In the twenty-first century pharmaceutical technology the dominating tendency is to seek a drug form which would provide a desired therapeutic effect with a minimum of side effects. Therefore, scientists create drug forms which both provide the correct dose of the medicinal substance to a specific organ and ensure its release for a specified period of time (1–3). In clinical practice the use of sustained release preparations (8–12 h) enables the use of a lower daily dose, which results in smaller variation of the concentration of medicinal substance in the blood. In order to obtain immediate and sustained release, the drug form technology has been enriched with newly developed multi-compartment systems whose structure makes it possible to meet the above-mentioned requirements. Thanks to this universal drug form it is possible to overcome many of the disadvantages arising from the use of conventional drug forms (4). The drug dose is divided into many sub-units – containers, each of which behaves like an individual form, providing medicinal substance in a predetermined place and in a predetermined way. If in the multi-compartment system several medicinal substances of different places of release are used, such a drug form can successfully compete with other forms, either in monotherapy or in combination therapy (5–7).

Multi-compartment system is superior to traditional drug forms in terms of more efficient control of release and absorption place. As a result, a better control of the concentration of medicinal substance in blood or tissues is obtained, leading to improved safety of pharmacotherapy (8–10). Furthermore, this kind of system provides the possibility to model the profile of medicinal substance release and absorption by placing in one capsule e.g., mini tablets of different compositions or of different coatings (5, 11, 12). Control of the rate of medicinal substance release is achieved *inter alia* through the use of polymer coatings of varied thickness, soluble at different pH values or through the use of excipients, delaying disintegration of the tablet or the release of the medicinal substance (11–13).

One of the main areas where modified release of medicinal substance is often used is the treatment of pain and inflammations. Ketoprofen (the II class

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**KINETICS STUDY ON KETOPROFEN RELEASE FROM MINI TABLETS AND MULTI-COMPARTMENT SYSTEMS**

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**Abstract:** Thanks to multi-compartment systems it is possible to modify drug release. Two types of mini tablets containing 12.5 mg of ketoprofen were made: mini tablets of immediate (IR) and sustained (SR) release. Some of the tablets of immediate release were coated with an enteric coating, thereby obtaining a delayed release effect (IRc). For each tablet type, release profiles were tested in three media: 0.1 M HCl, phosphate buffer pH 4.5 and phosphate buffer pH 6.8. Based on the obtained results, three appropriate multi-compartment models have been constructed and tested. The factor limiting the amount of available ketoprofen at the absorption place is pH of the environment. It was observed that the increase in pH caused the increase of ketoprofen solubility. Constructed multi-compartment systems allowed to change the composition and the dose of medicinal substances easily. Thanks to this it is possible to adjust the release profile of the active substance to the individual patient, which meets the expectations of personalized medicine.

**Keywords:** multi-compartment system, modified release, mini tablets, coated tablets, ketoprofen


In the twenty-first century pharmaceutical technology the dominating tendency is to seek a drug form which would provide a desired therapeutic effect with a minimum of side effects. Therefore, scientists create drug forms which both provide the correct dose of the medicinal substance to a specific organ and ensure its release for a specified period of time (1–3). In clinical practice the use of sustained release preparations (8–12 h) enables the use of a lower daily dose, which results in smaller variation of the concentration of medicinal substance in the blood. In order to obtain immediate and sustained release, the drug form technology has been enriched with newly developed multi-compartment systems whose structure makes it possible to meet the above-mentioned requirements. Thanks to this universal drug form it is possible to overcome many of the disadvantages arising from the use of conventional drug forms (4). The drug dose is divided into many sub-units – containers, each of which behaves like an individual form, providing medicinal substance in a predetermined place and in a predetermined way. If in the multi-compartment system several medicinal substances of different places of release are used, such a drug form can successfully compete with other forms, either in monotherapy or in combination therapy (5–7).

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of BCS system) (14) is a representative of the group of non-steroidal anti-inflammatory drugs (NSAID) (15) and it is widely used in the treatment of pain, in cases of inflammation and rheumatic diseases (16). When administered in the drug form of unmodified release, it is rapidly absorbed, achieving the maximum concentration in blood within 0.5 to 2 h (17, 18). After this time, its concentration decreases rapidly to a very low level, thus in the long-term treatment it is necessary to take multiple doses of the drug per day in order to maintain the therapeutic concentration (9).

Multi-compartment systems enable the release of desired amount of active substance in a selected section of the gastrointestinal tract (19, 20), according to a determined dosing schedule. Thanks to them it is often possible to reduce the quantity of drug doses to one per day (21).

The aim of the study was to construct and test a multi-compartment system, consisting of mini tablets of ketoprofen, enclosed in a capsule of hypromellose. The mini tablets obtained by the usage of different technologies and having different properties, created multi-compartment systems in suitable configurations. These systems allowed to change the composition and the dose of medicinal substances easily. It was also possible to modify the release profiles of applied substance.

