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In vitro and in vivo evaluation of potassium chloride sustained release formulation prepared with saturated polyglycolyed glycerides matrices

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Abstract

The aim of the present work was to evaluate the effect of sustained release of potassium chloride semi-solid matrices prepared with different kinds and added amounts of Gelucires by the in vitro dissolution test and in vivo oral absorption study, and compared with a commercial product (slow-K). The results indicating that the release rates of potassium from experimental formulations were dependent on the type of semi-solid matrices (Gelucires). The higher the melting point of the Gelucires was incorporated, the slower release rate of the active substance was observed. Moreover, the values of similarity factor of Formulae F05 and F09 versus the reference in three kinds of dissolution medium (f_2) were higher than 50, indicating that these experimental formulations had similar sustained release effects to the reference (slow-K) in dissolution test. In vivo study, the cumulative amount (mEq) of potassium excreted curve and the excretion rate curve of F05 and F09 were found to be similar to that of slow-K, and there were no significant differences ($P > 0.05$) in the maximum excretion rate and the mean time to reach the maximum rate between formulations and slow-K, indicating that the potassium chloride sustained release dosage form could be prepared using the Gelucires as lipid excipients.

Keywords: Potassium chloride; Dissolution test; Gelucire; In vivo study

1. Introduction

Gelucire excipients are total or partial glycerides (triacylglycerols) and polyethylene glycol mono and diesters of different molecular masses which have been used to prepare sustained release lipid matrices including nifedipine, ketoprofen, indomethacin and salbutamol (Dennis et al., 1990; Vial-Jato et al., 1990; Vial-Bernasconi et al., 1995; San-Vicente et al., 2000). The various grades are characterized by their hydrophile-lipophile-balance (HLB) value and melting point, which leads to a specific behaviour when placed in the gastrointestinal fluids in respect of hydrodispersibil-

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ity, melting and floatability (Mathis and Heimendinger, 1989; Vial-Bernasconi et al., 1995). The semi-solid matrix or liquid is filled into a hard gelatin capsule, which may offer many advantages including improvement in chemical stability, excellent homogeneity and content uniformity, easier formulation of oily drugs and preparation of oral sustained release formulations (Naidoo, 1989; Smith et al., 1990). It is also probable that semi-solids which are thermosoftening at body temperature may have the tendency to spread more readily and disperse their contents, thus preventing the effects of localized irritation of the mucus membrane of the oesophageal-gastro tract caused by dose-dumping of ulcerogenic drugs (Naidoo, 1989). The semi-solid matrix can modify drug release by controlling the drug's diffusion rate via altering the characteristic of the base such as the HLB value and melting point, as the more hydrophobic the base, the slower the release rate of the drug (Jones, 1985).

Potassium chloride is indicated for the treatment of hypokalemia or severe potassium loss of various etiologies (Lacy et al., 1998). But potassium chloride is known for its gastrointestinal complications such as ulcerations, hemorrhage, obstruction and perforation. In order to avoid or minimize the adverse effects induced by potassium chloride, the sustained release dosage form seems to be the ideal dosage form because of reduced possibility of a high local concentration of potassium chloride near the gastrointestinal mucosa. Therefore, a series of Gelucires were used as controlled release of base to prepare the potassium chloride semi-solid matrix capsule. The sustained release of potassium chloride from these experimental formulations was investigated via in vitro dissolution test and in vivo oral absorption study and compared with a commercial product (slow-K) which is also a wax-based tablet.

2. Materials and methods

2.1. Materials

Potassium chloride, Cesium chloride, potassium standard solution and sodium chloride were purchased from E. Merk (German). Samples of Gelucires 44/14, 46/07, 48/09, 53/10 and 62/05 were a gift from Gattefoss'e (France). The first two digits of the suffix are the nominal melting point (°C) and the last two digits denote the HLB value. All other chemicals and solvents were of analytical reagent grade.

2.2. Capsule preparation

The compositions of potassium chloride semi-solid formulations are shown in Table 1. The

Table 1
The formulations of potassium chloride of semi-solid matrix capsules (%)

Formulae	G 62/05	G 53/10	G 48/09	G 46/07	G 44/14	KCl	Olive oil
F01	2.5					50	47.5
F02	5.0					50	45.0
F03	10.0					50	40.0
F04		7.5				50	42.5
F05		8.5				50	41.5
F06		10.0				50	40.0
F07			10			50	40.0
F08			25			50	25.0
F09			30			50	20.0
F10				10		50	40.0
F11				30		50	20.0
F12				40		50	10.0
F13					10	50	40.0
F14					50	50	0.0

