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Development and bioequivalence study of potassium chloride extended release tablets✩

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A B S T R A C T

The purposes of this study are to prepare the generic extended release tablet of potassium chloride (PC) 600 mg and to compare the absorption of potassium ion from the experimental tablets to that of Kaleorid® LP 600 mg (Leo Pharmaceutical Products, Denmark). Carnauba wax was used as retardant in the matrix core tablets. The core tablets were coated with blends of ethyl cellulose (EC) and hydroxypropyl methyl cellulose (HPMC) to modulate the drug release. Results of a selective two-level, three-factor experiment design revealed that a blend of 41.75% of EC and 58.25% of HPMC at 4.5% weight gained could produce the coated tablets having dissolution profiles similar to those of Kaleorid®. A two-treatment, two-period, two-sequence crossover bioequivalence study was carried out on 24 healthy volunteers to compare the absorption of potassium ion from experimental tablets to that from Kaleorid®. The potassium ion in the urine was measured by a selective electrode of the ADVIA 1650 system (Bayer) and used to calculate cumulative urinary excretion and urinary excretion rate. Results of 90 percent confidence interval analysis showed that the limits for natural log-transformed cumulative urinary potassium excretion (Ln $AE_{0.95}$) of test product were in the range of 3.73–3.79 mEq, corresponding to 99.08%–100.92% of Kaleorid®, respectively, and the limits for natural log-transformed maximal potassium excretion rate ($R_{max}$) of test product were in the range of 1.72–1.82 mEq/h, corresponding to 97.34%–102.66% of reference product, respectively. Both of them fell within the bioequivalence interval (80%–125%) of reference product, proving that experimental product is bioequivalent to Kaleorid®.

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1. Introduction

Potassium is essential for a number of physiological processes including nerve transmission, muscle contraction and renal function. Potassium also plays a key role in the genesis and correction of imbalances of acid–base metabolism [1]. Potassium supplements are indicated for the treatment of patients with potassium depletion (hypokalemia) or prevention of hy-
pokalemia in patients who would be at particular risk if hypokalemia were to develop (e.g., patients receiving digitalis therapy or patients with significant cardiac arrhythmias). The depletion of this ion usually develops slowly in many cases, and the patients have to take the medicine in a long therapy period. Hence, extended release (ER) oral potassium supplements with a low incidence of gastrointestinal disturbance have found widely accepted [2]. Moreover, potassium chloride (PC) has been known for its gastrointestinal complication risks such as ulceration, hemorrhage, obstruction and perforation, and can even lead to necrosis and subsequent scarring. The ER dosage form seems to be the ideal one because of reduced possibility of a high local concentration of PC near the gastrointestinal mucosa [3]. ER dosage forms of PC have been developed in matrix structure or coated dosage forms.

Cellulosic polymer most often used for controlled release is ethyl cellulose (EC) due to its good film forming properties. EC is a water-insoluble polymer generally regarded as non-toxic and non-allergenic. It is stable under physiological as well as during normal storage conditions. Due to the low permeability of pure EC, polymer blends of EC and water-soluble polymers are often used as coatings [4]. Hydroxypropyl methyl cellulose (HPMC) is the most commonly used water-soluble polymer, and the release mechanism from pellets or tablets coated with EC:HPMC films with different polymer ratios has been extensively studied. EC:HPMC coatings are for instance used in osmotic controlled drug delivery systems [5].

Plasma potassium concentration is controlled by homeostatic mechanisms, thereby making it inaccurate to determine bioavailability by measuring blood levels. In order to determine the bioavailability of potassium preparations, some investigators have measured urinary potassium concentration [6]. This methodology is reasonable, since the major route of elimination for potassium is urinary excretion. Moreover, under steady state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. To achieve successfully these goals, it is necessary to control the diet and physical activity of the subjects. They must receive menus of known potassium and sodium content and abstain from exercises that may cause excessive perspiration and thus electrolyte losses [7].

Potassium is an intracellular cation and serum potassium level was maintained within a relatively narrow range, an accurate determination of bioavailability using potassium in plasma or serum is difficult [8]. Urinary potassium measurements were used in this study to estimate bioequivalence of products.

The objectives of present study were to develop a generic ER preparation containing 600 mg of PC and to compare the rate and extent of absorption of the potassium ion from experimental product with those of marketed product (Kaleorid® LP 600 mg, Leo Pharmaceutical Products, Denmark).

