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Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives

Wuryanto Hadinugroho[1]

[1] *Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, 60112, Indonesia.*

**Corresponding Author e-mail: wuryanto.hadinugroho@ymail.com*

1. Abstract

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. CA-LBG is a compound derived from the esterification of citric acid (CA) with locust bean gum (LBG). The experiment aimed to determine the potential and effect of CA-LBG as a glidant on microcrystalline cellulose (MCC). The CA-LBG concentrations in the experiments were 0.5%, 1%, 2%, and 4%. Talc and magnesium stearate (MgS) as a comparison. The mixtures were evaluated for flow rate and angle of repose. The mixture was compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability. The flow rate of the mixture containing CA-LBG 0.5%-4% was 12.77 $g.sec^{-1}$-15.96 $g.sec^{-1}$. The angle of repose of the mixture containing CA-LBG 0.5%-4% is 32.62°-35.52°. The weight of tablets containing CA-LBG 0.5%-4% is 700.0 mg-701.2 mg. The hardness of tablets containing CA-LBG 0.5%-4% is 6.30 kp-6.90 kp. The friability of tablets containing CA-LBG 0.5%-4% is 0.17%-0.36%. The CA-LBG has the potential as a glidant in MCC fillers. Increasing CA-LBG concentration causes the flow rate to increase, the angle of repose to decrease, and the hardness to increase. CA-LBG concentrations of 0.5% and 4% reduced tablet friability.

Keywords: CA-LBG, citric acid, esterification, glidant, locust bean gum

2. Introduction

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. The published uses of CA-LBG are as a tablet disintegration agent and negative matrix in controlled-release tablets (Hadinugroho et al., 2023; Hadinugroho, Martodihardjo, et al., 2022). CA-LBG is an ester material derived from the esterification of citric acid (CA) with locust bean gum (LBG) under acidic conditions. CA-LBG has been characterized by carbonyl ester group,

solubility, viscosity, esterified CA, glass transition temperature, crystallinity index, and particle morphology. CA-LBG particles have a non-polar and hydrophobic tendency, so CA-LBG has low solubility in water (Hadinugroho et al., 2017, 2019). CA-LBG is irregular in shape and has a wavy surface (Hadinugroho et al., 2017, 2019). This character can act as a glidant in granules or filler.

Glidant is a material that can interact with filler particles to improve flow properties. Glidant particles will be on the surface of the filler particles to cover porosity and smooth the surface of the filler particles. Changing the surface of the filler particles improves the movement of each particle(Awad et al., 2020). Glidant materials often used in pharmaceutical preparation formulations are talc and magnesium stearate (MgS). Talc and MgS particles are fines powders, hydrophobic, insoluble in water, irregular in shape and platy wavy (Lakio et al., 2013; Meng et al., 2022; Sheskey et al., 2017; Zarmpi et al., 2020). This character is similar to CA-BG particles, so CA-LBG has the potential to be a glidant agent.

The experiments aimed to determine the potential and influence of CA-LBG as a glidant on cellulose derivative fillers. The experiment used microcrystalline cellulose (MCC), commonly used as a filler in tablet formulations. The experiment used CA-LBG with concentrations of 0.5%, 1%, 2%, and 4%. Talc and magnesium stearate were used as a comparison with the same concentration. Each mixture was evaluated for flow rate and angle of repose. The mixture is then compressed directly into tablets 700 mg. Tablets were evaluated for weight, hardness, and friability. MCC was chosen as the filler model in this experiment because MCC is a filler that is often used in tablets using the direct compression method. MCC particles are water-insoluble, irregularly oval, porosity, and hydrophobic (Lakio et al., 2013; Sheskey et al., 2017).

The novelty of this experiment is using CA-LBG as a glidant in MCC tablet filler to observe its potency and effect at various concentrations. This experiment explores the function of CA-LBG as a glidant for tablet formulation. In addition, the experiment's success provides a choice of future glidant in pharmaceutical excipients.

3. Experimental Section

3.1. Materials

The materials are locust bean gum (food grade) (Viscogum, Cargill, France), citric acid monohydrate (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (pro analysis)

(Sigma Aldrich Chemie, GmbH, USA), water for injection (sterile water) (PT. Otsuka Indonesia), distilled water (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (technical grade) (Cawan Anugerah Chemika, Indonesia), spray dried lactose (food grade) (FlowLac 90, Meggle GmbH & Co. KG, Germany), talc (food grade) (PT. Bratachem, Indonesia) and magnesium stearate (food grade) (PT. Bratachem, Indonesia).

3.2. Methods

3.2.1. Synthesis of CA-LBG

The experiment used CA-LBG synthesized using methods adopted from previous research (Hadinugroho, Martodihardjo, et al., 2022). The manufacturing principle is that a certain amount of LBG (7.10 x 10^{-6} mol in 50 mL) that has been swollen is added to a certain amount of CA (0.42 mol) and HCl (0.24 mol) as a catalyst. The homogeneous mixture was UV irradiated. The mixture was then settled and washed repeatedly with acetone-distilled water. The CA-LBG precipitate was dried at room temperature and powdered using a blender. Before being used in experiments, CA-LBG powder was characterized, including Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), viscosity, and pH.

3.2.2. Characterization of CA-LBG

FTIR examination using UATR (Perkin Elmer Spectrum Version 10.4.3., USA). The spectrum is read at 400-4000 cm^{-1}. ^{1}H and ^{13}C NMR examination using a JEOL RESONANCE ECZ 500R liquid state spectrophotometer (Japan) operated at 500 MHz. Viscosity examination using a Brookfield viscometer (LVDV-I Prime, AP6510416, USA). The spindle (No. S61) rotates at 60 rpm, and the torque is achieved by more than 10%. Acidity check using a pH meter (Metrohm 913, Switzerland). pH meter electrode calibration was carried out for pH 4, 7, and 10.

3.2.3. Preparation of a mixture of MCC and glidant

Each glidant (talc, MgS, and CA-LBG) was weighed according to the concentration of each experiment (Table 1). A quantity of MCC (Avicel PH 102) was weighed to complete up to 100 g. For one minute, glidant and MCC were mixed in a cubic mixer (Erweka, Germany). Each mixture was evaluated for flow rate and angle of repose. The mixture is compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability.

3.2.4. Flow rate and angel of repose

The mixture (100 g) of glidant and MCC was poured into a flowability tester (Erweka, Germany). The equipment is pressed to start when the bottom valve of the funnel opens, and the mixture flows freely over the plate, forming a cone. The flow time is read on the monitor. The flow rate is obtained from the flow time ratio to the mixed powder's weight. The equipment then emits infrared light to measure the diameter and height of the cone. The angle of rest is read on the monitor.

3.2.5. Weight

A total of 20 tablets were randomly selected and weighed one by one (Mettler Toledo, Switzerland). All weights obtained are averaged, and the standard deviation is determined.

3.2.6. Hardness

A total of 6 tablets were randomly selected and placed on a hardness tester plate (Schleuniger, Netherlands). The moving metal rod presses the tablet to crack or break. The tablet hardness value is displayed on the monitor (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

3.2.7. Friability

Tablets were randomly selected and dusted to weigh the equivalent of 6500 mg on an analytical balance (Mettler Toledo, Switzerland). All tablets were placed in a friability tester apparatus tube (Erweka, Germany). The tube was rotated at 25 rpm for 4 minutes. Once the rotation stops, each tablet is dusted again. Friability is the ratio of the difference between the treatment's initial and final weight to the initial weight (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

4. Results and Discussion

4.1. Synthesis of CA-LBG

The synthesis for CA-LBG is divided into 30 batches because the synthesis is adjusted to lab scale capacity and facilities. The synthesis process followed fixed procedures in previous research (Hadinugroho, Martodihardjo, et al., 2022). Dry CA-LBG yield of all batches is 1.1% ± 1.24. The CA-LBG all batches were homogenized and pureed using a blender. CA-LBG fines powder was used for characterization and experiments as a glidant.

4.2. Characterization of CA-LBG

The FTIR spectra of CA-LBG are presented in Figure 1. The infrared spectrum shows that the wave number of the O-H group appears at 3318.20 cm^{-1}; C-H appears at 2923.66 cm^{-1} and 2851.10 cm^{-1}; and C=O ester appears at 1736.02 cm^{-1}. The NMR spectra of CA-LBG are presented in Figure 2. The ^{1}H NMR spectrum of CA-LBG presents two doublet peaks appearing at δ=2,927 ppm and δ=2,896 ppm, δ=2,744 and ppm, and δ=2.713 ppm, which corresponds to C–H_2 from CA. Both peaks originate from symmetric C protons in CA. These peaks indicate the presence of CA in LBG. One adjacent proton causes a twist of the bond and a signal rupture. Multiplet peaks of mannose and galactose appeared at δ=3.990–3.329 ppm. Previous research reported that the two CA double peaks were around δ=3,083–2.714 ppm (Hadinugroho 2022, 2023). The peaks of mannose and galactose appear between δ = 4.418–3.309 ppm (Hadinugroho 2012, 2023). The CA-LBG peaks in the 13C NMR examination were δ = 176.838 ppm; δ=173,449 ppm; δ = 173.363 ppm; δ = 100.154 ppm; δ = 98,762 ppm; 96,458 ppm; 76,550 ppm; δ = 75.034 ppm; δ = 73.316 ppm; 71.425 ppm; 69,946 ppm; 69,303 ppm; 60,981 ppm; 60,521 ppm; and 43,339 ppm. The peak δ=180–170 ppm corresponds to the C=O group. The peak δ=80–70 ppm corresponds to the central C atom. The peak δ=44–43 ppm corresponding to C–H and C–H_2 appears (Doll et al., 2006; Hadinugroho et al., 2019; Jans & Kinne, 1991; Zhang et al., 2016). The peak δ=105–60 ppm corresponds to mannose, and galactose appears at δ=105–60 ppm (Azero & Andrade, 2006; Bhatia et al., 2013; Gillet et al., 2014; Hadinugroho, Martodihardjo, et al., 2022; Parvathy et al., 2005). The CA-LBG test results for viscosity were 9.49 cP ± 0.08. This viscosity is close to previous research results of around 7.82-11.37 cP (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test result for pH was 4.83. This result was compared with a CA pH of 2.05 and an LBG pH of 5.85. The pH value of 4.83 proves that the presence of

CA in LBG results in a pH value between the pH values of CA and LBG. The results of CA-LBG characterization using FTIR, NMR, viscosity, and pH show that the CA-LBG used is similar to previous experiments and can be used for further experiments as a glidant in MCC filler.

4.3. Flow rate

The flow rate test results for all experiments are presented in Table I and Figure 2. In general, the mixture containing MgS (M0-M4) and CA-LBG (C0-C4) has a faster flow rate than the mixture containing talc. A good pharmaceutical flow rate for powder or powder mixture is ≥ 10 g.second^{-1} (Gustaman et al., 2021; Jayani et al., 2021; Luh Putu Wrasiati & Putra, 2021; Putri, 2023). MgS and CA-LBG particles can interact well on the surface of the MCC particles so that the two glidants can make it easier for them to flow. The mixture of each glidant showed a different flow rate profile. The mixture containing talc and CA-LBG showed that increasing the glidant concentration increased the flow rate of the mixture. The surface area of the MCC particles in the powder is sufficient to interact with many particles of talc and CA-LBG. The flow rate profile of the mixture containing MgS (M0-M2) was initially similar to the flow rate profile of the other two glidants, but at an MgS concentration of 4% (M4), the flow rate decreased. The number of MgS particles (M4) exceeds the number of MCC particles, so the surface area of the MCC particles in the powder is insufficient to interact with the MgS particles, and free MgS particles remain. MgS-free particles can inhibit the flow rate of the mixture because the MgS particles are in the form of fines.

4.4. Angel of repose

The angle of repose test results are presented in Table 1 and Figure 4. A pharmaceutically good angle of repose for powders or powder mixtures is $\leq 40^{\circ}$ (Beakawi Al-Hashemi & Baghabra Al-Amoudi, 2018; Clayton, 2018). In general, the mixture containing talc has the highest angle of repose (T0-T4). When forming a powder cone, the particles cannot move freely following the force of gravity because the particles below them restrain the movement of the particles above them. The powder cone becomes taller with a shorter base diameter. Irregular oval-shaped MCC particles dominate the mixture and have porosity so that the particle porosity becomes a stationary point holding the surrounding particles. The angle of repose improves along with increasing talc concentration (T0-T4). Talc particles can cover the porosity of MCC particles so that the MCC surface is flatter. This condition can reduce the stationary point holding particles, and the MCC

particles can quickly move.

A similar angle of repose profile occurred in the mixture containing CA-LBG, but the value of the angle of repose was lower than the other two glidants. CA-LBG is an ester compound that can close the porosity of MCC particles. In addition, CA-LBG particles become slippery when the particles rub against surrounding particles. The initial angle of repose profile of the mixture containing MgS (M0-M2) is similar to the profile of the angle of repose of the other two glidants. Still, the value of the angle of repose is between the other two glidants. The lubrication mechanism also involves closing porosity and leveling the surface of the MCC particles. MgS particles are cohesive, requiring sufficient energy to interact with other particles (Goh et al., 2021; Peddapatla et al., 2016).

This condition affects the strength of interaction with MCC particles and the quality of MCC particle movement in the powder. In experiment M4, the angle of repose increased again due to the excessive number of MgS particles in the mixture. MgS particles in the form of fines find it challenging to move and hold the particles around them.

4.5. Weight

Tablet weights for all experiments are presented in Table I. Experiments were carried out to confirm that the mixture could flow and move to form tablets with the weight according to design. All mixtures can be compressed into tablets weighing about 700 mg with a narrow deviation. All mixtures can flow and move stably to fill the volume of the die chamber in the tablet compression machine.

4.6. Hardness

Tablet hardness test results are presented in Table I and Figure 5. Tablet hardness represents the quality of the interlocking bonds between deformation particles that make up the tablet. Each glidant produces varying tablet hardness because the glidant concentration influences it. The hardness profile of tablets containing talc shows high in experiments T0 and T1. Tablet hardness T0 (talc 0.5%) is controlled by the interlocking and deformation porosity of the MCC particles. The deformation of the talc particles fills the porosity of the deformation of the MCC particles so that the deformation arrangement of the particles is more stable and compact. Tablet hardness T1 (talc 1%) is similar in mechanism to T0, but the porosity between the deformation of MCC

particles is full filled, more stable, and compact, so the tablet is more complex. The hardness of T2 and T4 is lower than T0 and T1 because the number of talc particles influences hardness. The large number of talc particles induces interlocking deformation of the talc particles when compressed. The interlocking formed is less strong because of the deformation of the talc particles in the form of fine particles.

The tablet hardness profile (M0-M4) in experiments containing MgS shows that the higher the MgS concentration, the lower the tablet hardness. MgS has a low density (0.159 g/cm^3), so that a low concentration produces a large number of particles (Sheskey et al., 2017). The higher the MgS concentration, the more interlocking deformation of MgS particles. This interlocking force makes the tablet hardness not strong because the MgS particles are in the form of fines. The hardness profile of tablets containing CA-LBG (C0-C4) contradicts those having MgS. The higher the CA-LBG concentration, the higher the tablet's hardness. CA-LBG is an ester derived from LBG with a density of around 0.600 g/cm^3(Botelho, 2018), so the deformation of the CA-LBG particles plays a greater role in filling and reducing the porosity of the deformation of the MCC particles so that the tablets are hard.

4.7. Friability

Tablet friability test results are presented in Table I and Figure 6. A pharmaceutically good friability for powders or powder mixtures is < 1% (Chee et al., 2017; Mehta et al., 2012; Osei-Yeboah & Sun, 2015; Sharma et al., 2014). The friability profile of tablets containing MgS (M0-M4) shows that the higher the MgS concentration, the higher the fragility. This condition is in line with the hardness profile of the tablet because the interlocking between deformation MgS particles is not strong, and the deformation MgS particles are easily separated. Apart from that, the low density of MgS and the fines tend to cause particle deformation on the tablet's surface so that they are easily separated when subjected to mechanical movement. The friability profile of tablets containing CA-LBG showed increased friability at three initial concentrations (C0-C2). This condition is because the deformation of the CA-LBG particles does not fill the porosity between the deformation of the MCC particles. Hence, the tablet is not strong and releases particles when there is mechanical movement. At high concentrations (C4), the porosity between the deformation of MCC particles is filled by the deformation of CA-LBG particles so that the tablet is more stable when subjected to mechanical movement.

5. Conclusion

Based on experiments CA-LBG with compared talc and MgS as glidants, CA-LBG has potential as a glidant in MCC fillers. The higher the concentration of CA-LBG, the higher the flow rate of the mixture, the lower the angle of repose of the mixture, and the harder the tablet. CA-LBG concentrations of 0.5% and 4% in the mixture produced tablets with low friability.

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8. Figures

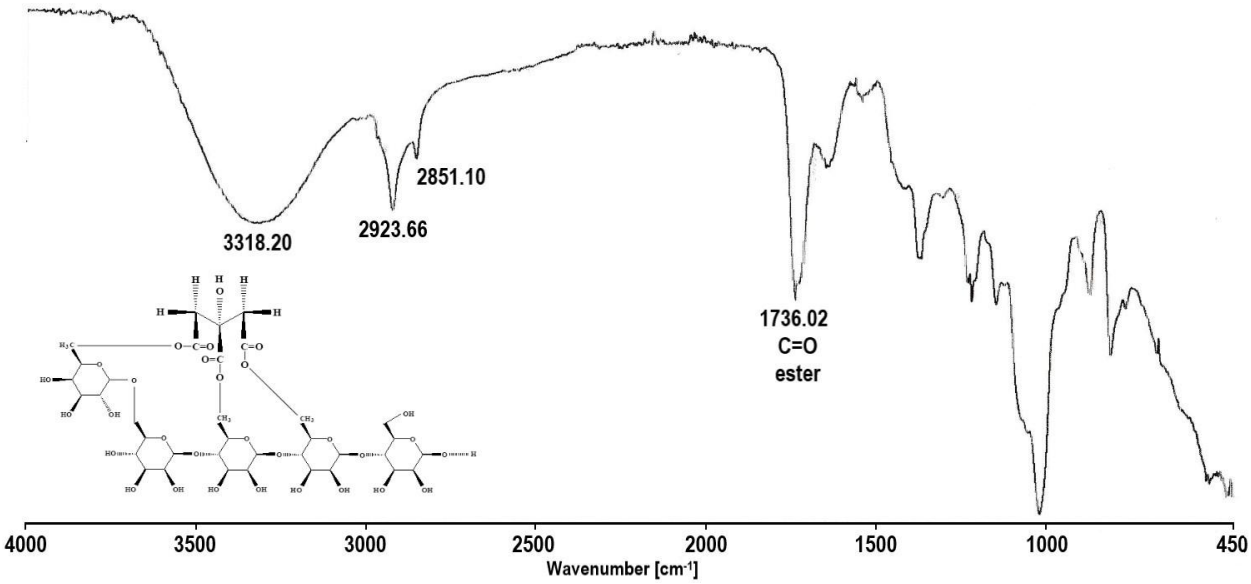

Figure 1. Infrared spectra of CA-LBG

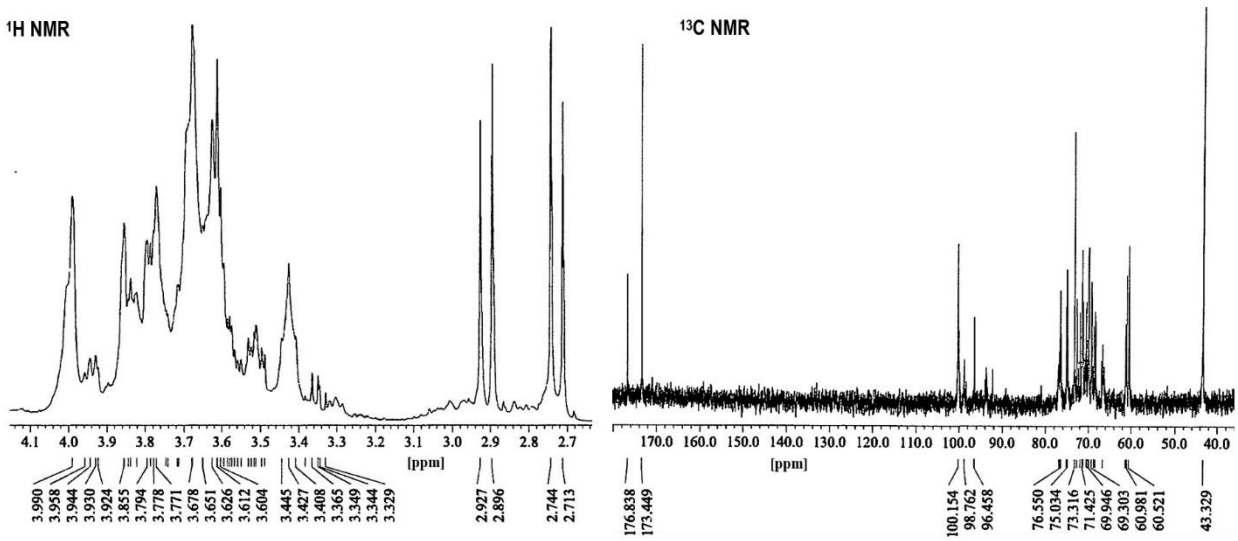

Figure 2. ^{1}H and ^{13}C NMR spectra of CA-LBG

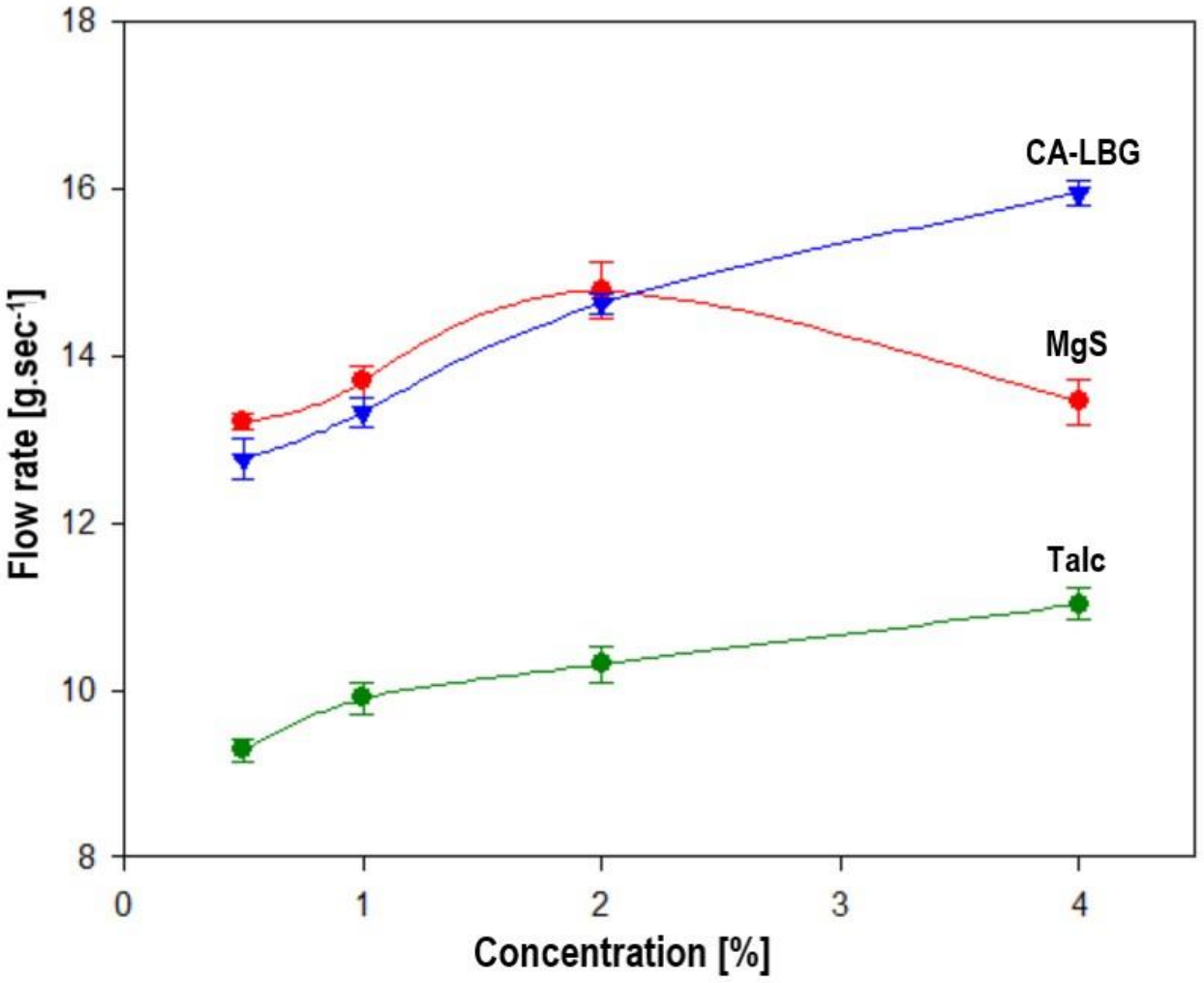

Figure 1. Profile of the relationship between glidant concentration and the flow rate of the mixture.

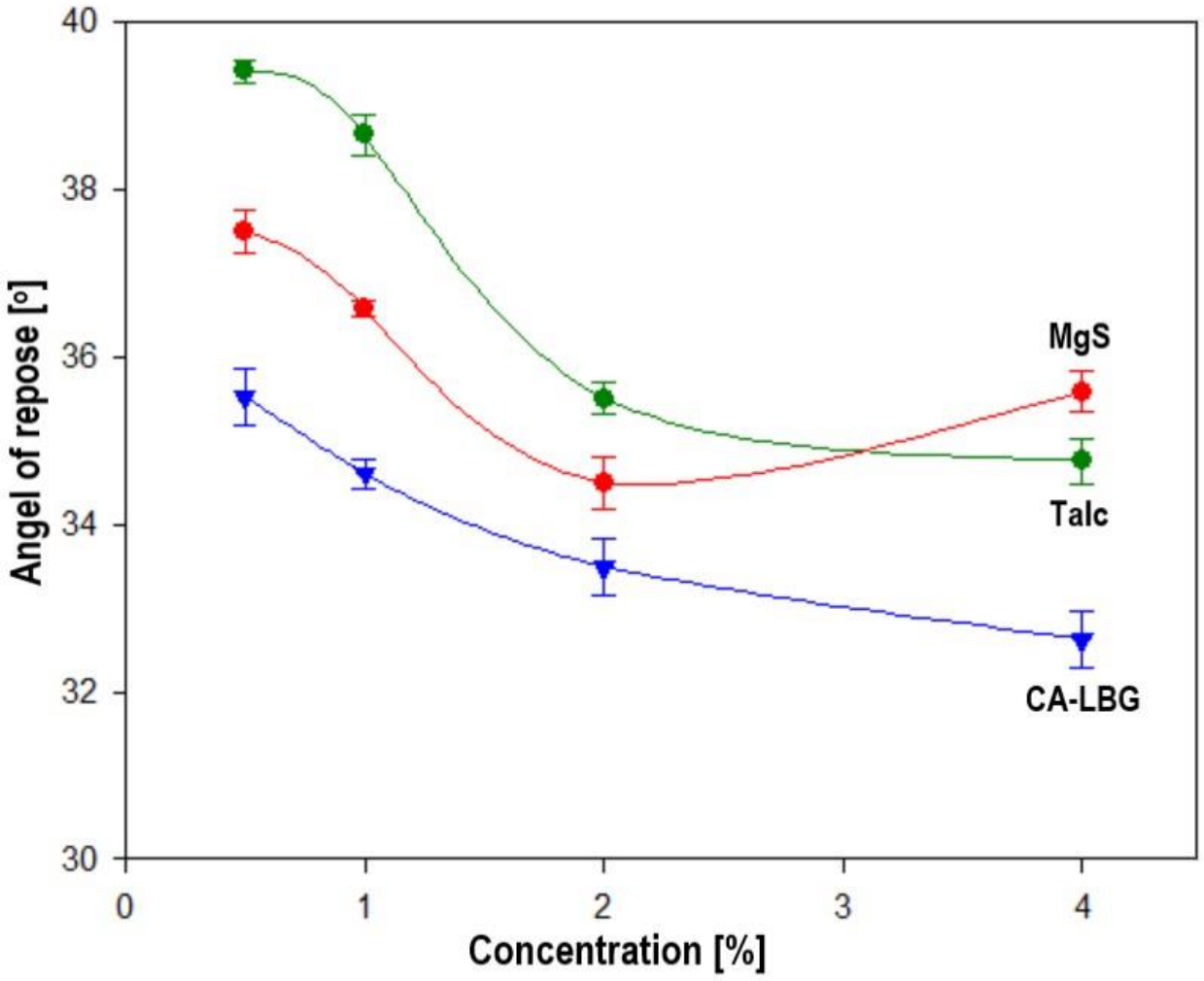

Figure 4. Profile of the relationship between glidant concentration and the angle of repose of the mixture.

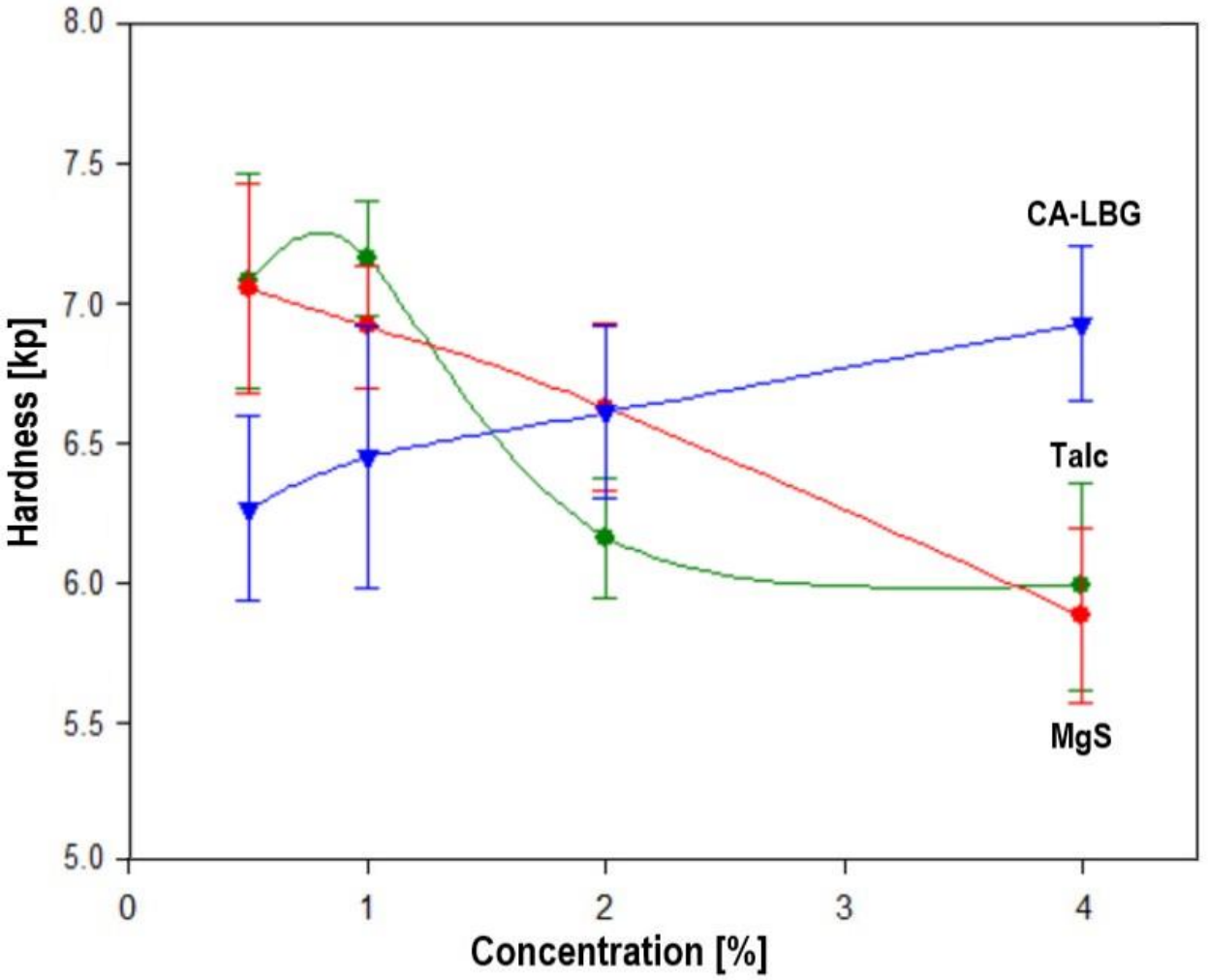

Figure 5. Profile of the relationship between glidant concentration and tablet hardness.

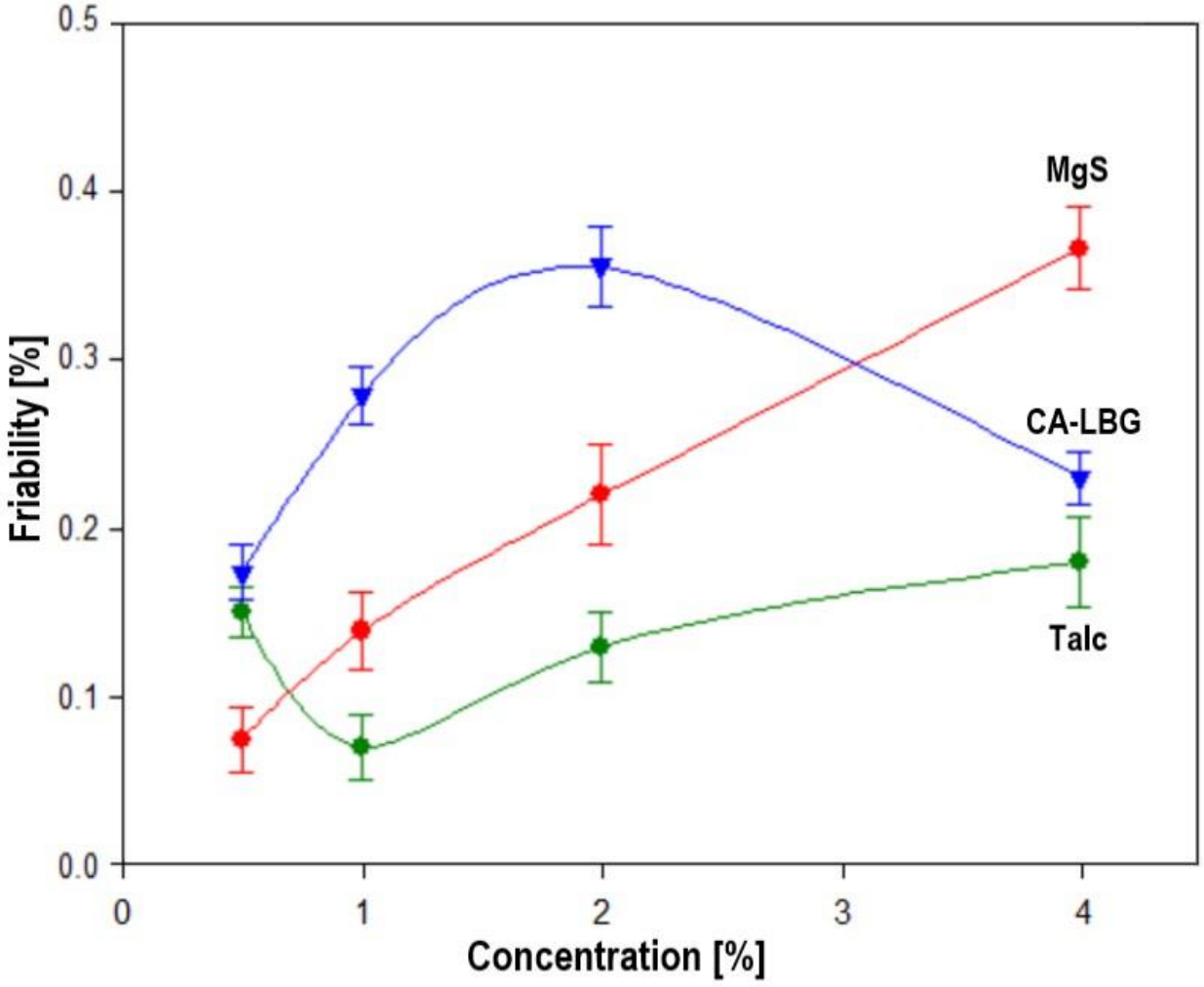

Figure 6. Profile of the relationship between glidant concentration and tablet friability.

