WALAILAK JOURNAL
http://wjst.wu.ac.th Health Sciences

Development of Tamarind Seed Gum as Dry Binder in Formulation of Diclofenac Sodium Tablets

Kampanart HUANBUTTA[1,*], Tanikan SANGMIN[1,2] and Wancheng SITTIKIJYOTHIN[3]

[1]*Faculty of Pharmaceutical Sciences, Burapha University, Chonburi 20131, Thailand*
[2]*Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakorn Pathom 73000, Thailand*
[3]*Department of Chemical Engineering, Faculty of Engineering, Burapha University, Chonburi 20131, Thailand*

([*]Corresponding author's e-mail: kampanart@go.buu.ac.th)

Received: 28 September 2015, Revised: 6 November 2015, Accepted: 16 December 2015

Abstract

Tamarind (*Tamarindus indica Linn*.) is tropical plant, which is generally found and planted in Thailand. The application of tamarind seed gum can raise the value of tamarind and minimize industrial waste. Tamarind seed gum powder offers a high viscosity solution. Therefore, researchers are interested in developing tamarind seed gum as a binder in the formulation of diclofenac sodium tablet, prepared by the dry granulation method. Physicochemical characterization results show that the carboxymethylation process can add a carboxymethyl group to the chemical structure of crude gum. The success of chemical modification was confirmed by Fourier transformed infrared (FTIR) result. A powder X-ray diffractogram expressed that the gum in, the crude and modified forms, were in amorphous form. The melting point, solubility properties, and viscosity of the polymer solution increased after the chemical structure modification. However, the disintegration time of the tablet made of the modified gum was too long. Consequently, an appropriate amount of gum powder (40 - 70 mg/tablet) was optimized. The result found that hardness of the tablet did not depend on the gum amount. Increasing the portion of the gum in the formulation retarded disintegration time and drug dissolution. The proper amount of the modified gum in the formulation was 60 mg (7.61 % w/w). The hardness of the tablet was 61 N, with 1.99 % of tablet friability. Disintegration time was less than 15 min, and drug release reached 76 % in 20 min.

Keywords: Tamarind seed gum, dry binder, tablets, diclofenac sodium, carboxy-methylation

Introduction

Dry granulation is a simple and low cost method used to fabricate pharmaceutical tablets, which was once extremely common and is becoming more popular again because of its simplicity, time, and cost efficiency. Therefore, the solid oral dosage formulation has led to a shift from the traditional wet granulation to the dry granulation manufacturing process [1]. The dry granulation method is suitable for medium and high dose drug formulation, and is particularly applicable for active pharmaceutical ingredients (APIs) which are heat and moisture sensitive. To prepare dry granules, the slugging process and roller compaction are common processing methods. In this method, excipients play a crucial role in the development of robust formulations, because they can influence the degree of granule compression and binding. Consequently, a dry binder is necessary to prepare dry granules. The required properties for the dry binder are good powder flowability, compatibility, stability in air, moisture and heat, and compatibility with APIs.

Gums are polysaccharides, with various molecular weights, and offer viscous or gel solutions after dissolving or dispersing in water [2]. Gum has been widely used in pharmaceutical applications, including tablet binders, drug release controllers, gelling agents, cream thickeners, stabilizers, emulsifiers, coating agents, and packaging films [2]. Gums can be obtained from several natural recourses, such as the secretions of plants, marine algae, or bacterial exopolysaccharide [3]. Plant seeds are also a common source of gums, and different seed gums have been studied and applied for diverse purposes [4-6]. Tamarind (*Tamarindus indica*) is in family of *Fabaceae* [7,8]. The specie is native to the Indian subcontinent and adjacent regions of Southeast Asia. The seed of tamarind contains high amounts of endosperm, which is source of gum. In general, tamarind seed has been underused; therefore, utilization of these plants can be value added, and also reduce the amount of waste. However, the application of seed gum is limited because of its low water solubility. Consequently, many attempts have been performed to ameliorate solubility property. Carboxymethylation of gum is reported to improve cold water solubility, improve viscosity, and increase swelling rate, as compared to native gum [9]. Consequently, chemical modification of gum could possibly develop crude tamarind seed gum as binding agent in the manufacturing process of tablets, by the dry granulation technique. The aim of this study is to develop tamarind seed gum as a dry binder in the formulation of diclofenac sodium tablets.

