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# Preparation and evaluation of sustained release microspheres of potassium chloride prepared with ethylcellulose

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**Abstract**

The water-insoluble polymer ethylcellulose is used as a retardant to prepare the sustained release of potassium chloride microspheres by drying in a liquid process. The effect of sustained release of potassium from ethylcellulose microspheres was evaluated by the in vitro dissolution test, and was compared to a commercial product (Slow-K). The results showed that ethylcellulose microspheres loaded with potassium chloride could be easily prepared and satisfactory results could be obtained considering size distribution and shapes of microspheres by incorporating aluminum stearate. The encapsulation efficiency and loading capacity were about 84–93 and 36%, respectively. However, the potassium/ethylcellulose 2/2 (30–45 mesh) microspheres showed the similar sustained release effect of commercial product.


*Keywords:* Potassium chloride; Ethylcellulose; Dissolution test

## 1. Introduction

Potassium chloride is used for the treatment of hypokalemia or severe potassium loss of various etiologies (Lacy et al., 1998). However, 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 the reduced possibility of a high local concentration of potassium chloride near the gastrointestinal mucosa (Lindstedt et al., 1991; Wu et al., 2002). There are some studies for potassium chloride sustained release dosage form, such as potassium chloride tablet coated with semipermeable membrane, potassium chloride matrix tablet or capsule, and microencapsulation with mastic (Arnold et al., 1980; Georgarakis et al., 1987; Caraballo et al., 1996, 2000; Wu et al., 2003).

Ethylcellulose is a water-insoluble and pH-independent polymer and has been widely used in the prepared sustained release dosage forms of a water-soluble material (Alpar and Walters, 1981; Al-Omran et al., 2002; Fan et al., 2001; Palmieri et al., 2001; Rao and Murthy, 2002). In this study, ethylcellulose was used as a retardant to prepare the potassium chloride microspheres by drying in a liquid process. The effect of sustained release of potassium chloride from ethylcellulose microspheres has been investigated via in vitro dissolution test and has been compared to a commercial sustained release product (Slow-K).

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## 2. Materials and methods

### 2.1. Materials

Potassium chloride, cesium chloride, potassium standard solution, aluminum stearate, and sodium chloride were purchased from E. Merck (Germany). Ethylcellulose was purchased from Riedel-de Hase (Germany). Slow-K tablets (Novartis) were purchased from the local market. All other chemicals and solvents were of analytical reagent grade.

### 2.2. Preparation of microspheres

Ethylcellulose (2 g) was dissolved completely in 100 ml acetone in a glass vessel. Aluminum stearate (1.0–1.5 g) and potassium chloride (2 g) were dispersed into the ethylcellulose solution. The mixture was stirred at a fixed stirring rate (150–350 rpm) in a water bath at 25 °C over 10 min, and then poured into 100 ml liquid paraffin which had been previously cooled to 25 °C. The emulsion was heated to 45 °C at a constant temperature and was continually stirred until the acetone was removed completely by evaporation. Then, 50 ml of *n*-hexane was added to the suspension of microspheres. After 10 min, the microspheres were separated by filtration, washed twice with 50 ml *n*-hexane, and dried at 40 °C for 12 h.

### 2.3. Scanning electron microscopy

The surface characteristics were examined by means of a scanning electron microscopy. The microspheres were coated with platinum/palladium alloy using an ion coater (Eiko Engineering counter) under vacuum, and then samples were examined with a scanning electron microscope (Hitachi S-450).

### 2.4. Sieve analysis

The separation of the microspheres into various size fractions was carried out using a mechanical sieve shaker (Sieving Machine, Retsch, Germany). A series of five standard stainless steel sieves (20, 30, 45, 60, and 80 mesh) were arranged in the order of decreasing aperture size. Five grams of drug-loaded microspheres was placed on the super-moist sieve. The sieves were shaken for a period of about 10 min, and then the particles on the screen were weighed. The procedure was carried out three times for each product.

### 2.5. Drug content determination

Microspheres were pulverized and dispersed in a 100 ml flask with 25 ml acetone. After shaking for 10 min, 50 ml of deionized water was added and was continually shaken for a further 30 min. The deionized water layer was diluted and determined by an atomic absorption spectrophotometer (Varian, 875 series with a lamp capable of measuring the absorbance of potassium at its secondary wavelength of 766.5 nm).

