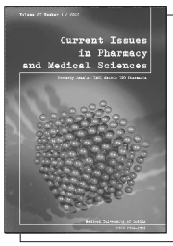

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Dissolution of lithium carbonate from three types extended-release capsules in paddle, basket and flow-through apparatus

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ABSTRACT

Three types of 24-h extended-release multiparticulate capsules containing a dose of 480-504 mg lithium carbonate in a form of either pellets or 2 mm minitablets or 6 mm tablets were prepared. Dissolutions tests were performed using three different pharmacopoeial apparatus: basket, paddle and flow-through apparatus. Only capsules filled with pellets showed the same dissolution profiles, irrespective of the apparatus used in the study. In the case of two other formulations, the slowest dissolution occurred in the flow-through apparatus. The largest difference between release profiles from different apparatus was observed for the capsule filled with 6 mm tablets. The observations may indicate that probability of good reproducibility of dissolution profiles obtained in different test conditions, including change of apparatus, is related to either size or a number of the units in a capsule.

Keywords: dissolution test, pellets, minitablets, lithium carbonate, extended-release capsules

INTRODUCTION

Lithium carbonate is a drug commonly used in the treatment of mania and in preventing the recurrence of both maniac and depressive symptoms. The therapeutic index of the drug is narrow, and side effects are common even in patients whose serum lithium levels are maintained within the therapeutic range [11]. Reduction of absorption peaks and gastrointestinal side effect of lithium is achieved in therapy with commercially available 12-h sustained-release lithium tablets intended for a twice-a-day administration. In order to prolong drug release up to 24 h, three different types of multiparticulate capsules were developed: the capsules were filled either with pellets or 2 mm minitablets or 6 mm tablets (Fig. 1).

The other goal of the present study was to compare the three formulations using three different pharmacopoeial dissolution apparatus: paddle, basket and flow-through apparatus.

There is no general dissolution method for all kind of dosage forms. The current sophistication in formulation of new modified release drug delivery systems and associated diversity in dosage form design necessitates the development of appropriate procedures for dissolution measurements [1-3, 12]. Moreover, the formulation scientists and regulatory authorities face a challenge of standardizing the test conditions for dissolution testing.

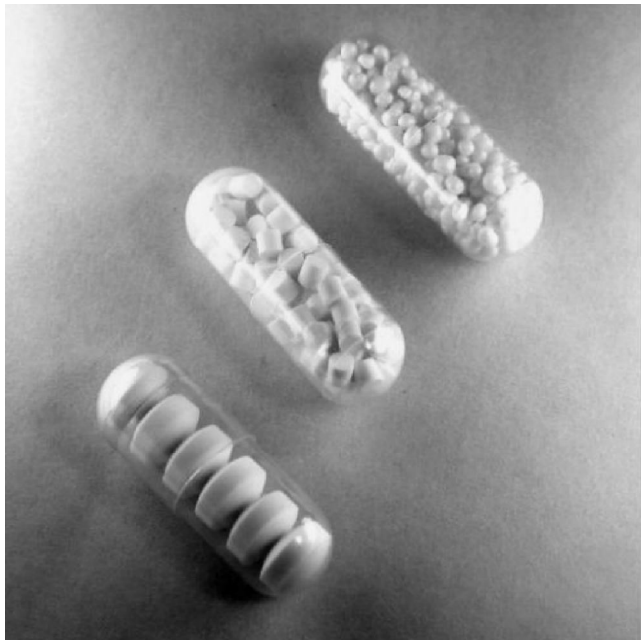

Fig. 1. Capsules filled with pellets, 2 mm minitablets and 6 mm tablets

The majority of studies focusing on dissolution profiles of extended release products use USP/Ph.Eur. dissolution apparatus with either paddle or basket method. An alternative is the flow-through method, introduced to Pharmacopoeias for testing dissolution profiles of extended release dosage forms. At present, there is no clear indication which appara-

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tus is the most suitable for dissolution studies of the multiparticulate capsules. Usually basket or paddle apparatus are recommended in pharmacopoeias for non-modified release capsules and these apparatus are indicated in published research, too [6-8]. In US Pharmacopoeia basket apparatus is proposed, for example, for immediate release lithium carbonate capsules. A pharmacopoeial flow-through apparatus has gained a lot of attention and can be used for hard and soft gelatin capsules as well [4]. The choice of the apparatus is more difficult when different filling (tablet or pellet type) of the capsule is considered [5]. Our investigation demonstrates the results obtained for different capsules depending on the type of apparatus used in the test.

