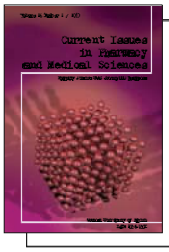

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The influence of coating on release of paracetamol from the multi-compartment systems

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ABSTRACT

A multi-compartment system enables modification of medicinal substance release. Nine series of multi-compartment systems were prepared, where each contained 5 minitablets. Application of different envelopes (OPADRY II WHITE and ACRYL EZE – PINK), coating the individual minitablets and complete multi-compartment systems, allowed for modeling medicinal substance release from the tested drug forms. Dissolution test of paracetamol was tested. The results were processed using the *Statistica 9.0* (StatSoft, USA).

Keywords: multi-compartment system, modified release, minitablets, coated tablets, paracetamol

INTRODUCTION

Pharmaceutical technology of the 21st century is dominated by a tendency to seek drug forms that would offer the expected pharmaceutical effect with the least possible unwanted results. Hence, forms are created which deliver an appropriate dose of medicinal substance to a specific organ and ensure release of the medicinal substance over a specific period of time. Use in clinical practice of extended-release preparations (8-12h) enables application of smaller daily dosage, leading to lower fluctuations of medicinal substance concentrations in the blood.

Coating of tablets enables prolongation of medicinal substance release. In turn, for the purpose of obtaining the effect of rapid and prolonged release, drug form technology has developed multi-compartment systems, whose structure enables satisfaction of the above requirements [1,4,5].

A multi-compartment system is superior to traditional drug forms with respect to more effective control of release and place of uptake. As a result, we are able to better control the concentration of medicinal substance in the blood or tissues, which leads to improved safety of pharmacotherapy. Moreover, such a system enables modeling of release profile of a medicinal substance, as well as of its uptake, by placement in a single tablet or capsule of e.g. minitablets, coated with different envelopes [2,3,6,8]. Control of release rate of medicinal substance is achieved by application of different thickness of envelopes of soluble polymers (the controlling factor is then the rate of swelling and dissolution of the envelope) or insoluble polymers (the controlling factor is then rate of diffusion through the envelope or time to breaking of continuity of the envelope) in the alimentary tract [4,7,9].

The objective of the work was to verify, in what degree the process of coating of tablets and minitablets contained therein, affects release of paracetamol. Owing to the performed tests, it was possible to specify in which section of the alimentary tract, after what time and in what quantity paracetamol is released from a programmed multi-compartment system.

MATERIALS AND METHODS

In the tests, a multi-compartment system was created with paracetamol (Mallinckrodt Chemical) as model substance. Using an impact tableting machine (Korsch – EKO, Erweka), with a 3mm diameter punch, minitablets were created with a mass of about 30 mg each. Subsequently, applying the direct tableting method, 9 series of multi-compartment systems were prepared – tablets with a diameter of 11 mm. Each of the tablets contained

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5 minitablets with paracetamol, of 3 mm in diameter. Their weight (5 units) prior to coating fell in the bracket of 0.1501-0.1511g, and following coating 0.1575-0.1599 g. The mass of the multi-compartment system – tablet was about 0.5 g. The contents of the tablet mass is given in table 1.

Table 1. Compositions of tablet mass of minitablets and the multi-compartment system (tablets – cores)

	Ingredient	Function	Amount (g)	
			Minitablets (5 minitabl.)	multi-compartment system
1.	Paracetamol	Active substance	0.125	0.125
2.	Microcrystalline cellulose	Binding substance, bodying agent, disintegrating, anti-adhesion substance	0.150	0.300
3.	Sodium starch glycolate	Disintegrating substance	0.010	0.020
4.	Colloidal silicon dioxide	disintegrating, lubricant, antistatic substance	0.005	0.012
5.	Magnesium stearate	lubricant, anti-adhesion substance	0.003	0.006
			Sum 0.293	Sum 0.463

Tablets and minitablets were coated with two types of coats: envelope soluble in acidic environment (OPADRY II WHITE, Colorcon) and respectively envelope dissolving only in the small intestine (ACRYL – EZE PINK, Colorcon).

