Development and evaluation of Ketoprofen sustained release matrix tablet using *Hibiscus rosa-sinensis* leaves mucilage

M. Kaleemullah a,*, K. Jiyauddin a, E. Thiban a, S. Rasha a, S. Al-Dhalli a, S. Budiasih a, O.E. Gamal b, A. Fadli a, Y. Eddy a

a School of Pharmacy, Management & Science University, 40100 Shah Alam, Selangor Darul Ehsan, Malaysia
b Unaizah College of Pharmacy, Qassim University, Qassim, Saudi Arabia

Received 22 October 2015; accepted 7 October 2016
Available online 10 November 2016

**KEYWORDS**
Ketoprofen; *Hibiscus rosa-sinensis*; Mucilage; HPMC; Sustained release

**Abstract** Currently, the use of natural gums and mucilage is of increasing importance in pharmaceutical formulations as valuable drug excipient. Natural plant-based materials are economic, free of side effects, biocompatible and biodegradable. Therefore, Ketoprofen matrix tablets were formulated by employing *Hibiscus rosa-sinensis* leaves mucilage as natural polymer and HPMC (K100M) as a synthetic polymer to sustain the drug release from matrix system. Direct compression method was used to develop sustained released matrix tablets. The formulated matrix tablets were evaluated in terms of physical appearance, weight variation, thickness, diameter, hardness, friability and in vitro drug release. The difference between the natural and synthetic polymers was investigated concurrently. Matrix tablets developed from each formulation passed all standard physical evaluation tests. The dissolution studies of formulated tablets revealed sustained drug release up to 24 h compared to the reference drug Apo Keto SR tablets. The dissolution data later were fitted into kinetic models such as zero order equation, first order equation, Higuchi equation, Hixson Crowell equation and Korsmeyer-Peppas equation to study the release of drugs from each formulation. The best formulations were selected based on the similarity factor ($f_2$) value of 50% and more. Through the research, it is found that by increasing the polymers concentration, the rate of drug release decreased for both natural and synthetic polymers. The best formulation was found to be F3 which contained 40% *Hibiscus rosa-sinensis* mucilage polymer and showed comparable dissolution profile to the reference drug with $f_2$ value of 78.03%. The release kinetics of this formulation has shown to follow non-Fickian type which involved both diffusion and erosion mechanism. Additionally, the statistical results indicated that there was no significant difference ($p > 0.05$).
between the F3 and reference drug in terms of MDT and T50% with p-values of 1.00 and 0.995 respectively.

© 2016 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Oral route being well known, advantageous, important and appealing drug delivery system with ease of administration, self-medication and cost-effective. Tablet adopted its popularity and availability in the market due to its ease of manufacturing, administration convenience, dosing accuracy and better stability than other dosage forms (Joshi et al., 2013).

Sustained release matrix tablets have given a new evolution towards novel drug delivery of pharmaceutical technology (Sharada et al., 2012). These dosage forms are a type of reservoir designed to release drug constantly and continuously over satisfactory prolonged period of time to maintain plasma drugs concentration within therapeutic level (Khan et al., 2010). Sustained release tablets provide patient convenient and compliance with cost effective made from the improved disease management.

Sustained release tablets involve were categorized into two basic types based on the mechanism of controlling the drug release which are active drug dissolution and diffusion of dissolved drugs and further explained clearly by four mechanisms which are hydrating of the device, diffusion of water into the device, dissolution of the drug, and diffusion of solubilized drug out of the device. These mechanisms may operate independently, together or consecutively (Taylor et al., 2007).

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) dedicated for anti-inflammatory, analgesic and antipyretic (Khan et al., 2010) (see Figs. 1 and 2).

