

DEVELOPMENT OF COPROCESSED EXCIPIENTS OF XANTHAN GUM AND ACACIA GUM AS A CONTROLLED RELEASE MATRIX FOR FAMOTIDINE FLOATING TABLETS

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ABSTRACT

Objective: Controlled release floating tablets require excipients, which act as a matrix to control the release of the active drug and facilitate the tablet floating in the gastric milieu. One potential excipient is coprocessed excipients of xanthan gum and acacia gum (Co-XG-GA), which is a physical modification of the two natural polymers. In this study, we produced several Co-XG-GA and used them as matrices in floating tablet formulations.

Methods: Several coprocessed excipients were prepared from xanthan gum and acacia gum at ratios of 1:1, 1:2, 2:1, 1:3, and 3:1. The obtained excipients were then characterized physically, chemically, and functionally. The coprocessed excipients were then formulated in floating tablets using famotidine as the drug model. The floating tablets were then evaluated in terms of the tablet floating capabilities and the drug release in HCl medium at pH 1.2 for 8 h.

Results: Our results showed that the coprocessed excipients were a fine powder, odorless, and a grayish-white color. The excipients had a good swelling index, fairly large viscosity, and good gel strength; hence, they were suitable to be applied as the matrices of floating tablet formulations. The floating tablets of F2, which contained the Co-XG-GA 1:2, demonstrated the best characteristics with 8.33 ± 0.58 min of floating lag time and 24 h of total floating time. Further release studies revealed that the famotidine floating tablets, which used Co-XG-GA (F1-F5) as matrices, controlled drug release with zero-order release kinetics and could be used for controlled release dosage forms.

Conclusion: Collectively, our results indicate that the Co-XG-GA can be applied as matrices in controlled release floating tablets.

Keywords: Acacia gum, Coprocessed excipient, Famotidine, Floating tablet, Xanthan gum.

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INTRODUCTION

Pharmaceutical preparations with gastroretentive drug delivery system are one of the ongoing developments to overcome absorption and bioavailability problems that often occur in ordinary oral dosage forms. This is particularly true for drugs with large absorption in certain areas of the digestive tract. Floating drug delivery systems (FDDSs) are delivery systems based on preparations that float in the gastric fluid due to their lower densities compared with gastric fluid. Accordingly, these preparations remain buoyant in the stomach for a long period without affecting the gastric emptying rate [1,2].

There are various types of natural gums, including those derived from natural polymers such as the natural polysaccharides, xanthan gum and acacia gum. Xanthan gum has good flow properties and is considered stable and non-toxic. In addition, it is a good gelling and viscosity-increasing agent (viscosity enhancer). Xanthan gum also has high swelling properties due to large water absorption and slight erosion [3]. However, xanthan gum has the disadvantage that it is not a tablet binder. In contrast, acacia gum is a stable material, a good gelling agent, and behaves like a tablet binder, but it has swelling properties with low viscosity. However, acacia gum is unique because it forms colloidal solutions with low viscosity compared with other gums. To obtain better overall characteristics of the two excipients, a modification of the coprocessed excipients of xanthan gum and acacia gum (Co-XG-GA) was performed. Modification of the coprocess was performed by combining the two excipients in the form of solution dispersion using a codrying process. The purposes of the coprocess excipient were to increase

synergy and functionality, change the physicochemical properties, and cover the shortcomings of each of its constituent excipient [4,5]. The coprocess excipient obtained from the xanthan gum and acacia gum was then used as a matrix in floating tablet formulations.

Famotidine, which is one of the drugs absorbed in the stomach, was used as the drug model in this study. Famotidine is a histamine 2 (H₂) receptor blocker with low bioavailability, ranging from 40% to 45% on oral administration. In addition, famotidine has an elimination half-life of 2.5–4 h. Drugs such as famotidine are suitable for preparation in the FDDS because they allow delivery to the H₂ receptors found in gastric parietal cells. Famotidine in the form of FDDS serves to reduce the known side effects of famotidine, including diarrhea, dizziness, headache, and anorexia. This is because famotidine is in a sustained release formulation, thereby reducing fluctuations in blood drug levels.