Materials and methods

Tamarind seed was collected from Uthaitanee province, Thailand. Diclofenac sodium was obtained from Amoli Organics Ltd. (Batch No. DS/0501/588A). Lactose was purchased from Ajax Finechem Pty Ltd. Microcrystalline Cellulose (Avicel PH-102) and magnesium stearate were received from P.C. Drug, Ph, Thailand. All other chemicals were of reagent grade.

Preparation of seed kernel powder (crude gum)

Tamarind seed was dried in a hot oven at 100 °C for 30 min, and the seed coat manually removed. Then, it was milled and ground through a 355 μm mesh sieve.

Carboxymethylation

Carboxymethylated gum was prepared following a previous modification [10]. As shown in **Table 1**, the condition of reaction used was at 70 °C for 1 h of reaction time. Methanol was used as a solvent medium. Different mole ratios of monochloroacetic acid to sodium hydroxide (n_{NaOH}/n_{MCA}) varied from 1 to 2.78, while 0.05 mole of seed gum was fixed.

Table 1 Proportion of reagents used in carboxymethylation process to modify seed gums.

Samples	Proportion of reagents used in carboxymethylation process (Mole)		
	Sodium hydroxide	Chloroacetic acid	Crude gum
Crude gum	-	-	-
Modified condition 1 (mod-1)	0.09	0.09	0.05
Modified condition 2 (mod-2)	0.25	0.09	0.05

Physicochemical property evaluation of gum

1. Degree of substitution (DS) determination

The degree of substitution (DS) of carboxymethylated gum was determined by using back titration. The mass fraction of acetyl group (W_A) was calculated as:

$$W_A = \frac{C_{NaOH} \cdot V_{NaOH} - C_{HCl} V_{HCl}}{m} \quad (1)$$

$$DS = \frac{162W_A}{58(100-W_A)} \quad (2)$$

where C_{NaOH} and C_{HCl} are the molar concentrations of standard NaOH and HCl solutions, respectively, V_{NaOH} and V_{HCl} are the volumes of NaOH and HCl used for the titration of the excess of NaOH, respectively, and m is the weight of gum taken. The number, 162 (g/mol), is the molar mass of the anhydroglucose unit.

2. Fourier transformed infrared (FTIR) spectroscopy

FTIR spectra of all crude and modified gums were obtained by the KBr method, using an FTIR spectrophotometer (Magna-IR system 750, Nicolet Biomedical Inc., USA) to investigate the effect of the carboxymethylation process on gum.

3. Appearance and particle morphology

The surface morphology of crude and modified gums was observed under a scanning electron microscope (SEM) (MX2000, Camscan, UK). Sample powders for SEM analyses were sprinkled onto a stub and sputter coated with gold to increase their conductance.

4. Viscosity measurements

Viscosities (η) were measured using a BROOKFIELD DV-II+ viscometer (USA). A sample solution was prepared by dissolving 1 g of gum in 100 mL of distilled water for 1 h. The rotation speed was kept constant during the experiment, at 75 rpm, and the temperature was controlled at 25±0.5 °C. Each set of the experiment was repeated 3 times to ensure reproducibility.

5. Moisture content

The moisture contents of crude and modified gums were examined after the preparation process. The gum powder was weighted for 2 g (initial weight) in a pre-dried and weighted evaporative dish. Then the gum was dried at 105 °C for 4 h. After that, the dried gum was weighted (dry weight), and then % moisture was calculated as:

$$\%\text{moisture} = \frac{initial\ weight - dry\ weight \times 100}{initial\ weight} \quad (3)$$

6. Carr's compressibility index

Carr's compressibility index was monitored to determine the flowability of the gum powder. To reveal Carr's compressibility, bulk and tapped densities were determined using the methods outlined in the USP [11]. The test started by pouring gum powder into 100 mL-cylinder until it reached the 50 mL-scale bar. Then, the opening of the cylinder was covered by paraffin film. The bulk volume was measured after manually tapping the cylinder 2 times on a flat table top surface. The tapped volume was measured by the tap density tester (TD1025, Labindia Analytical Instruments Pvt. Ltd., India) after tapping in increments of 500, 750, and 1250 taps, with 250 drops per minute. The %compressibility was calculated as:

$$\%\text{compressibility} = \frac{(\text{tapped density} - \text{bulk density}) \times 100}{\text{tapped density}} \quad (4)$$

