wider the enveloping and interlocking area of the CS particles, resulting in a thicker tablet. The thickness of the CS-5 and CS-6 formula tablets was dominated by the increase in the number of CS particles. CS particles in the CS-5 tablet mass forming long interlocking on surrounding SDL granules. The tablet mass contains limited SDL granules so produce thin tablets when compressed. The CS-6 tablet is thicker than the CS-5 tablet because the interlocking area enveloping the SDL granule is wider.

Break force and tensile strength

Evaluation of tablet resistance to mechanical stress is measured by the BF value and shown in Table 2. The resistance of the CL-1 tablet is influenced by the dominance of SDL granules interlocking bonds when compressed to result in deformation with a wide porosity so that the tablets have a low resistance to mechanical stress. The BF value of the CL-2 tablet is higher than CL-1tablet because the number of CA-LBG particles is more and fills the dense porosity between SDL granules so when compressed the interlocking bonds are stronger and the porosity is narrower. The CL-3 tablet shows the highest BF value than other CL tablets because the deformation of CA-LBG particles around the SDL granule when compressed is able to form interlocking bonds with narrow porosity so that the thick tablet and resistant to mechanical stress. In addition, the corners of the CA-LBG particles fill the surface porosity between the CA-LBG particles and the SDL granule surface porosity so strengthening the

interlocking bond. The CL-4 to CL-6 tablets have a similar mechanism as the CL-3 formula tablets, but the number of CA-LBG particles is increasing and SDL granules are decreasing so that when compressed, produce tablets with a lot of narrow porosity and a decrease in tablet resistance to mechanical stress. The tablet of CL-5 and CL-6 show similar BF values due to the CL-6 tablet, although the interlocking bonds between particles are more dominant with the number of narrow porosity increases.

The SSG particles in the SSG-1 tablet mass fill the surface porosity of the SDL granules so inducing the granules to be slightly moist and the interlocking bonds between the SDL deformation are weaker. In addition, SDL granules after being compressed produce wide porosity deformation. The resistance of the SSG-2 tablet is higher than the SSG-1 tablet because the narrow porosity between the SDL granules is filled with SSG particles so that the mass of the granules is compressed resulting in a narrower porosity deformation. The SSG-3 tablet shows the strongest resistance than other tablets because SSG particles surround SDL granules when compressed able to form deformation interlocking bonds with narrow and regular porosity so tablets are resistant to mechanical stress. SSG-4 to SSG-6 tablets have a similar mechanism to SSG-3 tablets, but the number of SSG particles is increasing and SDL granules are decreasing so the mass of SSG-5 and SSG 6 when compressed produces tablets with more narrow porosity and decrease in the resistance of the tablet to mechanical stress. In addition, the slightly hygroscopic character of SSG particles decreased the resistance of tablets shown in the SSG-4 tablet because the deformation interlocking bonds of SSG particles around the SDL granules were weak.

The little number of CS particles in the CS-1 tablet tends to fill the porosity of the SDL granules. When compressed, the interlocking bond is dominated by SDL deformation with wide porosity so the resistance of the tablets to mechanical stress is weak. The CS-2 tablet has a similar mechanism to the CS-1 tablet but the porosity between the SDL granules is filled with

CS particles so produces a tablet with narrower porosity and is more resistant to mechanical pressure. The CS-3 tablet has a similar mechanism to the CS-2 tablet but the number of CS particles is more so the CS particles form interlocking between particles and envelop the SDL granules. When compressed, the enveloping CS particles form an interlocking bond deformation with a narrow and large porosity so the tablet surface resistance is weak. In the CS-4 tablet, the interlocking CS particles to envelope the SDL granules and a wider area so produce tablets with interlocking narrow porosity and strong surface to withstand mechanical stress. The CS-5 and CS-6 tablets have a similar mechanism to the CS-4 tablets but the number of CS particles is increasing and the SDL granules are decreasing. In CS-5 tablets, reduced SDL granules have an impact on tablet resistance because SDL granules serve as a foundation to withstand the mechanical stress exerted on the tablet surface. In CS-6 tablets, the foundation of tablet resistance to mechanical stress is controlled more by the interlocking bonds between CS particles after being compressed so that the tablets are stronger than the CS-5 tablet.

The BF value was further confirmed by the tensile strength parameter to determine the comparison between tablets contain disintegrating agent variation according to the concentration in the experiment (Figure 7). The tensile strength profile of CA-LBG tablets is similar to that of SSG tablets due to the influence of the particle shape of CA-LBG and SSG. The irregular shape and coral surface of the CA-LBG particles produce tablets with strong deformation interlocking bonds. The tensile strength intensity of CA-LBG tablets is similar to that of SSG tablets showing a deformation interlocking bond that can adjust the concentration used in the tablets. In the experiment, the peak of tensile strength of CA-LBG tablets and SSG tablets was at a concentration of 2%, while the peak of tensile strength CS tablets was at a concentration of 4%. This concentration is the optimum condition for forming tablets with the most stable interlocking deformation bonds against mechanical stress.

Friability

Evaluation of tablet resistance to mechanical movement is measured by friability parameters and is shown in Table 2. The friability of the CL-1 tablet is influenced by the low BF value due to the interlocking bond of SDL deformation with wide porosity so that SDL deformation on the tablet surface releases particles when subjected to mechanical movement. In addition, the CA-LBG particles on the tablet surface were also released. The CL-2 tablet is more friable than the CL-1 tablet although the BF value is higher because the number of CA-LBG particles on the surface of the tablet is more so more particles are released when subject to mechanical movement. The CL-3 to CL-6 tablets showed a tendency to decrease in friability although the BF value was lower because of a strong interlocking bond on the deformation of granules and particles, so reducing the release of tablet surface particles when subjected to mechanical movement. The CL-6 tablet is more friable than the CL-5 tablet because the number of SDL deformation decreases so that the foundation to withstand mechanical movements is reduced.

The SSG-1 tablet is the most friable than SSG other tablets because of the low BF value due to SDL deformation interlocking bonds with wide porosity so that the tablet surface releases lactose and SSG particles when subjected to mechanical movement. The decrease in the friability of the SSG-2 and SSG-3 tablets proportional to the higher BF value indicates a strong interlocking bond from the deformation of granules and particles so resistant to mechanical movement. The friability of the SSG-4 to SSG-6 tablets tends to decrease because the strength of the interlocking bonding of SSG deformation is able to withstand mechanical movements. The SSG-6 tablet is more friable than the SSG-5 tablet because the number of SDL deformation is reduced so the foundation to withstand mechanical movements is reduced.

The CS-1 tablet is the most friable than the other CS tablets because the SDL deformation interlocking bond dominates with a wide porosity so the lactose and CS particles

on the surface are released when subject to mechanical movement. The friability of the CS-2 and CS-3 tablets increased proportionally to the BF values of the two tablet formulas decreased. The more SSG deformation interlocking bonds, the stronger the tablet withstands mechanical movements. The friability of the CS-4 to CS-6 tablets is proportional to the BF value and tends to decrease. The CS deformation on the tablet surface has a strong interlocking bond to withstand mechanical movements. The CS-6 tablet is more friable than the CS-5 tablet because of the reduced deformation of SDL as a foundation to resist mechanical movements.

The comparison of the effect of the presence of the disintegrating agent in each tablet formula to friability according to the concentration in the experiment is shown in Figure 8. The friability profile of the three CA-LBG tablets is similar but different at the peak of each disintegrating agent (CA-LBG 1%; CS 2%; SSG 4%). These peaks indicate that the tablet surface has bonds weakly of interlocking deformation and less stable to mechanical movements. The friability value before the peak concentration was also influenced by the release of particles from the SDL deformation, while after the peak concentration was influenced by the quality of the interlocking bond of deformation particles on the tablet surface so resistant to mechanical motion. CA-LBG tablets are more friable than other tablets due to the influence of the coral surface on the particles which tend to be friable when the porosity is not filled with other particles. The high friability profile of CA-LBG tablets appears at low concentrations because the surface porosity of the CA-LBG particles is not filled due to the limited number of CA-LBG particles. In addition, the irregularly shaped CA-LBG particles causing the porosity of tablets were number and wide.

Disintegration time

The evaluation of tablet disintegration rates for all formulas with various disintegrating agents and concentrations is shown in Table 2. The disintegration of tablets containing CA-

LBG showed a fast disintegration time proportional to the increasing concentration of CA-LBG. The value of BF and friability do not affect the function of the CA-LBG to disintegrate the tablet. The irregular particle shape and the corrugated surface of the CA-LBG particles resulted in a tablet with porosity for penetration of the disintegrating medium (Figure 4). The deformation porosity of CA-LBG formed on the tablet is proportional to the CA-LBG concentration in the tablet formula. The porosity of a large number on the tablet cause increases the channel for penetration of the disintegrating medium so that the tablet is disintegrating. The CA-LBG is an ester excipient that has low viscosity and low solubility in water (Table 1). This characteristic causes a repulsive force between deformations of CA-LBG on tablets when wet by disintegration medium. The repulsion force increases in proportion to the CA-LBG concentration in the tablet formula. The repulsive force between the CA-LBG deformations causes the tablets to disintegrate.

