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Citric acid-locust bean gum as a negative matrix for controlled release tablet

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Abstract

Purpose: This study aimed to determine the optimum concentration of HPMC as hydrogel matrix and CA-LBG as negative matrix on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC. CA-LBG accelerates the disintegration of tablets into granules so that the HPMC granule matrix swells immediately and controls drug release. The advantage of this method is that the tablets do not produce large hydroxypropyl methylcellulose (HPMC) gel lumps without drug (ghost matrix) but form HPMC gel granules which can be rapidly degraded after all the drug is released.

Methods: The experiment followed the simplex lattice design to obtain the optimum tablet formula with CA-LBG and HPMC concentrations as optimization factors. Tablets production by wet granulation method dan ketoprofen is the model of the active ingredient. The kinetics of ketoprofen release was studied using several models.

Results: Based on the coefficients of each polynomial equation that HPMC and CA-LBG increased the value of angle of repose (29.91 : 27.87), tap index (18.99 : 18.77), hardness (13.60 : 13.32), friability (0.41 : 0.73), and release of ketoprofen (52.48 : 99.44). Interaction of HPMC and CA-LBG increased the value of angle of repose (3.25), tap index (5.64), and hardness (2.42). Interaction of HPMC and CA-LBG too decreased the value friability (-1.10), and release of ketoprofen (-26.36). The Higuchi, Korsmeyer-Peppas, and Hixson-Crowell model is the kinetics of eight experimental tablet formulas.

Conclusion: The optimum concentrations of HPMC and CA-LBG for controlled release tablets are 32.97% and 17.03%. HPMC, CA-LBG, and a combination of both affect the physical quality of tablet and tablet mass. CA-LBG is a new excipient candidate that can control drug release from tablets by matrix disintegration mechanism on the tablet.

Keywords:

CA-LBG, citric acid, locust bean gum, control release, optimization

Introduction

Controlled-release tablets are drug delivery systems to prolong the therapeutic effect. The drug is released slowly and continuously over some time. Ion exchange resins, osmotic pumps, and reservoirs are examples of controlled release systems.[1,2] HPMC is one of the polymers often used to control drug release because the HPMC matrix can trap drug particles and release them slowly. HPMC matrices alone or with other polymers are often used to control drug release.[3–5]

CA-LBG is a new ester polymer derived from locust bean gum. CA-LBG is synthesized using a hydrochloric acid (HCl) catalyst and an ultraviolet light (UV 254 nm) energy source. O atoms of the carbonyl group of CA are to be protonated to form positive C atoms because of acid conditions created by HCl. The ester bond occurs at the OH (C-6) mannose and galactose groups in LBG with a positive C atom from the carbonyl group in CA to form a tetrahedral cation. OH were protonated to $^{+}OH_2$, continued loss of H_2O to form CA-LBG (ester).[6–11] Previous experiments reported that CA-LBG has an ester carbonyl group which LBG does not. The viscosity and solubility of CA-LBG are lower than that of LBG.[7] The CA-LBG character has the potential to control drug release.

This study aimed to determine the optimum concentration of HPMC and CA-LBG on the tablet. on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC. The activity of CA-LBG as a negative matrix with HPMC matrix to control drug release was studied by drug release kinetics. The novelty of this experiment is that the formulation using CA-LBG is a new polymer ester with low solubility. The CA-LBG as a negative matrix causes the tablets to disintegrate into granules. HPMC matrix gel derived from granules controls drug release. A negative matrix (CA-LBG) is a substance that causes the tablet's positive matrix (HPMC) to disintegrate into granules. The mechanism of action on tablets is that the wetted tablet surface causes disintegration into granules due to low solubility of CA-LBG and repulsion between CA-LBG particles. Granules containing HPMC swell to control drug release. CA-LBG controls drug release because CA-LBG is poorly soluble and has low viscosity, so CA-LBG inhibits

the wetting and dissolution of drug particles. The advantage of this method is that the tablets do not produce large hydroxypropyl methylcellulose (HPMC) gel lumps without drug (ghost matrix) but form HPMC gel granules which can be rapidly degraded after all the drug is released. Ketoprofen (100 mg) (see supplementary information Chapter S1) is a drug model added to the granules and compressed into tablets (400 mg). HPMC was chosen as the matrix because HPMC is a polymer that can swell when hydrated with water with a viscosity to control drug release.[1,5] Lactose monohydrate is a suitable filler for tablets because it has good compatibility and high density (1.545 g/cm^3).[5] These character can be suitable for wet granulation methods, so tablets are hard and of the ideal size. Ketoprofen is used in the drug model because ketoprofen has a dose of 25-200 mg and an elimination half-life of 2-4 hours.[12,13] Making tablets using the wet granulation method can improve the flow properties by increasing the particle size and the compatibility of the tablet mass. CA-LBG particles are shaped like coral-corrugated, HPMC particles like a rhizome, and irregularly shaped lactose monohydrate particles.[5,7] The experiment followed the simplex lattice design to obtain the optimum tablet formula. This method is quite simple for experiments by mixing internal factors (ingredients) in a formula without the influence of internal factors (process or technology). In addition, this method is quite effective for synthesized materials such as CA-LBG in limited quantities. The optimization factor is the concentration of CA-LBG and HPMC. The optimization response is the angle of repose, tap index, hardness, friability, and ketoprofen release.

Material and methods

Raw materials and chemicals

The materials used in this experiment include locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Brand KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich Chemie, GmbH, USA), distilled water (Sterilized Water For Injection, PT. Otsuka Indonesia), acetone (Cawan Anugerah Chemika, Indonesia), hydroxypropyl methylcellulose (Methocel K4M CR

Premium USP/EP, Colorcon, Singapore), lactose monohydrate (Leprino Foods, UDM, USA), ketoprofen (PT Kalbe Farma Tbk, Indonesia), potassium dihydrogen phosphate (KGaA Darmstadt Germany Brand), and sodium hydroxide (KGaA Darmstadt Germany Brand).

Manufacture of CA-LBG

The manufacturing of CA-LBG adopted the manufacturing method in the previous study. The LBG ($3.55\ 10^{-6}$ mol) was swelled in 50 mL of warm distilled water (55-60 ^{o}C), added CA ($21.00\ 10^{-3}$ mol), and HCl ($57.40\ 10^{-3}$ mol), homogenized for 10 minutes. The gel was irradiated with UV 254 nm for 100 min (8-Watt, CH-4132 Muttenz, Camag, Switzerland), then precipitated (acetone) and washed off (distilled water-acetone). The CA-LBG residue was dried at room temperature.[7,14]

The success of CA-LBG production was confirmed through the Fourier transform infrared spectroscopy (FTIR) characterization, nuclear magnetic resonance (NMR), solubility, and viscosity. Production is carried out for three batches to determine reproducibility through standard deviation.

Fourier transform infrared spectroscopy

The structure and specific groups of CA-LBG were identified by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.). The observations show that a spectrum wavelength is 4000-450 cm^{-1}. A certain amount of powder is placed on a diamond plate and pressed with a stick on the instrument. Spectra are visible on the monitor and recorded.

Nuclear magnetic resonance

The NMR spectroscopic examination confirmed the structure and specific group of CA-LBG. An amount of CA-LBG powder (5-10 mg) was dispersed in H_2O (deuterium) and stirred for 45 minutes at a vortex. The filtrate was transferred to a glass tube and analyzed by NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan).

Esterified CA

The amount of esterified CA was determined by the degree of esterification. Determination of the degree of esterification adopts the previous experiment.[7,14] Samples were derived from CA-LBG precipitating solven and washing solution (acetone and distilled water-acetone). Measurements using potentiometry with titrant NaOH (0.2 N) standardized by oxalic acid. The titrant volume endpoint determines the dissolved acid's total concentration [mEq]. The dissolved CA concentration [mEq] was obtained from the difference between the total acid concentration and the HCl concentration. The dissolved CA [gram] weight was obtained from the conversion of dissolved CA [mEq]. The reacted CA was obtained from the difference between the initial CA weight and dissolved CA. The degree of esterification [%] is the ratio of CA reacted with initial CA.

Solubility study

The CA-LBG powder (500 mg) was dispersed in distilled water (50 mL) and stirred for 24 hours (Wd). The swelled powder and filtrate are carefully separated. The filtrate was dried in a water bath (70^{o}C and reweighed (Wds) (Mettler Toledo AL204, Switzerland). The dissolved CA-LBG was determined according to Equation 1:

$$S\,[\%] = \frac{Wds}{Wd}.100\ \% \qquad \text{Equation 1}$$

where the solubility (S), the soluble weight (Wds), and initial dry weight (Wd).[15]

Viscosity

The viscosity of CA-LBG was determined by a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG powder (3% w/v) was swelled in warm distilled water (300 mL, 50-60^{o}C) and allowed to cool to ambient temperature. Spindle No. S61 mounted on Brookfield was dipped on swollen mass and rotated (100 rpm). Viscosity is shown on the monitor and recorded.

Manufacture of tablets

In this experiment, the method of making tablets by wet granulation adopted the previous study with the necessary adjustments.[14] Preparing granules by wet granulation contains HPMC and lactose monohydrate (50 %) according Table 2 (cubic mixer, rotary motor (Erweka)). A homogeneous mixture was moistened with CA-LBG dispersed in distilled water (± 5 mL) while being compressed to form a wet granule mass and sieved (mesh No. 18) to form granules. The wet granules were dried in an oven (50^0C; 15 min; RH 2-5%) (moisture analyzer OHAUS) and re-sieved (mesh No. 20). The granules were mixed with ketoprofen (100 mg) (3:1) and evaluated for the mass quality of the tablets. The tablet mass was compressed to form a 400 mg tablet and hardness ≥ 13 kp (single punch, Korch, Germany), assessed for the physical quality of the tablet and dissolution.

Optimization

Optimization of the granule formula according to the simplex lattice design of two factors used eight runs randomized of formulas, model quadratic, and optimization software (Design Expert ver. 10.0.8.0; Stat-Ease Inc., Minneapolis, MN, USA). Comparison of the proportion of HPMC and CA-LBG for each formula based on optimization software (Table 2), including 0:1 (2 formulas); 0.25:0.75 (1 formula); 0.50:0.5 (2 formulas); 0.75:0.25 (1 formula); and 1:0 (2 formulas). The concentration of HPMC in proportion 0 (30%) and proportion 1 (40%), while the concentration of CA-LBG in proportion 0 (10%) and proportion 1 (20%). The HPMC concentration and the CA-LBG concentration were optimization factors. The angle of repose, tap index, hardness, friability, and released ketoprofen were optimization responses. The values of the optimization response parameters were processed using optimization software to obtain polynomial equations and predict the optimum concentrations of HPMC and CA-LBG in granules.

Flowability

The mass of the tablet was weighed at about 50 g and placed on the funnel of a flowability tester (Erweka, Germany). The funnel valve opens, and the tablet mass flows freely. The flowability tester monitor observed the measured flow time of the tablet mass. The cone from tablet mass was measured using infrared to determine the angle of repose and watched on the flowability tester monitor.

Tap Index

The tablet mass was put in a measuring cup (50 mL). The measuring cup was tilted and filled with tablet mass. The filled measuring cup was placed on the volumenometer tap density and tapped 500 taps. Tap index (TI) was determined from the difference between the volume before and after tapping compared to the volume before tapping (Equation 2).[16–19]

$$TI\ [\%] = \frac{V0 - V1}{V0}\ x\ 100\% \qquad \text{Equation 2}$$

Weight

From randomly selected tablets (20), and each tablet was weighed using an analytical balance (Mettler Toledo, Switzerland).

Hardness

Tablet hardness test used randomly selected tablets (6 tablets).[20] The tablets were placed on a board in a hardness tester (Schleuniger, Netherlands), then a metal block pressed on the tablet until the tablet cracks. The tablet hardness was observed on the monitor hardness tester.

Friability

The tablet friability test used randomly selected tablets with a total weight of comparable tablets of 6500 mg.[20] Each tablet was cleaned from dust, then all tablets were weighed (W0). All tablets were placed in a drum friability tester (Erweka, Germany) and rotated (4 min; 25 rpm). All tablets were removed, cleaned from dust, and reweighed (W1). The friability (F) of tablets is determined according to Equation 3.

$$Fr\ (\%) = \frac{W0 - W1}{W0}\ 100\% \qquad \text{Equation 3}$$

Drug release

The release of ketoprofen was tested using a dissolution apparatus II USP paddle model.[12,13] The dissolution media used phosphate buffer pH 6.8 (900 mL; 37°C; 50 rpm) (Electrolab TDT-08L, India). Samples were taken at 0.5; 1; 1.5; 2; 2.5; 3; 4; 5; 6; 8; and 10 hour. Ketoprofen released from the tablet determined absorption value read by UV spectrophotometer (260 nm) (Hitachi U-1900, Japan).[13,21]

Kinetics of ketoprofen release

The release kinetics of ketoprofen from tablets was influenced by HPMC and CA-LBG in the granules. The kinetics of drug release is determined by the following equations:[22–25]

Zero order $: Q_t = Q_o + K_o.t$ Equation 4

First order $: \ln Q_t = \ln Q_o + K_o.t$ Equation 5

Qt: the amount of drug dissolved at the time (t), Qo: the amount of the initial drug, and Ko: drug release constant.

Higuchi $: Q_t = K_H.\sqrt{t}$ Equation 6

Qt: the amount of drug dissolved at the time (t), K_H: Higuchi constant, and t: time.

Korsmeyer-Peppas : $Q_t/Q_\infty = K_k . t^n$ Equation 7

Qt/Q∞: fraction of drug released, Kk: Korsmeyer-Peppas constant, and n: diffusion exponential.

Hixson-Crowell :$Q_o^{1/3} - Q_t^{1/3} = K_s.t$ Equation 8

Qo: the amount of initial drug, Qt: the amount of drug remaining at the time (t), and Ks: dissolution rate constant.

Weibull : $\log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 9

(1-m): fraction of insoluble drug, Ti: the lag time before dissolution, b: shape parameter obtained from the slope of the obtained curve. The value of b = 1 means that the curve is exponential. The importance of b > 1 is the shape of the sigmoid curve.

The release kinetics of ketoprofen from tablets of each granule formula was analyzed using DDSolver software.

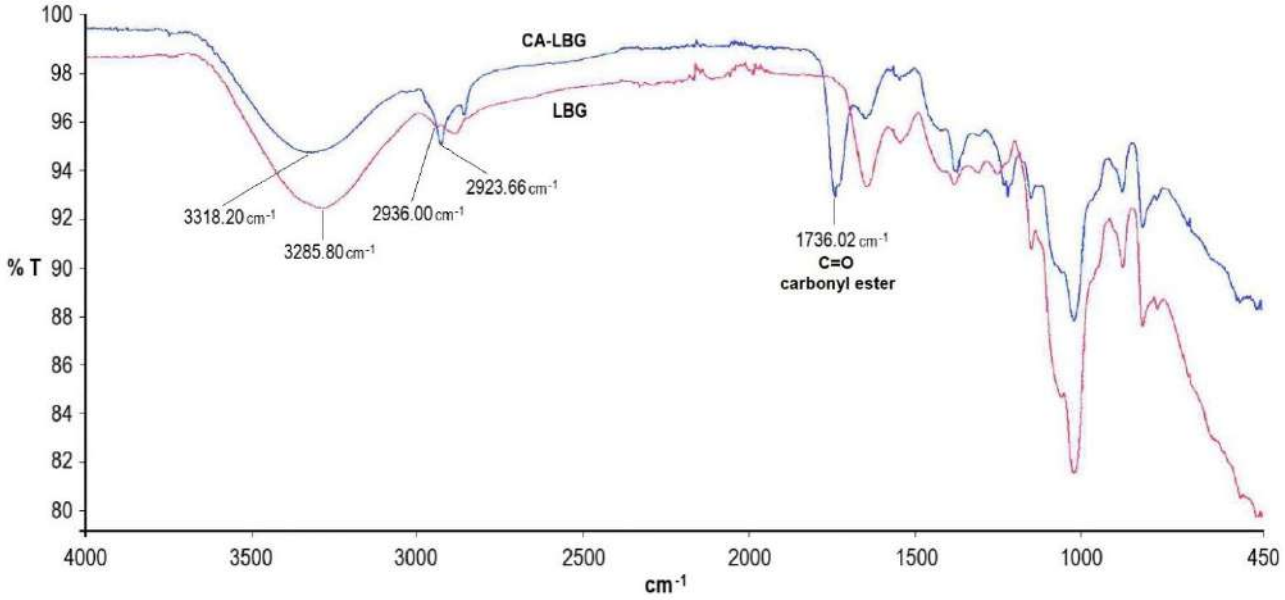

Figure 1. Infrared spectra of CA-LBG and LBG. The CA-LBG spectra have a carbonyl ester group (C=O) at a wavelength of 1736.02 cm^{-1}, presented by a blue line. LBG as control, presented with a red line.

Result and Discussion

Fourier transform infrared spectroscopy

Infrared spectra of CA-LBG and LBG are presented in Figure 1. Peaks at wavelengths of 3318.20 cm^{-1} and 3285.80 cm^{-1} indicate the hydroxyl (OH) groups of mannose and galactose. Peaks at wavelengths of 2923.66 cm^{-1} and 2936.00 indicate C-H bonds, where CA-LBG is sharper than LBG due to the influence of symmetrical C-H bonds from CA.[25,26] The specific peak of CA-LBG at 1736.02 cm^{-1} indicates an ester carbonyl group. Previous studies reported that the peak wavelength of the OH group appears at 3300 cm^{-1}, C-H appears at around 2900 cm^{-1}, and C=O appears at about 1750-1735 cm^{-1}.[7] The results of the infrared analysis were further confirmed using NMR.

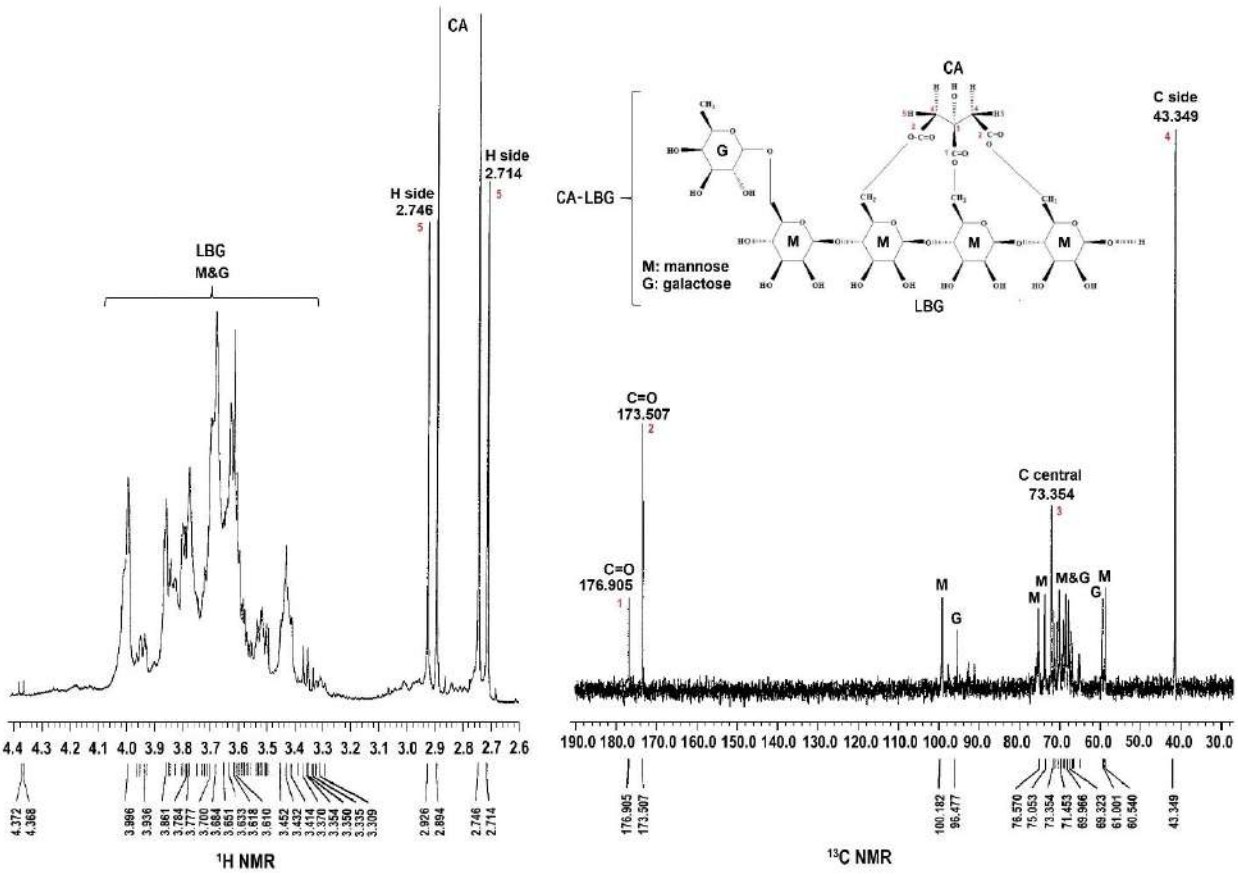

Figure 2. NMR observation spectra of CA-LBG. CA characters present in CA-LBG resented peaks 1, 2, 3, 4, and 5.

Nuclear magnetic resonance

The NMR examination further confirms the FTIR examination and is carried out representatively for the three manufacturing batches. The CA-LBG NMR spectra are presented in Figure 2. The ^{1}H NMR spectra, paired twin peaks at δ = 2.926 ppm and δ = 2.894 ppm, δ = 2.746 and ppm, δ = 2.714 ppm correspond to the presence of CH_2 (5) of CA in LBG. The sharp peak at δ = 3.996-3.309 ppm corresponds to the H atoms of mannose and galactose in LBG. Previous experiments reported that the paired twin peaks of CH_2 were seen at δ = 2.7-3.0 ppm. Sharp peaks of H atoms from mannose and galactose appear at δ = 4.5-3.0 ppm.[6,7]

The ^{13}C NMR spectra of CA-LBG at the peak δ = 176.905 ppm and δ = 173.507 ppm indicated the carbonyl group (C=O) (1,2), which was a specific group of CA-LBG. The central C atom of CA is shown at δ = 73.354 ppm (3). CH_2 of CA is shown at δ = 43.349 ppm (4). The C atoms that make up mannose and galactose from LBG are shown at δ = 100.182 ppm, δ = 96.477 ppm, δ = 76.570 ppm, δ = 75.053 ppm, δ = 71.453 ppm, δ = 69.966 ppm, δ = 69.323 ppm, δ = 61.001 ppm, δ = 60.540 ppm. Previous experiments show C=O group at δ = 180-170 ppm, central C atom at δ = 80-70 ppm, CH_2 appears at δ = 44-43 ppm.[6,7,27] The C atoms make up mannose, and galactose appears at δ = 105-60 ppm.[7,28–30] Finally, the peaks in the spectra indicate the success of the synthesis.

Esterified CA

The degrees of esterification in each batch are shown in Table 1. All batches had similar degrees of esterification, indicating reproducible manufacturing conditions. The experimental esterification degree of 29.30-29.55% corresponds to the previous experimental report of around 9.13%.[7,14] The degree of esterification of all batches indicated that the esterification conditions were stable and reproducible. The acidic condition created by HCl induces the O atom in the carbonyl group of CA to be protonated to a positive C atom. The OH group on C6 of mannose and galactose will react with a positive C atom.

Table 1. Evaluation degree of esterification, solubility, and viscosity of CA-LBG

Batch Code	Degree of esterification		Solubility		Viscosity	
	[%]	SD	[%]	SD	[cP]	SD
1	29.33	0.20	29.65	0.27	9.48	0.01
2	29.30	0.21	29.81	0.18	9.46	0.02
3	29.55	0.10	29.51	0.42	9.43	0.02

Solubility

The solubility of CA-LBG in each batch is presented in Table 1. All batches showed similar solubility and indicated reproducible manufacturing. The solubility is 29.51-29.81%, according to the solubility in the previous experiment (22.64-36.63%).[14] The ester bond of CA molecules influences the solubility of CA-LBG in LBG. The positive C atom of the carboxylate group (CA) binds to the O atom at C-6, inhibiting the interaction of CA-LBG with distilled water CA-LBG and reducing solubility.

Viscosity

Table 1 shows the respective viscosity of CA-LBG has similar values and indicates reproducible manufacturing. The viscosity shows a value of 9.43-9.48 cPs following the viscosity in the previous experiment (7.76-11.20 cPs).[14] Viscosity is influenced by the carbonyl ester group formed from the positive C atom of the carboxylic group (CA) with the O atom at C-6 in mannose and galactose so that the ability of CA-LBG to trap distilled water decreases.

Flowability

The results of testing the flow time and angle of repose of the tablet mass for each formula are presented in Table 2. Each formula produces a flow time of about 4.60-5.00 seconds and an angle of repose 27.89-30.04^0, indicating the tablet mass good flows because $\leq$ 10 seconds for 100 g and $\leq 40^0$ [17]. The tablet mass can occupy the die space inside the tablet machine. The tablet mass can be

continued to be compressed to form a tablet (400 mg). The response of the angle of repose according to the simplex lattice design is obtained by Equation 10.

$$Y = 29.91\ A + 27.87\ B + 3.25\ AB$$ Equation 10

The coefficient value of each component in the equation shows that HPMC (29.91) is the most dominant factor in increasing the angle of repose, followed with CA-LBG (27.87), and a combination of both (3.25). The CA-LBG is an ester polymer that is difficult to hydrate with distilled water, so CA-LBG inhibits the formation of bonds between the granule constituent particles and produces fine granules. A large number of refined grains inhibits the tablet mass flow. HPMC is a polymer that can absorb moisture from the surrounding environment.[5] The HPMC in the granules increases moisture impedes flow, forming high mounds. Combining CA-LBG with HPMC, which can absorb moisture, increases the tablet mass flow time. Flow time is one parameter that determines the diversity of weights in the tablet manufacturing process.

Based on the ANOVA analysis (see supplementary information Table S1), the response angle of repose has a Pred R-Squared (0.9596), similar to Adj R-Squared (0.9742) with less than 0.2. Meanwhile, the Adeq Precision (23.8130) greater than 4, indicating this model is acceptable.