Table I: Test results on mixtures and tablets for flow rate, angle of repose, weight, hardness and friability.

Glidant	Consentration [%]	Test code	Flow rate [g.sec.$^{-1}$]	Angel of repose [o]	Weight [mg]	Hardness [kp]	Friability [%]
Talc	**0.5**	**T0**	9.29 ± 0.13	39.40 ± 0.14	702.2 ± 1.67	7.10 ± 0.38	0.15 ± 0.01
	1.0	**T1**	9.90 ± 0.20	38.64 ± 0.25	701.1 ± 1.43	7.20 ± 0.21	0.07 ± 0.02
	2.0	**T2**	10.31 ± 0.21	35.50 ± 0.19	700.2 ± 1.51	6.20 ± 0.22	0.13 ± 0.02
	4.0	**T4**	11.03 ± 0.19	34.75 ± 0.27	702.5 ± 1.69	6.00 ± 0.37	0.18 ± 0.03
MgS	**0.5**	**M0**	13.22 ± 0.10	37.50 ± 0.25	703.1 ± 1.47	7.10 ± 0.38	0.07 ± 0.02
	1.0	**M1**	13.70 ± 0.19	36.57 ± 0.10	702.6 ± 1.98	6.90 ± 0.22	0.14 ± 0.02
	2.0	**M2**	14.78 ± 0.34	34.49 ± 0.31	702.7 ± 1.53	6.60 ± 0.30	0.22 ± 0.03
	4.0	**M4**	13.46 ± 0.27	35.58 ± 0.24	702.4 ± 0.96	5.90 ± 0.31	0.37 ± 0.02
CA-LBG	**0.5**	**C0**	12.77 ± 0.25	35.52 ± 0.35	700.7 ± 1.87	6.30 ± 0.33	0.17 ± 0.02
	1.0	**C1**	13.33 ± 0.18	34.61 ± 0.18	701.2 ± 1.59	6.50 ± 0.47	0.28 ± 0.02
	2.0	**C2**	14.63 ± 0.12	33.49 ± 0.34	700.0 ± 1.37	6.60 ± 0.31	0.36 ± 0.02
	4.0	**C4**	15.96 ± 0.15	32.62 ± 0.33	702.1 ± 1.27	6.90 ± 0.27	0.23 ± 0.02

Kind Reminder: Revision overdue (the 5th Liyang Conference 2023)

Dari: Liyang Conference (liyangconference@gmail.com)
Kepada: wuryanto.hadinugroho@ymail.com
Tanggal: Jumat, 16 Februari 2024 pukul 16.33 GMT+7

Ref: Submission ID LC-01

Dear Dr. Wuryanto Hadinugroho,

Your manuscript, "Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives", has now been reviewed, and the reviewer comments are appended below. You will see that, while the reviewers find your work of interest, they have raised points that must be addressed.

We therefore invite you to revise your paper, considering the points raised. At the same time, please make sure your manuscript complies with our format by reviewing our guidelines for preparing your manuscript, as attached to this email. After revision, the manuscript should have a less than 20% similarity index. In addition, please fulfil the requirement of copyright of transfer agreement form as attached to this email.

Once you have addressed each comment and completed each step listed below, the revised submission and final file can be uploaded via the link below.

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In order to process your paper, we require:

A point-by-point response to the comments, including a description of any additional experiments carried out and a detailed rebuttal of any criticisms or requested revisions you disagreed with. This must be uploaded as a 'Point-by-point response to reviewers' file. **All changes to the manuscript must be highlighted or indicated using tracked changes.**

At this stage, please also ensure you have replaced your initial submission image files with production-quality figures. These should be supplied at 300 dpi resolution for .jpeg and .tiff or as .eps files. Figures should not include Figure number labels in the image.

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If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone fluent in English. If you want professional help revising this manuscript, you can use any reputable English language editing service.

Please note that the final decision on the manuscript acceptance is based on the editors' decisions of each journal. Therefore, we do not guarantee the acceptance of your manuscript.

Please note that we expect revisions to be returned **within 7 (seven) days or maximum on February 25th 2024**. If this does not apply to you, please request an extension by replying to this email.

Sincerely,
Suciati
Andang Miatmoko

Scientific Committee
The 5th Liyang Conference 2023
"Global Health Transformation and Health Care Strategy in the New Era"
Email: liyangconference@gmail.com

Reviewer Comments:

Reviewer 1
"The article is well-written according to the research objectives.

1. Does only one person write the article?
2. Several improvements are related to writing the numbers after the comma of the CA-LBG concentration, experimental conditions, equipment used, and
3. Several statements require references to be referred to.
4. The statistical analysis must be included to compare test results.
5. Articles are written according to the template used."

Reviewer 2

1. please add some data or information of physicochemical characteristics that support the potential use of CA-LBG as a glidant for solid preparations
2. please add statistical analysis section for the method and their analysis results in the result section
3. please check for grammatical errors
4. P4 line 3-4: please give details about the tablet compression parameters including the tabletting machine, compression force, etc.
5. P5 line 3-5: how many grams for each batch? it should be clarified on the method and the recovery from all batches is really small. Does it really has potential as for glidant resources from the manufacturing perspectives?
6. P5 line 30-31: did the author check for pH of CA and LBG? please indicate it at the method
7. P8 line 8-10: these statements are not clearly understood. what is the interlocking deformation occured at high concentration of MgS and how does it occur? what is the relation of fines formation with this interlocking deformation? please clearly state it.
8. P8 line 12-15: does the density only affect the tablet hardness in this study? what is about the porosity of MCC and particle size of shape of the CA-LBG? did the author prove this idea? and about the hardness, the important parameter is about the presence of mannose and galactose of CA-LBG as it can form solidifed mass during or after the compression. Did the author prove it?
9. P.8 line 27-31: Why does the CA-LBG at low concentration do not fill the pores of MCC particles while it does at high concentration? Since there are some statements indicate that the MCC particles deformation produce porosity during the compression, it needs some clear or detail data about it to improve the clarity of the idea explanation well.

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Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives

Wuryanto Hadinugroho[1]

[1] *Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, 60112, Indonesia.*

**Corresponding Author e-mail: wuryanto.hadinugroho@ymail.com*

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1. Abstract

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. CA-LBG is a compound derived from the esterification of citric acid (CA) with locust bean gum (LBG). The experiment aimed to determine the potential and effect of CA-LBG as a glidant on microcrystalline cellulose (MCC). The CA-LBG concentrations in the experiments were 0.5%, 1%, 2%, and 4%. Talc and magnesium stearate (MgS) as a comparison. The mixtures were evaluated for flow rate and angle of repose. The mixture was compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability. The flow rate of the mixture containing CA-LBG 0.5%-4% was 12.77 $g.sec^{-1}$-15.96 $g.sec^{-1}$. The angle of repose of the mixture containing CA-LBG 0.5%-4% is 32.62°-35.52°. The weight of tablets containing CA-LBG 0.5%-4% is 700.0 mg-701.2 mg. The hardness of tablets containing CA-LBG 0.5%-4% is 6.30 kp-6.90 kp. The friability of tablets containing CA-LBG 0.5%-4% is 0.17%-0.36%. The CA-LBG has the potential as a glidant in MCC fillers. Increasing CA-LBG concentration causes the flow rate to increase, the angle of repose to decrease, and the hardness to increase. CA-LBG concentrations of 0.5% and 4% reduced tablet friability.

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Keywords: CA-LBG, citric acid, esterification, glidant, locust bean gum

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what is difference between CA-LBG and locust bean gum?

2. Introduction

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. The published uses of CA-LBG are as a tablet disintegration agent and negative matrix in controlled-release tablets (Hadinugroho et al., 2023; Hadinugroho, Martodihardjo, et al., 2022).

CA-LBG is an ester material derived from the esterification of citric acid (CA) with locust bean gum (LBG) under acidic conditions. CA-LBG has been characterized by carbonyl ester group, solubility, viscosity, esterified CA, glass transition temperature, crystallinity index, and particle morphology. CA-LBG particles have a non-polar and hydrophobic tendency, so CA-LBG has low solubility in water (Hadinugroho et al., 2017, 2019). CA-LBG is irregular in shape and has a wavy surface (Hadinugroho et al., 2017, 2019). This character can act as a glidant in granules or filler.

Glidant is a material that can interact with filler particles to improve flow properties. Glidant particles will be on the surface of the filler particles to cover porosity and smooth the surface of the filler particles. Changing the surface of the filler particles improves the movement of each particle(Awad et al., 2020). Glidant materials often used in pharmaceutical preparation formulations are talc and magnesium stearate (MgS). Talc and MgS particles are fines powders, hydrophobic, insoluble in water, irregular in shape and platy wavy (Lakio et al., 2013; Meng et al., 2022; Sheskey et al., 2017; Zarmpi et al., 2020). This character is similar to CA-BG particles, so CA-LBG has the potential to be a glidant agent.

The experiments aimed to determine the potential and influence of CA-LBG as a glidant on cellulose derivative fillers. The experiment used microcrystalline cellulose (MCC), commonly used as a filler in tablet formulations. The experiment used CA-LBG with concentrations of 0.5%, 1%, 2%, and 4%. Talc and magnesium stearate were used as a comparison with the same concentration. Each mixture was evaluated for flow rate and angle of repose. The mixture is then compressed directly into tablets 700 mg. Tablets were evaluated for weight, hardness, and friability. MCC was chosen as the filler model in this experiment because MCC is a filler that is often used in tablets using the direct compression method. MCC particles are water-insoluble, irregularly oval, porosity, and hydrophobic (Lakio et al., 2013; Sheskey et al., 2017).

The novelty of this experiment is using CA-LBG as a glidant in MCC tablet filler to observe its potency and effect at various concentrations. This experiment explores the function of CA-LBG as a glidant for tablet formulation. In addition, the experiment's success provides a choice of future glidant in pharmaceutical excipients.

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3. Experimental Section

3.1. Materials

The materials are locust bean gum (food grade) (Viscogum, Cargill, France), citric acid monohydrate (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (pro analysis) (Sigma Aldrich Chemie, GmbH, USA), water for injection (sterile water) (PT. Otsuka Indonesia), distilled water (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (technical grade) (Cawan Anugerah Chemika, Indonesia), spray dried lactose (food grade) (FlowLac 90, Meggle GmbH & Co. KG, Germany), talc (food grade) (PT. Bratachem, Indonesia) and magnesium stearate (food grade) (PT. Bratachem, Indonesia).

3.2. Methods

3.2.1. Synthesis of CA-LBG

The experiment used CA-LBG synthesized using methods adopted from previous research (Hadinugroho, Martodihardjo, et al., 2022). The manufacturing principle is that a certain amount of LBG (7.10×10^{-6} mol in 50 mL) that has been swollen is added to a certain amount of CA (0.42 mol) and HCl (0.24 mol) as a catalyst. The homogeneous mixture was UV irradiated. The mixture was then settled and washed repeatedly with acetone-distilled water. The CA-LBG precipitate was dried at room temperature and powdered using a blender. Before being used in experiments, CA-LBG powder was characterized, including Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), viscosity, and pH.

3.2.2. Characterization of CA-LBG

FTIR examination using UATR (Perkin Elmer Spectrum Version 10.4.3., USA). The spectrum is read at 400-4000 cm^{-1}. ^{1}H and ^{13}C NMR examination using a JEOL RESONANCE ECZ 500R liquid state spectrophotometer (Japan) operated at 500 MHz. Viscosity examination using a Brookfield viscometer (LVDV-I Prime, AP6510416, USA). The spindle (No. S61) rotates at 60 rpm, and the torque is achieved by more than 10%. Acidity check using a pH meter (Metrohm 913, Switzerland). pH meter electrode calibration was carried out for pH 4, 7, and 10.

3.2.3. Preparation of a mixture of MCC and glidant

Each glidant (talc, MgS, and CA-LBG) was weighed according to the concentration of each

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experiment (Table 1). A quantity of MCC (Avicel PH 102) was weighed to complete up to 100 g. For one minute, glidant and MCC were mixed in a cubic mixer (Erweka, Germany). Each mixture was evaluated for flow rate and angle of repose. The mixture is compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability.

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2. Please give details about the tablet compression parameters including the tabeltting machine, compression force, etc.

3.2.4. Flow rate and angel of repose

The mixture (100 g) of glidant and MCC was poured into a flowability tester (Erweka, Germany). The equipment is pressed to start when the bottom valve of the funnel opens, and the mixture flows freely over the plate, forming a cone. The flow time is read on the monitor. The flow rate is obtained from the flow time ratio to the mixed powder's weight. The equipment then emits infrared light to measure the diameter and height of the cone. The angle of rest is read on the monitor.

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3.2.5. Weight

A total of 20 tablets were randomly selected and weighed one by one (Mettler Toledo, Switzerland). All weights obtained are averaged, and the standard deviation is determined.

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3.2.6. Hardness

A total of 6 tablets were randomly selected and placed on a hardness tester plate (Schleuniger, Netherlands). The moving metal rod presses the tablet to crack or break. The tablet hardness value is displayed on the monitor (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

3.2.7. Friability

Tablets were randomly selected and dusted to weigh the equivalent of 6500 mg on an analytical balance (Mettler Toledo, Switzerland). All tablets were placed in a friability tester apparatus tube (Erweka, Germany). The tube was rotated at 25 rpm for 4 minutes. Once the rotation stops, each tablet is dusted again. Friability is the ratio of the difference between the treatment's initial and final weight to the initial weight (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

4. Results and Discussion

4.1. Synthesis of CA-LBG

The synthesis for CA-LBG is divided into 30 batches because the synthesis is adjusted to lab scale capacity and facilities. The synthesis process followed fixed procedures in previous research (Hadinugroho, Martodihardjo, et al., 2022). Dry CA-LBG yield of all batches is 1.1% ± 1.24. The CA-LBG all batches were homogenized and pureed using a blender. CA-LBG fines powder was used for characterization and experiments as a glidant.

4.2. Characterization of CA-LBG

The FTIR spectra of CA-LBG are presented in Figure 1. The infrared spectrum shows that the wave number of the O-H group appears at 3318.20 cm^{-1}; C-H appears at 2923.66 cm^{-1} and 2851.10 cm^{-1}; and C=O ester appears at 1736.02 cm^{-1}. The NMR spectra of CA-LBG are presented in Figure 2. The ^{1}H NMR spectrum of CA-LBG presents two doublet peaks appearing at δ=2,927 ppm and δ=2,896 ppm, δ=2,744 and ppm, and δ=2.713 ppm, which corresponds to C–H_2 from CA. Both peaks originate from symmetric C protons in CA. These peaks indicate the presence of CA in LBG. One adjacent proton causes a twist of the bond and a signal rupture. Multiplet peaks of mannose and galactose appeared at δ=3.990–3.329 ppm. Previous research reported that the two CA double peaks were around δ=3,083–2.714 ppm (Hadinugroho 2022, 2023). The peaks of mannose and galactose appear between δ = 4.418–3.309 ppm (Hadinugroho 2012, 2023). The CA-LBG peaks in the 13C NMR examination were δ = 176.838 ppm; δ=173,449 ppm; δ = 173.363 ppm; δ = 100.154 ppm; δ = 98,762 ppm; 96,458 ppm; 76,550 ppm; δ = 75.034 ppm; δ = 73.316 ppm; 71.425 ppm; 69,946 ppm; 69,303 ppm; 60,981 ppm; 60,521 ppm; and 43,339 ppm. The peak δ=180–170 ppm corresponds to the C=O group. The peak δ=80–70 ppm corresponds to the central C atom. The peak δ=44–43 ppm corresponding to C–H and C–H_2 appears (Doll et al., 2006; Hadinugroho et al., 2019; Jans & Kinne, 1991; Zhang et al., 2016). The peak δ=105–60 ppm corresponds to mannose, and galactose appears at δ=105–60 ppm (Azero & Andrade, 2006; Bhatia et al., 2013; Gillet et al., 2014; Hadinugroho, Martodihardjo, et al., 2022; Parvathy et al., 2005). The CA-LBG test results for viscosity were 9.49 cP ± 0.08. This viscosity is close to previous research results of around 7.82-11.37 cP (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test result for pH was 4.83. This result was compared with a CA pH of 2.05 and an LBG pH of 5.85. The pH value of 4.83 proves that the presence of

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CA in LBG results in a pH value between the pH values of CA and LBG. The results of CA-LBG characterization using FTIR, NMR, viscosity, and pH show that the CA-LBG used is similar to previous experiments and can be used for further experiments as a glidant in MCC filler.

4.3. Flow rate

The flow rate test results for all experiments are presented in Table I and Figure 2. In general, the mixture containing MgS (M0-M4) and CA-LBG (C0-C4) has a faster flow rate than the mixture containing talc. A good pharmaceutical flow rate for powder or powder mixture is ≥ 10 g.second^{-1} (Gustaman et al., 2021; Jayani et al., 2021; Luh Putu Wrasiati & Putra, 2021; Putri, 2023). MgS and CA-LBG particles can interact well on the surface of the MCC particles so that the two glidants can make it easier for them to flow. The mixture of each glidant showed a different flow rate profile. The mixture containing talc and CA-LBG showed that increasing the glidant concentration increased the flow rate of the mixture. The surface area of the MCC particles in the powder is sufficient to interact with many particles of talc and CA-LBG. The flow rate profile of the mixture containing MgS (M0-M2) was initially similar to the flow rate profile of the other two glidants, but at an MgS concentration of 4% (M4), the flow rate decreased. The number of MgS particles (M4) exceeds the number of MCC particles, so the surface area of the MCC particles in the powder is insufficient to interact with the MgS particles, and free MgS particles remain. MgS-free particles can inhibit the flow rate of the mixture because the MgS particles are in the form of fines.

4.4. Angel of repose

The angle of repose test results are presented in Table 1 and Figure 4. A pharmaceutically good angle of repose for powders or powder mixtures is ≤ 40° (Beakawi Al-Hashemi & Baghabra Al-Amoudi, 2018; Clayton, 2018). In general, the mixture containing talc has the highest angle of repose (T0-T4). When forming a powder cone, the particles cannot move freely following the force of gravity because the particles below them restrain the movement of the particles above them. The powder cone becomes taller with a shorter base diameter. Irregular oval-shaped MCC particles dominate the mixture and have porosity so that the particle porosity becomes a stationary point holding the surrounding particles. The angle of repose improves along with increasing talc concentration (T0-T4). Talc particles can cover the porosity of MCC particles so that the MCC surface is flatter. This condition can reduce the stationary point holding particles, and the MCC

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particles can quickly move.

A similar angle of repose profile occurred in the mixture containing CA-LBG, but the value of the angle of repose was lower than the other two glidants. CA-LBG is an ester compound that can close the porosity of MCC particles. In addition, CA-LBG particles become slippery when the particles rub against surrounding particles. The initial angle of repose profile of the mixture containing MgS (M0-M2) is similar to the profile of the angle of repose of the other two glidants. Still, the value of the angle of repose is between the other two glidants. The lubrication mechanism also involves closing porosity and leveling the surface of the MCC particles. MgS particles are cohesive, requiring sufficient energy to interact with other particles (Goh et al., 2021; Peddapatla et al., 2016).

This condition affects the strength of interaction with MCC particles and the quality of MCC particle movement in the powder. In experiment M4, the angle of repose increased again due to the excessive number of MgS particles in the mixture. MgS particles in the form of fines find it challenging to move and hold the particles around them.

4.5. Weight

Tablet weights for all experiments are presented in Table I. Experiments were carried out to confirm that the mixture could flow and move to form tablets with the weight according to design. All mixtures can be compressed into tablets weighing about 700 mg with a narrow deviation. All mixtures can flow and move stably to fill the volume of the die chamber in the tablet compression machine.

4.6. Hardness

Tablet hardness test results are presented in Table I and Figure 5. Tablet hardness represents the quality of the interlocking bonds between deformation particles that make up the tablet. Each glidant produces varying tablet hardness because the glidant concentration influences it. The hardness profile of tablets containing talc shows high in experiments T0 and T1. Tablet hardness T0 (talc 0.5%) is controlled by the interlocking and deformation porosity of the MCC particles. The deformation of the talc particles fills the porosity of the deformation of the MCC particles so that the deformation arrangement of the particles is more stable and compact. Tablet hardness T1 (talc 1%) is similar in mechanism to T0, but the porosity between the deformation of MCC

particles is full filled, more stable, and compact, so the tablet is more complex. The hardness of T2 and T4 is lower than T0 and T1 because the number of talc particles influences hardness. The large number of talc particles induces interlocking deformation of the talc particles when compressed. The interlocking formed is less strong because of the deformation of the talc particles in the form of fine particles.

The tablet hardness profile (M0-M4) in experiments containing MgS shows that the higher the MgS concentration, the lower the tablet hardness. MgS has a low density (0.159 g/cm^3), so that a low concentration produces a large number of particles (Sheskey et al., 2017). The higher the MgS concentration, the more interlocking deformation of MgS particles. This interlocking force makes the tablet hardness not strong because the MgS particles are in the form of fines. The hardness profile of tablets containing CA-LBG (C0-C4) contradicts those having MgS. The higher the CA-LBG concentration, the higher the tablet's hardness. CA-LBG is an ester derived from LBG with a density of around 0.600 g/cm^3(Botelho, 2018), so the deformation of the CA-LBG particles plays a greater role in filling and reducing the porosity of the deformation of the MCC particles so that the tablets are hard.

4.7. Friability

Tablet friability test results are presented in Table I and Figure 6. A pharmaceutically good friability for powders or powder mixtures is < 1% (Chee et al., 2017; Mehta et al., 2012; Osei-Yeboah & Sun, 2015; Sharma et al., 2014). The friability profile of tablets containing MgS (M0-M4) shows that the higher the MgS concentration, the higher the fragility. This condition is in line with the hardness profile of the tablet because the interlocking between deformation MgS particles is not strong, and the deformation MgS particles are easily separated. Apart from that, the low density of MgS and the fines tend to cause particle deformation on the tablet's surface so that they are easily separated when subjected to mechanical movement. The friability profile of tablets containing CA-LBG showed increased friability at three initial concentrations (C0-C2). This condition is because the deformation of the CA-LBG particles does not fill the porosity between the deformation of the MCC particles. Hence, the tablet is not strong and releases particles when there is mechanical movement. At high concentrations (C4), the porosity between the deformation of MCC particles is filled by the deformation of CA-LBG particles so that the tablet is more stable when subjected to mechanical movement.

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Commented [x27]: these statements are not clearly understood. what is the interlocking deformation occured at high concentration of MgS and how does it occur? what is the relation of fines formation with this interlocking deformation? please clearly state it.

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Since there are some statements indicate that the MCC particles deformation produce porosity during the compression, it needs some clear or detail data about it to improve the clarity of the idea explanation well.

5. Conclusion

Based on experiments CA-LBG with compared talc and MgS as glidants, CA-LBG has potential as a glidant in MCC fillers. The higher the concentration of CA-LBG, the higher the flow rate of the mixture, the lower the angle of repose of the mixture, and the harder the tablet. CA-LBG concentrations of 0.5% and 4% in the mixture produced tablets with low friability.

6. Acknowledgement

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8. Figures

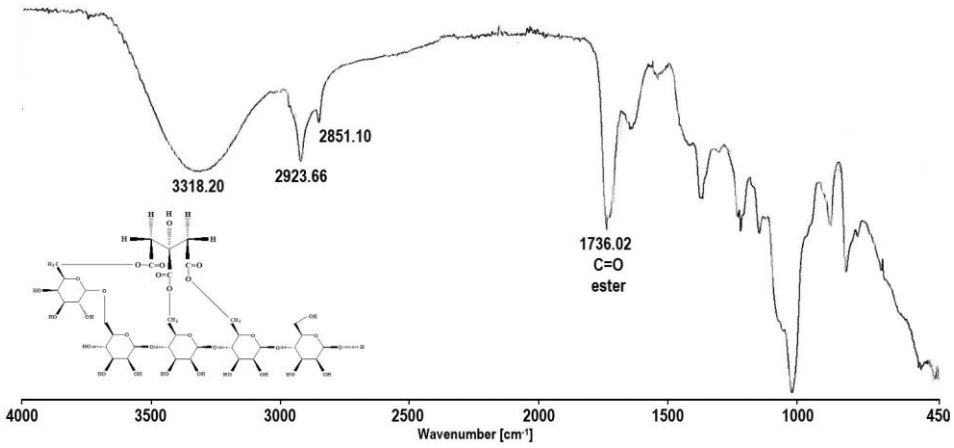

Figure 1. Infrared spectra of CA-LBG

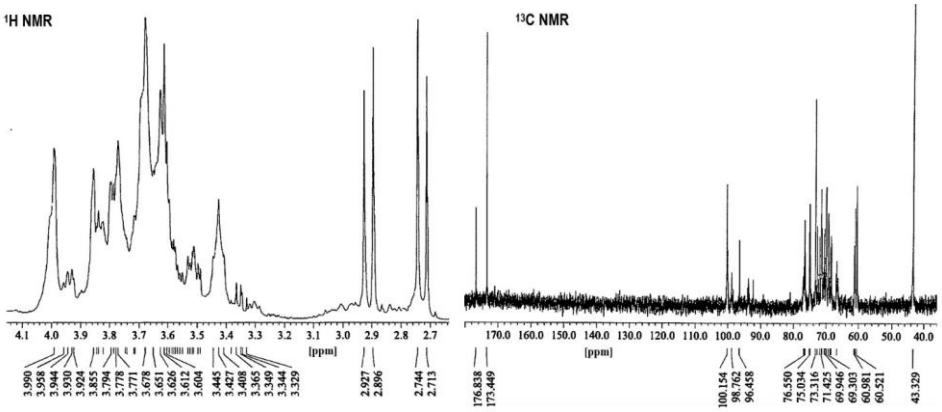

Figure 2. ^{1}H and ^{13}C NMR spectra of CA-LBG

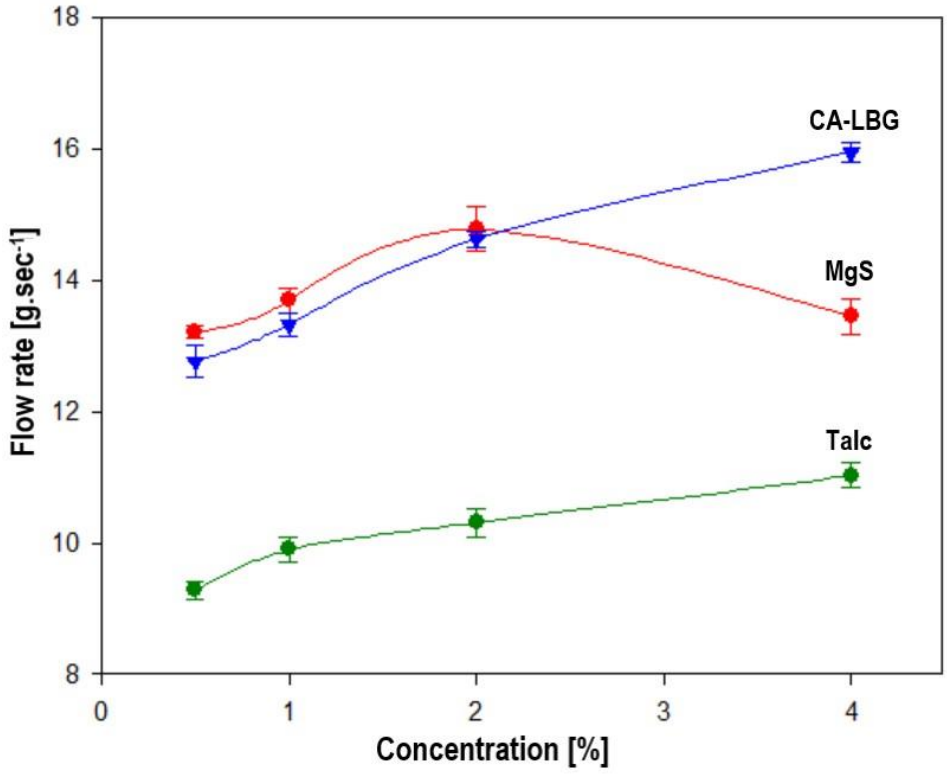

Figure 1. Profile of the relationship between glidant concentration and the flow rate of the mixture.

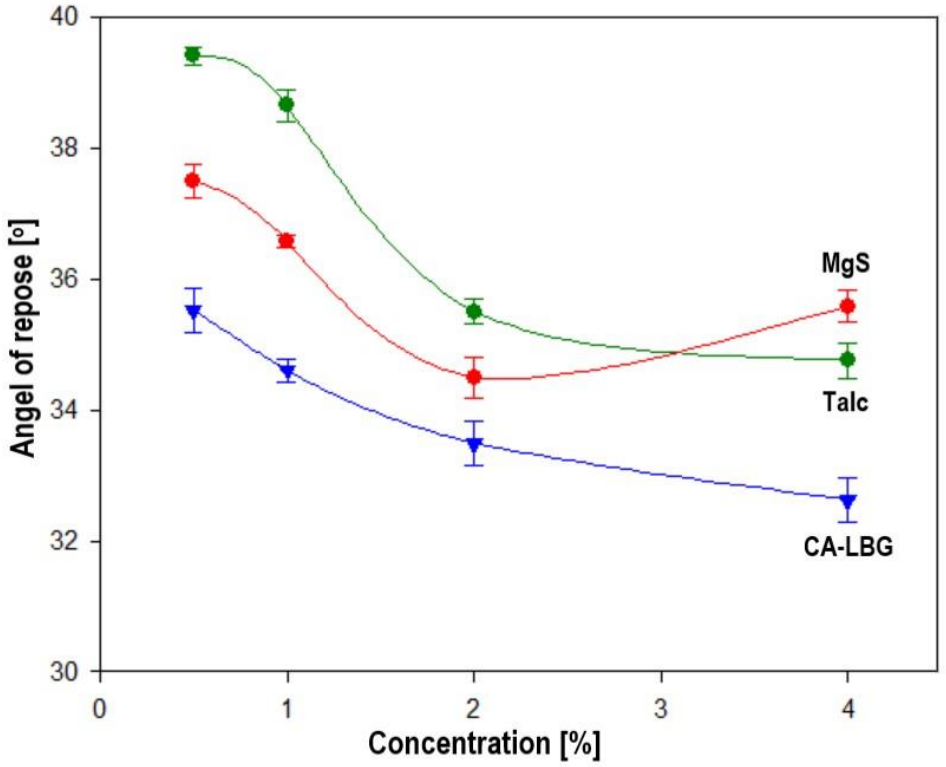

Figure 4. Profile of the relationship between glidant concentration and the angle of repose of the mixture.

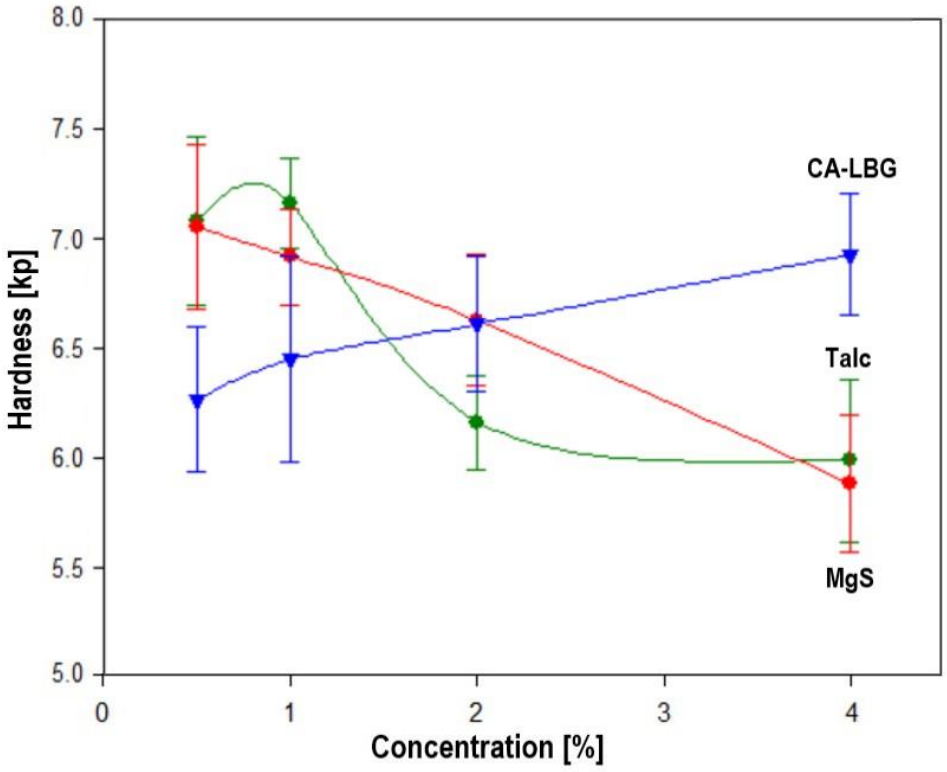

Figure 5. Profile of the relationship between glidant concentration and tablet hardness.