The type of coats used in individual series is presented in table 2.

Table 2. Diagram of coating minitablets and tablets of batches 1-9

Batch	Minitablets	Multi-compartment tablets
1.	No coating	No coating
2.	No coating	The coating soluble in the stomach
3.	The coating soluble in the stomach	No coating
4.	The coating soluble in the stomach	The coating soluble in the stomach
5.	No coating	Gastro-resistant coating
6.	Gastro-resistant coating	No coating
7.	The coating soluble in the stomach	Gastro-resistant coating
8.	Gastro-resistant coating	Gastro-resistant coating
9.	Gastro-resistant coating	The coating soluble in the stomach

Minitablets/cores and multi-compartment systems/cores were coated using a Unity Pharm type D-5 coating gun and dried with drier to prevent core clumping. Increase of tablet mass using the OPADRY II WHITE envelope was ca. 4.5%, while using the ACRYL – EZE PINK envelope – 5.4%.

Dissolution testing of paracetamol from the multi-compartment system was tested *in vitro* in a paddle machine (DT 70, Erweka, 50 rpm), utilizing the acceptor liquid exchange method. The test utilized two acceptor liquids:

1. 0.1M HCl – imitating the environment prevailing in the stomach,
2. phosphate buffer of pH 6.8 – imitating conditions in the small intestine.

Paracetamol in the tested samples was determined with the spectrophotometric method (UV-VIS) at the wavelength of 243 nm (correlation coefficient was 0.9875). The obtained results allowed for calculation of released paracetamol and determine active substance release profiles for each of the tablet series.

RESULTS

Results of paracetamol release profiles carried out for series 1-4 were tested for 60 minutes using only 0.1 M HCl as the acceptor liquid. Tablets of these series did not contain a coat resistant to operation of hydrochloric acid and within 30 minutes more than 80% of active substance was released.

A schedule of results of active substance release in 1, 3, 5, 10, 15, 30, 45 and 60 minutes in 0.1 M HCl from multi-compartment systems of series 1-4 is presented in figure 1.

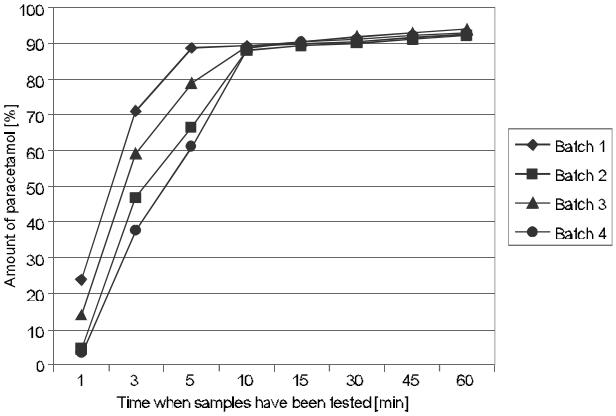

Fig. 1. Results of dissolution testing of paracetamol from tablets of batches 1-4 in 0.1 M HCl

For the other five series of tablets the test was conducted up to the 165 minute using 0.1 M HCl as acceptor liquid, provided that following 120 minutes the releasing medium was changed to phosphate buffer of pH 6.8.

A schedule of results of active substance release in 0.1 M HCl and in the phosphate buffer of pH 6.8 from multi-compartment systems of series 5-9 is presented in figure 2.