Tap Index

The tablet mass tap index for each formula is presented in Table 2. Each formula has a tap index of about 18.50-20.00%, indicating that the tablet mass has good homogeneity because ≤ 20% [17], so the space between the granules is filled with particles or fines. In addition, this condition shows that the tablet mass has good compressibility and creates low porosity tablets. The tap index for each formula is processed according to the simplex lattice design to obtain Equation 11.

$$Y = 18.99\ A + 18.77\ B + 5.64\ AB$$ Equation 11

The value of the HPMC coefficient (18.99) is the dominant factor in increasing the tap index, followed with CA-LBG (18.77) and a combination of both (5.64). HPMC can reduce the sensitivity

of the granules because the HPMC particles absorb moisture so that the granules change shape when granules receive mechanical stress. The difficulty of hydrating CA-LBG particles in the granulation process causes the bond between the granules to be not good so that the granules release fines and receive mechanical stress. The combination of the two factors can increase the tap index because the HPMC reduces the sensitivity due to moisture absorption. In addition, it is supported by less strong bonds between particles in the granules due to the difficulty of hydrating during the granulation process.

Based on the ANOVA analysis (see supplementary information Table S1), the response tap index has a Pred R-Squared (0.7862), similar to Adj R-Squared (0.8928) with less than 0.2. Meanwhile, the Adeq Precision (10.7420) greater than 4, indicates this model is acceptable.

Weight

The tablet weight of all formulas is shown in Table 2. Tablet mass was compressed into tablets with a weight of about 400 mg. The tablet mass of all formulas is free to flow and fill the die chamber, so tablet weight is according to design. The compression success is suitable for the value of flow time, angle of repose, and tap index.

Table 2. Details of HPMC and CA-LBG concentration, quality of the tablet mass, quality of the tablet, and release of ketoprofen (Dr)

Formula code	HPMC [%]	CA-LBG [%]	Flow time [sec.]	Angle of repose [°]	Tap index [%]	Weight [mg]	Hardness [kp]	Friability [%]	Dr [10 hr.] [%]
G1	40.00	10.00	4.80 ± 0.06	29.92 ± 0.10	19.00	401.34 ± 1.69	13.61 ± 0.70	0.39	53.75 ± 0.89
G2	32.50	17.50	4.60 ± 0.10	28.98 ± 0.08	20.00	400.87 ± 1.25	13.84 ± 1.05	0.45	83.34 ± 0.70
G3	35.00	15.00	5.00 ± 0.06	29.47 ± 0.18	20.00	402.08 ± 1.50	14.08 ± 0.84	0.28	69.33 ± 0.93
G4	40.00	10.00	4.60 ± 0.10	29.86 ± 0.53	18.50	400.07 ± 1.16	13.60 ± 0.61	0.43	51.71 ± 0.71
G5	30.00	20.00	4.80 ± 0.06	27.86 ± 0.18	19.00	399.69 ± 1.45	13.33 ± 0.46	0.74	99.21 ± 1.04
G6	37.50	12.50	4.80 ± 0.15	30.04 ± 0.06	20.00	400.12 ± 1.65	14.01 ± 0.83	0.34	58.16 ± 0.89
G7	35.00	15.00	5.00 ± 0.15	29.93 ± 0.94	20.00	400.36 ± 0.89	14.06 ± 0.87	0.28	69.82 ± 0.33
G8	30.00	20.00	5.00 ± 0.10	27.89 ± 0.54	19.00	399.67 ± 1.21	13.32 ± 0.84	0.73	99.32 ± 0.46
Ga	32.97	17.03	4.80 ± 0.06	29.17 ± 0.12	20.00	401.27 ± 1.15	13.97 ± 0.64	0.40	80.08 ± 0.60
Gb	32.97	17.03	4.60 ± 0.15	29.08 ± 0.23	20.00	399.00 ± 1.20	14.01 ± 0.58	0.41	80.44 ± 1.17
Gc	32.97	17.03	5.00 ± 0.10	29.22 ± 0.99	19.50	400.67 ± 0.79	13.86 ± 0.85	0.39	80.45 ± 0.55
Go	32.97	17.03	-	29.16	20.01	-	13.91	0.41	80.00

The proportion of HPMC and CA-LBG are G1 (1 : 0); G2 (0.25 : 0.75) G3 (0.5 : 0.5); G4 (1 : 0); G5 (0 : 1); G6 (0.75 : 0.25); G7 (0.5 : 0.5); G8 (0 : 1); Ga (0.30 : 0.70); Gb (0.30 : 0.70); Gc (0.30 : 0.70); and Go (0.30 : 0.70).

Hardness

The tablet hardness of each formula is presented in Table 2. Tablets of each formula have a hardness are around 13.32-14.08 kp, indicating that the tablet has strong resistance and good physical stability. The hardness of tablets comes from strong interlocking between the granules/particles making up the tablet when receiving compression so that the porosity of the tablet is low. The hardness of each formula is processed according to the simplex lattice design to obtain Equation 12.

$$Y = 13.60\ A + 13.32\ B + 2.42\ AB \qquad \text{Equation 12}$$

The coefficient value of HPMC (13.60) is the most dominant factor in increasing hardness, followed with CA-LBG (13.32) and a combination of both (2.42). HPMC can absorb moisture and is used as an adhesive between the deformation of granules/particles to produce a solid interlocking bond. The tablets have good stability to humidity even though the granules contain HPMC because the moisture absorption activity is inhibited by decreasing the absorption surface area in the tablets form than the granules. Although CA-LBG is difficult to hydrate, the deformation of the particles can form solid interlocking bonds. In addition, the presence of CA-LBG on the tablet surface inhibits moisture absorption. The combination of both can increase the hardness because the characters of HPMC and CA-LBG complement each other. The tablet has a solid interlocking bond between the deformation of the granules/particles, and the tablet can retain moisture. In addition, the tap index shows that the tablet mass has low porosity and good compressibility so that when compressed tablet mass produces a compact tablet.

Based on the ANOVA analysis (see supplementary information Table S1), the response hardness has a Pred R-Squared (0.9976), similar to Adj R-Squared (0.9985) with less than 0.2. Meanwhile the Adeq Precision (100.1700) greater than 4, indicates this model is acceptable.

Friability

The tablet friability of all formulas is presented in Table 2. Each formula has a friability of 0.28-0.74% (≤ 1%)[17], indicating that the tablet surface is strong enough to withstand mechanical movements because of solid interlocking bonds between the deformation of the particles on the tablet surface. Friability of all formulas is according to the simplex lattice design to obtain Equation 13.

$$Y = 0.41\ A + 0.73\ B - 1.10\ AB \qquad \text{Equation 13}$$

The coefficient value of HPMC (13.60) is the most dominant factor in increasing hardness, followed with CA-LBG (13.32) and a combination of both (2.42). HPMC can absorb moisture and is used as an adhesive between the deformation of granules/particles to produce a solid interlocking bond. The tablets have good stability to humidity even though the granules contain HPMC because the moisture absorption activity is inhibited by decreasing the absorption surface area in the tablets form than the granules. Although CA-LBG is difficult to hydrate, the deformation of the particles can form solid interlocking bonds. In addition, the presence of CA-LBG on the tablet surface inhibits moisture absorption. The combination of both can increase the hardness because the characters of HPMC and CA-LBG complement each other. The tablet has a solid interlocking bond between the deformation of the granules/particles, and the tablet can retain moisture. In addition, the tap index shows that the tablet mass has low porosity and good compressibility; thus, when compressed, tablet mass produces a compact tablet.

Based on the ANOVA analysis (see supplementary information Table S1), the response friability has a Pred R-Squared (0.9593) similar to Adj R-Squared (0.9747) with less than 0.2. Meanwhile, the Adeq Precision (24.6860) greater than 4, indicates this model is acceptable.

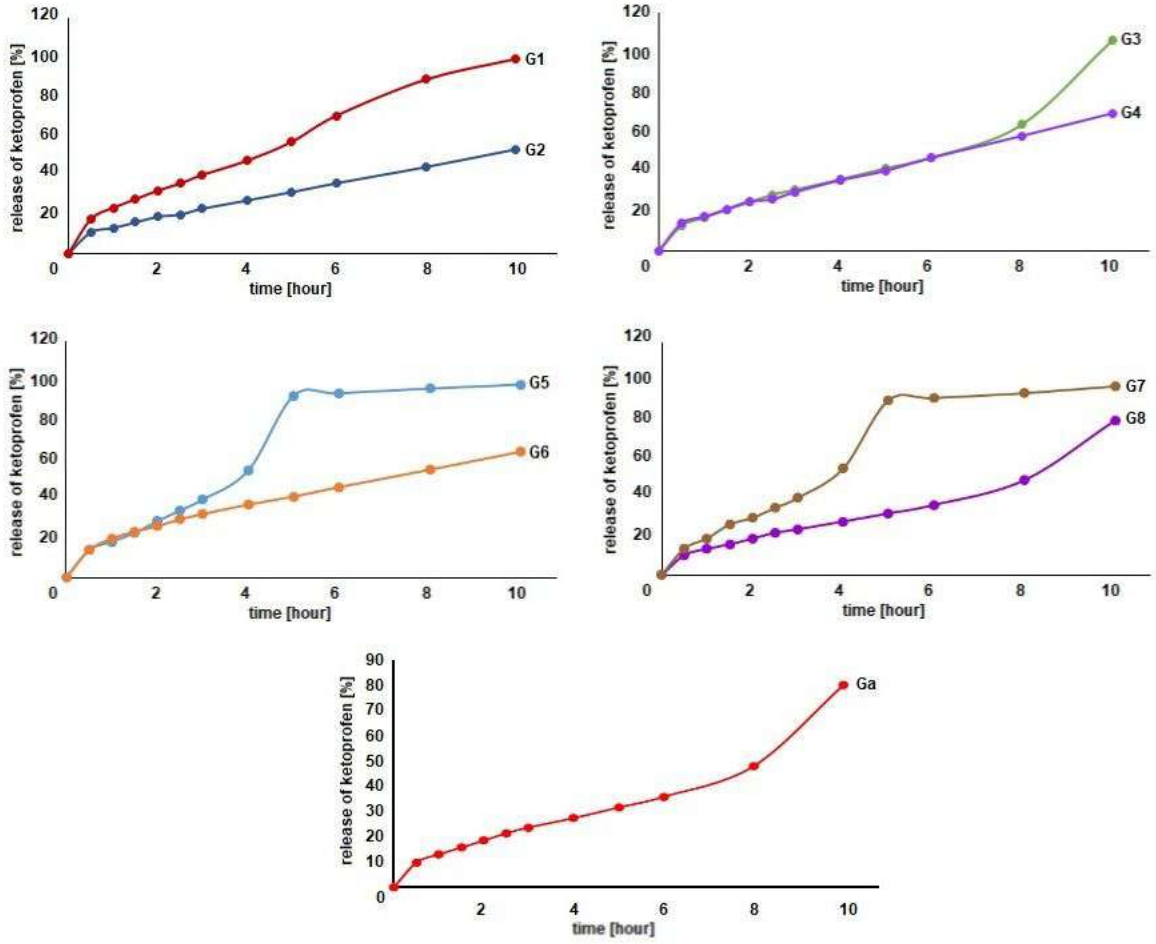

Figure 3. The ketoprofen dissolution profile of various tablet formulas contains HPMC [%] and CA-LBG [%]: G1 (40 : 10); G2 (32.5 : 17.5); G3 (35 : 15); G4 (40 : 10); G5 (30 : 20); G6 (37.5 : 12.5); G7 (35 : 15); G8 (30 : 20); and Ga (32.97 : 17.03).

Ketoprofen release

The concentration and profile of ketoprofen release for each tablet formula after 10 hours are presented in Table 2, Figure 3, and supplementary information Table S2-S3. All tablets of ketoprofen release around 51.71-99.32%, showing that HPMC and CA-LBG can control ketoprofen release from tablets. HPMC is a polymer that swells when hydrating by the dissolution medium. Ketoprofen release is inhibited because HPMC swells trap ketoprofen particles. The CA-LBG is a polymer that is difficult to hydrate and has low solubility. The CA-LBG character causes the tablet to disintegrate

and become granule. Releases of ketoprofen-controlled granule swelling form a gel. Based on the experimental design, ketoprofen released for 10 hours is ≥ 80% (see supplementary information Chapter 1). The processed concentration value of each tablet formula is according to the simplex lattice design to obtain Equation 14.

$$Y = 52.48\,A + 99.44\,B - 26.36\,AB \qquad \text{Equation 14}$$

The CA-LBG coefficient value (99.44) was the most dominant factor in increasing ketoprofen release, followed with HPMC (52.48). The combination of both (26.36) was the most dominant factor in reducing the release of ketoprofen. The deformation of CA-LBG particles on the tablet refuses each other when submerged in the dissolution medium, causing tablet disintegration. The granule porosity surface is used as a space for penetration of the dissolution medium into the granule, dissolved ketoprofen particles, and diffuses out of the granule. The high concentration of CA-LBG accelerates of disintegration of the tablet and forms HPMC gel. Combining the HPMC with CA-LBG can reduce the release of ketoprofen because the moisture of the deformation of the HPMC particles can bind hardly to the interlocking deformation of the CA-LBG and other particles, so that the tablet disintegrates longtime. In addition, the direct interaction of CA-LBG with particles inhibits the swelling of HPMC and hydrating of ketoprofen by the dissolution medium.

Based on the ANOVA analysis (see supplementary information Table S1), the response to the release of ketoprofen has a Pred R-Squared (0.9956), similar to Adj R-Squared (0.9978) with a difference of less than 0.2. Meanwhile the Adeq Precision (85.0460) greater than 4, indicates this model is acceptable.

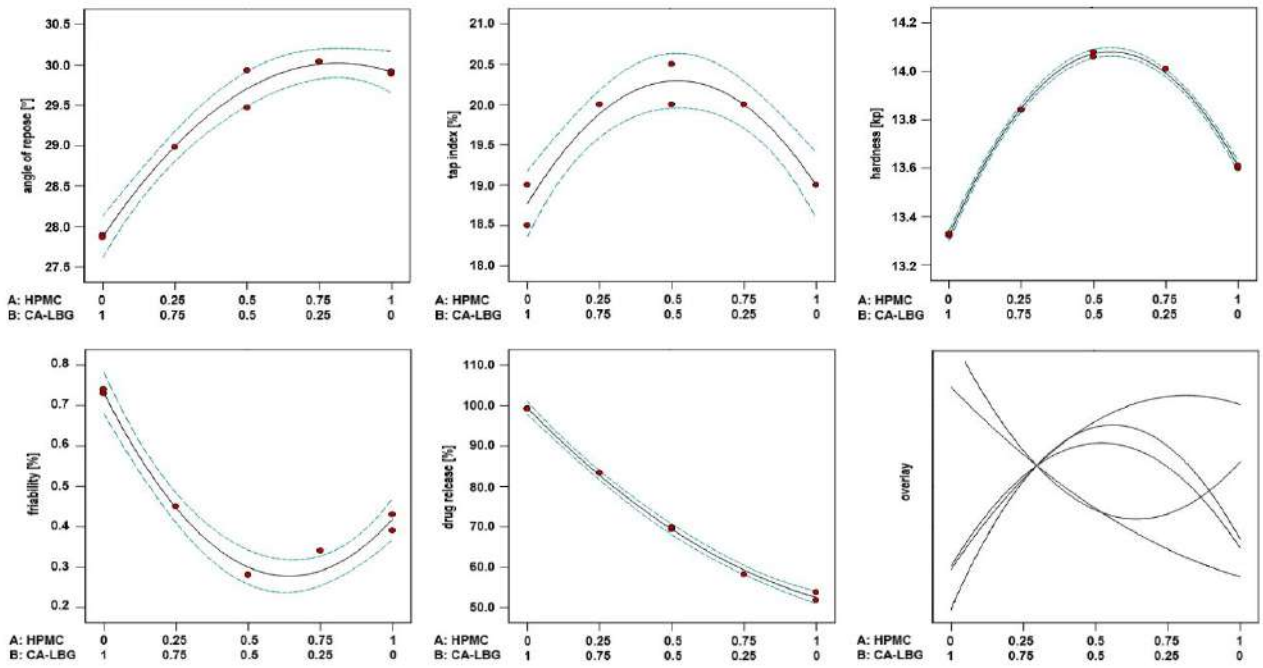

Figure 4. Comparison of actual (dotted line) and predicted (solid line) optimization response profiles. The red dot indicates the response value for each formula based on the respective proportions of HPMC and CA-LBG. The overlay shows the meeting point of all responses according to the predicted optimal proportions of HPMC and CA-LBG.

Optimum tablet formula

Determination of the optimum formula begins with the initial 8 experimental formula designs (G1-G8). The optimization factors and response parameter values were analyzed using design expert software using a simplex lattice design. The experimental comparison profiles and the predictions of each optimization response (Figure 4) show that the actual profiles are similar to the predictions. This profile follows the results of ANOVA analysis for each optimization response (flowability, tap index, hardness, friability, and release of ketoprofen). The optimization response overlay predicts the optimum proportion point to achieve the optimum response prediction. Design expert provides several alternative options for the optimum formula. The selected formula was determined from the response parameter specifications (angle of repose 27.86-30.04; tap index 18.5-20.5; hardness 13.32-

14.08 kp; friability 0.28-0.74%; drug release > 80%). Verification to the prediction of the optimum formula proportion (Go) to obtain the optimum formula was carried out in three batches (Ga, Gb, Gc) (Table 2 and Figure 3).

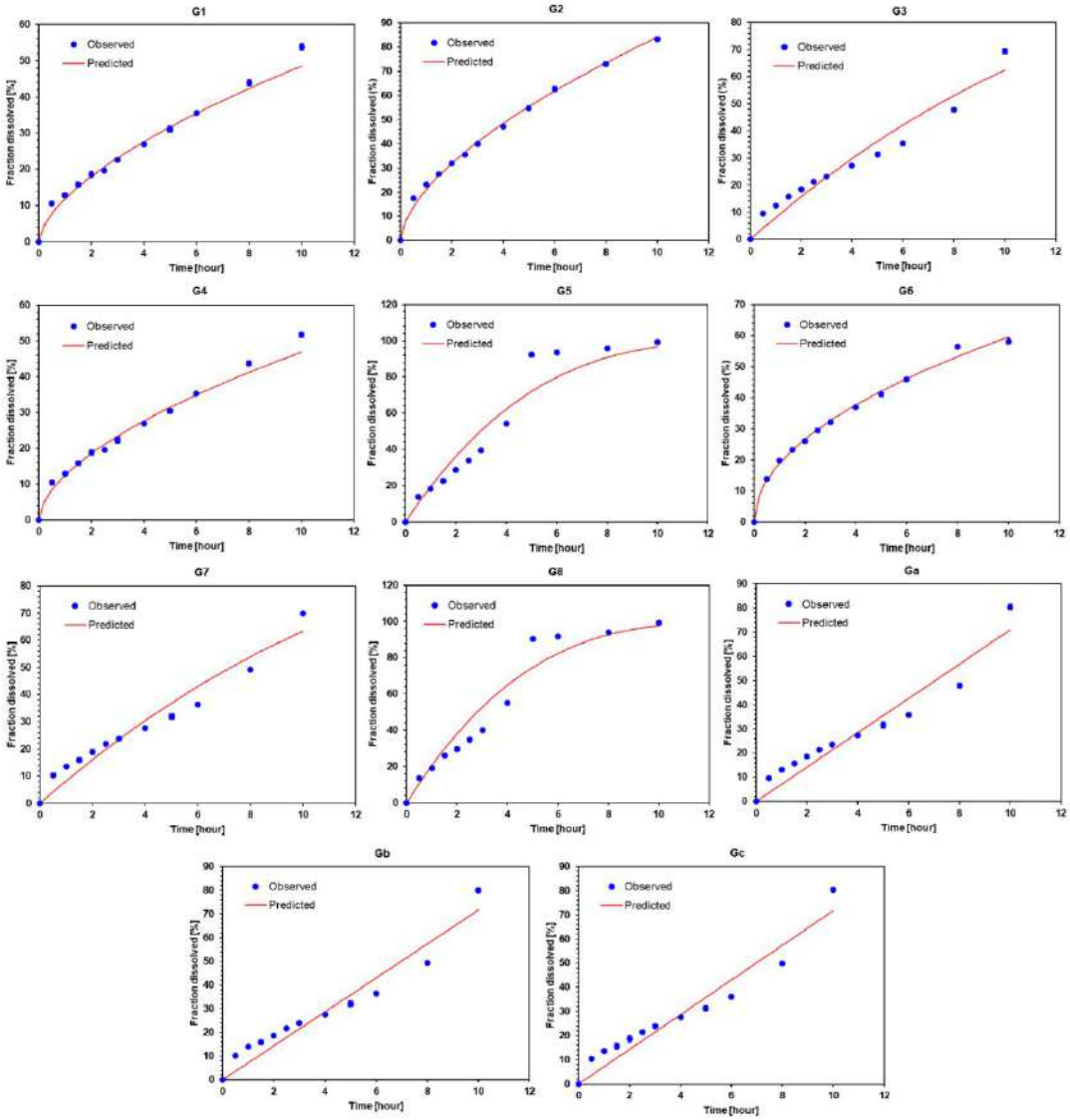

Figure 5. Drug release kinetics model (HPMC [%] : CA-LBG [%]): G1 (40 : 10) (Korsmeyer-Peppas); G2 (32.5 : 17.50) (Korsmeyer-Peppas); G3 (35 : 15) (Hixson-Crowell); G4 (40 : 10) (Korsmeyer-Peppas); G5 (30 : 20) (Hixson-Crowell); G6 (37.50 : 12.50) (Higuchi); G7 (35 : 15) (Hixson-Crowell); G8 (30 : 20) (Hixson-Crowell); Ga (32.97 : 17.03) (Zero order); Gb (32.97 : 17.03) (Zero order); and Gc (32.97 : 17.03) (Zero order).

One sample T-test results compare the experimental response formula verification with the predictive response. The values T of each parameter is T angle of repose (0.008), T tap index (1.096), T hardness (0.728), T friability (1.559), and T release of ketoprofen (2.657). The response parameter values between the prediction (Go) and the verification experiment (Ga-Gc) were not significantly different. These results indicate that the polynomial equations of each response parameter are valid for predicting the effect of HPMC, CA-LBG, and their combination. In addition, the selected optimum formula shows reproducibility in producing tablets and controlling ketoprofen's release. The variation of release shown by G1-G8 proves that tablets with irrelevant variations in physical quality produce varied drug releases.

Kinetics of ketoprofen release

The kinetics of ketoprofen release from the tablet is a non-linear approach using DDSolver (Table 3, Figure 5, and supplementary information Figure S1-S11). The kinetics parameters of ketoprofen release include high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC). The Rsqr_adj is the correlation value between dissolution time and released ketoprofen. MSE_root indicates the error value in correlation analysis. AIC is the value suitability to the equation to determine the release kinetics.[31–35] The results of DDSolver processing are presented in Table 3 and Figure 5.

The release kinetics of ketoprofen from tablets G1, G2, and G4 followed the Korsmeyer-Peppas kinetics. The exponential value (n) for tablets G1 (0.62), G2 (0.60), and G4 (0.58) indicates a non-Fickian diffusion mechanism (anomalous diffusion).[36] The release of ketoprofen released by diffusion is proportional to erosion. The surface of the granules forms a thin gel and cannot withstand the dissolution medium, so ketoprofen dissolves quickly. The ketoprofen release is not only through diffusion but also due to erosion of the surface of the gel formed. The CA-LBG is not tightly

integrated into the tablet and granule. This condition causes the dissolution rate to be faster with the increase in the dissolution medium that enters the tablet and granule.

The release kinetics of ketoprofen from tablets G3, G5, G7, and G8 followed Hixson-Crowell kinetics. The ketoprofen release was caused by hydrating the tablet surface, so the tablet disintegrated and become granule. This condition causes ketoprofen to be dissolved constantly. HPMC low concentration can tablet disintegration quickly when particles swell to form a gel and push against other particles. In addition, CA-LBG on the granule accelerates the decomposition of the HPMC gel because the repulsion forces between CA-LBG particles are difficult to dissolve.

The tablet G6 followed the release kinetics of Higuchi's model. The high viscosity gel of HPMC controlled the diffusion of ketoprofen from the granules. CA-LBG on the granule surface inhibited granule hydration and ketoprofen diffusion.

The release kinetics of ketoprofen from Ga, Gb, and Gc tablets followed zero order. HPMC on the tablet surface swells to form a gel when in contact with the dissolution medium. The trapped ketoprofen particles dissolve and are saturated, then diffuse from the gel. Simultaneously the rate of CA-LBG disintegrating tablets into granules is proportional to gel formation. The dissolving of ketoprofen comes from the ketoprofen particles in contact with the gel surface. The balanced concentrations of HPMC and CA-LBG formed a gel with a constant thickness. These conditions can control the diffusion and maintain the availability of saturated ketoprofen dissolved in the gel.

Table 3. The value of the kinetics parameters of the release of ketoprofen from tablets.

