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Research Article

COPROCESSED EXCIPIENTS OF CROSSLINKED AMYLOSE AND XANTHAN GUM FOR USE IN CONTROLLED RELEASE DOSAGE FORMS

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ABSTRACT

Objective: This study was aimed to obtain a new excipient that can be used as a polymer matrix for the formulation of controlled release dosage forms.

Methods: This study used coprocessing and crosslinking methods on amylose and xanthan gum (XG) to obtain a new excipient that can be used for controlled release matrix of pharmaceutical dosage forms. The coprocessing step was conducted by drum drying, and the crosslinking step was prepared using 6 and 12% sodium trimetaphosphate (STMP). The produced novel excipients were characterized in terms of infrared (IR) spectrum, substitution degree, moisture content, swelling index, and gel strength.

Results: Our results showed that amylose–XG excipients crosslinked using 6% STMP have greater gel strength and better swelling indexes than excipients crosslinked using 12% STMP. All coprocessed excipients exhibited no differences in their IR spectra, whereas the crosslinked excipients did, indicating a structural change due to the addition of phosphate groups. Crosslinking amylose–xanthan-coprocessed excipients using 6% STMP produced degrees of substitution (DSs) of 7–8 phosphates per 100 monomeric subunits. The excipients had a moisture content of 8.21–12.85%, and the pH of a 1% solution of excipients was 6.21–6.43. In addition, the swelling index and gel strength of the excipient where both amylose and XG were crosslinked together Were more than 1 where only amylose was crosslinked.

Conclusion: The crosslinking amylose–xanthan-coprocessed excipient using 6% STMP is more suitable for use in controlled release dosage forms, particularly when the polymer ratio is 1:1.

Keywords: Coprocessing, Crosslinking, High-amylose starch, Xanthan gum, Controlled release dosage forms.

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INTRODUCTION

Polysaccharides such as pectin, chitosan, starch, guar gum, and xanthan are commonly used in controlled release dosage forms of various pharmaceuticals due to their low cost, biocompatibility, low toxicity, ease of chemical modification, and biodegradability [1-4]. Among the various types of commercially available starch, high-amylose starch has been demonstrated to possess superior properties with regard to drug delivery compared with native starch [5]. Xanthan gum (XG) has also been studied as an ingredient for producing a direct compression matrix with high swelling properties [6,7].

Polymer modification can improve the physical and functional properties of each constituent polymer. Crosslinking has been proven to improve various characteristics of excipients such as swelling properties, solubility at various pHs, gel strength, mucoadhesive properties, and resistance to enzymatic modification or degradation. Many studies have demonstrated the successful application of high-amylose starch crosslinked using different agents, such as epichlorohydrin and sodium trimetaphosphate (STMP), in the development of controlled drug delivery systems [5,8,9]. Lenaerts *et al.* have demonstrated that crosslinked amylose (CLA) can be used in controlled drug release systems over periods of 18–24 h [10]. CLA with degrees of substitution (DSs) of 6–8 exhibits a good release profile when used as matrix in controlled-release tablets (15–20 h); in contrast, high DS (>10) results in a significant decrease in the drug release time profile (1–3 h), indicating that substitution can cause it to act as a disintegrants [11]. Meanwhile, according to Bejenariu *et al.*, crosslinking using STMP increases the gel strength of XG, which can then be used in controlled drug release systems [12].

Coprocessing is a new concept of manipulating the physical interaction of two or more excipients at the particulate level. The advantage of this method is that it can improve flow properties and compressibility and reduce weight variations by producing a single excipient with multiple functions. This can minimize the use of multiple excipients, produce excipients with improved functional properties with respect to viscosity or gel strength, and overcome the undesirable properties of the individual excipients to produce strong tablets with low compression pressure [13-15].

Based on these ideas, in this study, we modified high-amylose starch and XG using two methods. In the first, high-amylose starch was crosslinked using STMP and then coprocessed (Co) with XG. In the second, amylose and XG were coprocessed and then crosslinked using STPM to produce Co CLA–XG.

