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International Journal of Pharmaceutics 339 (2007) 19–24
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Rapid communication

Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings

Qing-Ri Cao, Tae-Wan Kim, Beom-Jin Lee *

National Research Laboratory for Bioavailability Control, College of Pharmacy, Kangwon National University, Chuncheon, Republic of Korea

Received 30 March 2007; received in revised form 3 April 2007; accepted 18 April 2007
Available online 24 April 2007

Abstract

Two types of the carnauba wax-based lipophilic matrix tablet using spray-dried granules (SDT) or directly compressible powdered mixtures (DCT) were prepared for sustained release. The model drug was a highly water-soluble potassium citrate and loaded about 74% of the total tablet weight. The SDT slowly eroded and disintegrated during the release study without showing sustained release when the hydrophilic excipients were added. In contrast, the DCT was more efficient for sustained release. The release rate decreased with increasing carnauba wax concentration. In particular, the sustained release rate was markedly pronounced when the lipophilic stearyl alcohol and stearic acid were combined with the carnauba wax. The surface of the intact DCT appeared to be smooth and rusty. The DCT rose to the surface from the bottom of the vessel during the release test, and numerous pores and cracks with no signs of disintegration were also observed after the release test. The release profile was dependent on the formulation composition and preparation method of the matrix tablet. Diffusion-controlled leaching through the channels of the pores and cracks of the lipophilic matrix tablet (DCT) is a key to the sustained release.

Keywords: Highly water-soluble potassium citrate; Sustained release; Lipophilic wax matrix tablet; Spray-dried granules; Directly compressible powdered mixtures; Release mechanism

1. Introduction

Potassium citrate is used clinically to treat nephrolithiasis by alkalizing the urinary pH (Tekin et al., 2002). However, its therapeutic efficacy in maintaining the pH level in urine after oral administration is limited due to its high water solubility (1.54 g/ml in water, 37 °C) and gastrointestinal complications such as ulcerations, hemorrhage, obstruction and perforation. Sustained release preparations of the potassium citrate may minimize these side effects and may also maintain an effective pH in the urine by alkalizing over an extended period (Harvey et al., 1989). However, considerable difficulties have been encountered in the preparation of sustained release matrix tablets containing highly water-soluble drugs with high drug loading.

Lipophilic carriers such as carnauba wax, glycerides, stearyl alcohol and stearic acid are preferred in the preparation of a sustained release matrix tablet in case of highly water-soluble drug like potassium citrate (Dakkuri et al., 1978; El-Shanawany, 1993; Lee et al., 1998; Wu et al., 2002; Hamdani et al., 2003). Various manufacturing processes using these lipophilic carriers have been used, including direct compression, hot-melt extrusion, melt granulation and solvent evaporation. The homogeneity of the drugs in the matrix type dosage forms is essential for the sustained release of drugs. However, until now, no report has been issued on simpler preparation of a sustained release lipophilic matrix tablet containing highly water-soluble potassium citrate.

The aim of this study was to prepare a lipophilic matrix tablet containing highly water-soluble potassium citrate with a high drug loading. The two types of the tablet (SDT or DCT) were prepared via compression of either a spray-dried granule or a directly compressible powdered mixture. The release mechanism and the photoimages of the sustained release lipophilic

* Corresponding author. Tel.: +82 33 250 6919; fax: +82 33 242 3654.
E-mail address: bjl@kangwon.ac.kr (B.-J. Lee).

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doi:10.1016/j.ijpharm.2007.04.016

matrix tablet (DCT) after the release test in water were then examined.