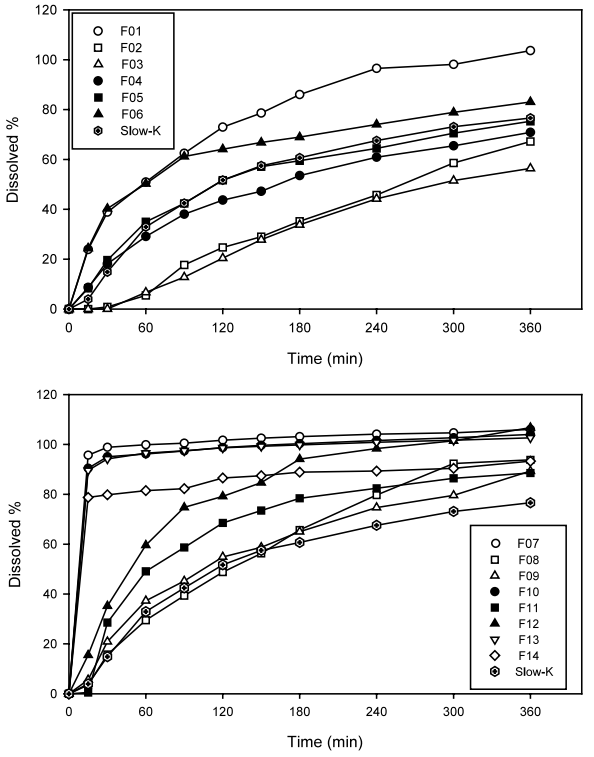

Fig. 1. Dissolution profiles of potassium chloride experimental formulations incorporated various types and amounts of Gelucires commercial product (slow-K) in deionized water.

bases were weighed into a glass beaker and slowly heated to 5–10 °C above the melting point on a hot plate and potassium chloride was added to the molten vehicle with continuous stirring, and then the semi-solid matrix was filled into the hard gelatin capsule. Capsules were kept upright until the mixture solidified, and they were stored at room temperature until testing.

2.3. In vitro dissolution test

Dissolution tests were performed in 900 ml aqueous solution including deionized water, artificial gastric fluid pH 1.2 and artificial intestinal fluid pH 6.8 using the basket method with a rotation speed of 100 rpm at 37 ± 0.5 °C. At fixed time intervals (15, 30, 60, 90, 120, 150, 180, 240, 300 and 360 min), 5 ml samples were withdrawn and replaced with the same volume of dissolution medium. The potassium contents in the dissolution samples were measured by atomic absorption spectrophotometer (Varian, 875 series with a lamp capable of measuring the absorbance of potassium at its secondary wavelength of 766.5 nm). The dissolved amount of drug at each time was expressed as a percentage of the dose.

2.4. Data analysis

The different release kinetics are assumed to reflect different release mechanisms. Therefore, three kinetic models including the zero-order release equation (Eq. (1)), Higuchi equation (Eq.

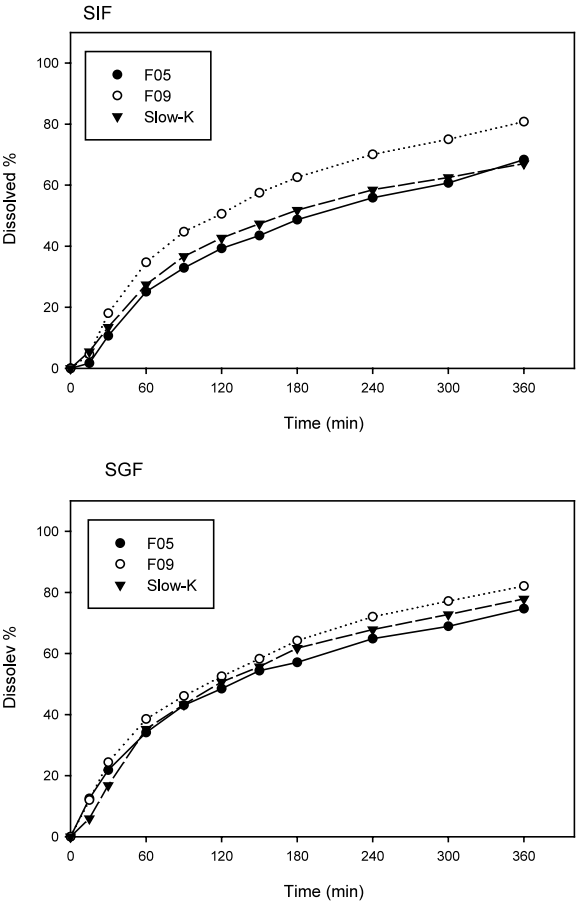

Fig. 2. Dissolution profiles of potassium chloride experimental formulations (F05 and F09) and commercial product (slow-K) in the artificial gastric fluid pH 1.2 and artificial intestinal fluid pH 6.8.