MATERIALS AND METHODS

In the first stage of the study, using a tablet press (EKO - Korsch) with a stamp having a diameter of 5 mm, two types of mini tablets with ketoprofen (Lee Pharma) as a model substance were prepared: immediate release mini tablets (IR) of a weight of 50 mg and the medicinal substance content of 12.5 mg as well as sustained release mini tablets (SR) of a weight of 60 mg and ketoprofen content of 12.5 mg. Both kinds of mini tablets were prepared using direct compression. Part of the immediate release mini-tablets were coated with enteric coating (ACRYL- EZE PINK, Colorcon), which resulted in mini tablets releasing drug substance with a delay (IRc). Mini tablets/cores were coated according to the Würster method (UNIGLATT, Glatt) (22). Weight gain of the tablets in the coating process was about 16%. The composition of the tablet mass of IR and SR mini tablets and its properties are shown in Table 1.

Release profiles were tested for each type of mini tablets, pursuant to the EMA (European Medicines Agency) guidelines, in three media: 0.1 M HCl, phosphate buffer pH 4.5 and phosphate buffer pH 6.8. In addition, release test in the phosphate buffer pH 6.8 over the course of 12 h was carried out for SR tablets. Concentration of ketoprofen in the tested samples was determined spectrophoto metrically (spectrophotometer UV 300 UV:Visible, Unicam) at a wavelength $\lambda = 259$ nm. The correlation coefficients for standard curves drawn for ketoprofen in particular media were respectively:

- 0.1 M HCl ($r^2 = 0.9995$)
- phosphate buffer, pH 4.5 ($r^2 = 0.9979$)
- phosphate buffer, pH 6.8 ($r^2 = 0.9912$)

The obtained results made it possible to calculate the amount of released ketoprofen for each series of mini tablets. Based on the obtained results,
multi-compartment systems were constructed, by placing mini tablets in a capsule of hypromellose.

The amount of released ketoprofen from the mini tablets and multi-compartment system were tested in vitro in the dissolution apparatus with a paddle (DT 70, Erweka), using the acceptor fluid replacement method (23). To avoid floating of multi-compartment systems on the surface of acceptor fluids aggravating elements (Sinkers) were used. The rotation speed of the agitator was 50/min while the water temperature in the bath was 37 ± 1°C. The volume of acceptor fluids was 900 mL. The following two acceptor fluids had been used in the study of multi-compartment systems:

- 0.1 M HCl - imitating the environment prevailing in the stomach,
- phosphate buffer, pH 6.8 – simulating the conditions in the small intestine.

Three types of multi-compartment systems were prepared, containing, respectively:

- **IR + IRc** – 2 immediate release mini tablets and 2 immediate release coated mini tablets. This model simulates the pulsatile release model in which half of the dose is released in the stomach and the other half in the small intestine;
- **IR + 3SR** – 1 immediate release mini tablet and 3 sustained release mini-tablets. This corresponds to a classic model of a drug of sustained action, wherein part of the substance, in initial dose form, is released in the stomach, and the other part as a maintenance dose is slowly released and absorbed in the small intestine;
- **IRc + 3SR** – 1 immediate release coated mini tablet and 3 sustained release mini-tablets where only a small, insignificant portion of ketoprofen is released from matrix tablets in the stomach while both, the initial dose and maintenance dose are released in the small intestine. This model can be proposed for the treatment of patients with damaged gastric mucosa and enables to avoid its irritation.

Studies on ketoprofen release from multi-compartment systems had been performed up to the 120th minute with the use of 0.1 M HCl as acceptor fluid and afterwards the releasing medium was changed to phosphate buffer pH 6.8.

**RESULTS AND DISCUSSION**

Use of Prosolv Easy Tab and Prosolv 90HD made it possible to carry out direct compression - the fastest and cheapest method of tableting. Obtained mini tablets with ketoprofen were characterized by high hardness (103 ± 2.26 N for IR mini tablets and 133.5 ± 3.24 N for SR mini tablets) and low friability (0.04% and 0.17%, respectively). It should be noted, that a considerable hardness of IR mini tablets did not lead to unfavorable prolong of their disintegration time (60 ± 2 s) (Table 1).

Results of dissolution testing show clearly, that the pH is the critical factor determining the quantity of ketoprofen, which may be dissolved in the medium, after release from the mini tablets. Solubility of ketoprofen increases substantially with increasing
pH (16, 24). In 0.1 M HCl, after 120 min, was dissolved 20% of ketoprofen, released from IR mini tablets. In the phosphate buffer pH 4.5 was dissolved almost 70% and in phosphate buffer pH 6.8 about 90%. The results of ketoprofen release from mini tablets are given in Figures 1 and 2.

The effect of pH on the dissolution rate of ketoprofen is also significant. In the first 30 min of the study, was dissolved in a medium, respectively:

- In 0.1 M HCl - 6.09% of ketoprofen, representing about 30% of the total amount of ketoprofen, dissolved within 120 min.
- In buffer pH 4.5 - 34.26%, representing approximately 50% of the total amount of ketoprofen, dissolved within 120 min.
- In buffer pH 6.8 - 81.95%, which is almost 90% of the dose of ketoprofen, which completely dissolved during the test.

