Acta Poloniae Pharmaceutica – Drug Research, Vol. 77 No. 4 pp. 619–628, 2020
DOI: 10.32383/appdr/126315
Received 29 June 2020, Received in revised form 10 July 2020, Accepted 11 August 2020.

ISSN 2353-5288
Polish Pharmaceutical Society

PHARMACEUTICAL TECHNOLOGY

THE EFFECT OF SIZE OF ENTERIC-COATED MINITABLETS AND TYPE OF THE CARRIER ON THE *IN VITRO* RELEASE OF DICLOFENAC

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Abstract: Minitablets are small tablets (1-3 mm in diameter) that can be easily swallowed by children. When administered in a certain number of units they enable flexible dosing for a broad range of age in pediatric patients. They can be designed as a modified-release formulation. Administration of a larger number of minitablets to small children may be possible with a standard polymeric hydrogel which facilitates swallowing. Enteric-coated minitablets (2 and 3 mm) with diclofenac sodium were developed and the main goal was to evaluate how carbomer and sodium carmellose gels influence the *in vitro* drug release from minitablets. The cores of minitablets composed of microcrystalline cellulose, lactose, pregelatinized maize starch, sodium starch glycolate, colloidal silica and sodium stearyl fumarate were coated with Eudragit L. Not only enteric film thickness but also the size of minitablet cores had a critical significance for the release of diclofenac. Smaller minitablets (2 mm) with thinner film thickness (40 μm) released diclofenac in pH 6.8 buffer quickly, however, larger cores (3 mm) with the same film thickness swelled in the acidic medium and in effect very slow drug release in the buffer phase was observed. The application of a thicker film (60 μm) eliminated this problem. Mixing of minitablets with a carmellose gel caused a prolonged release of diclofenac in the buffer stage. This effect was largely reduced if a carbomer gel was used as a dispersing medium, but still, the drug release was slower than from loose minitablets or minitablets filled in a gelatin capsule.

Keywords: minitablets, diclofenac, enteric-coated, *in vitro* release, gel carriers

The selection of appropriate drug formulations may improve patient compliance and is an important condition for effective pharmacotherapy in paediatry. Among traditional drug formulations, liquid forms (solutions, suspensions, syrups, oral drops) seem to be the most popular in pediatric practice, owing to the fact that they are easily administered orally and allow flexible dosing based on the weight and age of the child. However, due to poor stability, some of the active pharmaceutical ingredients (APIs) are not available in liquid forms. On the other hand, tablets which are the most popular form in adults, are inappropriate in smaller children, because of their size and swallowing difficulties (1-3). Moreover, these traditional solid forms are indivisible or divisible only into two or four parts, and therefore often the lower pediatric dose cannot be obtained (4). In adults, the improvement in pharmacotherapy can be achieved with modified-release tablets or capsules but the above-mentioned problems make this impossible in small children.

Only recently we can observe progress in the development of small size tablets, so-called minitablets or microtablets, which can solve the problem with swallowability in children and may be formulated as modified-release products. Minitablets (MT) are defined as tablets with a diameter from 1 to 3 mm (5). Administered not only as a single unit but also as several units at once, MT could easily allow appropriate pediatric dosing for a broad age range of children, based on the multiplication of dosage units instead of dividing as is used for tablets. In comparison to liquid pediatric products, MT allows to omit stability problems and taste-masking can be also easily achieved (6). Like in tablets, modification of a drug release rate may be obtained by coating. This technology was already applied in enteric and prolonged-released MT (7, 8).

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The acceptability of MT by children has been studied in numerous articles. An early study demonstrated that MT (3 mm of diameter) can be easily swallowed by children aged 2–6 years (1). The other recent cross-over studies showed that even younger children (above the age of 6 months) can cope with swallowing a single 1 mm or 2 mm unit (9, 10). The clinical trials performed in Germany confirmed, that even 25 units of minitablets (2 mm) are well-tolerated and safe in infants; moreover, children aged >1 year accept a large number of MT (= 400 units) even better than the equivalent dose of syrup (11). The up-to-date studies show that the administration of a larger number of minitablets to such small children may be possible with soft food (pudding, yogurt, mashed fruit mousse) or a drink (water, tea, fruit juice, lemonade, milk) of the child's choice. Unfortunately, this creates a risk of interactions between the drug and the food ingredients (12, 13), however, this risk can be much reduced by using a standard dispersing medium/carrier. The dispersing medium can be in the form of a semisolid gel composed of a hydrophilic organic polymer (14). In comparison to syrups or other liquids, semisolid dispersing vehicles may facilitate oral application due to the smooth texture and lubricating effect. An important advantage of the gelly carrier is that the suspended units are better protected against too fast disintegration prior to swallowing (15).

