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RESEARCH ARTICLE**THE ROLES OF CHANNELING AGENTS ON THE DRUG RELEASE FROM WAX MATRIX TABLET PREPARED BY MELT GRANULATION****Charumanee Suporn*, Yotsawimonwat Songwut, Wongpayapkul Ladda, Piyamongkol Sirivipa**

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ABSTRACT

The study aimed to investigate the effect of the channeling agents and to explore the mechanisms by which they affect the drug release from wax matrix tablets. The channeling agents were potato starch and icing sugar. The wax matrix tablet contained 4% w/w of chlorpheniramine maleate, a model drug. The matrix formers were carnauba wax, the mixtures of wax and potato starch or icing sugar with different weight ratio of wax: channeling agent, i.e., 1:1, 1:2, and 2:1. They were prepared by melt granulation and then compression into tablet. The *in vitro* drug release from the wax matrix tablets was studied using USP II (Paddle) method. Within 8 hours, only 22.26% of the drug released from the neat wax matrix tablet, whereas the drug release was significantly increased from tablets containing a channeling agent. The rate and the extent of the drug released increased linearly with the increasing amounts of potato starch. Unlike icing sugar, it had less effect on enhancing the drug release at concentrations of 33% and 50%, but at 67%, the dramatic increase of the drug release was attained. This discrepancy was attributed to the nature and different mechanisms of the two channeling agents on promoting the drug release. The SEM micrographs as well as the degree of water uptake and tablets erosion clearly demonstrated the roles of these two channeling agents on the drug release. The release profiles of the drug from all matrices followed Higuchi model showing the r^2 of 0.97-0.99.

Keywords: Carnauba wax; Chlorpheniramine maleate; Higuchi diffusion model; Icing sugar; Melt granulation; Potato starch;

1. INTRODUCTION

The development of oral controlled-release drug delivery systems is driven by clinical outcome benefits, aiming to improve the efficacy and the quality of drug administration. Ideally, the well-developed system should be able to control the release characteristics or in some instances, be able to target a drug directly to a specific absorption site. Accordingly, one or more of the following benefits can be achieved: the maintenance of the effective therapeutic drug level for the desired period of time, the reduction of frequency of dosing and/or dose required, the minimization of the incidence of side effects or toxicity, resulted from the fluctuation of drug concentration in circulation, and the improvement of patient compliance.^{1,2} Different types of controlled-release drug delivery systems are defined based on the compositions and/or the mechanism of controlling the drug release such as matrix-type, reservoir-type and solvent activated-controlled type². Among these, a matrix-type drug delivery system has been received more interest due to its simplicity and economy, ease to fabricate, high flexibility to modulate the drug release profiles and more feasibility to

manufacturability. Waxy substances have been widely used as a matrix forming agent for controlled-drug release systems and are still attractive at present³⁻⁶. Most of the waxy carriers are inert and considered as GRAS ingredients. They are for examples, carnauba wax, beeswax, cetyl alcohol, stearyl alcohol, glyceryl monostearate and hydrogenated oils. The release of drug from wax matrix is controlled by a combination of several processes including surface erosion, permeation of water through matrix and diffusion of drug through pores which generally occurs after the drug has dissolved in the penetrating water⁵. However, due to its high hydrophobicity, penetration of water into the dense wax matrix is quite limited. The desired characteristics of drug release can be manipulated by incorporating some additives into the wax. These agents are known as release-controlling agents or more specifically as channeling agents or wicking agent, depending on their mechanisms of action for enhancing the drug release. Substances employed as release-controlling agents are mannitol, PEG 4000, PEG 6000, PVP k30, sodium chloride,

microcrystalline cellulose, dicalcium phosphate and lactose^{4, 8-10}.

The wax matrix controlled-release systems can be prepared by several methods including direct compression^{11, 12}, hot-melt extrusion^{13, 14} and melt granulation¹⁵⁻¹⁷. Among these, the melt granulation technique has been used extensively because it is a solvent-free method and no sophisticated equipment is needed to prepare the system.