Formula code	Parameter	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	average	SD	average	SD	
G1	Rsqr_adj	0.8762	0.02	0.9441	0.01	0.9585	0.00	0.9776	0.01	0.9279	0.01	0.9333	0.00	Korsmeyer-Peppas
	MSE_root	5.2625	0.35	3.5357	0.26	3.0468	0.20	2.2216	0.34	4.0144	0.29	3.8687	0.11	
	AIC	70.5951	1.56	61.0431	1.72	57.4597	1.61	50.6125	3.52	64.0907	1.71	64.8308	0.66	
G2	Rsqr_adj	0.8049	0.01	0.9687	0.00	0.9861	0.00	0.9948	0.00	0.9426	0.01	0.9536	0.00	Korsmeyer-Peppas
	MSE_root	10.6069	0.28	4.2456	0.22	2.8232	0.37	1.7379	0.16	5.7451	0.32	5.1742	0.23	
	AIC	87.4453	0.63	65.4533	1.28	55.5400	3.24	44.8284	2.23	72.7095	1.35	71.7991	1.08	
G3	Rsqr_adj	0.9395	0.00	0.9296	0.01	0.8689	0.01	0.9113	0.01	0.9401	0.01	0.8651	0.01	Hixson-Crowell
	MSE_root	4.5672	0.13	4.9223	0.35	6.7233	0.38	5.5235	0.47	4.5427	0.27	6.8225	0.28	
	AIC	67.2211	0.72	68.9849	1.70	76.4828	1.36	72.5897	2.03	67.0722	1.38	78.4392	0.96	
G4	Rsqr_adj	0.8597	0.02	0.9358	0.01	0.9657	0.01	0.9777	0.01	0.9171	0.01	0.9414	0.01	Korsmeyer-Peppas
	MSE_root	5.4444	0.33	3.6827	0.21	2.6858	0.34	2.1496	0.36	4.1855	0.25	3.5175	0.31	
	AIC	71.4154	1.46	62.0355	1.40	54.3575	3.04	49.7755	3.97	65.1033	1.48	62.4881	2.17	
G5	Rsqr_adj	0.8594	0.01	0.6528	0.10	0.8570	0.01	0.9057	0.00	0.9231	0.00	0.9025	0.00	Hixson-Crowell
	MSE_root	13.6548	0.48	21.3289	3.31	13.7776	0.45	11.1888	0.34	10.1039	0.28	11.3789	0.30	
	AIC	93.5029	0.85	104.0112	3.90	93.7193	0.79	89.5817	0.73	86.2787	0.67	90.7234	0.63	
G6	Rsqr_adj	0.6618	0.02	0.8583	0.01	0.9945	0.00	0.9935	0.00	0.8093	0.01	0.9762	0.00	Higuchi
	MSE_root	9.9176	0.17	6.4175	0.16	1.2626	0.07	1.3745	0.10	7.4459	0.16	2.6266	0.17	
	AIC	85.8359	0.41	75.3863	0.60	36.3490	1.26	39.2239	1.71	78.9547	0.53	55.5081	1.61	
G7	Rsqr_adj	0.9360	0.01	0.9304	0.00	0.8758	0.01	0.9093	0.01	0.9398	0.00	0.8675	0.00	Hixson-Crowell
	MSE_root	4.7248	0.28	4.9359	0.11	6.5870	0.32	5.6328	0.20	4.5899	0.09	6.8079	0.13	
	AIC	68.0154	1.40	69.0873	0.55	75.9974	1.20	73.1077	0.84	67.3448	0.45	78.3976	0.46	
G8	Rsqr_adj	0.8582	0.01	0.7246	0.05	0.8753	0.01	0.9180	0.00	0.9286	0.01	0.9112	0.00	Hixson-Crowell
	MSE_root	13.3691	0.17	18.5895	1.66	12.5351	0.46	10.1662	0.37	9.4845	0.43	10.5795	0.28	
	AIC	93.0042	0.30	100.8549	2.10	91.4435	0.88	87.2783	0.87	84.7498	1.10	88.9752	0.63	

continue to the next page

Table 3. The value of the kinetics parameters of the release of ketoprofen from tablets.

Formula code	Parameter	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	average	SD	average	SD	
Ga	Rsqr_adj	0.9241	0.01	0.8628	0.01	0.7995	0.02	0.8441	0.02	0.8883	0.01	0.7823	0.03	Zero order
	MSE_root	5.7889	0.30	7.7879	0.24	9.4113	0.50	8.2963	0.58	7.0194	0.51	9.8002	0.73	
	AIC	72.8966	1.22	80.0290	0.73	84.5579	1.28	82.3715	1.68	77.5002	1.76	87.0994	1.81	
Gb	Rsqr_adj	0.9273	0.00	0.8670	0.01	0.8107	0.01	0.8481	0.02	0.8956	0.01	0.7874	0.03	Zero order
	MSE_root	5.6548	0.09	7.6500	0.20	9.1233	0.40	8.1484	0.47	6.7739	0.32	9.6602	0.66	
	AIC	72.3524	0.40	79.6025	0.62	83.8190	1.06	81.9522	1.39	76.6707	1.14	86.7613	1.66	
Gc	Rsqr_adj	0.9273	0.01	0.8648	0.01	0.8044	0.01	0.8408	0.02	0.8920	0.01	0.7809	0.03	Zero order
	MSE_root	5.6764	0.38	7.7581	0.22	9.3364	0.37	8.4134	0.49	6.9321	0.30	9.8658	0.69	
	AIC	72.4101	1.62	79.9382	0.68	84.3764	0.94	82.7199	1.40	77.2270	1.07	87.2649	1.70	

The ketoprofen release kinetics model of various tablet formulas contains HPMC [%] and CA-LBG [%]: G1 (40 : 10); G2 (32.5 : 17.5); G3 (35 : 15); G4 (40 : 10); G5 (30 : 20); G6 (37.5 : 12.5); G7 (35 :15); G8 (30 : 20); Ga (32.97 : 17.03); Gb (32.97 : 17.03); and Gc (32.97 : 17.03).

Conclusion

HPMC and CA-LBG increased the value of angle of repose, tap index, hardness, friability, and release of ketoprofen. The combination of HPMC with CA-LBG increased the angle of repose, tap index, and hardness. Besides, the combination decreased friability and release of ketoprofen. The optimum concentrations of HPMC and CA-LBG for controlled-release tablets is 32.97% and 17.03%, resulting in the angle of repose of 29.16^0; tap index of 20.01%; hardness of 13.91 kp; friability of 0.41%; and the drug release (10 hours) of 80%. The drug release kinetics from optimum tablets followed zero order. The constant thickness of gel can control the diffusion and maintain the saturated ketoprofen in the gel. CA-LBG as a negative matrix disintegrates tablets into granules. HPMC as a gel matrix controlled ketoprofen release by diffusion and erosion. The tablets did not produce a ghost matrix because the gel matrix came from granules which degraded quickly after all the ketoprofen was released.

Associated Content

Supporting Information

Tablet dosage calculation; Statistical analysis of ketoprofen tablets; The release of ketoprofen from tablets (G1-G8); The release of ketoprofen from optimum tablets (Ga-Gc); and The kinetics profile of ketoprofen release from tablets (G1-G8) (Ga-Gb)

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Declarations

Competing interest statement

The authors declare that authors have no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Suwaldi Martodihardjo, Achmad Fudholi, Sugeng Riyanto and, Jefri Prasetyo: analyzed and interpreted the data.

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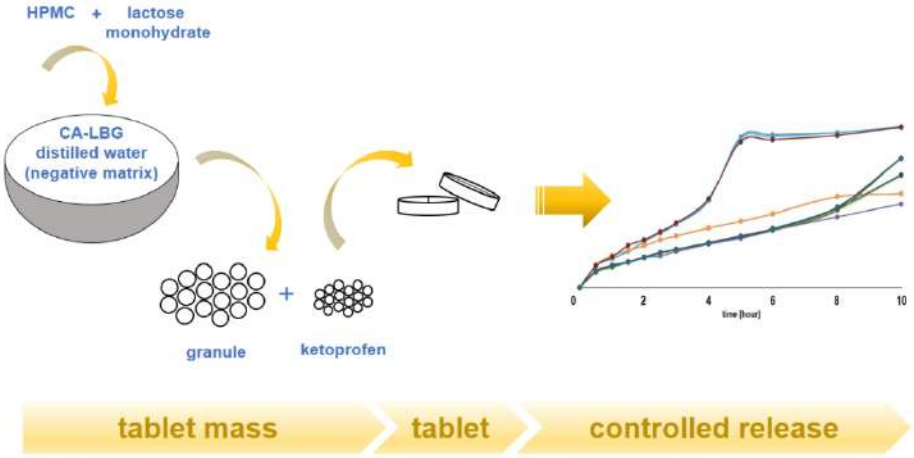

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Hadinugroho, Wuryanto ao-2022-07432u - Manuscript Revision Request 15-Dec-2022

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Kepada: wuryanto.hadinugroho@ymail.com

Tanggal: Kamis, 15 Desember 2022 pukul 22.15 GMT+7

15-Dec-2022

Journal: ACS Omega
Manuscript ID: ao-2022-07432u
Title: "Citric acid-locust bean gum as a negative matrix for controlled release tablet"
Author(s): Hadinugroho, Wuryanto; Martodihardjo, Suwaldi; Fudholi, Achmad; Riyanto, Sugeng; Prasetyo, Jefri

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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation: Publish after major revisions.

Comments:
The paper ‘Citric acid-locust bean gum as a negative matrix for controlled release tablet’ can be accepted after major revision. The following comments should addressed.
Comments:
1. ‘HPMC as hydrogel matrix and CA-LBG as negative matrix on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC’:
Here already it is said positive effect of HPMC……so why again it is sais to determine the effect of CA-LBG and HPMC?
2. ‘granulation method dan ketoprofen’ There is typo error.
3. Why Solubility study of CA-LGB was done? The method which is adopted, has any reference.
4. The similar works have already been done by authors. What is the novelty of this paper?
5. Why flow ability and tap index were measured for tablet mass instead of granules?
6. ‘dissolution apparatus II USP paddle model’ IT will be USP II
7. release of ketoprofen is expressed as Dr. Can it modified?
8. Can HPMC and CA-LBG network will interpenetrate? If it is so, then discuss on this. [citations removed by the editorial office]
9. This paper needs one graphical abstract.
10. simplex lattice design of two factors used eight runs should be shown in the manuscript.

Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes

Please evaluate the degree of novelty and originality of the research reported: Good

Are the conclusions adequately supported by the data presented?: Yes

Are the literature references appropriate and up to date?: No

Reviewer: 2

Recommendation: Publish after minor revisions.

Comments:
Journal: ACS Omega
Manuscript ID: ao-2022-07432u
Title of the Manuscript: Citric acid-locust bean gum as a negative matrix for controlled release tablet
In general, the present work determines the optimum concentration of HPMC as hydrogel matrix and citric acid-locust bean gum as negative matrix on controlled-release tablet formulation. The LGB and CA-LBG are characterized by the FTIR and NMR. Further, these tablets are evaluated by the dan ketoprofen drug release applications. As over all the work is well organed; results and discussions are well adequate. Hence the manuscript is recommended for publication with minor revision.
In specific
1) HPMC need be elaborated at once in starting of the manuscript and also need to appear in the title of the manuscript.
2) Page 2 line 25 ‘dan ketoprofen’? check this.
3) Page no 5 line 12 “Manufacture of CA-LBG” it is need to correct as ‘Preparation of CA-LBG matrix’; ‘manufacture’ word may be removed for the manuscript and use appropriate word.
4) It is not clear that ‘CA-LBG gel’ structure, either is chemical crosslinking or physical crosslinking, need to discuss in detail.
5) In the FTIR, X-axis need to labled as ‘Wavenumber (cm-1)’; H1 NMR spectrum need to provide 0-10 ppm also need to provide the units on X-axis

Additional Questions:
Is the technical quality of the research reported within valid and appropriate?: Yes

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Manuscript Type: Article
Title: "Citric acid-locust bean gum as a negative matrix for controlled release tablet"
Author(s): Hadinugroho, Wuryanto; Martodihardjo, Suwaldi; Fudholi, Achmad; Riyanto, Sugeng; Prasetyo, Jefri

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25-Dec-2022

Journal: ACS Omega
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Title: "Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet"
Authors: Hadinugroho, Wuryanto; Martodihardjo, Suwaldi; Fudholi, Achmad; Riyanto, Sugeng; Prasetyo, Jefri
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Date Submitted by the Author:	25-Dec-2022
Complete List of Authors:	Hadinugroho, Wuryanto; Widya Mandala Catholic University Surabaya, Faculty of Pharmacy Martodihardjo, Suwaldi; Gadjah Mada University, Faculty of Pharmacy Fudholi, Achmad; Gadjah Mada University, Faculty of Pharmacy Riyanto, Sugeng; Gadjah Mada University, Faculty of Pharmacy Prasetyo, Jefri; Widya Mandala Catholic University Surabaya, Faculty of Pharmacy

Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet

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Abstract

Purpose: This study aimed to determine the optimum concentration of hydroxypropyl methylcellulose (HPMC) as hydrogel matrix and citric acid-locust bean gum (CA-LBG) as negative matrix on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC. CA-LBG accelerates the disintegration of tablets into granules so that the HPMC granule matrix swells immediately and controls drug release. The advantage of this method is that the tablets do not produce large HPMC gel lumps without drug (ghost matrix) but form HPMC gel granules which can be rapidly degraded after all the drug is released.

Methods: The experiment followed the simplex lattice design to obtain the optimum tablet formula with CA-LBG and HPMC concentrations as optimization factors. Tablets production by wet granulation method and ketoprofen is the model of the active ingredient. The kinetics of ketoprofen release was studied using several models.

Results: Based on the coefficients of each polynomial equation that HPMC and CA-LBG increased the value of angle of repose (29.91 : 27.87), tap index (18.99 : 18.77), hardness (13.60 : 13.32), friability (0.41 : 0.73), and release of ketoprofen (52.48 : 99.44). Interaction of HPMC and CA-LBG increased the value of angle of repose (3.25), tap index (5.64), and hardness (2.42). Interaction of HPMC and CA-LBG too decreased the value friability (-1.10), and release of ketoprofen (-26.36). The Higuchi, Korsmeyer-Peppas, and Hixson-Crowell model is the kinetics of eight experimental tablet formulas.

Conclusion: The optimum concentrations of HPMC and CA-LBG for controlled release tablets are 32.97% and 17.03%. HPMC, CA-LBG, and a combination of both affect the physical quality of tablet and tablet mass. CA-LBG is a new excipient candidate that can control drug release from tablets by matrix disintegration mechanism on the tablet.

Keywords:

CA-LBG, citric acid, locust bean gum, control release, optimization

Introduction

Controlled-release tablets are drug delivery systems to prolong the therapeutic effect. The drug is released slowly and continuously over some time. Ion exchange resins, osmotic pumps, and reservoirs are examples of controlled release systems.[1,2] HPMC is one of the polymers often used to control drug release because the HPMC matrix can trap drug particles and release them slowly. HPMC matrices alone or with other polymers are often used to control drug release.[3–5]

CA-LBG is a new ester polymer derived from locust bean gum. CA-LBG is synthesized using a hydrochloric acid (HCl) catalyst and an ultraviolet light (UV 254 nm) energy source. O atoms of the carbonyl group of CA are to be protonated to form positive C atoms because of acid conditions created by HCl. The ester bond occurs at the OH (C-6) mannose and galactose groups in LBG with a positive C atom from the carbonyl group in CA to form a tetrahedral cation. OH were protonated to $^{+}OH_2$, continued loss of H_2O to form CA-LBG (ester).[6–11] Previous experiments reported that CA-LBG has an ester carbonyl group which LBG does not. The viscosity and solubility of CA-LBG are lower than that of LBG.[7] The CA-LBG character has the potential to control drug release.

This study aimed to determine the optimum concentration of HPMC and CA-LBG on the tablet. on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC. The activity of CA-LBG as a negative matrix with HPMC matrix to control drug release was studied by drug release kinetics. The novelty of this experiment is that the formulation using CA-LBG is a new polymer ester with low solubility. The CA-LBG as a negative matrix causes the tablets to disintegrate into granules. HPMC matrix gel derived from granules controls drug release. A negative matrix (CA-LBG) is a substance that causes the tablet's positive matrix (HPMC) to disintegrate into granules. The mechanism of action on tablets is that the wetted tablet surface causes disintegration into granules due to low solubility of CA-LBG and repulsion between CA-LBG particles. Granules containing HPMC swell to control drug release. CA-LBG controls drug release because CA-LBG is poorly soluble and has low viscosity, so CA-LBG inhibits

the wetting and dissolution of drug particles. The advantage of this method is that the tablets do not produce large hydroxypropyl methylcellulose (HPMC) gel lumps without drug (ghost matrix) but form HPMC gel granules which can be rapidly degraded after all the drug is released. Ketoprofen (100 mg) (see supplementary information Chapter S1) is a drug model added to the granules and compressed into tablets (400 mg). HPMC was chosen as the matrix because HPMC is a polymer that can swell when hydrated with water with a viscosity to control drug release.[1,5] Lactose monohydrate is a suitable filler for tablets because it has good compatibility and high density (1.545 g/cm^3).[5] These character can be suitable for wet granulation methods, so tablets are hard and of the ideal size. Ketoprofen is used in the drug model because ketoprofen has a dose of 25-200 mg and an elimination half-life of 2-4 hours.[12,13] Making tablets using the wet granulation method can improve the flow properties by increasing the particle size and the compatibility of the tablet mass. CA-LBG particles are shaped like coral-corrugated, HPMC particles like a rhizome, and irregularly shaped lactose monohydrate particles.[5,7] The experiment followed the simplex lattice design to obtain the optimum tablet formula. This method is quite simple for experiments by mixing internal factors (ingredients) in a formula without the influence of internal factors (process or technology). In addition, this method is quite effective for synthesized materials such as CA-LBG in limited quantities. The optimization factor is the concentration of CA-LBG and HPMC. The optimization response is the angle of repose, tap index, hardness, friability, and ketoprofen release.

Material and methods

Raw materials and chemicals

The materials used in this experiment include locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Brand KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich Chemie, GmbH, USA), distilled water (Sterilized Water For Injection, PT. Otsuka Indonesia), acetone (Cawan Anugerah Chemika, Indonesia), hydroxypropyl methylcellulose (Methocel K4M CR

Premium USP/EP, Colorcon, Singapore), lactose monohydrate (Leprino Foods, UDM, USA), ketoprofen (PT Kalbe Farma Tbk, Indonesia), potassium dihydrogen phosphate (KGaA Darmstadt Germany Brand), and sodium hydroxide (KGaA Darmstadt Germany Brand).

Preparation of CA-LBG matrix

The preparation of CA-LBG adopted the preparation method in the previous study. The LBG ($3.55\ 10^{-6}$ mol) was swelled in 50 mL of warm distilled water (55-60 ^{o}C), added CA ($21.00\ 10^{-3}$ mol), and HCl ($57.40\ 10^{-3}$ mol), homogenized for 10 minutes. The gel was irradiated with UV 254 nm for 100 min (8-Watt, CH-4132 Muttenz, Camag, Switzerland), then precipitated (acetone) and washed off (distilled water-acetone). The CA-LBG residue was dried at room temperature.[7,14]

The success of CA-LBG production was confirmed through the Fourier transform infrared spectroscopy (FTIR) characterization, nuclear magnetic resonance (NMR), solubility, and viscosity. Production is carried out for three batches to determine reproducibility through standard deviation.

Fourier transform infrared spectroscopy

The structure and specific groups of CA-LBG were identified by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.). The observations show that a spectrum wavelength is 4000-450 cm^{-1}. A certain amount of powder is placed on a diamond plate and pressed with a stick on the instrument. Spectra are visible on the monitor and recorded.

Nuclear magnetic resonance

The NMR spectroscopic examination confirmed the structure and specific group of CA-LBG. An amount of CA-LBG powder (5-10 mg) was dispersed in H_2O (deuterium) and stirred for 45 minutes at a vortex. The filtrate was transferred to a glass tube and analyzed by NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan).

Esterified CA

The amount of esterified CA was determined by the degree of esterification. Determination of the degree of esterification adopts the previous experiment.[7,14] Samples were derived from CA-LBG precipitating solven and washing solution (acetone and distilled water-acetone). Measurements using potentiometry with titrant NaOH (0.2 N) standardized by oxalic acid. The titrant volume endpoint determines the dissolved acid's total concentration [mEq]. The dissolved CA concentration [mEq] was obtained from the difference between the total acid concentration and the HCl concentration. The dissolved CA [gram] weight was obtained from the conversion of dissolved CA [mEq]. The reacted CA was obtained from the difference between the initial CA weight and dissolved CA. The degree of esterification [%] is the ratio of CA reacted with initial CA.

Solubility study

The CA-LBG powder (500 mg) was dispersed in distilled water (50 mL) and stirred for 24 hours (Wd). The swelled powder and filtrate are carefully separated. The filtrate was dried in a water bath (70^{o}C and reweighed (Wds) (Mettler Toledo AL204, Switzerland). The dissolved CA-LBG was determined according to Equation 1:

$$S\ [\%] = \frac{Wds}{Wd}.100\ \% \qquad \text{Equation 1}$$

where the solubility (S), the soluble weight (Wds), and initial dry weight (Wd).[15]

Viscosity

The viscosity of CA-LBG was determined by a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG powder (3% w/v) was swelled in warm distilled water (300 mL, 50-60^{o}C) and allowed to cool to ambient temperature. Spindle No. S61 mounted on Brookfield was dipped on swollen mass and rotated (100 rpm). Viscosity is shown on the monitor and recorded.

Manufacture of tablets

In this experiment, the method of making tablets by wet granulation adopted the previous study with the necessary adjustments.[14] Preparing granules by wet granulation contains HPMC and lactose monohydrate (50 %) according Table 2 (cubic mixer, rotary motor (Erweka)). A homogeneous mixture was moistened with CA-LBG dispersed in distilled water (± 5 mL) while being compressed to form a wet granule mass and sieved (mesh No. 18) to form granules. The wet granules were dried in an oven (50^0C; 15 min; RH 2-5%) (moisture analyzer OHAUS) and re-sieved (mesh No. 20). The granules were mixed with ketoprofen (100 mg) (3:1) and evaluated for the mass quality of the tablets. The tablet mass was compressed to form a 400 mg tablet and hardness $\geq$ 13 kp (single punch, Korch, Germany), assessed for the physical quality of the tablet and dissolution.

Optimization

Optimization of the granule formula according to the simplex lattice design of two factors used eight runs randomized of formulas, model quadratic, and optimization software (Design Expert ver. 10.0.8.0; Stat-Ease Inc., Minneapolis, MN, USA). Comparison of the proportion of HPMC and CA-LBG for each formula based on optimization software (Table 2), including 0:1 (2 formulas); 0.25:0.75 (1 formula); 0.50:0.5 (2 formulas); 0.75:0.25 (1 formula); and 1:0 (2 formulas). The concentration of HPMC in proportion 0 (30%) and proportion 1 (40%), while the concentration of CA-LBG in proportion 0 (10%) and proportion 1 (20%). The HPMC concentration and the CA-LBG concentration were optimization factors. The angle of repose, tap index, hardness, friability, and released ketoprofen were optimization responses. The values of the optimization response parameters were processed using optimization software to obtain polynomial equations and predict the optimum concentrations of HPMC and CA-LBG in granules.

Flowability

The mass of the tablet was weighed at about 50 g and placed on the funnel of a flowability tester (Erweka, Germany). The funnel valve opens, and the tablet mass flows freely. The flowability tester monitor observed the measured flow time of the tablet mass. The cone from tablet mass was measured using infrared to determine the angle of repose and watched on the flowability tester monitor.

Tap Index

The tablet mass was put in a measuring cup (50 mL). The measuring cup was tilted and filled with tablet mass. The filled measuring cup was placed on the volumenometer tap density and tapped 500 taps. Tap index (TI) was determined from the difference between the volume before and after tapping compared to the volume before tapping (Equation 2).[16–19]

$$TI\ [\%] = \frac{V0 - V1}{V0}\ x\ 100\% \qquad \text{Equation 2}$$

Weight

From randomly selected tablets (20), and each tablet was weighed using an analytical balance (Mettler Toledo, Switzerland).

Hardness

Tablet hardness test used randomly selected tablets (6 tablets).[20] The tablets were placed on a board in a hardness tester (Schleuniger, Netherlands), then a metal block pressed on the tablet until the tablet cracks. The tablet hardness was observed on the monitor hardness tester.

Friability

The tablet friability test used randomly selected tablets with a total weight of comparable tablets of 6500 mg.[20] Each tablet was cleaned from dust, then all tablets were weighed (W0). All tablets were placed in a drum friability tester (Erweka, Germany) and rotated (4 min; 25 rpm). All tablets were removed, cleaned from dust, and reweighed (W1). The friability (F) of tablets is determined according to Equation 3.

$$Fr\ (\%) = \frac{W0 - W1}{W0}\ 100\% \qquad \text{Equation 3}$$

Drug release

The release of ketoprofen was tested using a dissolution apparatus USP II paddle model.[12,13] The dissolution media used phosphate buffer pH 6.8 (900 mL; 37°C; 50 rpm) (Electrolab TDT-08L, India). Samples were taken at 0.5; 1; 1.5; 2; 2.5; 3; 4; 5; 6; 8; and 10 hour. Ketoprofen released from the tablet determined absorption value read by UV spectrophotometer (260 nm) (Hitachi U-1900, Japan).[13,21]

Kinetics of ketoprofen release

The release kinetics of ketoprofen from tablets was influenced by HPMC and CA-LBG in the granules. The kinetics of drug release is determined by the following equations:[22–25]

Zero order $: Q_t = Q_o + K_o.t$ Equation 4

First order $: \ln Q_t = \ln Q_o + K_o.t$ Equation 5

Qt: the amount of drug dissolved at the time (t), Qo: the amount of the initial drug, and Ko: drug release constant.

Higuchi $: Q_t = K_H.\sqrt{t}$ Equation 6

Qt: the amount of drug dissolved at the time (t), K_H: Higuchi constant, and t: time.

Korsmeyer-Peppas : $Q_t/Q_\infty = K_k . t^n$ Equation 7

Qt/Q∞: fraction of drug released, Kk: Korsmeyer-Peppas constant, and n: diffusion exponential.

Hixson-Crowell :$Q_o^{1/3} - Q_t^{1/3} = K_s.t$ Equation 8

Qo: the amount of initial drug, Qt: the amount of drug remaining at the time (t), and Ks: dissolution rate constant.

Weibull : $\log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 9

(1-m): fraction of insoluble drug, Ti: the lag time before dissolution, b: shape parameter obtained from the slope of the obtained curve. The value of b = 1 means that the curve is exponential. The importance of b > 1 is the shape of the sigmoid curve.

The release kinetics of ketoprofen from tablets of each granule formula was analyzed using DDSolver software.

Result and Discussion

Fourier transform infrared spectroscopy

Infrared spectra of CA-LBG and LBG are presented in Figure 1. Peaks at wavelengths of 3318.20 cm^{-1} and 3285.80 cm^{-1} indicate the hydroxyl (OH) groups of mannose and galactose. Peaks at wavelengths of 2923.66 cm^{-1} and 2936.00 indicate C-H bonds, where CA-LBG is sharper than LBG due to the influence of symmetrical C-H bonds from CA.[25,26] The specific peak of CA-LBG at 1736.02 cm^{-1} indicates an ester carbonyl group. Previous studies reported that the peak wavelength of the OH group appears at 3300 cm^{-1}, C-H appears at around 2900 cm^{-1}, and C=O appears at about 1750-1735 cm^{-1}. The reaction mechanism for making CA-LBG is a chemical esterification reaction. The reaction begins with the citric acid carbonyl group undergoing protonation and reacting with the hydroxyl group (OH) on the C-6 mannose and galactose atoms to form a tetrahedral cation. Oxygen

in the OH undergoes protonation ($^{+}OH_2$) to form loose OH so that the loss of H_2O and an ester (CA-LBG) is formed.[7] The results of the infrared analysis were further confirmed using NMR.