Tablets containing SSG showed that SSG concentration, BF value, and friability were influenced the disintegration time. The speed of tablet disintegration time is proportional to the increasing SSG concentration shown in the SSG-1 to SSG-4 tablets. Deformation of SSG in tablets attracts disintegration medium so SSG deformation swells and pushes deformation of other granules and particles to move away from each other so that the tablet is disintegrating. SSG-5 and SSG-6 tablets show the resistance of the tablets to pressure and mechanical movements affect the speed of disintegration. Increased BF value and low tablet friability caused long tablet disintegration time due to the strong interlocking bond between the deformation of granule or particle, thus inhibiting tablet disintegration.

Tablets containing CS showed an increase in CS concentration causing the disintegration time to rapidly. The resistance of tablets indicated by BF value and friability did not affect the function of CS as a tablet disintegrating agent. Tablets containing CS attracts the

disintegrating medium for penetration into the tablet so that the CS deformation swell and push deformation around. The more the CS deformation swell, the faster the tablet integrates.

The comparison of the ability of the disintegrating agent in each tablet formula according to the concentration in the experiment is shown in Figure 9. The time profile for the disintegration of CA-LBG tablets is similar to that of CS tablets because the two disintegrating agents perform their function not influenced by the quality of other tablets so that the increase in concentration is proportional to the increase in disintegration speed. tablet. In contrast to SSG tablets, the disintegration time is also influenced by the hardness and friability of the tablets, thus inhibiting the disintegration process in tablets with SSG concentrations of 8% and 12%. The disintegration time profile of CA-LBG tablets is longer than CS tablets because low solubility of CA-LBG so that the wetting time of CA-LBG tablets is longer and inhibits integration.

Dissolution

Experiments to study drug release from the dosage form were carried out using tablets of 1%, 2%, and 4% concentrations of each disintegrating agent. The effect of the disintegrating agent on the release of diclofenac sodium from the tablet is presented in Figure 10. The dissolution profile of the tablets containing CA-LBG showed that the release of diclofenac sodium from the tablets appeared to be different at 5 and 15 minutes. The higher the CA-LBG concentration on the cause tablet more rapidly disintegrates and releases more diclofenac sodium. All tablets with each concentration of CA-LBG meet the requirements for releasing diclofenac sodium [36].

A comparison of the release profile of diclofenac sodium from tablets with each of the disintegrating agents was shown in the dissolution profile (Figure 11). Tablets containing CA-LBG showed a slower release of diclofenac sodium than tablets containing SSG and CS

because of the gradual release at 5 and 15 minutes. The low solubility of CA-LBG inhibits the wetting of the tablets for disintegration thus inhibiting the solubility of diclofenac sodium in the dissolution medium.

Conclusion

Synthesis conditions using 0.24 mol HCl to produce CA-LBG 9.48 cP. Increasing the concentration of HCl in the synthesis causes a decrease in the viscosity of CA-LBG due to an increase in CA molecules bound to LBG. The presence of CA-LBG as a disintegrating agent has variation effects to thickness, break force, tensile strength, friability according to the concentration used. In the formulation process, increasing the concentration of CA-LBG in the tablet mass decreased the flow rate and increased compressibility. The increase in the concentration of CA-LBG in tablets accelerated the disintegration of tablets without the influence of other tablet parameters. The CA-LBG disintegration activity through repulsion between CA-LBG deformation on the tablet when wetted with disintegration medium. The repulsion force occurs due to the character of CA-LBG which has low solubility and low viscosity.

References

1. Das N, Triparthi N, Basu S, Bose C, Maitra S, Khurana S. Progress in the development of gelling agents for improved culturability of microorganisms. Front Microbiol. 2015;6:1–7.

2. Dey P, Maiti S, Sa B. Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide. J Biomater Sci Polym Ed. 2013;24:663–83.

3. Dionísio M, Grenha A. Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci. 2012;4:175–85.

4. Sheskey, Paul J Cook, Walter G Cable, Colin G. Handbook of Pharmaceutical Excipients

8th. London-Washington DC: Pharmaceutical Press and American Pharmacists Association; 2017.

5. Chudzikowski RJ. Guar gum and its applications. J Soc Cosmet Chem. 1971;22:43–60.

6. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Esterification of citric acid with locust bean gum. Heliyon. Elsevier Ltd; 2019; 5: e02337. https://doi.org/10.1016/j.heliyon.2019.e02337

7. Hadinugroho W, Martodihardjo S, Fudholi A, Riyanto S. Study of a catalyst of citric acid crosslinking on locust bean gum. J Chem Technol Metall. 2017;52:1086–91.

8. Samavati V, Razavi SH, Rezaei KA, Aminifar M. Intrinsic viscosity of locust bean gum and sweeteners mixture in dilute solutions. Electron J Environ Agric Food Chem. 2007;6:1879–89.

9. Tamaki Y, Teruya T, Tako M. The chemical structure of galactomannan isolated from seeds of Delonix regia. Biosci Biotechnol Biochem. 2010;74:1110–2.

10. Bhattacharya A, Rawlins JW, Ray P. Polymer Grafting and Crosslinking. Polym. Grafting Crosslink. Canada: A John Wiley & Sons, Inc, Publication; 2008.

11. Colas A. Cow Corning Silicones : Preparation Properties and Performance. Materials. Midland; 2005.

12. Santiago, E. V., Lopez, S. H. A, Romero AR. Photochemical cross-linking study of polymers containing diacetylene groups in their main chain and azobenzene compounds as pendant groups. Superf y vacío. 2006;19:1–7.

13. Tjandraatmadja GF, Burn LS, Jollands MJ. The effects of ultraviolet radiation on polycarbonate glazing. Proc 8th Int Conf Durab Build Constr Mater Vancouver, Canada. 1999;30:884–98.

14. Yeh CC, Chen CN, Li YT, Chang CW, Cheng MY, Chang HI. The effect of polymer molecular weight and UV radiation on physical properties and bioactivities of PCL films.

Cell Polym. 2011;30:261–76.

15. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res. Pharmaceutical Research; 2017;34:890–917.

16. Gulrez SKH, Al-Assaf S, Phillips GO. Hydrogels: Methods of Preparation, Characterisation and Applications. Prog Mol Environ Bioeng - From Anal Model to Technol Appl. 2011.

17. Michael E. Aulton, Kevin M. G. Taylor. Aulton's Pharmaceutics The Design and Manufacture of Medicines. BMC Public Health. New York: Churchill Livingstone Elsevier; 2017.

18. The United States Pharmacopeial Convention. Pharmacopeia 41-National Formulary 36. 41st ed. Rockville: Twinbrook Parkway; 2018.

19. Shang C, Sinka IC, Jayaraman B, Pan J. Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. Int J Pharm. Elsevier B.V.; 2013;442:57–64. http://dx.doi.org/10.1016/j.ijpharm.2012.09.005

20. Pitt KG, Newton JM, Richardson R, Stanley P. The Material Tensile Strength of Convex-faced Aspirin Tablets. J Pharm Pharmacol. 1989;41:289–92.

21. Uday Kumar M, Babu K. Design and evaluation of fast dissolving tablets containing diclofenac sodium using fenugreek gum as a natural superdisintegrant. Asian Pac J Trop Biomed. Hainan Medical University; 2014;4:S329–34. http://dx.doi.org/10.12980/APJTB.4.2014B672

22. Hammami MM, Hussein RF, Alswayeh R, Alvi SN. Eight enteric-coated 50 mg diclofenac sodium tablet formulations marketed in Saudi Arabia: In vitro quality evaluation. BMC Res Notes. BioMed Central; 2020;13:1–6. https://doi.org/10.1186/s13104-020-05270-4

23. Bertocchi P, Antoniella E, Valvo L, Alimonti S, Memoli A. Diclofenac sodium multisource prolonged release tablets - A comparative study on the dissolution profiles. J Pharm

Biomed Anal. 2005;37:679–85.

24. Zupančič Bozič D, Vrečer F, Kozjek F. Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur J Pharm Sci. 1997;5:163–9.

25. Ghasemi J, Niazi A, Ghobadi S. Simultaneous spectrophotometric determination of benzyl alcohol and diclofenac in pharmaceutical formulations by chemometrics method. J Chinese Chem Soc. 2005;52:1049–54.