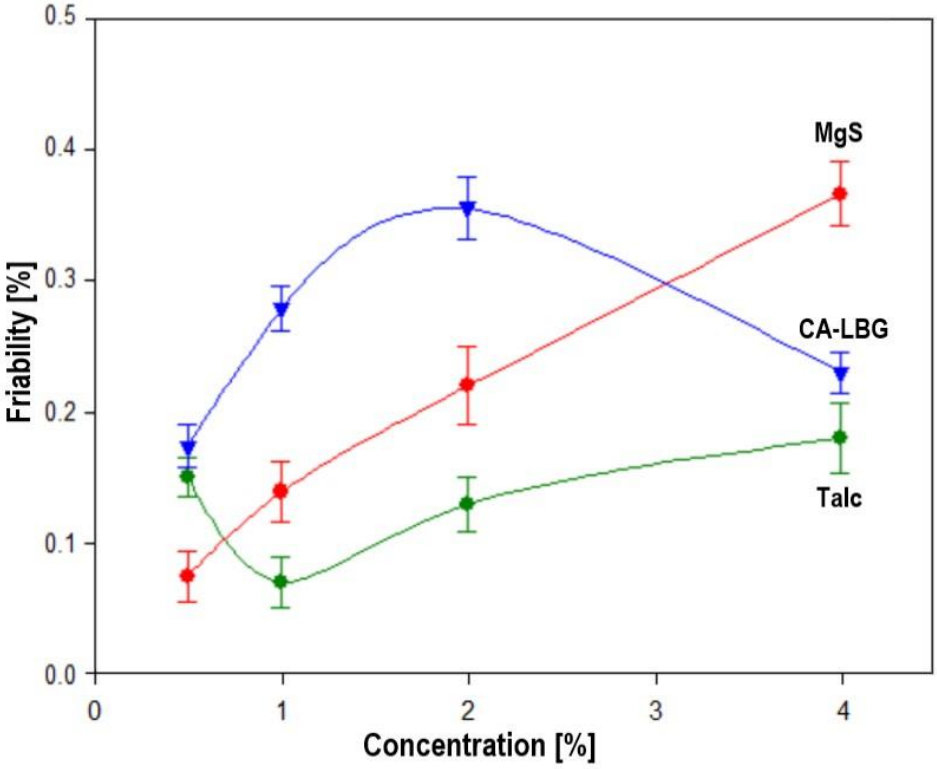

Figure 6. Profile of the relationship between glidant concentration and tablet friability.

Table I: Test results on mixtures and tablets for flow rate, angle of repose, weight, hardness and friability.

Glidant	Consentration [%]	Test code	Flow rate [g.sec.$^{-1}$]	Angel of repose [o]	Weight [mg]	Hardness [kp]	Friability [%]
Talc	0.5	T0	9.29 ± 0.13	39.40 ± 0.14	702.2 ± 1.67	7.10 ± 0.38	0.15 ± 0.01
	1.0	T1	9.90 ± 0.20	38.64 ± 0.25	701.1 ± 1.43	7.20 ± 0.21	0.07 ± 0.02
	2.0	T2	10.31 ± 0.21	35.50 ± 0.19	700.2 ± 1.51	6.20 ± 0.22	0.13 ± 0.02
	4.0	T4	11.03 ± 0.19	34.75 ± 0.27	702.5 ± 1.69	6.00 ± 0.37	0.18 ± 0.03
MgS	0.5	M0	13.22 ± 0.10	37.50 ± 0.25	703.1 ± 1.47	7.10 ± 0.38	0.07 ± 0.02
	1.0	M1	13.70 ± 0.19	36.57 ± 0.10	702.6 ± 1.98	6.90 ± 0.22	0.14 ± 0.02
	2.0	M2	14.78 ± 0.34	34.49 ± 0.31	702.7 ± 1.53	6.60 ± 0.30	0.22 ± 0.03
	4.0	M4	13.46 ± 0.27	35.58 ± 0.24	702.4 ± 0.96	5.90 ± 0.31	0.37 ± 0.02
CA-LBG	0.5	C0	12.77 ± 0.25	35.52 ± 0.35	700.7 ± 1.87	6.30 ± 0.33	0.17 ± 0.02
	1.0	C1	13.33 ± 0.18	34.61 ± 0.18	701.2 ± 1.59	6.50 ± 0.47	0.28 ± 0.02
	2.0	C2	14.63 ± 0.12	33.49 ± 0.34	700.0 ± 1.37	6.60 ± 0.31	0.36 ± 0.02
	4.0	C4	15.96 ± 0.15	32.62 ± 0.33	702.1 ± 1.27	6.90 ± 0.27	0.23 ± 0.02

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Study of Citric Acid-Locust Bean Gum as A Glidant to Fillers of Cellulose Derivatives

Wuryanto Hadinugroho[1,*]

[1] *Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, 60112, Indonesia.*

**Corresponding Author e-mail: wuryanto.hadinugroho@ymail.com*

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Author Response:
Thank you for the question. I am Wuryanto Hadinugroho, the sole author carrying out this research work. Work includes research design, research process, data collection, data processing, data analysis, data interpretation, and writing publication manuscripts.

Abstract

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. CA-LBG is a compound derived from the esterification of citric acid (CA) with locust bean gum (LBG). The experiment aimed to determine the potential and effect of CA-LBG as a glidant on microcrystalline cellulose (MCC). The CA-LBG concentrations in the experiments were 0.5%, 1.0%, 2.0%, and 4.0%. Talc and magnesium stearate (MgS) as a comparison. The mixtures were evaluated for flow rate and angle of repose. The mixture was compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability. The flow rate of the mixture containing CA-LBG 0.5%-4.0% was 12.77 $g.sec^{-1}$-15.96 $g.sec^{-1}$. The angle of repose of the mixture containing CA-LBG 0.5%-4.0% is 32.62°-35.52°. The weight of tablets containing CA-LBG 0.5%-4.0% is 700.0 mg-701.2 mg. The hardness of tablets containing CA-LBG 0.5%-4.0% is 6.30 kp-6.90 kp. The friability of tablets containing CA-LBG 0.5%-4.0% is 0.17%-0.36%. The CA-LBG has the potential as a glidant in MCC fillers. Increasing CA-LBG concentration causes the flow rate to increase, the angle of repose to decrease, and the hardness to increase. CA-LBG concentrations of 0.5% and 4.0% reduced tablet friability.

Keywords: citric acid-locust bean gum, citric acid, esterification, glidant, locust bean gum

1. Introduction

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. The published uses of CA-LBG are as a tablet disintegration agent and negative matrix in

controlled-release tablets (Hadinugroho et al., 2023; Hadinugroho, Martodihardjo, et al., 2022). CA-LBG is an ester material derived from the esterification of citric acid (CA) with locust bean gum (LBG) under acidic conditions. CA-LBG has been characterized by carbonyl ester group, solubility, viscosity, esterified CA, glass transition temperature, crystallinity index, and particle morphology. CA-LBG particles have a non-polar and hydrophobic tendency, so CA-LBG has low solubility in water (Hadinugroho et al., 2017, 2019). CA-LBG is irregular in shape and has a wavy surface (Hadinugroho et al., 2017, 2019). This character can act as a glidant in tablet formulation.

Glidant is a material that can interact with filler particles to improve flow properties. Glidant particles will be on the surface of the filler particles to cover porosity and smooth the surface of the filler particles. Changing the surface of the filler particles improves the movement of each particle (Awad et al., 2020). Glidant materials often used in pharmaceutical preparation formulations are talc and magnesium stearate (MgS). Talc and MgS particles are fines powders, hydrophobic, insoluble in water, irregular in shape and platy wavy (Lakio et al., 2013; Meng et al., 2022; Sheskey et al., 2017; Zarmpi et al., 2020). The character CA-BG particles similar the character talc and MgS particles, so CA-LBG has the potential to be a glidant agent.

The experiments aimed to determine the potential and influence of CA-LBG as a glidant in tablet formulation. The experiment used microcrystalline cellulose (MCC), commonly used as a filler in tablet formulations. MCC particles experience plastic deformation after compression, resulting in varying porosity in the tablet (Al-Ibraheemi et al., 2013). The experiment used CA-LBG with concentrations of 0.5%, 1.0%, 2.0%, and 4.0%. Talc and magnesium stearate were used as a comparison with the same concentration. Each mixture was evaluated for flow rate and angle of repose. The mixture is then compressed directly into tablets 700 mg. Tablets were evaluated for weight, hardness, and friability. MCC was chosen as the filler model in this experiment because MCC is a filler that is often used in tablets using the direct compression method. MCC particles are water-insoluble, irregularly oval, porosity, and hydrophobic (Lakio et al., 2013; Sheskey et al., 2017).

The novelty of this experiment is using CA-LBG as a glidant in MCC tablet filler to observe its potency and effect at various concentrations. This experiment explores the function of CA-LBG as a glidant for tablet formulation. In the fine form of CA-LBG, the shape of the CA-LBG particles is irregular, has a wavy surface, is difficult to dissolve in water, and is hydrophobic (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). In addition, the experiment's success

provides a choice of future glidant in pharmaceutical excipients.

2. Experimental Section

2.1. Materials

The materials are locust bean gum (food grade) (Viscogum, Cargill, France), citric acid monohydrate (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (pro analysis) (Sigma Aldrich Chemie, GmbH, USA), water for injection (sterile water) (PT. Otsuka Indonesia), distilled water (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (technical grade) (Cawan Anugerah Chemika, Indonesia), microcrystalline cellulose (pharmaceutical grade) (Flocel PH 102, Gujarat Microwax Ltd, Gujarat, India), talc (food grade) (PT. Bratachem, Indonesia) and magnesium stearate (food grade) (PT. Bratachem, Indonesia).

2.2. Methods

2.2.1. Synthesis of CA-LBG

The experiment used CA-LBG synthesized using methods adopted from previous research (Hadinugroho, Martodihardjo, et al., 2022). The manufacturing principle is that a certain amount of LBG (7.10 x 10^{-6} mol in 50 mL) that has been swollen is added to a certain amount of CA (0.42 mol) and HCl (0.24 mol) as a catalyst. The homogeneous mixture was UV irradiated. The mixture was then settled and washed repeatedly with acetone-distilled water. The CA-LBG precipitate was dried at room temperature (± 25°C for 72 hours) and powdered using a blender (Maspion, speed scale 4 for 8 x 5 minutes). Before being used in experiments, CA-LBG powder was characterized, including Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), viscosity, and pH.

2.2.2. Characterization of CA-LBG

A qualitative examination of chemical groups from CA-LBG infrared at 400-4000 cm^{-1} using UATR (Perkin Elmer Spectrum Version 10.4.3., USA). ^{1}H and ^{13}C examination of CA-LBG using liquid state NMR spectrophotometer (JEOL RESONANCE ECZ 500R, 500 MHz, Japan). Viscosity examination of CA-LBG on spindle No. S61, 60 rpm, and torque < 10% using a Brookfield viscometer (LVDV-I Prime, AP6510416, USA). The acidity examination of CA-LBG, CA, and LBG in solution (1% w/v) used a pH meter calibrated to pH 4.0; 7.0; and 10.0 (Metrohm

913, Switzerland).

2.2.3. Preparation of a mixture of MCC and glidant

Each glidant (talc, MgS, and CA-LBG) was weighed according to the concentration of each experiment (Table 1). A quantity of MCC (Avicel PH 102) was weighed to complete up to 100 g. For one minute, glidant and MCC were mixed in a cubic mixer (Erweka, Germany). Each mixture was evaluated for flow rate and angle of repose. The mixture was compressed (Single punch, Erweka EP-1, Germany) into tablets weighing 700 mg, diameter ± 15 mm, hardness 5-12 kp (equivalent to compression force ± 2 tons). Tablets were evaluated for weight, hardness, and friability.

2.2.4. Flow rate and angel of repose

The mixture (100 g) of glidant and MCC was poured into a flowability tester (Erweka, Germany). The equipment is pressed to start when the bottom valve of the funnel opens, and the mixture flows freely over the plate, forming a cone. The flow time is read on the monitor. The flow rate is obtained from the flow time ratio to the mixed powder's weight. The equipment then emits infrared light to measure the diameter and height of the cone. The angle of rest is read on the monitor (Aulton & Taylor, 2017; Hadinugroho, Foe, et al., 2022).

2.2.5. Weight

A total of 20 tablets were randomly selected and weighed one by one (Mettler Toledo, Switzerland). All weights obtained are averaged, and the standard deviation is determined (Hadinugroho, Martodihardjo, et al., 2022).

2.2.6. Hardness

A total of 6 tablets were randomly selected and placed on a hardness tester plate (Schleuniger, Netherlands). The moving metal rod presses the tablet to crack or break. The tablet hardness value is displayed on the monitor (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

2.2.7. Friability

Tablets were randomly selected and dusted to weigh the equivalent of 6500 mg on an analytical balance (Mettler Toledo, Switzerland). All tablets were placed in a friability tester apparatus tube (Erweka, Germany). The tube was rotated at 25 rpm for 4 minutes. Once the rotation stops, each tablet is dusted again. Friability is the ratio of the difference between the treatment's initial and final weight to the initial weight (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

2.2.8. Two-factor ANOVA

Apart from graphical analysis, the experiment was analyzed using a two-factor ANOVA for each parameter value. The factors used in ANOVA are the type of glidant and the experimental concentration. The parameters analyzed are flow rate, angle of repose, hardness and brittleness. Analysis using the alpha (α) value is 0.05.

3. Results and Discussion

3.1. Synthesis of CA-LBG

The synthesis for CA-LBG is divided into 30 batches because the synthesis is adjusted to lab scale capacity and facilities. The synthesis process followed fixed procedures in previous research (Hadinugroho, Martodihardjo, et al., 2022). Dry CA-LBG yield of all batches is 1.10 g ± 1.24 g. The CA-LBG all batches were homogenized and pureed using a blender (Maspion, speed scale 4 for 8 x 5 minutes). CA-LBG fines powder was used for characterization and experiments as a glidant.

3.2. Characterization of CA-LBG

The FTIR spectra of CA-LBG are presented in Figure 1. The infrared spectrum shows that the wave number of the O-H group appears at 3318.20 cm^{-1}; C-H appears at 2923.66 cm^{-1} and 2851.10 cm^{-1}; and C=O ester appears at 1736.02 cm^{-1}. The NMR spectra of CA-LBG are presented in Figure 2. The ^{1}H NMR spectrum of CA-LBG presents two doublet peaks appearing at δ=2,927 ppm and δ=2,896 ppm, δ=2,744 and ppm, and δ=2.713 ppm, which corresponds to C–H_2 from CA. Both peaks originate from symmetric C protons in CA. These peaks indicate the presence of CA

in LBG. One adjacent proton causes a twist of the bond and a signal rupture. Multiplet peaks of mannose and galactose appeared at δ=3.990–3.329 ppm. Previous research reported that the two CA double peaks were around δ=3,083–2.714 ppm (Hadinugroho 2022, 2023). The peaks of mannose and galactose appear between δ = 4.418–3.309 ppm (Hadinugroho 2012, 2023). The CA-LBG peaks in the 13C NMR examination were δ = 176.838 ppm; δ=173,449 ppm; δ = 173.363 ppm; δ = 100.154 ppm; δ = 98,762 ppm; 96,458 ppm; 76,550 ppm; δ = 75.034 ppm; δ = 73.316 ppm; 71.425 ppm; 69,946 ppm; 69,303 ppm; 60,981 ppm; 60,521 ppm; and 43,339 ppm. The peak δ=180–170 ppm corresponds to the C=O group. The peak δ=80–70 ppm corresponds to the central C atom. The peak δ=44–43 ppm corresponding to C–H and C–H_2 appears (Doll et al., 2006; Hadinugroho et al., 2019; Jans & Kinne, 1991; Zhang et al., 2016). The peak δ=105–60 ppm corresponds to mannose, and galactose appears at δ=105–60 ppm (Azero & Andrade, 2006; Bhatia et al., 2013; Gillet et al., 2014; Hadinugroho, Martodihardjo, et al., 2022; Parvathy et al., 2005). The CA-LBG test results for viscosity were 9.49 cP ± 0.08. This viscosity is close to previous research results of around 7.82-11.37 cP (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test result for pH was 4.83. This result was compared with a CA pH of 2.05 and an LBG pH of 5.85. Tests were carried out on 1% w/v solutions of CA-LBG, CA, and LBG by dipping the pH meter electrode (Metrohm 913, Switzerland), which had been previously calibrated. The pH value of 4.83 proves that the presence of CA in LBG results in a pH value between the pH values of CA and LBG (1% b/v, pH ± 5.3) (Sheskey et al., 2017). The results of CA-LBG characterization using FTIR, NMR, viscosity, and pH show that the CA-LBG used is similar to previous experiments and can be used for further experiments as a glidant in MCC filler.

3.3. Flow rate

The flow rate test results for all experiments are presented in Table 1 and Figure 2. In general, the mixture containing MgS (M0-M4) and CA-LBG (C0-C4) has a faster flow rate than the mixture containing talc. A good pharmaceutical flow rate for powder or powder mixture is ≥ 10 g.second^{-1} (Gustaman et al., 2021; Jayani et al., 2021; Luh Putu Wrasiati & Putra, 2021; Putri, 2023). MgS and CA-LBG particles can interact well on the surface of the MCC particles so that the two glidants can make it easier for them to flow. The mixture of each glidant showed a different flow rate profile. The mixture containing talc and CA-LBG showed that increasing the glidant concentration

increased the flow rate of the mixture. The surface area of the MCC particles in the powder is sufficient to interact with many particles of talc and CA-LBG. The flow rate profile of the mixture containing MgS (M0-M2) was initially similar to the flow rate profile of the other two glidants, but at an MgS concentration of 4% (M4), the flow rate decreased. The number of MgS particles (M4) exceeds the number of MCC particles, so the surface area of the MCC particles in the powder is insufficient to interact with the MgS particles, and free MgS particles remain. MgS-free particles can inhibit the flow rate of the mixture because the MgS particles are in the form of fines.

3.4. Angle of repose

The angle of repose test results are presented in Table 1 and Figure 4. A pharmaceutically good angle of repose for powders or powder mixtures is $\leq 40^{\circ}$ (Beakawi Al-Hashemi & Baghabra Al-Amoudi, 2018; Clayton, 2018). In general, the mixture containing talc has the highest angle of repose (T0-T4). When forming a powder cone, the particles cannot move freely following the force of gravity because the particles below them restrain the movement of the particles above them. The powder cone becomes taller with a shorter base diameter. Irregular oval-shaped MCC particles dominate the mixture and have porosity so that the particle porosity becomes a stationary point holding the surrounding particles (Sheskey et al., 2017). The angle of repose improves along with increasing talc concentration (T0-T4). Talc particles can cover the porosity of MCC particles so that the MCC surface is flatter. This condition can reduce the stationary point holding particles, and the MCC particles can quickly move.

A similar angle of repose profile occurred in the mixture containing CA-LBG, but the value of the angle of repose was lower than the other two glidants. CA-LBG is an ester compound that can close the porosity of MCC particles. In addition, CA-LBG particles become slippery when the particles rub against surrounding particles. The initial angle of repose profile of the mixture containing MgS (M0-M2) is similar to the profile of the angle of repose of the other two glidants. Still, the value of the angle of repose is between the other two glidants. The lubrication mechanism also involves closing porosity and leveling the surface of the MCC particles. MgS particles are cohesive, requiring sufficient energy to interact with other particles (Goh et al., 2021; Peddapatla et al., 2016).

This condition affects the strength of interaction with MCC particles and the quality of MCC particle movement in the powder. In experiment M4, the angle of repose increased again due to

the excessive number of MgS particles in the mixture. MgS particles in the form of fines find it challenging to move and hold the particles around them.

3.5. Weight

Tablet weights for all experiments are presented in Table 1. Experiments were carried out to confirm that the mixture could flow and move to form tablets with the weight according to design. All mixtures can be compressed into tablets weighing about 700 mg with a narrow deviation. All mixtures can flow and move stably to fill the volume of the die chamber in the tablet compression machine.

3.6. Hardness

Tablet hardness test results are presented in Table 1 and Figure 5. Tablet hardness represents the quality of the interlocking bonds between deformation particles that make up the tablet. Each glidant produces varying tablet hardness because the glidant concentration influences it. The hardness profile of tablets containing talc shows high in experiments T0 and T1. Tablet hardness T0 (talc 0.5%) is controlled by the interlocking and deformation porosity of the MCC particles. The deformation of the talc particles fills the porosity of the deformation of the MCC particles so that the deformation arrangement of the particles is more stable and compact. Tablet hardness T1 (talc 1%) is similar in mechanism to T0, but the porosity between the deformation of MCC particles is full filled, more stable, and compact, so the tablet is more complex. The hardness of T2 and T4 is lower than T0 and T1 because the number of talc particles influences hardness. The large number of talc particles induces interlocking deformation of the talc particles when compressed. The interlocking formed is less strong because of the deformation of the talc particles in the form of fine particles (Sheskey et al., 2017).

The tablet hardness profile (M0-M4) in experiments containing MgS shows that the higher the MgS concentration, the lower the tablet hardness. MgS has a low bulk density (0.159 g/cm^3), so that a low concentration produces a large number of particles (Sheskey et al., 2017). The higher the MgS concentration, the more MgS particles will experience interlocking deformation, and the higher the volume on dies in the tableting machine. The interlocking of low-density particles and fines results in weak tablet hardness. The hardness profile of tablets containing CA-LBG (C0-C4) contradicts those having MgS. The higher the CA-LBG concentration, the higher the tablet's

hardness. When compressed, the fine and irregular particles of CA-LBG experience deformation and fill porosity of the deformation of the MCC particles. This condition causes the compactibility of the mixture to increase due to decreased porosity, making the resulting tablet hard. Besides that, CA-LBG is an ester derivative of LBG containing mannose and galactose. When compressed, mannose and galactose form a hard solid mass, making the resulting tablet hard.

3.7. Friability

Tablet friability test results are presented in Table 1 and Figure 6. A pharmaceutically good friability for powders or powder mixtures is < 1% (Chee et al., 2017; Mehta et al., 2012; Osei-Yeboah & Sun, 2015; Sharma et al., 2014). The friability profile of tablets containing MgS (M0-M4) shows that the higher the MgS concentration, the higher the fragility. This condition is in line with the hardness profile of the tablet because the interlocking between deformation MgS particles is not strong, and the deformation MgS particles are easily separated. Apart from that, the low density of MgS and the fines tend to cause particle deformation on the tablet's surface so that they are easily separated when subjected to mechanical movement. The friability profile of tablets containing CA-LBG showed increased friability at three initial concentrations (C0-C2). This condition is because the deformation of the CA-LBG particles does not fill the porosity between the deformation of the MCC particles. Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. Apart from that, the character of CA-LBG in the form of an ester tends to be hydrophobic and cohesive so that small amounts of CA-LBG stick to the surface of the tablet after being compressed. Hence, the tablet is not strong and releases particles when there is mechanical movement. At high concentrations (C4), the porosity between the deformation of MCC particles is filled by the deformation of CA-LBG particles because the amount is excessive, so that the tablet is more stable when subjected to mechanical movement. In addition, irregularly shaped MCC particles, after compression, experience plastic deformation so that the size of the porosity formed varies (Al-Ibraheemi et al., 2013). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.

3.8. Two-factor ANOVA

The results of the ANOVA on the effect of glidant type on each parameter are flow rate F_{count} (1425.41) > F_{table} (3.40), angle of repose F_{count} (424.27) > F_{table} (3.40), hardness F_{count} (0.52) < F_{table}

Commented [x2]: Why does teh CA-LBG at low concentration do not fill the pores of MCC particles while it does at high concentration?
Author Response:
Thank you for the question. The author has added sentence: “Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. Apart from that, the character of CA-LBG in the form of an ester tends to be hydrophobic and cohesive so that small amounts of CA-LBG stick to the surface of the tablet after being compressed.”

Since there are some statements indicate that the MCC particles deformation produce porosity during the compression, it needs some clear or detail data about it to improve the clarity of the idea explanation well.
Author Response:
Thank you for the suggestion. The author has added sentence: “In addition, irregularly shaped MCC particles, after compression, experience plastic deformation so that the size of the porosity formed varies (Al-Ibraheemi et al., 2013). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.”

(3.40), and friability F_{count} (110.10) > F_{table} (3.40). The type of glidant influences the values of flow rate, angle of repose, and friability with a significance of 0.05. The type of glidant does not have a significant effect on tablet hardness. The results of the ANOVA on the effect of glidant concentration on each parameter are flow rate F_{count} (139.52) > F_{table} (3.01), angle of repose (331.92) > F_{table} (3.01), hardness F_{count} (46.74) > F_{table} (3.01), and friability F_{count} (69.34) > F_{table} (3.01). Glidant concentration influences the values of flow rate, angle of repose, and friability with a significance of 0.05.

4. Conclusion

Based on experiments CA-LBG with compared talc and MgS as glidants, CA-LBG has potential as a glidant in MCC fillers. The higher the concentration of CA-LBG, the higher the flow rate of the mixture, the lower the angle of repose of the mixture, and the harder the tablet. CA-LBG concentrations of 0.5% and 4.0% in the mixture produced tablets with low friability.

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Figures

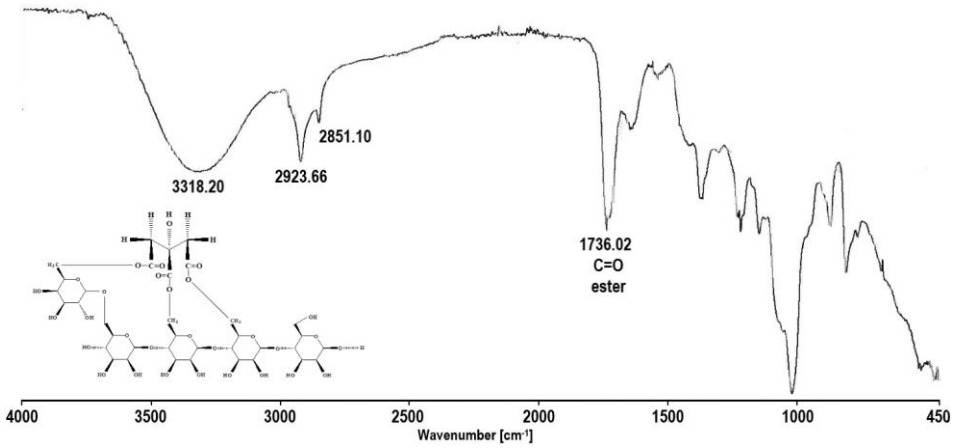

Figure 1. Infrared spectra of CA-LBG

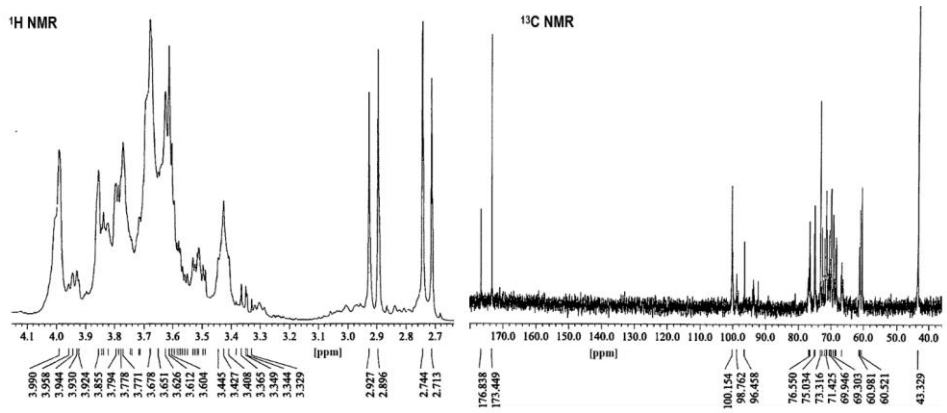

Figure 2. ^{1}H and ^{13}C NMR spectra of CA-LBG

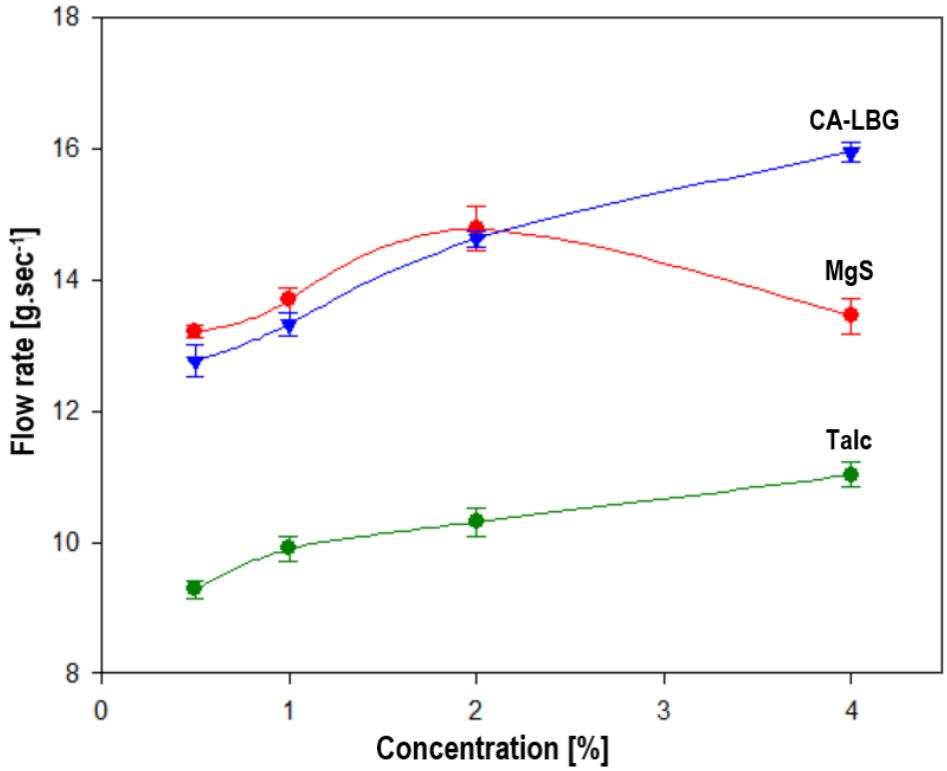

Figure 1. Profile of the relationship between glidant concentration and the flow rate of the mixture.

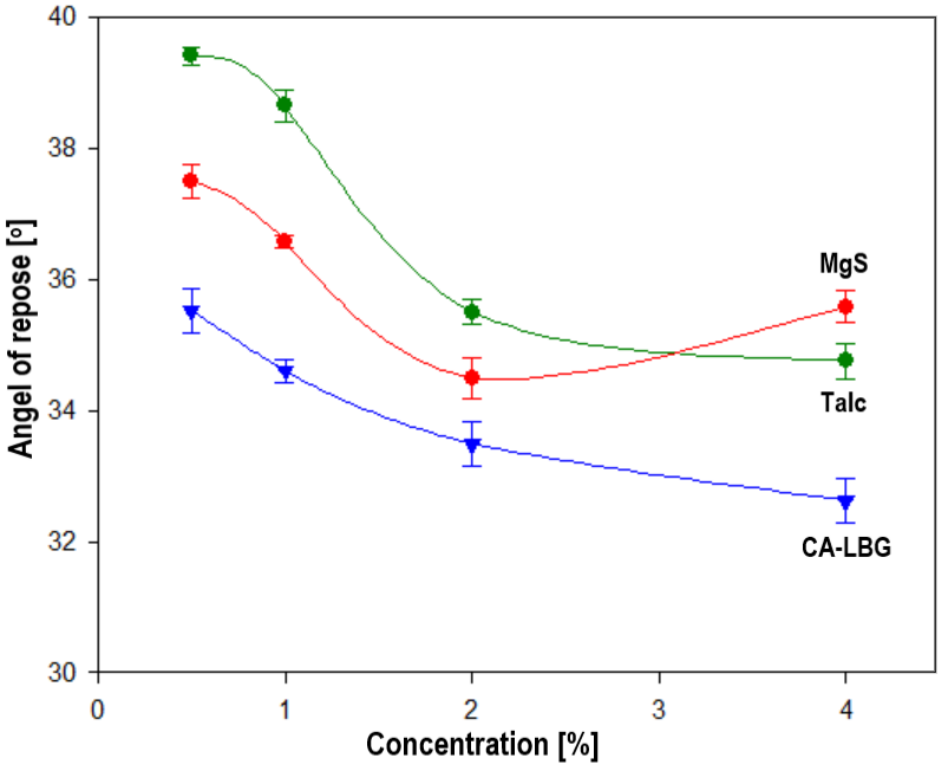

Figure 4. Profile of the relationship between glidant concentration and the angle of repose of the mixture.

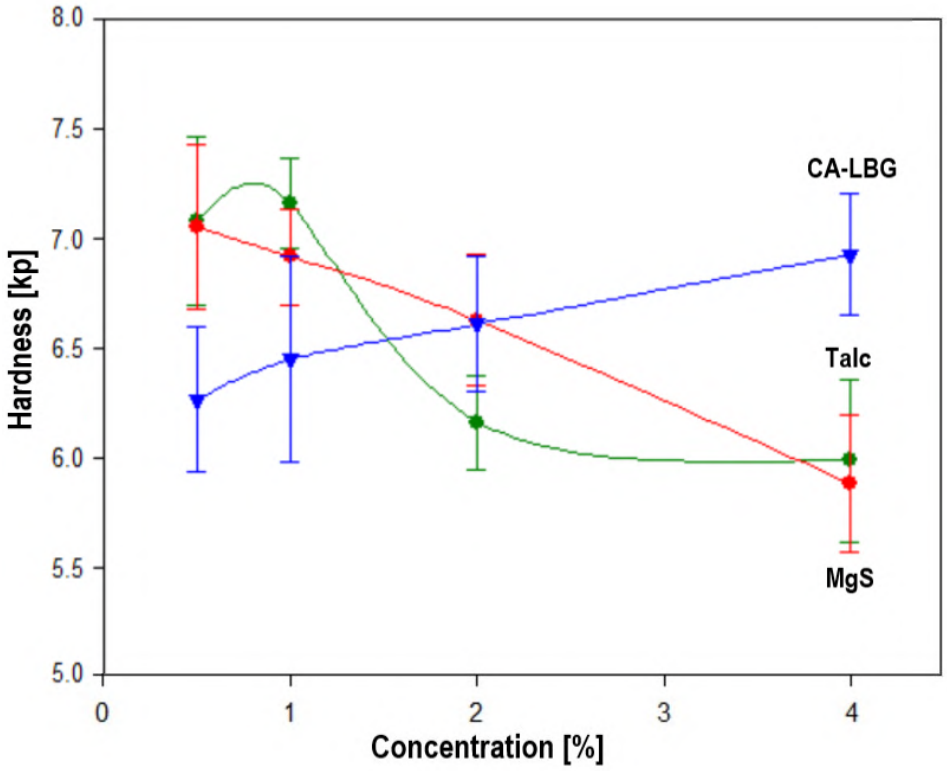

Figure 5**.** Profile of the relationship between glidant concentration and tablet hardness.