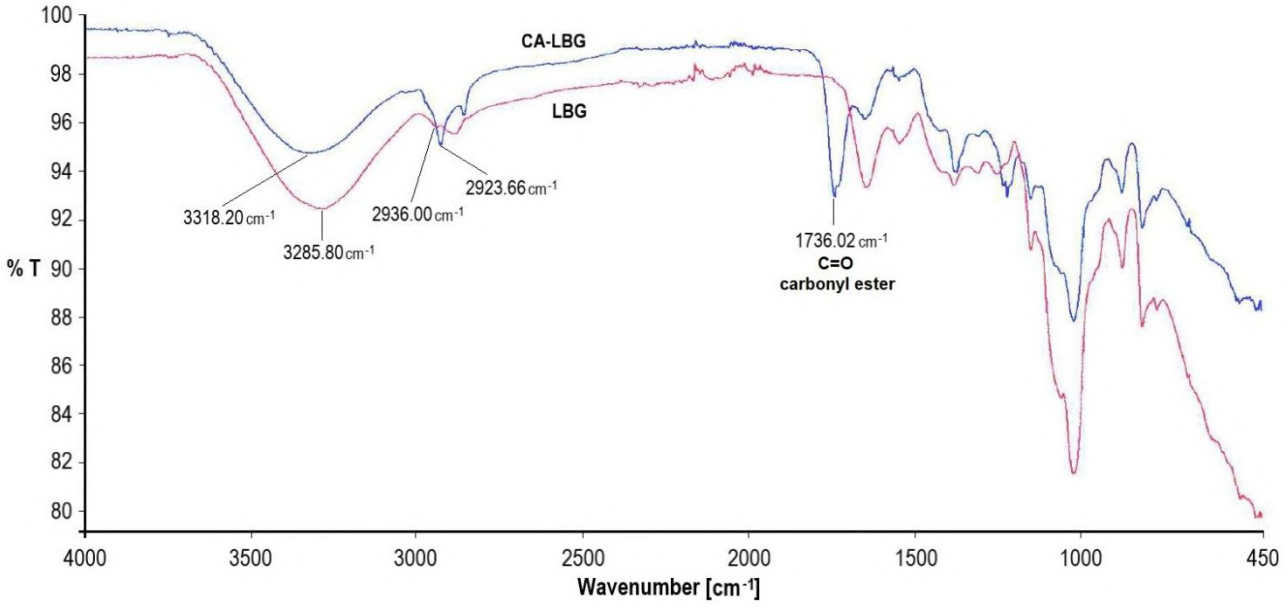

Figure 1. Infrared spectra of CA-LBG and LBG. The CA-LBG spectra have a carbonyl ester group (C=O) at a wavelength of 1736.02 cm^{-1}, presented by a blue line. LBG as control, presented with a red line.

Nuclear magnetic resonance

The NMR examination further confirms the FTIR examination and is carried out representatively for the three manufacturing batches. The CA-LBG NMR spectra are presented in Figure 2. The ^{1}H NMR spectra, paired twin peaks at δ = 2.926 ppm and δ = 2.894 ppm, δ = 2.746 and ppm, δ = 2.714 ppm correspond to the presence of CH_2 (5) of CA in LBG. The sharp peak at δ = 3.996-3.309 ppm corresponds to the H atoms of mannose and galactose in LBG. Previous experiments reported that the paired twin peaks of CH_2 were seen at δ = 2.7-3.0 ppm. Sharp peaks of H atoms from mannose and galactose appear at δ = 4.5-3.0 ppm.[6,7]

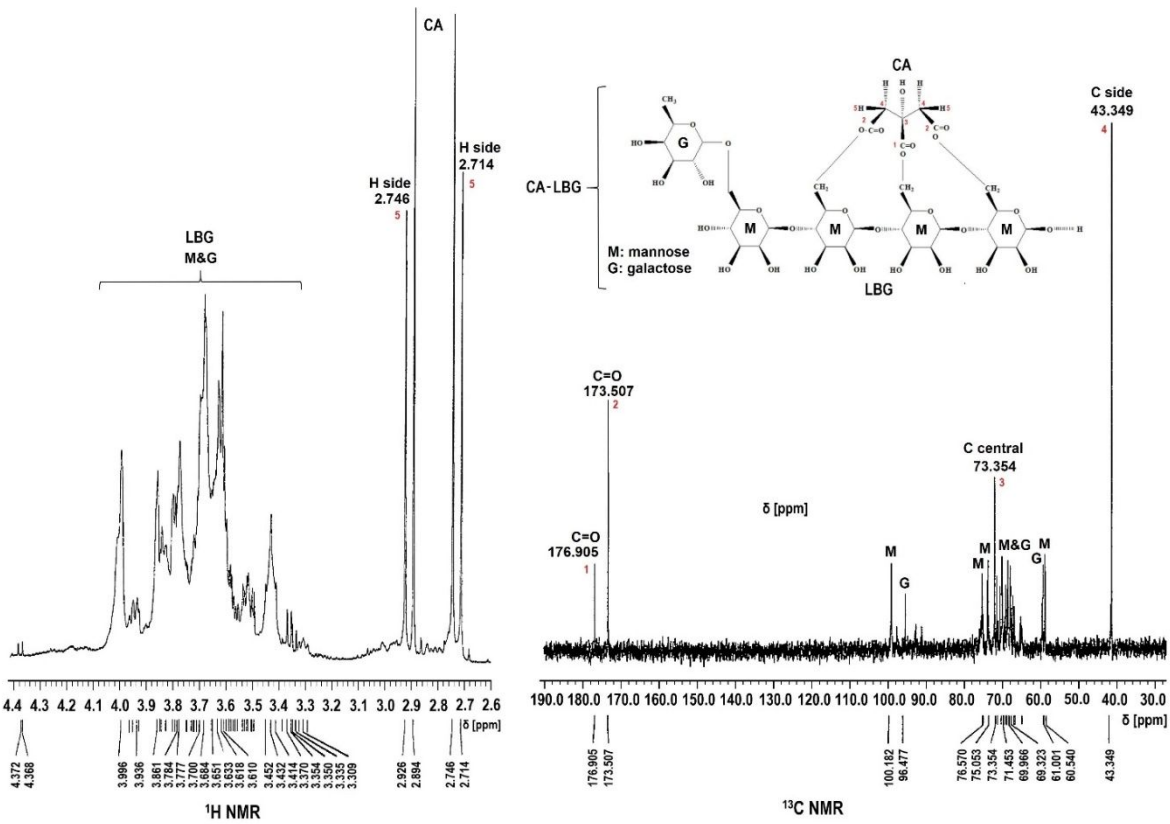

Figure 2. NMR observation spectra of CA-LBG. CA characters present in CA-LBG resented peaks 1, 2, 3, 4, and 5.

The ^{13}C NMR spectra of CA-LBG at the peak δ = 176.905 ppm and δ = 173.507 ppm indicated the carbonyl group (C=O) (1,2), which was a specific group of CA-LBG. The central C atom of CA is shown at δ = 73.354 ppm (3). CH_2 of CA is shown at δ = 43.349 ppm (4). The C atoms that make up mannose and galactose from LBG are shown at δ = 100.182 ppm, δ = 96.477 ppm, δ = 76.570 ppm, δ = 75.053 ppm, δ = 71.453 ppm, δ = 69.966 ppm, δ = 69.323 ppm, δ = 61.001 ppm, δ = 60.540 ppm. Previous experiments show C=O group at δ = 180-170 ppm, central C atom at δ = 80-70 ppm, CH_2 appears at δ = 44-43 ppm.[6,7,27] The C atoms make up mannose, and galactose appears at δ = 105-60 ppm.[7,28–30] Finally, the peaks in the spectra indicate the success of the synthesis.

Esterified CA

The degrees of esterification in each batch are shown in Table 1. All batches had similar degrees of esterification, indicating reproducible manufacturing conditions. The experimental esterification degree of 29.30-29.55% corresponds to the previous experimental report of around 9.13%.[7,14] The degree of esterification of all batches indicated that the esterification conditions were stable and reproducible. The acidic condition created by HCl induces the O atom in the carbonyl group of CA to be protonated to a positive C atom. The OH group on C6 of mannose and galactose will react with a positive C atom.

Table 1. Evaluation degree of esterification, solubility, and viscosity of CA-LBG

Batch Code	Degree of esterification		Solubility		Viscosity	
	[%]	SD	[%]	SD	[cP]	SD
1	29.33	0.20	29.65	0.27	9.48	0.01
2	29.30	0.21	29.81	0.18	9.46	0.02
3	29.55	0.10	29.51	0.42	9.43	0.02

Solubility

The solubility of CA-LBG in each batch is presented in Table 1. All batches showed similar solubility and indicated reproducible manufacturing. The solubility is 29.51-29.81%, according to the solubility in the previous experiment (22.64-36.63%).[14] The ester bond of CA molecules influences the solubility of CA-LBG in LBG. The positive C atom of the carboxylate group (CA) binds to the O atom at C-6, inhibiting the interaction of CA-LBG with distilled water CA-LBG and reducing solubility.

Viscosity

Table 1 shows the respective viscosity of CA-LBG has similar values and indicates reproducible manufacturing. The viscosity shows a value of 9.43-9.48 cPs following the viscosity in the previous experiment (7.76-11.20 cPs).[14] Viscosity is influenced by the carbonyl ester group

formed from the positive C atom of the carboxylic group (CA) with the O atom at C-6 in mannose and galactose so that the ability of CA-LBG to trap distilled water decreases.

Flowability

The results of testing the flow time and angle of repose of the tablet mass for each formula are presented in Table 2. Each formula produces a flow time of about 4.60-5.00 seconds and an angle of repose 27.89-30.04^0, indicating the tablet mass good flows because $\leq$ 10 seconds for 100 g and $\leq 40^0$ [17]. The tablet mass can occupy the die space inside the tablet machine. The tablet mass can be continued to be compressed to form a tablet (400 mg). The response of the angle of repose according to the simplex lattice design is obtained by Equation 10.

$$Y = 29.91\ A + 27.87\ B + 3.25\ AB \qquad \text{Equation 10}$$

The coefficient value of each component in the equation shows that HPMC (+29.91) is the most dominant factor in increasing the angle of repose, followed with CA-LBG (+27.87), and a combination of both (+3.25). The CA-LBG is an ester polymer that is difficult to hydrate with distilled water, so CA-LBG inhibits the formation of bonds between the granule constituent particles and produces fine granules. A large number of refined grains inhibits the tablet mass flow. HPMC is a polymer that can absorb moisture from the surrounding environment.[5] The HPMC in the granules increases moisture impedes flow, forming high mounds. Combining CA-LBG with HPMC, which can absorb moisture, increases the tablet mass flow time. Flow time is one parameter that determines the diversity of weights in the tablet manufacturing process.

Based on the ANOVA analysis (see supplementary information Table S1), the response angle of repose has a Pred R-Squared (0.9596), similar to Adj R-Squared (0.9742) with less than 0.2. Meanwhile, the Adeq Precision (23.8130) greater than 4, indicating this model is acceptable.

Tap Index

The tablet mass tap index for each formula is presented in Table 2. Each formula has a tap index of about 18.50-20.00%, indicating that the tablet mass has good homogeneity because ≤ 20% [17], so the space between the granules is filled with particles or fines. In addition, this condition shows that the tablet mass has good compressibility and creates low porosity tablets. The tap index for each formula is processed according to the simplex lattice design to obtain Equation 11.

$$Y = 18.99\ A + 18.77\ B + 5.64\ AB \qquad \text{Equation 11}$$

The value of the HPMC coefficient (+18.99) is the dominant factor in increasing the tap index, followed with CA-LBG (+18.77) and a combination of both (+5.64). HPMC can reduce the sensitivity of the granules because the HPMC particles absorb moisture so that the granules change shape when granules receive mechanical stress. The difficulty of hydrating CA-LBG particles in the granulation process causes the bond between the granules to be not good so that the granules release fines and receive mechanical stress. The combination of the two factors can increase the tap index because the HPMC reduces the sensitivity due to moisture absorption. In addition, it is supported by less strong bonds between particles in the granules due to the difficulty of hydrating during the granulation process.

Based on the ANOVA analysis (see supplementary information Table S1), the response tap index has a Pred R-Squared (0.7862), similar to Adj R-Squared (0.8928) with less than 0.2. Meanwhile, the Adeq Precision (10.7420) greater than 4, indicates this model is acceptable.

Weight

The tablet weight of all formulas is shown in Table 2. Tablet mass was compressed into tablets with a weight of about 400 mg. The tablet mass of all formulas is free to flow and fill the die chamber, so tablet weight is according to design. The compression success is suitable for the value of flow time, angle of repose, and tap index.

Table 2. Details of HPMC and CA-LBG concentration, quality of the tablet mass, quality of the tablet, and ketoprofen released

Formula code	HPMC [%]	CA-LBG [%]	Flow time [sec.]	Angle of repose [°]	Tap index [%]	Weight [mg]	Hardness [kp]	Friability [%]	Ketoprofen released [10 hr.] [%]
G1	40.00	10.00	4.80 ± 0.06	29.92 ± 0.10	19.00	401.34 ± 1.69	13.61 ± 0.70	0.39	53.75 ± 0.89
G2	32.50	17.50	4.60 ± 0.10	28.98 ± 0.08	20.00	400.87 ± 1.25	13.84 ± 1.05	0.45	83.34 ± 0.70
G3	35.00	15.00	5.00 ± 0.06	29.47 ± 0.18	20.00	402.08 ± 1.50	14.08 ± 0.84	0.28	69.33 ± 0.93
G4	40.00	10.00	4.60 ± 0.10	29.86 ± 0.53	18.50	400.07 ± 1.16	13.60 ± 0.61	0.43	51.71 ± 0.71
G5	30.00	20.00	4.80 ± 0.06	27.86 ± 0.18	19.00	399.69 ± 1.45	13.33 ± 0.46	0.74	99.21 ± 1.04
G6	37.50	12.50	4.80 ± 0.15	30.04 ± 0.06	20.00	400.12 ± 1.65	14.01 ± 0.83	0.34	58.16 ± 0.89
G7	35.00	15.00	5.00 ± 0.15	29.93 ± 0.94	20.00	400.36 ± 0.89	14.06 ± 0.87	0.28	69.82 ± 0.33
G8	30.00	20.00	5.00 ± 0.10	27.89 ± 0.54	19.00	399.67 ± 1.21	13.32 ± 0.84	0.73	99.32 ± 0.46
Ga	32.97	17.03	4.80 ± 0.06	29.17 ± 0.12	20.00	401.27 ± 1.15	13.97 ± 0.64	0.40	80.08 ± 0.60
Gb	32.97	17.03	4.60 ± 0.15	29.08 ± 0.23	20.00	399.00 ± 1.20	14.01 ± 0.58	0.41	80.44 ± 1.17
Gc	32.97	17.03	5.00 ± 0.10	29.22 ± 0.99	19.50	400.67 ± 0.79	13.86 ± 0.85	0.39	80.45 ± 0.55
Go	32.97	17.03	-	29.16	20.01	-	13.91	0.41	80.00

The proportion of HPMC and CA-LBG are G1 (1 : 0); G2 (0.25 : 0.75) G3 (0.5 : 0.5); G4 (1 : 0); G5 (0 : 1); G6 (0.75 : 0.25); G7 (0.5 : 0.5); G8 (0 : 1); Ga (0.30 : 0.70); Gb (0.30 : 0.70); Gc (0.30 : 0.70); and Go (0.30 : 0.70).

Hardness

The tablet hardness of each formula is presented in Table 2. Tablets of each formula have a hardness are around 13.32-14.08 kp, indicating that the tablet has strong resistance and good physical stability. The hardness of tablets comes from strong interlocking between the granules/particles making up the tablet when receiving compression so that the porosity of the tablet is low. The hardness of each formula is processed according to the simplex lattice design to obtain Equation 12.

$$Y = 13.60\ A + 13.32\ B + 2.42\ AB \qquad \text{Equation 12}$$

The coefficient value of HPMC (+13.60) is the most dominant factor in increasing hardness, followed with CA-LBG (+13.32) and a combination of both (+2.42). HPMC can absorb moisture and is used as an adhesive between the deformation of granules/particles to produce a solid interlocking bond. The tablets have good stability to humidity even though the granules contain HPMC because the moisture absorption activity is inhibited by decreasing the absorption surface area in the tablets form than the granules. Although CA-LBG is difficult to hydrate, the deformation of the particles can form solid interlocking bonds. In addition, the presence of CA-LBG on the tablet surface inhibits moisture absorption. The combination of both can increase the hardness because the characters of HPMC and CA-LBG complement each other. The tablet has a solid interlocking bond between the deformation of the granules/particles, and the tablet can retain moisture. In addition, the tap index shows that the tablet mass has low porosity and good compressibility so that when compressed tablet mass produces a compact tablet.

Based on the ANOVA analysis (see supplementary information Table S1), the response hardness has a Pred R-Squared (0.9976), similar to Adj R-Squared (0.9985) with less than 0.2. Meanwhile the Adeq Precision (100.1700) greater than 4, indicates this model is acceptable.

Friability

The tablet friability of all formulas is presented in Table 2. Each formula has a friability of 0.28-0.74% (≤ 1%)[17], indicating that the tablet surface is strong enough to withstand mechanical movements because of solid interlocking bonds between the deformation of the particles on the tablet surface. Friability of all formulas is according to the simplex lattice design to obtain Equation 13.

$$Y = 0.41\ A + 0.73\ B - 1.10\ AB \qquad \text{Equation 13}$$

The coefficient value of CA-LBG (+0.73) is the most dominant factor in increasing friability, followed by HPMC (+0.41) and a combination of both decreasing friability (-1.10). HPMC can absorb moisture and is used as an adhesive between the deformation of granules/particles to produce a solid interlocking bond. The tablets have good stability to humidity even though the granules contain HPMC because the moisture absorption activity is inhibited by decreasing the absorption surface area in the tablets form than the granules. Although CA-LBG is difficult to hydrate, the deformation of the particles can form solid interlocking bonds. In addition, the presence of CA-LBG on the tablet surface inhibits moisture absorption. The combination of the two can reduce the friability of the tablet because the HPMC and CA-LBG particles fill the space between the lactose monohydrate particles. The strong interlocking bonds of the granule mass components form compact and low-porosity granules. When compressed formed a tablet resistant to mechanical movement. The friability quality of this tablet is in line with the hardness quality of the tablet.

Based on the ANOVA analysis (see supplementary information Table S1), the response friability has a Pred R-Squared (0.9593) similar to Adj R-Squared (0.9747) with less than 0.2. Meanwhile, the Adeq Precision (24.6860) greater than 4, indicates this model is acceptable.

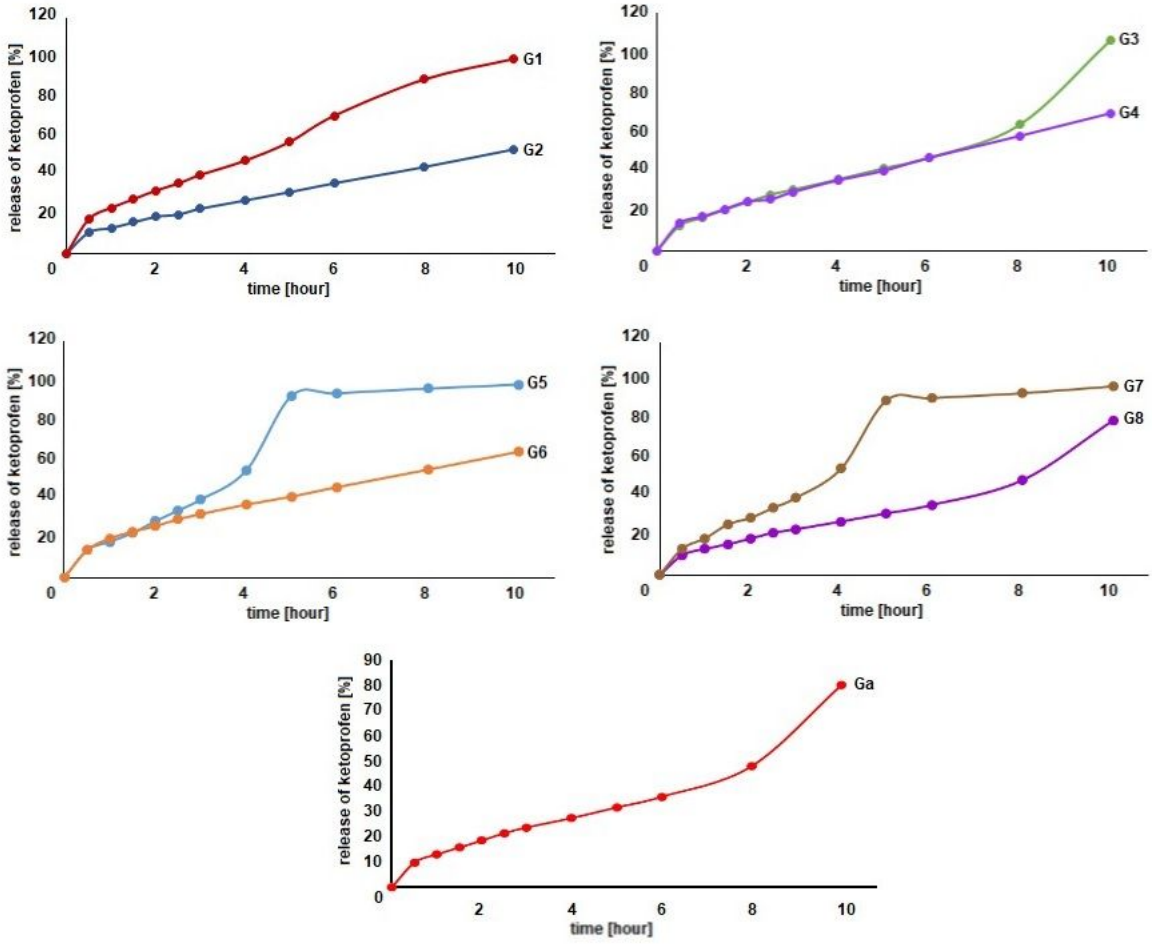

Figure 3. The ketoprofen dissolution profile of various tablet formulas contains HPMC [%] and CA-LBG [%]: G1 (40 : 10); G2 (32.5 : 17.5); G3 (35 : 15); G4 (40 : 10); G5 (30 : 20); G6 (37.5 : 12.5); G7 (35 : 15); G8 (30 : 20); and Ga (32.97 : 17.03).

Ketoprofen release

The concentration and profile of ketoprofen release for each tablet formula after 10 hours are presented in Table 2, Figure 3, and supplementary information Table S2-S3. All tablets of ketoprofen release around 51.71-99.32%, showing that HPMC and CA-LBG can control ketoprofen release from tablets. HPMC is a polymer that swells when hydrating by the dissolution medium. Ketoprofen release is inhibited because HPMC swells trap ketoprofen particles. The CA-LBG is a polymer that is difficult to hydrate and has low solubility. The CA-LBG character causes the tablet to disintegrate

and become granule. Releases of ketoprofen-controlled granule swelling form a gel. Based on the experimental design, ketoprofen released for 10 hours is ≥ 80% (see supplementary information Chapter 1). The processed concentration value of each tablet formula is according to the simplex lattice design to obtain Equation 14.

$$Y = 52.48\,A + 99.44\,B - 26.36\,AB \qquad \text{Equation 14}$$

The CA-LBG coefficient value (+99.44) was the most dominant factor in increasing ketoprofen release, followed with HPMC (+52.48). The combination of both (-26.36) was the most dominant factor in reducing the release of ketoprofen. The deformation of CA-LBG particles on the tablet refuses each other when submerged in the dissolution medium, causing tablet disintegration. The granule porosity surface is used as a space for penetration of the dissolution medium into the granule, dissolved ketoprofen particles, and diffuses out of the granule. The high concentration of CA-LBG accelerates of disintegration of the tablet and forms HPMC gel. Combining the HPMC with CA-LBG can reduce the release of ketoprofen because the moisture of the deformation of the HPMC particles can bind hardly to the interlocking deformation of the CA-LBG and other particles, so that the tablet disintegrates longtime. In addition, the direct interaction of CA-LBG with particles inhibits the swelling of HPMC and hydrating of ketoprofen by the dissolution medium. HPMC and CA-LBG particles can mix physically. Random distribution of HPMC and CA-LBG particles in granules. When these particles expand, the network of the two types of polymers can physically interact with each other (penetrate each other). In this condition, ketoprofen particles can be between these tissues so that these tissues control the release of ketoprofen. Ketoprofen release via diffusion or erosion mechanisms. The release of ketoprofen was studied through the kinetics of drug release.

Based on the ANOVA analysis (see supplementary information Table S1), the response to the release of ketoprofen has a Pred R-Squared (0.9956), similar to Adj R-Squared (0.9978) with a difference of less than 0.2. Meanwhile the Adeq Precision (85.0460) greater than 4, indicates this model is acceptable.

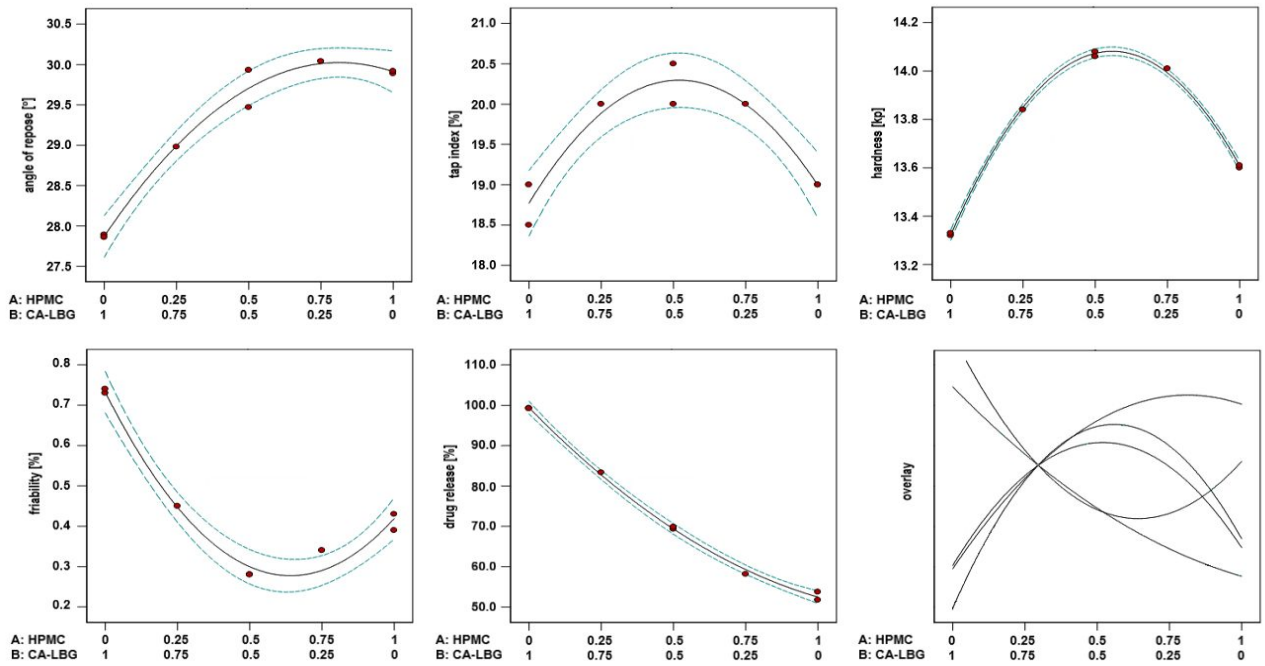

Figure 4. Comparison of actual (dotted line) and predicted (solid line) optimization response profiles. The red dot indicates the response value for each formula based on the respective proportions of HPMC and CA-LBG. The overlay shows the meeting point of all responses according to the predicted optimal proportions of HPMC and CA-LBG.