Coprocessed excipients consisting of XG and CLA were used as in the preparation of a sustained release matrix. Sustained release dosage forms have the advantages of reducing the frequency of drug administration, increasing patient compliance, minimizing drug level fluctuations in plasma, producing constant pharmacological effects (especially for drugs with short biological half-lives), and reducing the drug's side effects.

Sodium diclofenac is a nonsteroidal anti-inflammatory drug that is often used to treat a variety of pain, such as that due to migraines and osteoarthritis. This drug has a short half-life of 1–2 h and oral bioavailability of approximately 50% due to the first-pass metabolism in the liver. Frequent dosing is used for long-term treatment for osteoarthritis. For these reasons, sodium diclofenac was chosen as a model drug in this study as a slow release of the drug would be expected

to reduce administration frequency of the drug and provide constant pharmacological effects.

MATERIALS AND METHODS

Materials

Sodium diclofenac (Kimia Farma, Indonesia); high-amylose starch (Shangqiu Kangmedia Bio-Tech, China); XG (CV. Tristars Chemicals, Indonesia); STMP (Shangqiu Kangmedia Bio-Tech, China); sodium hydroxide (Merck, Jerman); chloride acid (Merck, Jerman); 96% ethanol (Brataco, Indonesia); and distilled water (Brataco, Indonesia) were used.

Methods

Synthesis of Co CLA-XG and CL Co-A-XG

Two methods, which were modified from the method of Cury *et al.* [16], were used. In the first, amylose was first crosslinked and then coprocessed with XG to produce Co CLA-XG. Amylose was crosslinked using STMP after adjusting the pH to 11–12 by adding 4% NaOH. STMP was used at concentrations of 6% or 12%, and the reaction time was 1–4 h. Once the reaction was completed, the amylose suspension was neutralized using HCl to pH±6 and then washed with 96% ethanol. The CLA was then air-dried and sieved using a 35-mesh sieve. CLA and XG were then dispersed in distilled water, homogenized for 15 min, and then dried in a drum drier at 80°C±5°C. The powder was then milled and sieved through a 35-mesh sieve. Three combinations of CLA and XG were produced at 1:1, 1:2, and 2:1.

In the second method, amylose and XG were first coprocessed and then crosslinked to produce CL Co-A-XG. A dispersion of amylose and XG in distilled water was homogenized for 15 min and then dried using drum drier at 80°C±5°C. The powder was then milled and sieved through a 35-mesh sieve. Three combinations of amylose and XG were produced at 1:1, 1:2, and 2:1. This material was suspended in distilled water, and the pH was adjusted to 11–12 with 4% NaOH. STMP was added at a concentration of 6% or 12% and reacted for 1–4 h. Once the reaction was completed, the suspension was neutralized using HCl to pH±6 and then washed with 96% ethanol. The final material was then air-dried and sieved using a 35-mesh sieve.

Characterization of Co CLA-XG and CL Co-A-XG

Physical characterization

Physical characterization of Co CLA-XG and CL Co-A-XG included its morphology, thermal properties, powder flowability, moisture content, hygroscopicity, and solubility. The shape and morphology of the powders were assessed using a scanning electron microscope. Thermal analysis was conducted using thermogravimetry-differential thermal analysis. Crystallinity was measured by X-ray diffraction. Moisture content was measured with a moisture balance using 1 g of sample powder, which was then heated to 105°C. Hygroscopicity testing was conducted on a 1-g sample placed in a desiccator at room temperature and a humidity of 70% relative humidity. The sample was divided into four different containers and changes in weight before and after treatment were recorded.

Chemical characterization

Chemical characterization of Co CLA-XG and CL Co-A-XG was conducted with respect to pH, number of functional groups, and degree of crosslinking. The excipient was dissolved in distilled water at a concentration of 10% and pH was measured using a pH meter. Substitution of phosphate groups in starch was ascertained using infrared (IR) spectrophotometer. IR spectra of Co CLA-XG and CL Co-A-XG were compared with those of amylose and XG. Phosphate groups exhibited specific absorption by ester bonds at wave numbers 1298.14 and 2362.88 cm^{-1}. The DS was measured using colorimetry.