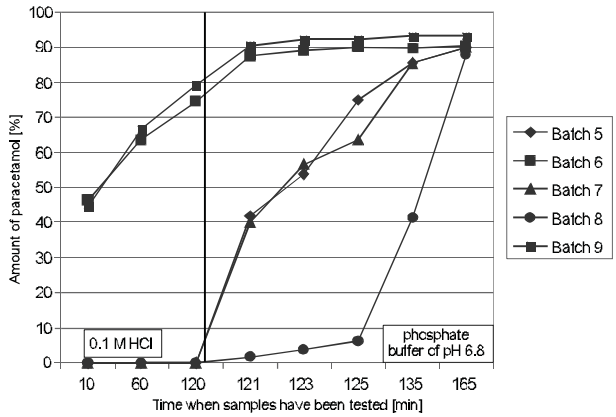

Fig. 2. Results of dissolution testing of paracetamol from tablets of batches 5-9 in 0.1 M HCl and phosphate buffer of pH 6.8

A line marks the time when the acceptor liquid was changed from 0.1M HCl to phosphate buffer of pH 6.8.

DISCUSSION

The obtained results of tests of pharmaceutical availability allowed for assessment of impact of the utilized envelopes on paracetamol release profiles from multi-compartment systems.

Analyzing the amount of released paracetamol it should be stated that up to the 10th minute paracetamol release was varied. Paracetamol was slowest to release from tablets of series coated with Opadry II White envelope. The fastest release was from uncoated tablets. Series 1 released over 80% of active substance already after 5 minutes, and for other series after 10 minutes. The quantity of released paracetamol of series 1-4, with the use of 0.1 M HCl, equalizes in the 10th minute of the test.

In case of series where tablets were coated with envelope resistant to action of 0.1 M HCl (series 5, 6, 7, 8, 9), the test was conducted for 120 minutes, as this is the approximate duration of paracetamol in the stomach prior to uptake in the small intestine. The active substance was released in 0.1 M HCl only in series 5,6,7 and 9, whereas results of series 5 and 9 were very similar to each other – after 10 minutes about 45% of paracetamol was released, after 60 minutes ca. 65%, after 120 minutes 75-80%. Release from these series occurred, however, twice slower than it took place in series 1-4. Results statistical analysis presented in table 3 showed no significant differences in the quantity of released paracetamol between series 6 and 9 – the OPADRY II WHITE envelope on multi-com- partment systems does not affect release in a situation, where minitablets are already coated.

Table 3. Comparison of results of paracetamol release for batches 6and 9, using 0.1M HCl. The probability test in the test T set with an independent estimation of variance

Time [min]	Amount of paracetamol [%]		The probability test
	Batch 6	Batch 9	
10	46.61	44.55	0.775536
60	63.88	66.64	0.702642
120	74.67	79.20	0.382223

Results of paracetamol release for series 6 and 9, using phosphate buffer of pH 6.8, were close, and release occurred twice as fast, due to the effect of disintegration of the coat on the minitablets already during release in 0.1 M HCl. Only after ca. 15 minutes of testing in phosphate buffer, the results of almost all series were comparable (85-90%), with the exception of series 8, where minitablets and the whole multi-compartment system were coated with intestinal coat (after 15 minutes only 41.48%) (Fig. 2).

Table 4. Comparison of results of paracetamol release for batches 6 and 9, using phosphate buffer of pH 6.8

Time [min]	Amount of paracetamol [%]		The probability test
	Batch 6	Batch 8	
121	87.54	1.88	0.000632
123	88.96	3.79	0.001626
125	90.06	6.34	0.000550
135	89.91	41.48	0.018384

Table 5. Comparison of results of paracetamol release for batches 8 and 9, using phosphate buffer of pH 6.8

Time [min]	Amount of paracetamol [%]		The probability test
	Batch 8	Batch 9	
121	1.88	90.42	0.000202
123	3.79	92.40	0.000070
125	6.34	92.16	0.000632
135	41.48	93.17	0.000726

It was found, that 5,4% weight gain of the enteric coat on minitablets was not enough to provide acid resistance.

Statistical analysis performed with the Kruskal-Wallis ANOVA test showed significant differences at significance level $p<0.05$ in the quantity of released paracetamol.

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