Optimum tablet formula

Determination of the optimum formula begins with the initial 8 experimental formula designs (G1-G8). The optimization factors and response parameter values were analyzed using design expert software using a simplex lattice design. The experimental comparison profiles and the predictions of each optimization response (Figure 4) show that the actual profiles are similar to the predictions. This profile follows the results of ANOVA analysis for each optimization response (flowability, tap index, hardness, friability, and release of ketoprofen). The optimization response overlay predicts the optimum proportion point to achieve the optimum response prediction. Design expert provides several alternative options for the optimum formula. The selected formula was determined from the response parameter specifications (angle of repose 27.86-30.04; tap index 18.5-20.5; hardness 13.32-

14.08 kp; friability 0.28-0.74%; drug release > 80%). Verification to the prediction of the optimum formula proportion (Go) to obtain the optimum formula was carried out in three batches (Ga, Gb, Gc) (Table 2 and Figure 3).

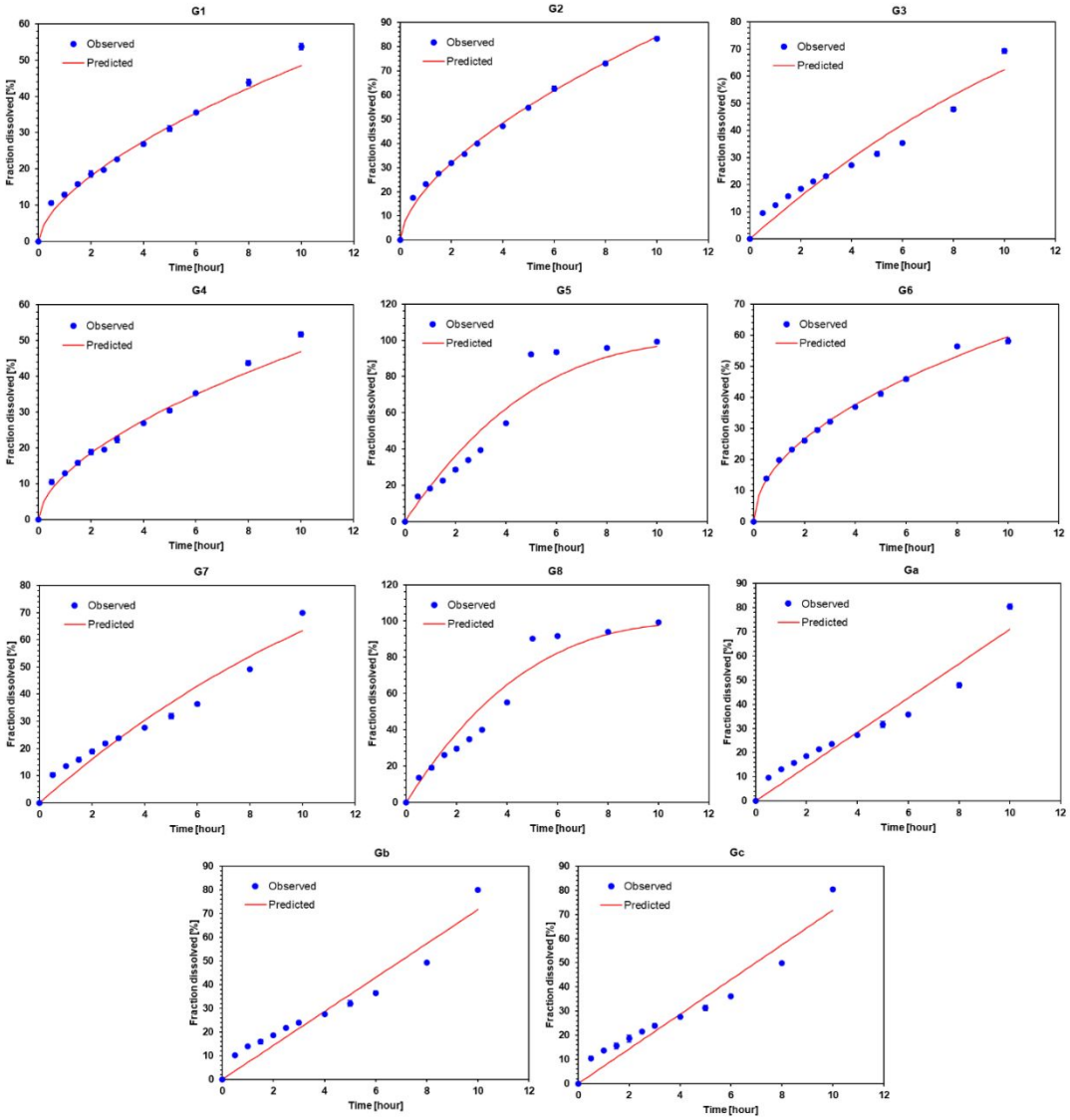

Figure 5. Drug release kinetics model (HPMC [%] : CA-LBG [%]): G1 (40 : 10) (Korsmeyer-Peppas); G2 (32.5 : 17.50) (Korsmeyer-Peppas); G3 (35 : 15) (Hixson-Crowell); G4 (40 : 10) (Korsmeyer-Peppas); G5 (30 : 20) (Hixson-Crowell); G6 (37.50 : 12.50) (Higuchi); G7 (35 : 15) (Hixson-Crowell); G8 (30 : 20) (Hixson-Crowell); Ga (32.97 : 17.03) (Zero order); Gb (32.97 : 17.03) (Zero order); and Gc (32.97 : 17.03) (Zero order).

One sample T-test results compare the experimental response formula verification with the predictive response. The values T of each parameter is T angle of repose (0.008), T tap index (1.096), T hardness (0.728), T friability (1.559), and T release of ketoprofen (2.657). The response parameter values between the prediction (Go) and the verification experiment (Ga-Gc) were not significantly different. These results indicate that the polynomial equations of each response parameter are valid for predicting the effect of HPMC, CA-LBG, and their combination. In addition, the selected optimum formula shows reproducibility in producing tablets and controlling ketoprofen's release. The variation of release shown by G1-G8 proves that tablets with irrelevant variations in physical quality produce varied drug releases.

Kinetics of ketoprofen release

The kinetics of ketoprofen release from the tablet is a non-linear approach using DDSolver (Table 3, Figure 5, and supplementary information Figure S1-S11). The kinetics parameters of ketoprofen release include high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC). The Rsqr_adj is the correlation value between dissolution time and released ketoprofen. MSE_root indicates the error value in correlation analysis. AIC is the value suitability to the equation to determine the release kinetics.[31–35] The results of DDSolver processing are presented in Table 3 and Figure 5.

The release kinetics of ketoprofen from tablets G1, G2, and G4 followed the Korsmeyer-Peppas kinetics. The exponential value (n) for tablets G1 (0.62), G2 (0.60), and G4 (0.58) indicates a non-Fickian diffusion mechanism (anomalous diffusion).[36] The release of ketoprofen released by diffusion is proportional to erosion. The surface of the granules forms a thin gel and cannot withstand the dissolution medium, so ketoprofen dissolves quickly. The ketoprofen release is not only through diffusion but also due to erosion of the surface of the gel formed. The CA-LBG is not tightly

integrated into the tablet and granule. This condition causes the dissolution rate to be faster with the increase in the dissolution medium that enters the tablet and granule.

The release kinetics of ketoprofen from tablets G3, G5, G7, and G8 followed Hixson-Crowell kinetics. The ketoprofen release was caused by hydrating the tablet surface, so the tablet disintegrated and become granule. This condition causes ketoprofen to be dissolved constantly. HPMC low concentration can tablet disintegration quickly when particles swell to form a gel and push against other particles. In addition, CA-LBG on the granule accelerates the decomposition of the HPMC gel because the repulsion forces between CA-LBG particles are difficult to dissolve.

The tablet G6 followed the release kinetics of Higuchi's model. The high viscosity gel of HPMC controlled the diffusion of ketoprofen from the granules. CA-LBG on the granule surface inhibited granule hydration and ketoprofen diffusion.

The release kinetics of ketoprofen from Ga, Gb, and Gc tablets followed zero order. HPMC on the tablet surface swells to form a gel when in contact with the dissolution medium. The trapped ketoprofen particles dissolve and are saturated, then diffuse from the gel. Simultaneously the rate of CA-LBG disintegrating tablets into granules is proportional to gel formation. The dissolving of ketoprofen comes from the ketoprofen particles in contact with the gel surface. The balanced concentrations of HPMC and CA-LBG formed a gel with a constant thickness. These conditions can control the diffusion and maintain the availability of saturated ketoprofen dissolved in the gel.

Table 3. The value of the kinetics parameters of the release of ketoprofen from tablets.

Formula code	Parameter	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	average	SD	average	SD	
G1	Rsqr_adj	0.8762	0.02	0.9441	0.01	0.9585	0.00	0.9776	0.01	0.9279	0.01	0.9333	0.00	Korsmeyer-Peppas
	MSE_root	5.2625	0.35	3.5357	0.26	3.0468	0.20	2.2216	0.34	4.0144	0.29	3.8687	0.11	
	AIC	70.5951	1.56	61.0431	1.72	57.4597	1.61	50.6125	3.52	64.0907	1.71	64.8308	0.66	
G2	Rsqr_adj	0.8049	0.01	0.9687	0.00	0.9861	0.00	0.9948	0.00	0.9426	0.01	0.9536	0.00	Korsmeyer-Peppas
	MSE_root	10.6069	0.28	4.2456	0.22	2.8232	0.37	1.7379	0.16	5.7451	0.32	5.1742	0.23	
	AIC	87.4453	0.63	65.4533	1.28	55.5400	3.24	44.8284	2.23	72.7095	1.35	71.7991	1.08	
G3	Rsqr_adj	0.9395	0.00	0.9296	0.01	0.8689	0.01	0.9113	0.01	0.9401	0.01	0.8651	0.01	Hixson-Crowell
	MSE_root	4.5672	0.13	4.9223	0.35	6.7233	0.38	5.5235	0.47	4.5427	0.27	6.8225	0.28	
	AIC	67.2211	0.72	68.9849	1.70	76.4828	1.36	72.5897	2.03	67.0722	1.38	78.4392	0.96	
G4	Rsqr_adj	0.8597	0.02	0.9358	0.01	0.9657	0.01	0.9777	0.01	0.9171	0.01	0.9414	0.01	Korsmeyer-Peppas
	MSE_root	5.4444	0.33	3.6827	0.21	2.6858	0.34	2.1496	0.36	4.1855	0.25	3.5175	0.31	
	AIC	71.4154	1.46	62.0355	1.40	54.3575	3.04	49.7755	3.97	65.1033	1.48	62.4881	2.17	
G5	Rsqr_adj	0.8594	0.01	0.6528	0.10	0.8570	0.01	0.9057	0.00	0.9231	0.00	0.9025	0.00	Hixson-Crowell
	MSE_root	13.6548	0.48	21.3289	3.31	13.7776	0.45	11.1888	0.34	10.1039	0.28	11.3789	0.30	
	AIC	93.5029	0.85	104.0112	3.90	93.7193	0.79	89.5817	0.73	86.2787	0.67	90.7234	0.63	
G6	Rsqr_adj	0.6618	0.02	0.8583	0.01	0.9945	0.00	0.9935	0.00	0.8093	0.01	0.9762	0.00	Higuchi
	MSE_root	9.9176	0.17	6.4175	0.16	1.2626	0.07	1.3745	0.10	7.4459	0.16	2.6266	0.17	
	AIC	85.8359	0.41	75.3863	0.60	36.3490	1.26	39.2239	1.71	78.9547	0.53	55.5081	1.61	
G7	Rsqr_adj	0.9360	0.01	0.9304	0.00	0.8758	0.01	0.9093	0.01	0.9398	0.00	0.8675	0.00	Hixson-Crowell
	MSE_root	4.7248	0.28	4.9359	0.11	6.5870	0.32	5.6328	0.20	4.5899	0.09	6.8079	0.13	
	AIC	68.0154	1.40	69.0873	0.55	75.9974	1.20	73.1077	0.84	67.3448	0.45	78.3976	0.46	
G8	Rsqr_adj	0.8582	0.01	0.7246	0.05	0.8753	0.01	0.9180	0.00	0.9286	0.01	0.9112	0.00	Hixson-Crowell
	MSE_root	13.3691	0.17	18.5895	1.66	12.5351	0.46	10.1662	0.37	9.4845	0.43	10.5795	0.28	
	AIC	93.0042	0.30	100.8549	2.10	91.4435	0.88	87.2783	0.87	84.7498	1.10	88.9752	0.63	

continue to the next page

Table 3. The value of the kinetics parameters of the release of ketoprofen from tablets.

Formula code	Parameter	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	average	SD	average	SD	
Ga	Rsqr_adj	0.9241	0.01	0.8628	0.01	0.7995	0.02	0.8441	0.02	0.8883	0.01	0.7823	0.03	Zero order
	MSE_root	5.7889	0.30	7.7879	0.24	9.4113	0.50	8.2963	0.58	7.0194	0.51	9.8002	0.73	
	AIC	72.8966	1.22	80.0290	0.73	84.5579	1.28	82.3715	1.68	77.5002	1.76	87.0994	1.81	
Gb	Rsqr_adj	0.9273	0.00	0.8670	0.01	0.8107	0.01	0.8481	0.02	0.8956	0.01	0.7874	0.03	Zero order
	MSE_root	5.6548	0.09	7.6500	0.20	9.1233	0.40	8.1484	0.47	6.7739	0.32	9.6602	0.66	
	AIC	72.3524	0.40	79.6025	0.62	83.8190	1.06	81.9522	1.39	76.6707	1.14	86.7613	1.66	
Gc	Rsqr_adj	0.9273	0.01	0.8648	0.01	0.8044	0.01	0.8408	0.02	0.8920	0.01	0.7809	0.03	Zero order
	MSE_root	5.6764	0.38	7.7581	0.22	9.3364	0.37	8.4134	0.49	6.9321	0.30	9.8658	0.69	
	AIC	72.4101	1.62	79.9382	0.68	84.3764	0.94	82.7199	1.40	77.2270	1.07	87.2649	1.70	

The ketoprofen release kinetics model of various tablet formulas contains HPMC [%] and CA-LBG [%]: G1 (40 : 10); G2 (32.5 : 17.5); G3 (35 : 15); G4 (40 : 10); G5 (30 : 20); G6 (37.5 : 12.5); G7 (35 :15); G8 (30 : 20); Ga (32.97 : 17.03); Gb (32.97 : 17.03); and Gc (32.97 : 17.03).

Conclusion

HPMC and CA-LBG increased the value of angle of repose, tap index, hardness, friability, and release of ketoprofen. The combination of HPMC with CA-LBG increased the angle of repose, tap index, and hardness. Besides, the combination decreased friability and release of ketoprofen. The optimum concentrations of HPMC and CA-LBG for controlled-release tablets is 32.97% and 17.03%, resulting in the angle of repose of 29.16^0; tap index of 20.01%; hardness of 13.91 kp; friability of 0.41%; and the drug release (10 hours) of 80%. The drug release kinetics from optimum tablets followed zero order. The constant thickness of gel can control the diffusion and maintain the saturated ketoprofen in the gel. CA-LBG as a negative matrix disintegrates tablets into granules. HPMC as a gel matrix controlled ketoprofen release by diffusion and erosion. The tablets did not produce a ghost matrix because the gel matrix came from granules which degraded quickly after all the ketoprofen was released.

Associated Content

Supporting Information

Tablet dosage calculation; Statistical analysis of ketoprofen tablets; The release of ketoprofen from tablets (G1-G8); The release of ketoprofen from optimum tablets (Ga-Gc); and The kinetics profile of ketoprofen release from tablets (G1-G8) (Ga-Gb)

Acknowledgment

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pharmaceutical technology equipment; and Widya Mandala Surabaya Catholic University (Indonesia) for funding the publication of this article.

Declarations

Competing interest statement

The authors declare that authors have no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Suwaldi Martodihardjo, Achmad Fudholi, Sugeng Riyanto and, Jefri Prasetyo: analyzed and interpreted the data.

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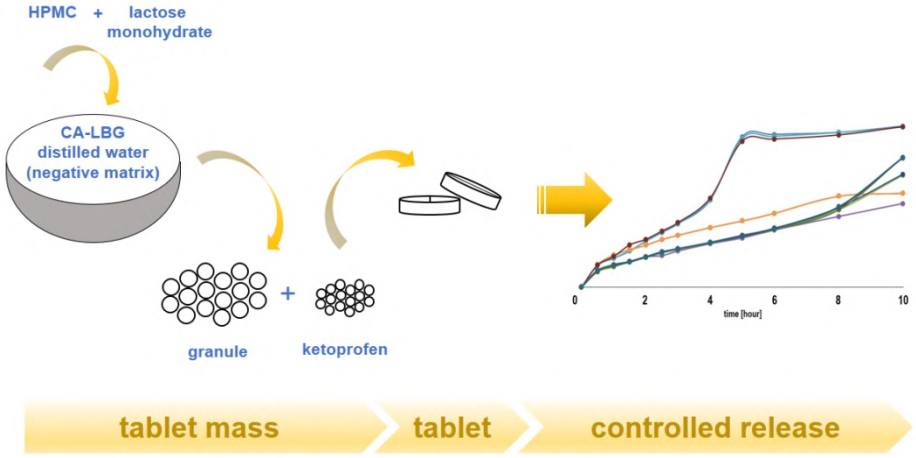


338x190mm (96 x 96 DPI)

Response to Reviewer comments

Comment of Reviewer 1

The paper 'Citric acid-locust bean gum as a negative matrix for controlled release tablet' can be accepted after major revision. The following comments should addressed.

Comments:

1. 'HPMC as hydrogel matrix and CA-LBG as negative matrix on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC':
   Here already it is said positive effect of HPMC……so why again it is sais to determine the effect of CA-LBG and HPMC?
   Response:
   Thank you for the comment and the suggestions. The influence in question is specific. The higher the concentration of CA-LBG or HPMC, the increases or decreases drug release. The coefficient value of the polynomial equation for each response parameter. If there is a positive sign (+) in the equation is concluded to increase and a negative sign (-) is concluded to decrease. If the higher the coefficient value is, the dominance of the influence is higher.
   An example of a ketoprofen release equation:
   Y=52.48 A+99.44 B-26.36 AB
   The CA-LBG coefficient value (+99.44) was the most dominant factor in increasing ketoprofen release, followed by HPMC (+52.48). The combination of both (-26.36) was the most dominant factor in reducing the release of ketoprofen.

2. 'granulation method dan ketoprofen' There is typo error.
   Response:
   Thank you for the comment and the suggestions. The correction has been fixed as follows: 'granulation method and ketoprofen'

3. Why Solubility study of CA-LGB was done? The method which is adopted, has any reference.
   Response:
   Thank you for the comment and the suggestions. CA-LBG solubility studies were carried out to ensure the physicochemical properties (solubility) of CA-LBG were available before being used in tablets. This is a pre-formulation study usually carried out before the formulation of pharmaceutical preparations.

4. The similar works have already been done by authors. What is the novelty of this paper?
   Response:
   Thank you for the comment and the suggestions. Compared to previous articles, the update in this manuscript is that CA-LBG is applied as a negative matrix in combination with HPMC to control drug release from tablets. This manuscript demonstrates the specific effect of HPMC or

CA-LBG on the quality of tablets and controlling drug release. In addition, the manuscript indicates the optimum concentration of HPMC and CA-LBG in tablets to control drug release.
Previous article:
Hadinugroho et al., 2019 determined the optimum conditions for making CA-LBG and its characterization. In addition, we show the potential of CA-LBG singly to control drug release compared to LBG (locust bean gum).
Hadinugroho et al., 2021 produce CA-LBG according to the optimum conditions and its characterization. In addition, we are applying CA-LBG singly as a tablet disintegrating agent.
These three topics are ongoing experiments to explore the potential of CA-LBG in pharmaceutical formulations.

5. Why flow ability and tap index were measured for tablet mass instead of granules?
   Response:
   Thank you for the comment and the suggestions. Granules are solid grains containing HPMC and CA-LBG. The tablet mass is granules (HPMC & CA-LBG) mixed with ketoprofen particles. Materials that can be compressed into tablets have good flow properties. In this experiment, the material to be compressed into tablets was granules (HPMC & CA-LBG) mixed with ketoprofen particles. Hence, the tablet mass had to be evaluated for its flow quality.

6. ‘dissolution apparatus II USP paddle model’ IT will be USP II
   Response:
   Thank you for the comment and the suggestions. The correction has been fixed as follows: dissolution apparatus USP II paddle model'

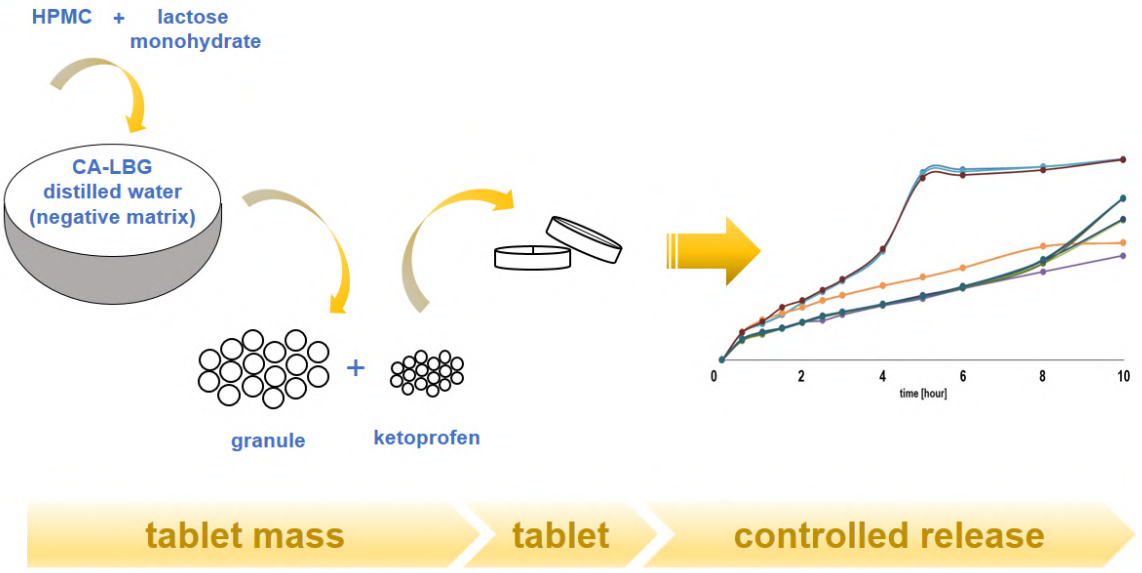
7. release of ketoprofen is expressed as Dr. Can it modified?
   Response:
   Thank you for the comment and the suggestions. 'Dr' was fixed by replacing 'Ketoprofen released'

8. Can HPMC and CA-LBG network will interpenetrate? If it is so, then discuss on this. [citations removed by the editorial office].
   Response:
   Thank you for the comment and the suggestions. HPMC and CA-LBG particles can mix physically. Random distribution of HPMC and CA-LBG particles in granules. When these particles expand, the network of the two types of polymers can physically interact with each other (penetrate each other). In this condition, ketoprofen particles can be between these tissues so that these tissues control the release of ketoprofen. Ketoprofen release via diffusion or erosion mechanisms. The release of ketoprofen was studied through the kinetics of drug release.

9. This paper needs one graphical abstract.

Response:

Thank you for the comment and the suggestions. We have provided a graphical abstract for this paper, as follows:



10. simplex lattice design of two factors used eight runs should be shown in the manuscript.

Response:

Thank you for the comment and the suggestions. The simplex lattice design of two factors of eight runs (G1-G8) according to the Design Expert software is shown in Table 2. The concentration of HPMC and CA-LBG (Columns 3 & 4) as optimization factors. The proportions of the two factors were randomized according to the Design Expert design. Columns 4-10 are the results of evaluating the physical quality of the mass of tablets, tablets, and released ketoprofen. The evaluation parameters that become the optimization response are the angle of repose (column 5), tap index (column 6), hardness (column 8), friability (column 9), and released ketoprofen (column 10). All responses were analyzed according to Design Expert to produce polynomial equations, optimal proportions of optimization factors (Go) (columns 2 & 3), and predictions of optimization responses (Go) (columns 5, 6, 8, 9, & 10). As a result of the analysis, the concentrations of the two factors were verified by experiment (Ga-Gc) (columns 2 & 3). Results of the evaluation of the verification experiment (Ga-Gc) (columns 4-10). The value of each optimization response verification experiment was tested for similarity by t-test.

Additional Questions:

Is the technical quality of the research reported within valid and appropriate?: Yes

Please evaluate the degree of novelty and originality of the research reported: Good

Are the conclusions adequately supported by the data presented?: Yes

Are the literature references appropriate and up to date?: No

Response:

Thank you for the comment.

Comment of Reviewer 2

Journal: ACS Omega

Manuscript ID: ao-2022-07432u

Title of the Manuscript: Citric acid-locust bean gum as a negative matrix for controlled release tablet

In general, the present work determines the optimum concentration of HPMC as hydrogel matrix and citric acid-locust bean gum as negative matrix on controlled-release tablet formulation. The LGB and CA-LBG are characterized by the FTIR and NMR. Further, these tablets are evaluated by the dan ketoprofen drug release applications. As over all the work is well organed; results and discussions are well adequate. Hence the manuscript is recommended for publication with minor revision.

In specific

1. HPMC need be elaborated at once in starting of the manuscript and also need to appear in the title of the manuscript.

   Response:

   Thank you for the comment and the suggestions. The correction has been fixed at the beginning of the manuscript and the title of the manuscript.