METHODS

Materials

Famotidine was gifted by Molex Ayus Co. Ltd. (Indonesia). Xanthan gum was purchased from Cargill Bioengineering (Canada). Acacia gum was purchased from Shangqiu Kangmedia Bio-Tech (China). Other chemicals and solvents were of analytical grade and purchased from commercial suppliers.

Preparation of Co-XG-GA

Xanthan gum and acacia gum, at concentrations of 3% each, were dispersed in distilled water. The xanthan gum and acacia gum were

mixed at varying ratios (1:1, 1:2, 2:1, 1:3, and 3:1) and homogenized with a rotation of 3000 rpm for 30 min to obtain a homogeneous mass. The mass was then dried with a double drum drier at $80\pm 5^\circ\text{C}$. The obtained layer or flakes were milled and sieved using a 35 mesh. Chemical, physical, and functional characterizations of the mass were then performed.

Functional group analysis

Chemical characterization was performed by functional group analysis using infrared spectrophotometers. Several Co-XG-GA were weighed, mixed until homogeneous with dried KBr powder, and then scanned in the region of wavenumbers $4000\text{--}400\text{ cm}^{-1}$.

Particle size distribution

Particle size distribution was determined using a sieve method. The sieve was arranged from the smallest mesh of 35 mesh, followed by 45 mesh, 60 mesh, 80 mesh, 120 mesh, and the largest at 230 mesh. The sample (25 g) was sieved with the smallest mesh at 30 rpm for 20 min. Each sieve that contained powder was weighed. Then, the weight percentage of the powder was displayed on a particle size distribution diagram.

Thermal analysis

Physical characterization was performed by thermal analysis using a differential scanning calorimeter (DSC). Approximately 5 mg of the sample was placed into an aluminum cylinder with a diameter of 5 mm. The cylinder was covered with aluminum plates and then the sample was put into a DSC. Measurements were examined at $30\text{--}35^\circ\text{C}$ with a heating rate of $10^\circ\text{C}/\text{min}$. Endothermic and exothermic processes that occurred in the sample were recorded [6].

Swelling index of floating tablets

The swelling index was performed using the powder excipient molded into a tablet with a weight of approximately 500 mg. The Petri dish and initial tablet (W_1) were weighed. Each tablet was placed into a Petri dish containing 10 mL of HCl at pH 1.2. After 15 min, the HCl was removed from the Petri dish and carefully dried, and the tablet and Petri dish were weighed to obtain the weight of the hydrated tablets (W_2). The same weighing procedure was performed at intervals of 30, 60, 120, 180, 240, 360, 480, 600, and 720 min. The time taken during the weighing process was not counted as a time interval. The volume of the HCl medium must remain at 10 mL at the time of the swelling index to the next interval [7].

Gel strength test

The powder was dispersed in aquadest at a concentration of 10% w/v and heated at 120°C to form a gel. Measurements were performed using a texture analyzer (Rheoner 3305, Germany). The gel preparation was placed into the sample container and then the penetration device was lowered to the surface of the gel. The gel strength was then measured when the gel breaks.

Preparation of famotidine floating tablets

For the preparation of the famotidine floating tablets, the wet granulation method was adopted. Polymer powder, famotidine, and NaHCO_3 were mixed until homogeneous. After that, talc, Mg stearate, and Avicel PH-101 were added and then molded manually using a tablet press machine. The composition of each formula is shown in Table 1.

Floating test

The tablets were placed in a 100 mL glass beaker containing simulated gastric fluid, pH 1.2 (HCl 0.1 N) at 37°C . The time required for the tablet to rise to the surface and to float was taken as the floating lag time (FLT). The duration of time in which the tablet constantly remained on the surface was considered as total floating time [8].

Famotidine content estimation in tablets

Three tablets of each formula were used to test for the drug content. Each tablet was crushed to a powder, weighed, and then placed into a 100 mL volumetric flask and dissolved with 0.1 N HCl. After

that, the solution was filtered and diluted suitably. The absorbance of the resultant solution was then measured with ultraviolet (UV) spectrophotometer at a wavelength of 265 nm. The amount of drug contained in the sample was calculated with the help of a calibration curve from a standard solution [6].

