Proceeding the Regional Conference on Chemical Engineering 2014
Yogyakarta, December 2-3, 2014

ISBN: 978-602-71398-0-0

Dissolution Rates of Mangosteen (*Garcinia mangostana L.*) Pericarps Extract Granules in Synthetic Human Gastrointestinal Fluid

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Abstract: Mangosteen (*Garcinia mangostana* L.) pericarps contain prenylated xanthone derivates, which exhibit some pharmacological activities, such as antiinflammatory, antihistamine, antibacterial, antivirus, antifungal, antioxidant, and antiulcerogenic. The purpose of this research was to study the dissolution rates of mangosteen pericarp extract granules in synthetic human gastrointestinal fluid at various pH and temperatures, which include experimental and modeling works. The granules were prepared by wet granulation of methanol extracts of mangosteen pericarps with addition of 25% w/v Arabic gum and 5% w/v maltodextrin. Dissolution rate study was performed by dissolving 0.5 g granules in 500 mL of 0.02M phosphate buffer solution with constant agitation at various pH (5.5, 6, 6.5, 7 and 7.5) and temperatures (30, 37 and 40^{o}C) for two hours. Every 20 minutes, a liquid sample was withdrawn from the system for xanthone analysis. The results showed that mangosteen pericarps granules dissolution rates increased with pH under acidic condition. At pH 7.5 (basic condition), the dissolution rate was faster than that at pH 7. As expected, the dissolution rates were higher at higher temperatures. The semi empirical Korsmeyer-Peppas model showed its superiority over other models to predict the mangosteen pericarps granules dissolution rates. However, the mass transfer model proposed in this work also agreed well with the experimental data with error percentages closely similar to that of Korsmeyer-Peppas model.

Key Words: *mangosteen pericarps; xanthones; granules; dissolution rates; models*

1 Introduction

Mangosteen (*Garcinia mangostana* L.) is a sessional fruit plant originated from tropical forests in the Southeast Asia regions. Mangosteen is well known as “Queen of Fruits” due to its yummy soft pulp and exotic taste, which a combination of sweet, sour and a bit of astringent. This fruit has even better reputations as a healthy food in the other areas, particulary Taiwan, Japan, Australia and Europe (Mohamad *et al*., 2006). Instead of the fruit pulp, mangosteen pericarp attracts more attention from researches around the world with regard to its pharmacological activities. Jung *et al*. (2006) reported that xanthone prenylated derivates contained in mangosteen pericarp exhibit antifungal, antimicrobial, antioxidant, and cytotoxic activities. Later, Nainwal *et al*. (2010) reported that mangosteen pericrap extracts display antiulcerogenic effect by which reducing the volume of gastric acid and total acidity, and finally raised gastric pH appreciably. Therefore, mangosteen pericarps have a great potential to be developed as drugs and supplements in the pharmaceutical technology.

Unfortunately, poor aqueous solubility and low oral bioavailability of xanthones in the mangosteen pericrap extracts have hindered their therapeutic applications (Aisha *et al*., 2012). A number of attempts have been done in order to improve the aqueous solubility

ISBN: 978-602-71398-0-0

and thereby the dissolution rate and oral bioavailability of poorly soluble drugs. Those attempts included particle size reduction, salt formation, solubilisation with surfactants, and solid dispersions (SDs). Solid dispersion is defined as the dispersion of a drug in water-soluble carriers in the solid state (Kanaujia *et al*., 2011; Manju dan Sreenivasan (2011).

Granulation is a method to convert fine particles into physically stronger and larger agglomerates called as granules with improved appearances, good flow property, better compression characteristics, mixing uniformity and reduce dustiness (Gabriel, 2005; Agrawal *et al*., 2011). Amongst the granulation processes, wet granulation is the most widely used granulation process in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, followed by drying of the mixture slightly above the glass transition temperature of the binder to forms granules, which enhanced particle size, flowing, and compression properties. In the pharmaceutical industry, good wettability between liquid binder and powder particles in the granules formulation are relied upon to produce strong granules with a narrow size distribution (Nguyen *et al*., 2010; Agrawal *et al*., 2011). Therefore, application of wet granulation to produce xanthones rich mangosteen pericarps extract granules in granules form pharmaceutical sector will be practically and economically advantageous.

