Formulation, Bioavailability, and Pharmacokinetics of Sustained-Release Potassium Chloride Tablets

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The release of potassium chloride incorporated into hydrogenated vegetable oil and hydroxypropyl methylcellulose matrix tablets was studied *in vitro*. The formulations containing 20% hydrogenated vegetable oil and hydroxypropyl methylcellulose showed a sustained-release profile comparable to that of a standard commercially available sustained-release preparation, containing 8 mEq potassium chloride embedded in a wax material. The formulated and standard sustained-release potassium chloride tablets were compared to a conventional enteric-coated potassium chloride tablet in 10 healthy subjects. Mean recoveries in 24-hr urine potassium levels from four dosage forms (after subtracting normal urine potassium excretion levels) were 76 ± 32% from hydroxypropyl methylcellulose, 95 ± 22% from hydrogenated vegetable oil-incorporated matrix tablets, 91 ± 29% from commercially available sustained-release tablets, and 97 ± 13% from enteric-coated tablets. There was no significant difference ($P > 0.05$) in the time to reach maximum excretion rates among the three sustained-release tablets. No significant adverse effect was experienced with any of the preparations.

KEY WORDS: potassium chloride; sustained-release tablets; formulation; *in vitro* evaluation; bioavailability; pharmacokinetics; *in vitro–in vivo* evaluation.

INTRODUCTION

Potassium, which is the principal intracellular cation, is essential for a number of physiological processes including nerve transmission, muscle contraction, and renal function. This cation also plays a key role in the genesis and correction of imbalance of acid–base metabolism. Potassium supplementation is, therefore, necessary when depletion of this cation occurs (1,2). Potassium chloride is the preferred salt for most situations, since chloride deficiency often coexists with that of potassium. Oral potassium supplementation has, however, been associated with a disturbing incidence of gastrointestinal side effects, primarily because of rapid disintegration of enteric-coated tablets (3–7). Hence, sustained-release potassium chloride tablets with a low incidence of gastrointestinal bleeding have found wide acceptance, avoiding localized release at high concentration (8,9).

Urinary excretion of potassium is commonly used as a measure of *in vivo* absorption in humans, because of known resistance in plasma level changes of potassium following oral supplementations (10–13).

One objective of the present study was to examine the *in vitro* release characteristics of potassium chloride from different matrix tablets in order to assess the suitability of such formulations for the production of sustained release dosage forms. The other objective was to evaluate the bioavailability and pharmacokinetics of sustained-release dosage forms of potassium chloride. In addition, circadian variation in urinary potassium excretion on control days with a fixed diet was examined. For evaluating the bioavailability and pharmacokinetics of the formulated sustained-release potassium chloride tablets, a commercially available enteric-coated tablet and a sustained-release tablet were used for comparison.

MATERIALS AND METHODS

Materials

The following materials were used: potassium chloride (E. Merck, Darmstadt, Germany), hydrogenated vegetable oil (Lubritab, E. Mendell Co. Inc., Carmel, New York 10512), hydroxypropyl methylcellulose (Metolose 60 SH 4000, Shinetsu Chemical Co., Japan), dibasic calcium phosphate dihydrate (Emcompress, E. Mendell Co. Inc., Carmel, New York 10512), magnesium stearate (E. Merck, GmbH Leverkusen, Germany), 600 mg potassium chloride sustained-release tablets (KCl-Retard, Zyma SA, Switzerland), and 572 mg enteric-coated potassium chloride tablets (K-Enteric, İ. E. Kimya Evi T.A.Ş., Turkey).

Methods

Preparation of Tablets

Hydroxypropyl methylcellulose (HPMC) and hydrogenated vegetable oil (Lubritab) were used as matrix materials. The powders were mixed and directly compressed with 1% magnesium stearate incorporated as a lubricant prior to compression. Tablets were compressed on a single-punch tablet machine Korsch EK/0, at a tablet weight of 1000 mg, using a flat nonbeveled punch of 12-mm diameter, and tablet hardness was kept constant within the range of 7.5–8.0 kp on a Heberlein hardness tester. Sustained-release matrix tablets were formulated to contain 600 mg or 60% potassium chloride and 10, 15, and 20% matrix material of total tablet weight. In order to obtain a constant tablet weight, different percentages of dibasic calcium phosphate dihydrate were added as a filler.