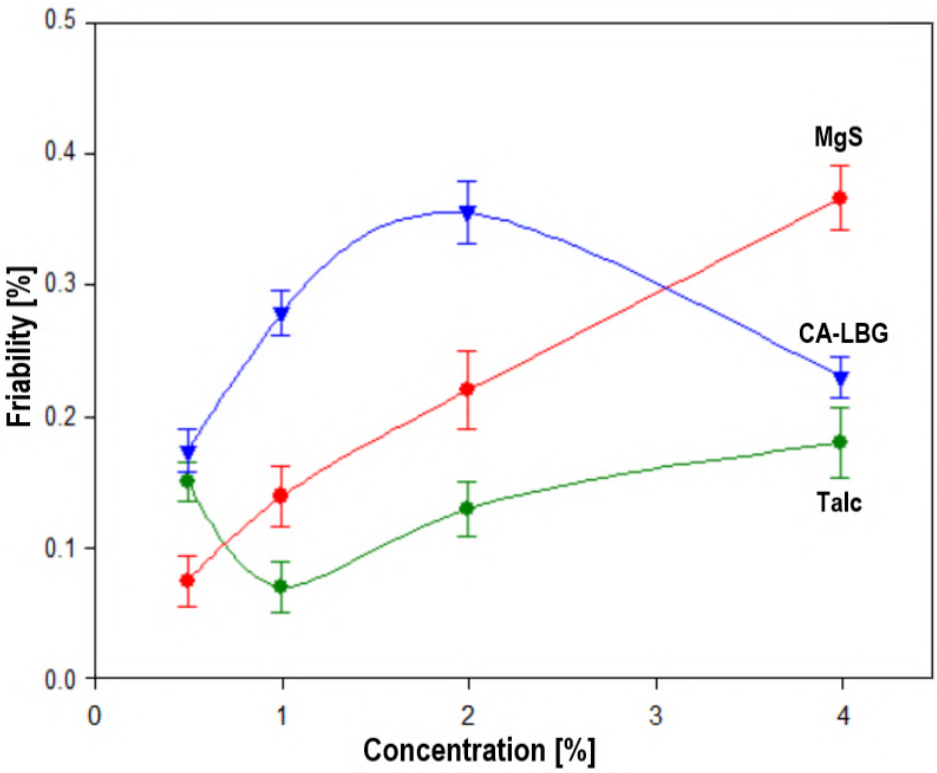

Figure 6**.** Profile of the relationship between glidant concentration and tablet friability.

Tables

Table 1. Test results on mixtures and tablets for flow rate, angle of repose, weight, hardness and friability.

Glidant	Consentration [%]	Test code	Flow rate [g.sec.$^{-1}$]	Angel of repose [o]	Weight [mg]	Hardness [kp]	Friability [%]
Talc	0.5	T0	9.29 ± 0.13	39.40 ± 0.14	702.2 ± 1.67	7.10 ± 0.38	0.15 ± 0.01
	1.0	T1	9.90 ± 0.20	38.64 ± 0.25	701.1 ± 1.43	7.20 ± 0.21	0.07 ± 0.02
	2.0	T2	10.31 ± 0.21	35.50 ± 0.19	700.2 ± 1.51	6.20 ± 0.22	0.13 ± 0.02
	4.0	T4	11.03 ± 0.19	34.75 ± 0.27	702.5 ± 1.69	6.00 ± 0.37	0.18 ± 0.03
MgS	0.5	M0	13.22 ± 0.10	37.50 ± 0.25	703.1 ± 1.47	7.10 ± 0.38	0.07 ± 0.02
	1.0	M1	13.70 ± 0.19	36.57 ± 0.10	702.6 ± 1.98	6.90 ± 0.22	0.14 ± 0.02
	2.0	M2	14.78 ± 0.34	34.49 ± 0.31	702.7 ± 1.53	6.60 ± 0.30	0.22 ± 0.03
	4.0	M4	13.46 ± 0.27	35.58 ± 0.24	702.4 ± 0.96	5.90 ± 0.31	0.37 ± 0.02
CA-LBG	0.5	C0	12.77 ± 0.25	35.52 ± 0.35	700.7 ± 1.87	6.30 ± 0.33	0.17 ± 0.02
	1.0	C1	13.33 ± 0.18	34.61 ± 0.18	701.2 ± 1.59	6.50 ± 0.47	0.28 ± 0.02
	2.0	C2	14.63 ± 0.12	33.49 ± 0.34	700.0 ± 1.37	6.60 ± 0.31	0.36 ± 0.02
	4.0	C4	15.96 ± 0.15	32.62 ± 0.33	702.1 ± 1.27	6.90 ± 0.27	0.23 ± 0.02

Response to Reviewers

Title: Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives
Manuscript number: LC-01
Revision Version: 1
Editor's Decision Received Date: February 16, 2024
Revision Submission Date: February 25, 2024

Author Response 1st revision

Reviewer 1

"The article is well-written according to the research objectives."

1. Reviewer Comments: Does only one person write the article?
   Author Response: Thank you for the question. I am Wuryanto Hadinugroho, the sole author carrying out this research work. Work includes research design, research process, data collection, data processing, data analysis, data interpretation, and writing publication manuscripts.

2. Reviewer Comments: Several improvements are related to writing the numbers after the comma of the CA-LBG concentration, experimental conditions, equipment used, and
   Author Response: The writing of numbers after the commas has been corrected in the manuscript with orange ink.

3. Reviewer Comments: Several statements require references to be referred to.
   Author Response: References have been added to the manuscript according to the suggestions provided on the side of the manuscript.

4. Reviewer Comments: The statistical analysis must be included to compare test results.
   Author Response: Thank you for the suggestion. The author has added statistic analysis (Two-factor ANOVA) to the methods section (2.2.8.) and result (3.8.).

5. Reviewer Comments: Articles are written according to the template used."
   Author Response: Thanks for the suggestion. The manuscript has been moved to the suggested template.

Reviewer 2

1. Reviewer Comments: please add some data or information of physicochemical characteristics that support the potential use of CA-LBG as a glidant for solid preparations
   Author Response: In the introduction part of the manuscript (paragraph of novelty), information about the physicochemical properties that support the potential use of CA-LBG as a glidant for solid dosage forms has been added. "In the fine form of CA-LBG, the

shape of the CA-LBG particles is irregular, the surface is wavy, difficult to dissolve in water, and is hydrophobic."

2. Reviewer Comments: please add statistical analysis section for the method and their analysis results in the result section
   Author Response: Thank you for the suggestion. The author has added statistic analysis (Two-factor ANOVA) to the methods section (2.2.8.) and result (3.8.).

3. Reviewer Comments: please check for grammatical errors
   Author Response: Thank you for the suggestion. The author has corrected the grammar of the manuscript according to suggestions. The corrected sentences are given orange ink.

4. Reviewer Comments: P4 line 3-4: please give details about the tablet compression parameters including the tabletting machine, compression force, etc.
   Author Response: Thank you for the suggestion. The author has added details about tablet compression parameters, including tablet machine and compression force, in section 2.2.3. Preparation of a mixture of MCC and glidant. The mixture is compressed (Single punch, Erweka EP-1, Germany) into tablets weighing 700 mg, diameter ± 15 mm, hardness 5-12 kp (equivalent to compression force ± 2 tons). Tablets were evaluated for weight, hardness, and friability.

5. Reviewer Comments: P5 line 3-5: how many grams for each batch? it should be clarified on the method and the recovery from all batches is really small. Does it really has potential as for glidant resources from the manufacturing perspectives?
   Author Response: Thank you for the question. The yield is 1.10 g ± 1.24 g. The author corrected that the experimental yield is in grams unit (g). Before in the manuscript, “1.1% ± 1.24” to “1.10 g ± 1.24 g.” Development research to obtain effective and efficient methods continues to be carried out today. The factors developed are the instrument and synthesis time. Specification parameters are post-synthesis polymer mass viscosity, pH, and yield.

6. Reviewer Comments: P5 line 30-31: did the author check for pH of CA and LBG? please indicate it at the method
   Author Response:
   Thank you for the question and suggestion. Yes, testing was done. The author has added testing methods in the methods and discussion sections.
   Method: "The acidity examination of CA-LBG, CA, and LBG in solution (1% w/v) used a pH meter calibrated to pH 4.0; 7.0; and 10.0 (Metrohm 913, Switzerland)."

Result and discussion: "Tests were carried out on 1% w/v solutions of CA-LBG, CA, and LBG by dipping the pH meter electrode (Metrohm 913, Switzerland), which had been previously calibrated."

7. Reviewer Comments: P8 line 8-10: these statements are not clearly understood. what is the interlocking deformation occured at high concentration of MgS and how does it occur? what is the relation of fines formation with this interlocking deformation? please clearly state it.
   Author Response: Thank you for the question and suggestion. The author has changed the previous paragraph on manuscript (orange ink):
   "The higher the MgS concentration, the more interlocking deformation of MgS particles. This interlocking force makes the tablet hardness not strong because the MgS particles are in the form of fines."
   to
   "The higher the MgS concentration, the more MgS particles will experience interlocking deformation, and the higher the volume on dies in the tableting machine. The interlocking of low-density particles and fines results in weak tablet hardness."

8. Reviewer Comments: P8 line 12-15: does the density only affect the tablet hardness in this study? what is about the porosity of MCC and particle size of shape of the CA-LBG? did the author prove this idea? and about the hardness, the important parameter is about the presence of mannose and galactose of CA-LBG as it can form solidifed mass during or after the compression. Did the author prove it?
   Author Response:
   Thank you for the question and suggestion. The author has changed the previous sentence:
   "CA-LBG is an ester derived from LBG with a density of around 0.600 g/cm3(Botelho, 2018), so the deformation of the CA-LBG particles plays a greater role in filling and reducing the porosity of the deformation of the MCC particles so that the tablets are hard."
   to
   "When compressed, the fine and irregular particles of CA-LBG experience deformation and fill porosity of the deformation of the MCC particles. This condition causes the compactibility of the mixture to increase due to decreased porosity, making the resulting tablet hard. Besides that, CA-LBG is an ester derivative of LBG containing mannose and galactose. When compressed, mannose and galactose form a hard solid mass, making the resulting tablet hard."

9. Reviewer Comments: P.8 line 27-31: Why does the CA-LBG at low concentration do not fill the pores of MCC particles while it does at high concentration?
   Author Response:

Thank you for the question. The author has added sentence (orange ink): “Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. Apart from that, the character of CA-LBG in the form of an ester tends to be hydrophobic and cohesive so that small amounts of CA-LBG stick to the surface of the tablet after being compressed.”

Since there are some statements indicate that the MCC particles deformation produce porosity during the compression, it needs some clear or detail data about it to improve the clarity of the idea explanation well.

Author Response:

Thank you for the suggestion. The author has added sentence (orange ink): “In addition, irregularly shaped MCC particles, after compression, experience plastic deformation so that the size of the porosity formed varies (Al-Ibraheemi et al., 2013). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.”

decision on your manuscript

Dari: Andang MIATMOKO (andang-m@ff.unair.ac.id)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Kamis, 28 Maret 2024 pukul 12.09 GMT+7

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we are forwarding the result of a review form STI editor. Please fulfill all questions and the similarity must be less than 20%. After revising, please send your files to this email address.
Please add your revision to the file we sent to the STI, please use a different color from the previous revision in the response to reviewer comments and revised manuscript file.

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We have reviewed the revised **manuscript LC-01**. We would like to inform you that the revised **manuscript LC-01** requires some improvements before it can be considered further to improve the quality of your article.

We hope that the author can make improvements in accordance with the attached notes and submit a revised version of your manuscript by **April 17, 2024**. Please attach a change note detailing the improvements made. If you need an extension of the revision time, please inform us. We thank you for your attention.

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Salam,

Andang Miatmoko, PhD., Apt.
1. Department of Pharmaceutical Sciences
Faculty of Pharmacy, Airlangga University
Nanizar Zaman Joenoes Building

2. Stem Cell Research and Development Center
Institute of Tropical Disease Building

Campus C Airlangga University, Mulyorejo, 60115
Surabaya

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Review LC-01 : Study of Citric Acid-Locust Bean Gum as A Glidant to Fillers of Cellulose Derivatives

1. Please add SEM data.
2. Please add XRD data.
3. in the materials section of the experimental section, please complete the chemical formula of the material you are using.
4. please note the order of the figures in your manuscript. please mention all the figures in your manuscript.
5. Your Figure 1 is very poor and does not meet the standard format of our journal. Please improve it. Pay attention to the x and y axes. I suggest you make a graph with the help of the Origin-LAB application.
6. please use the most recent year of reference. You are allowed to use references above the last 10 years up to 5%.

Re: decision on your manuscript

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

Kepada: andang-m@ff.unair.ac.id

Tanggal: Rabu, 17 April 2024 pukul 18.16 GMT+7

Dear
Mr Andang Miatmoko, PhD., Apt.

Thank you for the extension of time given by Prof. Aldes Lesbani, Ph.D. Editor-in-Chief of Science & Technology Indonesia. I have received similar results today. Along with this email, I am attaching manuscript revisions, responses to reviewers' comments, and similarity results.
If there are suggestions or other things to improve the manuscript in the future, please inform us again. I will be happy to make corrections to improve the quality of the manuscript.
Thank you for your attention and cooperation.

Yours Sincerely,
Wuryanto Hadinugroho

> Pada Rabu, 17 April 2024 pukul 12.10.19 GMT+7, Andang MIATMOKO <andang-m@ff.unair.ac.id> menulis:
>
> Dear Author,
> I am sending the reply from the journal editor, please see below
>
> Dear Commitee,
>
> Thank you for contacting us. We are pleased to inform you that we have accepted your request for an extension to submit the revision until April 24th for the LC-01 manuscript. We hope this additional time will facilitate you in making the necessary improvements. Should there be any other matters to discuss, please feel free to contact us again.
>
> Sincerely Yours,
>
> Editor-in-Chief
> **Prof. Aldes Lesbani, Ph.D.**
> Science & Technology Indonesia
> *http://sciencetechindonesia.com*
>
> On Sun, Apr 14, 2024 at 2:23 AM Wuryanto Hadinugroho <wuryanto.hadinugroho@ymail.com> wrote:
>
> > Dear
> > Mr. Andang Miatmoko, PhD., Apt.
> >
> > Happy Eid Al-Fitr 1445 H, sorry physically and mentally.
> > Thank you for the review you have submitted. In connection with assessing similarities and reprinting images according to reviewers' suggestions, I am requesting an extension until April 24, 2024. I will immediately send the revised manuscript if it is completed before that time.
> > I hope that this request will be granted. I thank you for your attention and cooperation.
> >
> > Yours Sincerely,
> > Wuryanto Hadinugroho
> >
> > Pada Kamis, 28 Maret 2024 pukul 12.09.03 GMT+7, Andang MIATMOKO <andang-m@ff.unair.ac.id> menulis:

Dear author,
we are forwarding the result of a review form STI editor. Please fulfill all questions and the similarity must be less than 20%. After revising, please send your files to this email address.
Please add your revision to the file we sent to the STI, please use a different color from the previous revision in the response to reviewer comments and revised manuscript file.

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We have reviewed the revised **manuscript LC-01**. We would like to inform you that the revised **manuscript LC-01** requires some improvements before it can be considered further to improve the quality of your article.

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Faculty of Pharmacy, Airlangga University
Nanizar Zaman Joenoes Building

2. Stem Cell Research and Development Center
Institute of Tropical Disease Building

Campus C Airlangga University, Mulyorejo, 60115
Surabaya

--
Salam,

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1. Department of Pharmaceutical Sciences
Faculty of Pharmacy, Airlangga University
Nanizar Zaman Joenoes Building

2. Stem Cell Research and Development Center
Institute of Tropical Disease Building

Campus C Airlangga University, Mulyorejo, 60115
Surabaya

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Study of Citric Acid-Locust Bean Gum as A Glidant to Fillers of Cellulose Derivatives

Wuryanto Hadinugroho[1,*]

[1] *Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, 60112, Indonesia.*

**Corresponding Author e-mail: wuryanto.hadinugroho@ymail.com*

Abstract

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. CA-LBG is a compound derived from the esterification of citric acid (CA) with locust bean gum (LBG). The experiment aimed to determine the potential and effect of CA-LBG as a glidant on microcrystalline cellulose (MCC). The CA-LBG concentrations in the experiments were 0.5%, 1.0%, 2.0%, and 4.0%. Talc and magnesium stearate (MgS) as a comparison. The mixtures were evaluated for flow rate and angle of repose. The mixture was compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability. The flow rate of the mixture containing CA-LBG 0.5%-4.0% was 12.77 $g.sec^{-1}$-15.96 $g.sec^{-1}$. The angle of repose of the mixture containing CA-LBG 0.5%-4.0% is 32.62°-35.52°. The weight of tablets containing CA-LBG 0.5%-4.0% is 700.0 mg-701.2 mg. The hardness of tablets containing CA-LBG 0.5%-4.0% is 6.30 kp-6.90 kp. The friability of tablets containing CA-LBG 0.5%-4.0% is 0.17%-0.36%. The CA-LBG has the potential as a glidant in MCC fillers. Increasing CA-LBG concentration causes the flow rate to increase, the angle of repose to decrease, and the hardness to increase. CA-LBG concentrations of 0.5% and 4.0% reduced tablet friability.

Keywords: citric acid-locust bean gum, citric acid, esterification, glidant, locust bean gum

1. Introduction

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. The published uses of CA-LBG are as a tablet disintegration agent and negative matrix in controlled-release tablets (Hadinugroho et al., 2023; Hadinugroho, Martodihardjo, et al., 2022).

CA-LBG is an ester material derived from the esterification of citric acid (CA) with locust bean gum (LBG) under acidic conditions. CA-LBG has been characterized by carbonyl ester group, solubility, viscosity, esterified CA, glass transition temperature, crystallinity index, and particle morphology. CA-LBG particles have a non-polar and hydrophobic tendency, so CA-LBG has low solubility in water (Hadinugroho et al., 2017, 2019). CA-LBG is irregular in shape and has a wavy surface (Hadinugroho et al., 2017, 2019). This character can act as a glidant in tablet formulation.

Glidant is a material that can interact with filler particles to improve flow properties. Glidant particles will be on the surface of the filler particles to cover porosity and smooth the surface of the filler particles. Changing the surface of the filler particles improves the movement of each particle (Awad et al., 2020). Glidant materials often used in pharmaceutical preparation formulations are talc and magnesium stearate (MgS). Talc and MgS particles are fines powders, hydrophobic, insoluble in water, irregular in shape and platy wavy (Meng et al., 2022; Pratiwi et al., 2017; Sheskey et al., 2017; Zarmpi et al., 2020). The character of CA-BG particles is similar to that of talc and MgS particles, thus indicating that CA-LBG is capable of glidant.

The experiments aimed to determine the potential and influence of CA-LBG as a glidant in tablet formulation. The experiment used microcrystalline cellulose (MCC), commonly used as a filler in tablet formulations. MCC particles experience plastic deformation after compression, resulting in varying porosity in the tablet (Krivokapić et al., 2020). The experiment used CA-LBG with concentrations of 0.5%, 1.0%, 2.0%, and 4.0%. Talc and magnesium stearate were used as a comparison with the same concentration. Each mixture was evaluated for flow rate and angle of repose. The mixture is then compressed directly into tablets 700 mg. Tablets were evaluated for weight, hardness, and friability. MCC was chosen as the filler model in this experiment because MCC is a filler that is often used in tablets using the direct compression method. MCC particles are water-insoluble, irregularly oval, porosity, and hydrophobic (Pratiwi et al., 2017; Sheskey et al., 2017).

The novelty of this experiment is using CA-LBG as a glidant in MCC tablet filler to observe its potency and effect at various concentrations. This experiment explores the function of CA-LBG as a glidant for tablet formulation. In the fine form of CA-LBG, the shape of the CA-LBG particles is irregular, has a wavy surface, is difficult to dissolve in water, and is hydrophobic (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). In addition, the experiment's success provides a choice of future glidant in pharmaceutical excipients.

2. Experimental Section

2.1. Materials

The materials are locust bean gum ($C_{32}H_{56}O_{26}$)(food grade) (Viscogum, Cargill, France), citric acid monohydrate ($C_6H_8O_7.H_2O$) (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (HCl) (pro analysis) (Sigma Aldrich Chemie, GmbH, USA), water for injection (H_2O) (sterile water) (PT. Otsuka Indonesia), distilled water (H_2O) (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (C_3H_6O) (technical grade) (Cawan Anugerah Chemika, Indonesia), microcrystalline cellulose ($C_{14}H_{26}O_{11}$) (pharmaceutical grade) (Flocel PH 102, Gujarat Microwax Ltd, Gujarat, India), talc ($Mg_3Si_4O_{10}(OH)_2$) (food grade) (PT. Bratachem, Indonesia) and magnesium stearate ($C_{36}H_{70}MgO_4$) (food grade) (PT. Bratachem, Indonesia).

2.2. Methods

2.2.1. Synthesis of CA-LBG

The experiment used CA-LBG synthesized using methods adopted from previous research (Hadinugroho, Martodihardjo, et al., 2022). The manufacturing principle is that a certain amount of LBG (7.10 x 10^{-6} mol in 50 mL) that has been swollen is added to a certain amount of CA (0.42 mol) and HCl (0.24 mol) as a catalyst. The homogeneous mixture was UV irradiated. The mixture was then settled and washed repeatedly with acetone-distilled water. The CA-LBG precipitate was dried at room temperature (± 25°C for 72 hours) and powdered using a blender (Maspion, speed scale 4 for 8 x 5 minutes). Before being used in experiments, CA-LBG powder was characterized, including Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), X-ray (XRD), scanning electron microscope (SEM), viscosity, and pH.

2.2.2. Characterization of CA-LBG

A qualitative examination of chemical groups from CA-LBG infrared at 400-4000 cm^{-1} using UATR (Perkin Elmer Spectrum Version 10.4.3., USA). ^{1}H and ^{13}C examination of CA-LBG using liquid state NMR spectrophotometer (JEOL RESONANCE ECZ 500R, 500 MHz, Japan). The CA-LBG diffractogram was recorded using X-ray of Cu; 1.54060A; speed 4º/minute; slit . DS: 1º, SS: 1º, RS: 0.30 mm, and range 3.0200º-80.0000º (θ-2θ) (Lab X XRD 6000, Shimadzu, Japan). The CA-LBG particle surface was recorded at a distance of 10 mm voltage of 10 kV (SEM JSM-6510LA, JEOL, Japan). Viscosity examination of CA-LBG on spindle No. S61, 60 rpm, and torque

< 10% using a Brookfield viscometer (LVDV-I Prime, AP6510416, USA). The acidity examination of CA-LBG, CA, and LBG in solution (1% w/v) used a pH meter calibrated to pH 4.0; 7.0; and 10.0 (Metrohm 913, Switzerland).

2.2.3. Preparation of a mixture of MCC and glidant

Each glidant (talc, MgS, and CA-LBG) was weighed according to the concentration of each experiment (Table 1). A quantity of MCC (Avicel PH 102) was weighed to complete up to 100 g. For one minute, glidant and MCC were mixed in a cubic mixer (Erweka, Germany). Each mixture was evaluated for flow rate and angle of repose. The mixture was compressed (Single punch, Erweka EP-1, Germany) into tablets weighing 700 mg, diameter ± 15 mm, hardness 5-12 kp (equivalent to compression force ± 2 tons). Tablets were evaluated for weight, hardness, and friability.

2.2.4. Flow rate and angel of repose

The mixture (100 g) of glidant and MCC was poured into a flowability tester (Erweka, Germany). The equipment is pressed to start when the bottom valve of the funnel opens, and the mixture flows freely over the plate, forming a cone. The flow time is read on the monitor. The flow rate is obtained from the flow time ratio to the mixed powder's weight. The equipment then emits infrared light to measure the diameter and height of the cone. The angle of rest is read on the monitor (Aulton & Taylor, 2017; Hadinugroho, Foe, et al., 2022).

2.2.5. Weight

A total of 20 tablets were randomly selected and weighed one by one (Mettler Toledo, Switzerland). All weights obtained are averaged, and the standard deviation is determined (Hadinugroho, Martodihardjo, et al., 2022).

2.2.6. Hardness

A total of 6 tablets were randomly selected and placed on a holder tester (Schleuniger, Netherlands). The hard block presses the tablet until the tablet starts to fracture. The tablet hardness value is displayed on the monitor (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

2.2.7. Friability

Tablets were randomly selected and dusted to weigh the equivalent of 6500 mg on an analytical balance (Mettler Toledo, Switzerland). All tablets were placed in a friability tester apparatus tube (Erweka, Germany). The tube was rotated at 25 rpm for 4 minutes. Once the rotation stops, each tablet is dusted again. Friability is the ratio of the difference between the treatment's initial and final weight to the initial weight (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

2.2.8. Two-factor ANOVA

Apart from graphical analysis, the experiment was analyzed using a two-factor ANOVA for each parameter value. The factors used in ANOVA are the type of glidant and the experimental concentration. The parameters analyzed are flow rate, angle of repose, hardness and friability. Analysis using the alpha (α) value is 0.05.

3. Results and Discussion

3.1. Synthesis of CA-LBG

The synthesis for CA-LBG is divided into 30 batches because the synthesis is adjusted to lab scale capacity and facilities. The synthesis process followed fixed procedures in previous research (Hadinugroho, Martodihardjo, et al., 2022). Dry CA-LBG yield of all batches is 1.10 g ± 1.24 g. The CA-LBG all batches were homogenized and pureed using a blender (Maspion, speed scale 4 for 8 x 5 minutes). CA-LBG fines powder was used for characterization and experiments as a glidant.

3.2. Characterization of CA-LBG

The FTIR spectra of CA-LBG are presented in Figure 1. The infrared spectrum shows that the wave number of the O-H group appears at 3318.20 cm^{-1}; C-H appears at 2923.66 cm^{-1} and 2851.10 cm^{-1}; and C=O ester appears at 1736.02 cm^{-1}. The NMR spectrum of CA-LBG are presented in Figure 2. Image ^{1}H CA-LBG NMR shows doublet peaks (2 pairs) at δ=2.927 ppm and δ=2.896 ppm; δ=2.744 ppm and δ=2.713 ppm, which correspond to C–H_2 of CA. Both peaks originate from symmetric C protons in CA. These peaks indicate the presence of CA in LBG. One adjacent proton

causes a twist of the bond and a signal rupture. Multiplet peaks of mannose and galactose appeared at δ=3.990–3.329 ppm. Previous research reported that the two CA double peaks were around δ=3,083–2.714 ppm (Hadinugroho 2022, 2023). The peaks of two monomers of LBG appear between δ = 4.418–3.309 ppm (Hadinugroho 2012, 2023). The CA-LBG peaks in the ^{13}C NMR examination were δ = 176.838 ppm; δ=173,449 ppm; δ = 173.363 ppm; δ = 100.154 ppm; δ = 98,762 ppm; 96,458 ppm; 76,550 ppm; δ = 75.034 ppm; δ = 73.316 ppm; 71.425 ppm; 69,946 ppm; 69,303 ppm; 60,981 ppm; 60,521 ppm; and 43,339 ppm. The peak δ=180–170 ppm corresponds to the C=O group. The peak δ=80–70 ppm corresponds to the central C atom. The peak δ=44–43 ppm corresponding to C–H and C–H_2 (Duan et al., 2020; Hadinugroho et al., 2019; Kim et al., 2017; Zhang et al., 2016). The peak δ=105–60 ppm corresponds to two monomers of LBG appearing at δ=105–60 ppm (Gillet et al., 2014; Hadinugroho, Martodihardjo, et al., 2022; Idström et al., 2016; Tian et al., 2023; Trabelsi et al., 2021). The diffractogram profile (Figure 3) shows that CA-LBG is an amorphous compound, as in previous research (Hadinugroho et al., 2019; Isasi, 2022; Singh et al., 2020). The amorphous character of CA-LBG is dominated by the LBG character, which is a galactomannan polymer with an irregular molecular arrangement (Tikhonov et al., 2019; Zheng et al., 2022). The shape of CA-LBG particles (Figure 4) is like irregular coral with a wavy surface. There are sheets attached to the coral to confirm the presence of CA in LBG (Hadinugroho et al., 2017; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test results for viscosity were 9.49 cP ± 0.08. This viscosity is close to previous research results of around 7.82-11.37 cP (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test result for pH was 4.83. This result was compared with a CA pH of 2.05 and an LBG pH of 5.85. Tests were carried out on 1% w/v solutions of CA-LBG, CA, and LBG by dipping the pH meter electrode (Metrohm 913, Switzerland), which had been previously calibrated. The pH value of 4.83 proves that the presence of CA in LBG results in a pH value between the pH values of CA and LBG (1% b/v, pH ± 5.3) (Sheskey et al., 2017). The results of CA-LBG characterization using FTIR, NMR, XRD, SEM, viscosity, and pH show that the CA-LBG used is similar to previous experiments and can be used for further experiments as a glidant in MCC filler.

3.3. Flow rate

The flow rate test results for all experiments are presented in Table 1 and Figure 5. In general,

the mixture containing MgS (M0-M4) and CA-LBG (C0-C4) has a faster flow rate than the mixture containing talc. A good pharmaceutical flow rate for powder or powder mixture is ≥ 10 g.second^{-1} (Gustaman et al., 2021; Jayani et al., 2021; Luh Putu Wrasiati & Putra, 2021; Putri, 2023). MgS and CA-LBG particles can interact well on the surface of the MCC particles so that the two glidants can make it easier for them to flow. The mixture of each glidant showed a different flow rate profile. The mixture containing talc and CA-LBG showed that increasing the glidant concentration increased the flow rate of the mixture. The surface area of the MCC particles in the powder is sufficient to interact with many particles of talc and CA-LBG. The flow rate graphic of the mixture containing MgS (M0-M2) was initially similar to the flow rate graphic of the other two glidants, but at an MgS concentration of 4% (M4), the flow rate decreased. The number of MgS particles (M4) exceeds the number of MCC particles, so the surface area of the MCC particles in the powder is insufficient to interact with the MgS particles, and free MgS particles remain. MgS-free particles can inhibit the flow rate of the mixture because the MgS particles are in the form of fines.

3.4. Angle of repose

The angle of repose test results are presented in Table 1 and Figure 6. A pharmaceutically good angle of repose for powders or powder mixtures is ≤ 40° (Beakawi Al-Hashemi & Baghabra Al-Amoudi, 2018; Clayton, 2018). In general, the mixture containing talc has the highest angle of repose (T0-T4). When forming a powder cone, the particles cannot move freely following the force of gravity because the particles below them restrain the movement of the particles above them. The powder cone becomes taller with a shorter base diameter. Irregular oval-shaped MCC particles dominate the mixture and have porosity so that the particle porosity becomes a stationary point holding the surrounding particles (Sheskey et al., 2017). The angle of repose improves along with increasing talc concentration (T0-T4). Talc particles can cover the porosity of MCC particles so that the MCC surface is flatter. This condition can reduce the stationary point holding particles, and the MCC particles can quickly move.

A similar angle of repose profile occurred in the mixture containing CA-LBG, but the value of the angle of repose was lower than the other two glidants. CA-LBG particles include esters, which can close the porosity of MCC particles and become slippery when rubbed against the surrounding particles. The initial angle of repose profile of the mixture containing MgS (M0-M2) is similar to the profile of the angle of repose of the other two glidants. Still, the value of the angle of repose is

between the other two glidants. The lubrication mechanism also involves closing porosity and leveling the surface of the MCC particles. MgS particles are cohesive, requiring sufficient energy to interact with other particles (Goh et al., 2021; Peddapatla et al., 2016).

This condition affects the strength of interaction with MCC particles and the quality of MCC particle movement in the powder. In experiment M4, the angle of repose increased again due to the excessive number of MgS particles in the mixture. MgS particles in the form of fines find it challenging to move and hold the particles around them.

3.5. Weight

Tablet weights for all experiments are presented in Table 1. Experiments were carried out to confirm that the mixture could flow and move to form tablets with the weight according to design. All mixtures can be compressed into tablets weighing about 700 mg with a narrow deviation. All mixtures can flow and move stably to fill the volume of the die chamber in the tablet compression machine.

3.6. Hardness

Tablet hardness test results are presented in Table 1 and Figure 7. Tablet hardness represents the interlocking strength between deformation particles of the tablet material. Each glidant produces varying tablet hardness because the glidant concentration influences it. The hardness profile of tablets containing talc shows high in experiments T0 and T1. Tablet hardness T0 (talc 0.5%) is controlled by the interlocking and deformation porosity of the MCC particles. The deformation of the talc particles fills the porosity of the deformation of the MCC particles so that the deformation arrangement of the particles is more stable and compact. Tablet hardness T1 (talc 1%) is similar in mechanism to T0, but the porosity between the deformation of MCC particles is full filled, more stable, and compact, so the tablet is more complex. The hardness of T2 and T4 is lower than T0 and T1 because the number of talc particles influences hardness. The large number of talc particles induces interlocking deformation of the talc particles when compressed. The interlocking formed is less strong because of the deformation of the talc particles in the form of fine particles (Sheskey et al., 2017).

The tablet hardness graphic (M0-M4) in experiments containing MgS shows that the higher the MgS concentration, the lower the tablet hardness. MgS has a low bulk density (0.159 g/cm^3),

so that a low concentration produces a large number of particles (Sheskey et al., 2017). The higher the MgS concentration, the more MgS particles will experience interlocking deformation, and the higher the volume on dies in the tableting machine. The interlocking of low-density particles and fines results in weak tablet hardness. The hardness graph of CA-LBG tablets (C0-C4) contradicts MgS tablets. A high concentration of CA-LBG increases tablet hardness. When compressed, the fine and irregular particles of CA-LBG experience deformation and fill porosity of the deformation of the MCC particles. This condition causes the compactibility of the mixture to increase due to decreased porosity, making the resulting tablet hard. Besides that, CA-LBG is an ester derivative of LBG containing mannose and galactose. When compressed, mannose and galactose form a hard solid mass, making the resulting tablet hard.

