Influence of water-soluble channeling agents on the release of diclofenac sodium from *Irvingia malayana* wax matrix tablets

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Abstract: *Irvingia malayana* wax (IW) is majorly composed of esters of medium chain fatty acids. Its melting point is low and closed to the body temperature. This study aimed at investigating the potential of IW as a matrix-forming agent and evaluate the effect of soluble channeling agents on the release of diclofenac sodium (DS) from IW matrix tablets. The preformulation study by infrared spectroscopy and differential scanning calorimetry showed no incompatibility between IW and DS or soluble channeling agents, namely PEG 4000, PEG 6000 and lactose. IW retarded the release of DS from the matrix tablets more efficiently than carnauba wax due to its greater hydrophobicity and its ability to become partial molten wax at 37°C. Factors affecting the release of DS from IW matrix were drug concentrations, and types and concentrations of channeling agents. The release of DS significantly improved when DS concentration reached approximately 33%. The fast dissolving channeling agent, lactose, could enhance the drug release rate more effectively than PEG 4000 and PEG 6000, respectively. The linear relationship between the DS release rate and the concentration of the chosen channeling agent, PEG 6000, was found (r^2=0.9866).

Keywords: *Irvingia malayana*, Wax matrix, Diclofenac sodium, Channeling agent

INTRODUCTION

Sustained and controlled release dosage forms are designed to improve the efficiency and safety of the administration of water soluble drugs which have relatively short plasma elimination half-lives. The application of these products offers the decrease in plasma drug fluctuation and in addition makes a once-a-day dose treatment possible. Matrix device is the system in which a drug is dispersed in an inert carrier (matrix forming agent) such as waxy substances or hydrophilic polymers. It is among the most frequently used sustained release solid dosage forms nowadays due to its simplicity to fabricate with low production cost, high flexibility to modulate the drug release profiles and high feasibility to scale up to the industrial production.

Waxy substances are insoluble in water and thus can be used as a matrix-forming agent for retarding drug release. Hydrophobic wax matrix was more effective in sustaining *in vitro* drug release for a longer duration than hydrophilic matrix tablets (Tiwari *et al.,* 2003). Waxy substances that were evaluated as a matrix forming agent included stearic acid (Hussain *et al.,* 2011; Quadir *et al.,* 2003; Gokce *et al.,* 2009), hydrogenated vegetable oil (Gokce, *et al.,* 2009, Yonezawa, *et al.,* 2001, Sudha *et al.,* 2010), glyceryl monostearate (Hussain *et al.,* 2011; Quadir *et al.,* 2003), cetyl alcohol (Quadir *et al.,* 2003), cetostearyl alcohol (Quadir *et al.,* 2003) beeswax (Quadir *et al.,* 2003; Basak *et al.,* 2008, Bhalekar *et al.,* 2008) and glyceryl behenate (Gokce, *et al.,* 2009). Among waxes used as a matrix forming agent, carnauba wax (Quadir *et al.,* 2003; Bhalekar *et al.,* 2008) is one of the most frequently used material and it exists in the commercial diclofenac sodium (DS) extended release matrix tablets.

A variety of waxes have different physicochemical properties and in designing wax matrix tablets with desired release pattern, the appropriate choice of wax should be selected based on these properties (Gokce *et al.,* 2009). Although a new kind of wax offers opportunity in designing matrix formulations with different drug release patterns, from our literature review it appears that investigation of a new type of wax for matrix forming agent is scarce recently. In this study, a new kind of natural wax extracted from seeds of *Irvingia malayana* Oliver Ex Bennett will be investigated for its potential as a matrix forming agent for diclofenac sodium (DS) extended release tablets. *Irvingia malayana* Oliver Ex Bennett is a tropical perennial tree of Ixonanthaceae family extensively found in Southeast Asia. *Irvingia malayana* seeds are edible (Cruz-Garcia *et al.,* 2011) and contain high amount of wax. Esters of medium chain saturated fatty acids, i.e. lauric acid 48.12% and myristic acid 42.18% were found to be the major composition of fatty acids in IW (Piyamongkol *et al.,* 2006). The preformulation study performed in this study will concentrate on evaluation of the primary chemical stability of IW and its compatibility with DS and channeling agents. Subsequently, the release profiles of DS from IW matrix tablets along with the effects of different water-soluble channeling agents will be investigated to obtain deep understanding of the release behavior of DS from the IW matrix tablets.