### 2.6. In vitro dissolution test

The model drug used is potassium chloride because its solubility in water is almost constant (approximately 350 mg/ml) over a physiological range. Ethylcellulose is also a pH-independent material. Thus, the drug release from the ethylcellulose microspheres would not be affected by pH of the medium. However, according to USP 23 monographs for potassium chloride extended-release capsules, the dissolution tests were performed in 900 ml deionized water using the basket method with a rotation speed of 100 rpm at $37 \pm 0.5$ °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 an 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 specific time interval was recorded as a percentage of the dose.

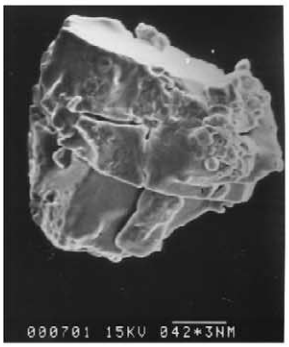
### 2.7. Data analysis

Three kinetic models, including the zero order release equation (Eq. (1)), Higuchi equation (Eq. (2)), and first order equation (Eq. (3)), were applied to process the in vitro data to find the equation with the best fit (James et al., 1997; Huang et al., 2003).

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

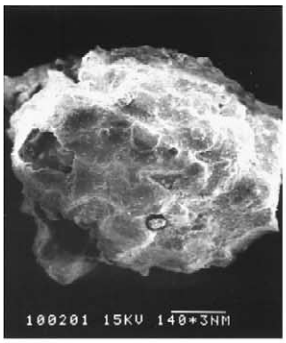
$$Q = k_2 (t)^{0.5} \quad (2)$$

(a)



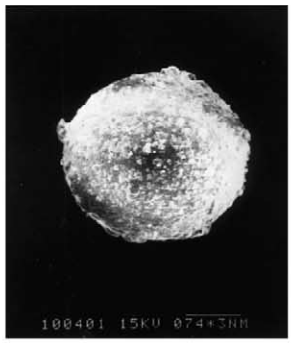

300 X

(b)



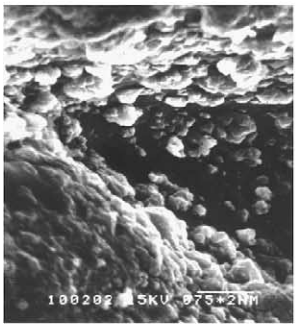

A:20-30 mesh 100X

B: 30-45 mesh 200X

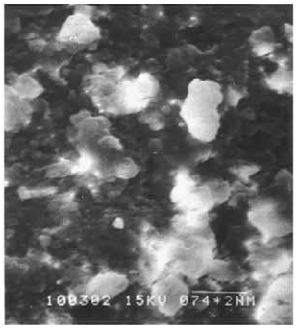



C: 45-60 mesh 200X

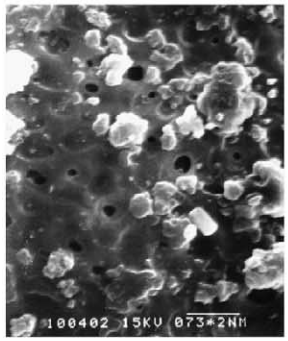

D: 60-80 mesh 200X




E: 20-30 mesh 2000X




F: 30-45 mesh 2000X




G: 45-60 mesh 2000X


H: 60-80 mesh 2000X

Fig. 1. Scanning electron micrographs of potassium chloride and ethylcellulose microspheres loading potassium chloride. (a) Potassium chloride, (b) drug/polymer 3/2 microspheres, (c) drug/polymer 2/2 microspheres.

(c)