Functional characterization

Functional characterization of Co CLA-XG and CL Co-A-XG powders was conducted on their flow properties, whereas viscosity and rheology, swelling index, and gel strength were assessed on their solutions/gels. The flow properties were measured with respect to flow rate, angle of repose, Hausner ratio, and compressibility index. Viscosity and rheology of Co CLA-XG and CL Co-A-XG were determined using their solutions at concentrations of 3%, 5%, 7%, and 10% w/v using a Brookfield viscometer. Swelling index was determined by comparing the weight of a dry tablet of excipient and the weight after it had been placed in 10 mL of the medium of various pHs. Gel strength was measured using a texture analyzer on a solid gel of 10% Co CLA-XG or CL Co-A-XG that has been cooled to ±4°C for 2 h.

RESULTS AND DISCUSSION

Synthesis of Co CLA-XG and CL Co-A-XG

Crosslinking was achieved by reacting a 3% mucilago of each polymer in distilled water with 6% of STMP. The pH was adjusted to 11–12 by continuous addition of 10 N NaOH solution. The hydroxyl groups of amylose and XG were ionized under alkaline conditions and could react with the phosphate groups.

The reaction was conducted while stirring at 3000 rpm in a homogenizer, and the crosslinking reaction is considered complete if there is no longer any change in the pH of the solution. The solution was then neutralized by adding HCl till a pH of 6.5–7 is reached.

A 50% ethanol solution was added to the neutralized suspension to form a white precipitate. The precipitate was then washed with 50% ethanol until no phosphate was detected in the final rinse (identified by an absorption peak at 820 nm). The precipitate was dried using a drum drier at a temperature of 80±5°C, milled using a disc mill, and sieved through a 60-mesh sieve to obtain Co CLA-XG or CL Co-A-XG.

Characterization of Co CLA-XG

Physical properties

CLA consisted of fine, white granules, whereas Co CLA-XG consisted of non-porous yellowish white fine flakes/fibers. The flake/fiber morphology of Co CLA-XG was due to the drying process with a double drum drier that broke the starch granules and turned them into irregular thin flakes (Fig. 1).

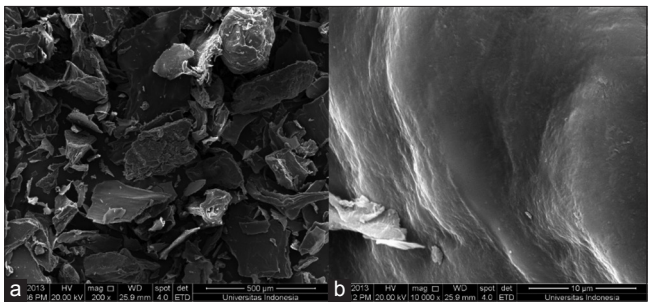

Fig. 1: Morphology of Co CLA-XG at ×200 (a) and ×10,000 magnifications (b)

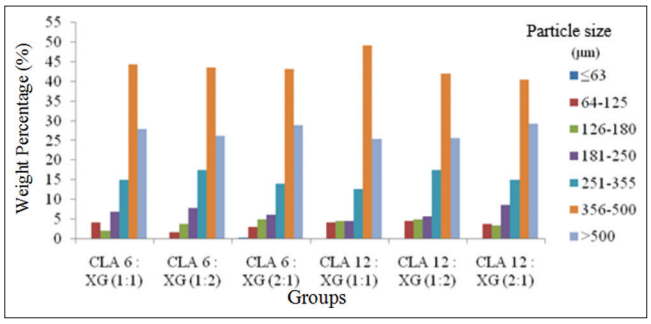

Fig. 2: Particle-size distribution of Co CLA-XG powders

The most common particle size of the various excipient powders was 356–500 µm, as shown in Fig. 2.

Table 1 shows that the moisture content of CLA was higher than that of Co CLA-XG. This was due to differences in drying methods; Co CLA-XG was dried using a drum drier at a higher temperature than CLA, which was dried at room temperature. Nevertheless, all excipients contained <15% water and flowed well (Table 2), so they could be used as excipients in pharmaceutical dosage forms.

Morphology, particle size, and moisture content contribute to the flow properties of powder excipients. Table 2 shows that all versions of Co CLA-XG performed well. High water levels can also cause poor flow rates due to adhesion between particles to form larger particles. However, while CLA6 had a higher water content, its spherical granules resulted in a good flow rate.