Dissolution study

Dissolution apparatus type 1 (the basket type) was used for the dissolution study. A drug release study was performed using 900 mL 0.1 N HCl at $37\pm 0.5^\circ\text{C}$ with a speed of 50 rpm. Sampling (10 mL) was performed at 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 min. The amount of solution taken was replaced by an equal amount of 0.1 N HCl solution. The absorbance of the sample was measured with a UV spectrophotometer at a wavelength of 265 nm. The drug release profile was determined by plotting the percentage of drug released against time. The dissolution data obtained were then calculated to determine the kinetic model of drug release and the mechanism of release.

Drug release mechanism

The mechanism of drug release from the preparations was determined by plotting the dissolution data in kinetic models of zero order, first order, Higuchi equation, and Korsmeyer–Peppas equation, as shown in Table 2 [9].

RESULTS AND DISCUSSION

Preparation of Co-XG-GA

The percentage yields of the Co-XG-GA were 40–70%, as shown in Table 3. Weight loss occurred during the process of dispersing the

Table 1: Formulas of famotidine floating tablets

Material	F1	F2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40	40	40	40	40	40
Co-XG-GA (1:1)	300	-	-	-	-	-	-	-
Co-XG-GA (1:2)	-	300	-	-	-	-	-	-
Co-XG-GA (2:1)	-	-	300	-	-	-	-	-
Co-XG-GA (1:3)	-	-	-	300	-	-	-	-
Co-XG-GA (3:1)	-	-	-	-	300	-	-	-
Physical mixture of XG-GA	-	-	-	-	-	300	-	-
Xanthan gum (XG)	-	-	-	-	-	-	300	-
Acacia gum (GA)	-	-	-	-	-	-	-	300
NaHCO_3 (15%)	75	75	75	75	75	75	75	75
Talc (2%)	10	10	10	10	10	10	10	10
Mg stearate (1%)	5	5	5	5	5	5	5	5
Avicel 101	70	70	70	70	70	70	70	70

Co-XG-GA: Coprocessed excipients of xanthan gum and acacia gum

Table 2: Drug release kinetic models

Model	Equation
Zero order	$Q_t/Q_0 = k_0 t$
First order	$\ln Q_t/Q_0 = k_1 t$
Higuchi	$Q_t/Q_0 = k_H t^{1/2}$
Korsmeyer–Peppas	$Q_t/Q_0 = k t^n$

Q_t/Q_0 : The drug fraction that is released at time t , k_0 , k_1 , k_H , k : The drug release constants for each equation, n : Peppas diffusion exponent

Table 3: Yield in preparation of Co-XG-GA excipients

Excipients	Yield (%)
Co-XG-GA (1:1)	61.67
Co-XG-GA (1:2)	53.33
Co-XG-GA (2:1)	71.67
Co-XG-GA (1:3)	48.33
Co-XG-GA (3:1)	76.67