Dissolution test is an in vitro analytical test used for testing of drug release characteristics of pharmaceutical product in humans. The rationale of conducting these tests is that the active pharmaceutical ingredient in the product must be controllable released from the product and should generally be dissolved in the fluids of the gastrointestinal tract at a desirable duration. This is because, in the solution form, the active pharmaceutical ingredient facilitates the absorption of the drug from the gastrointestinal tract into the blood circulation to reach its desired target to exert its effect (Qureeshi, 2007). A number of dissolution rate models to predict the dissolution profile of drug materials had been reported in the literature (Higuchi, 1963; Korsmeyer *et al*., 1983). Although some empirical models were reported to be satisfactorily predict the dissolution rate of a certain drug material, their extensive used remains questionable. One of the disadvantages of these empirical models is that they cannot be generally used for dissolution rate predictions. As far as literature studies have been conducted, no studies on mangosteen pericarp extract granules dissolution rate has been reported. The purposes of this research were to study the dissolution rates of mangosteen pericarp extract granules in synthetic human gastrointestinal fluid at various pH and temperature, which include experimental and modeling works. A theoretical model based on mass transfer and equilibrium mechanisms is proposed in this work. Table 1 shows the dissolution models used to predict the dissolution rates of mangosteen pericarp extract granules in this work.

ISBN: 978-602-71398-0-0

Table 1 Models Used for the Prediction of Mangosteen Pericarps Extract Granules Dissolution

Models	Equation	
Higuchi (Higuchi, 1963)	$Q_t = K_H t^{1/2}$	(1)
Korsmeyer-Peppas (Korsmeyer *et al*., 1983)	$\frac{C_t}{C_\infty} = K_k t^n$	(2)
Weibull (Langenbucher, 1972)	$\log\left[-\ln\left(1-\frac{Q_t}{Q_\infty}\right)\right] = b\log(t-T_i) - \log a$	(3)
Proposed in this work	$\frac{C_t}{C_\infty} = \left(1 - e^{-Kp\,\varepsilon\,t}\right)$	(4)
	$Q_t = C_t \times V$	(5)

where:

a = scale parameter (-)

b = shape parameter (-)

C_t = phenolic compound concentration at time t (mg/mL)

C_∞ = phenolic compound concentration of saturated solution (mg/mL)

Ko, K_H, K_k, K_p = dissolution rates constants (depending on the model)

n = release exponent (indicative of extract granules release mechanism)

Qt = amount of phenolic compound release at time t (mg)

$Q\infty$ = amount of phenolic compound in the saturated solution (mg)

t = time (min)

Ti = location parameter (-)

V = volume of solution (mL)

ε = granule porosity (-)

2 Methodology

Materials

Fresly harvested mangosteen pericarps were collected from a traditional plantation in hilly areas of Gunungpati-Semarang, Indonesia. All chemicals and reagents used in this work were of analytical grade (purity ≥ 99.5%) and purchased from an authorised distributor in Semarang.

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Extraction of mangosteen pericarps

Mangosteen pericarps were washed with clean water, cut into small size using a sharp knife, and oven dried at 45^{o}C for 48 hours. The dried mangosteen pericarps was then ground into powders using hammer mill. Extractions were performed by maceration of 50 grams dried mangosteen pericarps powders in 250 mL methanol for 48 hours at room temperature. Later, all extracts were combined, filtered through Whatman No. 1 paper, each of the filtrates was concentrated using vacuum rotary evaporator at 45^{o}C, and oven dried at 45^{o}C to dryness (Aisha *et al*., 2013).

Granulation of mangosteen pericarp extracts

The mangosteen pericarps extract granules was prepared according to the method previously used by Silva *et al*., (2013), which employed predetermined 25% w/v gum arabic and 5% w/v maltodextrin as a binder and filler, respectivley. Mangosteen pericarps extract was added to gum arabic and maltodextrin solution, and mixed well in a wet granulator for 3 hours to form granules. The granules obtained were then oven dried at 45^{o}C for 24 hours, passed through a 40 mesh sieve and stored in an air tight container at 4^{o}C prior to dissolution test study.

Dissolution test of mangosteen pericarp extracts granules

The dissolution test of the mangosteen pericaprs granules was evaluated as described previously by Manju and Sreenivasan (2011) with slight modification. Briefly, an excess amount of granule samples (containing 500 mg phenolic compound) was added to 500 mL of 0.02M phosphate-buffered saline (PBS) as the synthetic gastrointestinal fluid at studied pH (5.5-7.5) and temperatures (35^{o}C, 37^{o}C and 40^{o}C). The mixtures were shaken at 120 movements per minute with the assistance of a controllable temperature waterbath shaker to facilitate dissolution of the phenolic compounds from the granules for 120 min. Samples were withdrawn from the system at every 20 minutes interval for total phenolic compound analysis. Total phenol was determined by Folin- Ciocalteu reagent and was expressed as milligrams of gallic acid equivalents (GAE) per gram dry of the extract (Kujala *et al*., 2000). The experiments were carried out in tripiclates to ensure the reproducibility of the data. The dissolution rate models, namely the Higuchi, Kormeyers-Peppas, Weibull, and a proposed mass transfer model were validated their accuracy in describing the dissolution rates of mangosteen pericarp extract granules. The dissolution rate was expressed as (D%), which indicated the percentage amount of dissolved phenolic compound in the PBS solution calculated by the following equation:

$$D(\%) = \frac{Q_t}{Q_0} \times 100 \qquad (6)$$

The average relative deviations (ARDs) of the calculation to the experimental data were calculated as:

ISBN: 978-602-71398-0-0

$$ARD(\%) = \frac{ABS(Q_{cal} - Q_t)}{Q_t} \times 100 \quad (7)$$

where Q_{cal} is the amount of phenolic compound release at time t (mg) calculated using the models.