   The start of the manuscript

   before revision

   This study aimed to determine the optimum concentration of HPMC as hydrogel matrix and citric acid-locust bean gum (CA-LBG) as negative matrix on controlled-release tablet formulation.

   after revision

   This study aimed to determine the optimum concentration of hydroxypropyl methylcellulose (HPMC) as hydrogel matrix and citric acid-locust bean gum (CA-LBG) as negative matrix on controlled-release tablet formulation.

   Manuscript title

   before revision

   Citric acid-locust bean gum as a negative matrix for controlled release tablet

after revision

Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet

2. Page 2 line 25 ‘dan ketoprofen’? check this.

   Response:

   Thank you for the comment and the suggestions. The correction has been fixed as follows: ‘and ketoprofen’

3. Page no 5 line 12 “Manufacture of CA-LBG” it is need to correct as ‘Preparation of CA-LBG matrix’; ‘manufacture’ word may be removed for the manuscript and use appropriate word.

   Response:

   Thank you for the comment and the suggestions. We have corrected the sentence "Manufacture of CA-LBG" in the manuscript with the sentence "Preparation of CA-LBG matrix"

4. It is not clear that ‘CA-LBG gel’ structure, either is chemical crosslinking or physical crosslinking, need to discuss in detail.

   Response:

   Thank you for the comment and the suggestions. We have added a description of the reaction mechanism in the section on Fourier transform infrared spectroscopy.

   The reaction mechanism for making CA-LBG is a chemical esterification reaction. The reaction begins with the citric acid carbonyl group undergoing protonation and reacting with the hydroxyl group (OH) on the C-6 mannose and galactose atoms to form a tetrahedral cation. Oxygen in the OH undergoes protonation ($^{+}OH_2$) to form loose OH so that the loss of H_2O and an ester (CA-LBG) is formed (Hadinugroho, et al., 2019). Illustrations of the reaction mechanism can be studied further in previous studies (Hadinugroho, et al., 2019).

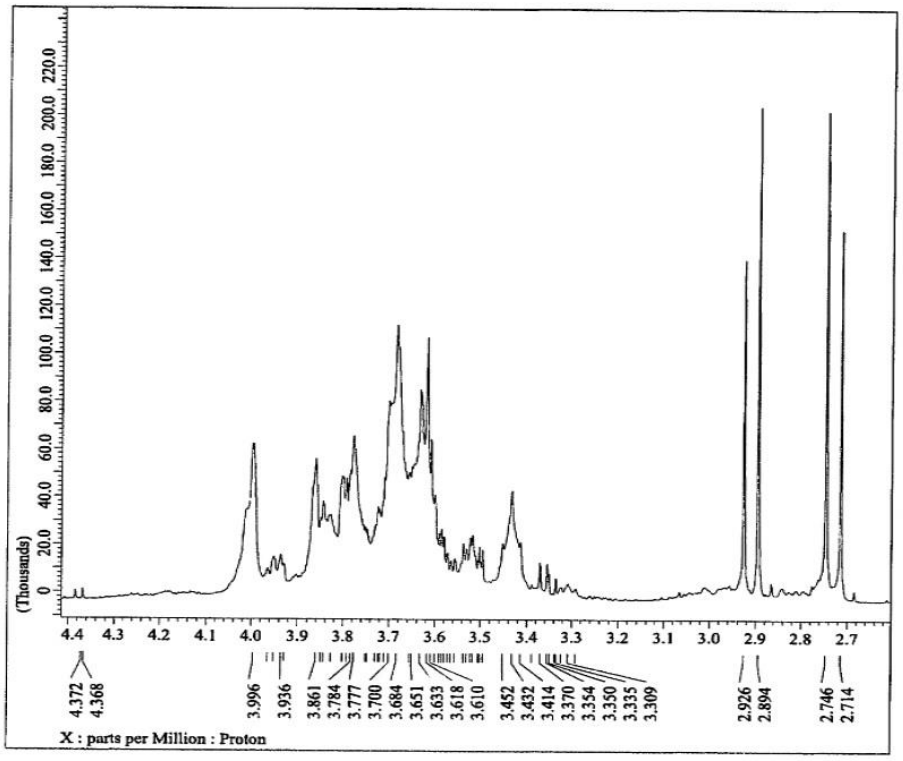
5. In the FTIR, X-axis need to labled as ‘Wavenumber (cm-1)’; H1 NMR spectrum need to provide 0-10 ppm also need to provide the units on X-axis

   Response:

   Thank you for the comment and the suggestions. A third institution conducted the evaluation using NMR due to the unavailability of instruments at our institution. The signal interval (ppm) of the spectra shown in the manuscript corresponds to the printout provided by the examining agency. Signal interval recording is performed only at signal intervals that appear optimum. We attach the original spectra. Sorry for the limitations of this condition.

   We have corrected the correction on the X-axis by adding the identity [δ] and units [ppm].

Original spectra



^{1}H NMR original spectra

before revision

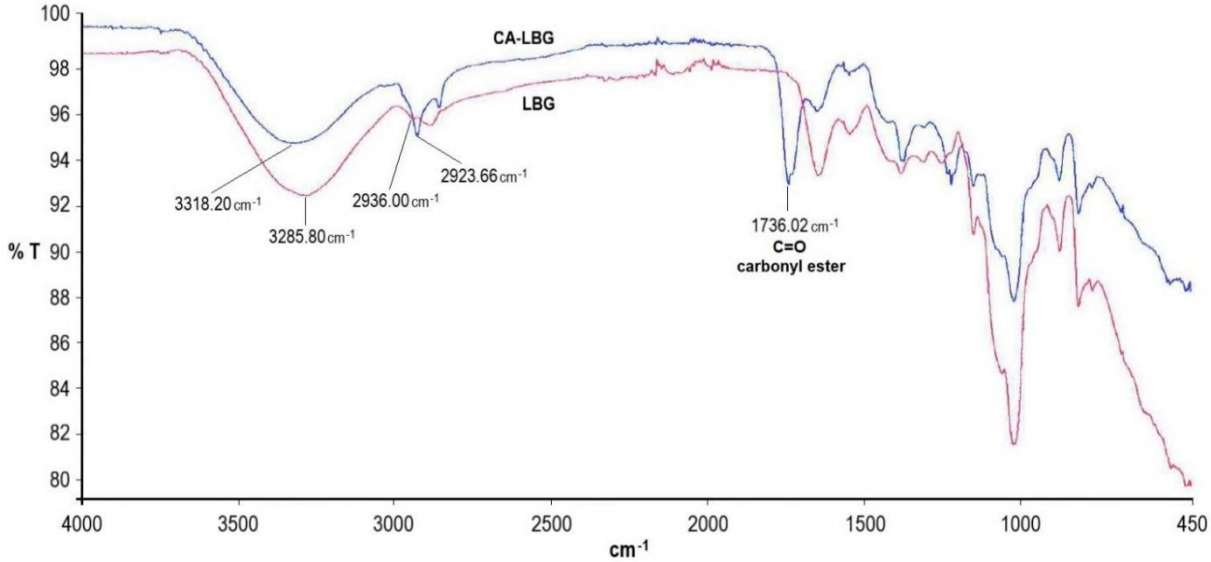


Figure 1. Infrared spectra of CA-LBG and LBG. The CA-LBG spectra have a carbonyl ester group (C=O) at a wavelength of 1736.02 cm^{-1}, presented by a blue line. LBG as control, presented with a red line.

after revision

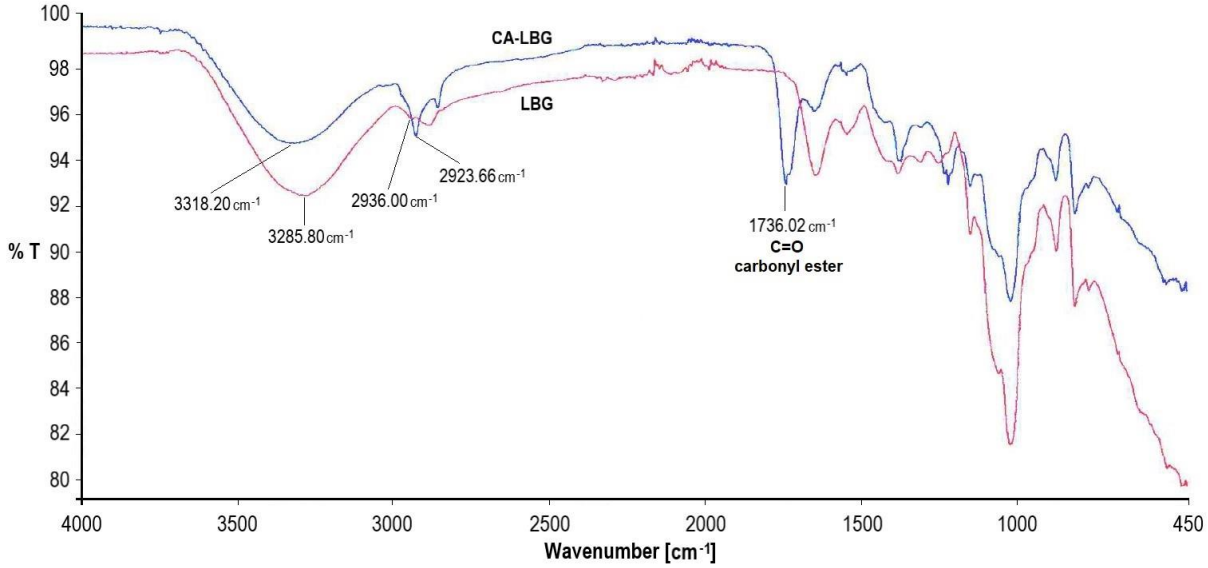


Figure 1. Infrared spectra of CA-LBG and LBG. The CA-LBG spectra have a carbonyl ester group (C=O) at a wavelength of 1736.02 cm^{-1}, presented by a blue line. LBG as control, presented with a red line.

before revision

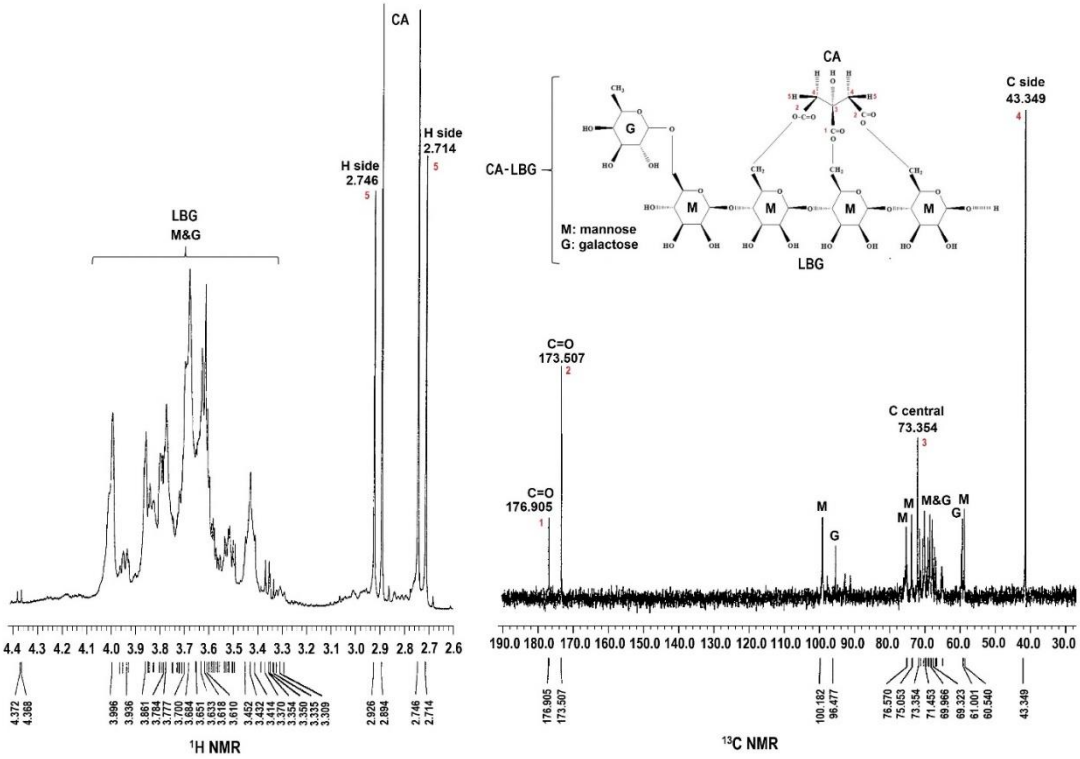


Figure 2. NMR observation spectra of CA-LBG. CA characters present in CA-LBG resented peaks 1, 2, 3, 4, and 5.

after revision

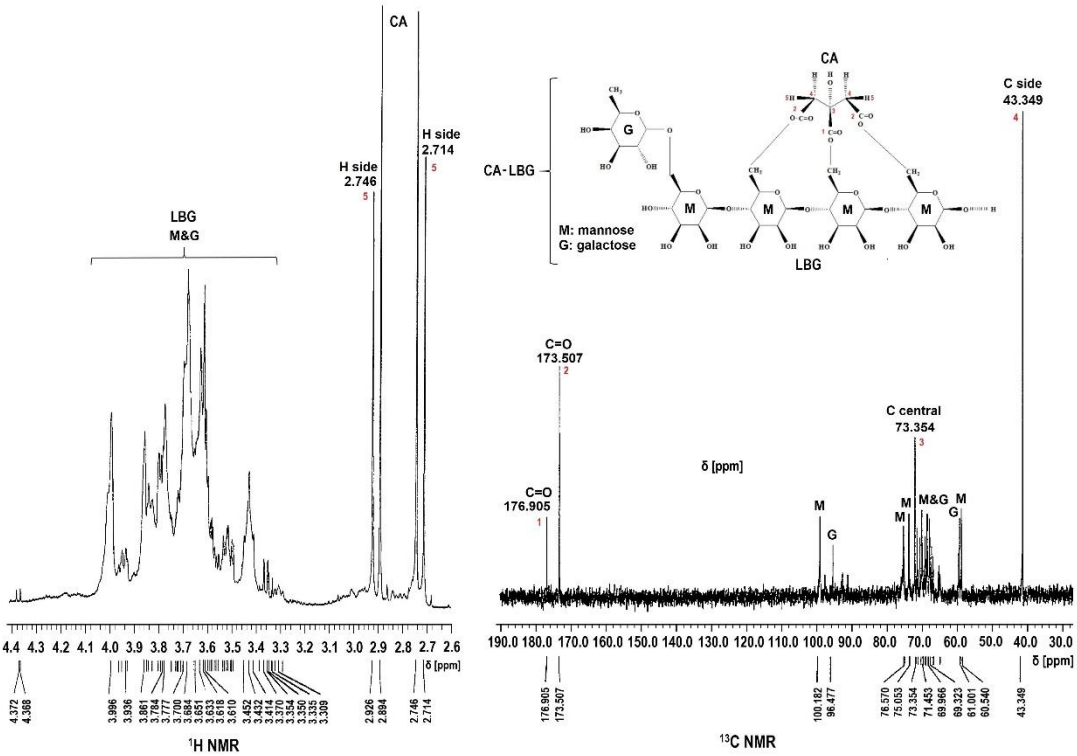


Figure 2. NMR observation spectra of CA-LBG. CA characters present in CA-LBG resented peaks 1, 2, 3, 4, and 5.

Additional Questions:

Is the technical quality of the research reported within valid and appropriate?: Yes

Please evaluate the degree of novelty and originality of the research reported: Good

Are the conclusions adequately supported by the data presented?: Yes

Are the literature references appropriate and up to date?: Yes

Response:

Thank you for the comment.

Hadinugroho, Wuryanto ao-2022-07432u.R1 - Manuscript Revision Request - Formatting Changes 06-Feb-2023

Dari: ACS Omega (onbehalfof@manuscriptcentral.com)

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Tanggal: Senin, 6 Februari 2023 pukul 17.18 GMT+7

06-Feb-2023

Journal: ACS Omega
Manuscript ID: ao-2022-07432u.R1
Title: "Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet"
Author(s): Hadinugroho, Wuryanto; Martodihardjo, Suwaldi; Fudholi, Achmad; Riyanto, Sugeng; Prasetyo, Jefri

Dear Dr. Hadinugroho:

Thank you for submitting your manuscript to ACS Omega.

We are pleased to inform you that your manuscript ao-2022-07432u.R1 is about to be accepted for publication in ACS Omega. Prior to formal acceptance please perform the following formatting changes:

- Remove color from the Manuscript file text.
- In reviewing the files it came to our attention that there is a title discrepancy:

In Paragon Plus and Manuscript file it appears as:
Hydroxypropyl methylcellulose as hydrogel matrix and citric acidlocust bean gum as a negative matrix for controlled release tablet

In Supporting file it appears as:
Citric acid-locust bean gum as a negative matrix for controlled release tablet

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Please upload manuscript file that is free of any annotations or highlights.

I would be pleased to receive the revised manuscript by 10-Feb-2023 at the latest, with the corrections of the mentioned issues.

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Sincerely,

Dr. Krishna Ganesh
Coeditor
ACS Omega
Phone: (202) 657-6323
Email: Ganesh-office@omega.acs.org

Thank you.

Hadinugroho, Wuryanto ao-2022-07432u.R2 - Revised Manuscript Submission to ACS Omega 06-Feb-2023

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Tanggal: Senin, 6 Februari 2023 pukul 23.27 GMT+7

06-Feb-2023

Journal: ACS Omega
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Title: "Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet"
Authors: Hadinugroho, Wuryanto; Martodihardjo, Suwaldi; Fudholi, Achmad; Riyanto, Sugeng; Prasetyo, Jefri
Manuscript Status: Submitted

Dear Dr. Hadinugroho:

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Thank you for submitting your manuscript to ACS Omega.

Sincerely,

Dr. Krishna Ganesh and Dr. Deqing Zhang
ACS Omega

Thank you.

Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet

Journal:	*ACS Omega*
Manuscript ID	ao-2022-07432u.R2
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Hadinugroho, Wuryanto; Widya Mandala Catholic University Surabaya, Faculty of Pharmacy Martodihardjo, Suwaldi; Gadjah Mada University, Faculty of Pharmacy Fudholi, Achmad; Gadjah Mada University, Faculty of Pharmacy Riyanto, Sugeng; Gadjah Mada University, Faculty of Pharmacy Prasetyo, Jefri; Widya Mandala Catholic University Surabaya, Faculty of Pharmacy

Hydroxypropyl methylcellulose as hydrogel matrix and citric acid-locust bean gum as a negative matrix for controlled release tablet

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Abstract

Purpose: This study aimed to determine the optimum concentration of hydroxypropyl methylcellulose (HPMC) as hydrogel matrix and citric acid-locust bean gum (CA-LBG) as negative matrix on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC. CA-LBG accelerates the disintegration of tablets into granules so that the HPMC granule matrix swells immediately and controls drug release. The advantage of this method is that the tablets do not produce large HPMC gel lumps without drug (ghost matrix) but form HPMC gel granules which can be rapidly degraded after all the drug is released.

Methods: The experiment followed the simplex lattice design to obtain the optimum tablet formula with CA-LBG and HPMC concentrations as optimization factors. Tablets production by wet granulation method and ketoprofen is the model of the active ingredient. The kinetics of ketoprofen release was studied using several models.

Results: Based on the coefficients of each polynomial equation that HPMC and CA-LBG increased the value of angle of repose (29.91 : 27.87), tap index (18.99 : 18.77), hardness (13.60 : 13.32), friability (0.41 : 0.73), and release of ketoprofen (52.48 : 99.44). Interaction of HPMC and CA-LBG increased the value of angle of repose (3.25), tap index (5.64), and hardness (2.42). Interaction of HPMC and CA-LBG too decreased the value friability (-1.10), and release of ketoprofen (-26.36). The Higuchi, Korsmeyer-Peppas, and Hixson-Crowell model is the kinetics of eight experimental tablet formulas.

Conclusion: The optimum concentrations of HPMC and CA-LBG for controlled release tablets are 32.97% and 17.03%. HPMC, CA-LBG, and a combination of both affect the physical quality of tablet and tablet mass. CA-LBG is a new excipient candidate that can control drug release from tablets by matrix disintegration mechanism on the tablet.

Keywords:

CA-LBG, citric acid, locust bean gum, control release, optimization

Introduction

Controlled-release tablets are drug delivery systems to prolong the therapeutic effect. The drug is released slowly and continuously over some time. Ion exchange resins, osmotic pumps, and reservoirs are examples of controlled release systems.[1,2] HPMC is one of the polymers often used to control drug release because the HPMC matrix can trap drug particles and release them slowly. HPMC matrices alone or with other polymers are often used to control drug release.[3–5]

CA-LBG is a new ester polymer derived from locust bean gum. CA-LBG is synthesized using a hydrochloric acid (HCl) catalyst and an ultraviolet light (UV 254 nm) energy source. O atoms of the carbonyl group of CA are to be protonated to form positive C atoms because of acid conditions created by HCl. The ester bond occurs at the OH (C-6) mannose and galactose groups in LBG with a positive C atom from the carbonyl group in CA to form a tetrahedral cation. OH were protonated to $^{+}OH_2$, continued loss of H_2O to form CA-LBG (ester).[6–11] Previous experiments reported that CA-LBG has an ester carbonyl group which LBG does not. The viscosity and solubility of CA-LBG are lower than that of LBG.[7] The CA-LBG character has the potential to control drug release.

This study aimed to determine the optimum concentration of HPMC and CA-LBG on the tablet. on controlled-release tablet formulation. In addition, the study was to determine the effect of CA-LBG and HPMC. The activity of CA-LBG as a negative matrix with HPMC matrix to control drug release was studied by drug release kinetics. The novelty of this experiment is that the formulation using CA-LBG is a new polymer ester with low solubility. The CA-LBG as a negative matrix causes the tablets to disintegrate into granules. HPMC matrix gel derived from granules controls drug release. A negative matrix (CA-LBG) is a substance that causes the tablet's positive matrix (HPMC) to disintegrate into granules. The mechanism of action on tablets is that the wetted tablet surface causes disintegration into granules due to low solubility of CA-LBG and repulsion between CA-LBG particles. Granules containing HPMC swell to control drug release. CA-LBG controls drug release because CA-LBG is poorly soluble and has low viscosity, so CA-LBG inhibits

the wetting and dissolution of drug particles. The advantage of this method is that the tablets do not produce large hydroxypropyl methylcellulose (HPMC) gel lumps without drug (ghost matrix) but form HPMC gel granules which can be rapidly degraded after all the drug is released. Ketoprofen (100 mg) (see supplementary information Chapter S1) is a drug model added to the granules and compressed into tablets (400 mg). HPMC was chosen as the matrix because HPMC is a polymer that can swell when hydrated with water with a viscosity to control drug release.[1,5] Lactose monohydrate is a suitable filler for tablets because it has good compatibility and high density (1.545 g/cm^3).[5] These character can be suitable for wet granulation methods, so tablets are hard and of the ideal size. Ketoprofen is used in the drug model because ketoprofen has a dose of 25-200 mg and an elimination half-life of 2-4 hours.[12,13] Making tablets using the wet granulation method can improve the flow properties by increasing the particle size and the compatibility of the tablet mass. CA-LBG particles are shaped like coral-corrugated, HPMC particles like a rhizome, and irregularly shaped lactose monohydrate particles.[5,7] The experiment followed the simplex lattice design to obtain the optimum tablet formula. This method is quite simple for experiments by mixing internal factors (ingredients) in a formula without the influence of internal factors (process or technology). In addition, this method is quite effective for synthesized materials such as CA-LBG in limited quantities. The optimization factor is the concentration of CA-LBG and HPMC. The optimization response is the angle of repose, tap index, hardness, friability, and ketoprofen release.

Material and methods

Raw materials and chemicals

The materials used in this experiment include locust bean gum (Viscogum, Cargill, France), citric acid monohydrate (Brand KgaA, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich Chemie, GmbH, USA), distilled water (Sterilized Water For Injection, PT. Otsuka Indonesia), acetone (Cawan Anugerah Chemika, Indonesia), hydroxypropyl methylcellulose (Methocel K4M CR

Premium USP/EP, Colorcon, Singapore), lactose monohydrate (Leprino Foods, UDM, USA), ketoprofen (PT Kalbe Farma Tbk, Indonesia), potassium dihydrogen phosphate (KGaA Darmstadt Germany Brand), and sodium hydroxide (KGaA Darmstadt Germany Brand).

Preparation of CA-LBG matrix

The preparation of CA-LBG adopted the preparation method in the previous study. The LBG ($3.55\ 10^{-6}$ mol) was swelled in 50 mL of warm distilled water (55-60 ^{o}C), added CA ($21.00\ 10^{-3}$ mol), and HCl ($57.40\ 10^{-3}$ mol), homogenized for 10 minutes. The gel was irradiated with UV 254 nm for 100 min (8-Watt, CH-4132 Muttenz, Camag, Switzerland), then precipitated (acetone) and washed off (distilled water-acetone). The CA-LBG residue was dried at room temperature.[7,14]

The success of CA-LBG production was confirmed through the Fourier transform infrared spectroscopy (FTIR) characterization, nuclear magnetic resonance (NMR), solubility, and viscosity. Production is carried out for three batches to determine reproducibility through standard deviation.

Fourier transform infrared spectroscopy

The structure and specific groups of CA-LBG were identified by Fourier transform infrared spectroscopy (UATR Perkin Elmer Spectrum Version 10.4.3.). The observations show that a spectrum wavelength is 4000-450 cm^{-1}. A certain amount of powder is placed on a diamond plate and pressed with a stick on the instrument. Spectra are visible on the monitor and recorded.

Nuclear magnetic resonance

The NMR spectroscopic examination confirmed the structure and specific group of CA-LBG. An amount of CA-LBG powder (5-10 mg) was dispersed in H_2O (deuterium) and stirred for 45 minutes at a vortex. The filtrate was transferred to a glass tube and analyzed by NMR spectroscopy (JEOL RESONANCE ECZ 500R Japan).

Esterified CA

The amount of esterified CA was determined by the degree of esterification. Determination of the degree of esterification adopts the previous experiment.[7,14] Samples were derived from CA-LBG precipitating solven and washing solution (acetone and distilled water-acetone). Measurements using potentiometry with titrant NaOH (0.2 N) standardized by oxalic acid. The titrant volume endpoint determines the dissolved acid's total concentration [mEq]. The dissolved CA concentration [mEq] was obtained from the difference between the total acid concentration and the HCl concentration. The dissolved CA [gram] weight was obtained from the conversion of dissolved CA [mEq]. The reacted CA was obtained from the difference between the initial CA weight and dissolved CA. The degree of esterification [%] is the ratio of CA reacted with initial CA.