7. Cold water solubility

The solubility of the gum in cold water was evaluated, which was adapted from the method of Chen and Jane [12]. The gum was weighted for 0.5 g, then dissolved in 100 mL of distilled water. The mixture of gum and water was agitated for 15 min, then centrifuged at 6000 rpm for 15 min. A supernate of the sample was collected, then dried at 105 °C for 4 h on a pre-weighted aluminum plate. The percentage of cold water solubility (%CWS) was calculated as:

$$\%CWS = \frac{(wieght\ of\ aluminium\ plate\ with\ sample\ after\ drying - weight\ of\ aluminium\ plate) \times 100}{weight\ of\ sample\ before\ drying} \quad (5)$$

8. Powder X-ray diffraction (PXRD)

PXRD patterns of crude and modified gums were analyzed using a powder X-ray diffractometer (D8, Bruker, Germany) under the following conditions: graphite monochromatized Cu Kα radiation; voltage 45 kV; electric current 40 mA; slit: DS1°, SS1°, RS, 0.15 nm; scanning ratio: 2θ = 5° min^{-1}.

9. Thermal analysis

Differential scanning calorimetry (DSC) thermograms of crude and modified gums were determined by a differential scanning calorimeter (Sapphire, PerkinElmer, USA) using indium as a standard. Each sample, 2 - 3 mg, was accurately weighed into a close aluminum solid pan. The scanning rate was run at 10 °C per min from 20 - 300 °C under nitrogen purge.

10. Tablet preparation

The tablets, containing a model drug, diclofenac sodium, were prepared by the dry granulation method. Various amounts of pharmaceutical excipients were incorporated in the tablets (**Table 2**). The dry slugs were compressed using a single-punch tableting machine (Yeo Heng, Thailand). Then, the dry granules were obtained from screening using a 10-mesh sieve. The pre-weighed granules (788 mg/tablet) were compressed by a manual hydraulic press (GS15011, Specac Ltd., UK).

Table 2 Formulation of diclofenac sodium loaded tablet prepared by different gum types.

Formulation	Amount of model drug and excipients (mg)							
	crude gum	mod-1 gum	mod-2 gum	Lactose	Microcrystalline cellulose	Crospovidone	Magnesium strearrate	Diclofenac sodium
F1	-	-	-	535	200	25	3	25
F2	60	-	-	475	200	25	3	25
F3	-	60	-	475	200	25	3	25
F4	-	-	60	475	200	25	3	25
F5	-	-	40	495	200	25	3	25
F6	-	-	50	485	200	25	3	25
F7	-	-	70	465	200	25	3	25

11. Physical properties of tablet

Profiles of the tablets, including weight, thickness, diameter, and hardness, were monitored by a Tablet Hardness Tester (TBH 325TD, Erweka GmbH, Germany). The friability of the prepared tablets was determined with an Erweka friabilator (TAR, Erweka GmbH, Germany). Ten tablets were analyzed at 25 rpm for 4 min. The means and standard deviations after triplicate determinations were calculated.

12. Disintegration time

The disintegration time of the prepared tablets was monitored following the USP30 NF25 standard by using a disintegration tester (ZT 322, Erweka, Germany).

13. *In-vitro* drug release profiles

Diclofenac sodium released from the gum tablets was investigated using USP dissolution apparatus II, equipped with a paddle, which were operated at a speed of 50 rpm. Nine hundreds milliliters of pH 6.8 phosphate buffer, as the dissolution media, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated to 37±0.5 °C. The samples (5 mL) were taken at various time intervals, i.e., 10, 20, 30, 40, 50, 60, and 120 min. After that, 5 mL of the pH 6.8 phosphate buffer was

replced back to keep the sink condition. Then, the amount of diclofenac sodium released was measured by UV-VIS spectrophotometer (model 2J1-0004, Hitachi, Japan) at a maximum wavelength of 276 nm. Each *in-vitro* release study was performed in triplicate.

Results and discussion

Physicochemical properties of gum

1. Degree of substitution (DS)

As illustrated in **Table 3**, mod-2 gum provided a higher DS than that of mod-1. This is because the amount of used sodium hydroxide was greater. Therefore, the hydroxyl group of gum was alkalized more than the modified condition-1, as described by chemical reaction 1 and 2. However, if sodium hydroxide is over utilized, it will interact with sodium chloroacetate (side reaction, chemical reaction 3), which reduces the carboxymethyl reaction. This result is in agreement with the previous study by Gong and colleagues [13], which found that the amount of sodium hydroxide noticeably influenced the reaction rate and the DS of carboxymethyl guar gum. A greater portion of sodium hydroxide offered an increment value of the DS.