3.7. Friability

Tablet friability test results are presented in Table 1 and Figure 8. A pharmaceutically good friability for powders or powder mixtures is < 1% (Aslani & Beigi, 2016; Chee et al., 2017; Fouad et al., 2020; Osei-Yeboah & Sun, 2015). The friability profile of tablets containing MgS (M0-M4) shows that the higher the MgS concentration, the higher the friability. This condition is in line with the hardness profile of the tablet because the interlocking between deformation MgS particles is not strong, and the deformation MgS particles are easily separated. In addition, the fines of MgS tend to be on the tablet's surface so that the fines are easily separated when the tablet is rotated. Tablets containing CA-LBG showed increased friability at three initial concentrations (C0-C2). This condition is caused by the CA-LBG deformation not occupying the porosity between the MCC deformation. Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. In addition, the ester nature causes CA-LBG to tend to be hydrophobic, cohesive, and stick to the outer part of the tablet. Hence, the tablet is not strong and releases particles when there is mechanical movement. At high concentrations (C4), the porosity between MCC deformations is occupied by CA-LBG deformations due to their excessive amount, so the tablet is more stable when rotated. The influence of the irregular shape of MCC after being compressed undergoes plastic deformation, causing the size of the porosity formed to vary (Krivokapić et al., 2020). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.

4. Conclusion

Based on experiments CA-LBG with compared talc and MgS as glidants, CA-LBG has potential as a glidant in MCC fillers. High concentration CA-LBG increases the mixture's flow rate, decreases the repose's angle, and hardens the tablet. CA-LBG concentrations of 0.5% and 4.0% in the mixture produced tablets with low friability.

Acknowledgement

The author would like to thank the Faculty of Pharmacy, Gadjah Mada University and the Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, for providing laboratory facilities. The author also thanks Dr. apt. Lannie Hadisoewignyo, M.Si., who provided raw materials for this research.

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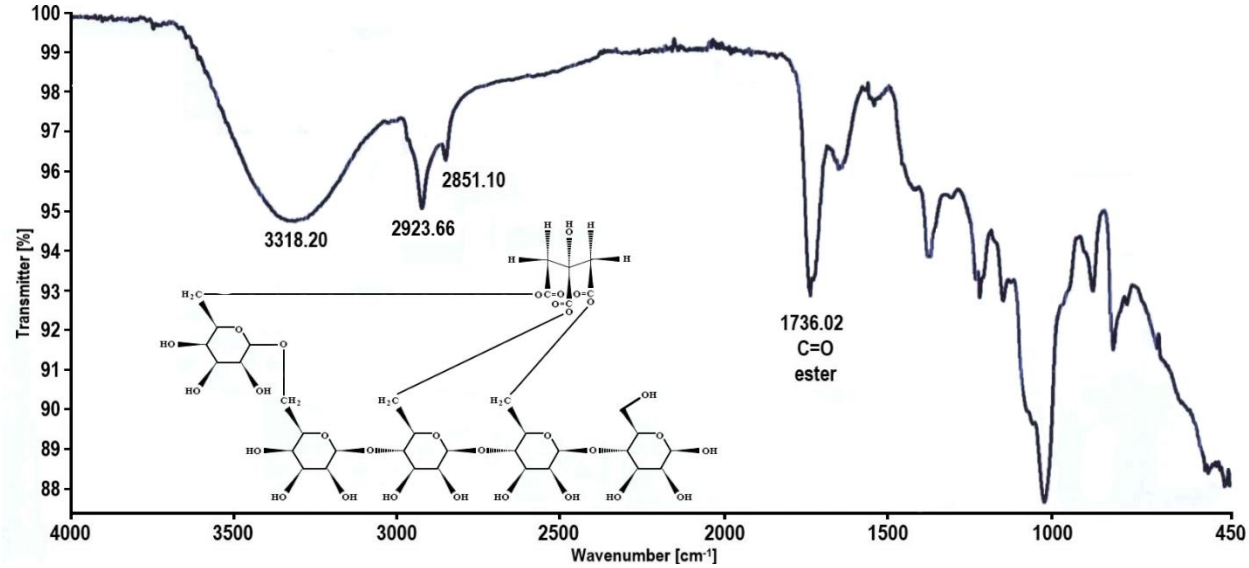


Figure 1. Infrared spectra of CA-LBG

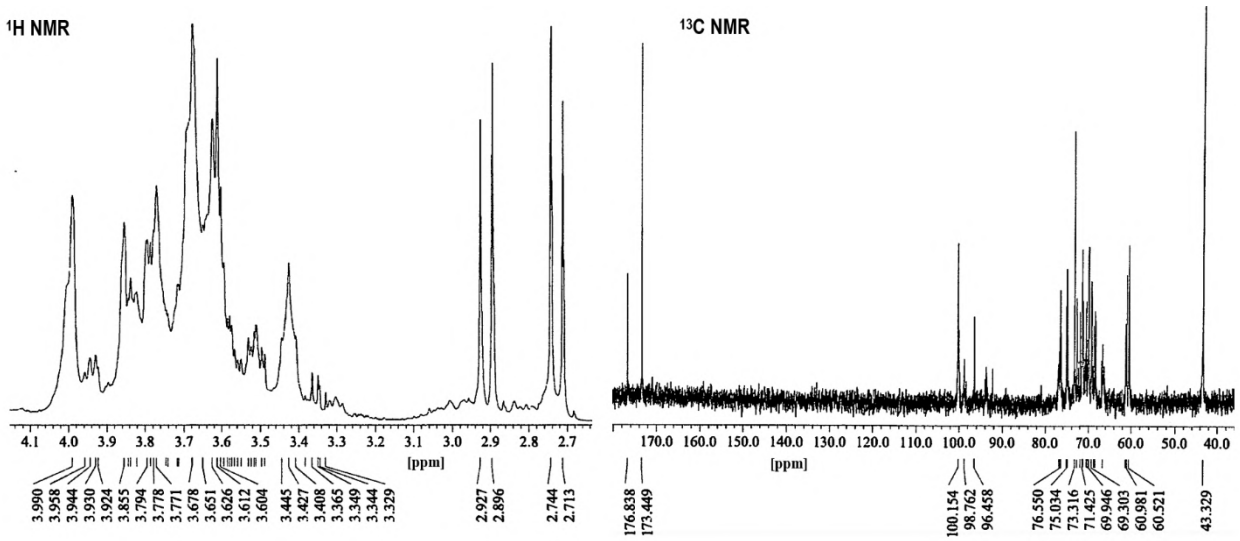


Figure 2**.** ^{1}H and ^{13}C NMR spectra of CA-LBG

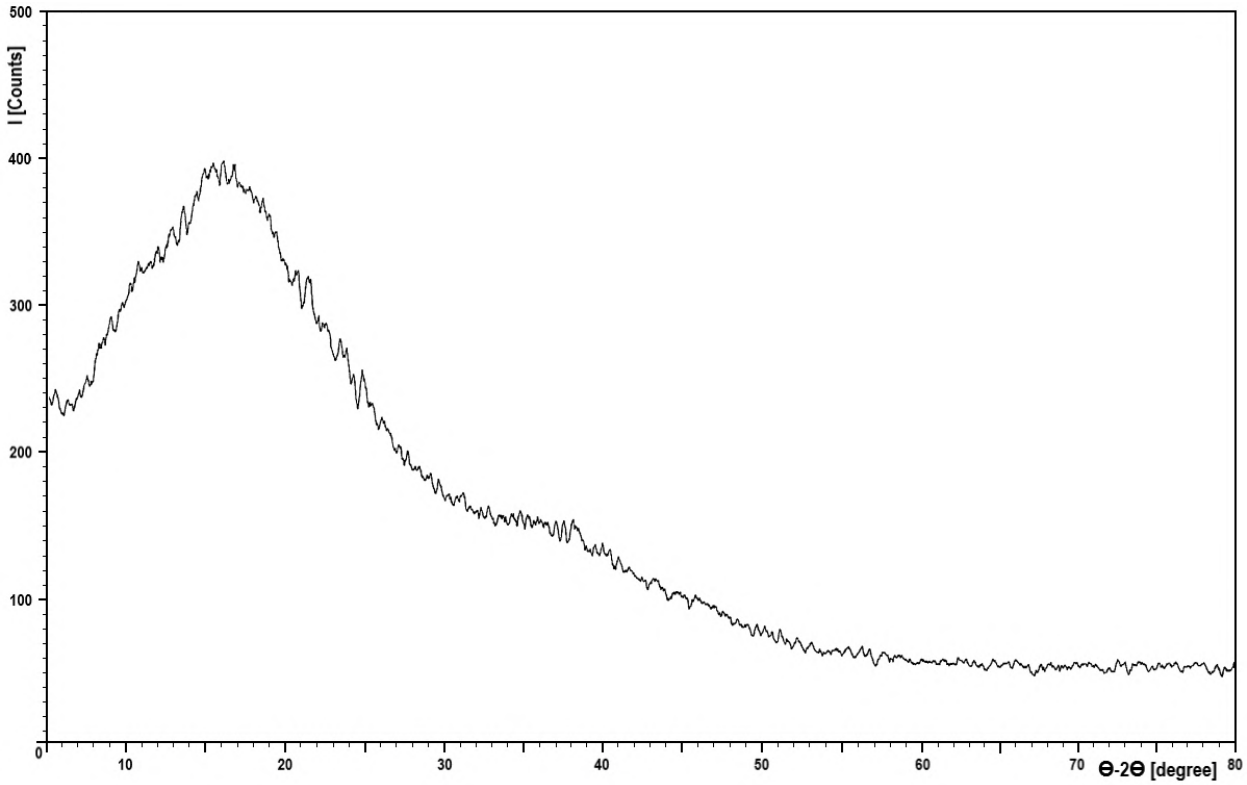


Figure 3. XRD diffractogram of CA-LBG

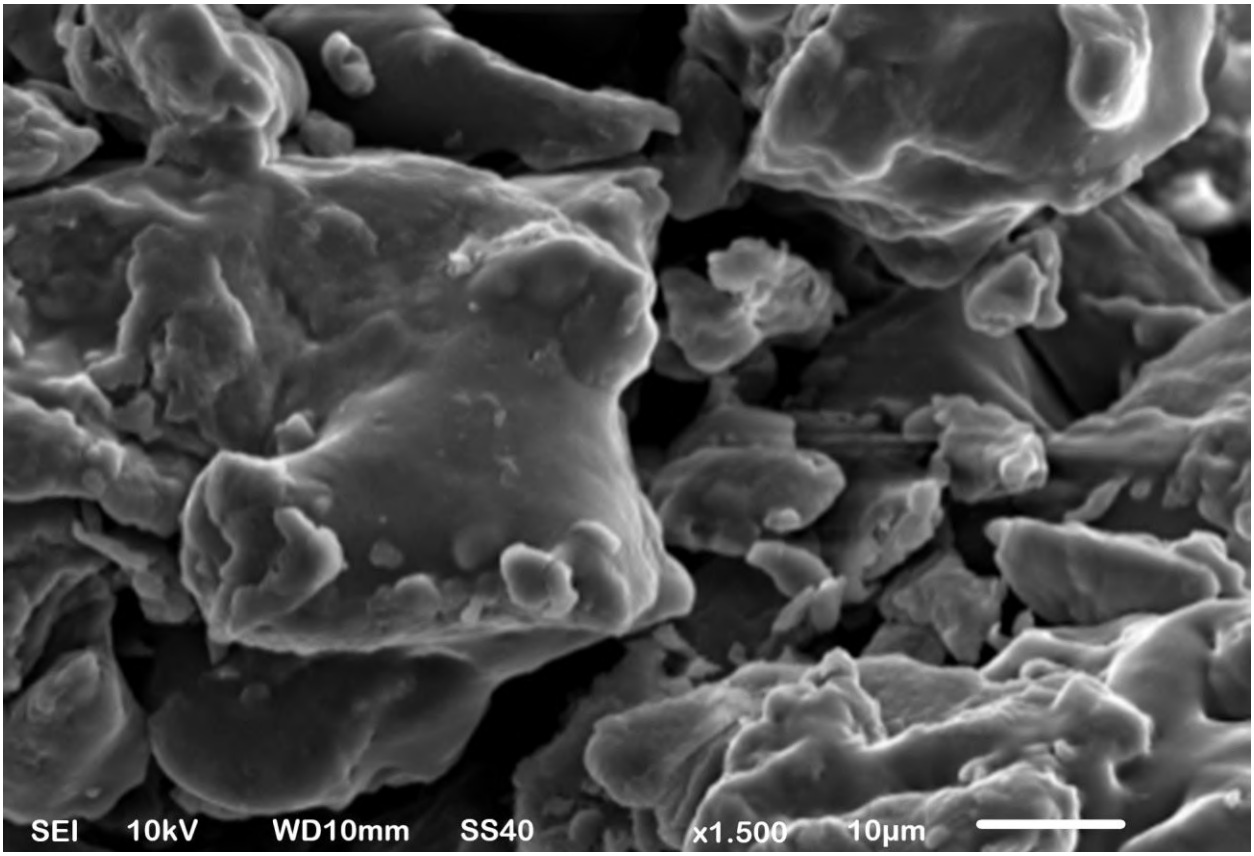


Figure 4. SEM images of CA-LBG

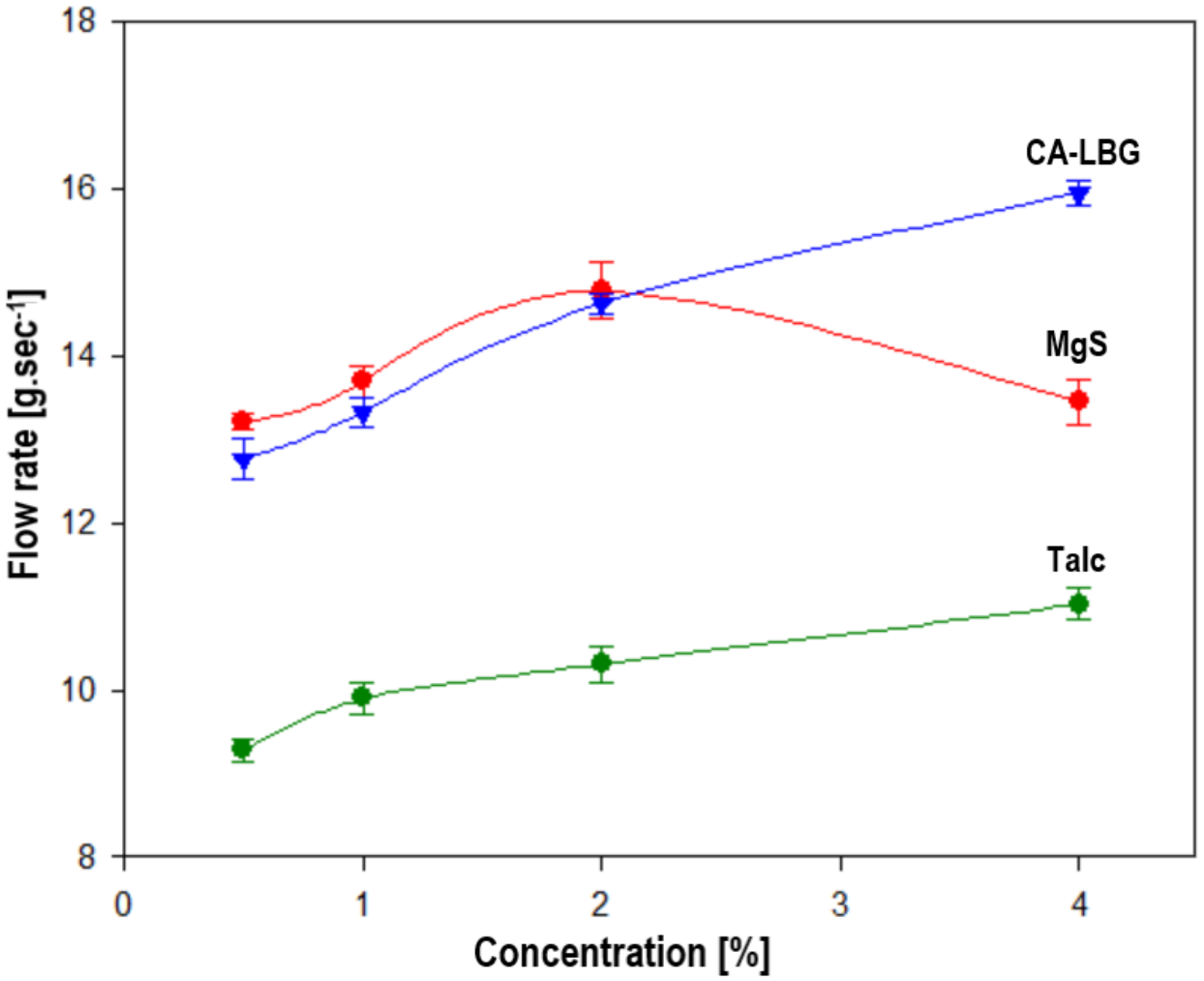


Figure 5. Profile of the relationship between glidant and the flow rate of the mixture. The ANOVA result of the type of glidant to flow rate is F_{count} (1425.41) > F_{table} (3.40) and glidant concentration to flow rate is F_{count} (139.52) > F_{table} (3.01), which means that the type of glidant and glidant concentration has an effect on the flow rate with a significance of 0.05.

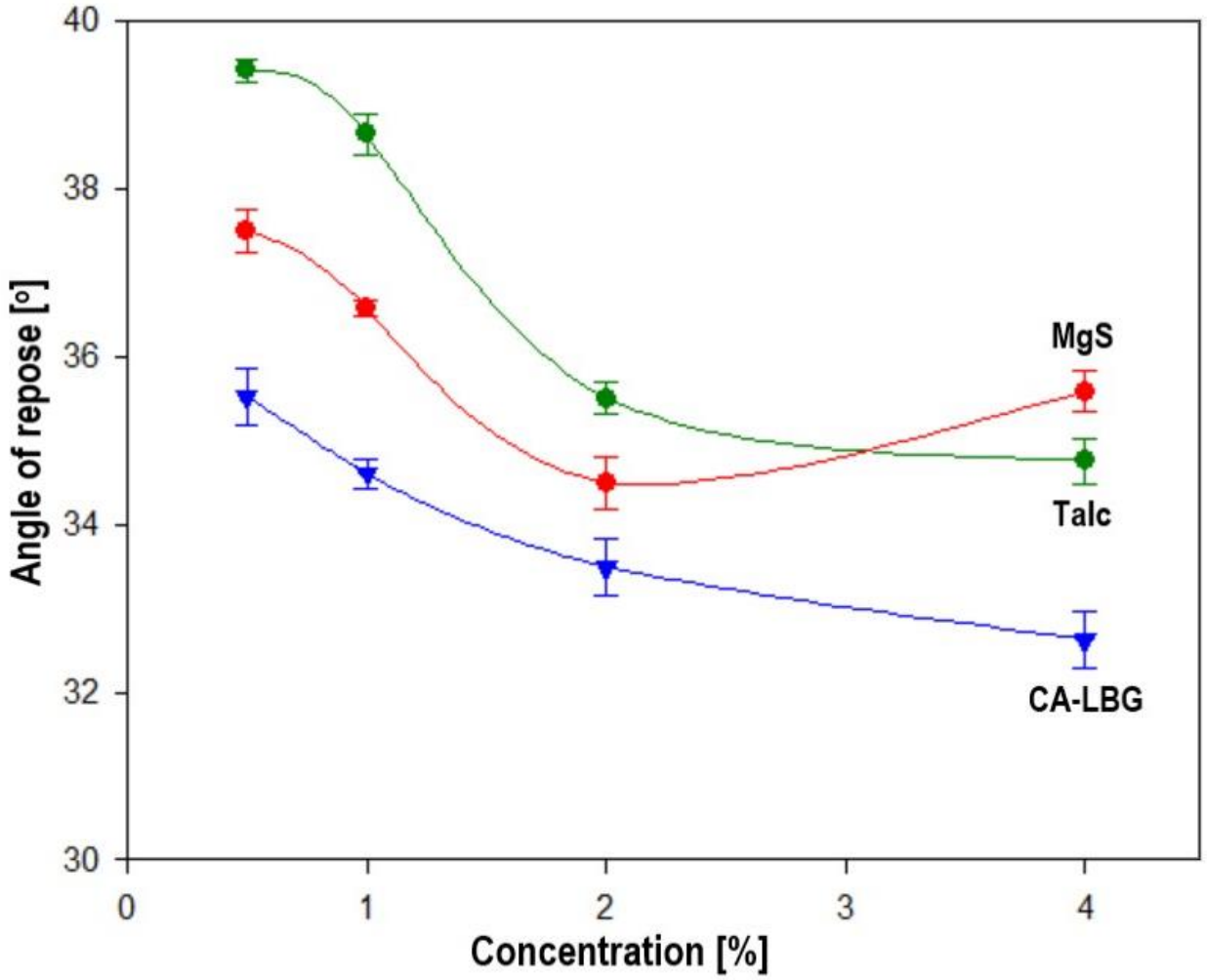


Figure 6. Profile of the relationship between glidant and the angle of repose of the mixture. The ANOVA result of the type of glidant to angle of repose is F_{count} (424.27) > F_{table} (3.40) and glidant concentration to angle of repose is F_{count} (331.92) > F_{table} (3.01), which means that the type of glidant and glidant concentration has an effect on the angle of repose with a significance of 0.05.

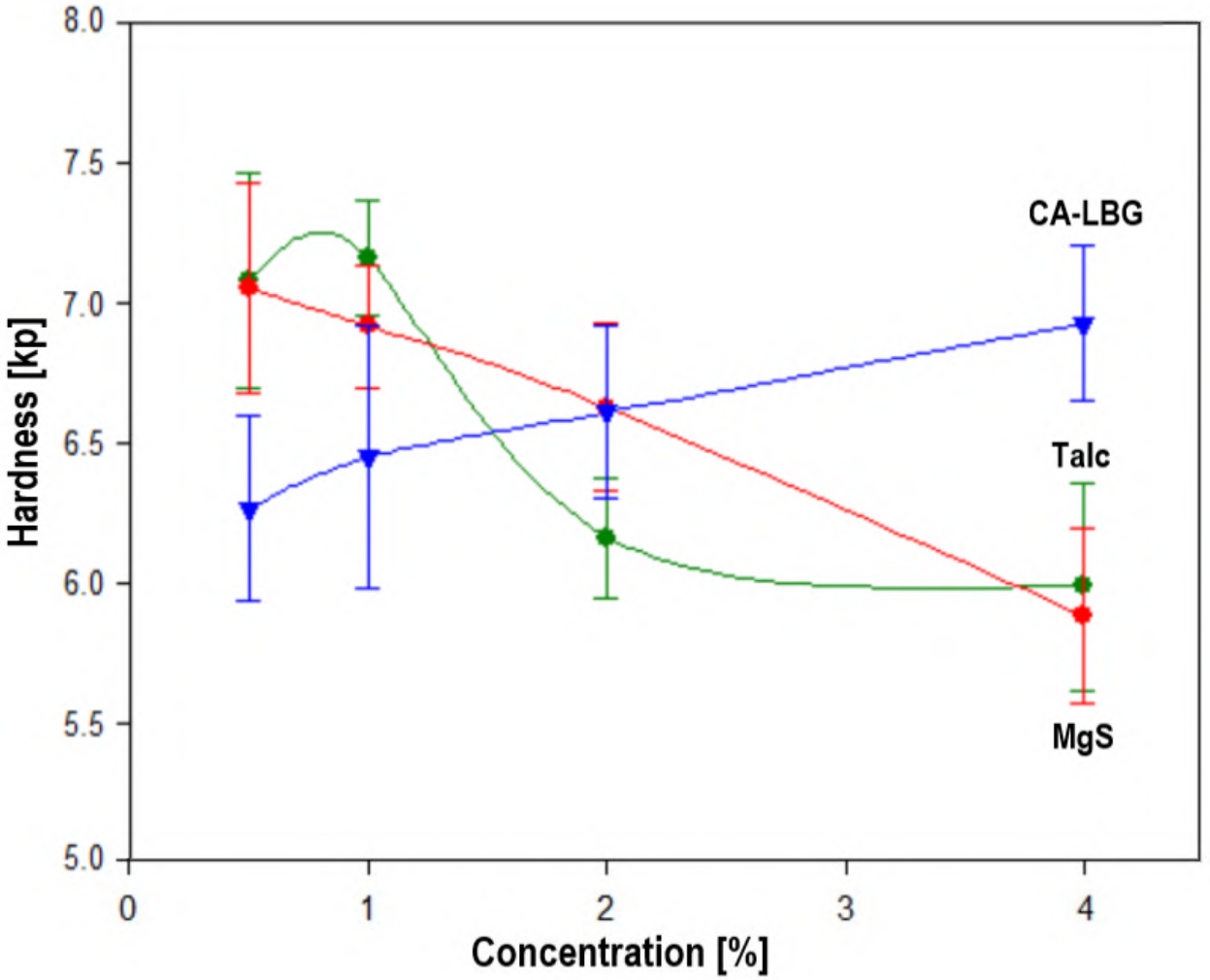


Figure 7**.** Profile of the relationship glidant and hardness. The ANOVA result of the type of glidant to the angle of repose is F_{count} (0.52) < F_{table} (3.40) and glidant concentration to the hardness is F_{count} (46.74) > F_{table} (3.01). The type of glidant has an effect that is not significant to the hardness, but glidant concentration has an effect on the hardness with a significance of 0.05.

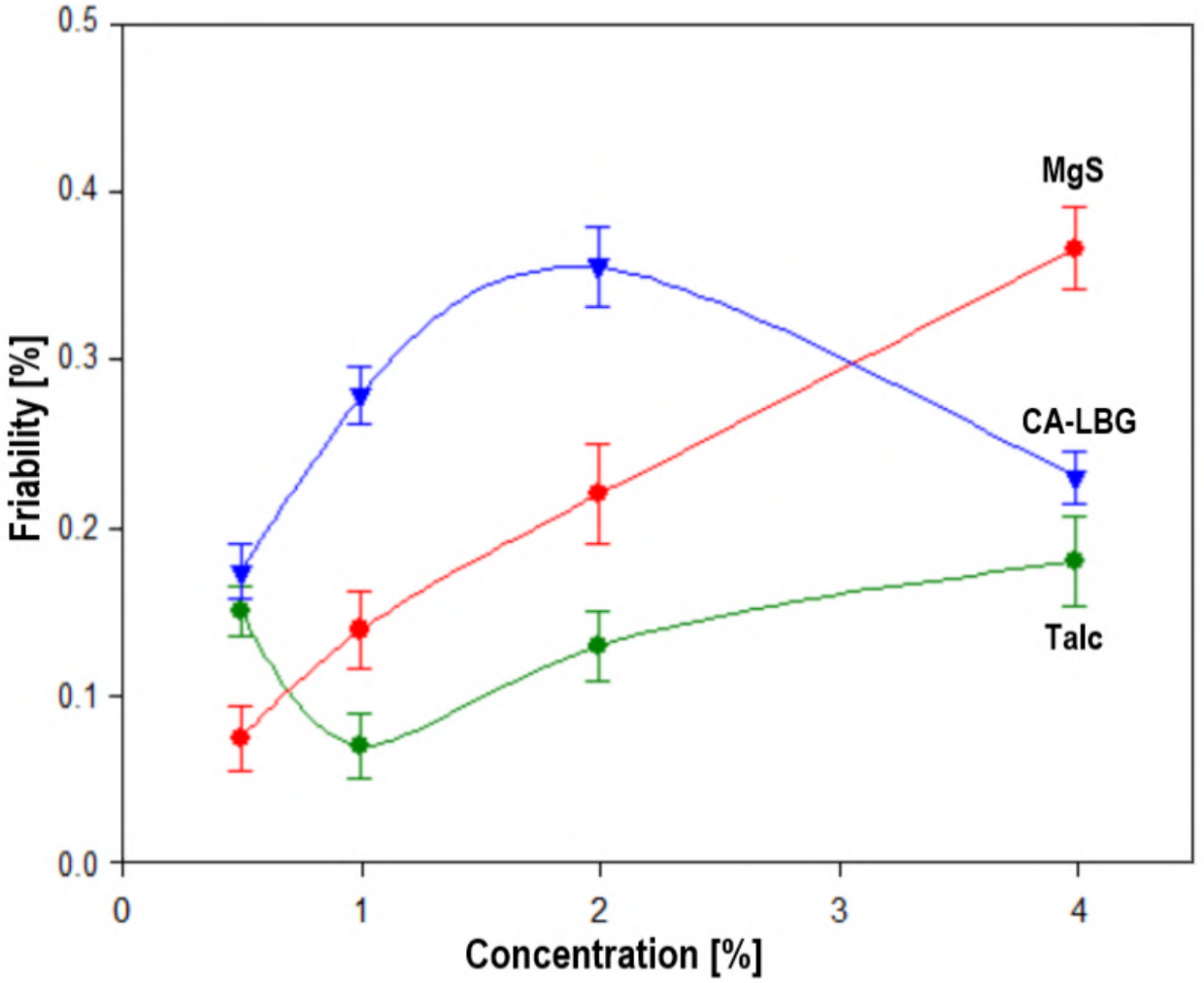


Figure 8**.** Profile of the relationship between glidant and tablet friability. The ANOVA result of the type of glidant to friability is F_{count} (110.10) > F_{table} (3.40) and glidant concentration to friability is F_{count} (69.34) > F_{table} (3.01), which means that the type of glidant and glidant concentration has an effect on the friability with a significance of 0.05.

Tables

Table 1. Test results on mixtures and tablets for flow rate, angle of repose, weight, hardness and friability.

Glidant	Consentration [%]	Test code	Flow rate [g.sec.$^{-1}$]	Angle of repose [º]	Weight [mg]	Hardness [kp]	Friability [%]
Talc	0.5	T0	9.29 ± 0.13	39.40 ± 0.14	702.2 ± 1.67	7.10 ± 0.38	0.15 ± 0.01
	1.0	T1	9.90 ± 0.20	38.64 ± 0.25	701.1 ± 1.43	7.20 ± 0.21	0.07 ± 0.02
	2.0	T2	10.31 ± 0.21	35.50 ± 0.19	700.2 ± 1.51	6.20 ± 0.22	0.13 ± 0.02
	4.0	T4	11.03 ± 0.19	34.75 ± 0.27	702.5 ± 1.69	6.00 ± 0.37	0.18 ± 0.03
MgS	0.5	M0	13.22 ± 0.10	37.50 ± 0.25	703.1 ± 1.47	7.10 ± 0.38	0.07 ± 0.02
	1.0	M1	13.70 ± 0.19	36.57 ± 0.10	702.6 ± 1.98	6.90 ± 0.22	0.14 ± 0.02
	2.0	M2	14.78 ± 0.34	34.49 ± 0.31	702.7 ± 1.53	6.60 ± 0.30	0.22 ± 0.03
	4.0	M4	13.46 ± 0.27	35.58 ± 0.24	702.4 ± 0.96	5.90 ± 0.31	0.37 ± 0.02
CA-LBG	0.5	C0	12.77 ± 0.25	35.52 ± 0.35	700.7 ± 1.87	6.30 ± 0.33	0.17 ± 0.02
	1.0	C1	13.33 ± 0.18	34.61 ± 0.18	701.2 ± 1.59	6.50 ± 0.47	0.28 ± 0.02
	2.0	C2	14.63 ± 0.12	33.49 ± 0.34	700.0 ± 1.37	6.60 ± 0.31	0.36 ± 0.02
	4.0	C4	15.96 ± 0.15	32.62 ± 0.33	702.1 ± 1.27	6.90 ± 0.27	0.23 ± 0.02

Response to Reviewers

Title: Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives
Manuscript number: LC-01
Revision Version: 2 **(blue ink)**
Editor's Decision Received Date: March 28, 2024
Revision Submission Date: April 20, 2024

1. Reviewer Comments: Please add SEM data.
   Author Response: Thank you for the suggestion. The author has added a SEM image (Figure 4) in the results and discussion section.

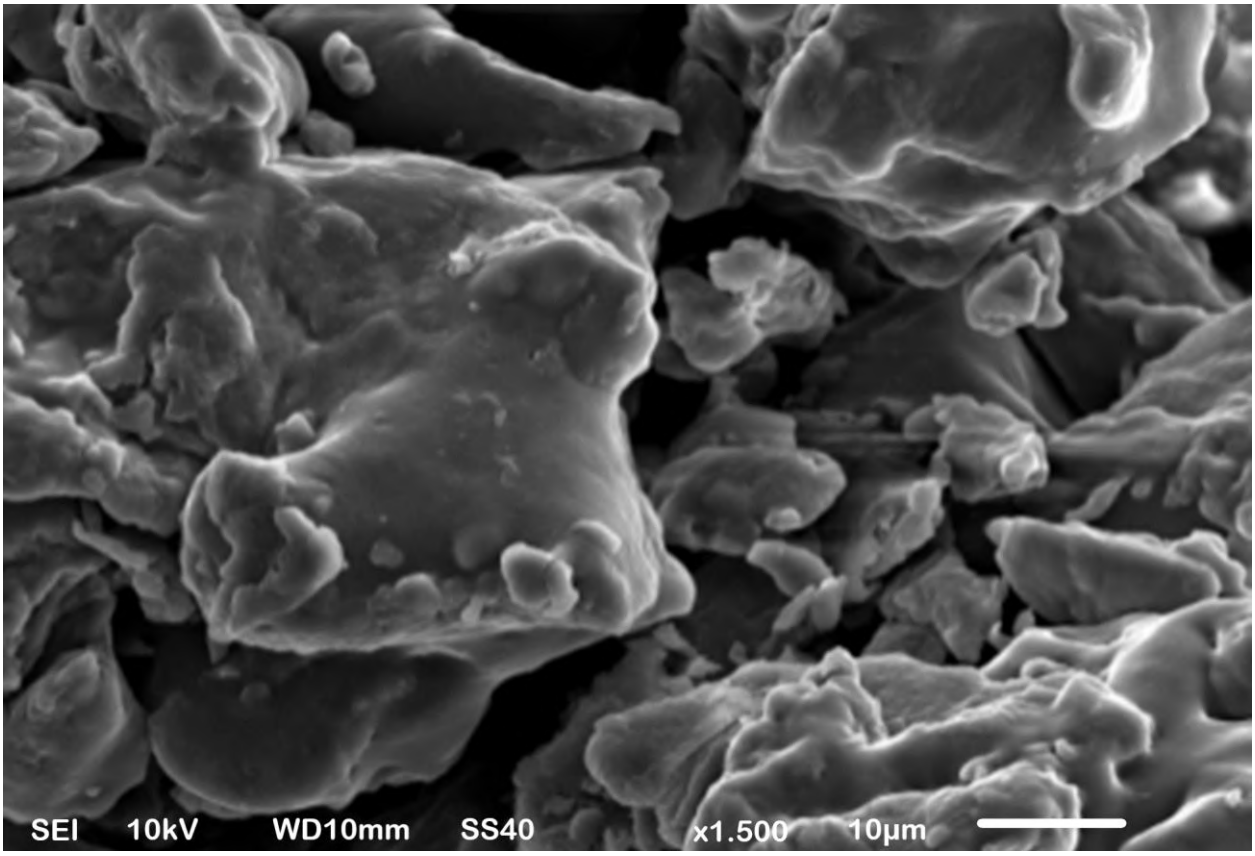


Figure 4. SEM images of CA-LBG

2. Reviewer Comments: Please add XRD data.
   Author Response: Thank you for the suggestion. The author has added a XRD diffractogram (Figure 3) in the results and discussion section.