Solubility study

The CA-LBG powder (500 mg) was dispersed in distilled water (50 mL) and stirred for 24 hours (Wd). The swelled powder and filtrate are carefully separated. The filtrate was dried in a water bath (70^{o}C and reweighed (Wds) (Mettler Toledo AL204, Switzerland). The dissolved CA-LBG was determined according to Equation 1:

$$S\ [\%] = \frac{Wds}{Wd}.100\ \% \qquad \text{Equation 1}$$

where the solubility (S), the soluble weight (Wds), and initial dry weight (Wd).[15]

Viscosity

The viscosity of CA-LBG was determined by a viscometer (Brookfield LVDV-I Prime, Middleboro, MA, USA). The CA-LBG powder (3% w/v) was swelled in warm distilled water (300 mL, 50-60^{o}C) and allowed to cool to ambient temperature. Spindle No. S61 mounted on Brookfield was dipped on swollen mass and rotated (100 rpm). Viscosity is shown on the monitor and recorded.

Manufacture of tablets

In this experiment, the method of making tablets by wet granulation adopted the previous study with the necessary adjustments.[14] Preparing granules by wet granulation contains HPMC and lactose monohydrate (50 %) according Table 2 (cubic mixer, rotary motor (Erweka)). A homogeneous mixture was moistened with CA-LBG dispersed in distilled water (± 5 mL) while being compressed to form a wet granule mass and sieved (mesh No. 18) to form granules. The wet granules were dried in an oven (50^0C; 15 min; RH 2-5%) (moisture analyzer OHAUS) and re-sieved (mesh No. 20). The granules were mixed with ketoprofen (100 mg) (3:1) and evaluated for the mass quality of the tablets. The tablet mass was compressed to form a 400 mg tablet and hardness $\geq$ 13 kp (single punch, Korch, Germany), assessed for the physical quality of the tablet and dissolution.

Optimization

Optimization of the granule formula according to the simplex lattice design of two factors used eight runs randomized of formulas, model quadratic, and optimization software (Design Expert ver. 10.0.8.0; Stat-Ease Inc., Minneapolis, MN, USA). Comparison of the proportion of HPMC and CA-LBG for each formula based on optimization software (Table 2), including 0:1 (2 formulas); 0.25:0.75 (1 formula); 0.50:0.5 (2 formulas); 0.75:0.25 (1 formula); and 1:0 (2 formulas). The concentration of HPMC in proportion 0 (30%) and proportion 1 (40%), while the concentration of CA-LBG in proportion 0 (10%) and proportion 1 (20%). The HPMC concentration and the CA-LBG concentration were optimization factors. The angle of repose, tap index, hardness, friability, and released ketoprofen were optimization responses. The values of the optimization response parameters were processed using optimization software to obtain polynomial equations and predict the optimum concentrations of HPMC and CA-LBG in granules.

Flowability

The mass of the tablet was weighed at about 50 g and placed on the funnel of a flowability tester (Erweka, Germany). The funnel valve opens, and the tablet mass flows freely. The flowability tester monitor observed the measured flow time of the tablet mass. The cone from tablet mass was measured using infrared to determine the angle of repose and watched on the flowability tester monitor.

Tap Index

The tablet mass was put in a measuring cup (50 mL). The measuring cup was tilted and filled with tablet mass. The filled measuring cup was placed on the volumenometer tap density and tapped 500 taps. Tap index (TI) was determined from the difference between the volume before and after tapping compared to the volume before tapping (Equation 2).[16–19]

$$TI\ [\%] = \frac{V0 - V1}{V0}\ x\ 100\% \qquad \text{Equation 2}$$

Weight

From randomly selected tablets (20), and each tablet was weighed using an analytical balance (Mettler Toledo, Switzerland).

Hardness

Tablet hardness test used randomly selected tablets (6 tablets).[20] The tablets were placed on a board in a hardness tester (Schleuniger, Netherlands), then a metal block pressed on the tablet until the tablet cracks. The tablet hardness was observed on the monitor hardness tester.

Friability

The tablet friability test used randomly selected tablets with a total weight of comparable tablets of 6500 mg.[20] Each tablet was cleaned from dust, then all tablets were weighed (W0). All tablets were placed in a drum friability tester (Erweka, Germany) and rotated (4 min; 25 rpm). All tablets were removed, cleaned from dust, and reweighed (W1). The friability (F) of tablets is determined according to Equation 3.

$$Fr\ (\%) = \frac{W0 - W1}{W0}\ 100\% \qquad \text{Equation 3}$$

Drug release

The release of ketoprofen was tested using a dissolution apparatus USP II paddle model.[12,13] The dissolution media used phosphate buffer pH 6.8 (900 mL; 37°C; 50 rpm) (Electrolab TDT-08L, India). Samples were taken at 0.5; 1; 1.5; 2; 2.5; 3; 4; 5; 6; 8; and 10 hour. Ketoprofen released from the tablet determined absorption value read by UV spectrophotometer (260 nm) (Hitachi U-1900, Japan).[13,21]

Kinetics of ketoprofen release

The release kinetics of ketoprofen from tablets was influenced by HPMC and CA-LBG in the granules. The kinetics of drug release is determined by the following equations:[22–25]

Zero order $: Q_t = Q_o + K_o.t$ Equation 4

First order $: \ln Q_t = \ln Q_o + K_o.t$ Equation 5

Qt: the amount of drug dissolved at the time (t), Qo: the amount of the initial drug, and Ko: drug release constant.

Higuchi $: Q_t = K_H.\sqrt{t}$ Equation 6

Qt: the amount of drug dissolved at the time (t), K_H: Higuchi constant, and t: time.

Korsmeyer-Peppas : $Q_t/Q_\infty = K_k . t^n$ Equation 7

Qt/Q∞: fraction of drug released, Kk: Korsmeyer-Peppas constant, and n: diffusion exponential.

Hixson-Crowell :$Q_o^{1/3} - Q_t^{1/3} = K_s.t$ Equation 8

Qo: the amount of initial drug, Qt: the amount of drug remaining at the time (t), and Ks: dissolution rate constant.

Weibull : $\log [\ln - (1 - m)] = b\log (t - Ti) - \log a$ Equation 9

(1-m): fraction of insoluble drug, Ti: the lag time before dissolution, b: shape parameter obtained from the slope of the obtained curve. The value of b = 1 means that the curve is exponential. The importance of b > 1 is the shape of the sigmoid curve.

The release kinetics of ketoprofen from tablets of each granule formula was analyzed using DDSolver software.

Result and Discussion

Fourier transform infrared spectroscopy

Infrared spectra of CA-LBG and LBG are presented in Figure 1. Peaks at wavelengths of 3318.20 cm^{-1} and 3285.80 cm^{-1} indicate the hydroxyl (OH) groups of mannose and galactose. Peaks at wavelengths of 2923.66 cm^{-1} and 2936.00 indicate C-H bonds, where CA-LBG is sharper than LBG due to the influence of symmetrical C-H bonds from CA.[25,26] The specific peak of CA-LBG at 1736.02 cm^{-1} indicates an ester carbonyl group. Previous studies reported that the peak wavelength of the OH group appears at 3300 cm^{-1}, C-H appears at around 2900 cm^{-1}, and C=O appears at about 1750-1735 cm^{-1}. The reaction mechanism for making CA-LBG is a chemical esterification reaction. The reaction begins with the citric acid carbonyl group undergoing protonation and reacting with the hydroxyl group (OH) on the C-6 mannose and galactose atoms to form a tetrahedral cation. Oxygen

in the OH undergoes protonation ($^{+}OH_2$) to form loose OH so that the loss of H_2O and an ester (CA-LBG) is formed.[7] The results of the infrared analysis were further confirmed using NMR.

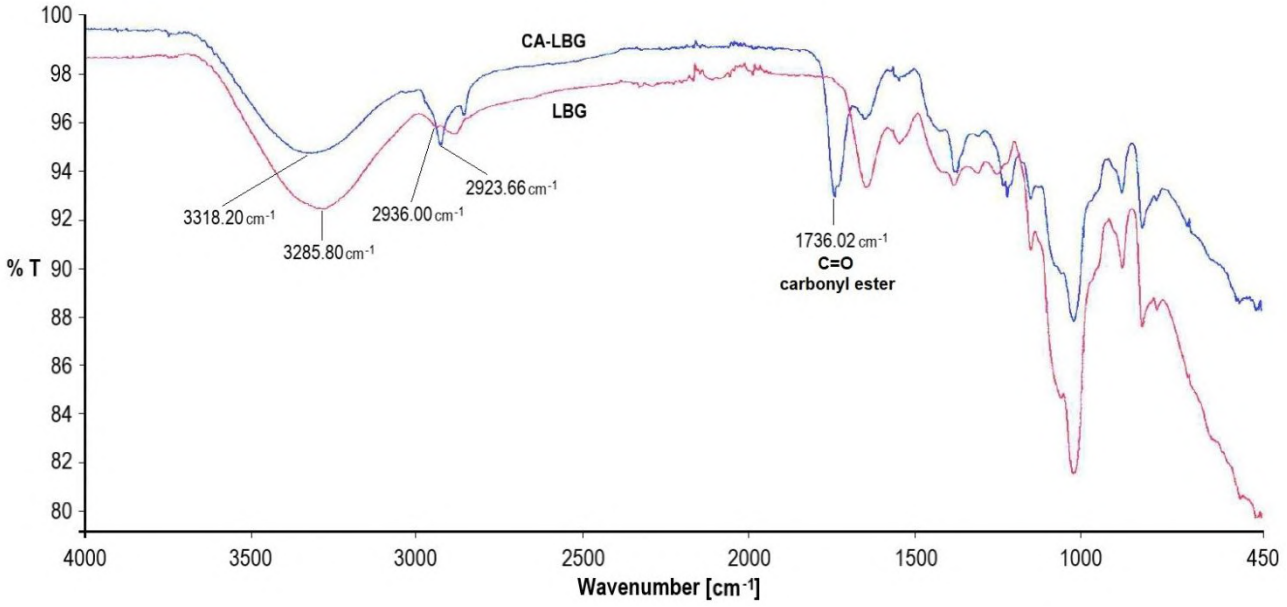

Figure 1. Infrared spectra of CA-LBG and LBG. The CA-LBG spectra have a carbonyl ester group (C=O) at a wavelength of 1736.02 cm^{-1}, presented by a blue line. LBG as control, presented with a red line.

Nuclear magnetic resonance

The NMR examination further confirms the FTIR examination and is carried out representatively for the three manufacturing batches. The CA-LBG NMR spectra are presented in Figure 2. The ^{1}H NMR spectra, paired twin peaks at δ = 2.926 ppm and δ = 2.894 ppm, δ = 2.746 and ppm, δ = 2.714 ppm correspond to the presence of CH_2 (5) of CA in LBG. The sharp peak at δ = 3.996-3.309 ppm corresponds to the H atoms of mannose and galactose in LBG. Previous experiments reported that the paired twin peaks of CH_2 were seen at δ = 2.7-3.0 ppm. Sharp peaks of H atoms from mannose and galactose appear at δ = 4.5-3.0 ppm.[6,7]

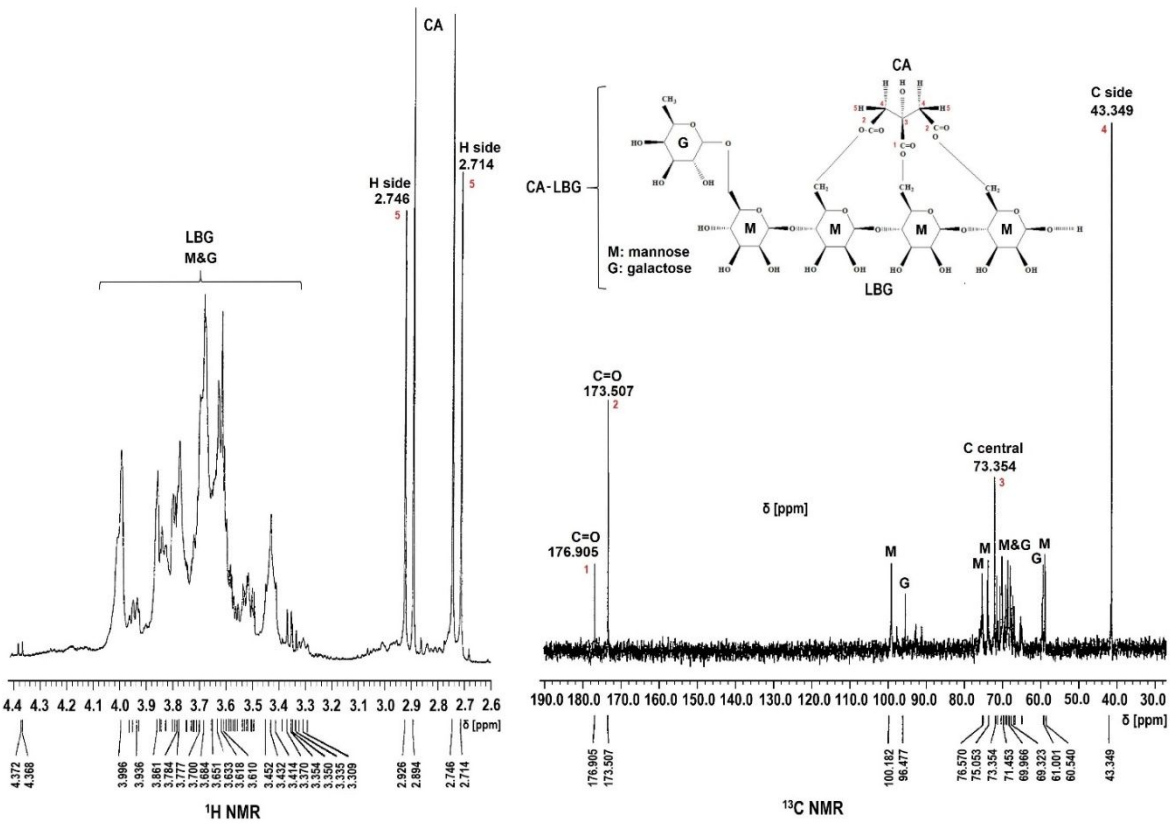

Figure 2. NMR observation spectra of CA-LBG. CA characters present in CA-LBG resented peaks 1, 2, 3, 4, and 5.

The ^{13}C NMR spectra of CA-LBG at the peak δ = 176.905 ppm and δ = 173.507 ppm indicated the carbonyl group (C=O) (1,2), which was a specific group of CA-LBG. The central C atom of CA is shown at δ = 73.354 ppm (3). CH_2 of CA is shown at δ = 43.349 ppm (4). The C atoms that make up mannose and galactose from LBG are shown at δ = 100.182 ppm, δ = 96.477 ppm, δ = 76.570 ppm, δ = 75.053 ppm, δ = 71.453 ppm, δ = 69.966 ppm, δ = 69.323 ppm, δ = 61.001 ppm, δ = 60.540 ppm. Previous experiments show C=O group at δ = 180-170 ppm, central C atom at δ = 80-70 ppm, CH_2 appears at δ = 44-43 ppm.[6,7,27] The C atoms make up mannose, and galactose appears at δ = 105-60 ppm.[7,28–30] Finally, the peaks in the spectra indicate the success of the synthesis.

Esterified CA

The degrees of esterification in each batch are shown in Table 1. All batches had similar degrees of esterification, indicating reproducible manufacturing conditions. The experimental esterification degree of 29.30-29.55% corresponds to the previous experimental report of around 9.13%.[7,14] The degree of esterification of all batches indicated that the esterification conditions were stable and reproducible. The acidic condition created by HCl induces the O atom in the carbonyl group of CA to be protonated to a positive C atom. The OH group on C6 of mannose and galactose will react with a positive C atom.

Table 1. Evaluation degree of esterification, solubility, and viscosity of CA-LBG

Batch Code	Degree of esterification		Solubility		Viscosity	
	[%]	SD	[%]	SD	[cP]	SD
1	29.33	0.20	29.65	0.27	9.48	0.01
2	29.30	0.21	29.81	0.18	9.46	0.02
3	29.55	0.10	29.51	0.42	9.43	0.02

Solubility

The solubility of CA-LBG in each batch is presented in Table 1. All batches showed similar solubility and indicated reproducible manufacturing. The solubility is 29.51-29.81%, according to the solubility in the previous experiment (22.64-36.63%).[14] The ester bond of CA molecules influences the solubility of CA-LBG in LBG. The positive C atom of the carboxylate group (CA) binds to the O atom at C-6, inhibiting the interaction of CA-LBG with distilled water CA-LBG and reducing solubility.

Viscosity

Table 1 shows the respective viscosity of CA-LBG has similar values and indicates reproducible manufacturing. The viscosity shows a value of 9.43-9.48 cPs following the viscosity in the previous experiment (7.76-11.20 cPs).[14] Viscosity is influenced by the carbonyl ester group

formed from the positive C atom of the carboxylic group (CA) with the O atom at C-6 in mannose and galactose so that the ability of CA-LBG to trap distilled water decreases.

Flowability

The results of testing the flow time and angle of repose of the tablet mass for each formula are presented in Table 2. Each formula produces a flow time of about 4.60-5.00 seconds and an angle of repose 27.89-30.04^0, indicating the tablet mass good flows because $\leq$ 10 seconds for 100 g and $\leq 40^0$ [17]. The tablet mass can occupy the die space inside the tablet machine. The tablet mass can be continued to be compressed to form a tablet (400 mg). The response of the angle of repose according to the simplex lattice design is obtained by Equation 10.

$$Y = 29.91\ A + 27.87\ B + 3.25\ AB \qquad \text{Equation 10}$$

The coefficient value of each component in the equation shows that HPMC (+29.91) is the most dominant factor in increasing the angle of repose, followed with CA-LBG (+27.87), and a combination of both (+3.25). The CA-LBG is an ester polymer that is difficult to hydrate with distilled water, so CA-LBG inhibits the formation of bonds between the granule constituent particles and produces fine granules. A large number of refined grains inhibits the tablet mass flow. HPMC is a polymer that can absorb moisture from the surrounding environment.[5] The HPMC in the granules increases moisture impedes flow, forming high mounds. Combining CA-LBG with HPMC, which can absorb moisture, increases the tablet mass flow time. Flow time is one parameter that determines the diversity of weights in the tablet manufacturing process.

Based on the ANOVA analysis (see supplementary information Table S1), the response angle of repose has a Pred R-Squared (0.9596), similar to Adj R-Squared (0.9742) with less than 0.2. Meanwhile, the Adeq Precision (23.8130) greater than 4, indicating this model is acceptable.

Tap Index

The tablet mass tap index for each formula is presented in Table 2. Each formula has a tap index of about 18.50-20.00%, indicating that the tablet mass has good homogeneity because ≤ 20% [17], so the space between the granules is filled with particles or fines. In addition, this condition shows that the tablet mass has good compressibility and creates low porosity tablets. The tap index for each formula is processed according to the simplex lattice design to obtain Equation 11.

$$Y = 18.99\ A + 18.77\ B + 5.64\ AB \qquad \text{Equation 11}$$

The value of the HPMC coefficient (+18.99) is the dominant factor in increasing the tap index, followed with CA-LBG (+18.77) and a combination of both (+5.64). HPMC can reduce the sensitivity of the granules because the HPMC particles absorb moisture so that the granules change shape when granules receive mechanical stress. The difficulty of hydrating CA-LBG particles in the granulation process causes the bond between the granules to be not good so that the granules release fines and receive mechanical stress. The combination of the two factors can increase the tap index because the HPMC reduces the sensitivity due to moisture absorption. In addition, it is supported by less strong bonds between particles in the granules due to the difficulty of hydrating during the granulation process.

Based on the ANOVA analysis (see supplementary information Table S1), the response tap index has a Pred R-Squared (0.7862), similar to Adj R-Squared (0.8928) with less than 0.2. Meanwhile, the Adeq Precision (10.7420) greater than 4, indicates this model is acceptable.

Weight

The tablet weight of all formulas is shown in Table 2. Tablet mass was compressed into tablets with a weight of about 400 mg. The tablet mass of all formulas is free to flow and fill the die chamber, so tablet weight is according to design. The compression success is suitable for the value of flow time, angle of repose, and tap index.

Table 2. Details of HPMC and CA-LBG concentration, quality of the tablet mass, quality of the tablet, and ketoprofen released

Formula code	HPMC [%]	CA-LBG [%]	Flow time [sec.]	Angle of repose [°]	Tap index [%]	Weight [mg]	Hardness [kp]	Friability [%]	Ketoprofen released [10 hr.] [%]
G1	40.00	10.00	4.80 ± 0.06	29.92 ± 0.10	19.00	401.34 ± 1.69	13.61 ± 0.70	0.39	53.75 ± 0.89
G2	32.50	17.50	4.60 ± 0.10	28.98 ± 0.08	20.00	400.87 ± 1.25	13.84 ± 1.05	0.45	83.34 ± 0.70
G3	35.00	15.00	5.00 ± 0.06	29.47 ± 0.18	20.00	402.08 ± 1.50	14.08 ± 0.84	0.28	69.33 ± 0.93
G4	40.00	10.00	4.60 ± 0.10	29.86 ± 0.53	18.50	400.07 ± 1.16	13.60 ± 0.61	0.43	51.71 ± 0.71
G5	30.00	20.00	4.80 ± 0.06	27.86 ± 0.18	19.00	399.69 ± 1.45	13.33 ± 0.46	0.74	99.21 ± 1.04
G6	37.50	12.50	4.80 ± 0.15	30.04 ± 0.06	20.00	400.12 ± 1.65	14.01 ± 0.83	0.34	58.16 ± 0.89
G7	35.00	15.00	5.00 ± 0.15	29.93 ± 0.94	20.00	400.36 ± 0.89	14.06 ± 0.87	0.28	69.82 ± 0.33
G8	30.00	20.00	5.00 ± 0.10	27.89 ± 0.54	19.00	399.67 ± 1.21	13.32 ± 0.84	0.73	99.32 ± 0.46
Ga	32.97	17.03	4.80 ± 0.06	29.17 ± 0.12	20.00	401.27 ± 1.15	13.97 ± 0.64	0.40	80.08 ± 0.60
Gb	32.97	17.03	4.60 ± 0.15	29.08 ± 0.23	20.00	399.00 ± 1.20	14.01 ± 0.58	0.41	80.44 ± 1.17
Gc	32.97	17.03	5.00 ± 0.10	29.22 ± 0.99	19.50	400.67 ± 0.79	13.86 ± 0.85	0.39	80.45 ± 0.55
Go	32.97	17.03	-	29.16	20.01	-	13.91	0.41	80.00

The proportion of HPMC and CA-LBG are G1 (1 : 0); G2 (0.25 : 0.75) G3 (0.5 : 0.5); G4 (1 : 0); G5 (0 : 1); G6 (0.75 : 0.25); G7 (0.5 : 0.5); G8 (0 : 1); Ga (0.30 : 0.70); Gb (0.30 : 0.70); Gc (0.30 : 0.70); and Go (0.30 : 0.70).

Hardness

The tablet hardness of each formula is presented in Table 2. Tablets of each formula have a hardness are around 13.32-14.08 kp, indicating that the tablet has strong resistance and good physical stability. The hardness of tablets comes from strong interlocking between the granules/particles making up the tablet when receiving compression so that the porosity of the tablet is low. The hardness of each formula is processed according to the simplex lattice design to obtain Equation 12.

$$Y = 13.60\ A + 13.32\ B + 2.42\ AB \qquad \text{Equation 12}$$

The coefficient value of HPMC (+13.60) is the most dominant factor in increasing hardness, followed with CA-LBG (+13.32) and a combination of both (+2.42). HPMC can absorb moisture and is used as an adhesive between the deformation of granules/particles to produce a solid interlocking bond. The tablets have good stability to humidity even though the granules contain HPMC because the moisture absorption activity is inhibited by decreasing the absorption surface area in the tablets form than the granules. Although CA-LBG is difficult to hydrate, the deformation of the particles can form solid interlocking bonds. In addition, the presence of CA-LBG on the tablet surface inhibits moisture absorption. The combination of both can increase the hardness because the characters of HPMC and CA-LBG complement each other. The tablet has a solid interlocking bond between the deformation of the granules/particles, and the tablet can retain moisture. In addition, the tap index shows that the tablet mass has low porosity and good compressibility so that when compressed tablet mass produces a compact tablet.

Based on the ANOVA analysis (see supplementary information Table S1), the response hardness has a Pred R-Squared (0.9976), similar to Adj R-Squared (0.9985) with less than 0.2. Meanwhile the Adeq Precision (100.1700) greater than 4, indicates this model is acceptable.

Friability

The tablet friability of all formulas is presented in Table 2. Each formula has a friability of 0.28-0.74% (≤ 1%)[17], indicating that the tablet surface is strong enough to withstand mechanical movements because of solid interlocking bonds between the deformation of the particles on the tablet surface. Friability of all formulas is according to the simplex lattice design to obtain Equation 13.

$$Y = 0.41\ A + 0.73\ B - 1.10\ AB \qquad \text{Equation 13}$$

The coefficient value of CA-LBG (+0.73) is the most dominant factor in increasing friability, followed by HPMC (+0.41) and a combination of both decreasing friability (-1.10). HPMC can absorb moisture and is used as an adhesive between the deformation of granules/particles to produce a solid interlocking bond. The tablets have good stability to humidity even though the granules contain HPMC because the moisture absorption activity is inhibited by decreasing the absorption surface area in the tablets form than the granules. Although CA-LBG is difficult to hydrate, the deformation of the particles can form solid interlocking bonds. In addition, the presence of CA-LBG on the tablet surface inhibits moisture absorption. The combination of the two can reduce the friability of the tablet because the HPMC and CA-LBG particles fill the space between the lactose monohydrate particles. The strong interlocking bonds of the granule mass components form compact and low-porosity granules. When compressed formed a tablet resistant to mechanical movement. The friability quality of this tablet is in line with the hardness quality of the tablet.

Based on the ANOVA analysis (see supplementary information Table S1), the response friability has a Pred R-Squared (0.9593) similar to Adj R-Squared (0.9747) with less than 0.2. Meanwhile, the Adeq Precision (24.6860) greater than 4, indicates this model is acceptable.

