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

Sevda Şenel,1 Yılmaz Çapan,1,4 Turgay Dalkara,2 Neriman İnanç,3 and A. Atilla Hincal1

Received September 26, 1990; accepted April 10, 1991

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 ± 25% 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 (Lubritat, 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 (KCI-Retard, Zyma SA, Switzerland), and 572 mg enteric-coated potassium chloride tablets (K-Enteric, I. E. Kimya Evi T.A.S., Turkey).

Methods

Preparation of Tablets

Hydroxypropyl methylcellulose (HPMC) and hydrogenated vegetable oil (Lubritat) 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.
**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):

\[
M_t/M_{∞} = k \cdot t^n
\]

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