The aim of the study was to develop enteric-coated MT with diclofenac sodium. Diclofenac is a non-steroidal anti-inflammatory drug generally used in children at least 6 years old who can swallow a tablet. However, in juvenile idiopathic arthritis, it is licensed for children above 1-year old and there is no appropriate formulation available for these youngest patients. The oral dose of diclofenac sodium for juvenile idiopathic arthritis is 1 to 3 mg/kg daily in divided doses, up to a maximum of 150 mg daily (16). Therefore, a single dose taking 2 times per day can start from 5 mg of diclofenac and may be increased with child age even to 75 mg. Appropriate pediatric dosing for a broad age range may be possible with MT by adjusting the number of administrated units, however, in small children for easy swallowing of several units mixing of MT with semisolid universal carriers, namely carbomer or carmellose gels was proposed.

For traditional tablets the standard pharmacopoeial dissolution tests are well-established, but the application of these methods for MT is still under discussion, especially regarding the dose composed of several units. The tests were done employing two pharmacopoeial dissolution apparatus to evaluate the impact of the test conditions on the release rate of diclofenac from the developed MT. This article also presents the results of the preliminary research, undertaken to estimate the impact of universal carriers, like gels and hard gelatin capsule, on the *in vitro* release of API from MT.

EXPERIMENTAL

Materials

Diclofenac sodium was kindly provided by Polpharma (Ph. Eur. grade, Starogard Gdanski, Poland). Minitablet cores were composed of microcrystalline cellulose (Avicel® PH 101, Sigma-Aldrich, Steinheim, Germany), colloidal silica (Aerosil® 200, Evonik Industries, Darmstadt, Germany), lactose monohydrate (GranuLac® 200, Meggle, Wasserburg, Germany), pregelatinized maize starch (Starch 1500®, Colorcon, Dartford, UK), sodium starch glycolate (Vivastar® P, JRS PHARMA, Rosenberg, Germany) and sodium stearyl fumarate (PRUV®, JRS PHARMA, Rosenberg, Germany). The enteric film was obtained spraying on the cores of MT an aqueous dispersion of methacrylic acid – ethyl acrylate copolymer (1 : 1): Eudragit® L 30D 55 (Evonik Industries, Darmstadt, Germany) containing triethyl citrate (TEC, Sigma-Aldrich, Steinheim, Germany) and talc (Luzenac VAL Chisone, Porte, Italy). The coated MT were placed either in hard gelatin capsules size 0 (Capsugel, Morristown, USA) or in a gel composed of carbomer (Carbopol® 974P NF, Lubrizol Corporation, Wickliffe, OH, USA) or carmellose sodium (Carboxymethylcellulose sodium salt, high viscosity – 1500-3000 cP, 1% solution; Sigma–Aldrich, Steinheim, Germany). Enteric-coated tablets Majamil® PPH 25 mg (Polpharma, Starogard Gdanski, Poland) with the coating film based on methacrylic acid – ethyl acrylate copolymer 1 : 1 (70 μm thickness) were used as a reference product.

Methods

Preparation and evaluation of enteric-coated minitablets

Preparation of minitablet cores

Tablet mass was prepared by a high-shear wet granulation in a granulator Prymus (Zelmer, Rzeszow, Poland). The batch size was 300 g. The cores were composed of diclofenac sodium (15% w/w), microcrystalline cellulose (40% w/w), lactose monohydrate (25% w/w), pregelatinized maize starch (10% w/w), sodium starch glycolate (5% w/w), colloidal silica (2% w/w) and sodium stearyl fumarate (3% w/w). The API, fillers and a binder

were mixed and wetted with water. After granulation, sodium starch glycolate as a disintegrant, colloidal silica and sodium stearyl fumarate as glidants were added. Biconvex MT with a diameter of 3 mm (21 mg) or 2 mm (8.5 mg) was prepared with a compression pressure of 200 MPa, using a rotary tablet press (RTP-D8, Erweka, Langen, Germany).