2. Materials and methods

2.1. Materials

Potassium citrate monohydrate ($C_6H_5K_3O_7$, Mw 306.4) from Junsei Chemical Co. Ltd., Tokyo, Japan was used as the model drug. Carnauba wax (Aldrich Chemical Co. Ltd., Milwaukee WI, USA) was used as the major matrix carrier. The shellac and microcrystalline cellulose (MCC) were purchased from Bee Dong Fine Co. Ltd. (Incheon, Korea). The stearyl alcohol, stearic acid and calcium sulfate were obtained from Junsei Chemical Co. Ltd. (Tokyo, Japan). The polysorbate 80, glycerol monooleate (GM) and polyethylene glycol 6000 (PEG 6000) were obtained from Sigma–Aldrich Co. (St. Louis. MO, USA). All other excipients were of pharmaceutical grade and used without further purification.

2.2. Preparation of spray-dried lipophilic matrix tablets (SDT)

Table 1 shows the formulation composition (mg) used for spray-dried lipophilic matrix tablet (SDT). Carnauba wax (10% polysorbate 80 in case), which was previously melted in an oil bath heated to 5 °C above the melting point, was added to 100 ml of boiling water. Three hundred milliliters of a 90% alcoholic solution containing GM/stearic acid or GM/shellac/stearic acid/PEG 6000 was then added to the above emulsion and mixed homogenously for 30 min. The final solution was then spray-dried using fluid bed equipment (STREA 1, Niro-Aeromatic, Switzerland). The inlet and outlet drying air temperature was set to 70 and 55 °C, respectively. The spray nozzle size was 0.8 mm in diameter and the feeding rate of the dispersion was 5 ml/min. The resulting dried granules were mixed with the drug/calcium sulfate/MCC/PEG6000 (SDT1, 2) or the drug (SDT3), and then compressed to prepare the tablet using a rotary tablet machine (Korea Machine, Anyang, Korea).

2.3. Preparation of directly compressed lipophilic matrix tablets (DCT)

Table 2 gives the formulation composition (mg) used for directly compressed lipophilic matrix tablet (DCT) using the powdered mixtures. The powdered mixtures were homogenously milled for 5 min in a mortar, and then sieved through a 40-mesh screen. The resulting powdered mixtures were then directly compressed to prepare the tablet using a rotary tablet machine, as reported above.

Each tablet contained 540 mg potassium citrate as the active ingredient. The total tablet weight ranged from 640 to 740 mg, depending on the formulation composition. The size of the tablet was 15.32 mm long and 8.27 mm wide.

2.4. Tablet characterization

The tablet hardness was measured in triplicate using an Erweka® hardness tester (Berlin, Germany). The hardness was measured in the height direction of the tablet (long direction). The friability of 10 randomly selected tablets was determined using a friabilator (Labfine Inc., Seoul, Korea) at 40 rpm for 10 min in a drum and the percentage weight loss was measured.

The disintegrating time of the tablet was measured in distilled water at 37 ± 0.5 °C using a disintegration tester according to the Korean Phamacopoeia (KP γ) disintegration test. The percentage compressibility (Carr's index) was then calculated using the following equation: Carr's index = $[(\rho_{tap} - \rho_{bulk})/\rho_{tap}] \times 100$, where ρ_{tap} and ρ_{bulk} are the tap density and bulk density of the granules, respectively. For the tap bulk density, the cylinder was tapped 500 times using an Erweka SVM12 tap density analyzer (Berlin, Germany).

Table 1
Formulation composition (mg) of the lipophilic matrix tablet prepared via the direct compression of granular mixtures

Codes	Drug	Carnauba wax	Polysorbate 80	Shellac	GM	Calcium sulfate	MCC	PEG 6000	Stearic acid
SDT1	540	30	3	10	3	32	5	10	10
SDT2	540	50	5	5	3	17	5	10	10
SDT3	540	90	–	–	3	–	–	–	10

Table 2
Formulation composition (mg) of lipophilic matrix tablet prepared via the direct compression of powdered mixtures

Codes	Drug	Carnauba wax	Stearyl alcohol	Calcium sulfate	MCC	PEG 6000	Stearic acid
DCT1	540	30	–	45	5	10	10
DCT2	540	100	–	–	–	–	10
DCT3	540	150	–	–	–	–	10
DCT4	540	100	40	–	–	–	10
DCT5	540	100	80	–	–	–	10
DCT6	540	100	60	–	–	–	40
DCT7	540	100	60	–	–	–	20
DCT8	540	100	60	–	–	–	30

2.5. Release test

The release rate of the tablet containing 540 mg potassium citrate was measured in triplicate using a DST-600A dissolution tester (Labfine, Seoul, Korea) according to the USP 26/NF 21 (2003) dissolution II paddle method at a rotation speed of 50 rpm in 900 ml of distilled water kept at 37 ± 0.5 °C.