In Vitro *Release of Potassium Chloride from Tablets*

The manufactured and commercially available tablets were tested for dissolution in 900 ml of distilled water using the USP XXI Apparatus II at 50 rpm. Samples were collected at appropriate time intervals, filtered, and assayed for potassium using a Dr Lange MD 70 flame photometer. Lithium was used as the internal standard. In addition, the disintegration of the commercially available enteric-coated tablets was carried out with the USP XXI–NF XVI method.

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In Vivo *Studies*

Ten healthy volunteers, eight females and two males, after the explanation of the experimental protocol, agreed to participate in the study. The age of the subjects ranged between 20 and 39 years (22.7 ± 5.8) and their weight was between 50 and 75 kg (59 ± 7.8). The subjects were clinically examined and found to have no hepatic, renal, or cardiovascular disease or history of gastrointestinal disorders. Routine laboratory determinations and physical examinations of the volunteers were conducted by a physician before admission to the study. The subjects remained under his supervision during the study. To avoid salt and water loss through perspiration, the subjects were not allowed to engage in strenuous exercise.

Study Design

The subjects were given each of the following formulations as a single oral dose on four separate occasions in an open-label four-way crossover treatment:

(A) five 1-g formulated sustained-release tablets containing 20% HPMC (40 mEq potassium),
(B) five 1-g formulated sustained-release tablets containing 20% Lubritab (40 mEq potassium),
(C) five 600-mg commercially available sustained-release tablets (40 mEq potassium), and
(D) six 572-mg enteric-coated tablets (46 mEq potassium).

The administration sequence was assigned randomly. The subjects were required to drink 2500 ml of water daily. They received a uniform diet containing an average of 90 mEq potassium. No additional food or snacks were permitted. Meals were served at 7:00 AM, 1:00 PM, and 6:00 PM. On treatment days (days 3, 5, 10, and 12) potassium dosing began at 9:00 AM. The first 2 days after admission (days 1 and 2) were control days for the first treatment on day 3. The third control day (day 4) was followed by the second treatment on day 5. The rest days (days 6 and 7) were followed by 2 control days (days 8 and 9), and the third treatment on day 10. After a control day (day 11), the final drug formulation was administered on day 12.

Collection of Samples

On both control and treatment days, urine was collected hourly for 8 hr and then every 2 hr up to 12 hr. The urine excreted during the remaining 12-hr interval (12–24 hr) was collected as a single specimen during the night. Urine potassium was determined by flame photometer using lithium as the internal standard.

Analysis of Data and Statistics

Changes in urine potassium levels for each collection from a subject were determined by subtracting the average urine potassium level of the six predosing control days of this subject from the urine potassium levels of treatment day. The net increase in the peak height of the urinary excretion curve, as well as the time to reach that peak was calculated in a similar fashion.

Comparisons of formulations between subjects were performed by use of two-way ANOVA. Significant differences identified at the 5% level were further defined by calculation of the 95% confidence interval of the difference between the two means by use of the pooled estimate of variance.

RESULTS

In Vitro

For Lubritab incorporated matrix tablets, the released amount of potassium chloride decreased as the matrix concentration was increased. But for tablets containing HPMC, the dissolution of the drug was independent of polymer concentration.

In order to investigate the mechanism of release, the following semiempirical equation was used (14,15):

$$M_t/M_\infty = k\,t^n \qquad (1)$$

where M_t/M_∞ is the fraction of drug released up to time t, k is a constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent indicative of the mechanism of release. The estimated parameters are given in Table I. When Eq. (1) is applied during early stages of release (fraction released, <0.7) to the geometries other than slabs (i.e., tablets), the value of the diffusional exponent, n, depends on the geometry of the system (14,15). In the case of a cylinder, Fickian diffusion is defined by $n = 0.45$ and Case II by $n = 0.89$. The correct values of exponent n for different geometries are reported in Table II.