Alkalization: $\text{Gum-OH} + \text{NaOH} \rightarrow \text{Gum-ONa} + H_2O$ (1)

Carboxymethylation: $\text{Gum-ONa} + ClCH_2COONa \rightarrow \text{Gum-}OCH_2COONa + NaCl$ (2)

Side reaction: $NaOH + ClCH_2COONa \rightarrow HOCH_2COONa + NaCl$ (3)

Table 3 Physicochemical properties of crude and modified gum.

	% DS*	Viscosity (cP)	%Moisture	%Compressibility	%CWS**
Crude gum	-	9.60	6.94	42.52	7.89
mod-1 gum	18.50	15.50	8.74	24.88	3.37
mod-2 gum	19.16	45.30	8.80	12.36	12.49

*DS stand for degree of substitution
**CWS stand for cold water solubility

2. FTIR spectroscopy

The FITR spectra of crude, mod-1, and mod-2 gum are presented in **Figure 1**. All gums showed characteristic absorption bands associated with the stretching vibration of -OH in the 3500 - 3300 cm^{-1} region, -CH in the 3000 - 2800 cm^{-1} region, and around 1400 cm^{-1} (bending vibration). The absorption band appearing around 1748 cm^{-1} corresponded to the OH bond of water molecules (moisture) and the bending vibration of -OH at 1654 cm^{-1} [3,14]. The IR spectrum of carboxymethylated gums show the higher wavelength shifting of the absorption band from the crude gums located at 3370 cm^{-1} to 3340 cm^{-1} (mod-1 gum) and 3429 cm^{-1} (mod-2 gum), due to OH stretching, indicating that some OH groups were carboxymethylated [15]. In addition, 3 new peaks emerged in the spectrum of carboxymethylation gum, due to carboxymethyl moiety. A peak around 1648 cm^{-1} was due to asymmetric stretching vibration, and peaks around 1542 and 1398 cm^{-1} for mod-1 gum and 1421 and 1395 cm^{-1} for mod-2 gum were concerned with the symmetrical stretching vibration of carboxylate ions in the modified gums [16].

3. Appearance and particle morphology

The physical appearance of crude gum was in form of aggregated white powder. Mod-1 gum was fine white powder, while the appearance of mod-2 gum was fine red-brown powder. **Figure 2** depicts SEM images of the crude and modified gums. As shown in **Figures 2B** and **2C**, the SEM images of crude and carboxymethylated gum were in an irregular shape, and their sizes were around 10 - 40 μm, while crude gum (**Figure 2A**) tended to aggregate more than those of carboxymethylated gum.

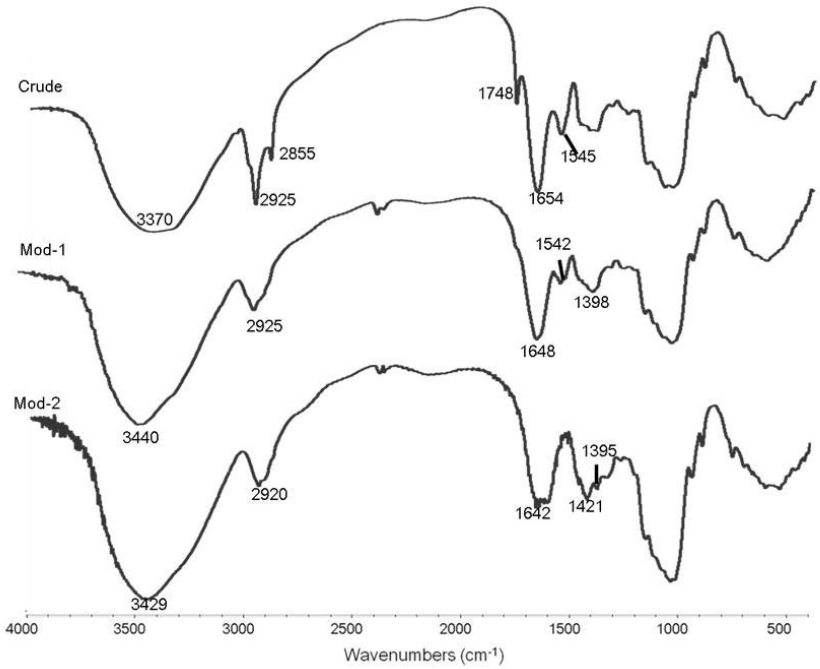

Figure 1 FTIR spectrum of crude, mod-1, and mod-2 gum.