26. Gouda AA, Kotb El-Sayed MI, Amin AS, El Sheikh R. Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: A review. Arab J Chem. 2013;6:145–63. http://dx.doi.org/10.1016/j.arabjc.2010.12.006

27. Coates J. Interpretation of Infrared Spectra, A Practical Approach. Encycl Anal Chem. 2006;10815–37.

28. Doll KM, Shogren RL, Willett JL, Swift G. Solvent-free polymerization of citric acid and D-sorbitol. J Polym Sci Part A Polym Chem. 2006;44:4259–67.

29. Jans AWH, Kinne RKH. 13C NMR spectroscopy as a tool to investigate renal metabolism. Kidney Int. 1991;39:430–7.

30. Zhang Y ling, Zhao C xia, Liu X dong, Li W, Wang J long, Hu Z guang. Application of poly(aspartic acid-citric acid) copolymer compound inhibitor as an effective and environmental agent against calcium phosphate in cooling water systems. J Appl Res Technol. 2016;14:425–33.

31. Azero EG, Andrade CT. Characterisation of Prosopis juliflora seed gum and the effect of its addition to κ-carrageenan systems. J Braz Chem Soc. 2006;17:844–50.

32. Bhatia H, Gupta PK, Soni PL, Division C. Extraction , Purification and Characterization of a Galactomannan From Prosopis Juliflora (Sw .) Dc . Seed. Int J Sci Enviroment Technol.

2013;2:708–24.

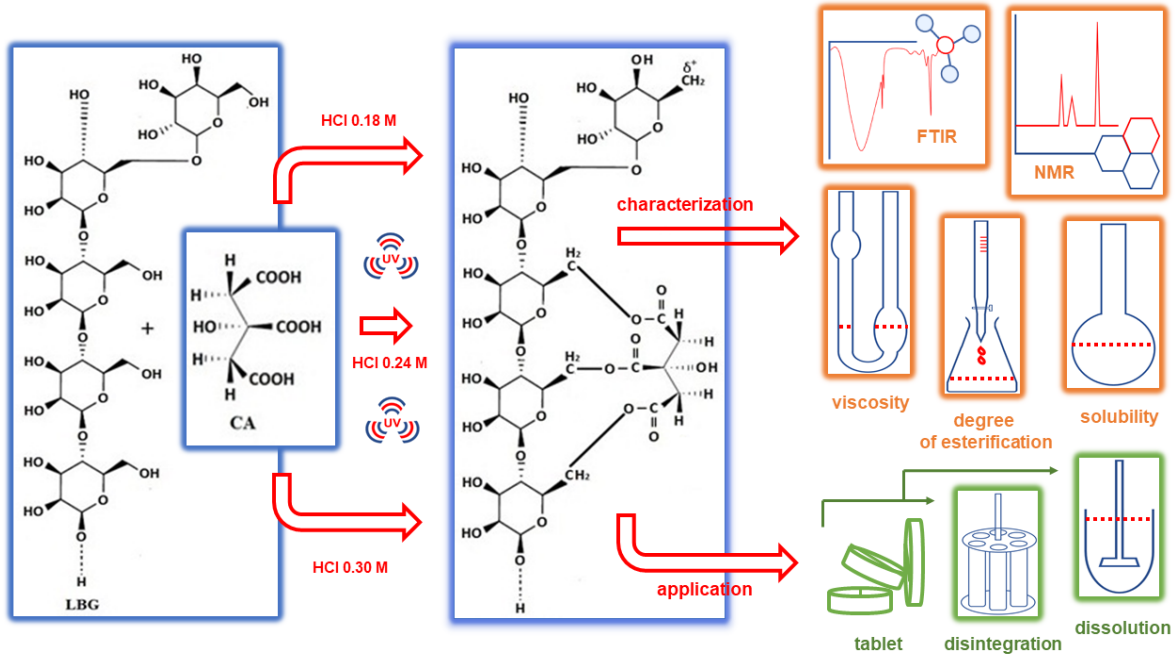
33. Gillet S, Aguedo M, Blecker C, Jacquet N, Richel A. Use of 13C-NMR in structural elucidation of polysaccharides: case of locust bean gum. Young Belgium Magn. Reson. Sci. Liege: University of Liege; 2014.

34. Parvathy KS, Susheelamma NS, Tharanathan RN, Gaonkar AK. A simple non-aqueous method for carboxymethylation of galactomannans. Carbohydr Polym. 2005;62:137–41.

35. Szumilo M, Belniak P, Swiader K, Holody E, Poleszak E. Assessment of physical properties of granules with paracetamol and caffeine. Saudi Pharm J. King Saud University; 2017;25:900–5. http://dx.doi.org/10.1016/j.jsps.2017.02.009

36. Directorate General of Medicine and Food. Indonesian Pharmacopoeia 4th edition. Jakarta: Ministry of Health Republic of Indonesia; 1995.

Graphical Abstract



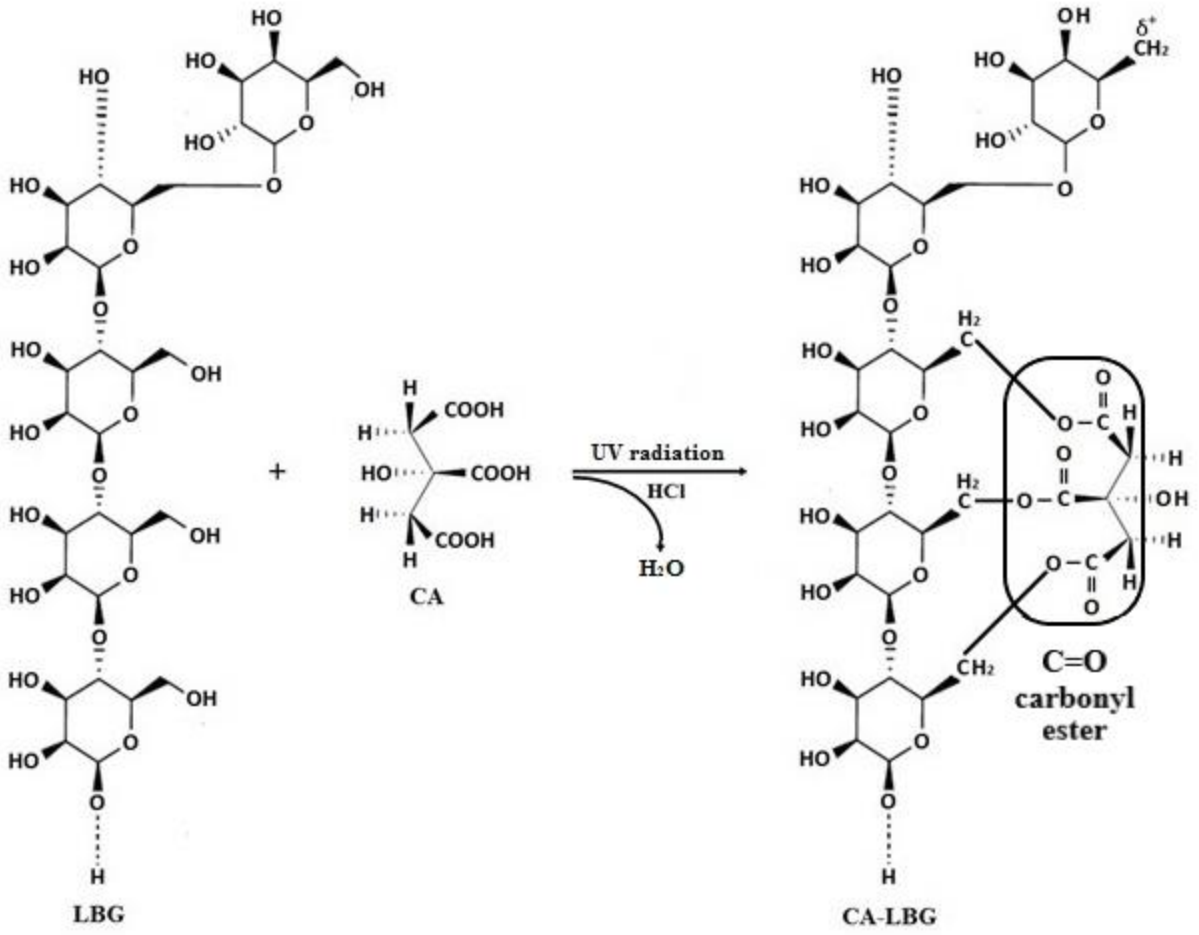


Figure 1. CA-LBG production mechanism. Synthesis of CA-LBG was carried out by adding 0.42 M CA to 7.10 x 10-6 M LBG which had swollen. The mixture was added with HCl (0.18-0.42 M) and UV irradiated (100 minutes).