The anti-inflammatory effects of Ketoprofen postulated by inhibition of cyclooxygenase-2 result depreciation in levels of prostaglandins that promote pain, fever and inflammation. Ketoprofen is indicated for symptomatic treatment of acute and chronic rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, primary dysmenorrhoea and mild to moderate pain associated with musculotendinous trauma (sprains and strains), postoperative (including dental surgery) or postpartum pain (DrugBank, 2014). Ketoprofen is a relevant model drug in formulating controlled release dosage forms due to its short plasma elimination half-life and poor solubility in water, and Ketoprofen is classified as Class II drugs according to BCS indicating low solubility and highly permeability (85% or more API is absorbed) with oral bioavailability 90% (Shohin et al., 2011). Ketoprofen is 99% bound primarily to albumin (DrugBank, 2014). Ketoprofen is instantaneously well-absorbed orally and highly metabolized in the liver through conjugation to glucuronic acid. Ketoprofen has dominance over other NSAIDs because it has no or very little addictive potential and also has no effect on sedation and depression of respiration (Jan et al., 2012).

Currently, usage of natural gums and mucilage is increasing importance in pharmaceutical formulations as valuable drug excipient. Natural plant based materials are economical, devoid of side effects, biocompatible, biodegradable, renewable source, environmental-friendly processing and better patient compliance (Sharada et al., 2012).

Hibiscus rosa-sinensis, (Malvaceae family) frequently known as China rose which is popular landscape shrub, creates a bold effect with its medium-textured, glossy dark green leaves and with 4–6 in. wide and up to 8 in. long, showy flowers, produced throughout the year and grows up to 7–12 feet (Abdul Ahad et al., 2011).

Hibiscus rosa-sinensis leaves mucilage was studied in one research on its release retardant activity in prepared sustained release formulations. The matrix tablets found to have improved uniformity of weight hardness, friability and drug content with low value variation. The swelling behaviour, release rate characteristics and the in vitro dissolution study...
proved that the dried *Hibiscus rosa-sinensis* leaves mucilage suits as matrix forming material for preparing sustained release matrix tablets. The kinetics of selected formulation followed zero order and concluded that *Hibiscus rosa-sinensis* leaves mucilage impressive matrix forming polymer, to retard the release of drugs from the formulation (Pawan et al., 2011).

In this experiment, direct compression is used for matrix tablet formulation as this method offers higher efficacy compared to wet granulation. Ketoprofen matrix tablet formulation involves incorporation of natural polymer which is *Hibiscus rosa-sinensis* leaves mucilage and synthetic hydrophilic polymer hydroxypropyl methylcellulose (HPMC) with various concentrations. The objective of the study aimed to develop and evaluate Ketoprofen sustained release matrix tablet using *Hibiscus rosa-sinensis* leaves mucilage having comparable dissolution profile with marketed Apo Keto® SR 200 mg.

### 2. Material and methods

#### 2.1. Materials

The fresh leaves *Hibiscus rosa-sinensis* were collected from Perak, Malaysia. Ketoprofen, Hydroxypropyl Methylcellulose (HPMC), Lactose DC, Magnesium Stearate, Talc, Microcrystalline Cellulose (Avicel PH102), and Disodium Hydrogen Phosphate were obtained from Pharmaniaga Manufacturing Berhad (PMB) Bangi, Malaysia, as free samples. Acetone (99.5%) AR grade and Methanol (99.98%) AR grade were obtained from Bendosen Laboratory Chemicals and HimBG Chemicals respectively. Distilled water was used throughout the experiment. Reference tablet for this experiment was Apo-Keto® SR 200 mg obtained from Apotex Pharma Malaysia Sdn Bhd.

#### 2.2. Methodology

##### 2.2.1. Mucilage extraction

The fresh leaves of *Hibiscus rosa-sinensis* were collected and cleaned repeatedly with adequate water to remove dirt and debris. The washed leaves then dried until crispy nature. The leaves were then crushed and then kept soaking for 5–6 h. The leaves then were boiled for 30 min and let stand for 1 h for complete release of the mucilage. The mucilage was extracted using an eightfold muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of the filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40 °C, collected, ground, passed through sieve mesh #80 and stored in a desiccator at 35 °C and 45% relative humidity till use.

##### 2.2.2. Characterization of mucilage

##### 2.2.2.1. Taxonomical classification

The collected *Hibiscus rosa-sinensis* leaves were classified for its kingdom, class, order, family, genus, and species (Abdul Ahad et al., 2011).

##### 2.2.3. Physical characterization

The collected mucilage was evaluated for its physical characteristics such as appearance, odour, solubility, percentage yield, percentage moisture content, and percentage weight loss on drying. All the values were evaluated in triplicate (Abdul Ahad et al., 2011).