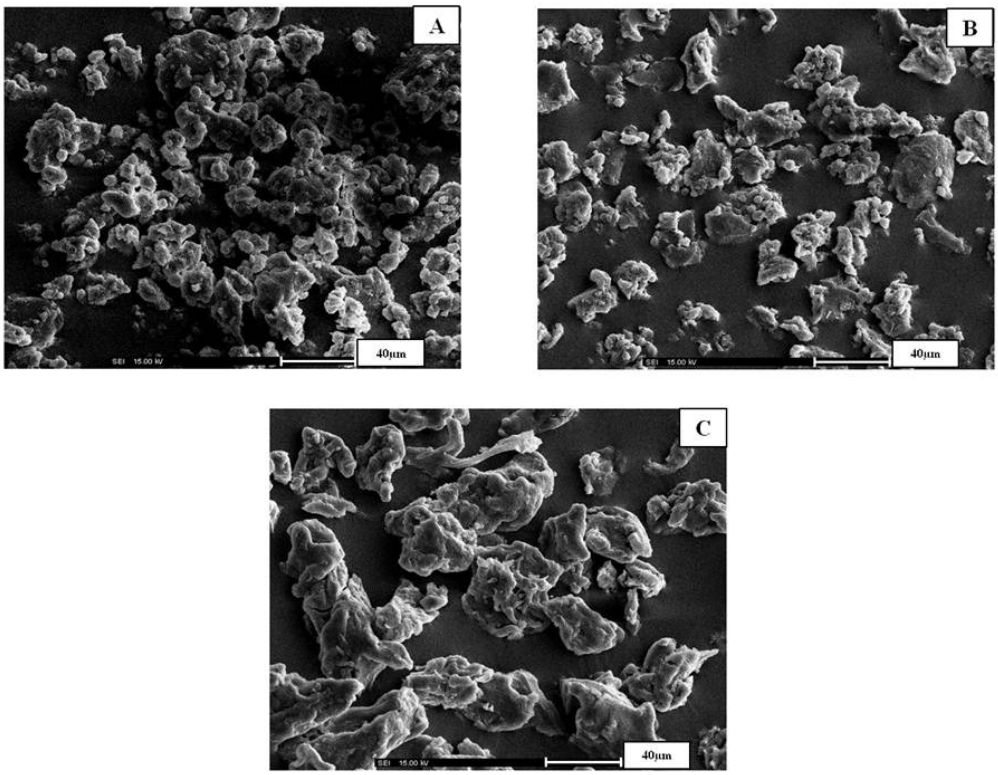

Figure 2 SEM images of (A) crude, (B) mod-1, and (C) mod-2 gum.

4. Viscosity and moisture content

Table 3 presents the viscosity property and %moisture of crude and modified gum solutions. The results found that the viscosity and %moisture of the carboxymethylated gums were higher than that of crude gum. Also, viscosity from mod-2 gum solution was greater than that of mod-1 gum solution. This is because the carboxymethylation process enhances the solubility of gum; therefore, the polymer chain of gum could expand better, and water molecules could penetrate into the polymer structure, leading to a viscous solution. Moreover, mod-2 gum has a higher DS compared to mod-1 gum, resulting in higher hydrophilicity and viscosity [3].

5. Carr's compressibility index

Carr's compressibility index result of the crude and modified gum is listed in **Table 3**. A low value of Carr's compressibility index refers to good flowability, according to the Carr's compressibility index table [17]. The results expressed that the flowability properties of mod-2, mod-1, and crude gum were in the level of good flow, poor flow, and extremely poor flow, respectively. These indicate that the carboxymethylation process of gum improves powder flowability. This result is supported by the morphology result from SEM, which found that carboxymethylation altered the characteristics of crude gum, from an aggregated form to a larger single particle, resulting in better flowability.

6. Cold water solubility

The percentages of cold water solubility (%CWS) of crude, mod-1, and mod-2 gum are exhibited in **Table 3**. Mod-2 gum could dissolve in purified water better than crude and mod-1 gum, respectively. This might have been because of the modified carboxymethyl group raised hydrophilicity of the gum structure [18]. However, the solubility of mod-1 gum was less than that of the crude gum. As reported in previous work, this might be due to crude gum containing soluble impurities, such as protein and other polysaccharides [19].

7. PXRD pattern

Figure 3 illustrates the PXRD patterns of crude, mod-1, and mod-2 gum. The PXRD pattern of all samples exhibited typical halo patterns of amorphous structures, and demonstrated broad peaks around 15°. This indicated that the crude, mod-1, and mod-2 gum were in amorphous states, and the carboxymethylation process did not alter the crystal structure of gum.