The drug release from inert matrix was first described by Higuchi¹⁸ as follows:

$$Q = \left[\left(\frac{D\varepsilon}{\tau} 2A - \varepsilon C_s \right) C_s t \right]^{\frac{1}{2}} = kt^{\frac{1}{2}} \quad (1)$$

where Q is the amount of drug released per unit surface area at time t, D is the drug diffusion coefficient in the matrix phase, C_s is the drug solubility in the dissolution medium, A represents the drug concentration in the matrix, ε is the porosity and τ denotes the tortuosity of the matrix, whereas k is the release rate constant.

According to equation (1), when the drug is highly soluble in water, i.e., C_s >> A, the cumulative amount of drug released is a linear function of the square root of time which can be simply illustrated in equation (2):

$$\frac{M_t}{M_\infty} = kt^{\frac{1}{2}} \quad (2)$$

Where, M_t/M_∞ denotes the drug fraction released at time, t

The objective of this study was to gain an insight into the mechanism of the release controlling agents by investigating the effect of two different channeling agents, potato starch (PS) and icing sugar (IS) on the release of chlorpheniramine maleate (CPM), the model drug from carnauba wax (CW) matrix tablets.

2. MATERIALS AND METHODS

Chlorpheniramine maleate, USP used in this study was from T.O. Chemicals, Co. Ltd., Carnauba wax, potato starch and icing sugar were of USP grade.

2.1 Preparation of wax matrix

The CPM-carnauba wax matrices with or without channeling agents were prepared by melt granulation method. Briefly, the drug and the channeling agents (PS or IS) were separately ground and passed through 200/325 mesh sieve prior to use. According to specified formula (Table 1), the calculated amount of the drug, PS or IS was added to the molten wax. The mixture was continuously stirred until congealed. The hard mass was then pulverized and passed through 60/70 mesh sieve (approx. 210-250 μm).

Table 1 Composition (% w/w) of wax and channeling agents in each formulation of wax matrix

Formulation	CPM	Carnauba wax (CW)	Potato starch (PS)	Icing sugar (IS)	Ratio of CW:PS/IS	% w/w PS/IS**
F1	4.0	96.0	-	-	1:0	0
F2	4.0	48.0	48.0	-	1:1	50.0
F2	4.0	32.0	64.0	-	1:2	67.0
F4	4.0	64.0	32.0	-	2:1	33.0
F5	4.0	48.0	-	48.0	1:1	50.0
F6	4.0	32.0	-	64.0	1:2	67.0
F7	4.0	64.0	-	32.0	2:1	33.0

** calculated as CW weight basis

2.2 Preparation of wax matrix tablets

The wax matrix powder was compressed into tablets using Hydraulic press, with a ¼" flat faced punch and dies set. A 300-mg matrix powder portion was filled into the die without any lubricant. The compression force was 20 kN with contact time of 30 seconds.

2.3 Physical characterization of wax matrix tablets

The diameter and the thickness of the wax matrix tablets were measured using a Vernier Caliper (Mitutoyo, Japan). The hardness and weight of the tablets were determined using ERWEKA TBT 28 apparatus (Erweka GmbH, Germany) and an electronic balance (Ohaus TS120S), respectively.

2.4 In vitro release study

The release of CPM from the matrix tablets was determined using the USP apparatus II, paddle method (Dissolution Tester, SR2 Hanson Research Co., Ltd. CA, USA). The dissolution medium was 500 ml of de-aerated distilled water maintained at 37±0.5 °C. The rotation speed of the paddle was kept constant at 100 rpm. The sample solution was withdrawn from vessels at various time intervals up to 8 hours. An equal volume of fresh dissolution medium maintained at the same temperature was immediately replaced at each sampling time. After appropriate dilution, when necessary, the sample solution was analyzed for the drug content by UV spectrophotometer (Spekol[®] 1200, Analytik Jena, Germany). All dissolution tests were performed in triplicate.