##### 2.2.3.1. Flow properties

The dried *Hibiscus rosa-sinensis* leaves mucilage was evaluated for the flow properties which include Angle of repose, Bulk density, Tapped density, Hausner’s ratio, and Carr’s index.

##### 2.2.3.1.1. Angle of repose

The angle of repose is determined by the funnel method. The granules allowed to flow through the funnel freely on to the surface. The diameter of the granules cone is measured and angle of repose is calculated using the following equation (Joshi et al., 2013).

\[
\tan \theta = \frac{h}{r} \quad \text{or} \quad \theta = \tan^{-1}\left(\frac{h}{r}\right)
\]

where

- \( \theta \) = angle of repose,
- \( h \) = height of the cone, and
- \( r \) = radius of the cone base.

##### 2.2.3.1.2. Bulk density

Bulk density (\( D_b \)) is determined through measuring the volume (\( V_b \)) of known weighed quantity (\( W \)) of granules using bulk density apparatus (Joshi et al., 2013).

\[
D_b = \frac{W}{V_b}
\]

##### 2.2.3.1.3. Tapped density

Tapped density (\( D_t \)) is calculated by measuring the volume (\( V_t \)) of known weighed quantity (\( W \)) of granules using bulk density apparatus and using the formula (Joshi et al., 2013).

\[
D_t = \frac{W}{V_t}
\]

##### 2.2.3.1.4. Hausner’s index

The Hausner’s index is calculated by dividing the tapped density by the bulk density of the granules (Joshi et al., 2013).

\[
\text{Hausner’s index} = D_t / D_b
\]

where

- \( D_t \) = tapped density
- \( D_b \) = bulk density

##### 2.2.3.1.5. Carr’s index

The Carr’s index that determines % of compressibility of the granules can be measured from the difference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage (Joshi et al., 2013).

\[
\text{Carr’s Index} = \left(\frac{D_t - D_b}{D_t}\right) \times 100
\]

where

- \( D_t \) = tapped density
- \( D_b \) = bulk density

##### 2.2.4. Preparation of Ketoprofen tablet

The sustained release matrix tablet of Ketoprofen was prepared by using direct compression method. Various concentrations 20%, 30%, and 40% of natural and synthetic polymers were used. Total seven formulations were developed using constant 200 mg of Ketoprofen with varying amount of...
2.2.5. Preparation of phosphate buffer pH 7.4

0.05 M of phosphate buffer is prepared using 8.9 g of Disodium hydrogen phosphate in 1 litre of distilled water. The pH of buffer was adjusted to 7.4 and measured using pH meter (Jiyauddin et al., 2014).

2.2.6. Standard curve of Ketoprofen

50 mg of Ketoprofen is diluted in 100 ml of methanol to prepare the stock solution. The prepared stock solution was subsequently diluted with 5 ml of 0.05 M phosphate buffer to get solution concentration of 1.563, 3.125, 12.5, 25, and 50 mcg/ml. The absorption of maximum Ketoprofen was measured at 260 nm using UV–Visible Evolution 60 spectrophotometer (Thermo Scientific). A new standard curve was freshly prepared for every dissolution test. The blank will be phosphate buffer pH 7.4 (Khan et al., 2010).

2.2.7. Post-compression evaluation

2.2.7.1. Physical appearance. The tablets are visually observed for capping, chipping, lamination and changes in colour (Taylor et al., 2007).

2.2.7.2. Tablet thickness. The thicknesses of the tablets can be determined by using Vernier calliper. Five tablets are required, and average values are calculated. Variation in tablet may cause problems in counting and packaging. Tablet thickness should be controlled within a ±5% of a standard value (Joshi et al., 2013; Rajesh et al., 2012).

2.2.7.3. Hardness. Hardness testing determines that tablet was able to withstand mechanical shocks while handling. The hardness of the tablets is determined by using Monsanto hardness tester. It is expressed in kg/cm². 10 tablets are randomly picked and hardness of the tablets is determined (Joshi et al., 2013).

2.2.7.4. Weight variation. 20 tablets are selected randomly and weighed individually to check for weight variation (Joshi et al., 2013).