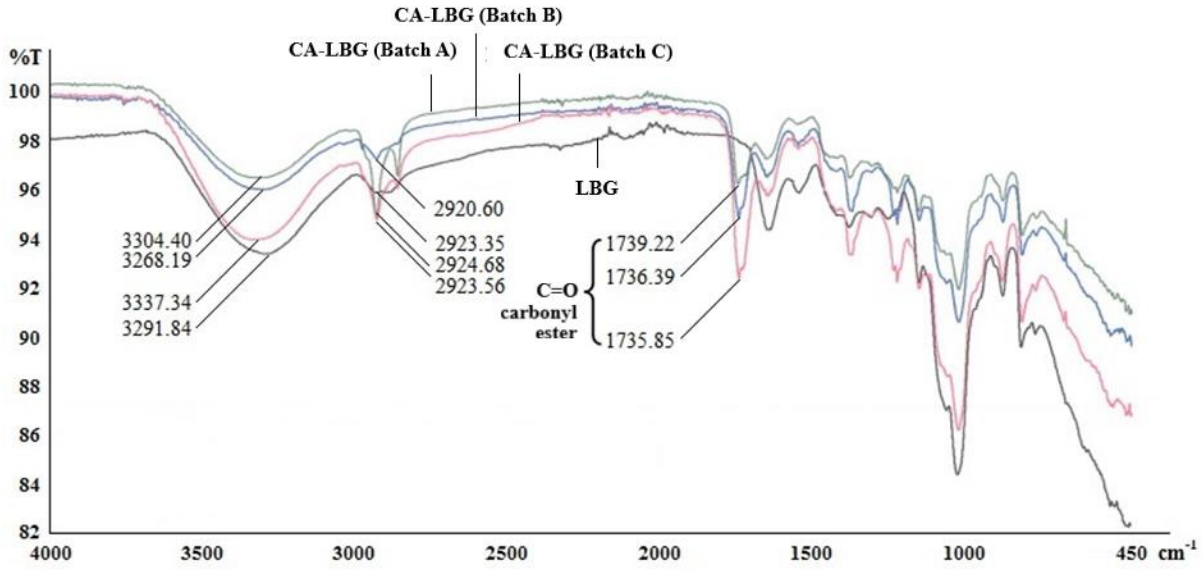


Figure 2. FTIR spectrum of LBG and CA-LBG. LBG as a comparison is shown in black spectra. CA-LBG was synthesized using a 0.18 M HCl catalyst (Batch A) shown in green spectra. CA-LBG was synthesized using a 0.24 M HCl catalyst (Batch B) shown in blue spectra. CA-LBG was synthesized using 0.30 M HCl catalyst (Batch C) shown in red spectra. The carbonyl ester group (C=O) is a specific group that presents at CA-LBG and absent at LBG.

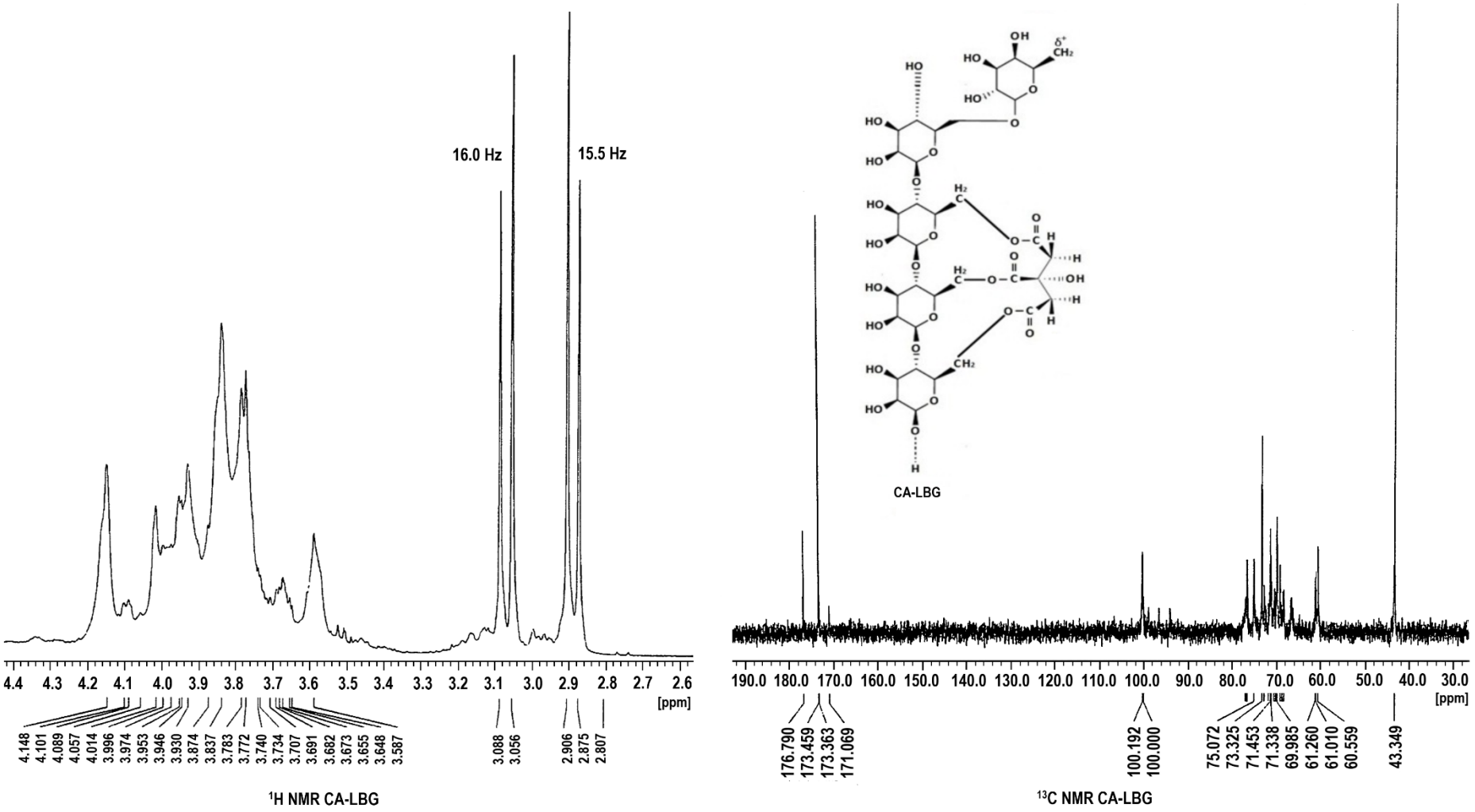
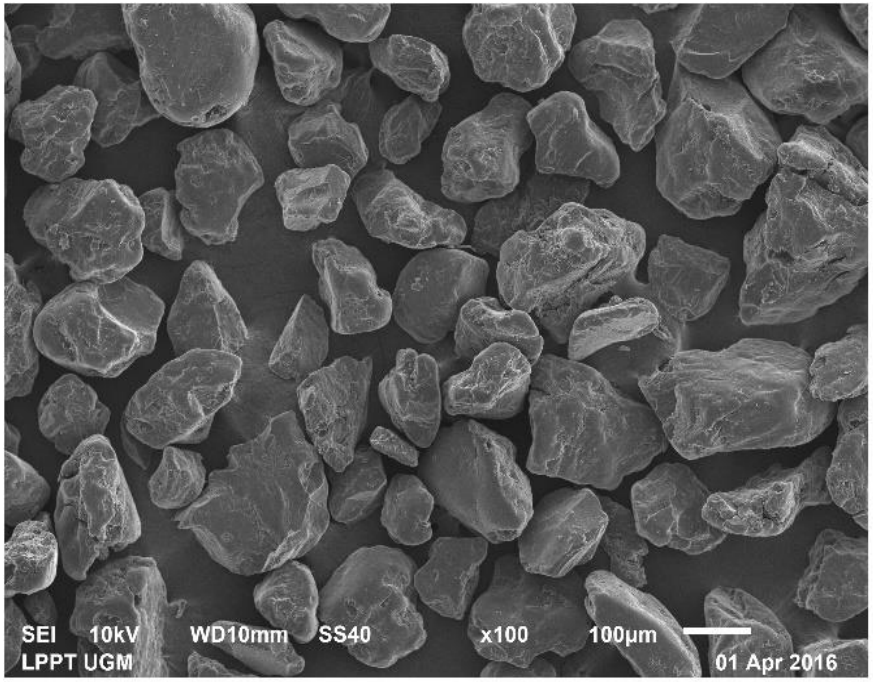
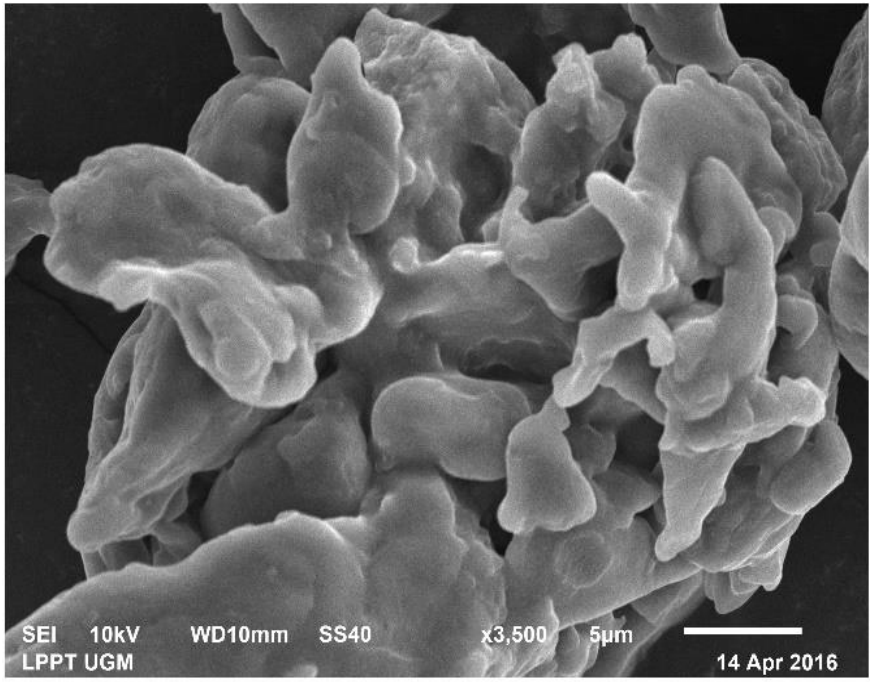