2.5 Water uptake and erosion determination

The water uptake by the wax matrix tablets was carried out according to those previously described¹⁹ with partial modification. The study was performed using the same procedure of the release study. At the end of the first and the fourth hour of the test, the tablets were taken from the vessel, removed excess water by blotting with tissue paper, weighed and then dried at 60 °C to constant weight. The percentage of water uptake and the percentage of matrix erosion were obtained by the following equations:

$$\text{Water uptake (\%)} = \frac{(\text{wet weight} - \text{dry weight})}{\text{dry weight}} \times 100$$

$$\text{Erosion (mass loss) (\%)} = \frac{[(W_i - W_f)/W_i] \times 100}{}$$

Where, W_f = remaining (dry) weight
 W_i = original weight

2.6 Microscopic and scanning electron microscopic investigation

The internal structures of the matrix tablets before and during the dissolution process were photographed using scanning electron microscope under electron radiation of 15kV (JSM- 5910LV, Jeol, Japan).

2.7 Analysis of the release data

The mean percentage of drug released from wax matrix tablets at any time intervals were fit against time according to Korsmeyer-Peppas and Higuchi diffusion models. K values were obtained from the slope of the linear relationships.

2.8. Statistical analysis

Descriptive statistics was used to summarize matrix tablets characteristics, i.e. weight, hardness, diameter

and thickness. The statistical difference between matrix tablets characteristics and k values obtained from various formulations were tested using one-way ANOVA at a significant level of 0.05.

3. RESULTS AND DISCUSSION

3.1 Preparation of wax matrix

The melt granulation method was selected to prepare CPM-wax matrix. Potato starch and icing sugar were representative candidates of water-insoluble and water-soluble channeling agents, respectively. As CPM, potato starch and icing sugar were not soluble, but thoroughly dispersed in wax matrix; the particle size of each ingredient was controlled to minimize its effect on the drug release. The molten mixture was continuously agitated until solidified in order to ensure the homogeneity of the resultant matrix. The solidified matrix was pulverized and passed through an optimal sieve mesh to obtain the uniform particle size.

3.2 Physical characterization of wax matrix tablets

Table 2 summarized the characteristics of the wax matrix tablets, including weight, hardness, diameter and thickness. There was no statistically significant difference ($p < 0.05$) for all tablet characteristics between formulations, except tablet diameters and thickness. It was noticed that the tablets with higher wax content exhibited higher thickness values due to low density of the wax. Although specific surface area of the tablet is directly proportional thickness, this appeared to have negligible effect when compared to the pronounced effect of channeling agents as will be demonstrated in the following topic.

Table 2 Matrix tablets characteristics

Formulation	Weight \pm SD* (g)	Hardness \pm SD [†] (N)	Diameter \pm SD [†] (mm)	Thickness \pm SD [†] (mm)
CW	0.297 \pm 0.001	> 13.7	10.008 \pm 0.001	3.870 \pm 0.002
CW:PS 1:1	0.299 \pm 0.001	13.4 \pm 0.02	10.030 \pm 0.001	3.231 \pm 0.001
CW:PS 1:2	0.299 \pm 0.001	13.2 \pm 0.03	10.039 \pm 0.001	3.025 \pm 0.001
CW:PS 2:1	0.299 \pm 0.001	13.7 \pm 0.02	10.012 \pm 0.001	3.471 \pm 0.001
CW:IS 1:1	0.298 \pm 0.001	> 13.7	10.018 \pm 0.001	3.174 \pm 0.001
CW:IS 1:2	0.299 \pm 0.002	13.6 \pm 0.01	10.034 \pm 0.001	2.929 \pm 0.001
CW:IS 2:1	0.299 \pm 0.001	> 13.7	10.024 \pm 0.001	3.438 \pm 0.001

(Mean \pm standard deviation, * n=20; †n=10)

3.3 In vitro release study

The profiles of drug release from wax matrix tablets containing PS and IS were illustrated in Figure 1 and Figure 2, respectively. It was shown that the drug release increased with the increasing amount of PS or IS. The extent of drug release was also affected by the types of channeling agents. PS could effectively

enhance the drug release at 33 %w/w and 50 %w/w (CW: PS 1:2 and CW: PS 1:1) and further increase of the drug release was obviously observed at 67 %w/w. The drug release from matrix tablets containing IS at low concentration of 33 %w/w was comparable to that of the neat wax matrix. However, IS produced the significant increase in drug release at 50% w/w and above.