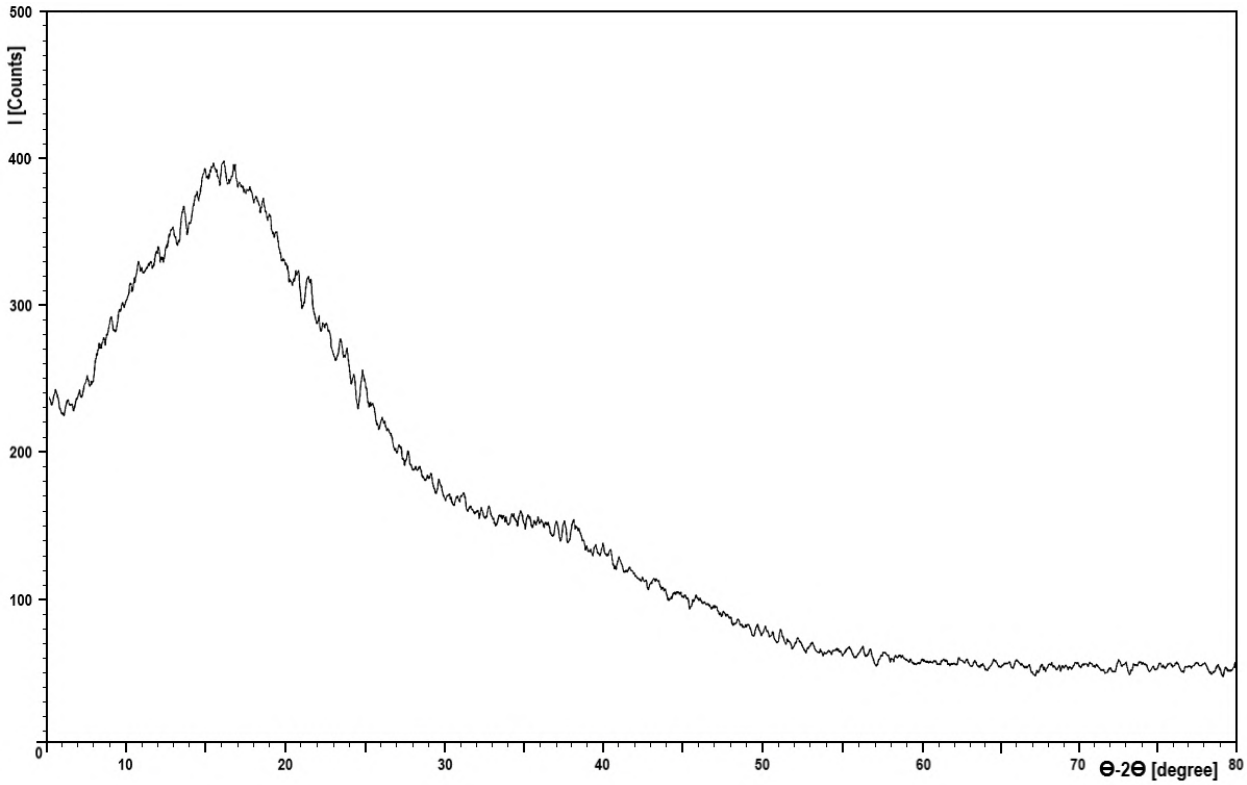


Figure 3. XRD diffractogram of CA-LBG

3. Reviewer Comments: in the materials section of the experimental section, please complete the chemical formula of the material you are using.

   Author Response: Thank you for the suggestion. The author has added the chemical structure of each material in the materials section.

   Materials

   The materials are locust bean gum ($C_{32}H_{56}O_{26}$)(food grade) (Viscogum, Cargill, France), citric acid monohydrate ($C_6H_8O_7.H_2O$) (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (HCl) (pro analysis) (Sigma Aldrich Chemie, GmbH, USA), water for injection (H_2O) (sterile water) (PT. Otsuka Indonesia), distilled water (H_2O) (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (C_3H_6O) (technical grade) (Cawan Anugerah Chemika, Indonesia), microcrystalline cellulose ($C_{14}H_{26}O_{11}$) (pharmaceutical grade) (Flocel PH 102, Gujarat Microwax Ltd, Gujarat, India), talc ($Mg_3Si_4O_{10}(OH)_2$) (food grade) (PT. Bratachem, Indonesia) and magnesium stearate ($C_{36}H_{70}MgO_4$) (food grade) (PT. Bratachem, Indonesia).

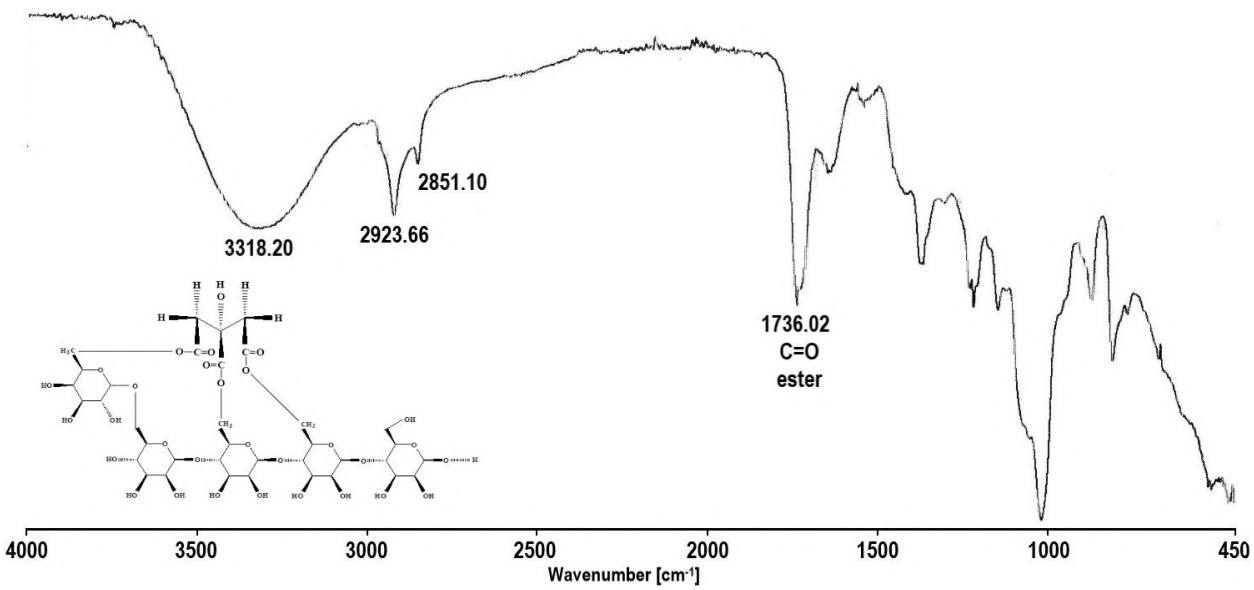
4. Reviewer Comments: please note the order of the figures in your manuscript. please mention all the figures in your manuscript.

   Author Response: Thank you for the suggestion. The author has corrected and ordered the figure according to the number. In the results and discussion sections, figure numbers have been given according to each subtopic.

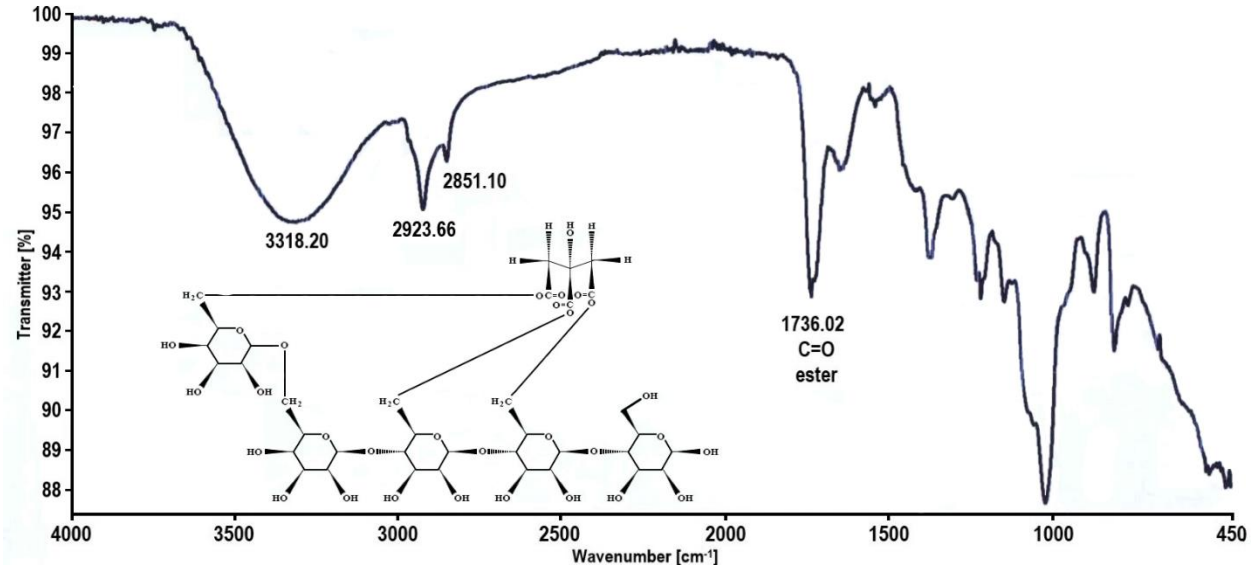
5. Reviewer Comments: Your Figure 1 is very poor and does not meet the standard format of our journal. Please improve it. Pay attention to the x and y axes. I suggest you make a graph with the help of the Origin-LAB application.

   Author Response: Thank you for the suggestion. The author has corrected figure 1 to make it clearer.

   before:



   after:



6. Reviewer Comments: please use the most recent year of reference. You are allowed to use references above the last 10 years up to 5%.
   Author Response: Thank you for the suggestion. The author has corrected the citations and references according to the reviewer's suggestions. The oldest reference used in this manuscript is in 2014.

Response to Reviewers
Title: Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives
Manuscript number: LC-01
Revision Version: 1 (Orange ink)
Editor's Decision Received Date: February 16, 2024
Revision Submission Date: February 25, 2024

Author Response 1st revision

Reviewer 1
"The article is well-written according to the research objectives."
1. Reviewer Comments: Does only one person write the article?
   Author Response: Thank you for the question. I am Wuryanto Hadinugroho, the sole author carrying out this research work. Work includes research design, research process, data collection, data processing, data analysis, data interpretation, and writing publication manuscripts.

2. Reviewer Comments: Several improvements are related to writing the numbers after the comma of the CA-LBG concentration, experimental conditions, equipment used, and
   Author Response: The writing of numbers after the commas has been corrected in the manuscript with orange ink.

3. Reviewer Comments: Several statements require references to be referred to.
   Author Response: References have been added to the manuscript according to the suggestions provided on the side of the manuscript.

4. Reviewer Comments: The statistical analysis must be included to compare test results.
   Author Response: Thank you for the suggestion. The author has added statistic analysis (Two-factor ANOVA) to the methods section (2.2.8.) and result (3.8.).

5. Reviewer Comments: Articles are written according to the template used."
   Author Response: Thanks for the suggestion. The manuscript has been moved to the suggested template.

Reviewer 2

1. Reviewer Comments: please add some data or information of physicochemical characteristics that support the potential use of CA-LBG as a glidant for solid preparations
   Author Response: In the introduction part of the manuscript (paragraph of novelty), information about the physicochemical properties that support the potential use of CA-LBG as a glidant for solid dosage forms has been added. "In the fine form of CA-LBG, the shape of the CA-LBG particles is irregular, the surface is wavy, difficult to dissolve in water, and is hydrophobic."

2. Reviewer Comments: please add statistical analysis section for the method and their analysis results in the result section
   Author Response: Thank you for the suggestion. The author has added statistic analysis (Two-factor ANOVA) to the methods section (2.2.8.) and result (3.8.).

3. Reviewer Comments: please check for grammatical errors
   Author Response: Thank you for the suggestion. The author has corrected the grammar of the manuscript according to suggestions. The corrected sentences are given orange ink.

4. Reviewer Comments: P4 line 3-4: please give details about the tablet compression parameters including the tabletting machine, compression force, etc.
   Author Response: Thank you for the suggestion. The author has added details about tablet compression parameters, including tablet machine and compression force, in section 2.2.3. Preparation of a mixture of MCC and glidant. The mixture is compressed (Single punch, Erweka EP-1, Germany) into tablets weighing 700 mg, diameter ± 15 mm, hardness 5-12 kp (equivalent to compression force ± 2 tons). Tablets were evaluated for weight, hardness, and friability.

5. Reviewer Comments: P5 line 3-5: how many grams for each batch? it should be clarified on the method and the recovery from all batches is really small. Does it really has potential as for glidant resources from the manufacturing perspectives?
   Author Response: Thank you for the question. The yield is 1.10 g ± 1.24 g. The author corrected that the experimental yield is in grams unit (g). Before in the manuscript, “1.1% ± 1.24” to “1.10 g ± 1.24 g.” Development research to obtain effective and efficient methods continues to be carried out today. The factors developed are the instrument and synthesis time. Specification parameters are post-synthesis polymer mass viscosity, pH, and yield.

6. Reviewer Comments: P5 line 30-31: did the author check for pH of CA and LBG? please indicate it at the method
   Author Response:
   Thank you for the question and suggestion. Yes, testing was done. The author has added testing methods in the methods and discussion sections.

Method: "The acidity examination of CA-LBG, CA, and LBG in solution (1% w/v) used a pH meter calibrated to pH 4.0; 7.0; and 10.0 (Metrohm 913, Switzerland)."
Result and discussion: "Tests were carried out on 1% w/v solutions of CA-LBG, CA, and LBG by dipping the pH meter electrode (Metrohm 913, Switzerland), which had been previously calibrated."

7. Reviewer Comments: P8 line 8-10: these statements are not clearly understood. what is the interlocking deformation occured at high concentration of MgS and how does it occur? what is the relation of fines formation with this interlocking deformation? please clearly state it.
   Author Response: Thank you for the question and suggestion. The author has changed the previous paragraph on manuscript (orange ink):
   "The higher the MgS concentration, the more interlocking deformation of MgS particles. This interlocking force makes the tablet hardness not strong because the MgS particles are in the form of fines."
   to
   "The higher the MgS concentration, the more MgS particles will experience interlocking deformation, and the higher the volume on dies in the tableting machine. The interlocking of low-density particles and fines results in weak tablet hardness."

8. Reviewer Comments: P8 line 12-15: does the density only affect the tablet hardness in this study? what is about the porosity of MCC and particle size of shape of the CA-LBG? did the author prove this idea? and about the hardness, the important parameter is about the presence of mannose and galactose of CA-LBG as it can form solidifed mass during or after the compression. Did the author prove it?
   Author Response:
   Thank you for the question and suggestion. The author has changed the previous sentence:
   "CA-LBG is an ester derived from LBG with a density of around 0.600 g/cm3(Botelho, 2018), so the deformation of the CA-LBG particles plays a greater role in filling and reducing the porosity of the deformation of the MCC particles so that the tablets are hard."
   to
   "When compressed, the fine and irregular particles of CA-LBG experience deformation and fill porosity of the deformation of the MCC particles. This condition causes the compactibility of the mixture to increase due to decreased porosity, making the resulting tablet hard. Besides that, CA-LBG is an ester derivative of LBG containing mannose and galactose. When compressed, mannose and galactose form a hard solid mass, making the resulting tablet hard."

9. Reviewer Comments: P.8 line 27-31: Why does the CA-LBG at low concentration do not fill the pores of MCC particles while it does at high concentration?

   Author Response:

   Thank you for the question. The author has added sentence (orange ink): “Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. Apart from that, the character of CA-LBG in the form of an ester tends to be hydrophobic and cohesive so that small amounts of CA-LBG stick to the surface of the tablet after being compressed.”

   Since there are some statements indicate that the MCC particles deformation produce porosity during the compression, it needs some clear or detail data about it to improve the clarity of the idea explanation well.

   Author Response:

   Thank you for the suggestion. The author has added sentence (orange ink): “In addition, irregularly shaped MCC particles, after compression, experience plastic deformation so that the size of the porosity formed varies (Al-Ibraheemi et al., 2013). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.”

Re: decision on your manuscript

Dari: Andang MIATMOKO (andang-m@ff.unair.ac.id)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Kamis, 18 April 2024 pukul 08.43 GMT+7

Dear Author,
I have checked your revised files, however before I forward to the STI editor, please consider revising some parts as the following:
1. In the file of response to the reviewer, please add the newer comments to the older one. please see the attached file. The older comments should be added to. Please put the newer comment in the first page, do not forget to change the revision date.
2. In the revised file of manuscript, there are 2 colors of revised text i.e., red and blue colored texts. please explain it in your comments, which refers to your revision, the newer or older revision.
3. For statistical analysis, it is better to directly put the significant sign/mark to the graphics or table, instead of writing it into a paragraph. Please see other published journals on how to state significance in scientific data.
4. For figure 1, there is a blue-colored background, please remove it.

> On Wed, Apr 17, 2024 at 6:16 PM Wuryanto Hadinugroho <wuryanto.hadinugroho@ymail.com> wrote:
>
> Dear
> Mr Andang Miatmoko, PhD., Apt.
>
> Thank you for the extension of time given by Prof. Aldes Lesbani, Ph.D. Editor-in-Chief of Science & Technology Indonesia. I have received similar results today. Along with this email, I am attaching manuscript revisions, responses to reviewers' comments, and similarity results.
> If there are suggestions or other things to improve the manuscript in the future, please inform us again. I will be happy to make corrections to improve the quality of the manuscript.
> Thank you for your attention and cooperation.
>
> Yours Sincerely,
> Wuryanto Hadinugroho
>
> Pada Rabu, 17 April 2024 pukul 12.10.19 GMT+7, Andang MIATMOKO <andang-m@ff.unair.ac.id> menulis:
>
> Dear Author,
> I am sending the reply from the journal editor, please see below
>
> Dear Commitee,
>
> Thank you for contacting us. We are pleased to inform you that we have accepted your request for an extension to submit the revision until April 24th for the LC-01 manuscript. We hope this additional time will facilitate you in making the necessary improvements. Should there be any other matters to discuss, please feel free to contact us again.
>
> Sincerely Yours,
>
> Editor-in-Chief
> **Prof. Aldes Lesbani, Ph.D.**
> Science & Technology Indonesia
> *http://sciencetechindonesia.com*

On Sun, Apr 14, 2024 at 2:23 AM Wuryanto Hadinugroho <wuryanto.hadinugroho@ymail.com> wrote:

Dear
Mr. Andang Miatmoko, PhD., Apt.

Happy Eid Al-Fitr 1445 H, sorry physically and mentally.
Thank you for the review you have submitted. In connection with assessing similarities and reprinting images according to reviewers' suggestions, I am requesting an extension until April 24, 2024. I will immediately send the revised manuscript if it is completed before that time.
I hope that this request will be granted. I thank you for your attention and cooperation.

Yours Sincerely,
Wuryanto Hadinugroho

Pada Kamis, 28 Maret 2024 pukul 12.09.03 GMT+7, Andang MIATMOKO <andang-m@ff.unair.ac.id> menulis:

Dear author,
we are forwarding the result of a review form STI editor. Please fulfill all questions and the similarity must be less than 20%. After revising, please send your files to this email address.
Please add your revision to the file we sent to the STI, please use a different color from the previous revision in the response to reviewer comments and revised manuscript file.

Dear Commitee,

We have reviewed the revised **manuscript LC-01**. We would like to inform you that the revised **manuscript LC-01** requires some improvements before it can be considered further to improve the quality of your article.

We hope that the author can make improvements in accordance with the attached notes and submit a revised version of your manuscript by **April 17, 2024**. Please attach a change note detailing the improvements made. If you need an extension of the revision time, please inform us. We thank you for your attention.

--
Salam,

Andang Miatmoko, PhD., Apt.
1. Department of Pharmaceutical Sciences
Faculty of Pharmacy, Airlangga University
Nanizar Zaman Joenoes Building

2. Stem Cell Research and Development Center
Institute of Tropical Disease Building

Campus C Airlangga University, Mulyorejo, 60115
Surabaya

--
Salam,

Andang Miatmoko, PhD., Apt.
1. Department of Pharmaceutical Sciences
Faculty of Pharmacy, Airlangga University
Nanizar Zaman Joenoes Building

2. Stem Cell Research and Development Center
Institute of Tropical Disease Building

> Campus C Airlangga University, Mulyorejo, 60115
> Surabaya

--

Salam,

Andang Miatmoko, PhD., Apt.
1. Department of Pharmaceutical Sciences
Faculty of Pharmacy, Airlangga University
Nanizar Zaman Joenoes Building

2. Stem Cell Research and Development Center
Institute of Tropical Disease Building

Campus C Airlangga University, Mulyorejo, 60115
Surabaya

LC-01 Response to Reviewer Comments.pdf
432kB

Revision 3 of Manuscript_LC 01

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

Kepada: andang-m@ff.unair.ac.id

Tanggal: Selasa, 7 Mei 2024 pukul 05.47 GMT+7

Dear.
Mr Andang Miatmoko, PhD., Apt.

Thank you for the suggestions, corrections, and revision opportunities provided. I am attaching revisions to the three manuscripts, reviewer comments, and graphic abstracts along with this email.
If there are suggestions or other things to improve the manuscript, please inform us again. I will be happy to make corrections to improve the quality of the manuscript.
Thank you for your attention and cooperation.

Yours sincerely,
Wuryanto Hadinugroho

LC-01 Revised Manuscript_3.docx
2MB

Response to Reviewer Comments_LC-01_Rev.3.pdf
972.7kB

LC-01 Graphical Abstract_rev 1.jpg
65.5kB

LC-01 Graphical Abstract_Rev 1.tiff
138kB

Study of Citric Acid-Locust Bean Gum as A Glidant to Fillers of Cellulose Derivatives

Wuryanto Hadinugroho[1,*]

[1] *Faculty of Pharmacy, Widya Mandala Surabaya Catholic University, Kalisari Selatan no. 1 Pakuwon City, Surabaya, 60112, Indonesia.*

**Corresponding Author e-mail: wuryanto.hadinugroho@ymail.com*

Abstract

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. CA-LBG is a compound derived from the esterification of citric acid (CA) with locust bean gum (LBG). The experiment aimed to determine the potential and effect of CA-LBG as a glidant on microcrystalline cellulose (MCC). The CA-LBG concentrations in the experiments were 0.5%, 1.0%, 2.0%, and 4.0%. Talc and magnesium stearate (MgS) as a comparison. The mixtures were evaluated for flow rate and angle of repose. The mixture was compressed into tablets weighing 700 mg. Tablets were evaluated for weight, hardness, and friability. The flow rate of the mixture containing CA-LBG 0.5%-4.0% was 12.77 $g.sec^{-1}$-15.96 $g.sec^{-1}$. The angle of repose of the mixture containing CA-LBG 0.5%-4.0% is 32.62°-35.52°. The weight of tablets containing CA-LBG 0.5%-4.0% is 700.0 mg-701.2 mg. The hardness of tablets containing CA-LBG 0.5%-4.0% is 6.30 kp-6.90 kp. The friability of tablets containing CA-LBG 0.5%-4.0% is 0.17%-0.36%. The CA-LBG has the potential as a glidant in MCC fillers. Increasing CA-LBG concentration causes the flow rate to increase, the angle of repose to decrease, and the hardness to increase. CA-LBG concentrations of 0.5% and 4.0% reduced tablet friability.

Keywords: citric acid-locust bean gum, citric acid, esterification, glidant, locust bean gum

1. Introduction

Citric acid-locust bean gum (CA-LBG) was introduced as an excipient in tablet preparations. The published uses of CA-LBG are as a tablet disintegration agent and negative matrix in controlled-release tablets (Hadinugroho et al., 2023; Hadinugroho, Martodihardjo, et al., 2022).

CA-LBG is an ester material derived from the esterification of citric acid (CA) with locust bean gum (LBG) under acidic conditions. CA-LBG has been characterized by carbonyl ester group, solubility, viscosity, esterified CA, glass transition temperature, crystallinity index, and particle morphology. CA-LBG particles have a non-polar and hydrophobic tendency, so CA-LBG has low solubility in water (Hadinugroho et al., 2017, 2019). CA-LBG is irregular in shape and has a wavy surface (Hadinugroho et al., 2017, 2019). This character can act as a glidant in tablet formulation.

Glidant is a material that can interact with filler particles to improve flow properties. Glidant particles will be on the surface of the filler particles to cover porosity and smooth the surface of the filler particles. Changing the surface of the filler particles improves the movement of each particle (Awad et al., 2020). Glidant materials often used in pharmaceutical preparation formulations are talc and magnesium stearate (MgS). Talc and MgS particles are fines powders, hydrophobic, insoluble in water, irregular in shape and platy wavy (Meng et al., 2022; Pratiwi et al., 2017; Sheskey et al., 2017; Zarmpi et al., 2020). The character of CA-BG particles is similar to that of talc and MgS particles, thus indicating that CA-LBG is capable of glidant.

The experiments aimed to determine the potential and influence of CA-LBG as a glidant in tablet formulation. The experiment used microcrystalline cellulose (MCC), commonly used as a filler in tablet formulations. MCC particles experience plastic deformation after compression, resulting in varying porosity in the tablet (Krivokapić et al., 2020). The experiment used CA-LBG with concentrations of 0.5%, 1.0%, 2.0%, and 4.0%. Talc and magnesium stearate were used as a comparison with the same concentration. Each mixture was evaluated for flow rate and angle of repose. The mixture is then compressed directly into tablets 700 mg. Tablets were evaluated for weight, hardness, and friability. MCC was chosen as the filler model in this experiment because MCC is a filler that is often used in tablets using the direct compression method. MCC particles are water-insoluble, irregularly oval, porosity, and hydrophobic (Pratiwi et al., 2017; Sheskey et al., 2017).

The novelty of this experiment is using CA-LBG as a glidant in MCC tablet filler to observe its potency and effect at various concentrations. This experiment explores the function of CA-LBG as a glidant for tablet formulation. In the fine form of CA-LBG, the shape of the CA-LBG particles is irregular, has a wavy surface, is difficult to dissolve in water, and is hydrophobic (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). In addition, the experiment's success provides a choice of future glidant in pharmaceutical excipients.

2. Experimental Section

2.1. Materials

The materials are locust bean gum ($C_{32}H_{56}O_{26}$)(food grade) (Viscogum, Cargill, France), citric acid monohydrate ($C_6H_8O_7.H_2O$) (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (HCl) (pro analysis) (Sigma Aldrich Chemie, GmbH, USA), water for injection (H_2O) (sterile water) (PT. Otsuka Indonesia), distilled water (H_2O) (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (C_3H_6O) (technical grade) (Cawan Anugerah Chemika, Indonesia), microcrystalline cellulose ($C_{14}H_{26}O_{11}$) (pharmaceutical grade) (Flocel PH 102, Gujarat Microwax Ltd, Gujarat, India), talc ($Mg_3Si_4O_{10}(OH)_2$) (food grade) (PT. Bratachem, Indonesia) and magnesium stearate ($C_{36}H_{70}MgO_4$) (food grade) (PT. Bratachem, Indonesia).

2.2. Methods

2.2.1. Synthesis of CA-LBG

The experiment used CA-LBG synthesized using methods adopted from previous research (Hadinugroho, Martodihardjo, et al., 2022). The manufacturing principle is that a certain amount of LBG (7.10 x 10^{-6} mol in 50 mL) that has been swollen is added to a certain amount of CA (0.42 mol) and HCl (0.24 mol) as a catalyst. The homogeneous mixture was UV irradiated. The mixture was then settled and washed repeatedly with acetone-distilled water. The CA-LBG precipitate was dried at room temperature (± 25°C for 72 hours) and powdered using a blender (Maspion, speed scale 4 for 8 x 5 minutes). Before being used in experiments, CA-LBG powder was characterized, including Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), X-ray (XRD), scanning electron microscope (SEM), viscosity, and pH.

2.2.2. Characterization of CA-LBG

A qualitative examination of chemical groups from CA-LBG infrared at 400-4000 cm^{-1} using UATR (Perkin Elmer Spectrum Version 10.4.3., USA). ^{1}H and ^{13}C examination of CA-LBG using liquid state NMR spectrophotometer (JEOL RESONANCE ECZ 500R, 500 MHz, Japan). The CA-LBG diffractogram was recorded using X-ray of Cu; 1.54060A; speed 4º/minute; slit . DS: 1º, SS: 1º, RS: 0.30 mm, and range 3.0200º-80.0000º (θ-2θ) (Lab X XRD 6000, Shimadzu, Japan). The CA-LBG particle surface was recorded at a distance of 10 mm voltage of 10 kV (SEM JSM-6510LA, JEOL, Japan). Viscosity examination of CA-LBG on spindle No. S61, 60 rpm, and torque

≥ 10% using a Brookfield viscometer (LVDV-I Prime, AP6510416, USA). The acidity examination of CA-LBG, CA, and LBG in solution (1% w/v) used a pH meter calibrated to pH 4.0; 7.0; and 10.0 (Metrohm 913, Switzerland).

2.2.3. Preparation of a mixture of MCC and glidant

Each glidant (talc, MgS, and CA-LBG) was weighed according to the concentration of each experiment (Table 1). A quantity of MCC (Avicel PH 102) was weighed to complete up to 100 g. For one minute, glidant and MCC were mixed in a cubic mixer (Erweka, Germany). Each mixture was evaluated for flow rate and angle of repose. The mixture was compressed (Single punch, Erweka EP-1, Germany) into tablets weighing 700 mg, diameter ± 15 mm, hardness 5-12 kp (equivalent to compression force ± 2 tons). Tablets were evaluated for weight, hardness, and friability.

2.2.4. Flow rate and angel of repose

The mixture (100 g) of glidant and MCC was poured into a flowability tester (Erweka, Germany). The equipment is pressed to start when the bottom valve of the funnel opens, and the mixture flows freely over the plate, forming a cone. The flow time is read on the monitor. The flow rate is obtained from the flow time ratio to the mixed powder's weight. The equipment then emits infrared light to measure the diameter and height of the cone. The angle of rest is read on the monitor (Aulton & Taylor, 2017; Hadinugroho, Foe, et al., 2022).

2.2.5. Weight

A total of 20 tablets were randomly selected and weighed one by one (Mettler Toledo, Switzerland). All weights obtained are averaged, and the standard deviation is determined (Hadinugroho, Martodihardjo, et al., 2022).

2.2.6. Hardness

A total of 6 tablets were randomly selected and placed on a holder tester (Schleuniger, Netherlands). The hard block presses the tablet until the tablet starts to fracture. The tablet hardness value is displayed on the monitor (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

2.2.7. Friability

Tablets were randomly selected and dusted to weigh the equivalent of 6500 mg on an analytical balance (Mettler Toledo, Switzerland). All tablets were placed in a friability tester apparatus tube (Erweka, Germany). The tube was rotated at 25 rpm for 4 minutes. Once the rotation stops, each tablet is dusted again. Friability is the ratio of the difference between the treatment's initial and final weight to the initial weight (Hadinugroho, Foe, et al., 2022; The United States Pharmacopeial Convention, 2018).

2.2.8. Two-factor ANOVA

Apart from graphical analysis, the experiment was analyzed using a two-factor ANOVA for each parameter value. The factors used in ANOVA are the type of glidant and the experimental concentration. The parameters analyzed are flow rate, angle of repose, hardness and friability. Analysis using the alpha (α) value is 0.05.

3. Results and Discussion

3.1. Synthesis of CA-LBG

The synthesis for CA-LBG is divided into 30 batches because the synthesis is adjusted to lab scale capacity and facilities. The synthesis process followed fixed procedures in previous research (Hadinugroho, Martodihardjo, et al., 2022). Dry CA-LBG yield of all batches is 1.10 g ± 1.24 g. The CA-LBG all batches were homogenized and pureed using a blender (Maspion, speed scale 4 for 8 x 5 minutes). CA-LBG fines powder was used for characterization and experiments as a glidant.

3.2. Characterization of CA-LBG

The FTIR spectra of CA-LBG are presented in Figure 1. The infrared spectrum shows that the wave number of the O-H group appears at 3318.20 cm^{-1}; C-H appears at 2923.66 cm^{-1} and 2851.10 cm^{-1}; and C=O ester appears at 1736.02 cm^{-1}. The NMR spectrum of CA-LBG are presented in Figure 2. Image ^{1}H CA-LBG NMR shows doublet peaks (2 pairs) at δ=2.927 ppm and δ=2.896 ppm; δ=2.744 ppm and δ=2.713 ppm, which correspond to C–H_2 of CA. Both peaks originate from symmetric C protons in CA. These peaks indicate the presence of CA in LBG. One adjacent proton

causes a twist of the bond and a signal rupture. Multiplet peaks of mannose and galactose appeared at δ=3.990–3.329 ppm. Previous research reported that the two CA double peaks were around δ=3,083–2.714 ppm (Hadinugroho 2022, 2023). The peaks of two monomers of LBG appear between δ = 4.418–3.309 ppm (Hadinugroho 2012, 2023). The CA-LBG peaks in the ^{13}C NMR examination were δ = 176.838 ppm; δ=173,449 ppm; δ = 173.363 ppm; δ = 100.154 ppm; δ = 98,762 ppm; 96,458 ppm; 76,550 ppm; δ = 75.034 ppm; δ = 73.316 ppm; 71.425 ppm; 69,946 ppm; 69,303 ppm; 60,981 ppm; 60,521 ppm; and 43,339 ppm. The peak δ=180–170 ppm corresponds to the C=O group. The peak δ=80–70 ppm corresponds to the central C atom. The peak δ=44–43 ppm corresponding to C–H and C–H_2 (Duan et al., 2020; Hadinugroho et al., 2019; Kim et al., 2017; Zhang et al., 2016). The peak δ=105–60 ppm corresponds to two monomers of LBG appearing at δ=105–60 ppm (Gillet et al., 2014; Hadinugroho, Martodihardjo, et al., 2022; Idström et al., 2016; Tian et al., 2023; Trabelsi et al., 2021). The diffractogram profile (Figure 3) shows that CA-LBG is an amorphous compound with a peak at 16.600 degrees, where this character is similar to previous research (Hadinugroho et al., 2019; Isasi & Ramón, 2022; Singh et al., 2020). The amorphous character of CA-LBG is dominated by the LBG character, which is a galactomannan polymer with an irregular molecular arrangement (Tikhonov et al., 2019; Zheng et al., 2022). The shape of CA-LBG particles (Figure 4) is like irregular coral with a wavy surface. There are sheets attached to the coral to confirm the presence of CA in LBG (Hadinugroho et al., 2017; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test results for viscosity were 9.49 cP ± 0.08. This viscosity is close to previous research results of around 7.82-11.37 cP (Hadinugroho et al., 2019, 2023; Hadinugroho, Martodihardjo, et al., 2022). The CA-LBG test result for pH was 4.83. This result was compared with a CA pH of 2.05 and an LBG pH of 5.85. Tests were carried out on 1% w/v solutions of CA-LBG, CA, and LBG by dipping the pH meter electrode (Metrohm 913, Switzerland), which had been previously calibrated. The pH value of 4.83 proves that the presence of CA in LBG results in a pH value between the pH values of CA and LBG (1% b/v, pH ± 5.3) (Sheskey et al., 2017). The results of CA-LBG characterization using FTIR, NMR, XRD, SEM, viscosity, and pH show that the CA-LBG used is similar to previous experiments and can be used for further experiments as a glidant in MCC filler.