## 2. Materials and methods

### 2.1. Materials

Potassium chloride was supplied from the Mekophar (Viet Nam); ethyl cellulose was kindly offered from Colorcon (Viet Nam). Carnauba wax (KahlWax, Germany) and stearyl alcohol (India) were purchased. All materials complied with the specification of pharmacopoeia or analytical grade. Kaleorid® LP (batch No. DA 8417, Leo Pharmaceutical Products, Denmark) was used as reference product to compare dissolution profiles and absorption in bioequivalence study.

### 2.2. Preparation of extended release tablets

Due to high solubility of PC in water, the ER tablets were designed in combination of matrix structure core and retard coating. Either stearyl alcohol or carnauba wax was used as retardant for the matrix. Tablets were prepared by direct compression process: PC was mixed with either stearyl alcohol or carnauba wax in a cubic mixer for 30 min. The mixture then was heated in an oven for 1 h at 100°C and passed through 1 mm sieve. The lubricant was added to the granules and the final mixture was mixed again for 5 min in a cubic mixer. The oblong-shaped tablets were compressed in the rotary tabletting machine. The average weight of tablets was in the range of 630–655 mg depending on the compositions of the tablets as could be seen in Table 1. The hardness of the tablets was maintained in the range of 180–200 Newtons.

The tablets were applied a subcoating of HPMC at 5% of weight before functional coating to enhance the adhesion of the functional coating. Polymer blends of EC and HPMC at various ratios were used as coatings to control the release of PC from the tablet. PEG 6000 was used as plasticizer. A selective two-level, three-factor experiment design (2³ factorial design) was adopted to study the dissolution profiles of drug from coated tablets. Experiment design for the optimization of percentage of EC in blends of EC was as follows: HPMC was taken as x₁, percentage of PEG 6000 was taken as x₂ and weight gained of coating was taken as x₃ and tabulated in Table 2. The percentage of drug released at 1, 2 and 6 h were taken as dependent variables and tabulated in Table 3.

### Table 1 - Compositions of the core tablets.

|          | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|----------|----|----|----|----|----|----|----|----|----|-----|
| PC (mg)  | 600| 600| 600| 600| 600| 600| 600| 600| 600| 600 |
| Stearyl alcohol (mg) | 50 | 45 | 40 | 35 | 50 | 45 | 40 | 35 | 30  | 25  |
| Carnauba wax (mg) | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5   | 5   |
| Aerosil (mg) | 655| 650| 645| 640| 655| 650| 645| 640| 635| 630 |
| Total (mg) | 7.63| 6.92| 6.20| 5.47| 7.63| 6.92| 6.20| 5.47| 4.72| 3.97 |

Percentage of retardant in tablet (%)
2.3. In vitro release test

In vitro release tests were performed using method II as per BP 2003: 900 ml of distilled water at 37.0 ± 0.5 °C was used as medium and rotation of the paddles was maintained at 50 rev/min. A sample of 10 ml of the medium was withdrawn at 1, 2, 3, 4, 5 and 6 h and the drug release was determined by the end point potentiometrical method in the following manner: add 25 ml of water, 5 ml of a 25% v/v solution of glacial acetic acid and 0.1 ml of a saturated solution of potassium sulfate and titrate with 0.01M silver nitrate VS determining the end point potentiometrically. Each ml of 0.01M silver nitrate VS is equivalent to 0.7455 mg of PC. The similar factor f2 was used to compare the difference of dissolution profiles between the reference product and experimental formulation. The f2 value greater than 50 (50–100) represents equivalence of the two curves.

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

n is the number of time points; R is the mean percent reference drug dissolved at time t after initiation of the study; T is the mean percent test drug dissolved at time t after initiation of the study.

2.4. Determination of potassium chloride content

The content of PC in the tablets was determined by the end point potentiometrical method as follows. Remove the coating of 10 tablets, shake the core of 10 tablets with about 800 ml of hot water then heat on a water bath for 30 min. Cool, add sufficient water to produce 1000 ml. Filter and dilute to give a concentration of about 0.6 mg/ml. Take 10 ml of solution and determine the content of PC in the same manner as described in drug release test.