3 Results And Discussion

Effect of pH on the dissolution rate

Depending on the location, the pH of human gastrointestinal tract fluid lies between 5.5-7.5 (Fallingborg, 1999). The effect of pH on the dissolution rates on mangosteen pericarp extract granules were performed at 37ºC which refer to normal human body temperature. The profile of the dissolution rates are presented in Figure 1. Theoretically, if changes in pH interfere with the hydrogen bonding between phenolic compounds and gum Arabic and maltodextrin, those phenolic compounds will be liberated from the granules and, consequently, dissolution will occur (Aisha *et al*., 2012). Figure 1 shows that the dissolution rate of the phenolic compounds from the mangosteen pericarp granules increased as the pH increased from 5.5 to 6.5, which was acidic. However, the dissolution rate was very low at pH 7 (neutral condition). Surprisingly, the dissolution rate of those compounds increased under basic condition (pH 7.5).

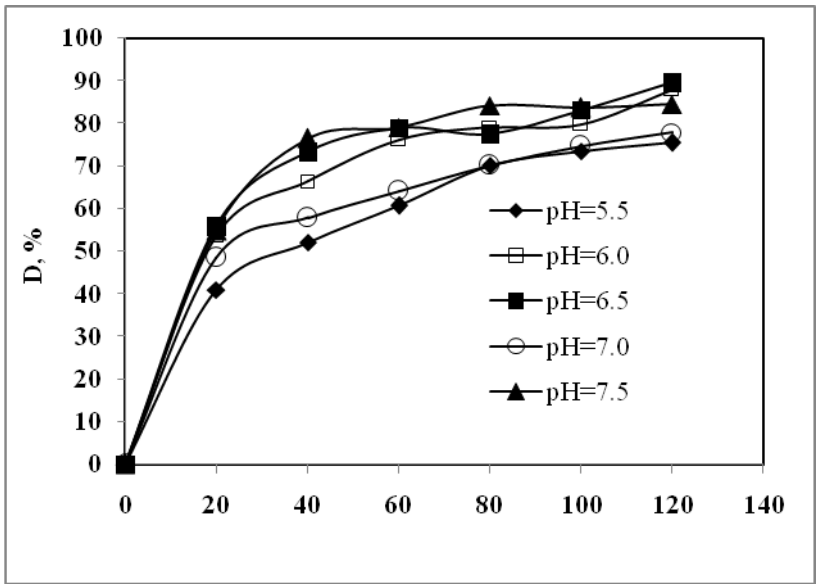

Figure 1 Effect of pH on the dissolution rate of mangosteen pericarp extract granules at 37ºC

The gum arabic and maltodextrin mixtures tend to form crystal at extremely low pH and transforms into big spherical shapes at pH 6 (Ahmad *et al*, 2013). Due to their crystal forms, the dissolution rates of the phenolic compounds were slower at lower pH. At higher pH, the phenolic compound granules were more amorphous, at which no energy is required to break up the crystal lattice that trigger faster dissolution process (Taylor and Zografi, 1997).

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Effect of temperatures on the dissolution rate

The effect of temperatures on the dissolution rates on mangosteen pericarp extract granules was studied at pH 7. Figure 2 depicts the dissolution profile of phenolic compounds from mangosteen