The absorbance of the solution was measured using an atomic absorption spectrophotometer (Shimadzu Corp.) at the potassium emission line of 766.5 nm with a potassium hollow-cathode lamp and an air-acetylene flame using water as the blank. The potassium concentration (μg/ml) was then determined from a standard calibration curve. The release rate is expressed as the percentage of potassium citrate released as a function of time.

2.6. Mathematical data analysis of release profiles

The following three kinetic equation models describing zero-order (1), Higuchi (2), and first-order (3) reactions were used to analyze the release data (Wu et al., 2002):

$$\frac{Q_t}{Q_\infty} = K_1 t \quad (1)$$

$$\frac{Q_t}{Q_\infty} = K_2 t^{0.5} \quad (2)$$

$$\frac{Q_t}{Q_\infty} = 100(1 - e^{-K_3 t}) \quad (3)$$

where Q_t/Q_∞ is the fraction of the release percentage at time t. K_1, K_2, and K_3 are the rate constant of the zero-order, Higuchi, and first-order model, respectively. In addition, the release data was also evaluated according to the well-known exponential Eq. (4), which is often used to describe the release behavior from a polymeric system (Brabander et al., 2000):

$$\frac{Q_t}{Q_\infty} = K_4 t^n \quad (4)$$

where K_4 is the rate constant with unit t^n and n is the release exponent, which indicates the mechanism of release.

2.7. Photoimages of lipophilic matrix tablet during release test

Photoimages of the lipophilic matrix tablet (DCT8), initially, during and after the release test in water were taken as a function of time using an Olympus digital camera (Tokyo, Japan) in the Central Laboratory, Kangwon National University in order to compare their disintegration and release behavior. After the release test, the tablets were carefully taken from the dissolution tester and dried at room temperature.

3. Results and discussion

3.1. Preliminary evaluation of lipophilic matrix tablet

Table 3 gives a comparison of the physical properties of the SDT and DCT. The SDT and DCT exhibited 50–70 N tablet hardness. The SDT experienced particle fracture leading to capping and lamination. The Carr indices of the spray-dried granules were approximately 35, which indicated that they were poorly flowing. Furthermore, the resulting matrix tablet showed a higher friability (2–3%). The SDT1 and SDT2 rapidly eroded and disintegrated within 30 min during the release test when hydrophilic excipients were combined with carnauba wax due to formation of channels. Contrarily, the tablet shape was retained without disintegration but the desired sustained release was not obtained when the lipophilic glycerol monooleate and stearic acid were added (SDT3). Manufacturing disorders such as lamination and capping also occurred.

Table 3
Preliminary evaluation of lipophilic matrix tablets prepared via the direct compression of granular mixtures or powdered mixtures

Codes	Hardness (N)	Manufacturing process	Release test	
			Profile	Disintegration
SDT1	57.6 ± 10.9	PF; L/C	SR	DI
SDT2	–	PF; L/C	SR	DI
SDT3	–	FF; NMD	IR	R
DCT1	47.4 ± 3.7	FF; NMD	IR	DI
DCT2	61.3 ± 5.0	FF; NMD	IR	R
DCT3	–	FF; NMD	SR	R
DCT4	–	FF; NMD	SR	R
DCT5	60.5 ± 3.4	FF; NMD	SR	R
DCT6	–	FF; NMD	SR	R
DCT7	–	FF; NMD	SR	R
DCT8	73.4 ± 5.3	FF; NMD	SR	R

IR: immediate release; SR: sustained release; PF: poorly flowing; FF: free flowing; L/C: lamination and capping; NMD: no manufacturing disorders; R: tablet was retained at 3 h without disintegration; DI: tablet was eroded and disintegrated within 30 min.