The derived values of n (Table I) were similar for each particular drug system. Peppas and Sahlin (15) stated that diffusional controlled (Fickian) release from planar surfaces gave a value of $n = 0.45$. Thus the values of n obtained for Lubritab emphasize that release of drug is Fickian diffusion controlled. The release rate constants determined from Eq. (1) are given in Table I. The decrease in percentage of Lubritab and HPMC increased the release rate, which may be because of the possible changes in the porosity and tortuosity of the matrix. The main objective was to have a release in

Table I. Values of Kinetic Constant (k), Release Exponent (n), and Determination Coefficient (r^2) Following Linear Regression of Dissolution Data of Formulations Containing Different Polymers and KCl-Retard Sustained-Release Tablets

Formulation	n (mean ± SD)	k	r^2
HPMC			
10%	0.483 ± 0.014	0.356	0.995
15%	0.469 ± 0.008	0.352	0.998
20%	0.490 ± 0.008	0.345	0.999
Lubritab			
10%	0.455 ± 0.030	0.515	0.990
15%	0.466 ± 0.043	0.460	0.979
20%	0.443 ± 0.021	0.410	0.990
KCl-Retard	0.753 ± 0.020	0.258	0.978

Table II. Geometric Dependence of the Diffusional Exponent (n) in Eq. (1)

Diffusional exponent (n)			Transport mechanism
Slab	Cylinder	Sphere	
0.5	0.45	0.43	Fickian (Case I)
>0.5	>0.45	>0.43	Anomalous
<1	<0.89	<0.85	
1	0.89	0.85	Case II

the range of 40–65% by 3 hr and 55–80% by 6 hr for the sustained-release potassium chloride tablets (16). The 20% Lubritab and 20% HPMC and KCl-Retard tablets gave the desired release and were evaluated further *in vivo*. Drug released from conventional enteric-coated tablets conforms with the requirements of USP XXI.

In Vivo

The mean control value for 10 subjects was 45.0 ± 9.5 mEq (Table III). An analysis of variance with repeated measurements on subjects was carried out and showed no significant differences between the control days ($P > 0.05$) but significant differences between the subjects were observed ($P < 0.05$). These results suggest that there was no significant carryover in urinary potassium excretion because of the treatment received during the previous period. It is, therefore, reasonable to proceed without consideration of treatment order.

The net increase in the 24-hr potassium level after administration of preparations is given in Table III. According to the results of ANOVA, the mean cumulative 24-hr urinary potassium values (%), corrected for sustained-release and enteric-coated tablets, did not differ significantly from one another ($P > 0.05$, Fig. 1).

The 24-hr urine collection was divided into five fractions to determine the potassium elimination patterns of formulated and commercially available sustained-release tablets in comparison to K-Enteric tablets. The results (Table III) indicate that significantly greater excretions were observed

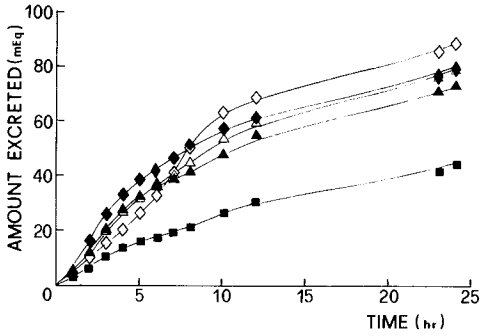

Fig. 1. Cumulative amount of potassium excreted following oral administration of sustained-release and enteric-coated tablets. ■, Control; ▲, HPMC; ♦, Lubritab; △, KCl-Retard; ◇, K-Enteric.

after the sustained-release tablet treatments than after the enteric-coated tablets during the first two intervals (0–2 and 2–4 hr, $P < 0.05$). During the 4- to 6-hr postdose period, the excretion in the sustained-release and enteric-coated tablets was essentially the same ($P > 0.05$). In the fourth period, more potassium was excreted in the urine after K-Enteric tablets ($P < 0.05$). In this interval, no difference was observed between Lubritab and KCl-Retard sustained-release tablets ($P > 0.05$). Significant differences were observed between 40-mEq Lubritab matrix tablets and 40-mEq KCl-Retard tablets only for the 0- to 2-hr interval (i.e., 9.3 ± 4.0 vs 4.4 ± 2.1; $P < 0.05$) and for the 6- to 8-hr interval when HPMC matrix was compared with KCl-Retard tablets ($P < 0.05$). The differences in the levels of potassium excretion during the final interval (8–24 hr postdose) of sustained-release tablets were not significant ($P > 0.05$). However a significant difference was notable between the sustained-release and the enteric-coated tablets ($P < 0.05$).