Chemical properties

Amylose was first crosslinked using STMP at two different concentrations (6% and 12%) before Co with XG. Crosslinking produced CLA with different DSs: 0.07 and 0.11 (Table 3). This means that there are approximately 7 or 11 phosphate groups for every 100 anhydroglucose units in amylose depending on the STMP concentration. Crosslinking is expected to occur at C positions 2, 3, and 6 of the starch, with a higher probability at the C2 position because it has the highest reactivity [17].

pH measurement on 1% solutions of the various Co CLA-XGs showed that they had a pH close to neutral (Table 4). This shows that there was no/very little residual phosphate in this crosslinked excipient and indicates that it is safe to use since its pH is close to physiological pH.

Analysis of the functional groups of CL6 was performed using FTIR. This showed a specific absorption for P (O) O at 1298.14 cm^{-1}, a peak for oxygen single bonds (–PO) of the phosphate group at 933.58 cm^{-1}, and an oxygen double bond (–P = O) at 1062.81 cm^{-1}. Amylose and CLA6 produced different spectra between 4000 and 2000 cm^{-1}. The additional peak at 2362.88 cm^{-1} in CLA6 that was due to the phosphate groups from STMP has reacted with amylose, while the loss of the peak at 2945.40 cm^{-1} in CLA6 was due to the partial loss of hydroxyl groups through reaction with STMP.

Analysis of the functional groups of the Co-CLA6-XG was performed to identify the physical interactions between XG and CLA6. The absence of a new group that emerged proving that there were no chemical interactions.

Functional properties

Co CLA6-XG exhibited greater gel strength than Co CLA12-XG, suggesting that Co-CLA6 PVA might be more suitable as a controlled release matrix (Fig. 3).

Table 1: Moisture content of Co CLA-XG

Excipient	Water content (%)
CLA6	12.58±0.62
CLA6:XG (2:1)	8.21±1.11
CLA6:XG (1:1)	8.22±1.08
CLA6:XG (1:2)	8.41±0.94

Swelling index measurements were performed in distilled water and phosphate buffer at pH 7.4. Co CLA-XG exhibited greater swelling in water than in buffer. All Co CLA-XG variants swelled to 2 times their original volume in the first 90 min, suggesting that the Co excipients could potentially be used as slow-release dosage forms. Co CLA6-XG 1:1 was the most promising excipient for use as a matrix with the ability to better retain and then release drugs. Results can be seen in Fig. 4.

Low viscosity is an indicator of a low gel strength, which can influence drug release. Co CLA-XG dispersed in distilled water exhibited pseudoplastic thixotropic flow properties, meaning that the viscosity of the solution decreased as the shear rate increased; however, when share rate is low, the viscosity of the solution does not immediately return to normal (Fig. 5).

Characterization of CL Co-A-XG

Physical properties

All Co-A-XG formulations were yellowish white flakes/fibers caused using a drum drier. In contrast, Co CLA-XG was non-porous, yellowish white, and granule-shaped. Differences in the shape of these modified excipients could impact their functional properties, such as flow rate and density. Morphology of CL Co-A-XG can be seen in Fig. 6.

Most of the powder particles were in the size range of 356–500 µm, as shown in Fig. 7.

Moisture content of Co A-XG was higher than that of CL Co-A-XG due to the different drying processes (Table 5). Co-A-XG was dried using the drum drying method; thus, its water content was lower than that of CL Co-A-XG, which was dried at room temperature.

Shape, size, and water content of the excipients impact the flow rate of the powder. Powder flow properties of all powders were in the fine category and their flow rates were quite good (Table 6).

Chemical properties

Crosslinking of Co-A-XG using STMP at concentrations of 6% and 12% resulted DSs listed in Table 7. Crosslinking of Co-A-XG with 6% STMP produced CL Co-A-XG with a DS of 0.08 while crosslinking using 12% STMP produced a DS of 0.11–0.12.