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MATERIALS AND METHODS

Materials

IW was obtained by compressing *Irvingia malayana* seeds using screw-typed machine at temperature of 110°C. Activated charcoal (1% w/w) was added to the molten oil and the mixture was agitated for 30min to eliminate impurities. Activated charcoal was removed by filtration and the oil was cooled down to room temperature and became white solid wax. Diclofenac sodium (Henan Dongtai Pharm Co., LTD., China) was used as a drug. Carnauba wax (Acros Organics, USA) was used as another matrix forming agent for comparison. Lactose (DMV International, Netherland), PEG 4000 and PEG 6000 (Chemekij, Thailand) were used as channeling agents to improve DS release. All reagents used in this study were of analytical grade.

Methods

Preformulation study

Infrared spectrophotometry

A physical mixture of IW and DS at a ratio of 1:1 w/w was prepared and then stored at either 4±2°C or 30±2°C for 30 days. The infrared spectra of the samples after storage were investigated by KBr disk method using Fourier Transform Infrared Spectrophotometer (FT-IR, Nexus, USA) at wave number from 500 to 4000cm^{-1} and compared to that of before storage.

Differential scanning calorimetry

Physical mixtures of IW and either PEG 4000, PEG 6000 or lactose at a weight ratio of 1:1 were prepared by trituration method. Three to five milligrams of the mixtures were hermetically sealed in an aluminum pan and analyzed using differential scanning calorimeter (DSC7, Perkin Elmer, USA) in order to observe thermal behavior that indicates incompatibility such as eutectic mixture. The thermal scan condition was heating from 0°C to 80°C at a rate of 5°C/min, cooling from 80°C to 0°C at a rate of 5°C/min and heating once again following the condition in the former heating step.

Factors affecting DS release from IW matrix tablets

DS concentration

Cylindrical matrix tablets containing DS 100mg with varying amount of IW (200, 300 and 400mg) were prepared by melting granulation method. Briefly, IW was melted at 60°C and DS (fine powder) was thoroughly dispersed in the molten wax to obtain DS concentrations of 20%, 25% and 33% w/w (Formulations F 1, F 2 and F 3 in table 1). The mixture was continuously stirred and gradually cooled down to room temperature. The homogeneous solid was granulated by using sieve no 16. DS-wax granules corresponding to DS 100mg were compressed into tablets using a hydraulic press (Carver, USA) at a compression force of 2 tons and the matrix tablets were investigated for their release profiles of DS according to the following *in-vitro* release study. For comparison, carnauba wax matrix tablets containing DS of 20% w/w (Formulation F 4) were prepared and evaluated for their release characteristics in the same manner.

Types of channeling agent

A water-soluble channeling agent, i.e. lactose, PEG 4000 or PEG 6000 of an equal weight portion to the wax (200 mg) was added into formulation F3 (as shown in formulations F5, F6 and F7 in table 1) in order to enhance the release rate and release extent of DS. The channeling agent was dispersed in the molten wax at the same time as DS and the obtained solid mixtures were compacted into tablets in the same manner as described previously. The release study was performed.

Concentration of channeling agent

Five formulations of 100 mg DS matrix tablets containing different concentrations of the selected channeling agent, i.e. PEG 6000 from 10% to 40% (Formulations F 7-F11 in table 1) were prepared. The total weights of all tablet formulations were maintained equally at 500 mg to ensure that their tablet sizes and surface area were similar. The release behaviors were examined.