2.5. Bioequivalence study

2.5.1. Subjects

Twenty four healthy male volunteers, aged 21–27 y (22.75 ± 1.49 y) with body mass index in the range of 18.5–24.9 (21.8 ± 1.22), participated in this study. Female volunteers were excluded to avoid variability in physiological status peculiar to female like menstruation, lactation, etc. The subjects were examined and found to have no hepatic, renal, or cardiovascular disease or history of GI disorders. Routine laboratory determinations, ECGs, and physical examinations were conducted before admission to the study center. Informed consents were obtained after the study protocol was approved by the Ethics Committee of The Bioequivalence Evaluation Center in Ho Chi Minh City, Viet Nam.

2.5.2. Test product and reference product

Test product was experimental formulation coated with a blend of EC and HPMC at a suitable ratio and reference product was Kaleorid® LP (batch No. DA 8417, Leo Pharmaceutical Products, Denmark).

2.5.3. Study design

A two-treatment, two-period, two-sequence crossover study was carried out. To avoid salt and water loss through perspiration, the subjects stayed indoors in air-conditioned rooms under the supervision of the medical and nursing staff. Physical activities were restricted to avoid excessive sweating. A standardized diet, with known amounts of potassium and sodium, was supplied to the subjects at fixed times. The fluid intake was maintained at 3700 ml per day to ensure an adequate rate of urine flow. Each subject administered 500 ml of water at 7:00 a.m. and 200 ml every hour afterwards up to 11:00 p.m. Extensive urine sampling for determination of urinary potassium excretion was performed, with creatinine clearance determined to ensure that urine collection has been adequate.

The first day was controlled day for baseline potassium urine. The samples of urine were divided into 10 collections over 24 h for each subject. The volume of each urine collection was recorded to calculate the level of potassium excreted. After the aliquots were drawn for potassium assay, all remaining urine samples for each subject over a 24 h period were pooled for urine creatinine determination. A blood sample was drawn at 2:00 p.m. for serum creatinine determination.

The second day was the dosing day. After a fasted overnight, the subjects were dosed 80 mEq of potassium in a single dose of either the test or reference product at 7:00 a.m. with 500 ml of water. The schedules of fluid intake, blood sample, and urine collection were similar to those of day 1. Stool tests were performed on all feces to determine any loss of blood.

The third day was postdosing day for calculating the cumulative potassium urinary excretion from 0–48 h (Ae0–48). A washout period of 1 week was given before crossover to the next formulation.
2.5.4. **Potassium determination**

The potassium ion in the urine was measured by an ion selective electrode of the ADVIA 1650 system (Bayer). In this method, the urine sample was automatically determined by a potassium electrode.

2.5.5. **Pharmacokinetic analysis**

Cumulative potassium urinary excretion in 24 h (Ae0-24) and in 48 h (Ae0-48) was calculated after subtracting normal urine potassium excretion. The rate of potassium urine excretion (R) was calculated by dividing the amount of potassium excreted in the urine during a collection interval by the time elapsed. T was the time of each corresponding R. Statistical analysis (P = 0.05) were performed for raw data and natural log-transformed data. The two one-sided t tests were used to determine 90 percent confidence intervals of 24 h cumulative urinary excretion (Ae0-24) and maximal rate of urinary excretion (Rmax).

3. **Results and discussion**

3.1. **Formulation of the core tablets**

Results of drug release tests, as illustrated in Fig. 1A and Fig. 1B, showed that both of retardants could prolong the release of PC from the tablets. However, the tablets containing stearyl alcohol (formulation F1–F4) were stuck to the upper punches after a short time of compress process, maybe due to the low melting point (50°C) of this excipient.

The tablets using carnauba wax as retardant could release PC at the percentage lower than those using stearyl alcohol at the same ratio of retardant. The sticking did not occur with tablets containing carnauba wax in compressing. As could be seen in Fig. 1B, formulation F10 released over 80% of drug at 3h, indicating that the percentage of carnauba was about 4% could not retard the release of drug effectively. Among the remaining, formulation F9 was considered to be promising due to the small amount of carnauba wax used to retard the release, hence the smallest weight of the core tablets makes it easy to be swallowed.

![Figure 1](image_url)  
**Fig. 1** – Dissolution profiles of core formulations. A: with stearyl alcohol as retardants (F1–F4); B: with carnauba wax as retardants (F5–F10) (each point represents the mean ± SD, n = 6).