Figure 3. ^{1}H NMR and ^{13}C NMR spectrum of CA-LBG representative (Batch B). CA-LBG was synthesized using catalyst 0.24 M HCl. The presence of CA at CA-LBG was shown in the peaks of a, b, c, d, and e.



CA-LBG [magnification 100x]



CA-LBG [magnification 3500x]

Figure 4. SEM images of CA-LBG representative, synthesized using catalyst 0.24 M HCl (Batch B)

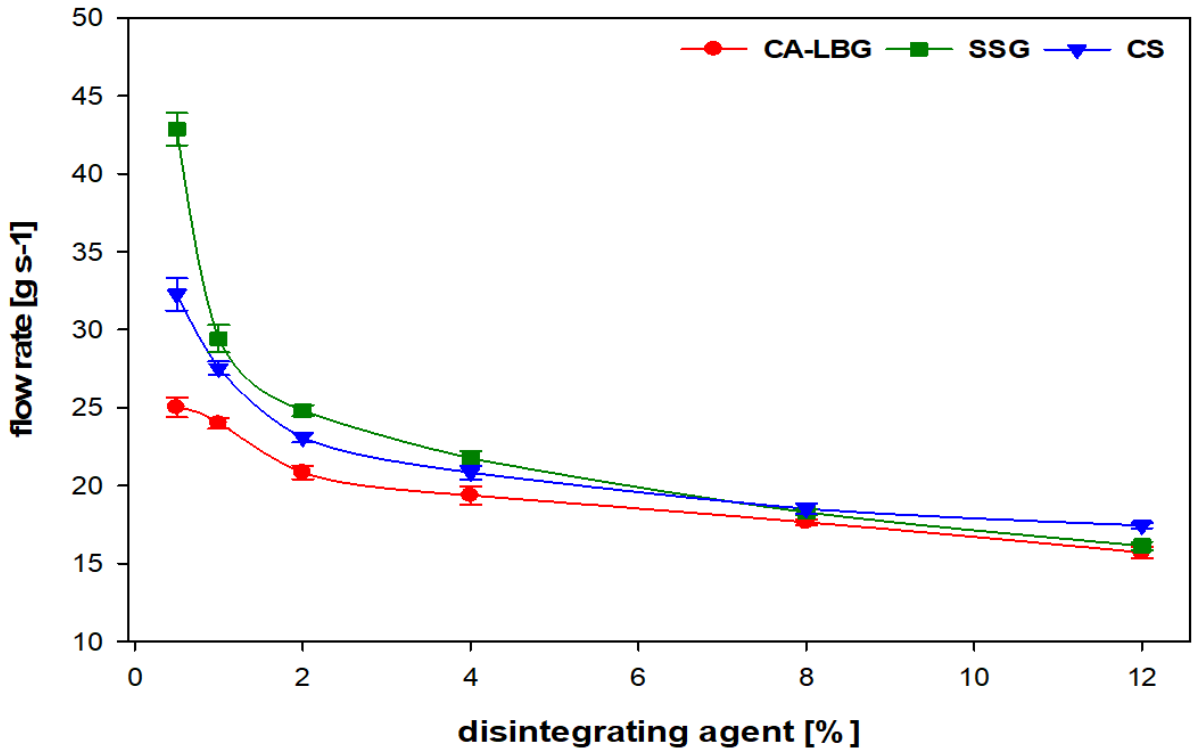


Figure 5. The flow rate profile of the mass of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

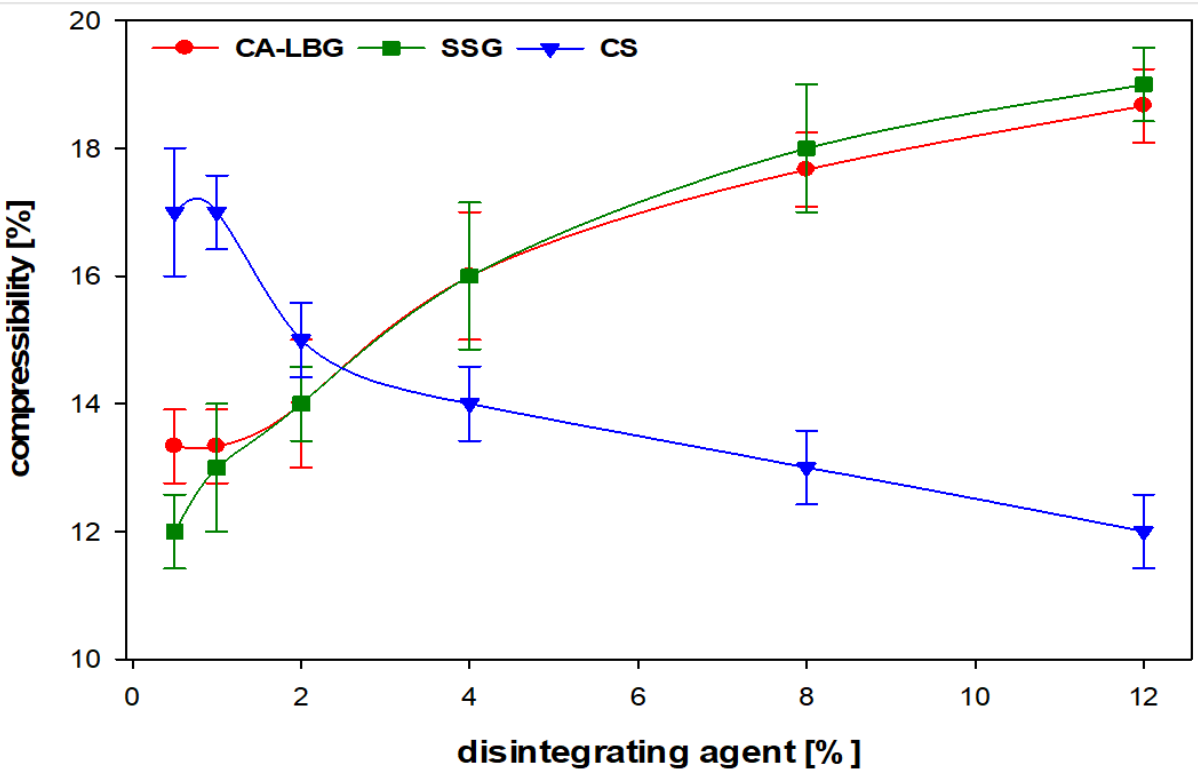


Figure 6. The compressibility profile of the tablet mass contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