The DCT showed a relatively lower friability (0.2–0.5%). The Carr indices of the size distributed powdered mixtures were approximately 21, and were likely to be free flowing. No manufacturing imperfections such as lamination or capping were observed throughout the experiments. The tablet shape also disintegrated within 30 min during the release test when the hydrophilic excipients were incorporated (DCT1). However, the tablet shape was retained without disintegration for more than 3 h when lipophilic stearyl alcohol and/or stearic acid were combined with carnauba wax (DCT2–8).

3.2. Release characteristic and mechanism of lipophilic matrix tablet

Fig. 1 shows the SDT release profiles in water. The release rate decreased with increasing carnauba wax content even though the hydrophilic excipients had been incorporated (SDT1 and SDT2). The SDT containing the hydrophilic excipients slowly eroded and disintegrated during the release study due to the increased wetting. Otherwise, the tablet shape (SDT3) was retained without disintegration. The SDT was not efficient to control the release rate of the drug even though there was a much larger amount of carnauba wax.

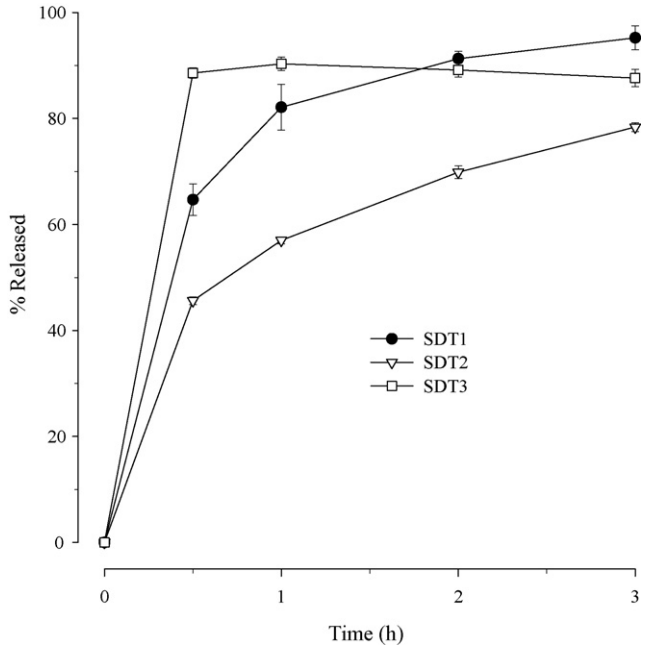

Fig. 1. The SDT release profiles in water.

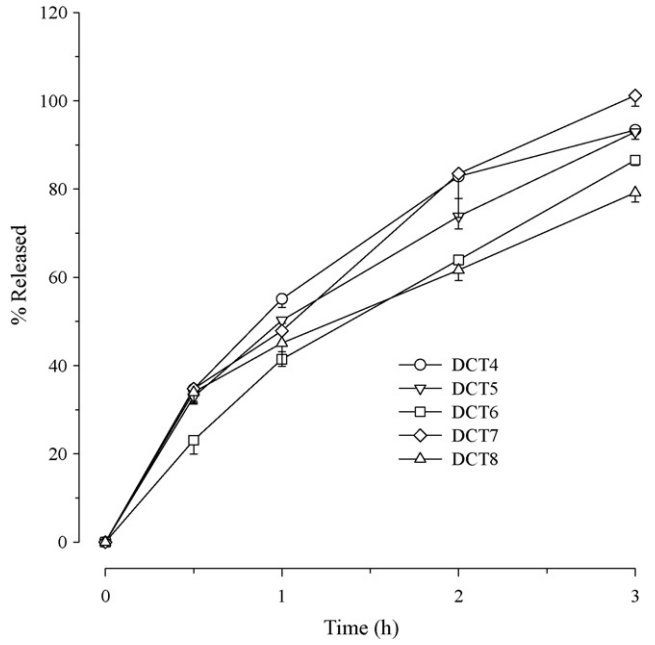

Fig. 3. Effect of stearyl alcohol and stearic acid combined with carnauba wax on the DCT release profiles in water.