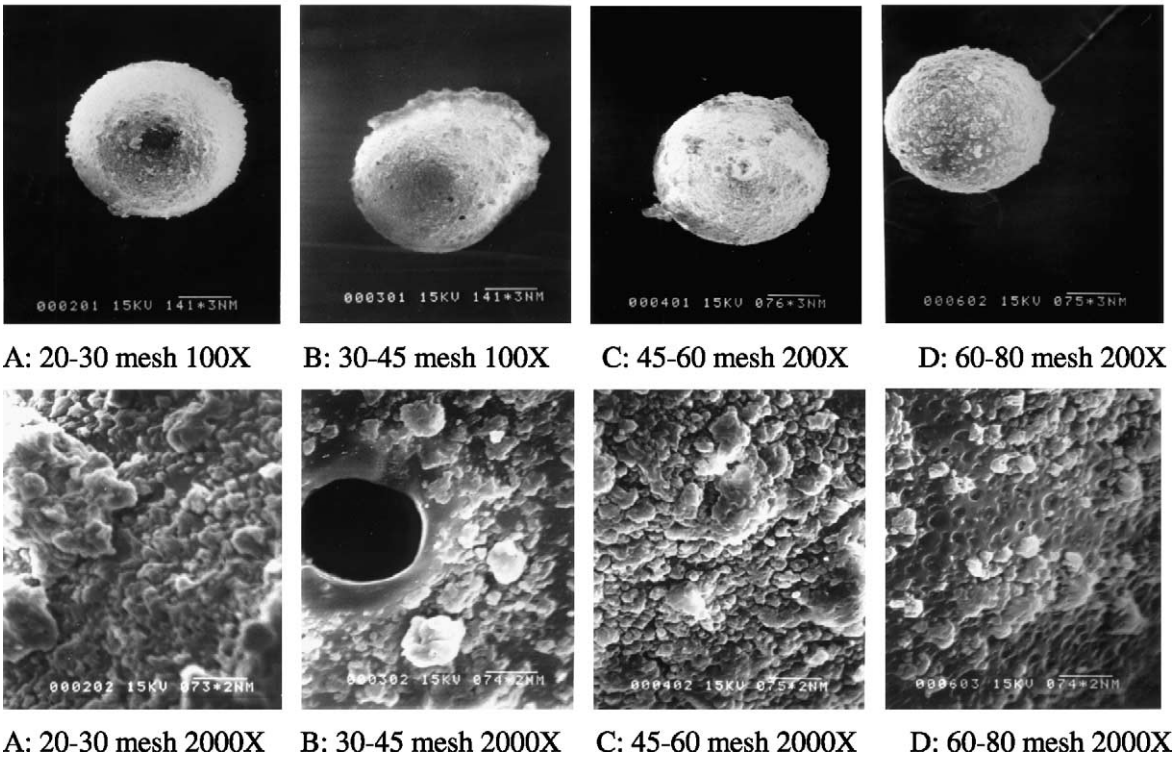



Fig. 1. (*Continued*).

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

where $Q$ is the release percentage at time $t$. The $k_1$, $k_2$, and $k_3$ are the rate constants 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:

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

where $n$ is the number of dissolution sample times, and $R_t$ and $T_t$ 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.

## 3. Results and discussion

Previous studies (Kawata et al., 1986; Goto et al., 1986) point that the aluminum stearate is a useful additive for microencapsulation process, due to the reduction of the interfacial tension and prevention of electrification and flocculation in the microencapsulation dispersion system, and thus improves the yield ratio and the shape and internal structure of microspheres. In this study, the different amounts of aluminum stearate (1.0, 1.25, and 1.5 g) were used to prevent flocculation and aggregation of microspheres in all studied systems and to enable the isolation of final products. The surface morphologies of potassium chloride and different particle size of Eudragit RS microspheres containing potassium chloride with 100–2000 times of ampliation are shown in Fig. 1a–c, respectively. The shape of the potassium chloride crystal is irregular. The Eudragit RS microspheres are nearly spherical in shape except the large size particles

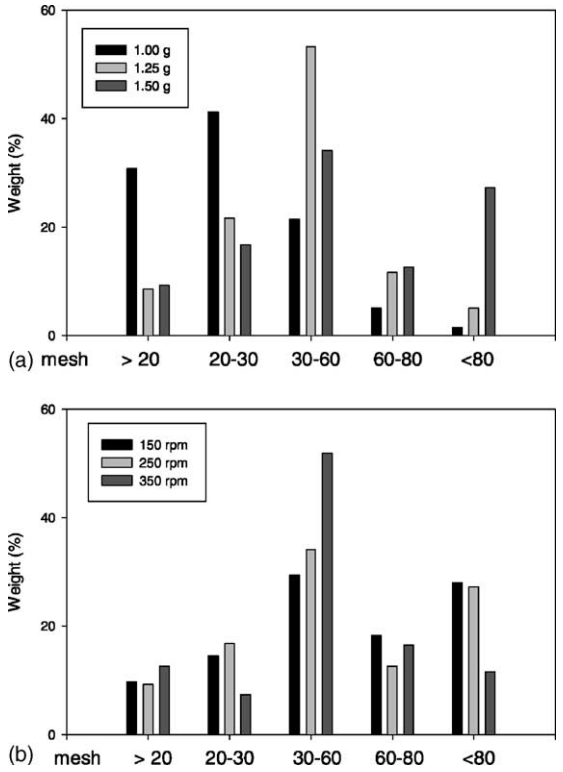



Fig. 2. The size distribution of ethylcellulose microspheres with the addition of different amounts of aluminum stearate and stirring rate.