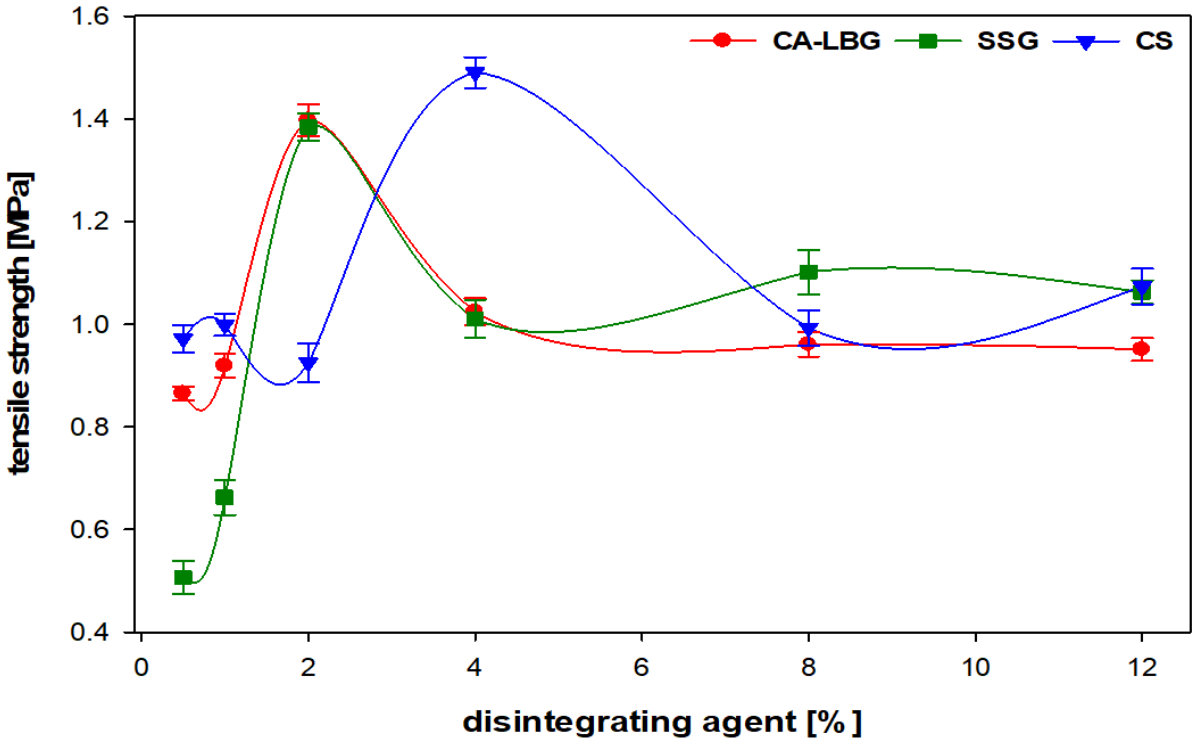


Figure 7. The tensile strength profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

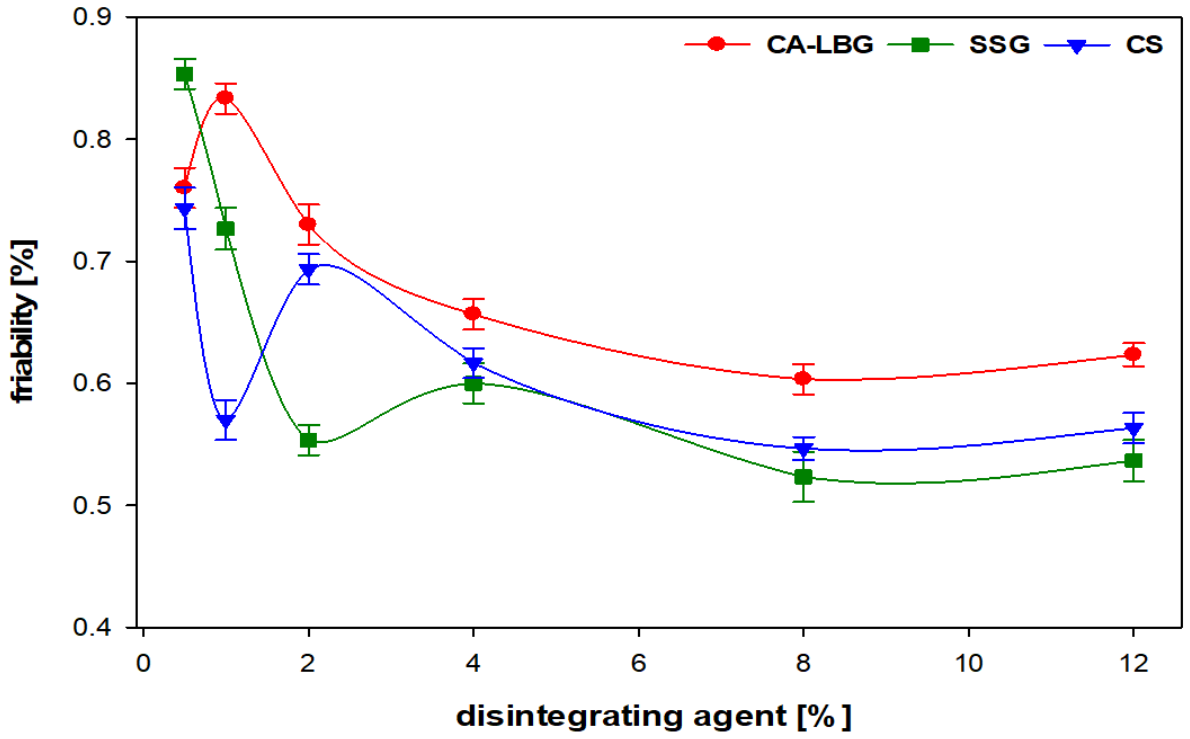


Figure 8. The friability profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

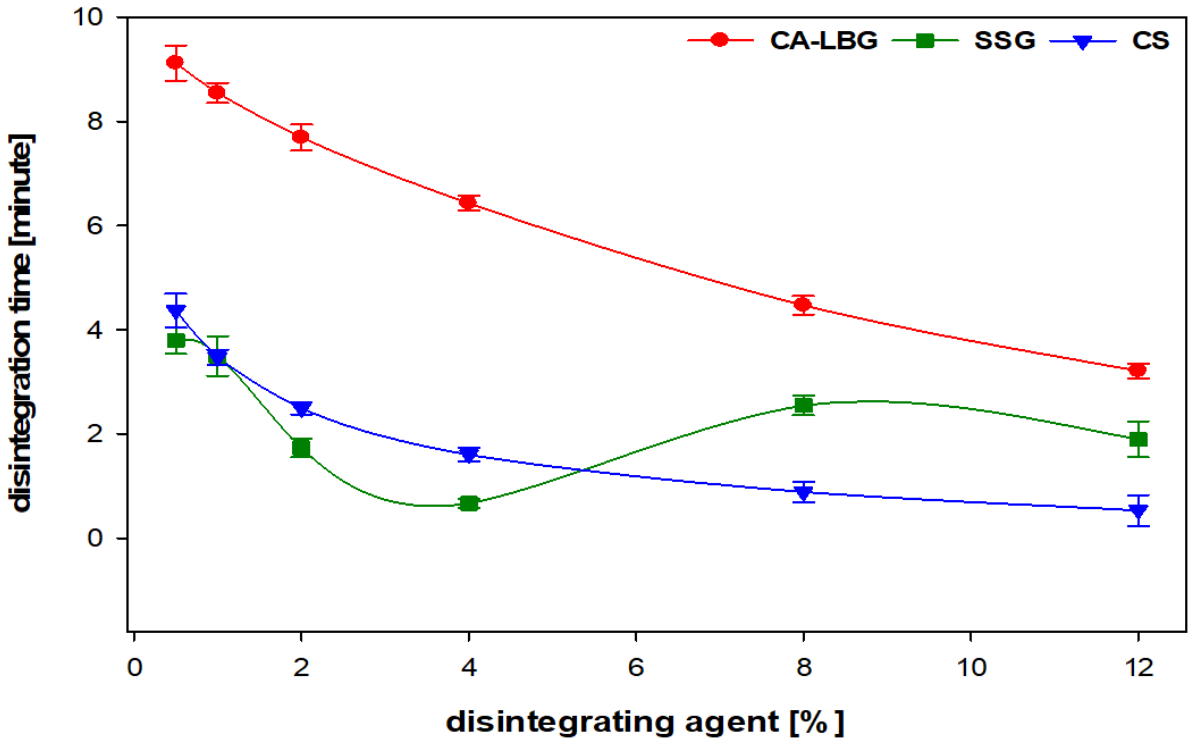


Figure 9. The disintegration time profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 0.5%; 1%; 2%; 4%; 8%; and 12%.