Fig. 2 shows the effect of carnauba wax contents on DCT release profiles in water. The tablet (DCT1 and DCT2) containing less than 100 mg carnauba wax or hydrophilic excipients had no sustaining effect on the release rate, showing 100% release within 30 min. The DCT3 containing a higher amount of carnauba wax (150 mg) has a tendency to decrease the release rate due to the enhanced strength of the matrix network, as discussed previously (Brabander et al., 2000).

Lipophilic excipients such as stearyl alcohol and stearic acid can be combined with the carnauba wax in the formulation in order to efficiently control the DCT release rate. It was previously reported that stearyl alcohol is useful in controlling the release rate of water-soluble melatonin from a matrix pellet via microencapsulation (Lee et al., 1998). Fig. 3 shows effect of stearyl alcohol and stearic acid combined with carnauba wax on the DCT release profiles in water. Interestingly, a combination of stearyl alcohol and carnauba wax markedly improved the sustained release rate. The release rate further decreased due to the water resistance when the amount of stearyl alcohol was doubled. Furthermore, release rate was further modified in a sustained manner with increasing stearic acid content. The release profiles were dependent on the type and content of the lipophilic excipients (carnauba wax, stearyl alcohol and/or stearic acid).

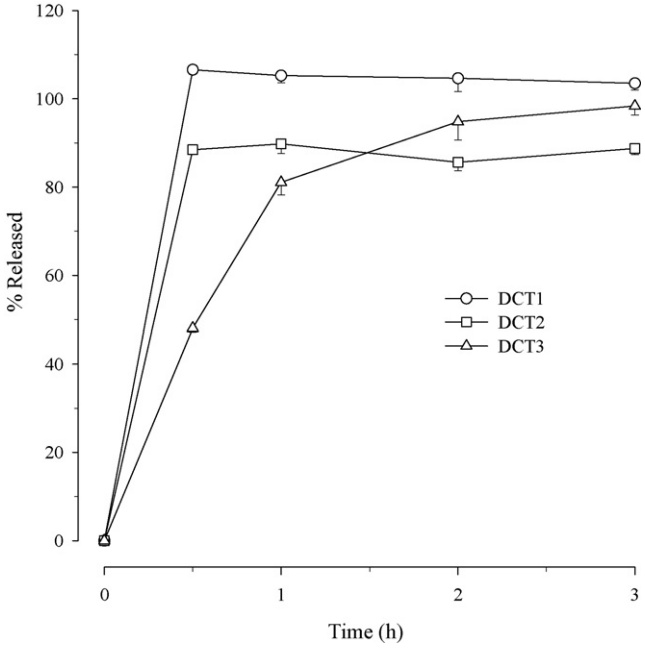

Fig. 2. Effect of carnauba wax contents on the DCT release profiles in water.

A direct compression of powdered mixtures of the lipophilic excipients would be preferable to that of granular mixtures because it forms a more hydrophobic environment in aqueous media. The incorporation of hydrophilic excipients in the lipophilic carriers was not efficient for sustaining the release rate of a highly water-soluble drug. The optimally formulated lipophilic matrix tablet (DCT8), exhibited sustained release profiles, giving <40%, <60% and approximately 80% at 30 min, 1 h and 3 h in water, respectively.

