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

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**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 ($p > 0.05$).
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 accurateness 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 anti-pyretic (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