In vitro release study of DS from the matrix

The *in-vitro* release tests were performed using USP apparatus 2 (paddle) (Pharma Test, Germany). Phosphate buffer (pH 6.8, 900ml) was used as dissolution medium and was maintained at 37±0.5°C throughout the study. The rotation speed of the paddle was 50 rpm. The dissolution samples were taken at predetermined time intervals up to 8 h and replaced with equal volume of fresh medium to maintain the total volume. Samples were filtered and analyzed by UV spectrophotometry at 276nm. The percent labeled strength of DS dissolved was determined (n=3). The microscopic cross section of matrix tablets before and after release study for 0, 1 and 8 h were investigated using Scanning Electron Microscope (JSM-5910LV, JEOL, Japan). The following simple semi-empirical exponent relation (Ritger *et al.,* 1987) was used to obtain the release rate constant (k).

$$\frac{M_t}{M_\infty} = kt^n$$

Where:

$\frac{M_t}{M_\infty}$ is the fractional release of DS at time t

k is a release rate constant

n is the diffusional exponent

RESULTS

Infrared spectrophotometry

The infrared spectra of the physical mixture of IW and DS at a ratio of 1:1 before and after storage at 4 °C and 30 °C for 30 days are illustrated in fig. 1. Peaks representing functional groups of DS (Bartolomei *et al.*, 2006), wave number 3394 cm^{-1} (N-H stretching, peak no. 1), 3270 cm^{-1}

(NH-O stretching, peak no. 1), 1577 cm^{-1} (-C=O stretching, peak no. 4) and 746cm^{-1} (C-Cl stretching, peak no. 5) and those of IW (Knuutinen and Norrman, 2000) wave number 2931cm^{-1} (C-H stretching, peak no. 2) and 1745cm^{-1} (C=O stretching, peak no. 3) remained unchanged after storage.

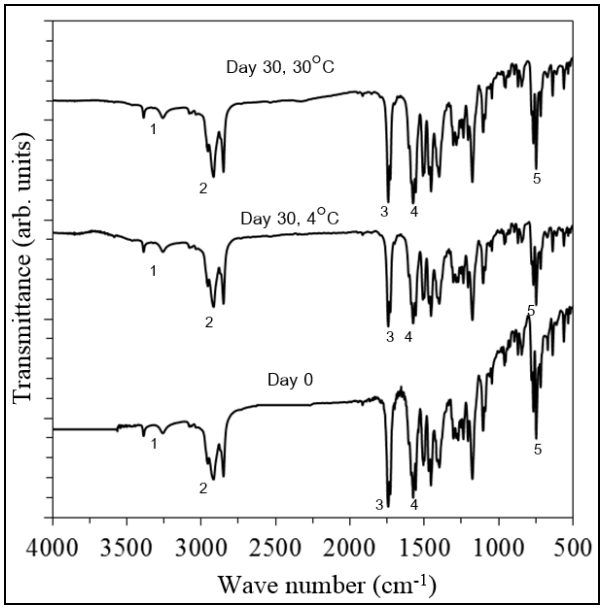

Fig. 1: Infrared spectra of the physical mixture of IW and DS (1:1 w/w) before and after storage at 4°C and 30°C for 30 days (refer details for peak numbers in text)