Co-XG-GA: Coprocessed excipients of xanthan gum and acacia gum

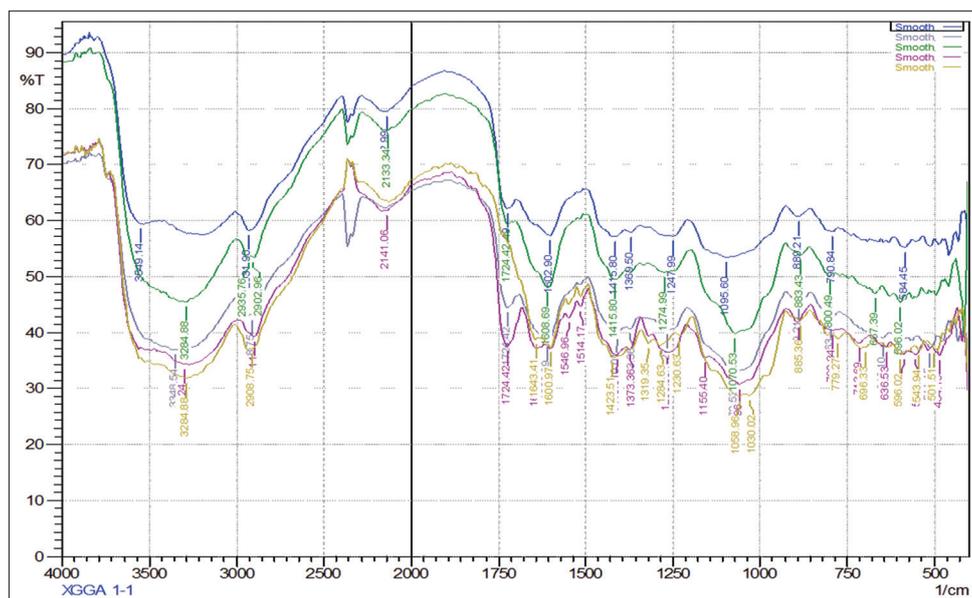


Fig. 1: Infrared spectrum of excipients: (a) Xanthan gum, (b) acacia gum, (c) coprocessed excipients of xanthan gum and acacia gum (CO-XG-GA) 1:1, (d) CO-XG-GA 1:2, and (e) CO-XG-GA 2:1

excipients in distilled water, along with material left behind during the drying, milling, and sifting process.

Functional group analysis

The purpose of the functional group analysis was to ascertain whether a chemical reaction occurred between each of the functional groups of the two excipients. Xanthan gum and acacia gum only interact or mix physically. No new functional groups presented in the spectrum (Fig. 1), indicating that these interactions do not involve chemical changes. The Fourier-transform infrared spectroscopy spectrum of xanthan gum, at wavenumber 1724.42 cm^{-1} showed a sharp peak, suggesting the presence of -C=O carboxylic bonds. This is reinforced by the presence of wide peaks with strong intensities in the range of wavenumbers $2400\text{--}3700\text{ cm}^{-1}$, indicating the presence of the -OH carboxylate group.

Particle size distribution

The particle size distributions of the coprocessed excipients are shown in Fig. 2. The excipients of Co-XG-GA 1:1, Co-XG-GA 1:2, Co-XG-GA 2:1, Co-XG-GA 1:3, and Co-XG-GA 3:1 were distributed on the particle size of $64\text{--}125\text{ }\mu\text{m}$, with the percentages at 40.00%, 48.70%, 27.03%, 44.62%, and 26.27%, respectively. Particle size can affect the flowability of a powder: The smaller the particle size of the powder, the more difficult it is to flow, or it shows poor flow properties due to high interparticle cohesiveness.

Thermal analysis

Fig. 3 displays thermal analysis of the Co-XG-GA using DSC (PerkinElmer, USA). The results show that the Co-XG-GA 1:1, 1:2, and 2:1 excipients were first degraded at temperatures $<100^\circ\text{C}$. According to the previous research, polysaccharides first degrade at a temperature of $40\text{--}110^\circ\text{C}$. Degradation at this temperature was associated with heat loss. Physical interactions involving high-temperature heating causes thermal stability to decrease [10]. The physical interaction of the polymer causes the formation of two descending peaks on the curve.

Swelling index

The results of the swelling index of the famotidine floating tablets are shown in Fig. 4. The Co-XG-GA excipient could swell for 12 h in HCl pH 1.2. The Co-XG-GA 3:1 (F5) excipient had the highest swelling index at 307.35%, whereas the Co-XG-GA 1:3 (F4) excipient had the lowest swelling index at 131.16%. The Co-XG-GA 1:1 (F1), 1:2 (F2), and 2:1 (F3) excipients had swelling indexes of 193.87%, 150.47%, and 270.63%, respectively.

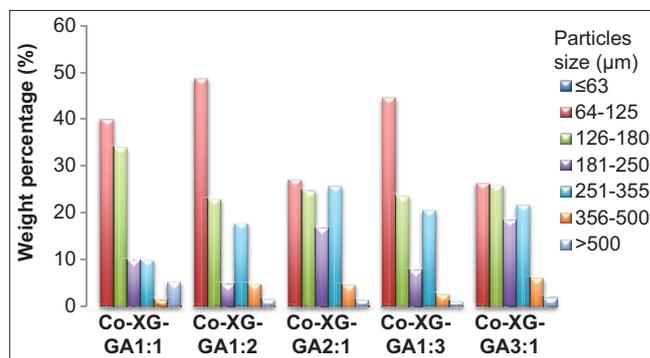


Fig. 2: Particle size distribution of coprocessed excipients of xanthan gum and acacia gum (Co-XG-GA) 1:1, Co-XG-GA 1:2, Co-XG-GA 2:1, Co-XG-GA 1:3, and Co-XG-GA 3:1