Table 2
The kinetic parameters for potassium chloride release from semi-sold matrix in difference dissolution medium

Dissolution medium	Formulae	Zero-order model		Higuchi model		First order model	
		r	*k*	*r*	*k*	*r*	*k*
Deionized water	F05	0.9479	0.183	0.9912	4.454	0.8043	0.006
	F09	0.9474	0.218	0.9906	5.303	0.7659	0.006
	Slow-K	0.9180	0.194	0.9769	4.807	0.7511	0.006
Gastric fluid pH 1.2	F05	0.9440	0.166	0.9896	4.045	0.8438	0.004
	F09	0.9446	0.186	0.9897	4.546	0.8312	0.004
	Slow-K	0.9264	0.190	0.9811	4.683	0.7754	0.005
Intestinal fluid pH 6.8	F05	0.9509	0.177	0.9920	4.285	0.7413	0.007
	F09	0.9305	0.199	0.9833	4.901	0.7567	0.006
	Slow-K	0.9359	0.167	0.9860	4.087	0.7973	0.006

r: correlation coefficient; *k* (%/min): release rate constant.

(2)) and first-order equation (Eq. (3)) were applied to process the in vitro data to find the equation with the best fit (Moore and Flanner, 1996; James et al., 1997).

$$Q = k_1 t \quad (1)$$

$$Q = k_2 (t)^{0.5} \quad (2)$$

$$Q = 100(1 - e^{-k_3 t}) \quad (3)$$

where Q is the release percentage at time t. The k_1, k_2 and k_3 are the rate constant of zero-order, Higuchi and first order model, respectively.

In addition, the similarity factor f_2 is defined by the following equation and is used to compare the difference of dissolution profiles between the commercial product and experimental formulation.

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

where n is the number of dissolution sample times, and Rt and Tt are the individual percentages dissolved at each time point, t, for the reference and test dissolution profiles, respectively. The f_2 values greater than 50 (50–100) represent equivalence of the two curves.

2.5. In vivo absorption study

Male New Zealand white rabbits (10–12 weeks old, 2.0–2.5 kg) were used and fasted 12 h prior to the experiment. During the study, 8 ml of deionized water was supplied hourly for the 12 h after treatment to ensure adequate urine flow. The first day was the control day for the treatment on the second day. The 600 mg potassium chloride of experimental formulations or commercial product was orally administered with 10 ml deionized water. All urine voided was collected hourly up to the 12th hour and pooled from 12 to 24 h by Nelaton Catheter tube No. 3. The volume of each collection was recorded, and a sample was centrifuged and analyzed for its potassium content by atomic absorption spectrophotometer.

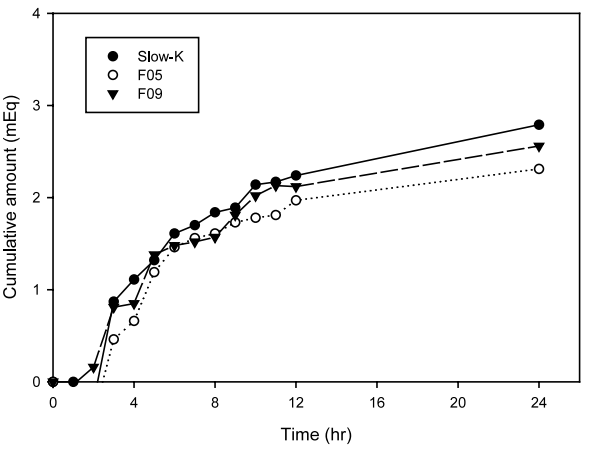

Fig. 3. Cumulative amount (mEq) of potassium excreted in the urine corrected for the control after oral administration of 600 mg potassium chloride in rabbits ($n = 6$).