3.2. **Coating of the potassium chloride tablets**

The core tablets from F9 were chosen to coat with blends of EC and HPMC, in which HPMC was used as pore former of the coating. As per 2^3 factorial design, 8 coating formulations (FC) were conducted and the results of drug released were depicted in Table 4.

| Table 4 | Drug released from PC tablets coated with various blends of EC and HPMC in coating formulations of factorial design (n = 6 for formulation FC 1–FC 8 and n = 12 for Kaleorid®). |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Formulation code | x1 | x2 | x3 | Drug release (%) (Mean ± SD) | 1h (y1) | 2h (y2) | 6h (y3) |
|-----------------|---|---|---|-------------------------------|--------|--------|--------|
| FC 1            | 35| 20| 3.5| 27.40 ± 2.96                 | 53.40 ± 4.36 | 88.34 ± 1.84 |
| FC 2            | 50| 20| 3.5| 17.15 ± 1.40                 | 34.55 ± 2.71 | 77.63 ± 3.78 |
| FC 3            | 35| 25| 3.5| 29.73 ± 1.88                 | 54.98 ± 3.22 | 89.83 ± 1.65 |
| FC 4            | 50| 25| 3.5| 17.71 ± 1.79                 | 35.88 ± 4.27 | 81.17 ± 2.15 |
| FC 5            | 35| 20| 6 | 15.66 ± 0.79                 | 34.01 ± 1.78 | 82.28 ± 0.82 |
| FC 6            | 50| 20| 6 | 11.93 ± 0.84                 | 24.70 ± 1.64 | 75.48 ± 1.87 |
| FC 7            | 35| 25| 6 | 16.31 ± 0.96                 | 35.88 ± 1.08 | 83.68 ± 1.57 |
| FC 8            | 50| 25| 6 | 12.77 ± 1.25                 | 25.07 ± 1.71 | 76.13 ± 1.56 |
| Kaleorid®       |    |    |    | 19.12 ± 1.59                 | 40.40 ± 2.15 | 82.25 ± 2.66 |
### Table 5 – Variables and corresponding P-values.

| Variables | \( y_1 \) | \( y_2 \) | \( y_3 \) |
|-----------|----------|----------|----------|
| \( b_0 \) | 18.58 (\( P = 0.00 \)) | 37.31 (\( P = 0.00 \)) | 81.82 (\( P = 0.00 \)) |
| \( b_1 \) | −3.69 (\( P = 0.02 \)) | −7.26 (\( P = 0.00 \)) | −4.22 (\( P = 0.00 \)) |
| \( b_2 \) | 0.55 (\( P = 0.60 \)) | 0.64 (\( P = 0.60 \)) | 0.89 (\( P = 0.10 \)) |
| \( b_3 \) | −4.41 (\( P = 0.01 \)) | −7.39 (\( P = 0.00 \)) | −2.42 (\( P = 0.00 \)) |

Polynomial equation for 2³ full factorial design is given in the following equation:

\[
y = b_0 + b_1x_1 + b_2x_2 + b_3x_3
\]

where \( y \) is dependent variable, \( b_0 \) is arithmetic mean response of eight formulations, and \( b_1, b_2, b_3 \) are estimated co-efficients for factor \( x_1, x_2, x_3 \), respectively.

Significant terms at 95% confidence interval (\( P < 0.05 \)) revealed that \( b_2 \) co-efficient attained the \( P \)-value greater than 0.05, as shown in Table 5, indicating that the variable \( b_2 \) (concentration of PEG 6000) did not affect the percentage released. Therefore the equations for drug released should be:

\[
y_1 = 18.58 – 3.69x_1 – 4.41x_3
\]

\[
y_2 = 37.31 – 7.26x_1 – 7.39x_3
\]

\[
y_3 = 81.82 – 4.22x_1 – 2.42x_3
\]

As seen in Table 4, formulation FC 8 contained \( x_1 \) and \( x_3 \) at high value, hence the drug released at 1, 2 and 6 h were slower than those of Kaleorid®; therefore the value of \( x_1 \) and \( x_3 \) were changed backward in 4 additional trials using −2.75 and −0.5 for \( x_3 \) and \( x_2 \), respectively. Concentration of PEG 6000 was kept at 20% with respect to polymer weight.