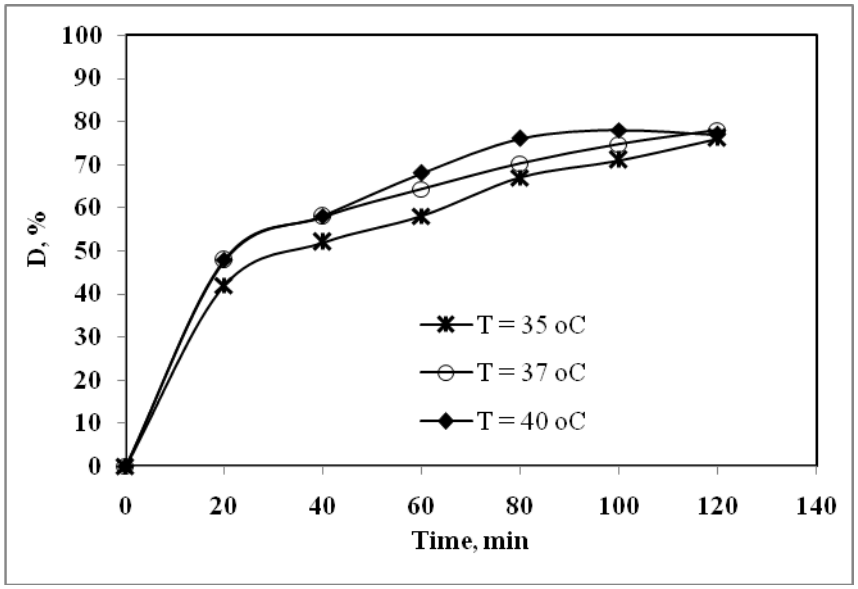

Figure 2 Effect of temperature on the dissolution rate of mangosteen pericarp extract granules

pericarp extract granules. It is clear that the dissolution rate of phenolic compound from the granules increased with temperatures. This finding is expected as the aqueous solubility of solution also increased with temperatures (Kara´sek *et al*., 2009). In addition, the granules will swell and expand to some extent that ease the solubilized phenolic compounds to leach out. Increasing the system temperature also increases the diffusion coefficient of the phenolic compounds and reduces the viscosity of the dissolution media (Craig, 2002).

Modelling of the dissolution rate

Refer to most of microbial infection cases, people with *Staphylococcal* infection may experience fever close to 40^{o}C. Therefore, the dissolution rate models in this study were evaluated at pH 7.0 and temperature 40^{o}C. The modelling results are presented in Figure 3 and Table 2. Figure 3 and Table 2 show that the Korsmeyer-Peppas model performed its superiority over other models as seen by its closest dissolution curve profile and lowest absolute relative deviation with the experimental data. The proposed model also presented good prediction results, while the Higuchi and Weibull models did not perform as good as the other models.

ISBN: 978-602-71398-0-0

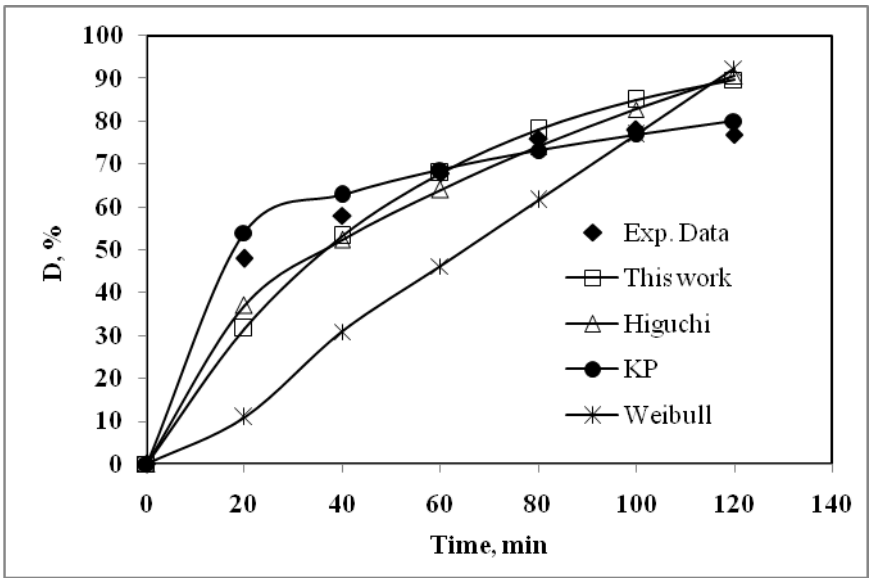

Figure 3 Comparison of the the dissolution rate modelling results

Table 2 Optimised parameters of the studied dissolution rate models

Models	Parameters							
	k_H	K_k	K_p	a	b	n	Ti	ARD (%)
Higuchi	41.3845	-	-	-	-	-	20	12.10
Korsmeyer-Peppas	-	139.22	-	-	-	0.22	-	6.75
Weibull	-	-	-	0.7057	1	-	0	28.98
Proposed in this work	-	-	0.0296	-	-	-	-	8.76

4 Conclusions

From the results of experimental and modeling works some conclusions can be drawn. Mangosteen pericarps granules dissolution rates increased with pH under acidic condition. Under basic condition, the dissolution rate was also faster than that at neutral condition. The dissolution rates of mangosteen pericarps granules were faster at higher temperatures. The semi empirical Korsmeyer-Peppas model showed its superiority over the other models to predict the mangosteen pericarps granules dissolution rates. However, the mass transfer model proposed in this work also agreed well with the experimental data with error percentages closely similar to that of Korsmeyer-Peppas model.

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