8. Thermal analysis

The thermal behavior of crude, mod-1, and mod-2 gum was investigated by DSC technique, as presented in **Figure 4**. The DSC thermograms of crude, mod-1, and mod-2 exhibited broad endothermic peaks at 82.4, 90.1, and 104.3 °C, respectively. The shift in the endothermic peak indicated that modification of gum has taken place on carboxymethylation [20].

9. Tablet preparation

The tablets were fabricated using gum as a dry binder, following **Table 2**. The average thickness and diameter of all prepared tablets were 4.71±0.11 mm and 9.11±0.02 mm, respectively. A profile of the tablets (F1-F7), including hardness and friability, are expressed in **Figure 5**. The effects of gum type on tablet property were compared in F1 to F4. The tablet made of crude gum (F2) offered low hardness with a high percentage of friability. The optimum formulation was F4 prepared form mod-2 gum (60 mg). This indicated that the binding property of the gum was improved after the carboxymethylation process. Furthermore, the consequences from amounts of mod-2 gum were equated in F4 to F7 (40 - 70 mg). The result exhibited that the proper amount of mod-2 was 60 mg (F4), which can provide appropriate hardness with low friability.

10. Disintegration time

The results for disintegration time (**Figure 6**) show that the prepared tablets containing mod-2 gum (F4-F7) as a dry binder had a disintegration time of between 14 and 16 min, which were longer than no

binder, crude, and mod-1 gum tablets (F1-F3). This can be explained by a previous study [21] which reported that high DS gum swells better than low DS gum, resulting in retardation of disintegration time from swelling gum gel. Furthermore, the portion of mod-2 gum (F4-F7) rarely impinged on disintegration time.

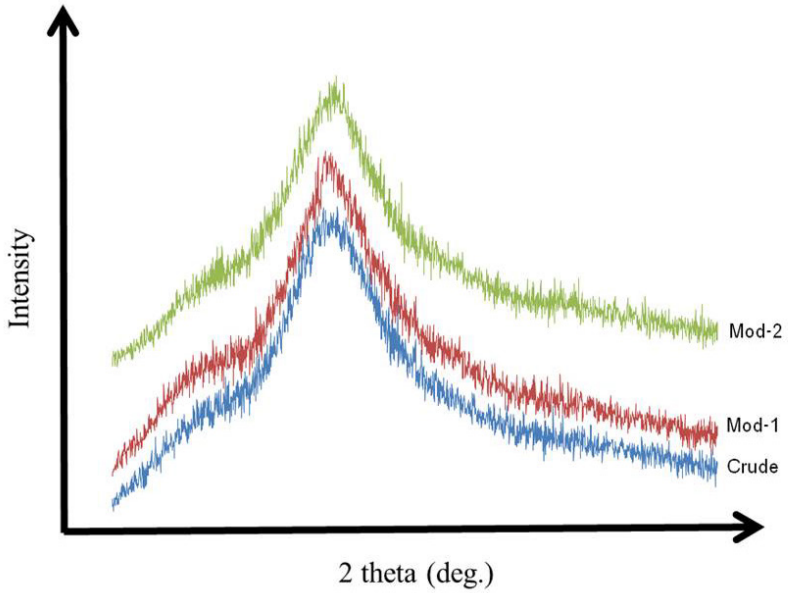

Figure 3 PXRD patterns of crude, mod-1, and mod-2 gum.

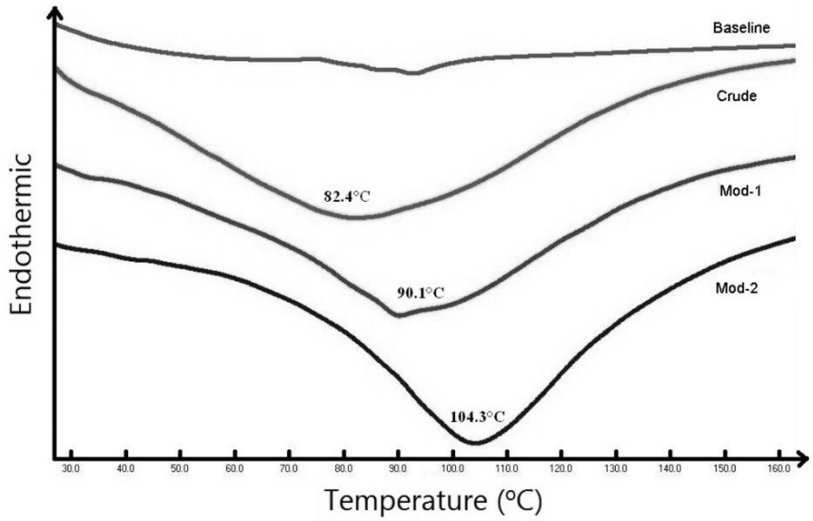

Figure 4 DSC thermograms of crude, mod-1, and mod-2 gum.