3.3. Flow rate

The flow rate test results for all experiments are presented in Table 1 and Figure 5. In general,

the mixture containing MgS (M0-M4) and CA-LBG (C0-C4) has a faster flow rate than the mixture containing talc. A good pharmaceutical flow rate for powder or powder mixture is ≥ 10 g.second^{-1} (Fitrya, Najma Annuria Fithri1, 2021; Gustaman et al., 2021; Jayani et al., 2021; Luh Putu Wrasiati & Putra, 2021; Putri, 2023; Zebua et al., 2023). MgS and CA-LBG particles can interact well on the surface of the MCC particles so that the two glidants can make it easier for them to flow. The mixture of each glidant showed a different flow rate profile. The mixture containing talc and CA-LBG showed that increasing the glidant concentration increased the flow rate of the mixture. The surface area of the MCC particles in the powder is sufficient to interact with many particles of talc and CA-LBG. The flow rate graphic of the mixture containing MgS (M0-M2) was initially similar to the flow rate graphic of the other two glidants, but at an MgS concentration of 4% (M4), the flow rate decreased. The number of MgS particles (M4) exceeds the number of MCC particles, so the surface area of the MCC particles in the powder is insufficient to interact with the MgS particles, and free MgS particles remain. MgS-free particles can inhibit the flow rate of the mixture because the MgS particles are in the form of fines.

3.4. Angle of repose

The angle of repose test results are presented in Table 1 and Figure 6. A pharmaceutically good angle of repose for powders or powder mixtures is ≤ 40° (Beakawi Al-Hashemi & Baghabra Al-Amoudi, 2018; Clayton, 2018; Zebua et al., 2023). In general, the mixture containing talc has the highest angle of repose (T0-T4). When forming a powder cone, the particles cannot move freely following the force of gravity because the particles below them restrain the movement of the particles above them. The powder cone becomes taller with a shorter base diameter. Irregular oval-shaped MCC particles dominate the mixture and have porosity so that the particle porosity becomes a stationary point holding the surrounding particles (Sheskey et al., 2017). The angle of repose improves along with increasing talc concentration (T0-T4). Talc particles can cover the porosity of MCC particles so that the MCC surface is flatter. This condition can reduce the stationary point holding particles, and the MCC particles can quickly move.

A similar angle of repose profile occurred in the mixture containing CA-LBG, but the value of the angle of repose was lower than the other two glidants. CA-LBG particles include esters, which can close the porosity of MCC particles and become slippery when rubbed against the surrounding particles. The initial angle of repose profile of the mixture containing MgS (M0-M2) is similar to

the profile of the angle of repose of the other two glidants. Still, the value of the angle of repose is between the other two glidants. The lubrication mechanism also involves closing porosity and leveling the surface of the MCC particles. MgS particles are cohesive, requiring sufficient energy to interact with other particles (Goh et al., 2021; Peddapatla et al., 2016).

This condition affects the strength of interaction with MCC particles and the quality of MCC particle movement in the powder. In experiment M4, the angle of repose increased again due to the excessive number of MgS particles in the mixture. MgS particles in the form of fines find it challenging to move and hold the particles around them.

3.5. Weight

Tablet weights for all experiments are presented in Table 1. Experiments were carried out to confirm that the mixture could flow and move to form tablets with the weight according to design. All mixtures can be compressed into tablets weighing about 700 mg with a narrow deviation. All mixtures can flow and move stably to fill the volume of the die chamber in the tablet compression machine.

3.6. Hardness

Tablet hardness test results are presented in Table 1 and Figure 7. Tablet hardness represents the interlocking strength between deformation particles of the tablet material. Each glidant produces varying tablet hardness because the glidant concentration influences it. The hardness profile of tablets containing talc shows high in experiments T0 and T1. Tablet hardness T0 (talc 0.5%) is controlled by the interlocking and deformation porosity of the MCC particles. The deformation of the talc particles fills the porosity of the deformation of the MCC particles so that the deformation arrangement of the particles is more stable and compact. Tablet hardness T1 (talc 1%) is similar in mechanism to T0, but the porosity between the deformation of MCC particles is full filled, more stable, and compact, so the tablet is more complex. The hardness of T2 and T4 is lower than T0 and T1 because the number of talc particles influences hardness. The large number of talc particles induces interlocking deformation of the talc particles when compressed. The interlocking formed is less strong because of the deformation of the talc particles in the form of fine particles (Sheskey et al., 2017).

The tablet hardness graphic (M0-M4) in experiments containing MgS shows that the higher

the MgS concentration, the lower the tablet hardness. MgS has a low bulk density (0.159 g/cm^3), so that a low concentration produces a large number of particles (Sheskey et al., 2017). The higher the MgS concentration, the more MgS particles will experience interlocking deformation, and the higher the volume on dies in the tableting machine. The interlocking of low-density particles and fines results in weak tablet hardness. The hardness graph of CA-LBG tablets (C0-C4) contradicts MgS tablets. A high concentration of CA-LBG increases tablet hardness. When compressed, the fine and irregular particles of CA-LBG experience deformation and fill porosity of the deformation of the MCC particles. This condition causes the compactibility of the mixture to increase due to decreased porosity, making the resulting tablet hard. Besides that, CA-LBG is an ester derivative of LBG containing mannose and galactose. When compressed, mannose and galactose form a hard solid mass, making the resulting tablet hard.

3.7. Friability

Tablet friability test results are presented in Table 1 and Figure 8. A pharmaceutically good friability for powders or powder mixtures is < 1% (Aslani & Beigi, 2016; Chee et al., 2017; Fouad et al., 2020; Osei-Yeboah & Sun, 2015). The friability profile of tablets containing MgS (M0-M4) shows that the higher the MgS concentration, the higher the friability. This condition is in line with the hardness profile of the tablet because the interlocking between deformation MgS particles is not strong, and the deformation MgS particles are easily separated. In addition, the fines of MgS tend to be on the tablet's surface so that the fines are easily separated when the tablet is rotated. Tablets containing CA-LBG showed increased friability at three initial concentrations (C0-C2). This condition is caused by the CA-LBG deformation not occupying the porosity between the MCC deformation. Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. In addition, the ester nature causes CA-LBG to tend to be hydrophobic, cohesive, and stick to the outer part of the tablet. Hence, the tablet is not strong and releases particles when there is mechanical movement. At high concentrations (C4), the porosity between MCC deformations is occupied by CA-LBG deformations due to their excessive amount, so the tablet is more stable when rotated. The influence of the irregular shape of MCC after being compressed undergoes plastic deformation, causing the size of the porosity formed to vary (Krivokapić et al., 2020). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.

4. Conclusion

Based on experiments CA-LBG with compared talc and MgS as glidants, CA-LBG has potential as a glidant in MCC fillers. High concentration CA-LBG increases the mixture's flow rate, decreases the repose's angle, and hardens the tablet. CA-LBG concentrations of 0.5% and 4.0% in the mixture produced tablets with low friability.

Acknowledgement

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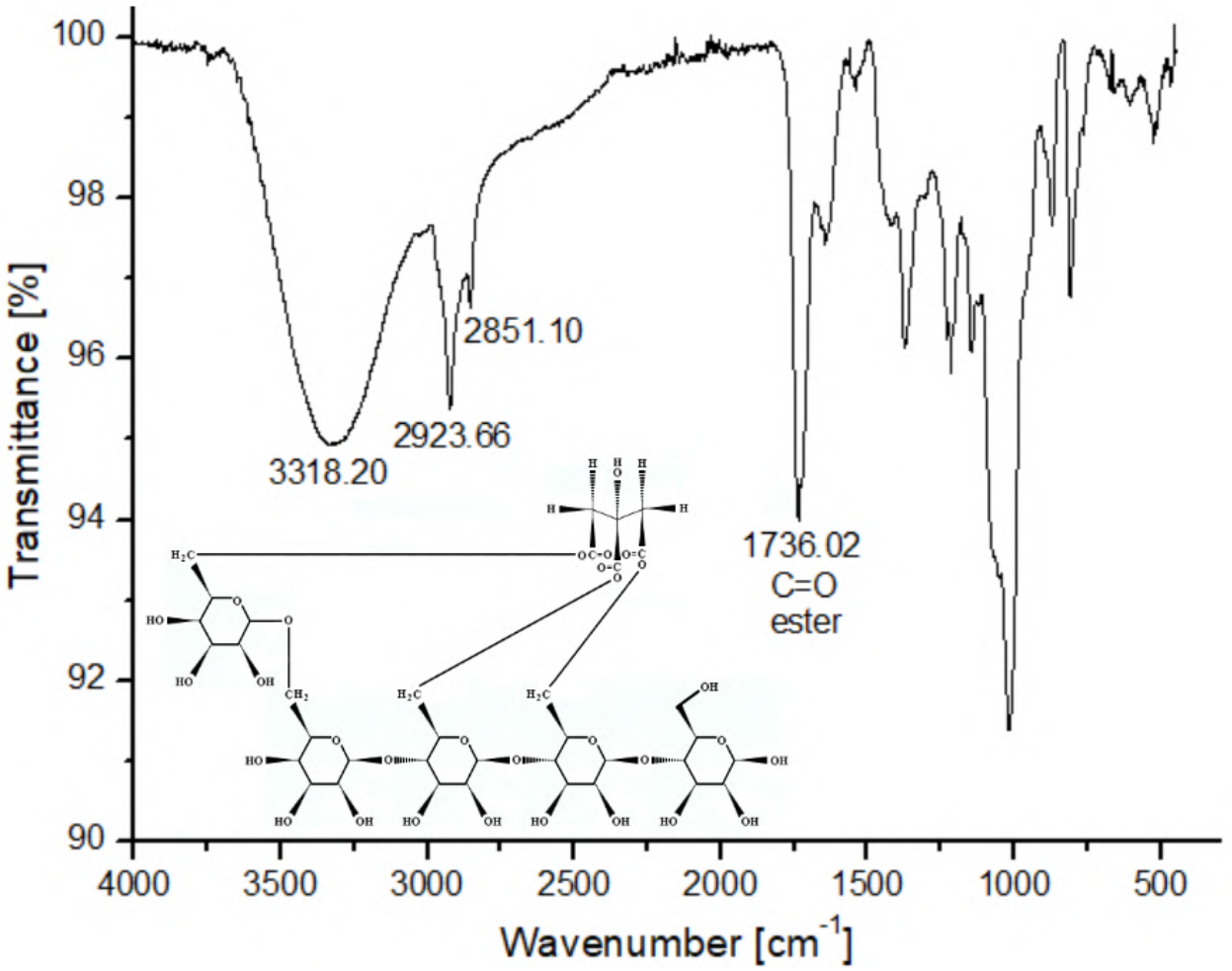

Figure 1. Infrared spectra of CA-LBG

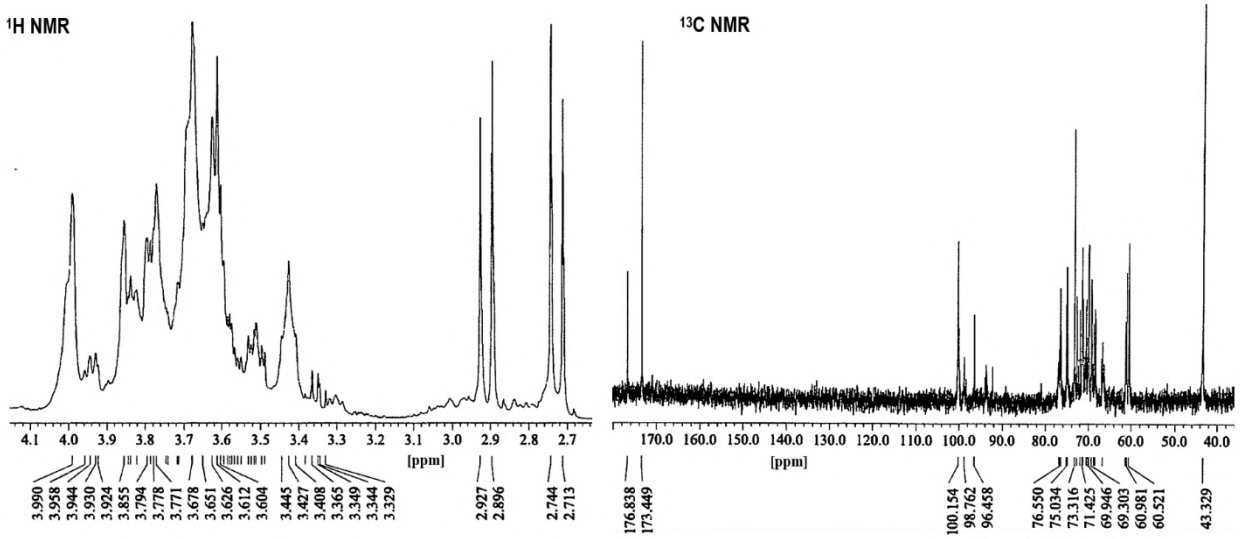

Figure 2**.** ^{1}H and ^{13}C NMR spectra of CA-LBG

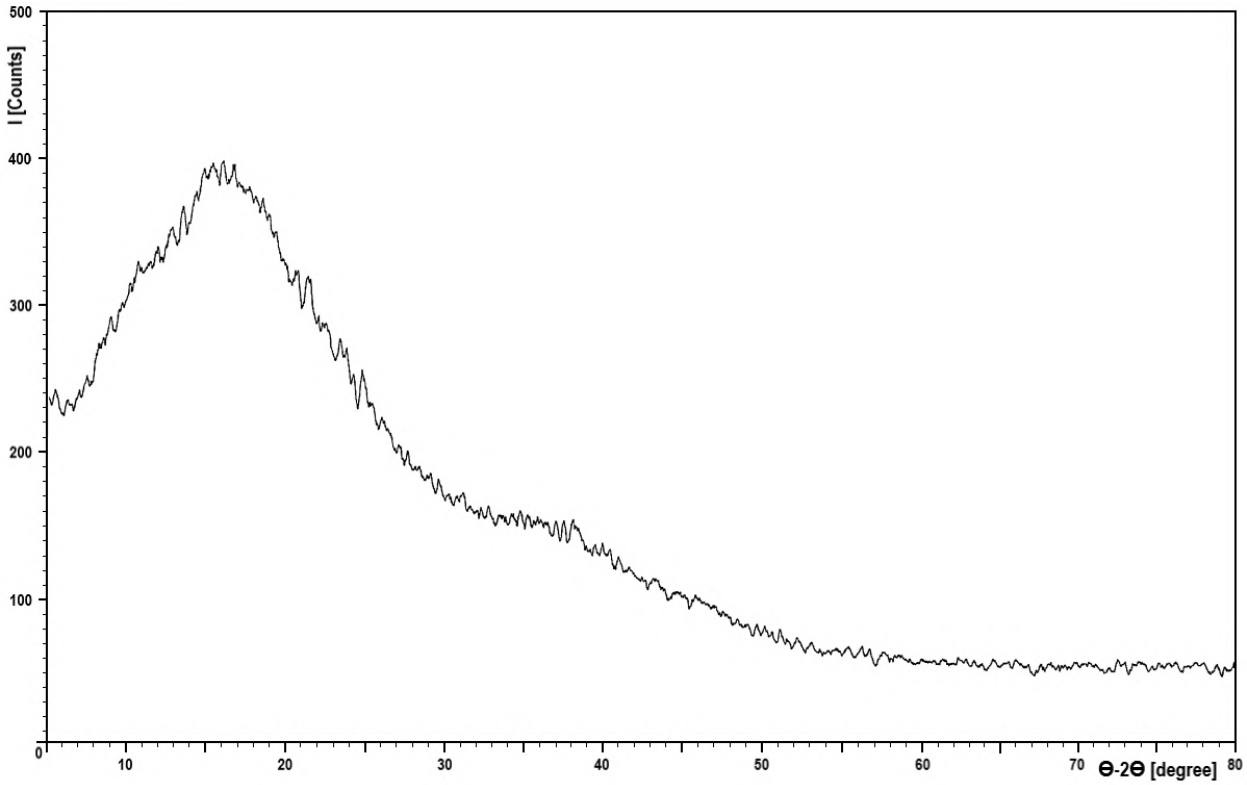

Figure 3. XRD diffractogram of CA-LBG

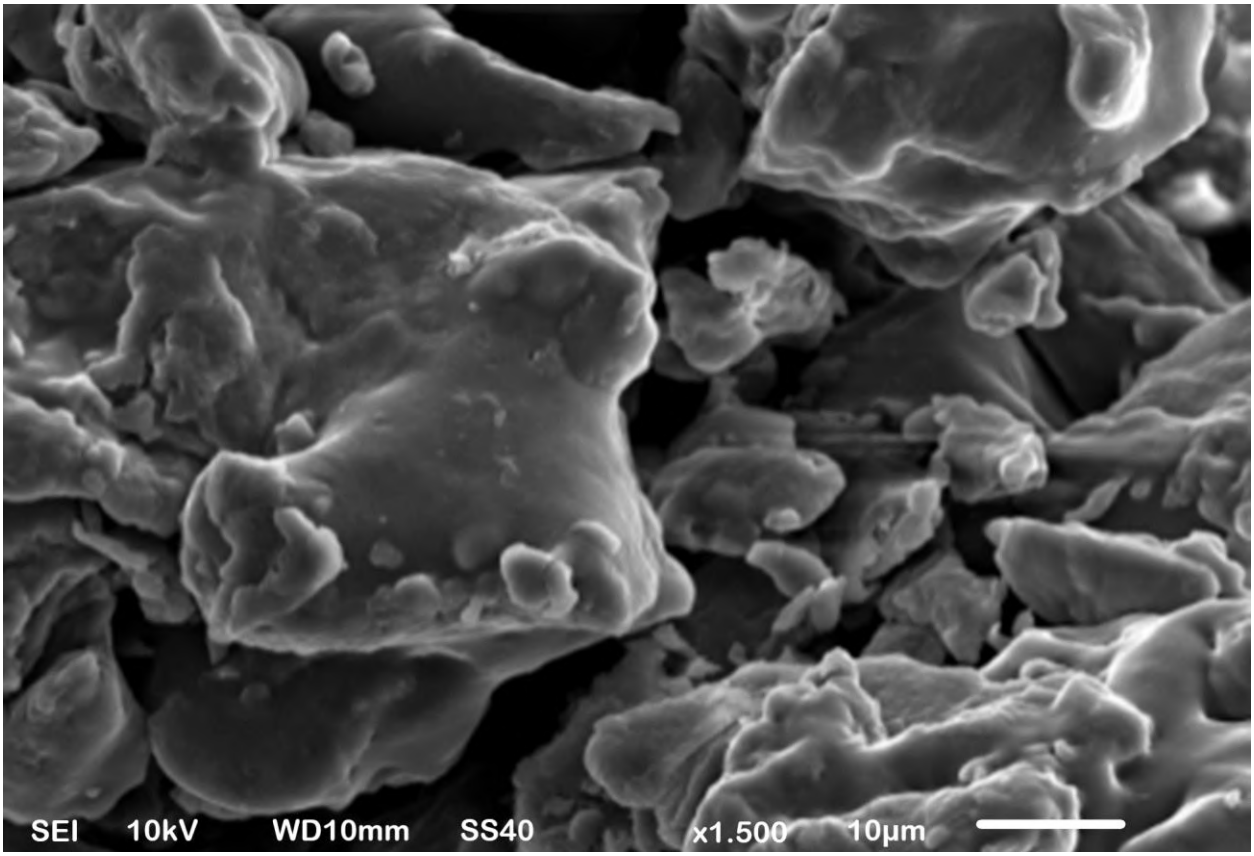

Figure 4. SEM images of CA-LBG

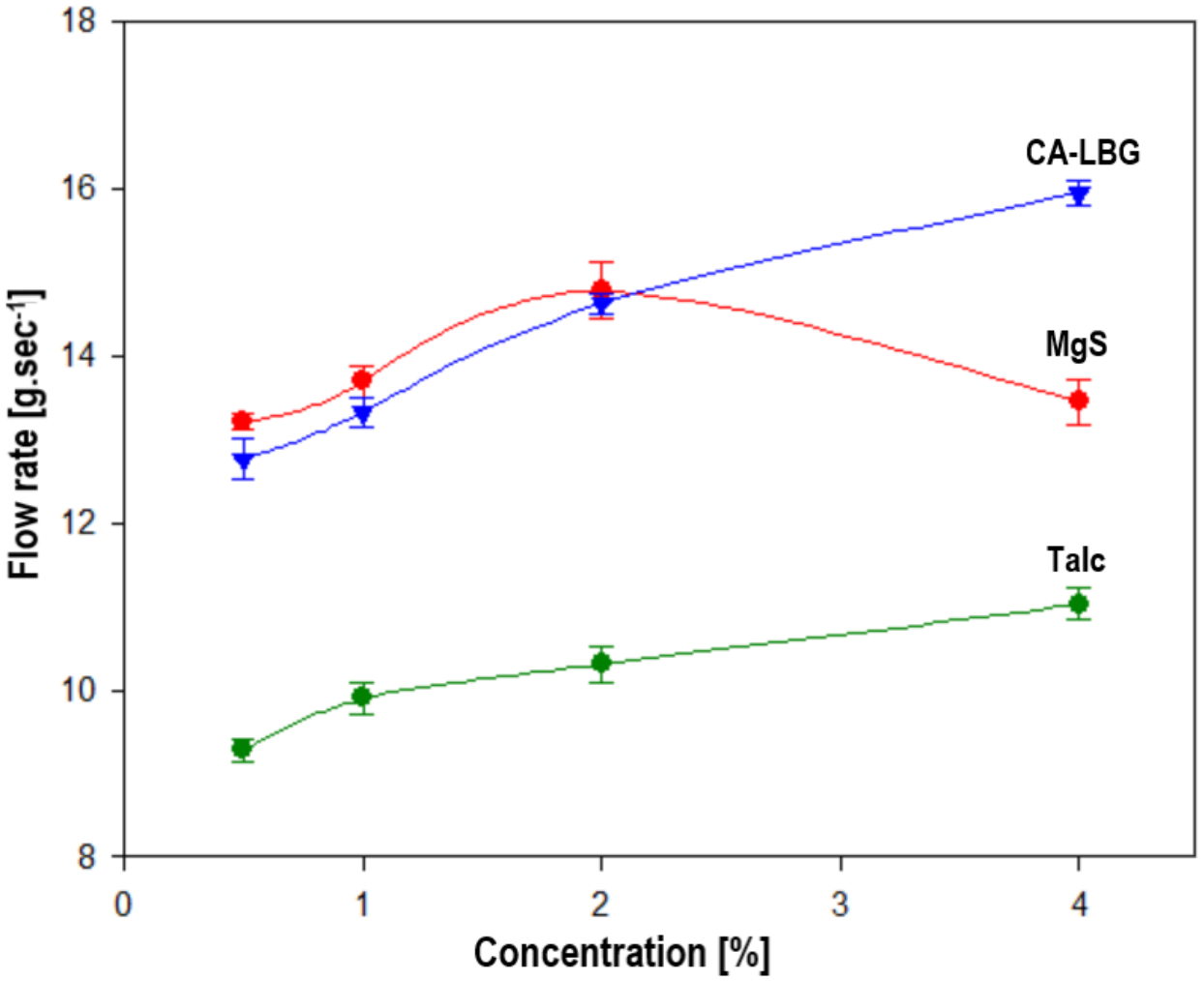

Figure 5. Profile of the relationship between glidant and the flow rate of the mixture. The ANOVA result of the type of glidant to flow rate is F_{count} (1425.41) > F_{table} (3.40) and glidant concentration to flow rate is F_{count} (139.52) > F_{table} (3.01), which means that the type of glidant and glidant concentration has an effect on the flow rate with a significance of 0.05.

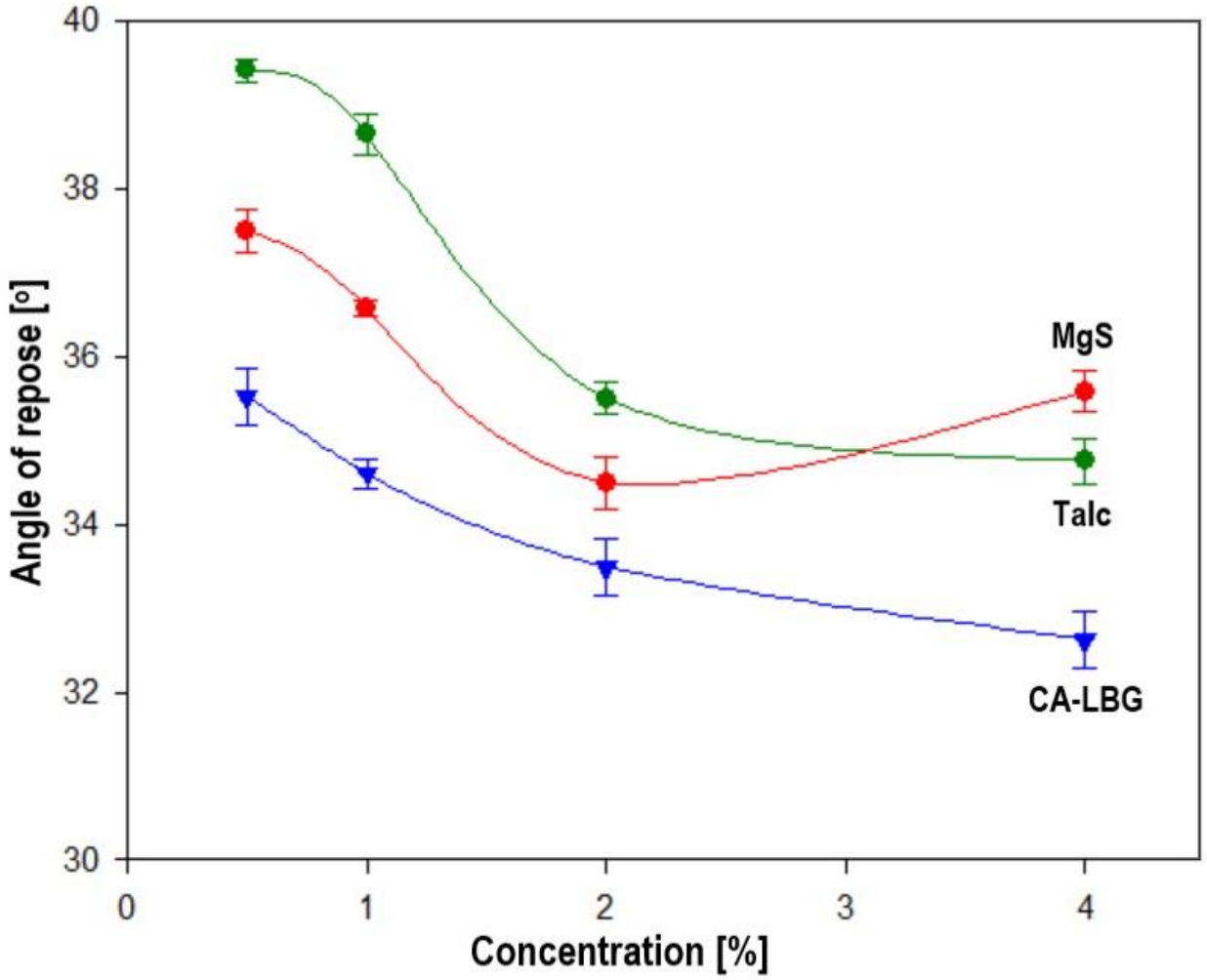

Figure 6. Profile of the relationship between glidant and the angle of repose of the mixture. The ANOVA result of the type of glidant to angle of repose is F_{count} (424.27) > F_{table} (3.40) and glidant concentration to angle of repose is F_{count} (331.92) > F_{table} (3.01), which means that the type of glidant and glidant concentration has an effect on the angle of repose with a significance of 0.05.

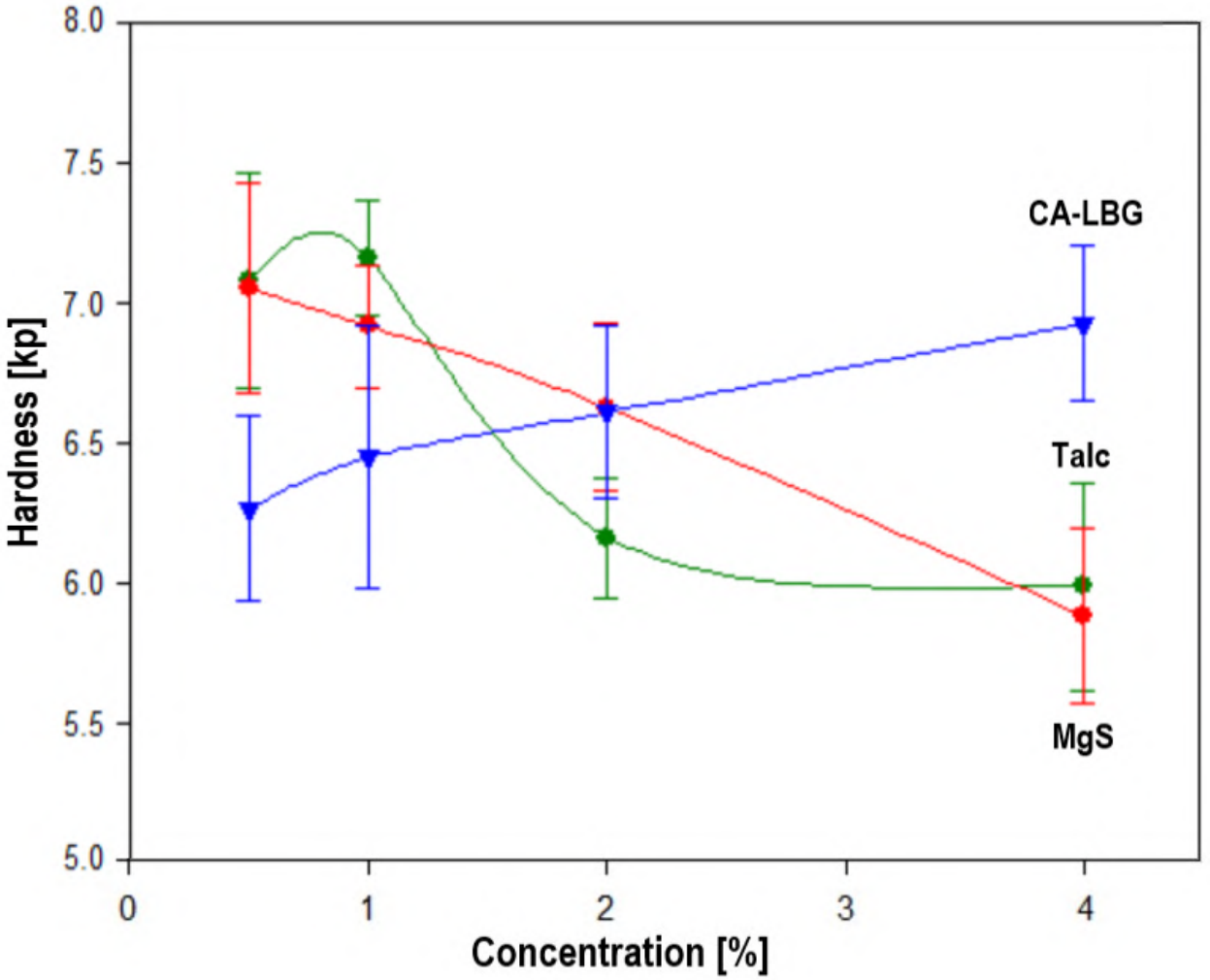

Figure 7**.** Profile of the relationship glidant and hardness. The ANOVA result of the type of glidant to the angle of repose is F_{count} (0.52) < F_{table} (3.40) and glidant concentration to the hardness is F_{count} (46.74) > F_{table} (3.01). The type of glidant has an effect that is not significant to the hardness, but glidant concentration has an effect on the hardness with a significance of 0.05.