MATERIALS AND METHODS

Preparation of tablets, minitablets, pellets and multiparticulate capsules

The composition of the formulations is shown in Table 1.

Table 1. Composition of cores and coatings of 1-1.5 mm pellets, 2 mm minitablets and 6 mm tablets [% w/w]

Formulation / Ingredient	Pellets		Minitablets		Tablets
Cores					
Lithium carbonate	70.0		70.0		70.0
Avicel PH 101	16.25		10.0		10.0
Sucrose	10.0		–		–
Tablettose 80	–		8.5		8,5
PVP K-30	3.75		1.0		1.0
Macrogol 6000	–		10.0		10.0
Magnesium stearate	–		0.5		0.5
Coating					
	1st layer	2nd layer	1st layer	2nd layer	
Eudragit RS30D	23.3	–	23.3	–	–
Eudragit RL30D	16.7	–	16.7	–	–
Eudragit L30D55	–	40.0	–	40.0	–
Talc	6.0	6.0	6.0	6.0	–
Triethyl citrate	2.4	2.4	2.4	2.4	–
Antifoam emulsion	0.2	0.2	0.2	0.2	–
Kollicoat MAE30DP	–	–	–	–	60.0
Propylene glycol	–	–	–	–	1.8

In order to prepare cores of the tablets and minitablets lithium carbonate, microcrystalline cellulose – Avicel PH 101 and lactose – Tablettose 80 were mixed and agglomerated with an aqueous polyvinylpyrrolidone K-30 solution. The granules (for minitablets the proper size was achieved using 0.25 mm mesh sieve) were blended with magnesium stearate and polyethylene glycol 6000. Tablets or minitablets were produced using an eccentric tabletting machine (Korsch EK-0, Frankfurt, Germany) equipped with 6 mm hemispherical or 2 mm flat punches, respectively. The minitablets were cylindrical, 1.9 mm in heigth with an average mass 9 mg.

The 6 mm tablets were enteric-coated in a drum-coater (Farma-Tech, Kutno, Poland) with Kollicoat MAE30DP dispersion. A hard gelatin capsule, size 1 was filled with one uncoated and five coated tablets, which corresponded to 504 mg (3.0 %) of lithium carbonate.

The cores of minitablets were coated with Eudragits aqueous dispersion in a Uni-Glatt fluidized-bed Würster system (Glatt, Dresden, Germany). The first layer (50 μm) was prepared with a mixture of Eudragit RS/RL (ratio 7:5) and the second one was made of Eudragit L (25 μm). Each capsule was filled manually with 100 mg of uncoated and 600 mg of coated minitablets (approximately 75 units in total). Lithium carbonate content was on an average 480 mg (4.2 %).

The third type of capsule was prepared by filling with 700 mg pellets of 1.0-1.5 mm grain size. The pellets were prepared by a standard extrusion-spheronization method [10]. Shortly, the drug, Avicel PH 101 and sucrose were blended and the mass for extrusion was prepared by wetting the powders with PVP K-30 solution. The granules were obtained in an extruder type 25 (Caleva, Dorset, UK) equipped with a 1.0 mm mesh and finally spherical pellets were prepared in a Caleva spheronizer. The pellets were coated with two layers of Eudragits, as described for minitablets. The ratio of coated and uncoated pellets in a capsule was 6 : 1. Each capsule contained on an average 480 mg (±5.0 %) of lithium carbonate.