Differential scanning calorimetry

DSC thermograms of the physical mixtures between IW and PEG 4000, PEG 6000 or lactose at the ratio of 1:1 w/w are shown in fig. 2. The endothermic peaks with the onset temperature of 32.4±0.1°C in heating 1 step of all thermograms were of the melting peak of IW. The conclusion temperature of melting was approximately 40.0°C. The second peaks in the first heating step (heating 1) in figs. 2 (a) and (b) were results from melting of PEG 4000 (onset temperature 54.3±0.2°C, corresponding to the reported melting point of 50-58°C (Rowe *et al.*, 2009)) and PEG 6000 (onset temperature 56.1±0.6°C, corresponding to the reported melting point of 55-63°C (Rowe *et al.*, 2009)). The melting peak of lactose was not detected in the temperature range of 0-80°C. The exothermic peaks during cooling were crystallization of IW (onset temperature 18.1±0.3°C for PEG 4000 and 11.3±0.1°C for PEG 6000) and PEG 4000 (onset temperature 36.4±2.1°C) and 6000 (onset temperature 35.2±1.9°C), indicating the solidification points of the wax and polymers occurred at a temperature lower than that of the melting peak. The melting peaks of IW, PEG 4000 and PEG 6000 in the second heating step (heating 2) occurred at temperatures closed to those of the first run. The split melting peaks of PEG 4000 was also found when heating PEG 4000 alone under the same thermal condition (Data not shown).

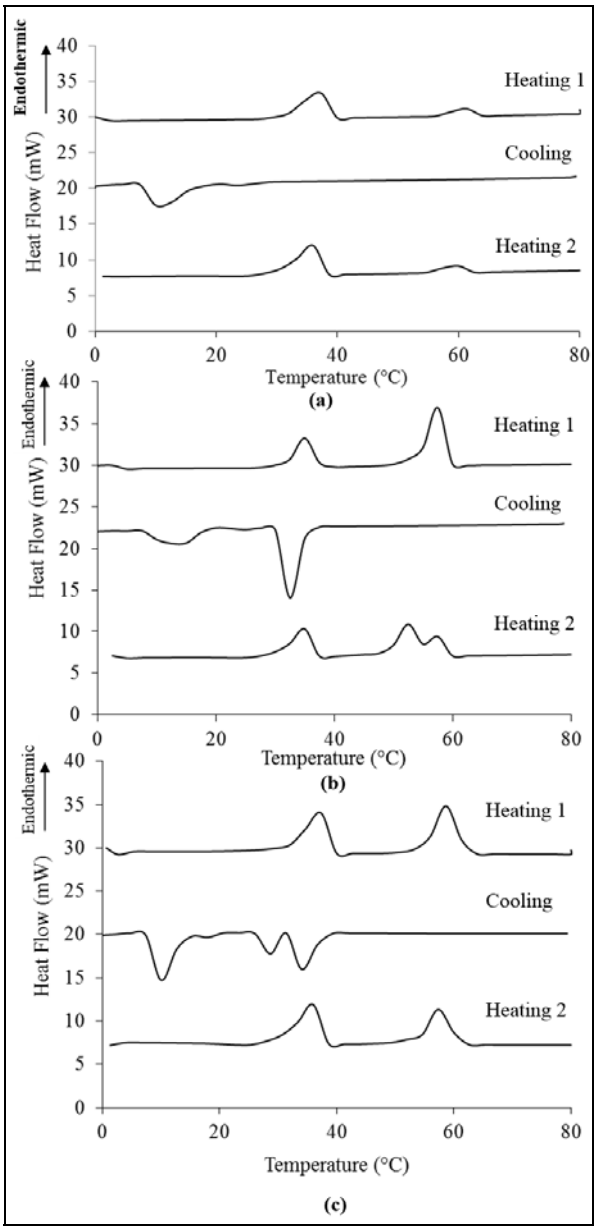

Fig. 2: DSC thermograms of the physical mixtures of IW and PEG 4000 (a), PEG 6000 (b) and lactose (c) in a ratio of 1:1 w/w after first heating from 0°C to 80°C (heating 1), cooling from 80°C to 0°C (cooling) and second heating from 0°C to 80°C (heating 2) at the constant scanning rate of 5°C/min

Effect DS concentrations on releasing behavior of DS from matrix tablets

The release profiles of 100mg DS IW matrix tablets prepared with varying DS concentrations, namely 20, 25 and 33% w/w together with 100mg DS CW matrix tablets containing DS 20% w/w are shown in fig. 3. IW was more effective in retarding DS release than CW.