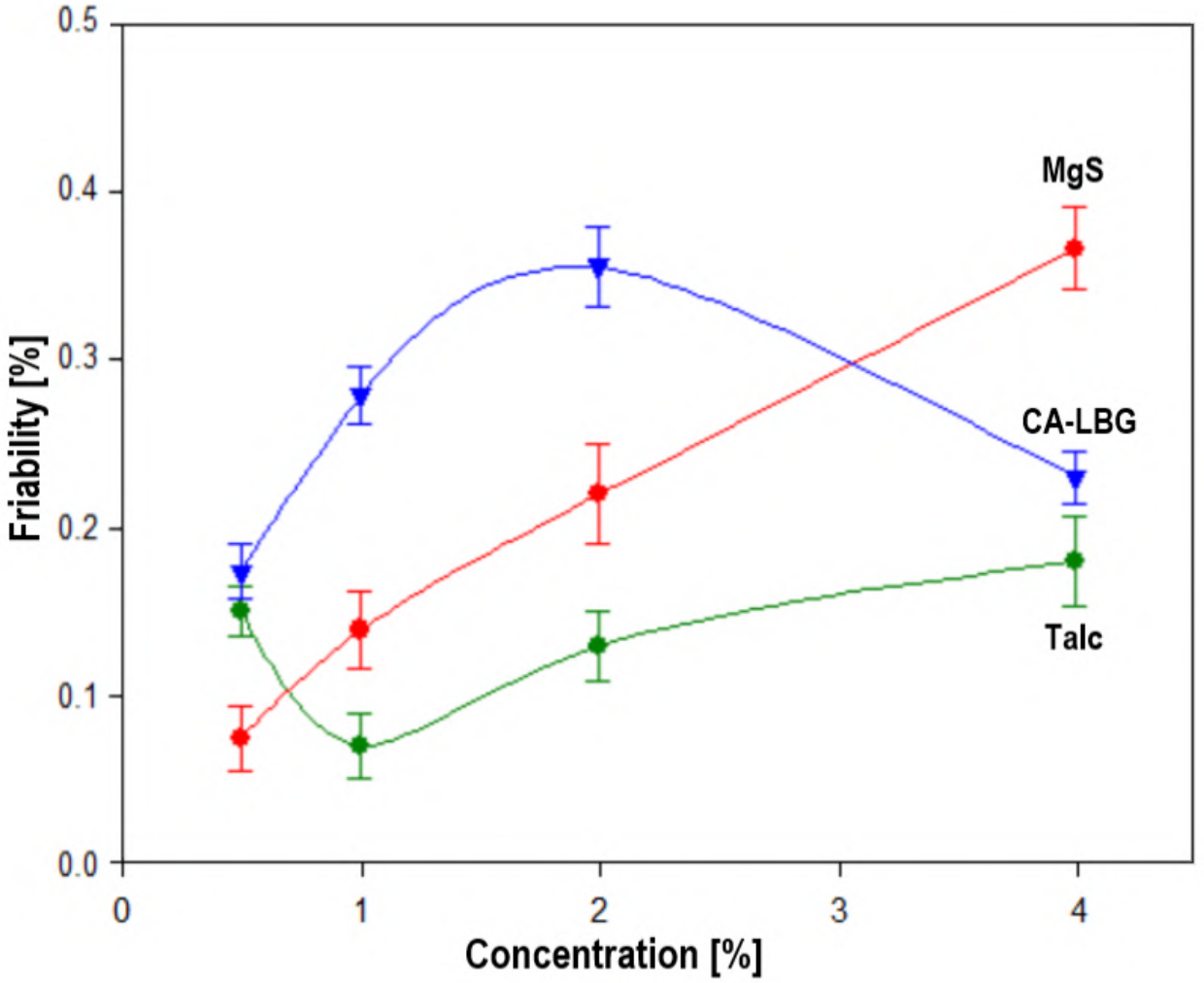

Figure 8**.** Profile of the relationship between glidant and tablet friability. The ANOVA result of the type of glidant to friability is F_{count} (110.10) > F_{table} (3.40) and glidant concentration to friability is F_{count} (69.34) > F_{table} (3.01), which means that the type of glidant and glidant concentration has an effect on the friability with a significance of 0.05.

Tables

Table 1. Test results on mixtures and tablets for flow rate, angle of repose, weight, hardness and friability.

Glidant	Consentration [%]	Test code	Flow rate [g.sec.$^{-1}$]	Angle of repose [º]	Weight [mg]	Hardness [kp]	Friability [%]
Talc	0.5	T0	9.29 ± 0.13	39.40 ± 0.14	702.2 ± 1.67	7.10 ± 0.38	0.15 ± 0.01
	1.0	T1	9.90 ± 0.20	38.64 ± 0.25	701.1 ± 1.43	7.20 ± 0.21	0.07 ± 0.02
	2.0	T2	10.31 ± 0.21	35.50 ± 0.19	700.2 ± 1.51	6.20 ± 0.22	0.13 ± 0.02
	4.0	T4	11.03 ± 0.19	34.75 ± 0.27	702.5 ± 1.69	6.00 ± 0.37	0.18 ± 0.03
MgS	0.5	M0	13.22 ± 0.10	37.50 ± 0.25	703.1 ± 1.47	7.10 ± 0.38	0.07 ± 0.02
	1.0	M1	13.70 ± 0.19	36.57 ± 0.10	702.6 ± 1.98	6.90 ± 0.22	0.14 ± 0.02
	2.0	M2	14.78 ± 0.34	34.49 ± 0.31	702.7 ± 1.53	6.60 ± 0.30	0.22 ± 0.03
	4.0	M4	13.46 ± 0.27	35.58 ± 0.24	702.4 ± 0.96	5.90 ± 0.31	0.37 ± 0.02
CA-LBG	0.5	C0	12.77 ± 0.25	35.52 ± 0.35	700.7 ± 1.87	6.30 ± 0.33	0.17 ± 0.02
	1.0	C1	13.33 ± 0.18	34.61 ± 0.18	701.2 ± 1.59	6.50 ± 0.47	0.28 ± 0.02
	2.0	C2	14.63 ± 0.12	33.49 ± 0.34	700.0 ± 1.37	6.60 ± 0.31	0.36 ± 0.02
	4.0	C4	15.96 ± 0.15	32.62 ± 0.33	702.1 ± 1.27	6.90 ± 0.27	0.23 ± 0.02

Response to Reviewers

Title: Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives
Manuscript number: LC-01
Revision Version: 3 **(purple ink)**
Editor's Decision Received Date: Aprill 24, 2024
Revision Submission Date: May 7, 2024

1. Reviewer Comments: Please correct Figures 1-3 in your manuscript. The figures are not in accordance with our journal format. We recommend that you create the graphs using the Origin-LAB application.

   Thank you for the corrections and suggestions. The author has replaced Figure 1 (FTIR) with a figure from the Origin-Lab application. NMR and X-ray tests use the services of instrumental institutions. The author has made an effort, but the institution only provides results in hard files. The document is then scanned in PDF format and prepared for the journal manuscript. The author apologizes for the limitations in obtaining soft file data, which means figures cannot be repaired via the Origin-Lab application. The author asks for suggestions on alternative methods that can be used to improve image quality by the standards of Science and Technology Indonesia.

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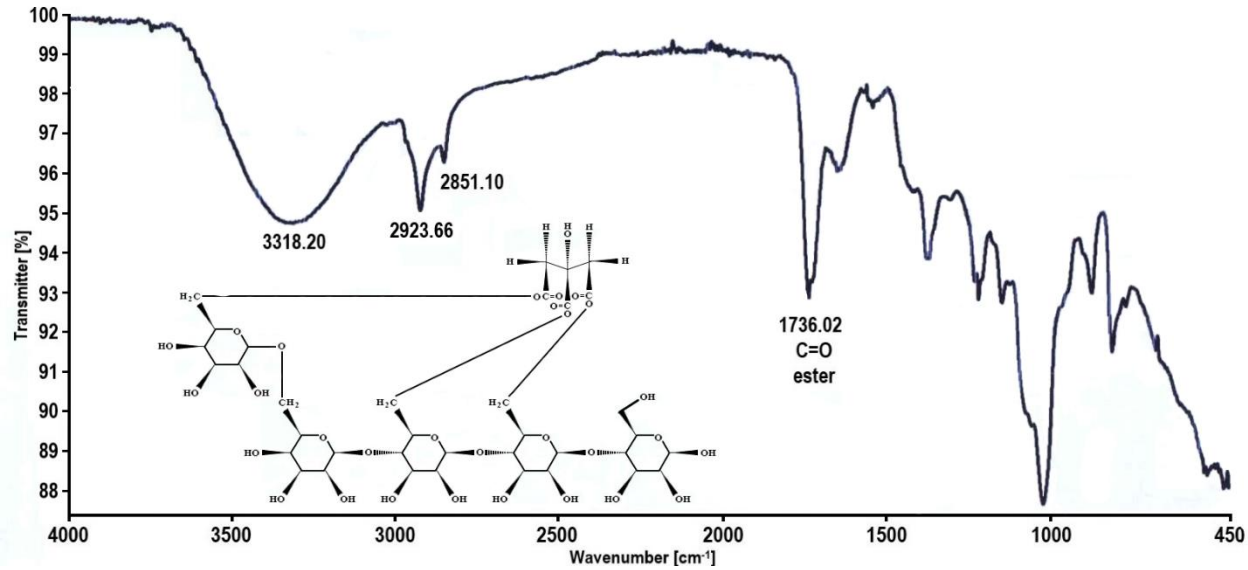

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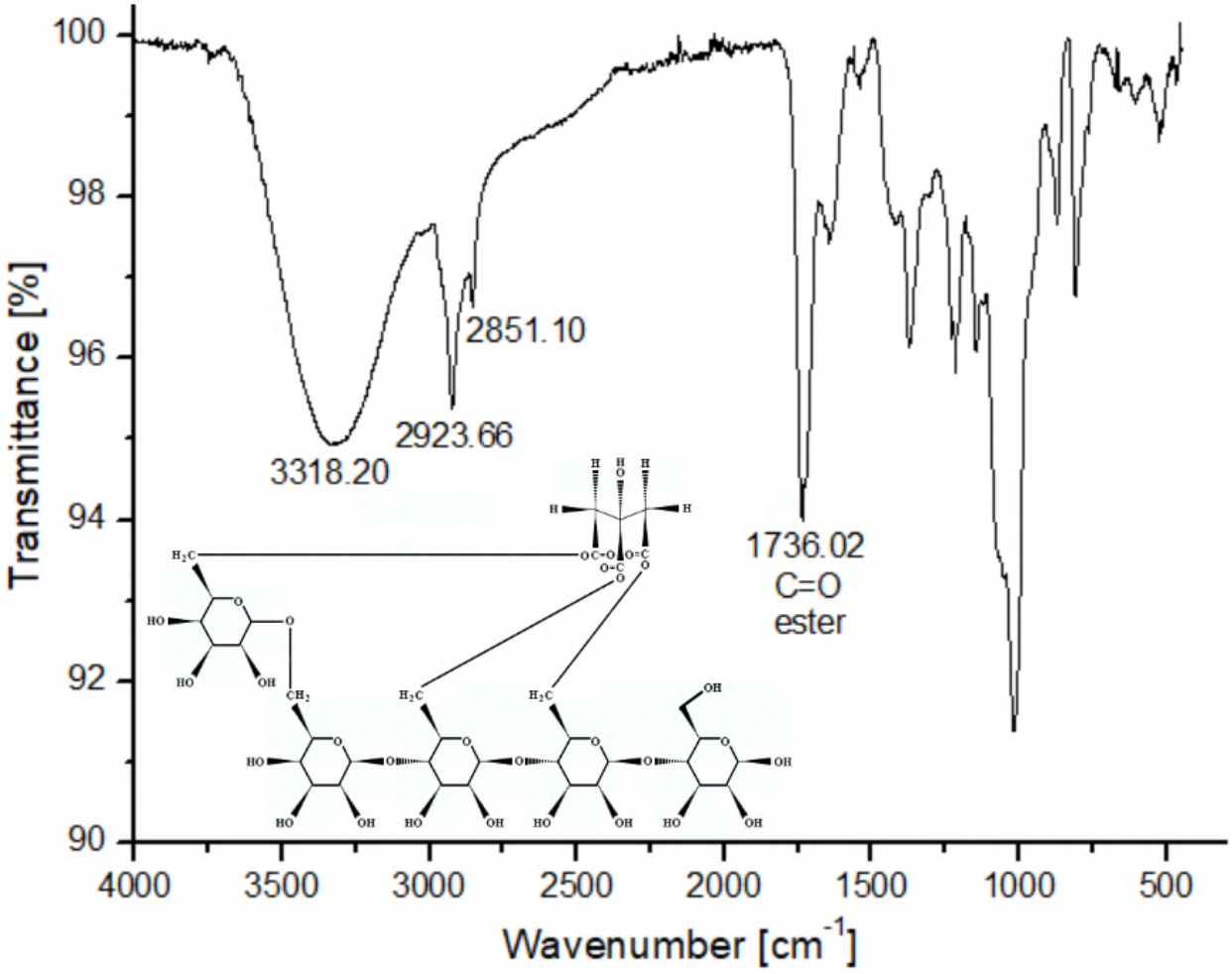


2. Reviewer Comments: If possible, please add citations to your manuscript from 1-2 Science & Technology Indonesia journals related to your research.
   Thank you for the suggestion. The author has cited two articles from Science and Technology Indonesia on the friability in the results and discussion section. Following are additional references:

   Fitrya, Najma Annuria Fithri1, B. U. A. (2021). Tablet Formula Optimization From Helminthostachys Zaylanica Extract Using A Simplex Lattice Design. *Science and Technology Indonesia*, *6*(3), 131–136. https://doi.org/https://doi.org/10.26554/sti.2021.6.3.131-136

   Zebua, N. F., Alexandro, T., Pratiwi, V. W., Nadia, S., Hidayat, S., Fujiko, M., Saputri, M., Bakri, T. K., & Nerdy. (2023). Tablet Formulation with Galactomannan Binding Agent and Acute Toxicity Test from Terminalia catappa L. *Science and Technology Indonesia*, *8*(1), 129–136. https://doi.org/10.26554/sti.2023.8.1.129-136

3. Reviewer Comments: Please review the explanation regarding the XRD results in your manuscript. Please specify at which angle the peak was generated.
   Thank you for the corrections and suggestions. The author has added a description of the diffractogram peaks to the results and discussion of the characterization. Here's the sentence:

   The diffractogram profile (Figure 3) shows that CA-LBG is an amorphous compound with a peak at 16.600 degrees, where this character is similar to previous research (Hadinugroho et al., 2019; Isasi & Ramón, 2022; Singh et al., 2020). The amorphous character of CA-LBG is dominated by the LBG character, which is a galactomannan polymer with an irregular molecular arrangement (Tikhonov et al., 2019; Zheng et al., 2022).

Response to Reviewers

Title: Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives
Manuscript number: LC-01
Revision Version: 2 **(blue ink)**
Editor's Decision Received Date: March 28, 2024
Revision Submission Date: April 20, 2024

1. Reviewer Comments: Please add SEM data.
   Author Response: Thank you for the suggestion. The author has added a SEM image (Figure 4) in the results and discussion section.

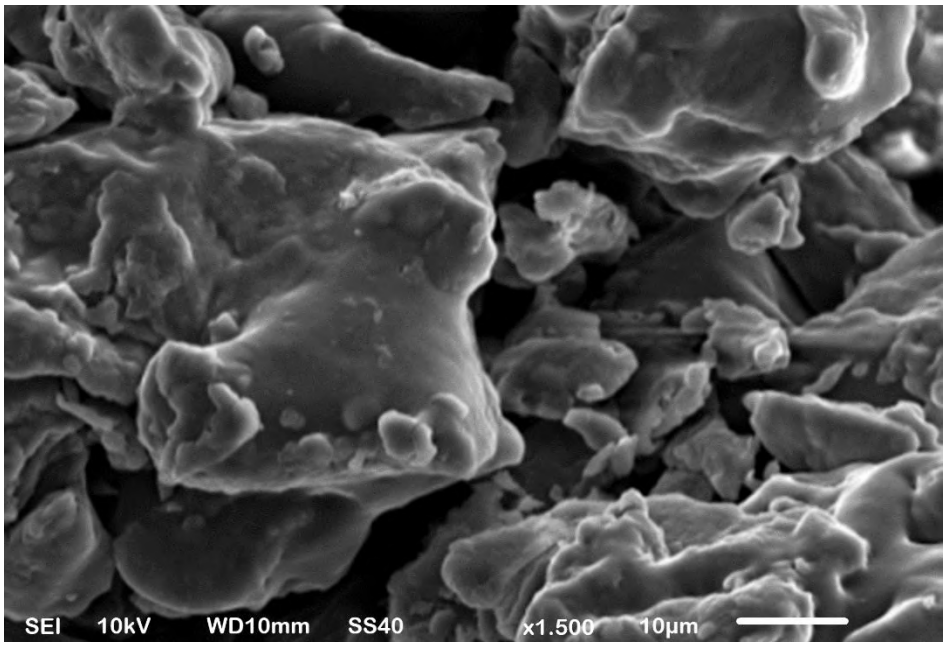


Figure 4. SEM images of CA-LBG

2. Reviewer Comments: Please add XRD data.
   Author Response: Thank you for the suggestion. The author has added a XRD diffractogram (Figure 3) in the results and discussion section.

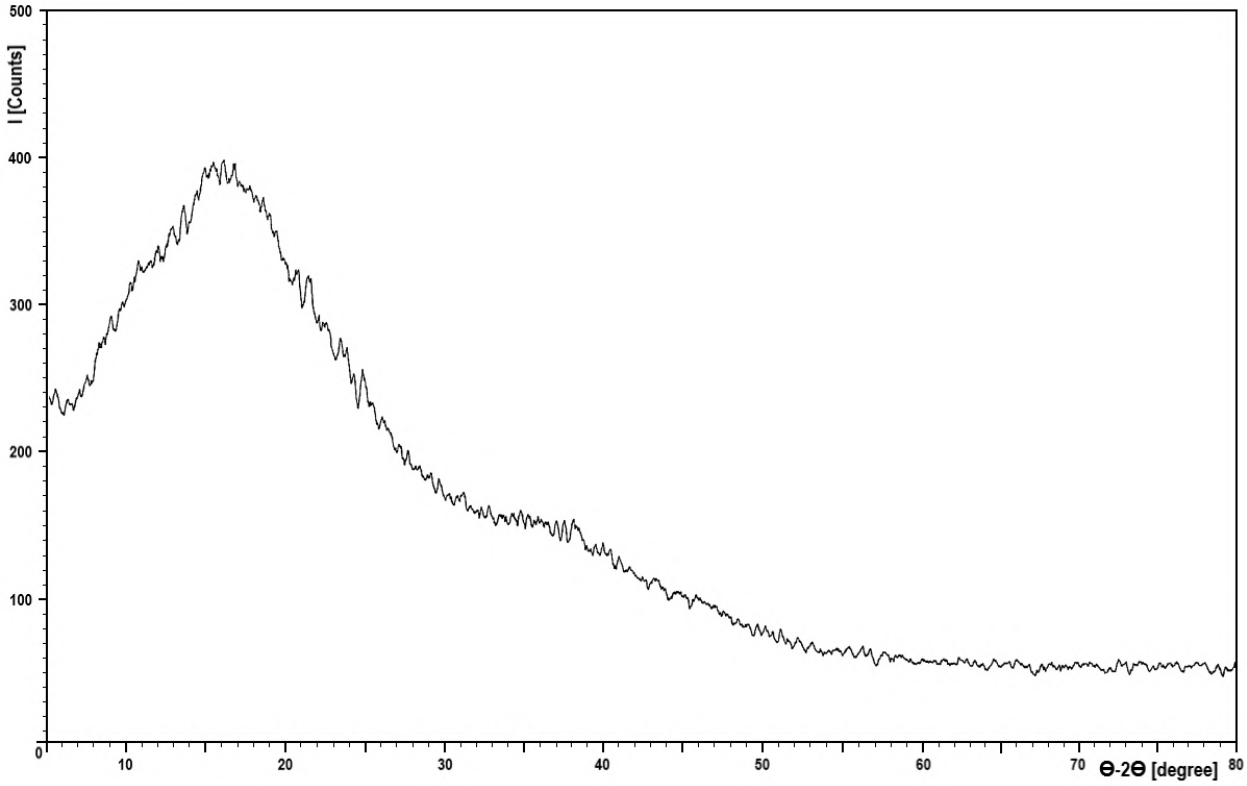


Figure 3. XRD diffractogram of CA-LBG

3. Reviewer Comments: in the materials section of the experimental section, please complete the chemical formula of the material you are using.
   Author Response: Thank you for the suggestion. The author has added the chemical structure of each material in the materials section.

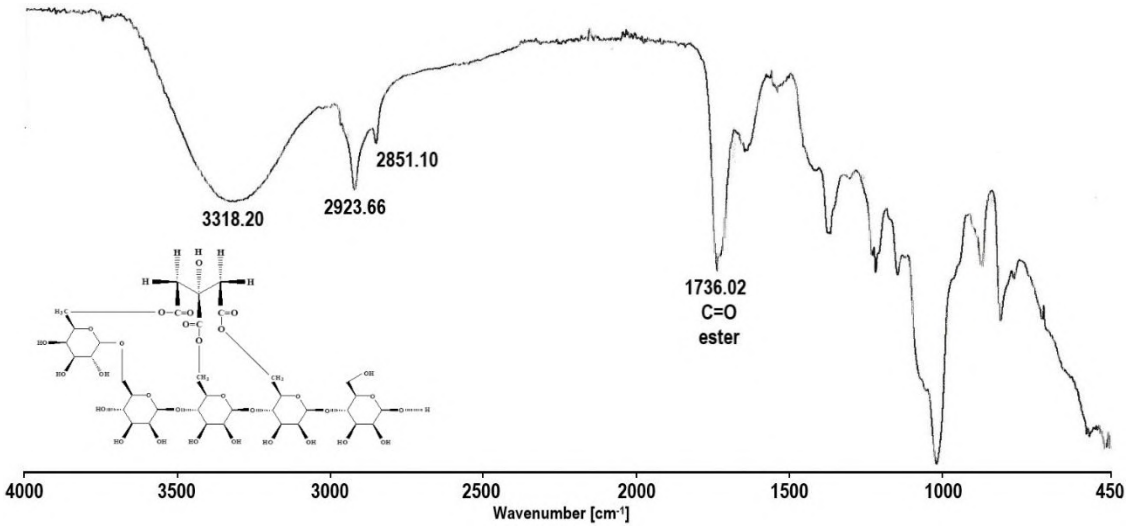
Materials

The materials are locust bean gum ($C_{32}H_{56}O_{26}$)(food grade) (Viscogum, Cargill, France), citric acid monohydrate ($C_6H_8O_7.H_2O$) (pro analysis) (Merk KgaA, Darmstadt, Germany), hydrochloric acid (HCl) (pro analysis) (Sigma Aldrich Chemie, GmbH, USA), water for injection (H_2O) (sterile water) (PT. Otsuka Indonesia), distilled water (H_2O) (technical grade) (Cawan Anugerah Chemika, Indonesia), acetone (C_3H_6O) (technical grade) (Cawan Anugerah Chemika, Indonesia), microcrystalline cellulose ($C_{14}H_{26}O_{11}$) (pharmaceutical grade) (Flocel PH 102, Gujarat Microwax Ltd, Gujarat, India), talc ($Mg_3Si_4O_{10}(OH)_2$) (food grade) (PT. Bratachem, Indonesia) and magnesium stearate ($C_{36}H_{70}MgO_4$) (food grade) (PT. Bratachem, Indonesia).

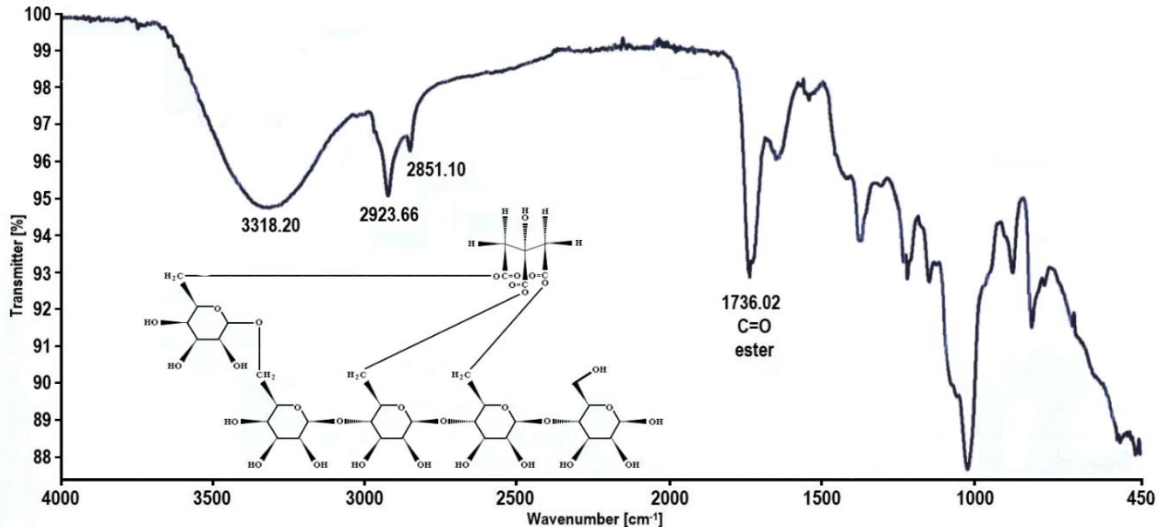
4. Reviewer Comments: please note the order of the figures in your manuscript. please mention all the figures in your manuscript.
   Author Response: Thank you for the suggestion. The author has corrected and ordered the figure according to the number. In the results and discussion sections, figure numbers have been given according to each subtopic.

5. Reviewer Comments: Your Figure 1 is very poor and does not meet the standard format of our journal. Please improve it. Pay attention to the x and y axes. I suggest you make a graph with the help of the Origin-LAB application.
   Author Response: Thank you for the suggestion. The author has corrected figure 1 to make it clearer.

before:



after:



6. Reviewer Comments: please use the most recent year of reference. You are allowed to use references above the last 10 years up to 5%.
   Author Response: Thank you for the suggestion. The author has corrected the citations and references according to the reviewer's suggestions. The oldest reference used in this manuscript is in 2014.

Response to Reviewers

Title: Study of Citric acid-locust bean gum as A Glidant to Fillers of Cellulose Derivatives
Manuscript number: LC-01
Revision Version: 1 (Orange ink)
Editor's Decision Received Date: February 16, 2024
Revision Submission Date: February 25, 2024

Author Response 1st revision

Reviewer 1

"The article is well-written according to the research objectives."

1. Reviewer Comments: Does only one person write the article?
   Author Response: Thank you for the question. I am Wuryanto Hadinugroho, the sole author carrying out this research work. Work includes research design, research process, data collection, data processing, data analysis, data interpretation, and writing publication manuscripts.

2. Reviewer Comments: Several improvements are related to writing the numbers after the comma of the CA-LBG concentration, experimental conditions, equipment used, and
   Author Response: The writing of numbers after the commas has been corrected in the manuscript with orange ink.

3. Reviewer Comments: Several statements require references to be referred to.
   Author Response: References have been added to the manuscript according to the suggestions provided on the side of the manuscript.

4. Reviewer Comments: The statistical analysis must be included to compare test results.
   Author Response: Thank you for the suggestion. The author has added statistic analysis (Two-factor ANOVA) to the methods section (2.2.8.) and result (3.8.).

5. Reviewer Comments: Articles are written according to the template used."
   Author Response: Thanks for the suggestion. The manuscript has been moved to the suggested template.

Reviewer 2

1. Reviewer Comments: please add some data or information of physicochemical characteristics that support the potential use of CA-LBG as a glidant for solid preparations
   Author Response: In the introduction part of the manuscript (paragraph of novelty), information about the physicochemical properties that support the potential use of CA-LBG as a glidant for solid dosage forms has been added. "In the fine form of CA-LBG, the shape of the CA-LBG particles is irregular, the surface is wavy, difficult to dissolve in water, and is hydrophobic."

2. Reviewer Comments: please add statistical analysis section for the method and their analysis results in the result section
   Author Response: Thank you for the suggestion. The author has added statistic analysis (Two-factor ANOVA) to the methods section (2.2.8.) and result (3.8.).

3. Reviewer Comments: please check for grammatical errors
   Author Response: Thank you for the suggestion. The author has corrected the grammar of the manuscript according to suggestions. The corrected sentences are given orange ink.

4. Reviewer Comments: P4 line 3-4: please give details about the tablet compression parameters including the tabletting machine, compression force, etc.
   Author Response: Thank you for the suggestion. The author has added details about tablet compression parameters, including tablet machine and compression force, in section 2.2.3. Preparation of a mixture of MCC and glidant. The mixture is compressed (Single punch, Erweka EP-1, Germany) into tablets weighing 700 mg, diameter ± 15 mm, hardness 5-12 kp (equivalent to compression force ± 2 tons). Tablets were evaluated for weight, hardness, and friability.

5. Reviewer Comments: P5 line 3-5: how many grams for each batch? it should be clarified on the method and the recovery from all batches is really small. Does it really has potential as for glidant resources from the manufacturing perspectives?
   Author Response: Thank you for the question. The yield is 1.10 g ± 1.24 g. The author corrected that the experimental yield is in grams unit (g). Before in the manuscript, “1.1% ± 1.24” to “1.10 g ± 1.24 g.” Development research to obtain effective and efficient methods continues to be carried out today. The factors developed are the instrument and synthesis time. Specification parameters are post-synthesis polymer mass viscosity, pH, and yield.

6. Reviewer Comments: P5 line 30-31: did the author check for pH of CA and LBG? please indicate it at the method
   Author Response:
   Thank you for the question and suggestion. Yes, testing was done. The author has added testing methods in the methods and discussion sections.

Method: "The acidity examination of CA-LBG, CA, and LBG in solution (1% w/v) used a pH meter calibrated to pH 4.0; 7.0; and 10.0 (Metrohm 913, Switzerland)."
Result and discussion: "Tests were carried out on 1% w/v solutions of CA-LBG, CA, and LBG by dipping the pH meter electrode (Metrohm 913, Switzerland), which had been previously calibrated."

7. Reviewer Comments: P8 line 8-10: these statements are not clearly understood. what is the interlocking deformation occured at high concentration of MgS and how does it occur? what is the relation of fines formation with this interlocking deformation? please clearly state it.
   Author Response: Thank you for the question and suggestion. The author has changed the previous paragraph on manuscript (orange ink):
   "The higher the MgS concentration, the more interlocking deformation of MgS particles. This interlocking force makes the tablet hardness not strong because the MgS particles are in the form of fines."
   to
   "The higher the MgS concentration, the more MgS particles will experience interlocking deformation, and the higher the volume on dies in the tableting machine. The interlocking of low-density particles and fines results in weak tablet hardness."

8. Reviewer Comments: P8 line 12-15: does the density only affect the tablet hardness in this study? what is about the porosity of MCC and particle size of shape of the CA-LBG? did the author prove this idea? and about the hardness, the important parameter is about the presence of mannose and galactose of CA-LBG as it can form solidifed mass during or after the compression. Did the author prove it?
   Author Response:
   Thank you for the question and suggestion. The author has changed the previous sentence:
   "CA-LBG is an ester derived from LBG with a density of around 0.600 g/cm3(Botelho, 2018), so the deformation of the CA-LBG particles plays a greater role in filling and reducing the porosity of the deformation of the MCC particles so that the tablets are hard."
   to
   "When compressed, the fine and irregular particles of CA-LBG experience deformation and fill porosity of the deformation of the MCC particles. This condition causes the compactibility of the mixture to increase due to decreased porosity, making the resulting tablet hard. Besides that, CA-LBG is an ester derivative of LBG containing mannose and galactose. When compressed, mannose and galactose form a hard solid mass, making the resulting tablet hard."

9. Reviewer Comments: P.8 line 27-31: Why does the CA-LBG at low concentration do not fill the pores of MCC particles while it does at high concentration?

   Author Response:

   Thank you for the question. The author has added sentence (orange ink): “Fine particles from CA-LBG in small amounts choose to occupy the deformation surface of the MCC particles. Apart from that, the character of CA-LBG in the form of an ester tends to be hydrophobic and cohesive so that small amounts of CA-LBG stick to the surface of the tablet after being compressed.”

   Since there are some statements indicate that the MCC particles deformation produce porosity during the compression, it needs some clear or detail data about it to improve the clarity of the idea explanation well.

   Author Response:

   Thank you for the suggestion. The author has added sentence (orange ink): “In addition, irregularly shaped MCC particles, after compression, experience plastic deformation so that the size of the porosity formed varies (Al-Ibraheemi et al., 2013). This porosity is filled by fine deformation of CA-LBG so that the tablet is stable when subjected to mechanical movement.”

[STI] Editor Decision

Dari: Prof. Aldes Lesbani (scitechindones@gmail.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Sabtu, 11 Mei 2024 pukul 08.17 GMT+7

Dear Wuryanto Hadinugroho:

We have reached a decision regarding your submission to Science and Technology Indonesia, "Study of Citric Acid-Locust Bean Gum as A Glidant to Fillers of Cellulose Derivatives".

Our decision is to accept your submitted manuscript for publication in

Thank you for publishing with us and please do not hesitate to contact us if you have any inquiry.

Science and Technology Indonesia

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B-LC-01 Revised Manuscript_3 Ter.docx
1.9MB

Proofread and Invoice Article (LC-01)

Dari: Aldes Lesbani (sciencetechindonesia@gmail.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Sabtu, 11 Mei 2024 pukul 22.33 GMT+7

Dear Author,

I am sending the proof of the manuscript for your approval and final check before publishing it in Science and Technology Indonesia. If anything needs to be changed, please inform us as soon as possible.

-Please complete the references in your manuscript that are colored red

To cover processing costs and provide open access for articles that have been accepted, the Journal now charges a publication fee of 4,013,750 IDR. This publication fee should be transferred to the bank account shown below, and details of the transfer either e-mailed to <admin@sciencetechindonesia.com> and <sciencetechindonesia@gmail.com>.

The payment must be made to Science and Technology Indonesia to the below bank account.

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Bank: Bank Central Asia (BCA)
Account Name: Aldes Lesbani
Account No: 0214167855
Bank SWIFT Code: CENAIDJA

Your accepted manuscript will be transferred to the production section after your payment has been confirmed by our administration department.

Sincerely Yours,

Editor-in-Chief
Prof. Aldes Lesbani, Ph.D.
Science & Technology Indonesia
http://sciencetechindonesia.com

STI-INVOICE ARTICLE (LC-01).pdf
72.4kB

STI_template (LC-01).pdf
1.1MB

Final correction and proof of transfer of APC Manuscript LC-01

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

Kepada: sciencetechindonesia@gmail.com; admin@sciencetechindonesia.com

Tanggal: Sabtu, 18 Mei 2024 pukul 06.26 GMT+7

Dear.
Prof. Aldes Lesbani, Ph.D.
Editor-in-Chief
Science & Technology Indonesia

Thank you for the opportunity to finalize corrections for the LC-01 manuscript. I am attaching the corrected manuscript, figure 2, ^{1}H and ^{13}C NMR Spectra of CA-LBG, and proof of APC payment transfer to this email.
Thank you for your attention and cooperation. If you have questions or need anything else, please contact me again.

Yours sincerely,
Wuryano Hadinugroho

Figure 2..jpg
193.1kB

Figure 2..tiff
327.3kB

STI_template (LC-01)_Proofread Rev.pdf
1.1MB

Proof of transfer of APC Manuscript LC-01.jpeg
56.6kB

[STI] Editor Decision

Dari: Prof. Aldes Lesbani (scitechindones@gmail.com)

Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Minggu, 19 Mei 2024 pukul 17.26 GMT+7

Dear Wuryanto Hadinugroho:

Your article "Study of Citric Acid-Locust Bean Gum as a Glidant to Fillers of Cellulose Derivatives," is has been pre-published in upcoming issue.

URL of the issue in progress is here: https://sciencetechindonesia.com/index.php/jsti/

Thank you for your great contribution.

Best regards

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Study of Citric Acid-Locust Bean Gum as a Glidant to Fillers of Cellulose Derivatives

Wuryanto Hadinugroho

https://doi.org/10.26554/sti.2024.9.3.613-620