All the CL Co A-XG excipients at 1% concentration exhibited pHs close to neutrality (Table 8); however, all CL Co A-XG excipients had slightly

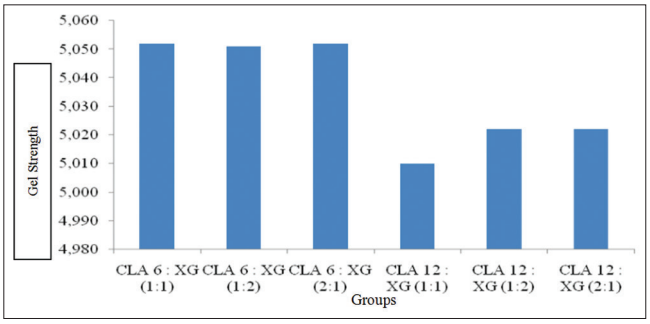

Fig. 3: Gel strength of Co CLA-XG

Table 2: Flow properties of Co CLA-XG

Excipient	Flow rate (g/det)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
CLA6:XG (1:1)	4.08	0.89	25.00	1.33
CLA6:XG (1:2)	4.05	0.87	24.59	1.33
CLA6:XG (2:1)	3.97	0.87	23.33	1.30
CLA12:XG (1:1)	4.17	0.89	25.00	1.33
CLA12:XG (1:2)	4.00	0.89	25.00	1.33
CLA12:XG (2:1)	4.14	0.89	25.00	1.33

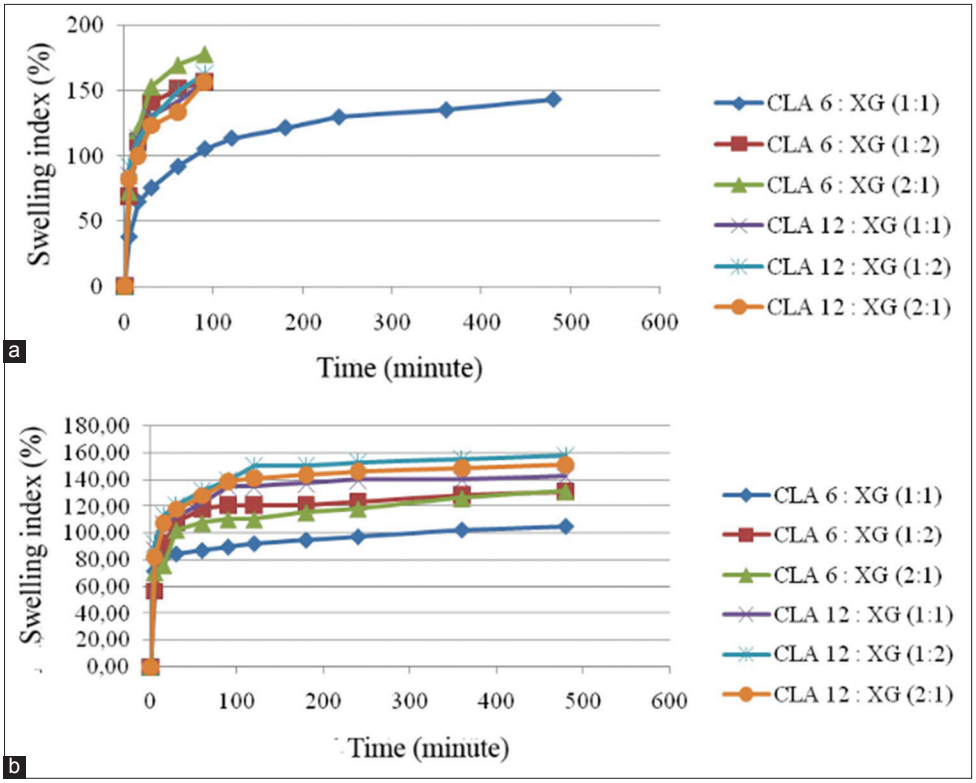

Fig. 4: Swelling indices of Co CLA-XG in (a) distilled water and (b) phosphate buffer at pH 7.4

Table 3: Degree of substitution of crosslinked amylose

Excipient	% p	DS
CLA6	1.43±0.175	0.07±0.010
CLA12	2.12±0.418	0.11±0.025

Table 4: pH of Co CLA-XG

Sample (1%)	pH
CLA6:XG (1:1)	6.44±0.03
CLA6:XG (1:2)	6.42±0.04
CLA6:XG (2:1)	6.44±0.02
CLA12:XG (1:1)	6.37±0.03
CLA12:XG (1:2)	6.39±0.05
CLA12:XG (2:1)	6.32±0.06