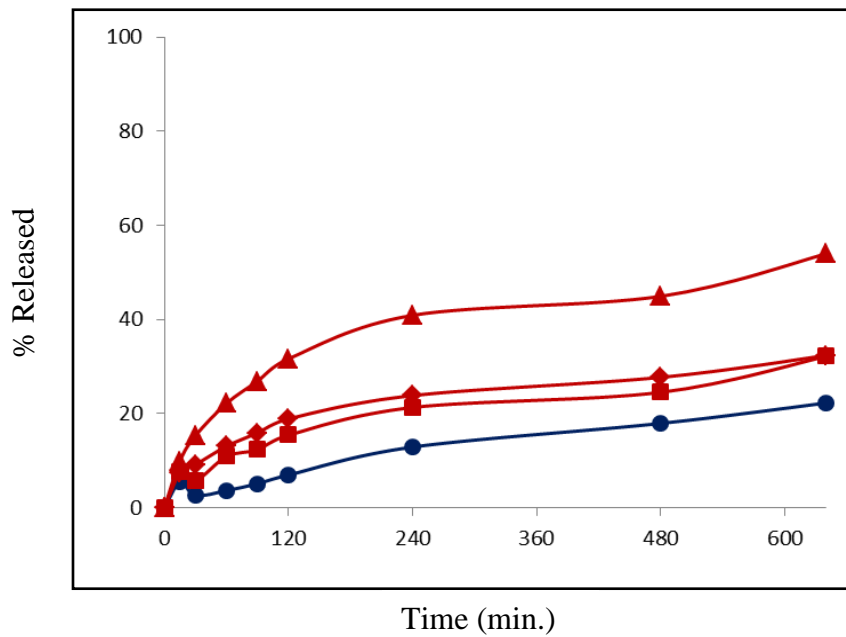


Figure 1: Release profiles of CPM from wax matrix tablets; using PS as a channeling agent ● CW; ■ CW: PS 1:1, ▲ CW: PS 1:2, ◆ CW: PS 2:1

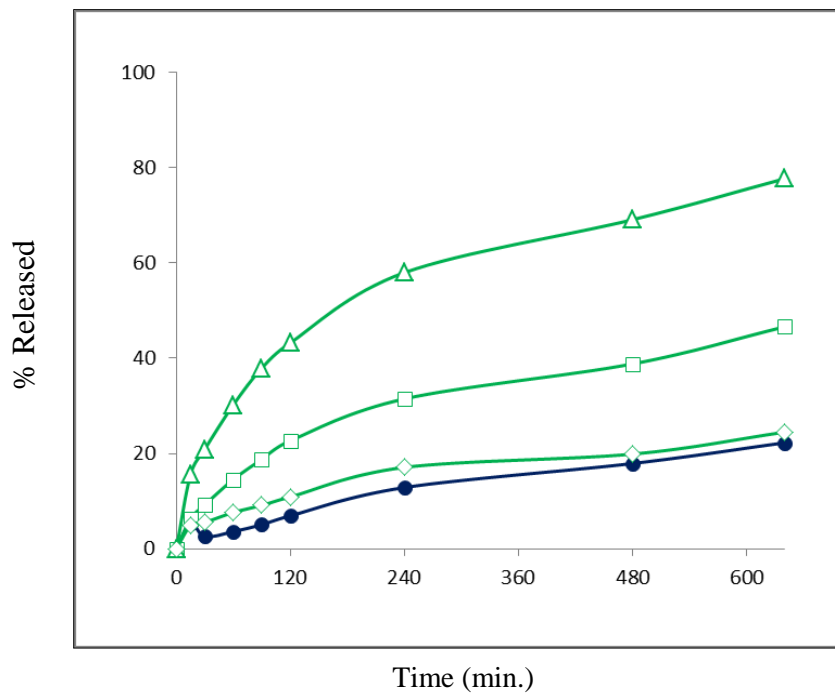


Figure 2 Release profiles of CPM from wax matrix tablets; using IS as a channeling agent ● CW; □ CW: IS 1:1, △ CW: IS 1:2, ◇ CW: IS 2:1