Physical evaluation of the minitablets cores

The crushing resistance of MT cores (n=10) was evaluated with a texture analyzer TA.XT Plus (Stable Micro Systems, Godalming, UK) with a cylindrical probe at a compression mode and constant speed (0.5 mm/s). The Friability test was performed according to the European Pharmacopoeia (Ph. Eur. 9.0) test for tablets (monograph 2.9.7): dedusted MT (batch size 6.5 g) were placed in a friability tester (TAR-10, Erweka, Langen, Germany) and after 100 rotations, the loss of the MT mass was determined.

Enteric coating process

The delayed release of API was achieved by coating the cores with Eudragit L 30D 55 using an Aircoater 025 (Romaco Innojet, Steinen, Germany) apparatus. An aqueous dispersion (20% of solids) of Eudragit L 30D 55® with added TEC as a plasticizer and talc as a glidant was prepared (17). The coating process parameters were applied accordingly to the previous research based on the design of the experiment's approach (18). The product temperature, spraying pressure and coating mixture flow rate were 27°C, 0.85 bar and 1 g/min respectively. The inlet airflow rate was adjusted to the size of MT: 16 m^3/h for MT 2 mm and 17.5 m^3/h for MT 3 mm. MT (batch size 50 g) were coated until 40 or 60 µm thick enteric films were achieved. The amount of the aqueous dispersion needed to achieve the desired film thickness was calculated and the actual thickness obtained was proved using microscopic methods. To prepare samples for film thickness measurements individual MT was frozen at -20°C and cut it in a vertical axis using Cryostat (CM1850, Leica Biosystems, Wetzlar, Germany). The flat surface of the cross-sections, without artifacts, was obtained by multiple shearing (every 10 µm). After thawing and de-dusting cross-sections of five MT from each batch were analyzed using a stereoscopic microscope and scanning electron microscope (SEM).

Microscopic analysis

Stereoscopic microscope Olympus SZX12 (Olympus Corporation, Tokyo, Japan) with a zoom ranging from 7x to 90x was equipped with a computer-controlled image analysis system Optomax V (Optomax Inc, Hollos, NH, USA). All samples were observed in reflected light and images were taken at 72x magnification.

The cross-sections of MT were set up on double-sided carbon tape (Oxon, Oxford Instruments, Oxford, UK). SEM (Supra 35 VP, Carl Zeiss, Oberkochen, Germany) imaging was performed using an acceleration voltage of 1 kV and a secondary electron detector. The images of MT cross-sections from SEM were taken at a 500x magnification.

***In vitro* dissolution test**

Dissolution tests were performed accordingly to the United States Pharmacopoeia (USP 43-NF 38) monograph for Diclofenac Delayed-Release Tablets; therefore, the pharmacopoeial paddle apparatus (DT 720 Series, Erweka, Langen, Germany) rotating at 50 rpm was used. The test was performed in 900 ml of 0.1 M HCl at 37°C ± 0.5°C. After 2 hours, the dissolution medium was replaced for 1 hour with 900 ml of 0.05 M potassium phosphate buffer (pH 6.8). The amount of API released was determined in-line using a UV–VIS spectrometer with flow-through spectrophotometric cuvettes (Agilent, Santa Clara, CA, USA), at the wavelength of 276 nm. The API content was calculated on the basis of the calibration curves (the method was validated). In addition, a pharmacopoeial basket apparatus (DT 720 Series, Erweka, Langen, Germany) was used to evaluate and optimize the dissolution tests for MT. The rotation speed also was 50 rpm and other test conditions were the same. To receive a dose similar to the reference product, 8 MT 3 mm or 20 MT 2 mm were placed in one vessel of a dissolution apparatus, corresponding to 25 mg of diclofenac.