Table 5: Moisture content of excipient

Excipient	Moisture content (%)
Co-A-XG (1:1)	9.31±1.02
Co-A-XG (1:2)	9.58±1.00
Co-A-XG (2:1)	9.12±0.75
Co CLA-XG (1:1)	12.65±0.41
Co CLA-XG (1:2)	12.85±0.46
Co CLA-XG (2:1)	12.83±0.69

higher pHs than their non-crosslinked counterparts. Nevertheless, all the excipients produced were considered to be compatible for use in formulations because they were close to the physiological pH of the body.

There was a difference in the IR spectra of Co A-XG and CL Co A-XG, indicating that crosslinking had altered the chemical structure of the excipient.

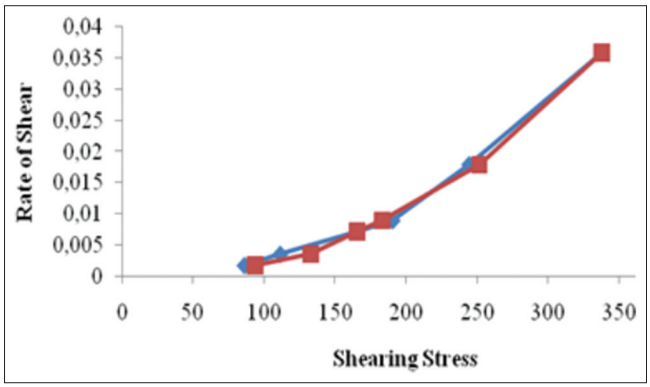

Fig. 5: Viscosity of Co CLA-XG

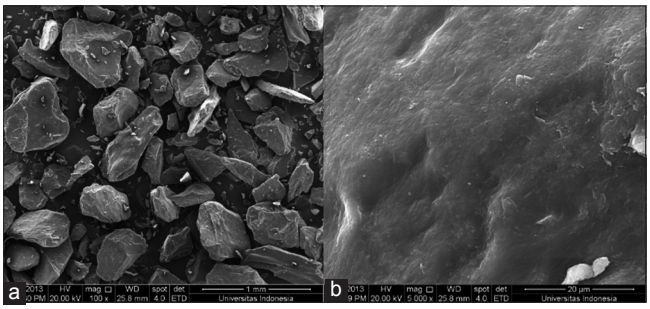

Fig. 6: Morphology of CL Co-A-XG at 100× (a) and 5000× magnifications (b)

Chemical properties

CL Co A-XG showed more swelling in the buffer than in distilled water (Fig. 8) and expanded up to 800% in the buffer (10 times higher than that in distilled water).