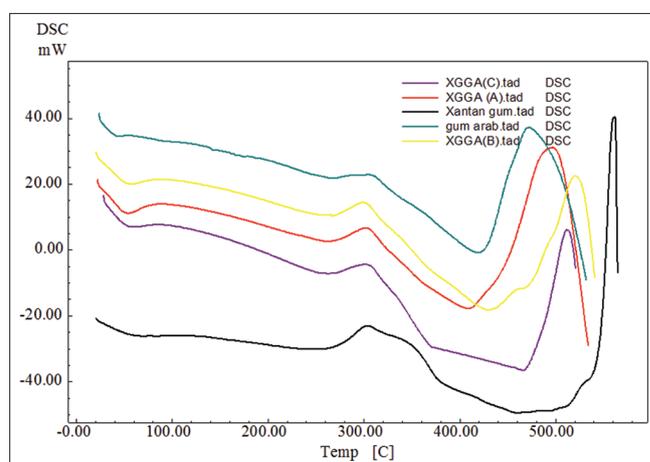


Fig. 3: Endothermic and exothermic curves: (A) Coprocessed excipients of xanthan gum:acacia gum (Co-XG-GA) 1:1, (B) Co-XG-GA 2:1, (C) Co-XG-GA 1:2, (D) XG, and (E) GA

Gel strength test

Observation data on the strength of the excipient gel are shown in Table 4. The gel strength is the resistance of a gel to external pressure

Table 4: Gel strength of the excipients

Material	Gel strength (gF)
Co-XG: GA 1:1	17.5±0.87
Co-XG: GA 1:2	14.67±0.58
Co-XG: GA 2:1	32.67±1.53
Co-XG: GA 1:3	7.83±0.29
Co-XG: GA 3:1	36.17±0.76
Physical mixture	13.83±0.29
Xanthan gum (XG)	55.67±0.76
Acacia gum (GA)	0±0

Co-XG: GA: Coprocessed excipients of xanthan gum: acacia gum

Table 5: Floating lag time and total floating time of the famotidine floating tablets composed of the Co-XG-GA

Formula	FLT (min)	TFT (h)
F1	8.67±0.58	24
F2	8.33±0.58	24
F3	13.33±0.58	24
F4	10.33±0.58	24
F5	15.67±0.58	24
F6	18.33±0.58	24
F7	8.67±0.58	24
F8	0.00±0	0

Co-XG-GA: Coprocessed excipients of xanthan gum and acacia gum, FLT: Floating lag time, TFT: Total floating time

Table 6: Evaluation results of famotidine content in the floating tablets

Formula	Content (%)
F1	97.50±1.18
F2	102.56±1.17
F3	105.61±0.25
F4	101.21±1.12
F5	106.33±0.97
F6	99.54±1.48
F7	100.33±0.90
F8	99.29±1.44

Table 7: Drug release rate constant (k) of the famotidine floating tablets

Formula	Kinetics parameters	
	k (h ⁻¹)	r
F1	0.050±0.003	0.9969
F2	0.046±0.001	0.9980
F3	0.050±0.001	0.9960
F4	0.045±0.002	0.9980
F5	0.048±0.002	0.9940

and shows the nature of the cohesiveness of a gel in maintaining its shape.