Drug release study

In vitro release of lithium from each kind of the multiparticulate capsules was carried out at temperature 37±0.5°C in the Ph. Eur. paddle and basket apparatus (PTWS-3, Pharma Test, Hainburg, Germany). The rotation speed was 75 rpm. Change of dissolution medium (900 ml) was performed in order to imitate physiological conditions: HCl (0.1 mol/l) was replaced after 2 h with pH 6.8 phosphate buffer (0.2 mol/l). Samples of the dissolution medium were withdrawn after 2, 4, 6, 12 and 24 h. The test was also performed in the Ph. Eur. flow-through apparatus (SSE-343, Sotax, Allschwil, Switzerland). For the first 2 h 0.1 mol/l HCl was used as the dissolution medium, followed by pH 6.8 phosphate buffer (0.2 mol/l). The flow rate of the media was 4 ml/min.

The amount of lithium in the collected dissolution medium was determined using an atomic absorption spectrometry (AAS) at the analytical wavelength 670.1 nm (Unicam SP 1900 spectrometer, Unicam, Manchester, UK). The method was evaluated and precision (SD 4.5%) and linearity (r^2=0.99968) in the range of lithium concentration 0.1-5.0 mg/l was demonstrated. Two-way ANOVA was used to test statistical significance of the observed differences between dissolution profiles.

RESULTS AND DISCUSSION

In the acidic medium, all uncoated formulations released the total dose of lithium carbonate in less than 45 min. In the pH 6.8 phosphate buffer, more than 80% of the dose was released after 2 h from pellets, after 4 h from 2 mm minitablets and after more than 12 h from 6 mm tablets. In order to achieve 24 h extended-release forms coating of the cores was performed. Since the cores of the 6 mm tablets demonstrated extended-release profile in the pH 6.8 buffer but too fast release in an acidic medium [9], they were enteric-coated with Kollicoat MAE30DP. In contrast to 6 mm tablets,

the cores of minitablets, despite of the same composition (Table 1), did not show any retardation of the drug release, what can be explained by different geometry and hardness of the tablets (110.9 N and 10.3 N for 6 mm and 2 mm tablet, respectively). In order to achieve slow drug release for up to 24 h, the minitablets were coated with two-layer Eudragit films. The same coating was appropriate for prolongation of drug release from pellets.