The release profiles of 100mg DS IW matrix tablets containing the drug of 20, 25 and 33% w/w were different (repeated measure ANOVA, $p<0.001$). The cumulative

DS release at 8 h was only 6.7%, 9.3% and 41.8% for tablets containing DS 20, 25 and 33% w/w, respectively. This revealed the high efficiency of IW in retarding the release of DS as a model of a highly water-soluble drug. The release profiles of DS from IW matrix tablets could be described fairly well with a Higuchi model (Higuchi, 1963) where a direct proportionality between the cumulative amount of drug released and the square root of time can be demonstrated (r^2=0.9335-0.9782). The plot of the Higuchi release rate constants (k) against the drug concentrations was shown in fig. 4. It was found that the concentration of drug itself influenced the extent and the rate of drug release. The release rate constants of DS were quite low and slightly increased at 20 and 25% of drug concentration and markedly increased when the drug concentration reached 33%.

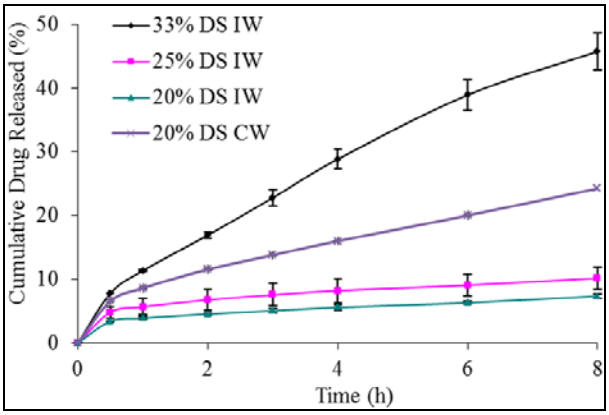

Fig. 3: Cumulative percentage drug released of IW matrix tablets containing DS of 20% (F 3), 25% (F 2) and 33% w/w (F 1) and CW matrix tablets containing DS of 20% w/w (F 4).

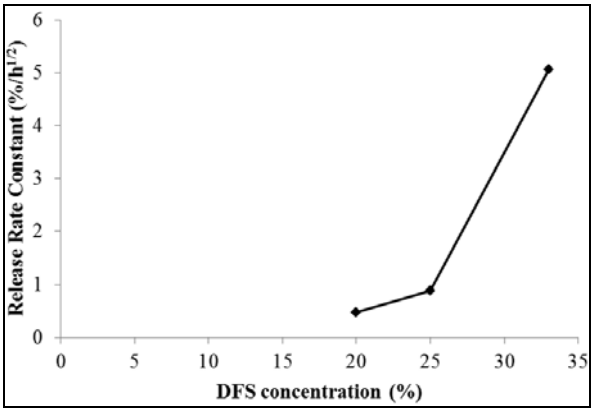

Fig. 4: Release rate constant calculated based on Higuchi square root of time release model of 100mg DS IW matrix tablets with varying drug concentrations, 20% (F3), 25% (F 2) and 33% (F 1) w/w

Effect of types of channeling agent on DS release from IW matrix tablets

Different water-soluble channeling agents i.e. lactose, PEG 4000 and PEG 6000 were chosen based on their different dissolution properties. The release profiles of matrix tablets containing 100mg DS, 200mg channeling agent and 200 mg IW are shown in fig. 5. The release profiles of F1, F 5, F6 and F7 were statistically different (repeated measure ANOVA, $p<0.001$). The incorporation of a channeling agent significantly improved the release of DS. DS release from tablets containing lactose (F5) occurred at a faster rate than PEG 4000 (F6) and PEG 6000 (F7). To obtain more insight into the behavior of DS release from each formulation, the scanning electron micrographs (SEM) of the cross section of IW tablets composing of PEG 4000 and PEG 6000 as a channeling agent after the release study had been carried out for 1 and 8 hours were taken as shown in fig. 6. The SEM characteristics of formulation without any channeling agent after the release study had performed for 1h demonstrated almost no evidence of dissolution of drug particles and after 8 hours it was observed that only DS particles near the tablet surface disappeared from the matrix. Numerous channels were obviously found in the cross-sectional micrographs of IW tablets containing PEG 4000 and PEG 6000 even as soon as 1h of the release study, indicating rapid dissolution of drug particles. After 8h, the formation of channels was found deep further inside the tablets of both formulations, with slightly faster dissolution of DS observed from formulation containing PEG 4000 than PEG 6000.