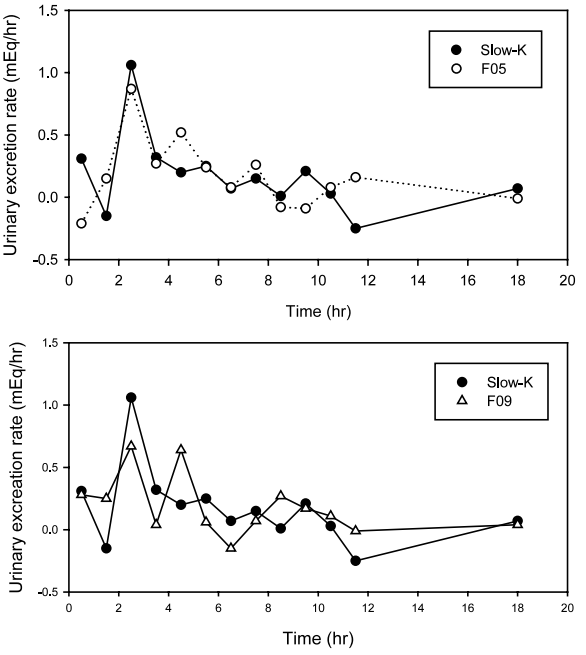

Fig. 4. The curve of urinary potassium excretion rate (mEq/h) corrected for the control vs. the midpoint of the collection interval after oral administration of 600 mg potassium chloride in rabbits ($n = 6$).

3. Results and discussion

3.1. In vitro drug release test

Fig. 1 presents the dissolution profiles of potassium chloride experimental formulations incorporated various types and amounts of Gelucires in deionized water. It shows that with the addition of 10% Gelucires into the capsules, the release rate increased in the following order of Gelucire $62/05 < 53/10 < 48/09 < 46/07 < 44/14$. The higher the melting point, the later the active substance is released, indicating that the melting point of Gelucire was the most influential factor on the release of potassium chloride. In the effect of added amounts of excipients, as was expected, the higher concentrations of Gelucires results in slower release of potassium chloride except for the Gelucire 53/10. The release rate of potassium chloride gradually increased following the added amount of Gelucire 53/10 from 7.5 upto 10%. The results might be presumed that the influence of the HLB value was greater than that of melting point while the small amount of Gelucire 53/10 base (7.5 up to 10%) was incorporated into the formulation. Gelucire 53/10 is a hydrophilic surfactant, since the added amount increased would increase the dispersion of potassium chloride and lead to the fast dissolution from the formulation. Moreover, the dissolution profile of F05 and F09 were similar to the profiles of the commercial product (slow-K), since the f_2 values of F05 and F09 versus slow-K were 74.99 and 51.04, respectively.

The dissolution profile of F05, F09 and the commercial product in the artificial gastric fluid (pH 1.2) and artificial intestinal fluid (pH 6.8) were also investigated and are shown in Fig. 2. The dissolution patterns in these medium were similar and f_2 values were higher than 50 (data not shown), indicating that the pH values of dissolution medium had no effect on the potassium release from the Gelucires matrices.

The release mechanisms of experimental formulations were evaluated on the basis of theoretical dissolution equations including zero-order, Higuchi equation and first order kinetic model (James et al., 1997), since different release kinetics are assumed to reflect different

Table 3
The potassium excretion kinetics in rabbit ($n = 6$)

	F05	F09	Slow-K
Mean maximum excretion rate (mEq/h)	0.93 ± 0.73	0.98 ± 0.32	1.07 ± 0.89
Mean time of maximum excretion rate (h)	4.60 ± 1.14	3.33 ± 1.37	4.17 ± 2.37

There were no significant difference between F05 or F09 and Slow-K ($P > 0.05$, t-test).

release mechanisms. The obtained results are given in Table 2. It is obvious that the correlation coefficients of the Higuchi equation were the highest in different dissolution medium (pH 1.2, 6.8 and deionized water) indicating that the release mechanisms of these potassium chloride matrices were similar in gastrointestinal tract. The better fitting of Higuchi model to the potassium chloride release from semi-solid is due to the fact that the experimental formulations are in a matrix system form in which the release is normally diffusion controlled and the Higuchi model is originally proposed to describe the release of drugs from such systems.

3.2. In vivo absorption study

The cumulative amount of potassium excreted in the urine over 24 h for the two experimental formulations and the commercial product (Slow-K) is shown in Fig. 3. The cumulative urinary potassium values corrected for the control were equivalent to 35.6, 39.0 and 41.9% of the state dose for the F06, F12 and Slow-K, respectively. There were no significant differences ($P > 0.05$), indicating that the sustained release effect of F05 and F09 were similar to that of slow-K. The excretion rate curves are shown in Fig. 4. The excretion rate curves of F05 and F09 were found to be similar to that of slow-K. Moreover, there were no significant differences ($P > 0.05$) in the maximum excretion rates and the mean times to reach the maximum rate between experimental formulations and slow-K as shown in Table 3 indicating that the experimental formulations indeed possessed sustained release effects. The above in vitro and in vivo results demonstrate that the potassium chloride sustained release dosage form could be prepared using the Gelucires as lipid excipients.

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