2.2.7.5. Friability. 20 tablets from each batch are selected randomly and weight. The friability of tablets is determined by using Roche Friabilator for 100 revolutions. The friabilator is operated at 25 rpm for 4 min. The tablets are subject to combine effect of abrasion and shock in a plastic chamber and dropping a tablet at height of 6 in. in each revolution. The tablets were removed, de-dusted and weighed again. It is expressed in percentage (%). % Friability of tablets less than 1% is considered acceptable. The % friability was then calculated by Joshi et al. (2013), Rajesh et al. (2012).

\[
\% \text{Friability} = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Initial Weight}} \times 100
\]

where

\[
S.I. = \frac{(Mt - M0)}{M0} \times 100
\]

2.2.7.6. Swelling behaviour. The extent of swelling is measured in terms of per cent weight gain by the tablet. To study the swelling behaviour, one tablet from each formulation is kept in a petri dish containing 20 ml phosphate buffer pH 7.4. At the end of 1 h, the tablet is removed, placed on tissue paper and weighed. The process was continued for every 2 h, till the end of 12 h. The formula is as follows (Joshi et al., 2013).

2.2.7.7. In vitro dissolution study. Rotating basket (USP method I) was adopted for the dissolution study of all tablet formulations. Ketoprofen dissolution media would be pH 7.4 phosphate buffers. The pH value of 7.4 was chosen in order to achieve a maximum drug release from the tablet, since the drug is poorly soluble at low pH conditions. Temperature of dissolution medium should maintain at 37 ± 0.5 °C and the rotating speed adjusted to 100 rpm. Samples of 5 ml are taken at time intervals of 0.5, 1, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0 and 24 h and filtered using filter paper of 0.45 μm. Then all samples should be observed spectrophotometrically (UV–Visible spectrophotometer evolution 60, Thermo Scientific) with wavelength of 260 nm and note their respective absorbance. Then, the per cent release is calculated for all tablets from the standard curves (Jan et al., 2012; Khan et al., 2010). The dissolution experiments were conducted in triplicate.

2.2.8. Drug release analysis

2.2.8.1. Similarity factor calculation. To compare test and reference products, dissolution profiles should be compared using

---

**Table 1** Formulation of Ketoprofen sustained release matrix tablets.

<table>
<thead>
<tr>
<th>Component</th>
<th>F1 (mg)</th>
<th>F2 (mg)</th>
<th>F3 (mg)</th>
<th>F4 (mg)</th>
<th>F5 (mg)</th>
<th>F6 (mg)</th>
<th>F7 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td><em>Hibiscus rosa-sinensis</em> mucilage</td>
<td>80</td>
<td>120</td>
<td>160</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>80</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>120</td>
<td>160</td>
<td>80</td>
</tr>
<tr>
<td>Lactose</td>
<td>54</td>
<td>34</td>
<td>14</td>
<td>54</td>
<td>34</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>54</td>
<td>34</td>
<td>14</td>
<td>54</td>
<td>34</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Talc</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total weight of each tablet</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

excipients. The polymers being used in formulations are Hydroxypropyl Methylcellulose (HPMC) and *Hibiscus rosa-sinensis* leaves mucilage (see Table 1).
similarity factor (F2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the per cent (%) of dissolution between the two curves. Two dissolution profiles are considered similar when the F2 value is 50 or more than 50 (Khan et al., 2010).

$$f_2 = 50\log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(R_i - T_i)^2\right]^{-0.5}\right\} \times 100$$

2.2.8.2. Drug release kinetics. To study the kinetic profile of drug release from the formulations (Ullah Shah et al., 2012).

2.2.8.2.1. Zero order kinetics.

$$C = K_0t$$

It describes the system in which the drug release rate is independent of its concentration (Chime Salome et al., 2013). C represents the cumulative amount of drug released in time t and $K_0$ is zero order release constant.

2.2.8.2.2. First order kinetics.

$$\log C_t = \log C_0 - K_1t/2.303$$

It describes the drug release from the systems in which the release rate is concentration dependent (Chime Salome et al., 2013). Whereby, $C_t$ is the amount of drug released in time t, $C_0$ is the initial concentration of drug and $K_1$ is the first order release constant.