To gain more insight into the mechanism of drug release, the CPM release data were fitted in Korsmeyer-Peppas model, a simple relationship that describes a fraction of drug release versus time according to the following equation.

$$\frac{M_t}{M_\infty} = k t^n$$

Where,

$\frac{M_t}{M_\infty}$ is a fraction of drug release at time t

k is a release rate constant

n is a release rate exponent

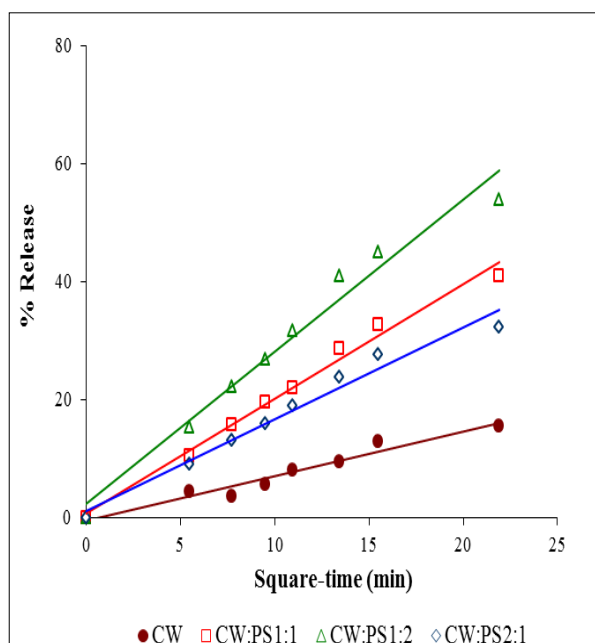


Figure 3 Higuchi's Plots of CPM from wax matrix tablets; using PS as channeling agent ● CW; □ CW: PS 1:1, △ CW: PS 1:2, ◇ CW: PS 2:1

The value of n describes the release mechanism of drug release from the matrix. It was found that the n values obtained from the release profiles of all matrix tablets in this study were close to 0.50, indicating that they followed Higuchi model. The results agreed with the studies previously reported^{8, 15, 20-21}. The curve fittings for Higuchi model of the drug release from the matrix tablets containing PS and IS were illustrated in Figure 3 and Figure 4, respectively. The release rate

constant, k values, as well as r^2 obtained from the curve fitting were summarized in Table 3. It can be observed that the k values significantly increased with the increasing amount of PS or IS in the matrix tablets. This finding was in agreement with those previously reported; the incorporation of hydrophilic excipients can enhance the drug release from hydrophobic matrix^{4, 8, 15}.

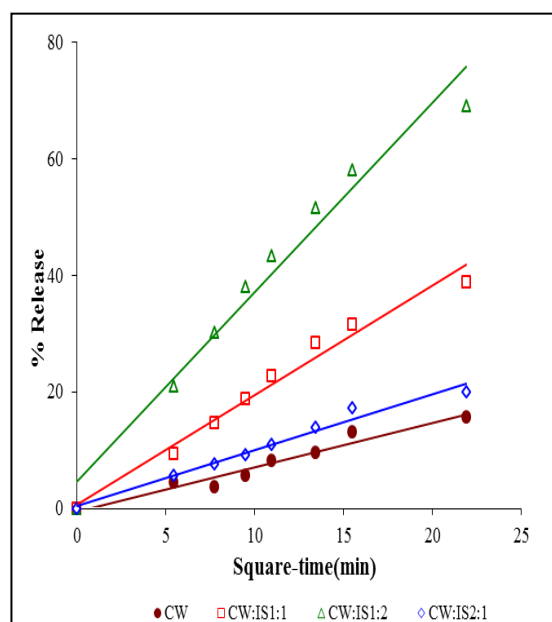


Figure 4 Higuchi's Plots of CPM from wax matrix tablets; using IS as channeling agent ● CW; □ CW: IS 1:1, △ CW: IS 1:2, ◇ CW: IS 2:1