Table 4 gives a comparison of the release kinetics of potassium citrate from the lipophilic matrix tablets (SDT and DCT) according to four different kinetic models. The release mechanism from the lipophilic matrix tablet was quite different, depending on the composition and the preparation method. The SDT and DCT including hydrophilic excipients showed diffusion-controlled erosion and disintegration (see also Table 3). The release mechanism showed a non-Fickian model that was fitted by the first-order equation because the correlation coefficients were the highest. On the other

Table 4
Release kinetics of potassium citrate from lipophilic matrix tablets prepared via the direct compression of granular mixtures or powdered mixtures in water according to four different kinetic models

Codes	Zero order		Higuchi		First-order		Exponential		
	r^2	K_1	r^2	K_2	r^2	K_3	n	r^2	K_4
SDT1	0.6300	25.76	0.8028	52.32	0.9315	0.9534	0.2129	0.9305	77.75
SDT2	0.7562	22.16	0.9455	43.97	0.9217	0.4658	0.3018	0.9992	56.53
DCT1	0.4527	41.56	0.4387	65.71	0.4667	2.7631	−0.0131	0.9602	105.48
DCT2	0.3541	19.50	0.3433	41.18	0.3267	0.4583	−0.0081	0.0989	88.33
DCT3	0.7430	29.45	0.8672	57.11	0.9924	1.3876	0.3916	0.8732	69.72
DCT4	0.9044	29.74	0.9841	55.33	0.9985	0.9089	0.5649	0.9858	53.09
DCT5	0.9382	29.02	0.9973	53.95	0.9706	0.8488	0.3498	0.9995	49.54
DCT6	0.9751	27.76	0.9794	50.27	0.9115	0.4771	0.726	0.9960	39.29
DCT7	0.9523	32.47	0.9869	59.65	0.7121	1.5191	0.3762	0.9869	51.64
DCT8	0.9031	23.64	0.9951	45.09	0.9818	0.4877	0.4661	0.9936	46.00

K_1, K_2, and K_3 are the rate constants for a zero-order, Higuchi, and first-order model, respectively. K_4 is the rate constant with unit t^n and n is the release exponent, which indicate the release mechanism.

hand, the lipophilic matrix tablet with a sustained release manner was best fitted by the Higuchi equation and agreed with the Fickian model regardless of the preparation methods used.

3.3. Photoimages and surface morphology of lipophilic matrix tablet

Fig. 4 shows photoimages of the lipophilic matrix tablet (DCT8) during release test in water. The DCT8 incorporating stearyl alcohol and stearic acid in the carnauba wax retained its shape without disintegration. The tablet density should decrease gradually as the highly water-soluble drug diffused out. As a result, the lipophilic matrix tablet began to rise from the bottom of the vessel to the surface of the release medium approximately 3 h after the dissolution test.

Fig. 5 shows the surface morphology of the lipophilic matrix tablet (DCT8) before and after the release test for 3 h in water. Before the release test, the surface of the intact lipophilic matrix tablet appeared to be smooth and rusty. After the release test, the tablet maintained its shape but there was slight erosion on the tablet surface with many pores and cracks. The release of the drug through these diffusion channels of pores and cracks of lipophilic matrix tablet occurred progressively via a diffusion-controlled leaching process (Yonezawa et al., 2003).