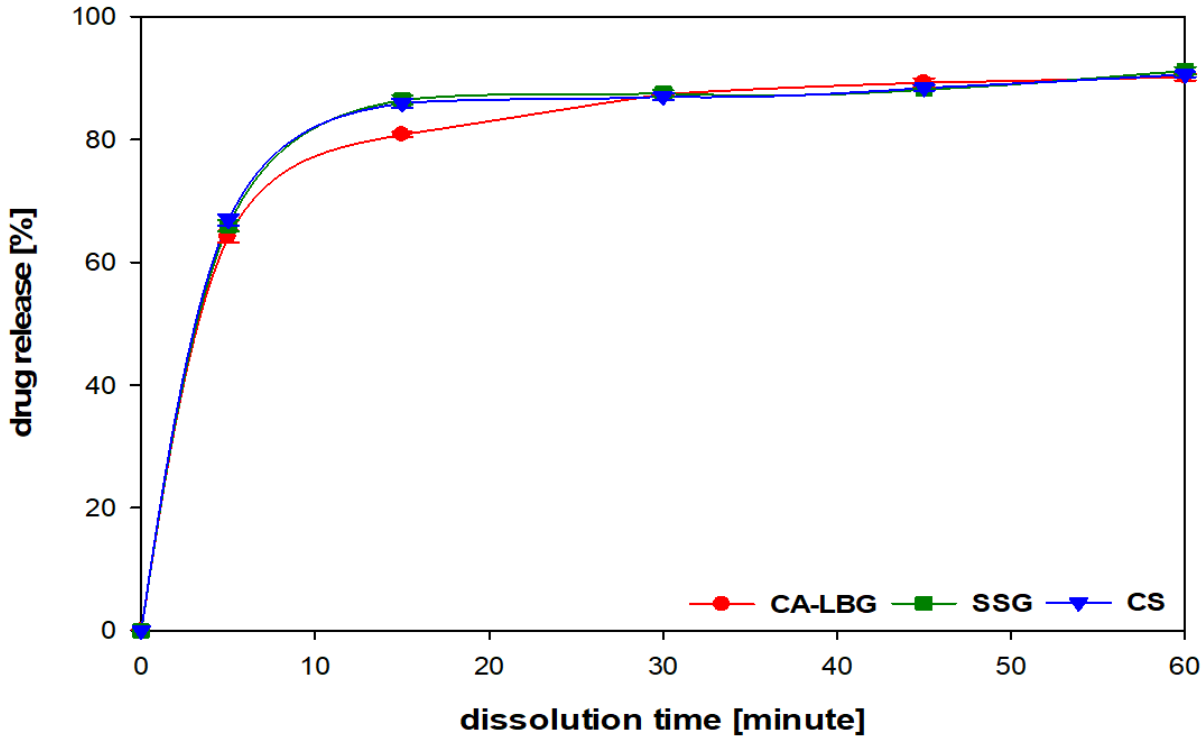
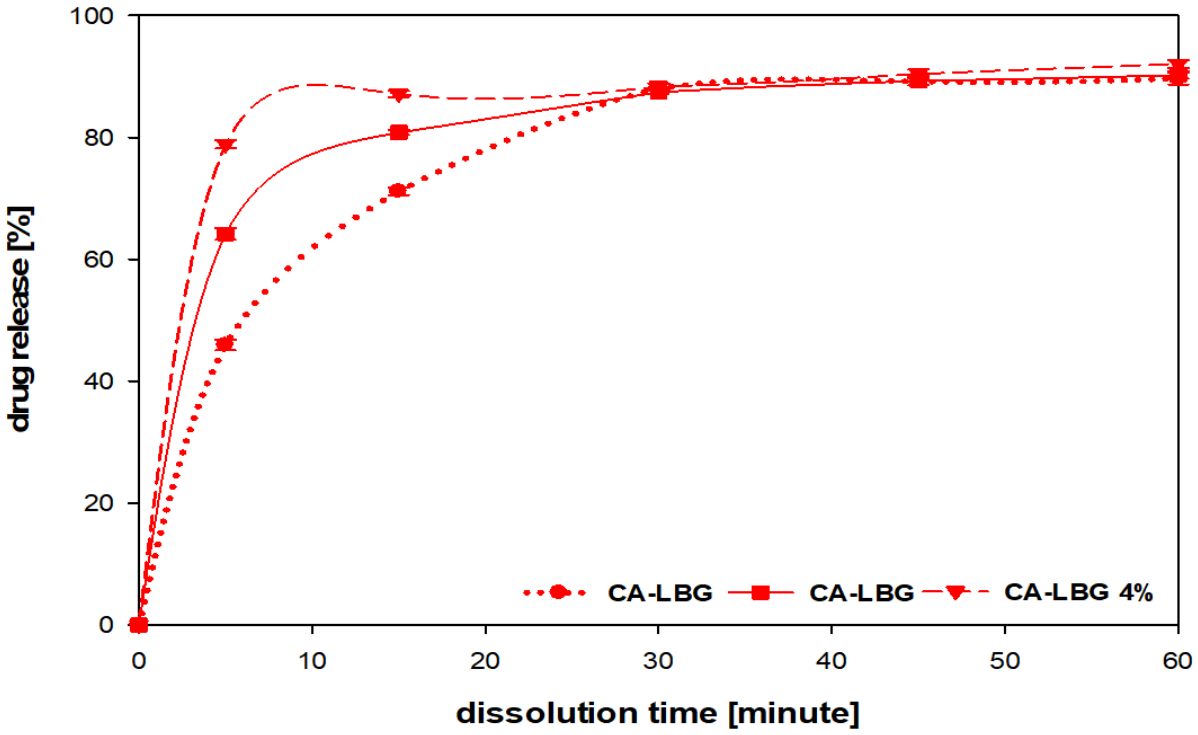


Figure 10. The dissolution profile of the tablet contains a disintegrating agent. The concentration of each disintegrating agent 2%.



106

107 **Figure 11.** The dissolution profile of the tablet contains CA-LBG 1%; 2% and 4%.

Table (must NOT contain author information)

Table 1. Detail synthesis of CA-LBG using the concentration of HCl and irradiated with UV (254 nm,100 minutes). Value physical parameters of CA-LBG: yield, the degree of esterification, carbonyl ester wavelength, solubility, and viscosity.

Batch Code	LBG 10^{-6} [mol]	CA [mol]	HCl [mol]	Carbonyl Ester [cm^{-1}]	Yield [%]	Degree of Esterification [%]	Solubility [%]	Viscosity [cP]
A	7.10	0.42	0.18	1739.22	26.62 ± 0.05	8.27 ± 0.19	36.63 ± 1.14	11.20 ± 0.10
B	7.10	0.42	0.24	1736.39	27.13 ± 0.09	9.13 ± 0.13	29.30 ± 1.16	9.48 ± 0.06
C	7.10	0.42	0.30	1735.85	27.66 ± 0.06	9.69 ± 0.23	22.64 ± 1.15	7.76 ± 0.07

Table 2. Details of tablet formulations using disintegrating agents. Evaluate the physical quality of the tablet mass and the tablet.

formula code	disintegrating agent			flow time	ρ_{tapped}-ρ_{bulk}	actual weight	thickness	break force	friability	disintegration time
	CA-LBG	SSG	CS							
	[%]	[%]	[%]	[sec.]	[g.mL^{-1}]	[mg]	[mm]	[kp]	[%]	[min.]
CL-1	0.5	-	-	4.0 ± 0.10	0.041 ± 0.00	201.0 ± 0.25	4.39 ± 0.01	4.0 ± 0.06	0.76 ± 0.02	9.12 ± 0.34
CL-2	1	-	-	4.2 ± 0.06	0.041 ± 0.00	201.2 ± 0.47	4.38 ± 0.01	4.2 ± 0.10	0.83 ± 0.01	8.54 ± 0.19
CL-3	2	-	-	4.8 ± 0.10	0.044 ± 0.01	201.2 ± 0.12	4.40 ± 0.01	6.4 ± 0.15	0.73 ± 0.02	7.69 ± 0.25
CL-4	4	-	-	5.2 ± 0.15	0.053 ± 0.01	201.1 ± 0.21	4.41 ± 0.01	4.7 ± 0.12	0.66 ± 0.01	6.43 ± 0.14
CL-5	8	-	-	5.7 ± 0.06	0.059 ± 0.01	200.9 ± 0.26	4.38 ± 0.01	4.4 ± 0.10	0.60 ± 0.01	4.47 ± 0.18
CL-6	12	-	-	6.4 ± 0.15	0.061 ± 0.00	201.1 ± 0.36	4.39 ± 0.01	4.4 ± 0.12	0.62 ± 0.01	3.21 ± 0.14
SSG-1	-	0.5	-	2.3 ± 0.06	0.036 ± 0.00	200.8 ± 0.06	4.40 ± 0.01	2.3 ± 0.15	0.85 ± 0.01	3.79 ± 0.25
SSG-2	-	1	-	3.4 ± 0.10	0.042 ± 0.00	201.1 ± 0.44	4.38 ± 0.01	3.0 ± 0.15	0.73 ± 0.02	3.49 ± 0.38
SSG-3	-	2	-	4.0 ± 0.06	0.047 ± 0.01	201.0 ± 0.51	4.35 ± 0.01	6.3 ± 0.12	0.55 ± 0.01	1.73 ± 0.18
SSG-4	-	4	-	4.6 ± 0.10	0.051 ± 0.00	200.7 ± 0.21	4.37 ± 0.01	4.6 ± 0.17	0.60 ± 0.02	0.67 ± 0.09
SSG-5	-	8	-	5.5 ± 0.06	0.057 ± 0.00	201.1 ± 0.32	4.38 ± 0.01	5.0 ± 0.21	0.52 ± 0.02	2.55 ± 0.19
SSG-6	-	12	-	6.2 ± 0.10	0.063 ± 0.00	200.7 ± 0.15	4.38 ± 0.01	4.9 ± 0.12	0.54 ± 0.02	1.90 ± 0.35
CS-1	-	-	0.5	3.1 ± 0.10	0.056 ± 0.00	200.8 ± 0.60	4.43 ± 0.01	4.5 ± 0.12	0.74 ± 0.02	4.37 ± 0.33
CS-2	-	-	1	3.6 ± 0.06	0.052 ± 0.00	200.8 ± 0.35	4.46 ± 0.01	4.7 ± 0.10	0.57 ± 0.02	3.47 ± 0.15
CS-3	-	-	2	4.3 ± 0.06	0.050 ± 0.00	201.0 ± 0.31	4.42 ± 0.01	4.3 ± 0.17	0.69 ± 0.01	2.49 ± 0.12
CS-4	-	-	4	4.8 ± 0.10	0.045 ± 0.00	201.1 ± 0.60	4.40 ± 0.01	6.9 ± 0.12	0.62 ± 0.01	1.60 ± 0.13
CS-5	-	-	8	5.4 ± 0.10	0.038 ± 0.00	201.2 ± 0.35	4.34 ± 0.01	4.5 ± 0.15	0.55 ± 0.01	0.89 ± 0.20
CS-6	-	-	12	5.7 ± 0.06	0.038 ± 0.01	200.9 ± 0.15	4.45 ± 0.01	5.0 ± 0.15	0.56 ± 0.01	0.53 ± 0.30