Table 3 Curve fitting parameters from of the release data according to Higuchi model

Formula	k	r^2
F1, CW	1.345 ± 0.070	0.975
F2, CW:PS 1:1	1.868 ± 0.030	0.989
F3, CW:PS 1:2	2.413 ± 0.029	0.969
F3, CW:PS 2:1	1.514 ± 0.032	0.982
F2, CW:IS 1:1	1.859 ± 0.037	0.981
F3, CW:IS 1:2	3.048 ± 0.049	0.970
F3, CW:IS 2:1	0.942 ± 0.076	0.985

Figure 5 illustrated the internal structures of the matrix tablets by SEM micrographs, at initial and after one and four hours of the drug release study. In case of PS, small cracks or channels were observed in matrix tablets after exposed to the release medium as clearly demonstrated in Figure 5(b). This was attributed to the swelling property of potato starch on contact with penetrating water. The swelling force was sufficiently strong to produce small cracks or channels, thus

resulting in an increase of matrix porosity and consequently enhanced the rate of drug release²². The penetration of water into wax matrix progressed with time and cracks and channels were formed deeper inside the matrix tablets as shown in Figure 5(c). The appearance of the internal structure conformed very well with the release study results. Accordingly, swelling of PS was proved to be the major mechanism to enhance the drug release from the matrix.