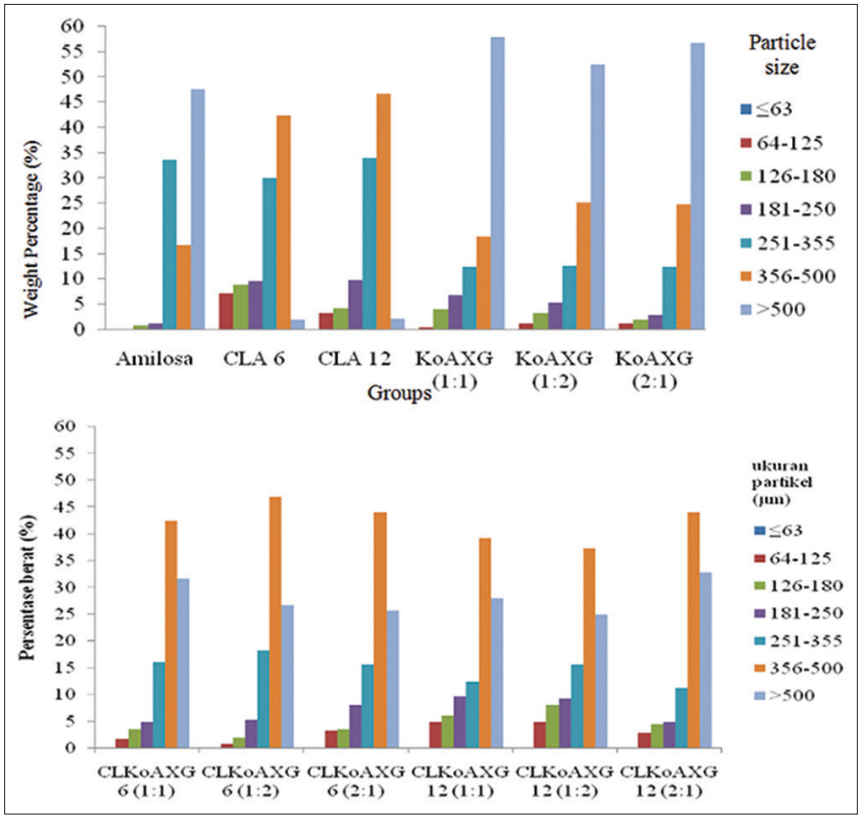

Fig. 7: Particle size distribution of coprocessed amylose-xanthan gum (Co-A-XG) (above) and CL Co-A-XG (below)

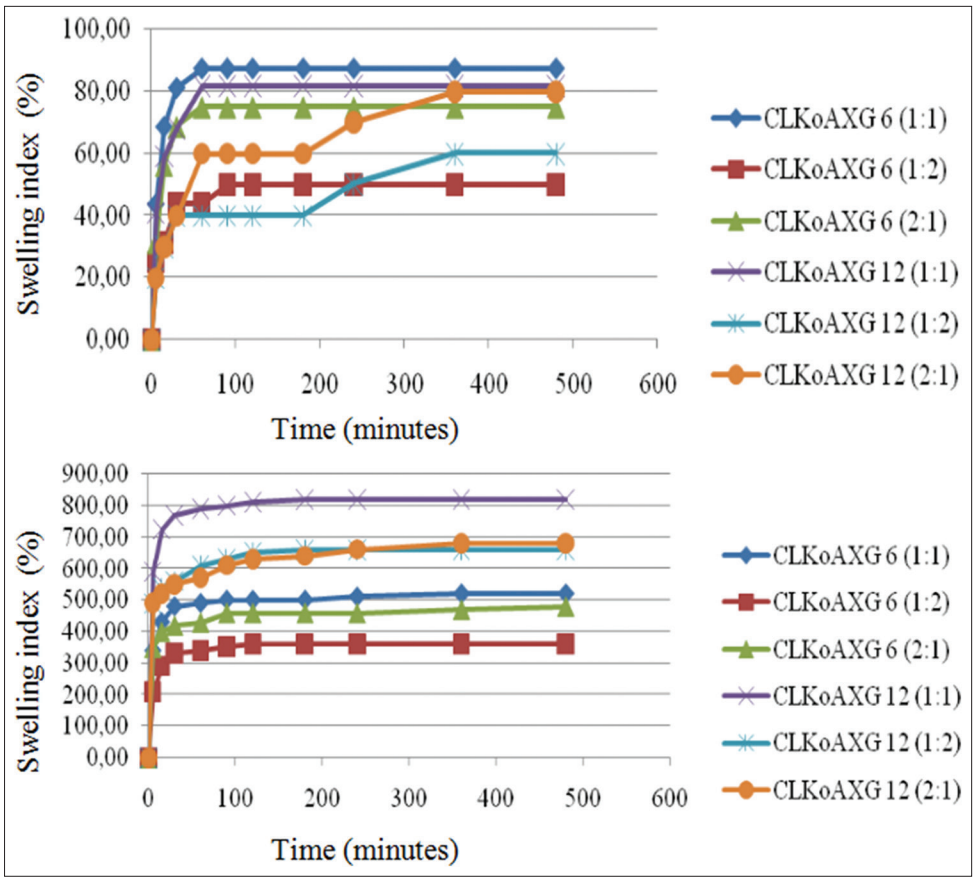

Fig. 8: Swelling index of CL Co-A-XG

Table 6: Flowability properties of Co CLA-XG

Excipient	Flow rate (g/s)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
Co CLA6:XG (1:1)	4.08	0.80	16.67	1.20
Co CLA6:XG (1:2)	4.05	0.82	18.33	1.22
Co CLA6:XG (2:1)	3.97	0.80	18.03	1.22
Co CLA12:XG (1:1)	4.17	0.80	18.03	1.22
Co CLA12:XG (1:2)	4.00	0.82	18.33	1.22
Co CLA12:XG (2:1)	4.14	0.82	18.33	1.22