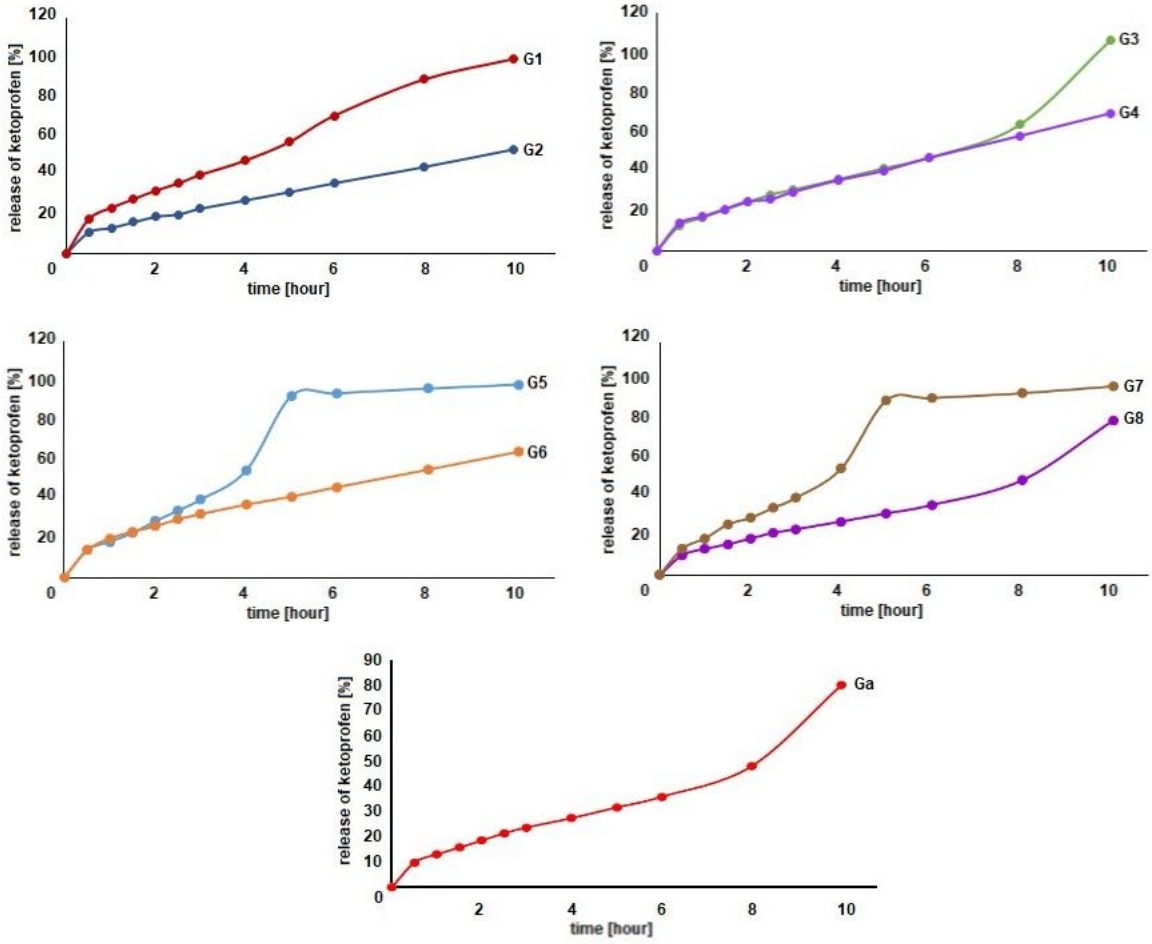

Figure 3. The ketoprofen dissolution profile of various tablet formulas contains HPMC [%] and CA-LBG [%]: G1 (40 : 10); G2 (32.5 : 17.5); G3 (35 : 15); G4 (40 : 10); G5 (30 : 20); G6 (37.5 : 12.5); G7 (35 : 15); G8 (30 : 20); and Ga (32.97 : 17.03).

Ketoprofen release

The concentration and profile of ketoprofen release for each tablet formula after 10 hours are presented in Table 2, Figure 3, and supplementary information Table S2-S3. All tablets of ketoprofen release around 51.71-99.32%, showing that HPMC and CA-LBG can control ketoprofen release from tablets. HPMC is a polymer that swells when hydrating by the dissolution medium. Ketoprofen release is inhibited because HPMC swells trap ketoprofen particles. The CA-LBG is a polymer that is difficult to hydrate and has low solubility. The CA-LBG character causes the tablet to disintegrate

and become granule. Releases of ketoprofen-controlled granule swelling form a gel. Based on the experimental design, ketoprofen released for 10 hours is ≥ 80% (see supplementary information Chapter 1). The processed concentration value of each tablet formula is according to the simplex lattice design to obtain Equation 14.

$$Y = 52.48\,A + 99.44\,B - 26.36\,AB \qquad \text{Equation 14}$$

The CA-LBG coefficient value (+99.44) was the most dominant factor in increasing ketoprofen release, followed with HPMC (+52.48). The combination of both (-26.36) was the most dominant factor in reducing the release of ketoprofen. The deformation of CA-LBG particles on the tablet refuses each other when submerged in the dissolution medium, causing tablet disintegration. The granule porosity surface is used as a space for penetration of the dissolution medium into the granule, dissolved ketoprofen particles, and diffuses out of the granule. The high concentration of CA-LBG accelerates of disintegration of the tablet and forms HPMC gel. Combining the HPMC with CA-LBG can reduce the release of ketoprofen because the moisture of the deformation of the HPMC particles can bind hardly to the interlocking deformation of the CA-LBG and other particles, so that the tablet disintegrates longtime. In addition, the direct interaction of CA-LBG with particles inhibits the swelling of HPMC and hydrating of ketoprofen by the dissolution medium. HPMC and CA-LBG particles can mix physically. Random distribution of HPMC and CA-LBG particles in granules. When these particles expand, the network of the two types of polymers can physically interact with each other (penetrate each other). In this condition, ketoprofen particles can be between these tissues so that these tissues control the release of ketoprofen. Ketoprofen release via diffusion or erosion mechanisms. The release of ketoprofen was studied through the kinetics of drug release.

Based on the ANOVA analysis (see supplementary information Table S1), the response to the release of ketoprofen has a Pred R-Squared (0.9956), similar to Adj R-Squared (0.9978) with a difference of less than 0.2. Meanwhile the Adeq Precision (85.0460) greater than 4, indicates this model is acceptable.

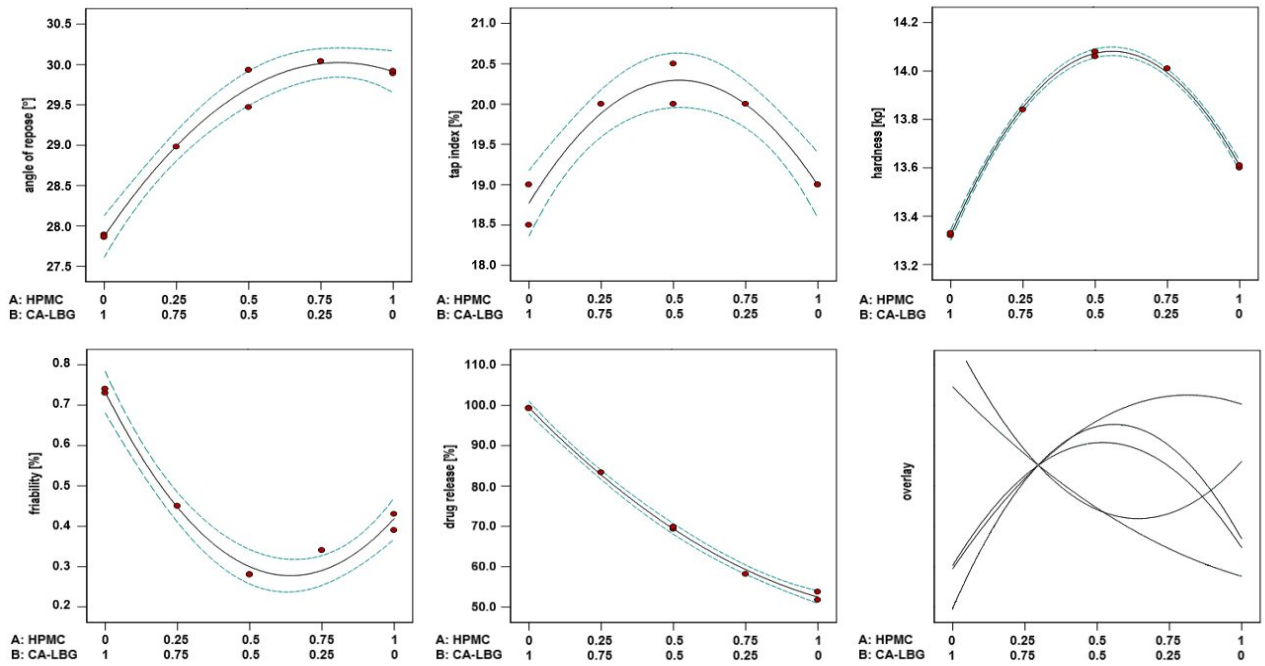

Figure 4. Comparison of actual (dotted line) and predicted (solid line) optimization response profiles. The red dot indicates the response value for each formula based on the respective proportions of HPMC and CA-LBG. The overlay shows the meeting point of all responses according to the predicted optimal proportions of HPMC and CA-LBG.

Optimum tablet formula

Determination of the optimum formula begins with the initial 8 experimental formula designs (G1-G8). The optimization factors and response parameter values were analyzed using design expert software using a simplex lattice design. The experimental comparison profiles and the predictions of each optimization response (Figure 4) show that the actual profiles are similar to the predictions. This profile follows the results of ANOVA analysis for each optimization response (flowability, tap index, hardness, friability, and release of ketoprofen). The optimization response overlay predicts the optimum proportion point to achieve the optimum response prediction. Design expert provides several alternative options for the optimum formula. The selected formula was determined from the response parameter specifications (angle of repose 27.86-30.04; tap index 18.5-20.5; hardness 13.32-

14.08 kp; friability 0.28-0.74%; drug release > 80%). Verification to the prediction of the optimum formula proportion (Go) to obtain the optimum formula was carried out in three batches (Ga, Gb, Gc) (Table 2 and Figure 3).

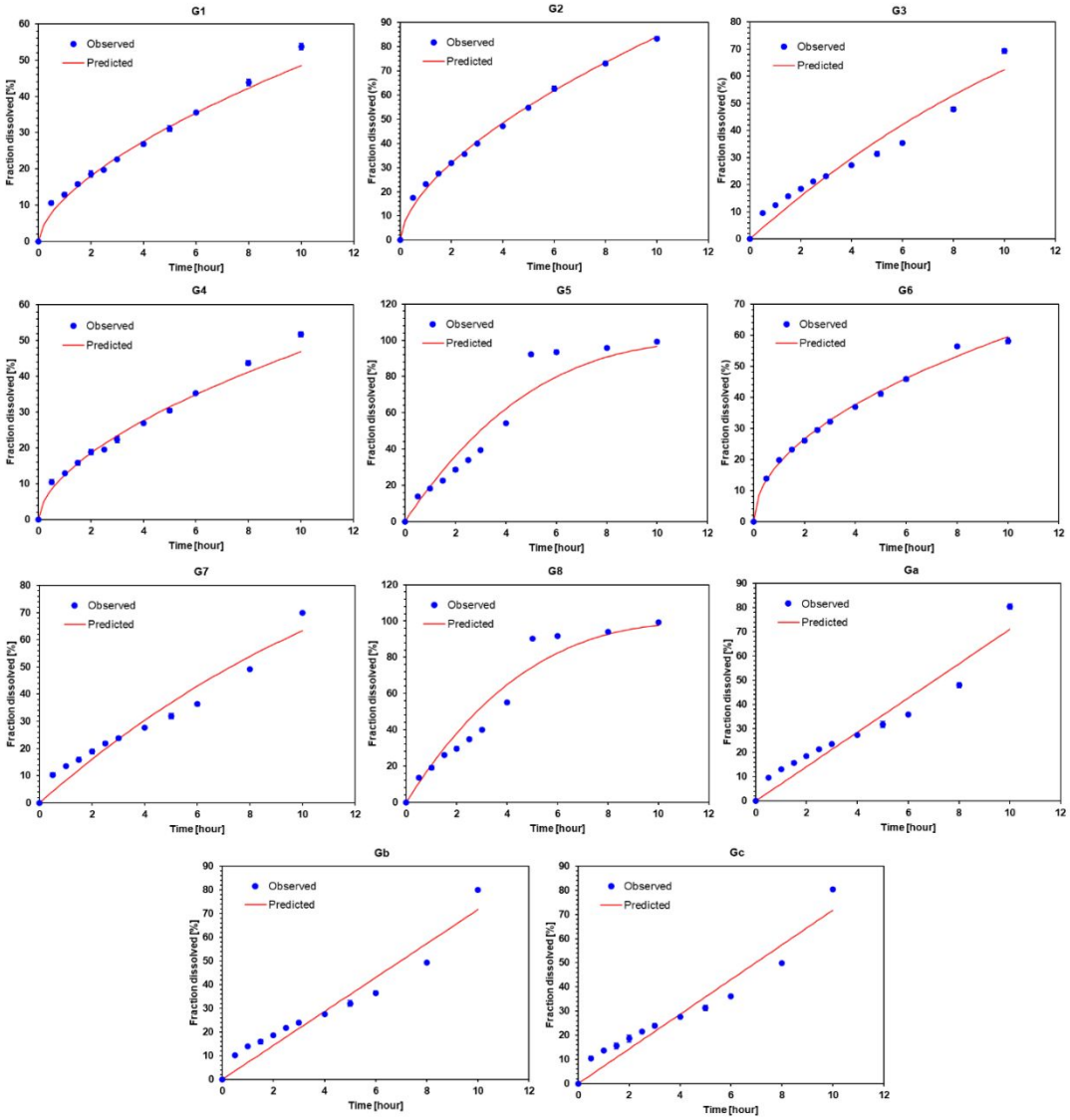

Figure 5. Drug release kinetics model (HPMC [%] : CA-LBG [%]): G1 (40 : 10) (Korsmeyer-Peppas); G2 (32.5 : 17.50) (Korsmeyer-Peppas); G3 (35 : 15) (Hixson-Crowell); G4 (40 : 10) (Korsmeyer-Peppas); G5 (30 : 20) (Hixson-Crowell); G6 (37.50 : 12.50) (Higuchi); G7 (35 : 15) (Hixson-Crowell); G8 (30 : 20) (Hixson-Crowell); Ga (32.97 : 17.03) (Zero order); Gb (32.97 : 17.03) (Zero order); and Gc (32.97 : 17.03) (Zero order).

One sample T-test results compare the experimental response formula verification with the predictive response. The values T of each parameter is T angle of repose (0.008), T tap index (1.096), T hardness (0.728), T friability (1.559), and T release of ketoprofen (2.657). The response parameter values between the prediction (Go) and the verification experiment (Ga-Gc) were not significantly different. These results indicate that the polynomial equations of each response parameter are valid for predicting the effect of HPMC, CA-LBG, and their combination. In addition, the selected optimum formula shows reproducibility in producing tablets and controlling ketoprofen's release. The variation of release shown by G1-G8 proves that tablets with irrelevant variations in physical quality produce varied drug releases.

Kinetics of ketoprofen release

The kinetics of ketoprofen release from the tablet is a non-linear approach using DDSolver (Table 3, Figure 5, and supplementary information Figure S1-S11). The kinetics parameters of ketoprofen release include high Rsqr_adj, low Mean Square Error-Root (MSE_root), and low Akaike Information Criterion (AIC). The Rsqr_adj is the correlation value between dissolution time and released ketoprofen. MSE_root indicates the error value in correlation analysis. AIC is the value suitability to the equation to determine the release kinetics.[31–35] The results of DDSolver processing are presented in Table 3 and Figure 5.

The release kinetics of ketoprofen from tablets G1, G2, and G4 followed the Korsmeyer-Peppas kinetics. The exponential value (n) for tablets G1 (0.62), G2 (0.60), and G4 (0.58) indicates a non-Fickian diffusion mechanism (anomalous diffusion).[36] The release of ketoprofen released by diffusion is proportional to erosion. The surface of the granules forms a thin gel and cannot withstand the dissolution medium, so ketoprofen dissolves quickly. The ketoprofen release is not only through diffusion but also due to erosion of the surface of the gel formed. The CA-LBG is not tightly

integrated into the tablet and granule. This condition causes the dissolution rate to be faster with the increase in the dissolution medium that enters the tablet and granule.

The release kinetics of ketoprofen from tablets G3, G5, G7, and G8 followed Hixson-Crowell kinetics. The ketoprofen release was caused by hydrating the tablet surface, so the tablet disintegrated and become granule. This condition causes ketoprofen to be dissolved constantly. HPMC low concentration can tablet disintegration quickly when particles swell to form a gel and push against other particles. In addition, CA-LBG on the granule accelerates the decomposition of the HPMC gel because the repulsion forces between CA-LBG particles are difficult to dissolve.

The tablet G6 followed the release kinetics of Higuchi's model. The high viscosity gel of HPMC controlled the diffusion of ketoprofen from the granules. CA-LBG on the granule surface inhibited granule hydration and ketoprofen diffusion.

The release kinetics of ketoprofen from Ga, Gb, and Gc tablets followed zero order. HPMC on the tablet surface swells to form a gel when in contact with the dissolution medium. The trapped ketoprofen particles dissolve and are saturated, then diffuse from the gel. Simultaneously the rate of CA-LBG disintegrating tablets into granules is proportional to gel formation. The dissolving of ketoprofen comes from the ketoprofen particles in contact with the gel surface. The balanced concentrations of HPMC and CA-LBG formed a gel with a constant thickness. These conditions can control the diffusion and maintain the availability of saturated ketoprofen dissolved in the gel.

Table 3. The value of the kinetics parameters of the release of ketoprofen from tablets.

Formula code	Parameter	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	average	SD	average	SD	
G1	Rsqr_adj	0.8762	0.02	0.9441	0.01	0.9585	0.00	0.9776	0.01	0.9279	0.01	0.9333	0.00	Korsmeyer-Peppas
	MSE_root	5.2625	0.35	3.5357	0.26	3.0468	0.20	2.2216	0.34	4.0144	0.29	3.8687	0.11	
	AIC	70.5951	1.56	61.0431	1.72	57.4597	1.61	50.6125	3.52	64.0907	1.71	64.8308	0.66	
G2	Rsqr_adj	0.8049	0.01	0.9687	0.00	0.9861	0.00	0.9948	0.00	0.9426	0.01	0.9536	0.00	Korsmeyer-Peppas
	MSE_root	10.6069	0.28	4.2456	0.22	2.8232	0.37	1.7379	0.16	5.7451	0.32	5.1742	0.23	
	AIC	87.4453	0.63	65.4533	1.28	55.5400	3.24	44.8284	2.23	72.7095	1.35	71.7991	1.08	
G3	Rsqr_adj	0.9395	0.00	0.9296	0.01	0.8689	0.01	0.9113	0.01	0.9401	0.01	0.8651	0.01	Hixson-Crowell
	MSE_root	4.5672	0.13	4.9223	0.35	6.7233	0.38	5.5235	0.47	4.5427	0.27	6.8225	0.28	
	AIC	67.2211	0.72	68.9849	1.70	76.4828	1.36	72.5897	2.03	67.0722	1.38	78.4392	0.96	
G4	Rsqr_adj	0.8597	0.02	0.9358	0.01	0.9657	0.01	0.9777	0.01	0.9171	0.01	0.9414	0.01	Korsmeyer-Peppas
	MSE_root	5.4444	0.33	3.6827	0.21	2.6858	0.34	2.1496	0.36	4.1855	0.25	3.5175	0.31	
	AIC	71.4154	1.46	62.0355	1.40	54.3575	3.04	49.7755	3.97	65.1033	1.48	62.4881	2.17	
G5	Rsqr_adj	0.8594	0.01	0.6528	0.10	0.8570	0.01	0.9057	0.00	0.9231	0.00	0.9025	0.00	Hixson-Crowell
	MSE_root	13.6548	0.48	21.3289	3.31	13.7776	0.45	11.1888	0.34	10.1039	0.28	11.3789	0.30	
	AIC	93.5029	0.85	104.0112	3.90	93.7193	0.79	89.5817	0.73	86.2787	0.67	90.7234	0.63	
G6	Rsqr_adj	0.6618	0.02	0.8583	0.01	0.9945	0.00	0.9935	0.00	0.8093	0.01	0.9762	0.00	Higuchi
	MSE_root	9.9176	0.17	6.4175	0.16	1.2626	0.07	1.3745	0.10	7.4459	0.16	2.6266	0.17	
	AIC	85.8359	0.41	75.3863	0.60	36.3490	1.26	39.2239	1.71	78.9547	0.53	55.5081	1.61	
G7	Rsqr_adj	0.9360	0.01	0.9304	0.00	0.8758	0.01	0.9093	0.01	0.9398	0.00	0.8675	0.00	Hixson-Crowell
	MSE_root	4.7248	0.28	4.9359	0.11	6.5870	0.32	5.6328	0.20	4.5899	0.09	6.8079	0.13	
	AIC	68.0154	1.40	69.0873	0.55	75.9974	1.20	73.1077	0.84	67.3448	0.45	78.3976	0.46	
G8	Rsqr_adj	0.8582	0.01	0.7246	0.05	0.8753	0.01	0.9180	0.00	0.9286	0.01	0.9112	0.00	Hixson-Crowell
	MSE_root	13.3691	0.17	18.5895	1.66	12.5351	0.46	10.1662	0.37	9.4845	0.43	10.5795	0.28	
	AIC	93.0042	0.30	100.8549	2.10	91.4435	0.88	87.2783	0.87	84.7498	1.10	88.9752	0.63	

continue to the next page

Table 3. The value of the kinetics parameters of the release of ketoprofen from tablets.

Formula code	Parameter	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell		Weibull		Kinetics model
		average	SD	average	SD	average	SD	average	SD	average	SD	average	SD	
Ga	Rsqr_adj	0.9241	0.01	0.8628	0.01	0.7995	0.02	0.8441	0.02	0.8883	0.01	0.7823	0.03	Zero order
	MSE_root	5.7889	0.30	7.7879	0.24	9.4113	0.50	8.2963	0.58	7.0194	0.51	9.8002	0.73	
	AIC	72.8966	1.22	80.0290	0.73	84.5579	1.28	82.3715	1.68	77.5002	1.76	87.0994	1.81	
Gb	Rsqr_adj	0.9273	0.00	0.8670	0.01	0.8107	0.01	0.8481	0.02	0.8956	0.01	0.7874	0.03	Zero order
	MSE_root	5.6548	0.09	7.6500	0.20	9.1233	0.40	8.1484	0.47	6.7739	0.32	9.6602	0.66	
	AIC	72.3524	0.40	79.6025	0.62	83.8190	1.06	81.9522	1.39	76.6707	1.14	86.7613	1.66	
Gc	Rsqr_adj	0.9273	0.01	0.8648	0.01	0.8044	0.01	0.8408	0.02	0.8920	0.01	0.7809	0.03	Zero order
	MSE_root	5.6764	0.38	7.7581	0.22	9.3364	0.37	8.4134	0.49	6.9321	0.30	9.8658	0.69	
	AIC	72.4101	1.62	79.9382	0.68	84.3764	0.94	82.7199	1.40	77.2270	1.07	87.2649	1.70	

The ketoprofen release kinetics model of various tablet formulas contains HPMC [%] and CA-LBG [%]: G1 (40 : 10); G2 (32.5 : 17.5); G3 (35 : 15); G4 (40 : 10); G5 (30 : 20); G6 (37.5 : 12.5); G7 (35 :15); G8 (30 : 20); Ga (32.97 : 17.03); Gb (32.97 : 17.03); and Gc (32.97 : 17.03).

Conclusion

HPMC and CA-LBG increased the value of angle of repose, tap index, hardness, friability, and release of ketoprofen. The combination of HPMC with CA-LBG increased the angle of repose, tap index, and hardness. Besides, the combination decreased friability and release of ketoprofen. The optimum concentrations of HPMC and CA-LBG for controlled-release tablets is 32.97% and 17.03%, resulting in the angle of repose of 29.16^0; tap index of 20.01%; hardness of 13.91 kp; friability of 0.41%; and the drug release (10 hours) of 80%. The drug release kinetics from optimum tablets followed zero order. The constant thickness of gel can control the diffusion and maintain the saturated ketoprofen in the gel. CA-LBG as a negative matrix disintegrates tablets into granules. HPMC as a gel matrix controlled ketoprofen release by diffusion and erosion. The tablets did not produce a ghost matrix because the gel matrix came from granules which degraded quickly after all the ketoprofen was released.

Associated Content

Supporting Information

Tablet dosage calculation; Statistical analysis of ketoprofen tablets; The release of ketoprofen from tablets (G1-G8); The release of ketoprofen from optimum tablets (Ga-Gc); and The kinetics profile of ketoprofen release from tablets (G1-G8) (Ga-Gb)

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Declarations

Competing interest statement

The authors declare that authors have no conflict of interest.

Author contribution statement

Wuryanto Hadinugroho: designed the experiments, performed the experiments, analyzed and interpreted the data, wrote the manuscript. Suwaldi Martodihardjo, Achmad Fudholi, Sugeng Riyanto and, Jefri Prasetyo: analyzed and interpreted the data.

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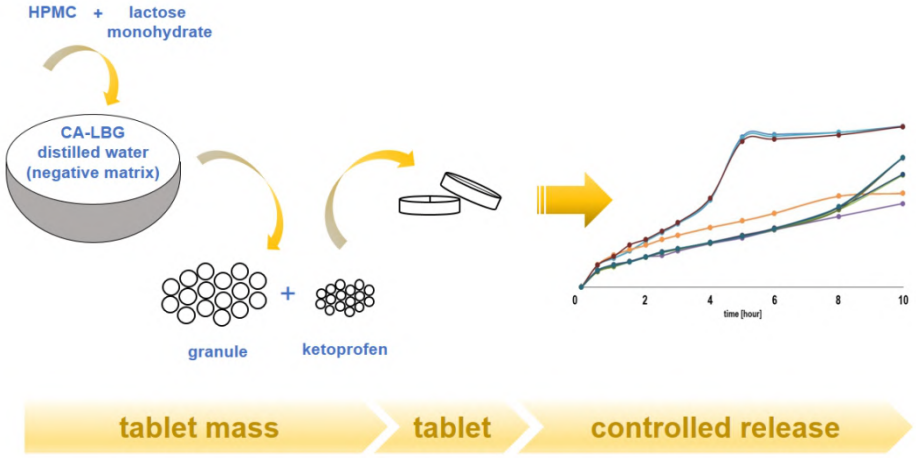

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