Drug released from 4 additional coating formulations were depicted in Table 6. As seen in Table 6, formulation FC 11 containing 41.75% EC in mixture of EC:HPMC (e.g., 41.75:58.25, equivalent to 1.67% and 2.33% of EC and HPMC, respectively, in coating solution of 4% polymer blend) and the weight gained of coating layer at 4.5% to core weight could produce the coated tablet possessed dissolution profile similar to that of Kaleorid® as could be seen in Fig. 2, and the similarity factor was at 83.41. The coating solution was designed as follows: EC

![Fig. 2 – Dissolution profiles of PC from tablets coated with EC:HPMC vs. those from Kaleorid® (each point represents the mean ± SD, n = 12).](image)

at 1.67%; HPMC at 2.33%, PEG 6000 at 0.8% and solvent to make 100%.

### 3.3. Bioequivalence study

#### 3.3.1. The baseline urinary potassium excretion

The mean cumulative baseline urinary potassium excretions on the controlled day were 36.61 ± 9.81 mEq and 37.02 ± 10.06 mEq in the group dosing test product and dosing reference product, respectively. As seen on Fig. 3, the mean cumulative baseline potassium excretion profiles of both superimposed and statistical analysis showed no significant difference (\( P = 0.143 \)).

The rates of potassium excretions depicted in Fig. 4, and expressed as units of mEq/h, were calculated by dividing the amount of potassium excreted in the urine during a collection interval by the time elapsed during the interval. Excretion rate data of this type was very variable but provide useful patterns to analyze the excretion kinetic. In Fig. 4, it could be seen that the 0-24 h urinary potassium excretion on the controlled day from the test and reference product virtually superimposed, indicating that the rates of potassium excretion were not different from each other at the specific time during the controlled day.

![Fig. 4 – Urinary potassium excretion in the control and test groups.](image)

#### Table 6 – Drug released from PC tablets coated with blends of EC and HPMC in additional coating formulations of factorial design (n = 12).

| Formulation code | \( x_1 \) | \( x_3 \) | Drug release (%) (Mean ± SD) | \( f_2 \) (vs. Kaleorid®) |
|------------------|--------|--------|-----------------------------|------------------------|
| FC 8             | 50     | 6      | 12.77 ± 1.43                | 25.07 ± 1.60           | 41.25 ± 2.03           | 52.65 ± 2.11           | 63.83 ± 2.13           | 76.13 ± 2.13           | 45.78                |
| FC 9             | 47.25  | 5.5    | 14.65 ± 1.55                | 30.57 ± 1.33           | 49.39 ± 2.12           | 61.60 ± 2.19           | 71.83 ± 2.11           | 79.02 ± 2.74           | 60.68                |
| FC 10            | 44.5   | 5      | 16.87 ± 1.63                | 34.39 ± 1.66           | 51.81 ± 2.06           | 64.77 ± 1.86           | 76.32 ± 2.17           | 81.23 ± 2.61           | 73.64                |
| FC 11            | 41.75  | 4.5    | 20.97 ± 1.93                | 41.56 ± 1.82           | 54.05 ± 1.75           | 66.72 ± 1.72           | 79.49 ± 2.01           | 83.87 ± 1.89           | 83.41                |
| FC 12            | 39     | 4      | 22.09 ± 1.96                | 43.15 ± 2.06           | 57.13 ± 1.95           | 70.92 ± 1.86           | 80.61 ± 2.11           | 84.62 ± 2.07           | 74.32                |
| Kaleorid®        | 19.12  | 1.59   | 40.40 ± 2.15                | 55.26 ± 2.52           | 67.55 ± 1.93           | 76.01 ± 2.71           | 82.25 ± 2.66           | 83.41                |
The similarity in the excretion patterns would result from the normal creatinine clearances of the subjects and the well designed menus. From the potassium urinary excretion profiles, some peaks could be seen at 5, 9, and 13 h from the starting of the first collection. The increasing of the urinary potassium excretion rates at these moments would be the effect of the meals because they were observed about 1–2 h after taking the meals.

3.3.2. Pharmacokinetic parameters of the potassium excretion
The net effect of drug administration was calculated by subtracting the amount obtained on the drug dosing day to baseline excretion of potassium for subject specific and collection specific. As seen in Fig. 5, the values of mean baseline-adjusted cumulative urinary potassium excretion of test product were lower than those of reference product at the specific times in the 4–16 h interval.