Table 7: Degree of substitution of CL Co-A_XG

Excipient	% P	DS
CLCoAXG 6 (1:1)	1.56±0.039	0.08±0.002
CLCoAXG 6 (1:2)	1.62±0.03	0.08±0.002
CLCoAXG 6 (2:1)	1.66±0.041	0.08±0.002
CLCoAXG 12 (1:1)	2.18±0.123	0.11±0.007
CLCoAXG 12 (1:2)	2.27±0.093	0.12±0.006
CLCoAXG 12 (2:1)	2.33±0.038	0.12±0.002

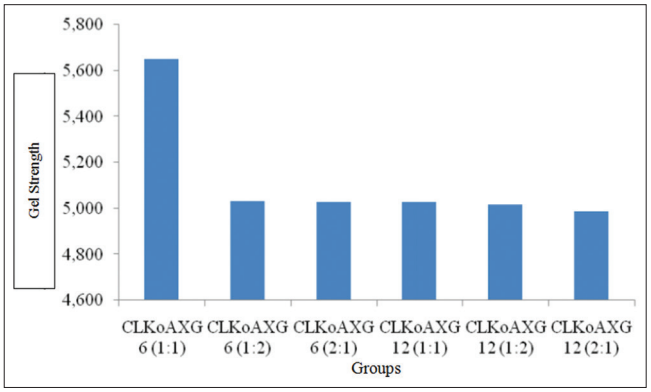

Fig. 9: Gel Strength of CL Co-A-XG

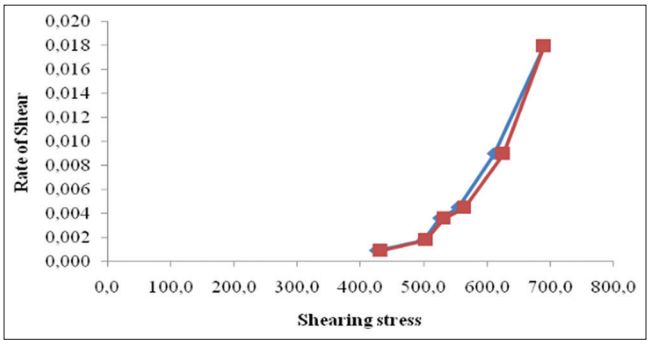

Fig. 10: Rheology of CL Co-A-XG

CL6 Co A-XG (1:1) has the highest gel strength compared with other excipients (Fig. 9).

Based on its swelling index and gel strength, CL6-Co-A-XG (1:1) is a prospective excipient for use in slow-release preparations. This is supported by the fact that a suspension of CL-Co-A-XG in distilled water exhibited pseudoplastic thixotropic flow properties; thus, CL6-Co-A-XG (1:1) is a suitable excipient for slow-release dosage forms. Rheology of CL Co A-XG is presented in Fig. 10.

CONCLUSION

Based on its swelling index and gel strength, the CL6-Co-A-XG excipient was superior to Co-CLA6-XG for use in slow-release dosage forms. Among the entire collections of crosslinked coprocessed excipients

Table 8: pH of the dispersion

Sample (1%)	pH
CoAXG (1:1)	6.21±0.02
CoAXG (1:2)	6.19±0.07
CoAXG (2:1)	6.31±0.12
CLCoAXG 6 (1:1)	6.39±0.05
CLCoAXG 6 (1:2)	6.39±0.03
CLCoAXG 6 (2:1)	6.41±0.03
CLCoAXG 12 (1:1)	6.38±0.03
CLCoAXG 12 (1:2)	6.43±0.03
CLCoAXG 12 (2:1)	6.43±0.03

produced and tested, CL6 Co-A-XG (1:1) is the most suitable excipient for this purpose.

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CONFLICTS OF INTEREST

All authors have none to declare

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