2.2.8.2.3. Higuchi kinetics.

$$W = K_2t^{1/2}$$

It describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion (Chime Salome et al., 2013). $W$ represents the cumulative amount of drug released in time t and $K_2$ is the Higuchi dissolution constant.

2.2.8.2.4. Hixson Crowell kinetics.

$$(100 - W)^{1/3} = 100^{1/3} - K_3t$$

It describes the release from the systems, where it depends on the change in surface area and diameter of the tablets with time and mainly applies in systems, which erode over time (Ullah Shah et al., 2012). $W$ represents the cumulative amount of drug dissolved at time t and $K_3$ is the release constant.

2.2.8.2.5. Korsmeyer Peppas equation,

$$M_t/M_\infty = K_4t^n$$

It describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation. Where $K_4$ is release constant, $n$ is release exponent, indicative of the drug release mechanism and $F$ represents the cumulative amount of drug dissolved in time t. For matrix tablets, if the release exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion (Khan et al., 2010). An exponent value of 0.89 is indicative of Case-II Transport or typical zero order release.

2.2.9. Mean dissolution time (MDT)

$$MDT = \frac{\sum_{j=1}^{n}t_j\Delta Q_j}{\sum_{j=1}^{n}\Delta Q_j}$$

Characterizing the drug-release process, the mean dissolution time (MDT) was calculated according to the equation. Where $j$ is the sample number, $n$ the number of time increments considered, $t_j$ the time at midpoint between $t_j$ and $t_{j-1}$; and $\Delta Q_j$ the additional amount of drug dissolved (Vueba et al., 2004).

3. Results and discussion

3.1. Mucilage characterization

3.1.1. Taxonomical classification

Based on Taxonomical classification Hibiscus rosa-sinensis is classified under the Kingdom of Plantae, Class of Magnoliopsida, Order of Malvales, and family as Malvaceae (Abdul Ahad et al., 2011). The detail classification is shown in Table 2.

3.1.2. Physical characterization

The extracted leaves mucilage powder appeared in brownish colour with characteristic odour. The granules are slowly soluble in water producing viscous solution. Fresh Hibiscus rosa-sinensis leaves produced 21.58 g of dried mucilage per kg. The percentage weight loss on drying is 12.82 ± 0.58 and percentage moisture content is 14.70 ± 0.77. All the values are shown in Table 3.

3.1.3. Flow properties

Dried Hibiscus rosa-sinensis leaves mucilage powder has an excellent flow properties based on Angle of repose 25.37° ± 0.434°, Bulk density 0.75 ± 0.014 g/cm³, and Tapped density 0.83 ± 0.017 g/cm³. Based on USP, Carr’s index with value of 9.44 ± 0.178% and Hausner’s ratio of 1.10 ± 0.002 noted values in excellent range of flowability. The mucilage now regarded very suitable to be used in tablet manufacturing. All these values are shown in Table 4.

3.2. Standard curve of Ketoprofen

The Ketoprofen peak wavelength of 260 nm was determined from the screening method using the lowest concentration of
Ketoprofen dilution using UV–Visible Evolution 60 spectrophotometer. With using the selected wavelength, the absorbance value of 0.051, 0.096, 0.220, 0.465, 0.944, and 1.299 was determined as the sample absorbs the light when light beam passes through the solution with concentrations of 0.997, 1.953, 3.906, 7.813, 15.625, and 31.250 mcg/ml. The blank solution was set to be phosphate buffer pH 7.4. The graphical presentation was determined by plotting absorbance against concentration and obtained a fine linear regression line with R value of 0.9999 as shown in Fig. 3. This standard line became a standard reference graph which later used to quantify the concentration of drug released with corresponded absorbance value at particular time during in vitro dissolution studies.