Figure 2. Amount of released ketoprofen (% ± SD) from SR mini tablets in buffer pH 6.8 over 12 h (n = 12)

Figure 3. Amounts of released ketoprofen (% ± SD) from multi-compartment systems (n = 12)
This clearly shows that a relatively small change in pH in the stomach may have a significant impact on the solubility and absorption of ketoprofen, and through it, on the time, after which a therapeutic effect is observed (16). The situation when the pH of the stomach is higher than the physiological, can take place, inter alia, during long term use of proton pump inhibitors (omeprazole, pantoprazole), as well as during the concomitant use of ketoprofen and antacids (magnesium hydroxide, aluminum hydroxide) (25).

In studies of ketoprofen release from sustained release mini tablets (SR), the effect of pH on the dissolution rate of released ketoprofen is also observed. However, the main factor, controlling the amount of ketoprofen released into the medium is the diffusion rate through the swollen matrix. The amount of dissolved ketoprofen increases with an increase of pH, but in any medium, an increase of its concentration is quite uniform. There is no rapid dissolving of substantial amount of the active substance in the first 30 min of the release, as it was observed in the IR mini tablets studies. In the initial stage, when the mini tablet absorbs the medium and forms a matrix, we can see the graph curve slightly flattened (Fig. 2). Only when the diffusion rate of ketoprofen to the medium stabilizes, the curve is steeper and close to a straight line.

In the study on the multi-compartment system #3 (Fig. 3), where the SR mini tablets are one of the components of the system, the effect of pH change on the release rate of ketoprofen is also clearly visible. For 120 min, about 7% of ketoprofen, originating from IR and IRc mini tablets was dissolved, which is an initial dose. When in the 120th minute the medium was changed (the vertical, dashed line) to phosphate buffer pH 6.8, the rest of the initial dosage rapidly dissolved. The remainder of ketoprofen contained in SR mini-tablets was released more slowly than would be apparent from the results, obtained in the study on SR mini tablets in a phosphate buffer pH 6.8 (Fig. 2). From 150th to 240th minute of testing, the curve has a flatter course than in the distal section. This means, that ketoprofen releases from the matrix slower, despite the relatively long residence of SR mini-tablets in the buffer, with the best observed solubility of the active substance. It seems that this is due to soaking mini-tablets by hydrochloric acid during their residence in 0.1 M HCl solution. Formed matrix, restricts the exchange of ketoprofen with the surrounding buffer. It was not until 240th minute that the curve is of steeper course, which may indicate a change in the permeability of the matrix. This leads to the suspicion that in a clinical conditions similar phenomenon may occur. When a tablet administered to a patient is surrounded by chyme with a low pH, the diffusion rate of active substance from the dosage may be lower than in vitro. Summary of the results of the active ingredient release from multi-compartment systems, as well as types of analyzed multi-compartment systems are given in Figure 3.

Comparison of the amounts of released ketoprofen from the IR and the IRc mini tablets, shows
significant difference in the release rate of ketoprofen in phosphate buffer pH 6.8 (Fig. 4). The percentage of the released ketoprofen at 30th and 60th min is higher for IR mini tablets than for IRc mini tablets, although the compositions of both are the same, and the envelope covering the core of the IRc mini tablet dissolved very quickly. Amounts of ketoprofen released in the 90th and 120th min of a study are similar, and the differences between them are statistically insignificant. The observed phenomenon indicates that the presence of the enteric coating on the core has an impact on the release rate of ketoprofen. All data are shown as the mean values ± standard deviation and were evaluated with Statistica 10.0 (StatSoft, Poland).

The proposed design of multi-compartment systems, based on the results of the mini tablets ketoprofen dissolution testing, makes it easier to design the composition of the dosage form. Thanks to this it is possible to adjust the release profile of the active substance to the individual patient, which meets the expectations of personalized medicine (26). Preparation of the proposed form of drug in the present embodiments, can be also less expensive than developing a complex form of the drug in tablet form (27, 28). In addition, dividing the total dose into smaller subunits accelerates the release of the active substance compared to the release of the same dose, contained in one tablet (29). This is particularly important in the treatment with NSAID and helps to avoid local irritation of the gastric mucosa by slowly disintegrating tablet.

CONCLUSIONS

The factor limiting the amount of available ketoprofen at the absorption place is pH of the environment. A relatively small change in pH in the stomach may have a significant impact on the solubility and absorption of ketoprofen, and through it, on the time, after which a therapeutic effect is observed. Multi-compartment systems are superior to traditional drug forms in terms of more efficient control of release and absorption place. Preparation of the proposed form of drug in the present embodiments, can be also easier and less expensive than developing a complex form of the drug in tablet form.

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Received: 19. 03. 2015