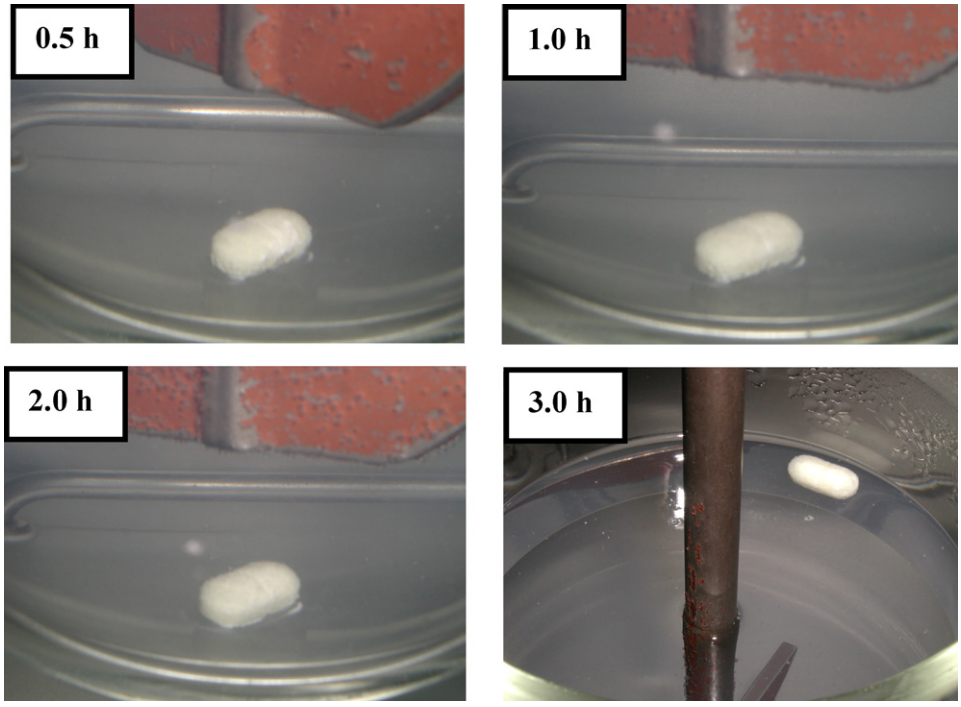

Fig. 4. Photoimages of a lipophilic matrix tablet (DCT8) during release test in water.

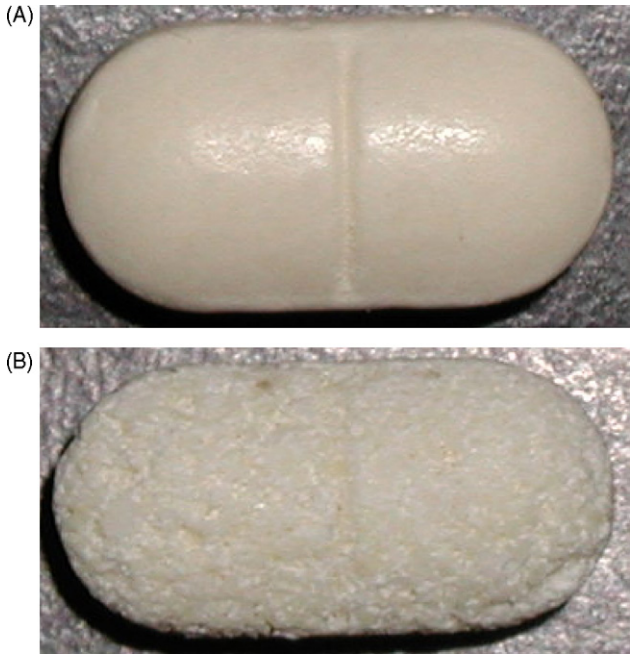

Fig. 5. Surface morphology of a lipophilic matrix tablet (DCT8) before (A) and after the 3 h release test in water (B).

4. Conclusions

Release mechanism by either leaching or disintegration of the lipophilic matrix tablet was dependent on the preparation method as well as the composition of the formulation. The incorporation of lipophilic stearyl alcohol and stearic acid in carnauba wax was essential for obtaining a sustained release lipophilic matrix tablet containing highly water-soluble potassium citrate at a high loading dose. Release profile of the sustained release matrix tablet was well fitted by the Higuchi equation model and was explained by the diffusion-controlled leaching through the channels of pores and cracks. This lipophilic matrix tablet might be a useful tool for delivering highly soluble potassium citrate at high loading doses in a sustained release manner, and is currently being marketed for clinical use as an Urocitra-K SR tablet in Korea.

Acknowledgments

This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the National Research Lab. Program funded by the Ministry of Science and Technology (M10300000-06J0000-31910). This research was awarded the best poster presentation in Korean Society of Pharmaceutical Science and Technology annual meeting held in Seoul, Korea. We also thank the Research Institute of Pharmaceutical Sciences, Kangwon National University for allowing the use of their fluid-bed coating apparatus.

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