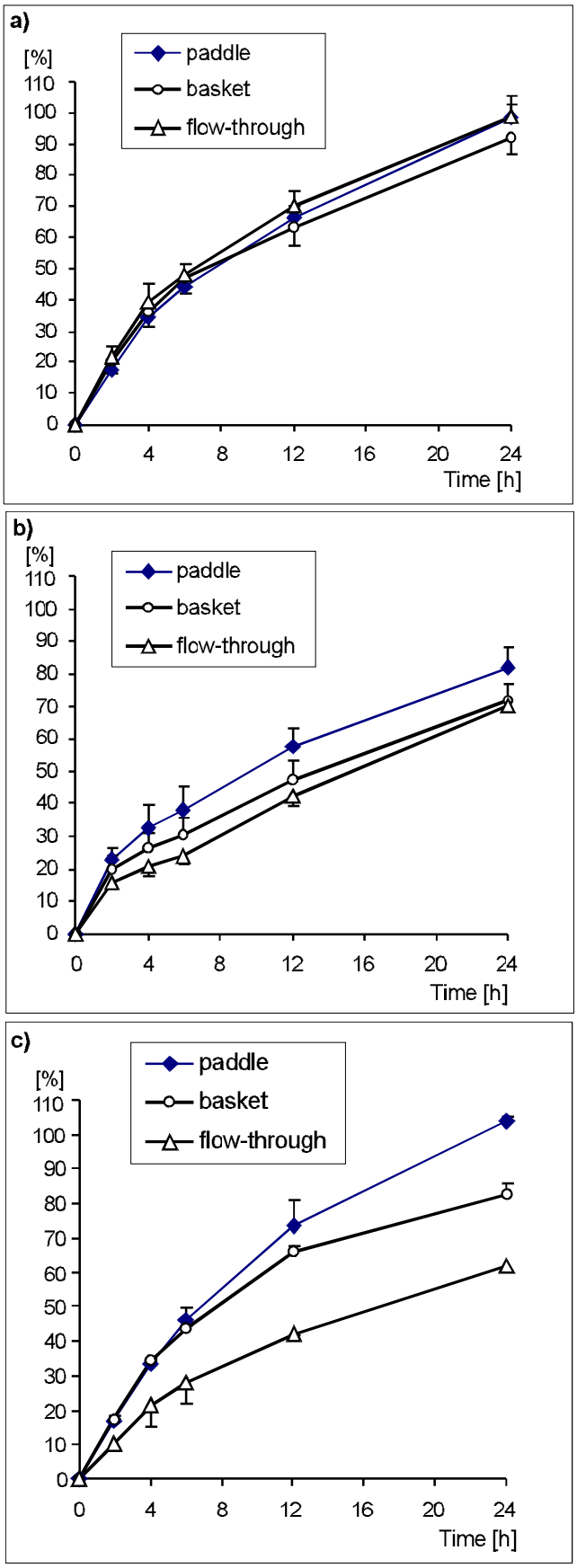

Fig. 2. Lithium release profile from capsules filled with : a) pellets (1-1.5 mm), b) 2 mm minitablets or c) 6 mm tablets observed in paddle, basket (75 rpm) and flow-through (4 ml/min) apparatus (mean and SD, n=6)

The coated units showed initial delay in drug release, but this was eliminated by combining in one capsule both, coated and uncoated, forms. The number of units containing 480-500 mg of lithium carbonate fitted well in a size 1 hard gelatin capsule. The 1:6 ratio of uncoated and coated pellets or minitablets or 1 uncoated and 5 coated 6 mm tablets allowed for achieving 24 h extended-release profiles what is demonstrated in Fig. 2.

The drug release study was performed in paddle, basket and flow-through apparatus in order to compare results and to evaluate which of them may be the most suitable for each type of the capsule. If the three apparatus were regarded, only for the pellet-capsule the profiles would be identical ($p < 0.05$). That was not a case, for the minitablet-capsule or tablet-capsule formulations, for which the slowest dissolution occurred in the flow-through apparatus. In comparison to the paddle apparatus, slower release during first 4 h was also observed for the minitablet-capsule when the basket apparatus was used.

The 4 ml/min flow rate employed in the flow-through apparatus, was the slowest recommended in USP (4-16 ml/min). Tests with the flow-rate 16 ml/min were also carried out for 6 mm tablet-capsule and for pellet-capsule. The four-fold increase in the flow rate resulted only in 10-23% increase of the drug release rate from the tablet-capsule but the difference was not statistically significant ($p < 0.05$) and still the process was slower than observed in two other apparatus ($p < 0.01$). On the other hand the release profile from the pellet-capsule remained unchanged (data not shown).

The flow-through apparatus is often indicated for pellets. Our results demonstrate that capsules filled with pellets could be tested in this apparatus and that the results are comparable with those obtained in two other apparatus. An interesting problem can be raised, however, regarding high irresponsivity of the dissolution profiles to varying test conditions (change of the flow rate), what is not necessarily a desired feature of a dissolution test, since a significant level of the discriminating power for such test is required [2].

Opposite to the pellet-capsule, tablet- and minitablet-capsules are the systems for which good reproducibility of the results obtained with different test conditions, including change of the type of apparatus, is less probable. The most significant variability in dissolution profiles, related to the type of the apparatus, was observed for the capsules filled with large and few units – 6 mm tablets (Fig. 2).

The above observations may indicate that reproducibility of results obtained with different test conditions, including change of the apparatus, may be related either to the size or to the number of the units in the capsule. The choice of the apparatus may be less critical for pellet-capsule than for tab-

let- or minitablet-capsule. However, this hypothesis requires confirmation and further studies for different active substances.

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