The mean baseline-adjusted 24 h cumulative urine levels were 43.52 ± 10.19 mEq for test product and 44.34 ± 11.81 mEq for reference product, corresponding to 54.40% and 55.43% recoveries from the dose of 80 mEq, respectively. The mean baseline-adjusted 48 h cumulative urine levels were 55.42 ± 16.79 mEq for test product and 55.45 ± 18.48 mEq for reference product, corresponding to 69.27% and 69.31% recoveries from the dose of 80 mEq, respectively.

The mean maximal rate of urinary potassium excretion was 5.56 ± 1.57 mEq/h for the test product and 6.12 ± 1.87 mEq/h for the reference product. The mean time of maximum excretion of potassium was 3.79 ± 2.19 h for the test and 4.54 ± 2.29 h for the reference product. The excretion rates of potassium decreased gradually after 4 h of administration, as shown in Fig. 6.

3.3.3. Statistical analysis and bioequivalence evaluation
Statistical analysis (P = 0.05) showed no significant differences for all raw data (e.g., $A_{0-24}$, $P = 0.810$; $A_{0-48}$, $P = 0.995$; $R_{max}$, $P = 0.246$; $T_{max}$, $P = 0.295$) and natural log-transformed data (e.g., $\ln (A_{0-24})$, $P = 0.878$; $\ln (R_{max})$, $P = 0.223$) of 24 subjects.

The 90 percent confidence interval was determined for each natural log-transformed data using the two one-sided t test. The limits for log-transformed cumulative urinary potassium excretion of test product were in the range of 3.73–3.79 mEq, corresponding to 99.08%–100.92% of reference product, respectively. The limits for natural log-transformed maxi-
nal potassium excretion rate of test product were in the range of 1.72–1.82 mEq/h, corresponding to 97.34%–102.66% of reference product, respectively. Both of them fell within the bioequivalence interval (80%–125%) of reference product.

4. Conclusion

The results of drug release test in this study proved that combination of matrix structure (using carnauba wax) and coating technique (using blend of EC and HPMC) is effective in controlling the release of PC from experimental tablets and can prevent the dose dumping of the system. The blend of polymer in this case led to forming the diffusion pores during drug release test.

The bioequivalent study revealed that the time to reach the maximal rate of potassium excretion for test product was shorter than that of reference drug, however both of them reflected the extended release properties of these products. The results of statistical analysis on pharmacokinetic parameters proved that the experimental product is bioequivalent to Kaleorid® LP 600 mg (Leo Pharmaceutical Products, Denmark).

Conflicts of interest

The authors declare that there are no conflicts of interest.

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REFERENCES

[1] Ashok R, Srikumaran M, John DA, et al. Kinetics of potassium excretion following oral supplements: evidence of induced natriuresis. Pharm Res 1987;4:531–5.
[2] Pao CW, Min JT, Yaw BH, et al. In vitro and in vivo evaluation of potassium chloride sustained release formulation prepared with saturated polyglycolyed glycerides matrices. Int J Pharm 2002;243:119–24.
[3] Pao CW, Yaw BH, Jui SC, et al. Design and evaluation of sustained release microspheres of potassium chloride prepared by Eudragit®. Eur J Pharm Sci 2003;19:115–22.
[4] Siepmann F, Siepmann J, Walther M, et al. Polymer blends for controlled release coatings. J Control Release 2008;125:1–15.
[5] Nasser N, Stephen WH. Assessment of polymer-polymer interactions in blends of HPMC and film forming polymers by modulated temperature differential scanning calorimetry. Pharm Res 2000;17:625–31.
[6] Sevda S, Yılmaz C, Turgay D, et al. Formulation, bioavailability and pharmacokinetics of sustained release potassium chloride tablets. Pharm Res 1991;8:1313–17.
[7] Charles JB, John DA, Wayne FR, et al. Bioavailability and pharmacokinetics of a new sustained-release potassium chloride tablet. Pharm Res 1987;4:409–11.
[8] Moller H, Ali SL, Steinbach D. Pharmaceutical and biological availability of sustained release preparations of potassium chloride. Int J Pharm 1987;7:157–67.