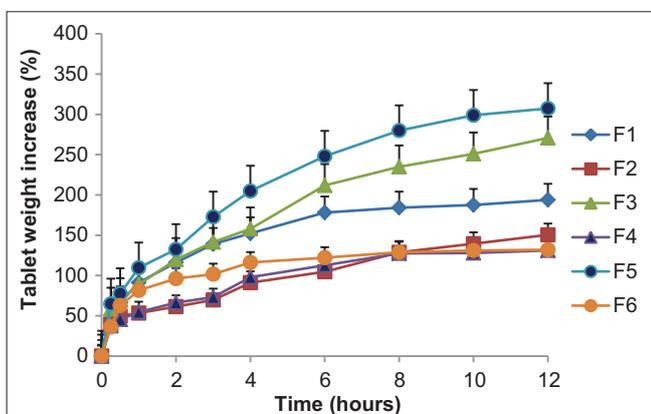


Fig. 4: Swelling index of the F1-F5 floating tablets for 12 h in HCl pH 1.2, F6 as a comparison. Each point represents the mean value±SD (n=3)

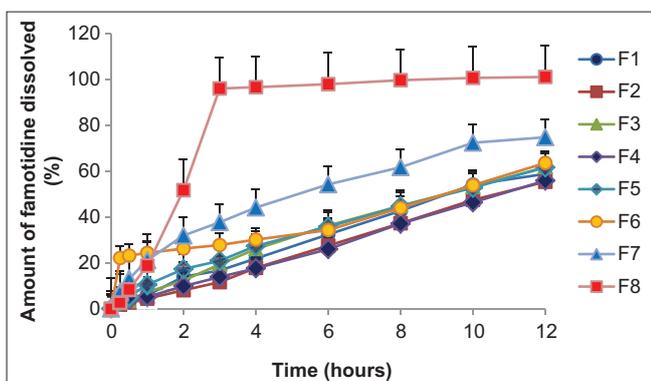


Fig. 5: The release profile of the famotidine floating tablets of F1-F5 formulation in HCl medium of pH 1.2 for 12 h, F6-F8 as a comparison. Each point represents the mean value±standard deviation (n=3)

Floating test

From the results of the floating test shown in Table 5, the F2 tablets composed of Co-XG-GA 1:2 excipient as the matrix had the fastest FLT value at 8.33 min. In contrast, the F5 tablets composed of Co-XG-GA excipient 3:1 as a matrix had the longest FLT value of 15.67 min. The best formula was the F2 formula, which contained the Co-XG-GA 1:2 excipient matrix on each tablet, and this formula had the fastest floating time among the five formulas at 8.33±0.58 min. This is because the Co-XG-GA 1:2 excipient was a combination of the natural polymers, which had a swelling index of 150.47% and a gel strength 14.67 gF; thus, it could absorb water immediately when in contact with the HCl at pH 1.2 medium [11]. This served to wet the gas-forming portion so that the formation of carbon dioxide gas was faster, which causes the preparation to float faster, and the resulting carbon dioxide gas can be retained by the Co-XG-GA 1:2 excipient matrix.

Famotidine content in the floating tablets

The famotidine content in the tablets is shown in Table 6 and is in the range of 90.0–110.0% and thereby meeting the requirements of the United States Pharmacopoeia 30th edition.

Drug release study

Fig. 5 shows the drug release profiles of the famotidine floating tablets. It shows that all the formulas that used a matrix of the coprocessed excipients could sustain drug release for 12 h with the cumulative amount released: F1 58.75%, F2 55.32%, F3 61.75%, F4 55.86%, F5 61.65%, F6 63.59%, F7 74.75%, and F8 101.08%. The release profile of the famotidine floating tablets of formulas 1–5 followed by the zero-order kinetics model and the drug release rate constants (k) is shown in Table 7. In this zero-order kinetics model, the drug release profile from the dosage form had a constant release rate from time to time without being affected by the concentration of the drug in the dosage form. This release kinetics model is also ideal for a controlled release dosage form because it can produce constant drug levels in the blood.

CONCLUSION

In this study, we produced the Co-XG-GA at ratios of 1:1, 1:2, 2:1, 1:3, and 3:1 in the form of odorless and slightly grayish-white fine powders. The

Co-XG-GA excipients had a characteristic swelling index and viscosity that were quite large, with gel strength of 7.83–36.17 gF; thus, this excipient was considered favorable for use in floating matrix tablets. The best formula was the second formula (F2), which contained a 1:2 Co-XG-GA excipient matrix on each tablet and had the fastest floating time among the five formulas at 8.33 ± 0.58 min, with drug release for 8 h at 37.26%. All floating tablets with a Co-XG-GA excipient matrix showed a controlled release of famotidine over 24 h.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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