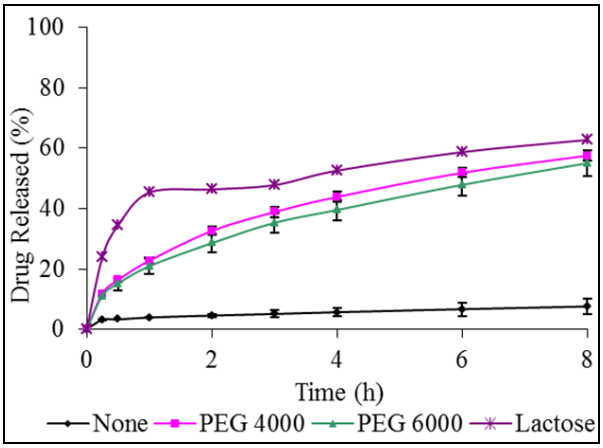

Fig. 5: Release profiles of 100mg DS IW matrix tablets containing different types of channeling agents (none (F 1), lactose (F 5), PEG 4000 (F 6) and PEG 6000 (F 7))

The kinetics and the rates of DS release from IW matrix comprising of PEG 4000 and PEG 6000 were evaluated. The release of DS from the matrix could be described well with Higuchi model. The release rate constants for PEG 4000 and PEG 6000 were 20.55 mg/$h^{1/2}$ (r^2=0.9949) and 19.23mg/$h^{1/2}$ (r^2=0.9989), which was almost ten time higher than that contained no channeling agent (2.13 mg/$h^{1/2}$, r^2=0.9460).

Effect of channeling agent concentrations on DS release from matrix tablets

The release study of IW matrix tablets containing 100mg DS and PEG 6000 of different concentrations: 10, 20, 30,

35 and 40% was carried out to obtain the release rate constants based on to Higuchi equation. The linear relationship between the concentrations of PEG 6000 and the release rate constants of DS was found as shown in fig. 7, which can be described as the following equation: Y= -3.864 + 0.577X (r^2=0.9866); where X represents PEG 6000 concentration (%) and Y is a release rate constant.

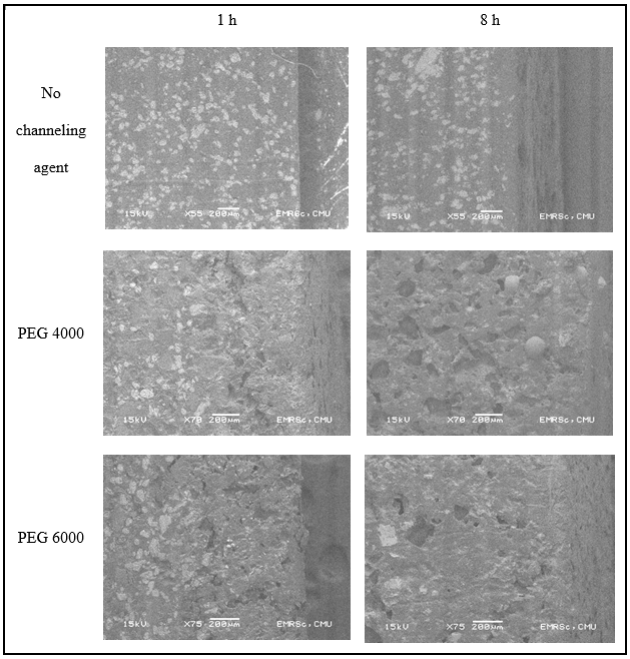

Fig. 6: Scanning electron micrographs of cross section of 100 mg DS IW matrix tablets containing no channeling agent (F 1), PEG 4000 (F 6) and PEG 6000 (F 7) after the release study for 1 and 8 h