### Table 3: Physical characterization of Hibiscus rosa-sinensis leaves mucilage.

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Brownish powder</td>
</tr>
<tr>
<td>Odour</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Solubility</td>
<td>Progressive soluble in water forming viscous solution</td>
</tr>
<tr>
<td>Percentage yield (g/kg)</td>
<td>21.58 ± 0.58</td>
</tr>
<tr>
<td>% Of moisture content</td>
<td>14.70 ± 0.77</td>
</tr>
<tr>
<td>% Of weight loss on drying</td>
<td>12.82 ± 0.58</td>
</tr>
</tbody>
</table>

### Table 4: Muclilage flow properties.

<table>
<thead>
<tr>
<th>Flow properties</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose (°)</td>
<td>25.37 ± 0.434</td>
</tr>
<tr>
<td>Bulk density (g/cm³)</td>
<td>0.75 ± 0.014</td>
</tr>
<tr>
<td>Tapped density (g/cm³)</td>
<td>0.83 ± 0.017</td>
</tr>
<tr>
<td>Carr’s index (%)</td>
<td>9.44 ± 0.178</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.10 ± 0.002</td>
</tr>
</tbody>
</table>

### 3.3. Post compression tablet evaluation

The Ketoprofen sustained release tablet was produced using direct compression method as this method is very economic and less time consuming. The compressed tablets were evaluated for its physical parameters such as appearance, weight variation, diameter, thickness, hardness and friability.

Through the research conducted it is found that all the tablets from various polymer concentrations do not show any sign of capping, chipping, and lamination. Tablets containing mucilage polymers appeared to be in light brown colour with increasing darkness as the mucilage concentration increasing. From the weight variation evaluation, all the formulations noted fitted within the 5% difference allowed for tablet weight more than 324 mg. This ensures the dose or amount of drugs was said to be accurate within formulations. Diameter and thickness parameter tablets from all the formulations show value within ±5% difference. This value is also significant for maintaining the drug amount to be in same dose and reproducibility during manufacturing. The percentage friability evaluation for all formulations falls within the range which is less than 1% satisfactory. The significant data of friability shown the tablets can withstand the shock and abrasion during transportation and storage. The hardness for all formulation was found to be satisfactory. Values for physical parameters are shown in Table 5.

### 3.4. Swelling index

Swelling index involves intake of liquid by tablets resulting in an increase in the weight and volume of tablets. This is due to hydration of the macromolecule. The liquid gains access into tablets through small pores and bounds to large molecule by breaking the hydrogen bond. This phenomenon has resulted in swelling of the tablet (Kshirsagar et al., 2009). Basically hydrophilic polymers have nature to swell when in contact with water and the tablet weight increases as time increases. This research has shown that both natural and synthetic polymers used in the formulation are hydrophilic in nature due to its ability to absorb water and swell. Apart from that, Hibiscus rosa-sinensis has higher swelling ability compared to HPMC polymers. It is also being noted that, as the polymer concentration increases the swelling behaviour of the tablet increases and this is applicable for both natural and synthetic polymers used in the study. F3 formulations containing 40% mucilage have shown highest swelling index compared to F2 and F1 containing 30% and 20% mucilage polymers respectively. On the other hand, formulations using HPMC polymers, F6 with 40% HPMC noted highest swelling index compared to F5 and F6 containing lesser polymers. When comparing between 40% mucilage and 40% HPMC, the mucilage has shown higher hydrophilic nature as well as showing higher swelling rate compared to HPMC polymer. The swelling behaviour of each formulations has been shown in Fig. 4.

### 3.5. In vitro dissolution study

In present study of dissolution profile as shown in Fig. 5, all the formulations have shown more than 50% of drugs being released within 24 h in 0.05 M phosphate buffer pH 7.4, which proved to be a dissolution medium with an acceptable discriminating power as it can be seen from Fig. 5. In fact, the same dissolution conditions were used in many studies on ketoprofen (Khan et al., 2010; Jan et al., 2012). From the observation, F1 has achieved drug release more than 98% within 9 h whereas F6 was maximally able to achieve 57% drug release within 24 h. This particular comparison can be concluded that F1 polymer which is 20% mucilage not able to sustain the...
release of drugs for more than 9 h. However, it is totally con-
tradicd with F6 containing 40% HPMC where it highly
retards the drugs being release from the tablet. On the other
part, F2 and F4 have similarly achieved more than 95% drug
release at interval of 18 h. These F2 and F4 formulations con-
taining 30% mucilage and 20% HPMC polymers respectively