The excretion rate curve of each product is shown in Fig. 2. The sustained-release tablets resulted in lower h_{max} values than for enteric-coated tablets ($P < 0.05$), and the t_{max} for enteric-coated tablets was longer ($P < 0.05$, Table III). No significant difference was obtained between the t_{max} values of sustained-release tablets ($P > 0.05$). Also, there were no significant differences among the subjects for h_{max} and t_{max} values for all products ($P > 0.05$).

Table III. Cumulative Potassium Recovery in 24 hr and Potassium Excretion Kinetics

Interval (hr)	Mean control potassium level (mEq ± SD)[a]	Net increase in urine potassium level in 24 hr (mEq ± SD)			
		Lubritab	HPMC	KCl-Retard	K-Enteric
0–2	7.4 ± 1.3	9.3 ± 4.0	5.7 ± 5.0	4.4 ± 2.1	3.6 ± 2.5
2–4	6.9 ± 0.7	9.9 ± 2.9	8.6 ± 3.9	8.7 ± 3.1	3.6 ± 2.5
4–6	4.3 ± 0.8	5.4 ± 2.1	4.6 ± 1.8	5.7 ± 3.6	6.9 ± 4.2
6–8	3.7 ± 0.5	4.5 ± 4.3	1.8 ± 1.6	4.9 ± 2.6	13.2 ± 5.9
8–24	22.6 ± 2.3	8.8 ± 6.5	9.8 ± 8.4	12.7 ± 6.9	17.3 ± 8.0
Total	45.0 ± 9.5	37.9 ± 8.8	30.5 ± 12.9	36.3 ± 11.5	44.6 ± 6.8
CV (%)	18	23	42	32	15
Cumulative recovery (%)		94.8 ± 21.9	76.2 ± 32.1	90.9 ± 28.8	96.7 ± 12.9
h_{max} (mEq/hr ± SD)		7.1 ± 1.6	5.2 ± 2.2	5.6 ± 1.6	9.8 ± 2.7
t_{max} (hr ± SD)		2.3 ± 0.8	2.4 ± 0.6	2.4 ± 0.9	6.7 ± 1.5

[a] Average of 6 control days.

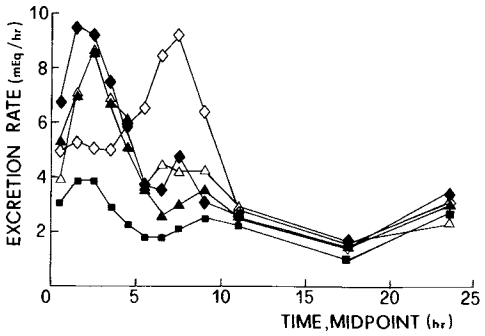

Fig. 2. Mean urinary potassium excretion rate before and after administration. ■, Control; ▲, HPMC; ♦, Lubritab; △, KCl-Retard; ◇, K-Enteric.

In Vitro/in Vivo Correlation

Quantitative relationships were obtained between the percentage potassium excreted and its *in vitro* release for Lubritab, HPMC, and KCl-Retard sustained-release tablets. Figure 3 was constructed by taking corresponding amounts (in percentage) for *in vivo* and *in vitro* release of the same 1-hr interval up to 8 hr of the sustained-release tablets. However, no correlation was obtained between the excretion and the dissolution rates of commercial enteric-coated tablets, whereas there was a high *in vitro–in vivo* correlation, with a determination coefficient of 0.995 ($P = 0.0001$) for HPMC, 0.948 ($P = 0.0001$) for Lubritab, and 0.986 ($P = 0.0001$) for KCl-Retard sustained-release tablets.