DISCUSSION

The infrared spectra and the physical appearance of the mixture of IW and DS at a ratio of 1:1 did not change after storage at 4 °C and 30 °C for 30 days**,** indicating no degradation of IW and no interaction formed between IW and DS. No obvious change in the DSC thermograms of the physical mixtures between IW and PEG 4000, PEG 6000 or lactose at the ratio of 1:1 was observed, demonstrating that IW did not form eutectic mixture or complex with lactose and PEG. It could further signify that matrix preparation by melting granulation at 60°C did not introduce any significant change in thermal behaviors to IW and the selected channeling agents. The Infrared spectrophotometry and DSC findings suggested the potential of IW for pharmaceutical applications in terms of its stability and inertness.

IW showed more effective drug release retarding property than CW. This might come from two contributions. First, the composition of CW is a mixture of aliphatic esters (wax esters), α-hydroxyl esters and cinnamic aliphatic diesters (ANS, 2012). The esters of cinnamic acid and α-hydroxyl esters is considered less hydrophobic than esters of lauric acid and myristic acid in IW and this introduced the release of DS from CW faster than IW matrix tablets. Second, IW has a melting point close to the body temperature, while CW has a higher melting point of 64°C. When IW matrix tablets were exposed to the release medium at 37°C, it was similar to apply heat treatment to tablets which resulted in redistribution of partial molten wax and caused increased tortuosity of the matrix (Zhang *et al.,* 2001). In addition, molten wax would form film-like structure coating around drug particles, and thus further retarded drug release.

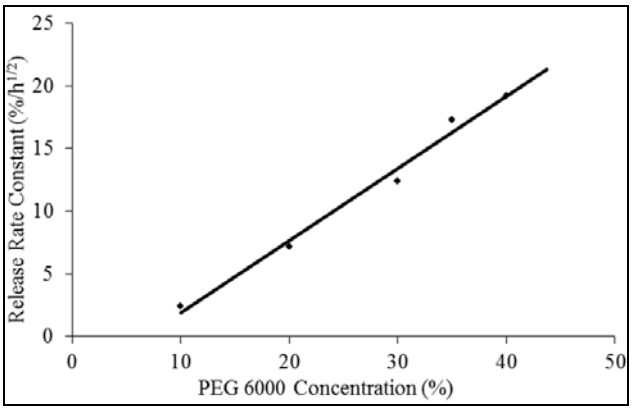

Fig. 7: Linear relationship between release rates of DS from IW matrix compacts and PEG 6000 concentrations

The effect DS concentrations on releasing behavior of DS from matrix tablets can be explained by percolation theory (Kaewvichit *et al.*, 1994). When a concentration of drug is low, drug powder distributed in a matrix tablet is discontinuous. Dissolution of drug occurs mostly from particles near the tablet surface, while the rest of drug powder inside the tablet remains intact with dissolution medium and cannot be released. When a drug concentration is increased, a chance of drug particles to become in contact with each other is increased. As a result, water penetration can proceed inside a tablet more rapidly because of drug particle network formed throughout the tablet, resulting in higher extent and faster rate of drug release. Moreover, after drug diffusing out of the compact, interconnected pores are formed which facilitate the dissolution and the release of the remaining drug. It was previously proposed that the concentration of drug that could form continuous structure of capillaries and led to the enhancement of drug release was 33.8% (Burns *et al.*, 1990), which is close to the results obtained from this study. In order to increase the extent of drug release, it is likely that the concentration of drug in the tablet should be increased. However, the limitation was found when DS concentration reached 50%, the mixture could not be compressed into a tablet. In addition, the dose of drug is always fixed and therefore other components in the formulation should be varied to modify the release rate instead.