### Table 5 Physical parameters evaluation of Ketoprofen formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Average weight (mg) n = 10</th>
<th>Diameter (mm) n = 10</th>
<th>Thickness (mm) n = 10</th>
<th>Hardness (N) n = 10</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>394.36 ± 2.34</td>
<td>10.12 ± 0.02</td>
<td>4.88 ± 0.03</td>
<td>49.2 ± 1.44</td>
<td>0.79</td>
</tr>
<tr>
<td>F2</td>
<td>396.02 ± 3.69</td>
<td>10.11 ± 0.02</td>
<td>4.84 ± 0.07</td>
<td>45.8 ± 1.63</td>
<td>0.70</td>
</tr>
<tr>
<td>F3</td>
<td>394.96 ± 4.87</td>
<td>10.11 ± 0.02</td>
<td>4.72 ± 0.10</td>
<td>57.7 ± 2.08</td>
<td>0.54</td>
</tr>
<tr>
<td>F4</td>
<td>388.63 ± 1.96</td>
<td>10.11 ± 0.02</td>
<td>4.77 ± 0.06</td>
<td>62.0 ± 1.68</td>
<td>0.23</td>
</tr>
<tr>
<td>F5</td>
<td>390.56 ± 4.32</td>
<td>10.10 ± 0.02</td>
<td>4.74 ± 0.02</td>
<td>55.5 ± 1.56</td>
<td>0.21</td>
</tr>
<tr>
<td>F6</td>
<td>391.82 ± 2.60</td>
<td>10.11 ± 0.02</td>
<td>4.82 ± 0.04</td>
<td>54.9 ± 2.37</td>
<td>0.17</td>
</tr>
<tr>
<td>F7</td>
<td>393.16 ± 3.53</td>
<td>10.10 ± 0.02</td>
<td>4.85 ± 0.03</td>
<td>60.8 ± 3.91</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**Figure 4** Swelling behaviour of Ketoprofen formulations.

**Figure 5** Drug release analysis for all Ketoprofen formulations.
show comparable dissolution to each other. From the dissolution studies, F5 and F7 show slightly higher percentage drug release from the reference drug (Apo Keto® SR) which are 97% and 98% respectively. Dissolution studies of F5 and F7 can be regarded as similar as the percentage release very close to each other. This phenomenon was able to prove that combination of natural and synthetic polymer able to retard the drug release comparable with HPMC alone. In contrast, F3 formulation contains 30% mucilage showing slightly lower drug release compared with reference drug which noted value of 90% within 24 h. Reference drug shows 94% of drug release within 24 h. To wrap up it can be said that F3, F5 and F7 perform percentage drugs release of 90% and more within 24 h and are closely related to reference drugs.

With comparison of all the formulations, only three formulations can be sort out which is said to be having percentage drug release near to the reference drug. These three formulations also show same pattern of drug release with reference drug. Those formulations are F3, F5 and F7. Among these three formulation comparisons, F5 and F3 show the release pattern near to the reference drug Apo Keto SR. The dissolution studies can be concluded that 40% mucilage shows comparable retarding activity with 30% HPMC at first 6 h interval and then mucilage dominates the retarding properties after 6 h interval up to 24 h. The selective comparison is shown in Fig. 6. Furthermore, formulations F3, F5 and F7 were found to be stable, in terms of dissolution rate and extent, after 6 months of storage at room temperature (see Table 6).

3.6. Drug release analysis

Drug dissolution from solid dosage forms has been described by some kinetic models which include zero-order...

<table>
<thead>
<tr>
<th>Table 6 Release kinetics for all ketoprofen formulations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation code</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>F1</td>
</tr>
<tr>
<td>F2</td>
</tr>
<tr>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
</tr>
<tr>
<td>F5</td>
</tr>
<tr>
<td>F6</td>
</tr>
<tr>
<td>F7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7 Summary of similarity factor of Ketoprofen formulations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation code</td>
</tr>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>F1</td>
</tr>
<tr>
<td>F2</td>
</tr>
<tr>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
</tr>
<tr>
<td>F5</td>
</tr>
<tr>
<td>F6</td>
</tr>
</tbody>
</table>

Figure 6  Comparison between selective formulations with reference drug.
The phenomenon when a drug shows evident that F3, F4, F5 and F7 show value more than 50%.