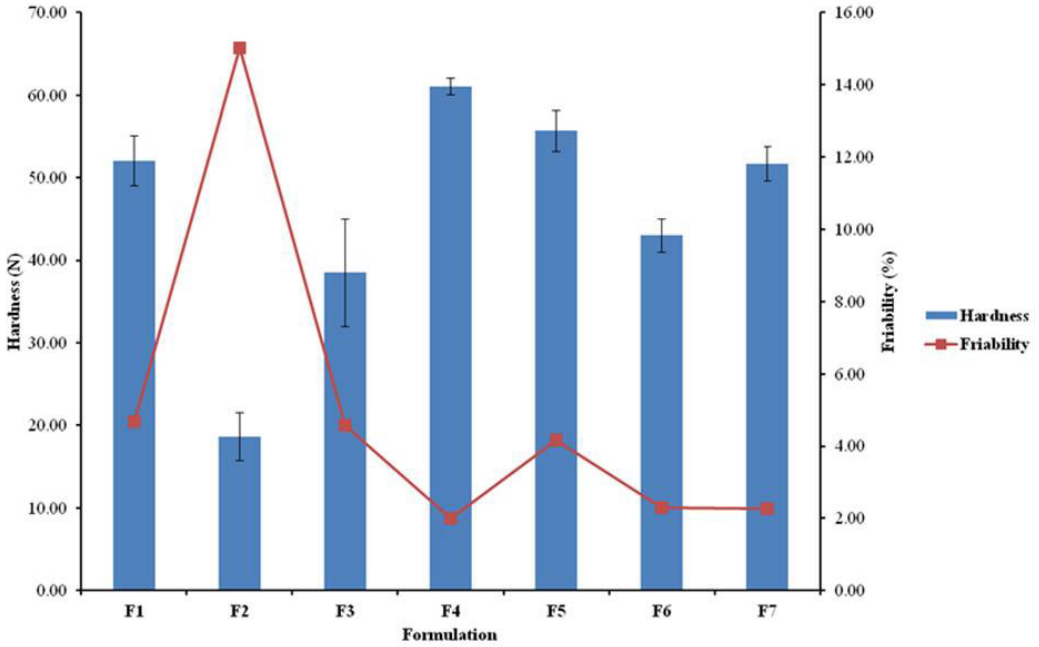

Figure 5 Hardness and friability (%) profiles of the prepared tablets.

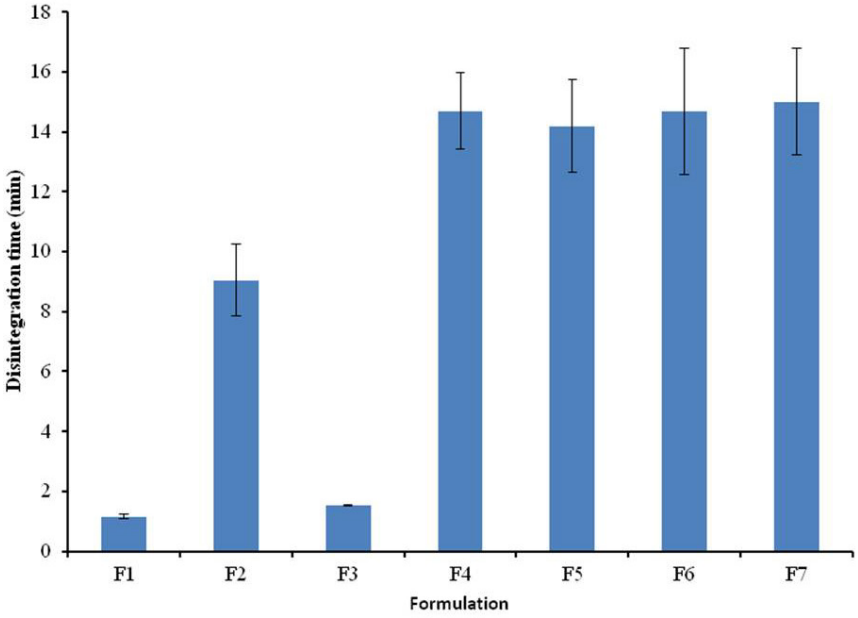

Figure 6 Disintegration time of the prepared tablets.