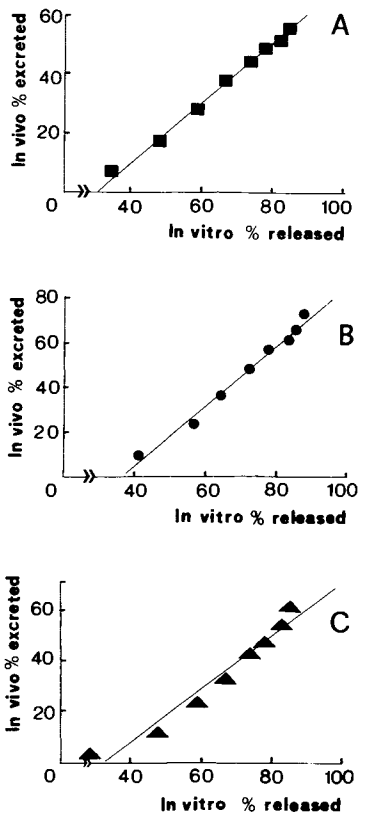

Fig. 3. Plot of the percentage of cumulative potassium excreted in the first 8 hr following oral administration vs *in vitro* release in the corresponding times: (A) HPMC; (B) Lubritab; (C) KCl-Retard.

DISCUSSION

In Vitro

For formulations containing potassium chloride and Lubritab, an increase in the percentage of polymer decreased the release rate in a nonlinear manner. These results showed that for Lubritab, a Fickian diffusion mechanism predominates ($n = 0.45$), while for HPMC and KCl-Retard matrix tablets a non-Fickian mechanism occurs ($n > 0.45$), and release rates were not reduced by increasing the polymer concentration. Owing to slow erosion of the outer gel layer of HPMC matrices, the diffusional path length for the drug increased with time and hence the release rate decreased with time.

Preliminary studies revealed that the criterion of acceptance might be that, at 3 hr, between 40 and 65% and, at 6 hr, between 55 and 80% of label claim is released (16,17). The results of the present study support this observation.

In Vivo

In investigations on the bioavailability of potassium-containing preparations, problems encountered were often because of the nonstandardization of dietary intake, since uncontrolled ingestion of potassium immediately causes a change in the pattern of urinary potassium excretion. In addition to diet, fluid intake and physical activity should also be carefully controlled in bioavailability studies of potassium. The diet used in this investigation was satisfying since it provided a steady intake of potassium, particularly in the first 8 hr after administration of the preparations, when fluctuating levels of ingested potassium could interfere with the results. Studies on the bioequivalance of sustained-release preparations containing potassium generally require approximately 40 mEq potassium to be given orally if clear differences in potassium excretion compared to control days are to be shown (10,11,18).

This study did not demonstrate any statistical difference in the formulated Lubritab and HPMC matrix or commercially available KCl-Retard sustained-release tablets of potassium chloride in terms of the total amount of potassium excreted over a 24-hr period or in the rate of potassium excretion. However, the K-Enteric tablet, which has a solid core of potassium chloride, released potassium rapidly when it reached the alkaline environment of the small intestine. The observed variation in delay results from such factors as gastric emptying time and pH and motility of the small intestine. The sustained-release preparations of potassium chloride are formulated to release potassium and chloride ions slowly over time. As a result, these preparations avoid a sudden high concentration of potassium.

Our data differ from those of other authors reporting bioavailability values for potassium chloride slow-release tablets of 27% (10), 47% (18), 50–53% (12), and 50% (13). One explanation for this discrepancy could be the use of different slow-release potassium chloride preparations. Another possibility could be the duration of renal excretion sampling (8 hr in earlier studies and 24 hr in this report) after a single administration. The higher recoveries of potassium in this study are in agreement with the previous single-dose data of Moller *et al.* (11) and Skoutakis *et al.* (19).

The maximum urinary excretion rate values (Table III) were significantly different between sustained-release and enteric-coated tablets, thus lending credibility to the sustained release of potassium from Lubritab, HPMC, and KCl-Retard tablets. If the sustained-release tablets had released potassium chloride in a nonprolonged fashion, the maximum rate from the sustained-release tablets would have been greater than from enteric-coated tablets.

The linear relationship between the mean *in vitro* release pattern of the sustained-release formulations and that *in vivo* indicates that the rate of absorption of the drug is almost constant. Thus, for this type of formulation, *in vitro* release profiles are a reasonable reflection of the availability rate *in vivo*. It is noteworthy that although five potassium chloride sustained-release tablets were administered as a single dose, there were no adverse reactions in any of the 10 subjects.

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