Table 1: Formulations of 100 mg DS matrix tablets used for testing the effect of DS concentration and the effect of types and concentrations of channeling agent

Formulation	IW (mg)	CW* (mg)	DS (mg)	Channeling agent				Total Weight (mg)
				Lactose (mg)	PEG 4000 (mg)	PEG 6000 (mg)	Concentration (%)	
F 1	200	-	100	-	-	-	-	300
F 2	300	-	100	-	-	-	-	400
F 3	400	-	100	-	-	-	-	500
F 4	-	400	100	-	-	-	-	500
F 5	200	-	100	200	-	-	40	500
F 6	200	-	100	-	200	-	40	500
F 7	200	-	100	-	-	200	40	500
F 8	225	-	100	-	-	175	35	500
F 9	250	-	100	-	-	150	30	500
F 10	300	-	100	-	-	100	20	500
F11	350	-	100	-	-	50	10	500

* CW = carnauba wax

Due to the fact that the cumulative percent release of DS from IW matrix tablets containing the drug in a concentration of 33.3% w/w (Formulation F1) was lower than 50% even after 8 hours of the release study, enhancement of drug release from IW matrix tablets by an additional intervention was thus considered necessary. A channeling agent is usually added into hydrophobic matrix to adjust the release rate of an active ingredient to a required level. The release rate of DS from matrix tablets containing lactose was higher than those containing PEG 4000 and PEG 6000 because lactose can dissolve faster in water. However, the abnormal increase of DS release in the profile of lactose originated from tablet lamination after 0.5 h of the release study. Thus, it was not further investigated by SEM.

Scanning electron micrographs of cross section of matrix tablets showed that water could not penetrate well into the tablet and triggered DS to dissolve and diffuse out of the tablet without the aid of a channeling agent. As a result, the low extent of DS release was found in the formulation without any channeling agent. The addition of water-soluble channeling agents, i.e. PEG 4000 and PEG 6000 into IW matrix could enhance drug release by generation of capillaries inside matrix tablet. A channeling agent possessing fast dissolution property provides fast formation of capillaries and leads to rapid release of a drug.

Increased rate and extent of the DS release were observed when using higher concentrations of PEG 6000 due to higher porous network were formed in the matrix tablets. The results were similar to the release study of DS from carnauba wax matrix tablets (Ahmed and Khalil, 2014) and theophylline from hydrophilic polymer matrix tablets (Razzak *et al.*, 2009). The linear relationship between the concentrations of PEG 6000 and the release rate constants of DS is beneficial for development of DS matrix tablet formulation to achieve the desired release rate.

The rate of a drug release can be controlled by selecting appropriate types and concentrations of channeling agents based on their dissolution properties. The addition of channeling agents had negligible effect on the release mechanism as the release of the drug and channeling agent was similarly governed by diffusion and the whole matrix compact was considered as diffusion controlled system.

CONCLUSION

IW is an inert fatty material that has a high potential for pharmaceutical uses. It produced neither chemical reaction with DS nor eutectic mixture or complex formation with lactose, PEG 4000 and PEG 6000. IW could sustain the release of DS effectively and thus it can be used as a matrix-forming agent in an extended release tablet formulation. A channeling agent can be added to modify the release rate and release extent of DS to the desired level. As a channeling agent, lactose offered higher release rate than PEG 4000 and PEG 6000. Rate of capillary formation was found to depend on how fast the channeling agent could dissolve in the medium and this directly affected the release rate of DS. The release rate of DS from IW can also be enhanced by increasing the concentration of a channeling agent. In this study, the linear relationship was found between DS release rate constant and the concentration of PEG 6000 in the range of 10-40%. In summary, IW demonstrates a high potential for use as a matrix-forming agent in a sustained release formulation of DS and the desired release rate can be possibly manipulated by addition of a suitable channeling agent at an appropriate concentration.

ACKNOWLEDGEMENTS

This work was financially supported by Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand.

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