11. *In-vitro* drug release profiles

The drug release data for diclofenac sodium from the gum tablets are presented in **Figure 7**. The cumulative drug release from all formulations reached 100 % within 120 min. As presented in **Figure 7a**, drug release from the mod-2 gum tablet (F4) was slower than for F1, F2, and F3 formulations, referring to without gum, crude gum, and mod-1 gum, respectively. In addition, **Figure 7b** shows that the amount of mod-2 gum had an effect on the release rate. The active drug rapidly released in the formulation of low mod-2 gum portion (F5). Greater mod-2 gum incorporation (F4, F6 and F7) translated to delayed active release. Such an increase in concentration of mod-2 gum is expected to lead to improved wettability, enhanced water uptake, and greater swelling of the hydrophilic matrix and, hence, gel barrier formation, which is consistent with the observed reduction in drug release rates from formulations with greater amounts of hydrophilic polymers [22].

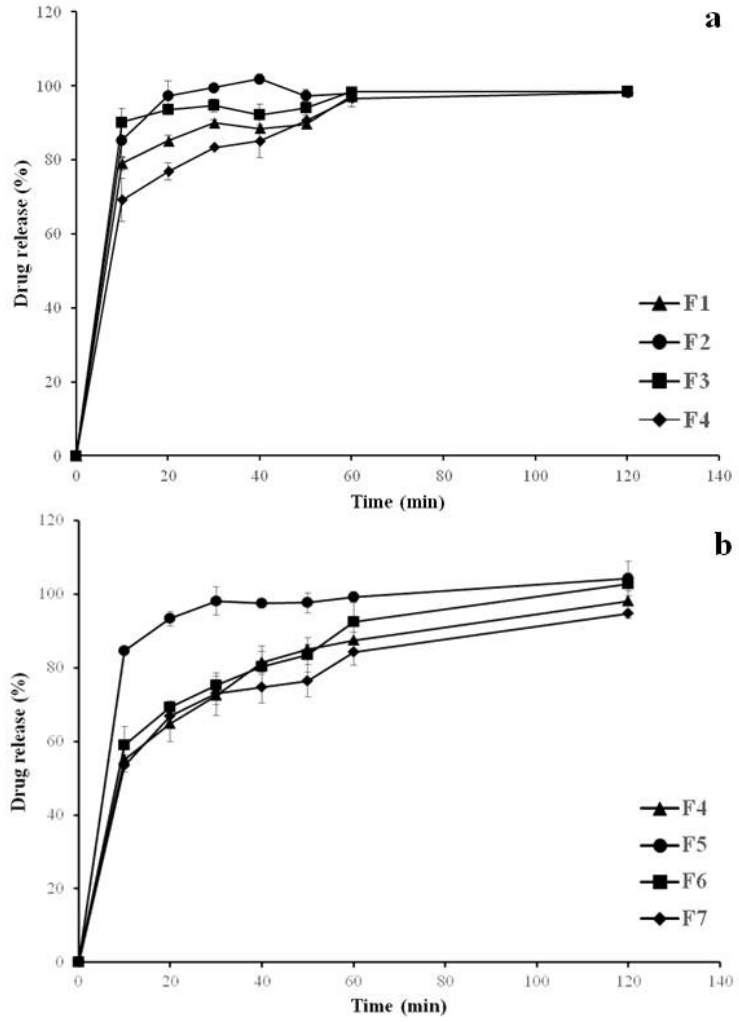

Figure 7 Drug release profiles of the gum tablets from different formulations.

Conclusions

Tamarind gum was modified by carboxymethylation, which was confirmed by FTIR spectroscopy and DSC. The characterization of carboxymethylation gum revealed an increase in water solubility and flowability properties. Further, mod-2 gum could work well as a dry binder in tablet formulation, by increasing hardness and dropping tablet friability. The tablet made from mod-2 gum minimally retarded the active drug release by its swelling property. It can be concluded on the basis of the present study that mod-2 gum is a promising biopolymer, which should be developed for further applications as a pharmaceutical dry binder in tablet formulation.

Acknowledgements

This work was financially supported by the Research Grant of Burapha University through National Research Council of Thailand (Grant no. 3/2559). The assistance for laboratory work by Kanoknat Nakhonthai, Benjawan Ninwalaikul and Suebpong Eampakun is greatly appreciated

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