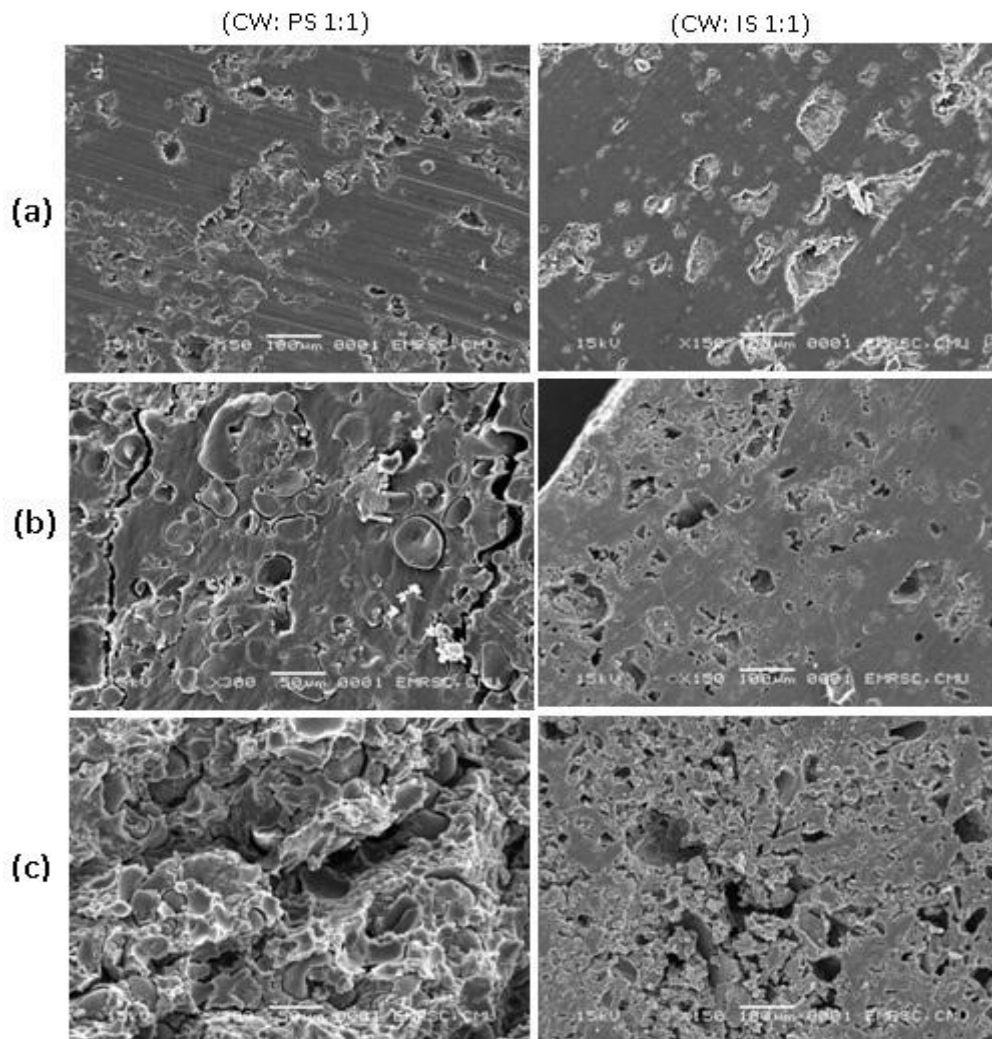


Figure 5- Internal structure of CPM matrix tablets containing PS (left) and IS (right) 1:1 (a) initial and after dissolution; (b) 1 hour and (c) 4 hours under SEM analysis (x 150 and x 300 magnification)

The internal structures of the matrix tablets containing IS as a channeling agent from the drug release study by SEM micrograph were also shown in Figure 5. IS dissolves readily in water upon exposure to penetrating water. As a result, a great number of small holes were subsequently produced after IS dissolved and left from the matrix tablet. The formation of holes inside the tablets increased the release surface for the drug and also accelerated the rate of water penetration into the matrix tablet. These could enhance the drug release from inert wax matrix. At low concentration of IS, a limited numbers of small holes was created and they were rarely connected, the release of drug thus could be enhanced to some extent due to the increase in matrix porosity. As the concentration of IS increased, the number of these small holes increased (Figure not shown). At longer time, not only the number and the size of holes increased, a large channel were also built up resulting from interconnection of these holes as shown in Figure 5(c). From such loosed matrix structure, the release of drug was thus dramatically increased.

3.4 Water uptake and erosion determination

Figure 6 showed the effect of PS and IS on the percentage of water uptake and the percentage of tablet erosion at the end of 4 hours of the release study. It was shown that the channeling agent, either water-insoluble or water-soluble type increased water uptake and tablet erosion of wax matrix tablets, however, at different extents. The values were not significantly different in tablets containing 33 %w/w for each channeling agent (wax: PS/IS 1: 2 by weight). However, both values markedly increased at PS or IS concentrations of 50% w/w and above. It was of interest that, at certain concentration above 50 %w/w, PS exhibited higher water uptake than IS as showed in Figure 6 (a), whereas IS exhibited higher erosion at the comparable concentration. This attributed to the different property of channeling agent on controlling the drug release. PS had strong water attraction, then swelled and created cracks thereafter, whereas IS, readily dissolves then leached out from the matrix. On comparison, the phenomenon produced by IS induced more tablet erosion than PS did. The changes in tablet internal structure were evidenced by SEM micrographs in Figure 5.