RE: Decision on your manuscript #JOPI-D-21-00339R1 [JOPI] [AU] [STATUS] [R]

Dari: Jed Joseph Adel (jedjoseph.adel@springernature.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Senin, 13 September 2021 pukul 08.37 GMT+7

Dear Dr. Hadinugroho,

Thank you for your email.

Please be informed that I addressed your concern to Dr. Scypinski to provide further details regarding with the minor revision decision on your paper.

Rest assure that you will be notified once updates received.

Kind regards,

Jed

Jed Joseph Adel
(he/him/his)
JEO Assistant
Journals Editorial Office (JEO)

Springer Nature
T +1-818-665-3733| +1-818-665-3734

JedJoseph.Adel@springernature.com
springernature.com

--

From: Wuryanto Hadinugroho <wuryanto.hadinugroho@ymail.com>
Sent: Saturday, September 11, 2021 11:56 AM
To: Jed Joseph Adel <jedjoseph.adel@springernature.com>
Subject: Re: Decision on your manuscript #JOPI-D-21-00339R1

[External - Use Caution]

Dear
Prof. Stephen Scypinski
Editor-in-Chief
Journal of Pharmaceutical Innovation

Thank you for your email. Regarding the manuscript revision process that my team will do, I ask for information. Where can I find new comments from reviewers? In the comments column in the email, I did not find any comments. I also didn't find any new documents attached to the View Attachments column https://www.editorialmanager.com/jopi/l.asp?i=48098&l=2FGZ8OZG

On August 30th, 2021, I have received the manuscript decision by email from Prof. Robert A Lodder by attaching reviewer comments and documents in the View Attachments column. I have submitted a revised manuscript on September 5th, 2021, as directed by the editorial manager.

I ask for information if the revised manuscript that I have sent has shortcomings and does not comply with the procedure. My team will gladly revise if there are still corrections and suggestions from reviewers or editors.

Thank you for your attention and cooperation.

Yours sincerely,
Wuryanto Hadinugroho

Pada Sabtu, 11 September 2021 02.01.28 WIB, Journal of Pharmaceutical Innovation <em@editorialmanager.com> menulis:

Dear Dr Hadinugroho:

We have received the reports from our advisors on your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms", which you submitted to Journal of Pharmaceutical Innovation.

Based on the advice received, your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions.
When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments.
Your list of responses should be uploaded as a file in addition to your revised manuscript.

In order to submit your revised manuscript electronically, please access the following web site:

https://www.editorialmanager.com/jopi/

Your username is: wuryanto.hadinugroho@ymail.com
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.

Please click "Author Login" to submit your revision.

We look forward to receiving your revised manuscript.

Sincerely yours,

Stephen Scypinski

Journal of Pharmaceutical Innovation

COMMENTS FOR THE AUTHOR:

Please note that this journal is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted.

Authors may need to take specific actions to achieve compliance with funder and institutional open access mandates. If your research is supported by a funder that requires immediate open access (e.g. according to Plan S principles) then you should select the gold OA route, and we will direct you to the compliant route where possible. For authors selecting the subscription publication route our standard licensing terms will need to be accepted, including our self-archiving policies. Those standard licensing terms will supersede any other terms that the author or any third party may assert apply to any version of the manuscript.

 Find out more about compliance

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Acknowledgement of Receipt of #JOPI-D-21-00339R2

Dari: Journal of Pharmaceutical Innovation (em@editorialmanager.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Selasa, 28 September 2021 pukul 20.36 GMT+7

Dear Dr Hadinugroho:

We acknowledge, with thanks, receipt of the revised version of your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms", submitted to Journal of Pharmaceutical Innovation. The manuscript number is JOPI-D-21-00339R2.
You may check the status of your manuscript at any time by accessing the following web site:

https://www.editorialmanager.com/jopi/

Your username is: wuryanto.hadinugroho@ymail.com
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.

We will inform you of the Editor's decision as soon as possible.

Best regards,

The Editorial Office
Journal of Pharmaceutical Innovation

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Decision on your manuscript #JOPI-D-21-00339R2 - [EMID:4c7dafbffbba5b42]

Dari: Journal of Pharmaceutical Innovation (em@editorialmanager.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Minggu, 3 Oktober 2021 pukul 21.53 GMT+7

Dear Dr Hadinugroho:

I am pleased to inform you that your manuscript, "Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the disintegrating agent of tablet dosage forms" has been accepted for publication in Journal of Pharmaceutical Innovation.

For queries regarding your accepted paper, you may email the following contacts in regards to your concern.

https://www.springer.com/journal/12247/contact-the-journal?IFA

Please remember to always include your manuscript number, #JOPI-D-21-00339R2, whenever inquiring about your manuscript.
Thank you.

Sincerely,

Stephen Scypinski

Journal of Pharmaceutical Innovation

Please note that this journal is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted.

Authors may need to take specific actions to achieve compliance with funder and institutional open access mandates. If your research is supported by a funder that requires immediate open access (e.g. according to Plan S principles) then you should select the gold OA route, and we will direct you to the compliant route where possible. For authors selecting the subscription publication route our standard licensing terms will need to be accepted, including our self-archiving policies. Those standard licensing terms will supersede any other terms that the author or any third party may assert apply to any version of the manuscript.

 Find out more about compliance

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/jopi/login.asp?a=r). Please contact the publication office if you have any questions.

Your article in Journal of Pharmaceutical Innovation is now online

Dari: Springer (springeralerts@springeronline.com)
Kepada: wuryanto.hadinugroho@ymail.com
Tanggal: Selasa, 12 Oktober 2021 pukul 18.03 GMT+7

Online First: your article is published 2021-10-12

Congratulations

Dear Author,

We are pleased to inform you that your article has just been published:

Title
Preparation of Citric Acid-Locust Bean Gum (CA-LBG) for the Disintegrating Agent of Tablet Dosage Forms

Journal
Journal of Pharmaceutical Innovation, (), 1-16

DOI
10.1007/s12247-021-09591-0

Your article is available as 'Online First':
http://link.springer.com/article/10.1007/s12247-021-09591-0

We're committed to making your article as accessible and discoverable as possible:

- Your article is fully accessible to all users at libraries and institutions that have purchased access to SpringerLink.
- SharedIt: Springer Nature's innovative content-sharing initiative means that research articles can also be posted anywhere. Find out more.
- Open access: If your article is published open access, it will be freely accessible to any user, immediately, with no access fees. Open access also allows for unrestricted re-use. Find out more.

Announce your publication
We encourage you to forward this email to your co-authors. Additionally we recommend you mention your article's publication and its DOI on your website or your social media profiles.
Use the buttons below to share your article on social media.

Citation Information
Your article can be cited by its DOI 10.1007/s12247-021-09591-0 in the following form:

Author, Journal Title, Year, DOI

We will notify you once your article completed production and is assigned to a specific journal issue. After that any additional (printed) offprints or posters you might have ordered will be shipped to you.

Author services to amplify your research
From video abstracts to article metrics to research data support, find out about the author services and how these could benefit you and your research.
Read more.

Thank you again for publishing with Springer. We look forward to your future contributions!

Best regards,

Alison Mitchell
Managing Director Journals

Did you know?
If you are using an ORCID iD and allow for auto-update, your article will appear in your ORCID record automatically. ORCID iDs create a unique, persistent and internationally recognized identifier that attaches your identity to your work, such as articles and their citations. More on ORCID benefits at springernature.com/orcid .