(20–30 mesh) (Fig. 1b(A–D)), indicating that spherical solid microspheres could be prepared by adding a small amount of aluminum stearate. In comparison, the surface of microspheres at 2000 times amplification (Fig. 1b(E–H)) shows that the smaller particles had smoother and closer surface structure than that of larger particles. The encapsulation efficiency of these formulations was about 83–93%. Fig. 2a illustrates the size distribution of ethylcellulose microspheres incorporated with various amounts of aluminum stearate. The result indicated that by increasing the addition of aluminum stearate, there was a trend in size distribution towards increasing percentages of smaller sized microspheres. More than 53% of particles were gathered up between 30 and 60 mesh while the added amount of aluminum stearate rose up to 1.25 g. The loading capacity of potassium was about 36%. The stirring rate in microencapsulation process is the other obvious factor influencing the size of the microspheres (Jalsenjak et al., 1976; Alpar and Walters, 1981). As shown in Fig. 2b, by increasing the stirring rate there was a trend in the size distribution towards increasing percentages of smaller sized microspheres.

Studies of the in vitro dissolution rates allow a comparison to be made between the different microsphere size fractions and may give an indication of their relative efficiencies as potential delayed release dosage forms. The dissolution profiles of potassium from microsphere fraction with differing drug/polymer ratios into deionized water are shown in Fig. 3. The dissolution efficiencies of 360 min ($DE_{360}$) which were calculated from the area under the dissolution curves are listed in Table 1. In potassium/ethylcellulose 3/2 microspheres, there were significant burst effects in these different size fractions. The $DE_{360}$ values were about 445, 396, 296, and 230 for 20–30, 30–45, 45–60, and 60–80 mesh microspheres, respectively. The result indicated that the release rate depended on the particle size. In comparison to the dissolution patterns with the commercial product (Slow-K), the $f_2$ values of these four microspheres were below 50 (Table 1), and thus showed that these dissolution curves were not similar to that of Slow-K. The release rate of potassium from larger size particles (20–30 and 30–45 mesh) were faster than that from Slow-K. In contrast, the smaller size particles (45–60 and 60–80 mesh) showed remarkable sustained release effect than that of Slow-K. In the case of potassium/ethylcellulose 2/2 microspheres, the release rates were slower than that of drug/polymer 3/2 in different microsphere size fractions. Only the larger size particles (20–30 and 30–45 mesh) had burst effects which were less than that of potassium/ethylcellulose 3/2 microspheres. The release rate of potassium increased in the following order: 60–80 mesh = 45–60 mesh < 30–45 mesh < 20–30 mesh. The $f_2$ value of 30–45 fraction was 55.59, and thus indicated that the release pattern was similar to that of Slow-K. The above results showed that the larger microspheres had a faster release rate. The SEM graphs of ethylcellulose (Fig. 1b and c) showed that the surfaces of the larger microspheres were rougher and there were some pores. Therefore, it might be proposed that very small amount of potassium chloride were aggregated on the surface of microspheres or/and some individual microspheres coagulated together to form larger sized microspheres in the evaporating process.