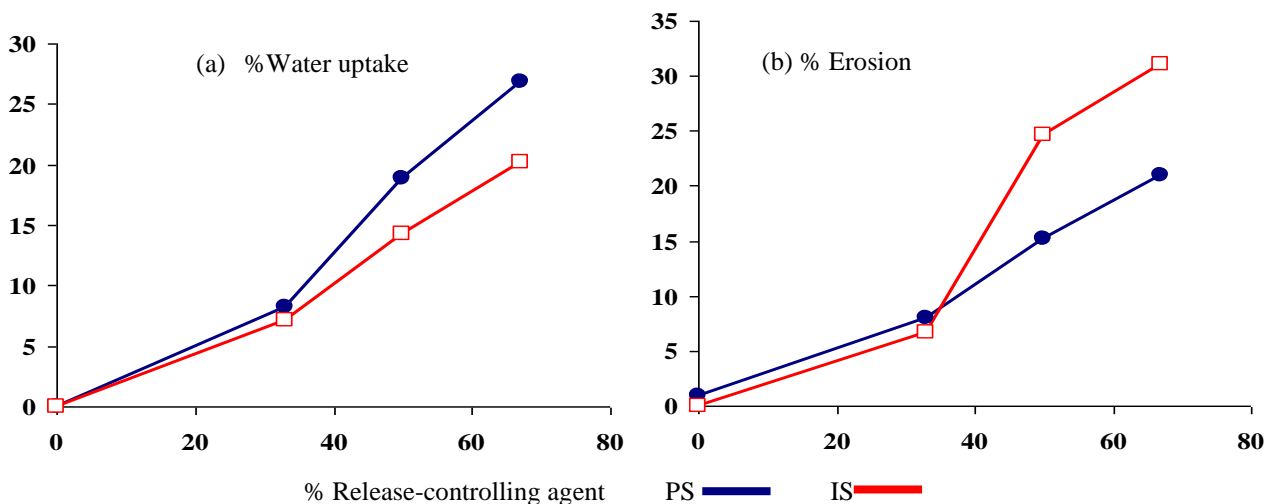


Figure 6 Relationships between percent of release-controlling agents and % water uptake (a), and % erosion (b) of CPM matrix tablets after the end of dissolution test

The relationship between the rate constant of drug release and the percentage of channeling agents was showed in Figure 7. The linear relationship was observed for PS containing matrix tablets, implying that the cracks or capillaries that promoted the drug release were generated dependently on the concentration of PS.

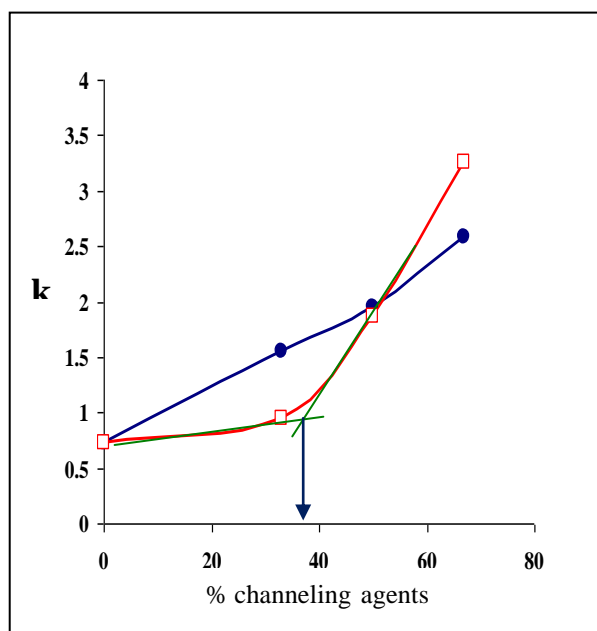


Figure 7 Relationship between the release rate constant, k of CPM from tablet containing ● PS and □ IS

In case of IS containing matrix tablets, the biphasic curve was obtained. At low concentration of IS, the release of drug occurred with almost the constant rate, and it abruptly increased following the concentration when the percentage of IS reached approximately 40% and above. This was clearly demonstrated by SEM micrographs of matrix tablet containing IS of 50%

which showed a network of interconnected holes after the release study at 4 hours in Figure 5(C) and clearly demonstrated by the high percentage of tablet erosion. Understanding of the difference between the mechanisms of PS and IS on promoting the drug release as aforementioned is very important. It provides a great help for a formulator to achieve the wax matrix formulation with the desired release rate of the drug without wasting much time.

4. CONCLUSIONS

The roles and the mechanisms of water-insoluble and water-soluble channeling agents, i.e., potato starch and icing sugar respectively on the release of chlorpheniramine maleate, water-soluble drug from carnauba wax matrix tablets were clearly demonstrated. The kinetics of the drug release from wax matrix fit well with Higuchi’s diffusion model. The incorporation of the two additives did not alter the kinetics of drug release. The rate of drug release significantly increased with the increasing amount of potato starch or icing sugar. However, the extent of drug release and the drug release profiles were directly affected by their properties. SEM micrographs were good visible evidences to provide insight how these additives work on enhancing the drug release. The results of this study could be helpful to give an idea for selecting suitable released-controlling agent in hydrophobic modified release formulation.

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CONFLICTS OF INTEREST

The authors disclose any financial or relationship with people or organization that could be conflict of interest to this manuscript.

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