$p$ and to that reference drugs with drugs, but F3 has shown extremely no significant different show no significant difference compared with reference drug compared with F5 and F7. Even though F5 and F7 significant difference ($T50\%$, among the selected formulations, F4 is statistically based on one way ANOVA using data of MDT and drug which was also regarded as bioequivalent. However, formulations when compared with drug release of reference drug was from the matrix system. The Korsmeyer peppas equation suggests non-Fickian type of drug release (0.45 $< n < 0.89$) for all the formulations in which $n$ value ranges from 0.446 to 0.750 indicating combination of both diffusion and erosion drug release mechanism. This has been further explained by when the dissolution data fitted into Higuchi and Hixon Crowell, formulations F1, F4, and F6 show high Higuchi $R^2$ values whereby diffusion mechanism dominates. On the other hand, F2, F3, F5, F7 and reference drug have shown high Hixon Crowell $R^2$ value in which erosion mechanism dominated.

Based on similarity factor ($f_2$) presented in Table 7, it is evident that F3, F4, F5 and F7 show value more than 50%. The phenomenon when a drug shows $f_2$ equal or more than 50% demonstrates similar drug release properties of test formulations when compared with drug release of reference drug which was also regarded as bioequivalent. However, based on one way ANOVA using data of MDT and T50%, among the selected formulations, F4 is statistically significant difference ($p < 0.05$) as compared with reference drug compared with F5 and F7. Even though F5 and F7 show no significant difference compared with reference drugs, but F3 has shown extremely no significant different to that reference drugs with $p = 1.00$ in terms of MDT and $p = 0.995$ for T50%. The values for MDT and T50% are shown in Table 8.

4. Conclusions

In conclusion, based on all the formulations studied, Ketoprofen matrix tablet containing mucilage 40% (F3) showed comparable dissolution profile to that of reference drug. This has further proven by no significant difference between F3 and reference drug Apo Keto® SR. Through various evaluations, *Hibiscus rosa-sinensis* leaves mucilage has been proven as effective natural polymer in retarding the drug release and this mucilage acted as hydrophilic polymer which can be employed in formulating successful matrix tablets.

Acknowledgement

The author gratefully acknowledges the Research Management Centre of Management & Science University for providing the necessary facilities to carry out the research project successfully. Furthermore, sincere thank also goes to Pharna Niagara Manufacturing Berhad for pharmaceutical support of this study.

References


### Table 8 MDT and T50% values for all formulations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>T50%</th>
<th>Significant difference with reference drug</th>
<th>MDT</th>
<th>Significant difference with reference drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>8.39 ± 0.10</td>
<td>–</td>
<td>9.03 ± 0.44</td>
<td>–</td>
</tr>
<tr>
<td>F1</td>
<td>2.96 ± 0.65</td>
<td>$P = 0.000$</td>
<td>3.34 ± 0.64</td>
<td>$P = 0.000$</td>
</tr>
<tr>
<td>F2</td>
<td>4.31 ± 0.16</td>
<td>$P = 0.000$</td>
<td>5.55 ± 0.15</td>
<td>$P = 0.000$</td>
</tr>
<tr>
<td>F3</td>
<td>8.88 ± 0.13</td>
<td>$P = 0.995$</td>
<td>8.90 ± 0.09</td>
<td>$P = 1.000$</td>
</tr>
<tr>
<td>F4</td>
<td>6.24 ± 0.88</td>
<td>$P = 0.089$</td>
<td>7.19 ± 0.41</td>
<td>$P = 0.003$</td>
</tr>
<tr>
<td>F5</td>
<td>8.04 ± 0.23</td>
<td>$P = 0.999$</td>
<td>8.61 ± 0.32</td>
<td>$P = 0.941$</td>
</tr>
<tr>
<td>F6</td>
<td>16.00 ± 2.07</td>
<td>$P = 0.000$</td>
<td>7.25 ± 0.87</td>
<td>$P = 0.004$</td>
</tr>
<tr>
<td>F7</td>
<td>7.51 ± 0.08</td>
<td>$P = 0.891$</td>
<td>8.37 ± 0.14</td>
<td>$P = 0.647$</td>
</tr>
</tbody>
</table>

$P < 0.05$