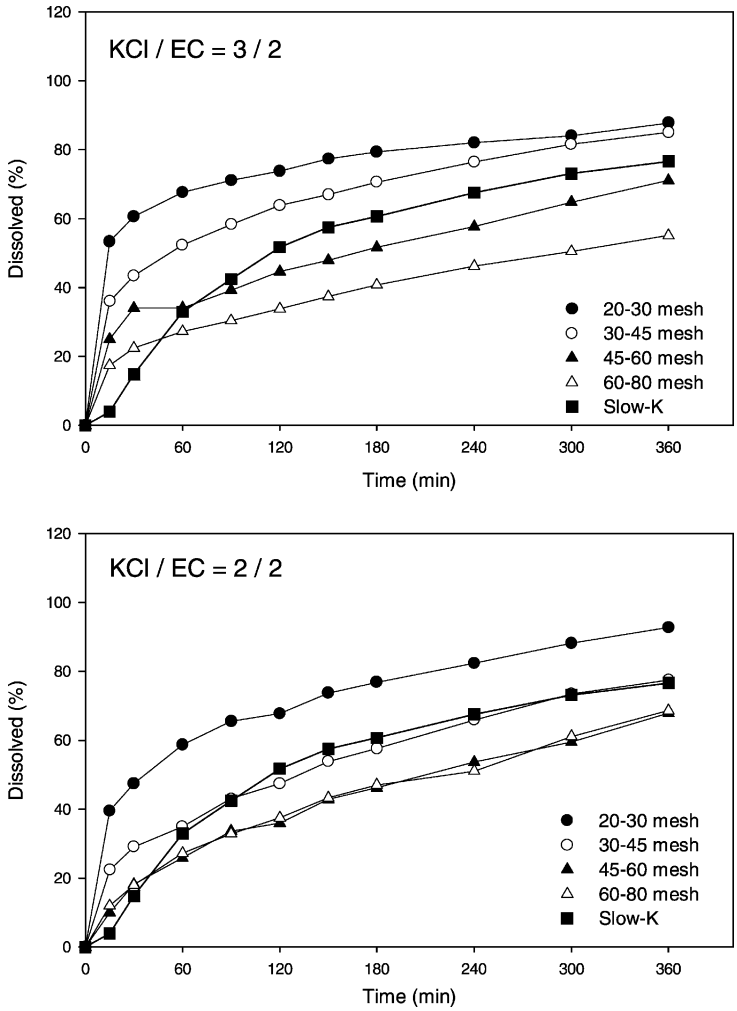



Fig. 3. Dissolution profiles of potassium chloride from ethylcellulose microspheres and the commercial product (Slow-K) in deionized water ($n = 6$).

Table 1
Dissolution efficiency at 360 min ($DE_{360}$), $f_2$ values, and release mechanism of correlation coefficients of potassium chloride from ethylcellulose microspheres in deionized water

| Formulae | $DE_{360}$ | $f_2$ | Zero order ($r$) | Higuchi ($r$) | First order ($r$) |
|---|---|---|---|---|---|
| Slow-K | 323.31 ± 10.77 | | 0.9162 | 0.9750 | 0.7463 |
| KCl/EC 3/2 (20–30 mesh) | 444.51 ± 59.08 | 27.06 | 0.9400 | 0.9807 | 0.8931 |
| KCl/EC 3/2 (30–45 mesh) | 395.66 ± 14.91 | 37.91 | 0.9776 | 0.9943 | 0.9315 |
| KCl/EC 3/2 (45–60 mesh) | 296.22 ± 34.25 | 47.58 | 0.9661 | 0.9881 | 0.8628 |
| KCl/EC 3/2 (60–80 mesh) | 230.41 ± 23.14 | 34.69 | 0.9702 | 0.9885 | 0.8942 |
| KCl/EC 2/2 (20–30 mesh) | 430.72 ± 58.06 | 32.45 | 0.9037 | 0.9615 | 0.8746 |
| KCl/EC 2/2 (30–45 mesh) | 325.04 ± 46.92 | 55.59 | 0.9516 | 0.9897 | 0.9096 |
| KCl/EC 2/2 (45–60 mesh) | 259.41 ± 66.95 | 47.05 | 0.9458 | 0.9454 | 0.9169 |
| KCl/EC 2/2 (60–80 mesh) | 260.81 ± 59.45 | 47.31 | 0.9841 | 0.9959 | 0.9424 |

EC: ethylcellulose; $r$: correlation coefficient; $DE_{360}$: the area under the dissolution curves from 0 to 360 min.

In addition, the release mechanisms of potassium released from these Eudragit microspheres were also 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 release mechanisms. The obtained results are given in Table 1. It shows that the release pattern of potassium chloride from ethylcellulose microspheres corresponded best to the Higuchi equation, thus indicating that a diffusion process is responsible for the release of the drug.

## 4. Conclusions

Therefore, it would appear that polymer separation can be used to prepare sustained microspheres of water-soluble drugs and the release of drugs from these ethylcellulose microspheres was both a function of the drug/polymer ratio and the overall microsphere size. The release occurs by a diffusion process as in the case of insoluble polymer microspheres. However, potassium/ethylcellulose 2/2 (30–45 mesh) microspheres exhibited a similar sustained release effect of the commercial product.

## Acknowledgements

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