The release rate of API from MT placed in transparent hard gelatin capsules or in hydrogels used as universal carriers was also investigated. High viscosity dispersing gels were obtained by dissolving in water either carmellose sodium (2% w/w) or carbomer (0.5% w/w). To gelify carbomer, the dispersion was neutralized to pH 7.0 with 20% solution of sodium hydroxide. The apparent viscosity measured at shear speed 10 s^{-1}, was 5000 mPas and 8000 mPas for carmellose sodium and carbomer gels, respectively. 20 units of 2 mm MT were mixed with 5 g of the gel and left for 5 min before placing in the dissolution apparatus. The capsules were filled with 8 or 20 MT to obtain 25 mg of diclofenac. Conditions of the performed dissolution test are described in detail in Table 1. Additionally, the

results of the drug release test were compared with results for the reference formulation (Majamil PPH 25 mg).

Statistical analysis

Statistical analysis of the dissolution data (% released) was carried out using Statistica 13.1 software (TIBCO Software Inc, CA, USA). Non-parametric Mann-Whitney U-Test was used, where p-value <0.05 denoted significance, to indicate the influence of a hard gelatin capsule on dissolution rate and to compare the use of basket or paddle apparatus during the test.

RESULTS

Minitablets cores

MT (2 and 3 mm) containing 15% (w/w) of diclofenac sodium were successfully produced in a rotary tablet press. For both types of the cores good mass uniformity, with deviation less than 10% was demonstrated (MT 3 mm – 20.7 mg ± 0.16 mg; MT 2 mm – 8.5 mg ± 0.25 mg). The hardness values of 24.3 N (± 3.56 N) for MT 3 mm and 16.5 N (± 1.34 N) for MT 2 mm were measured. The friability for all batches was below 0.2%. The satisfactory mechanical strength of the cores was essential for the proper fluid bed coating process.

Enteric-coated minitablets

MT were successfully coated in the Aircoater 025 fluid bed system using the aqueous dispersion of Eudragit L 30D 55 with additives. Enteric-coated MT (2 and 3 mm in diameter) with two different film thicknesses (40 and 60 µm) were prepared to evaluate the influence of film thickness on gastro-resistance, depending on the core size. Direct measurement of the film thickness was performed using SEM with additional stereoscopic microscopy evaluation to confirm the suitability of both methods in the quality control of coated minitablets. In Figure 1 images of MT cross-sections obtained with stereoscopic microscopy (A) and SEM (B) are presented. Clear boundaries between the core and the film layer indicate that there was no diffusion of the coating material to MT cores. Both microscopic techniques resulted in similar film thickness (Table 2) with the only difference that higher deviations of the film thickness for MTs 3mm/60µm were observed with SEM method.

In vitro dissolution test

The requirements of Ph.Eur. state that from gastro-resistant tablets or capsules no more than 10% of the declared API dose can be released in an acidic medium, and more than 80% of the dose should be released in a buffer medium, typically in

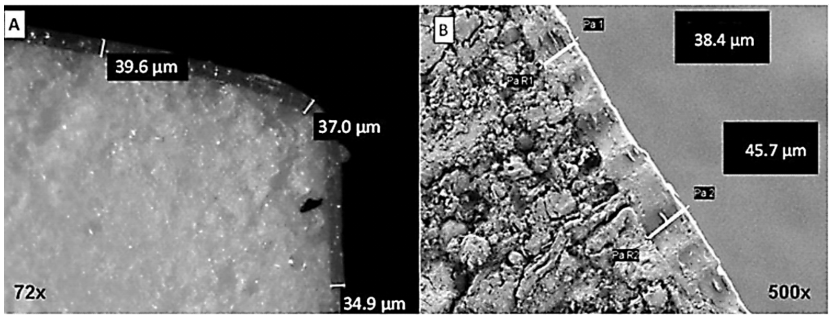

Figure 1. Stereoscopic microscope (A) and SEM (B) images of MT 3 mm/40 µm cross-sections.

Table 1. Methodology of dissolution test for minitablets.

Size of MT	Number of MT per vessel	Film thickness [µm]	Type of a carrier	Type of apparatus
3 mm (20.7 mg)	8	40	• Loose MT	• Paddle (with sinkers - for capsules)
		60	• MT in a capsule	
2 mm (8.5 mg)	20	40		
		60	• MT in a gel*	• Basket

*before the test MT 2 mm (20 units) were mixed with 5 g of carbomer or carmellose gels.

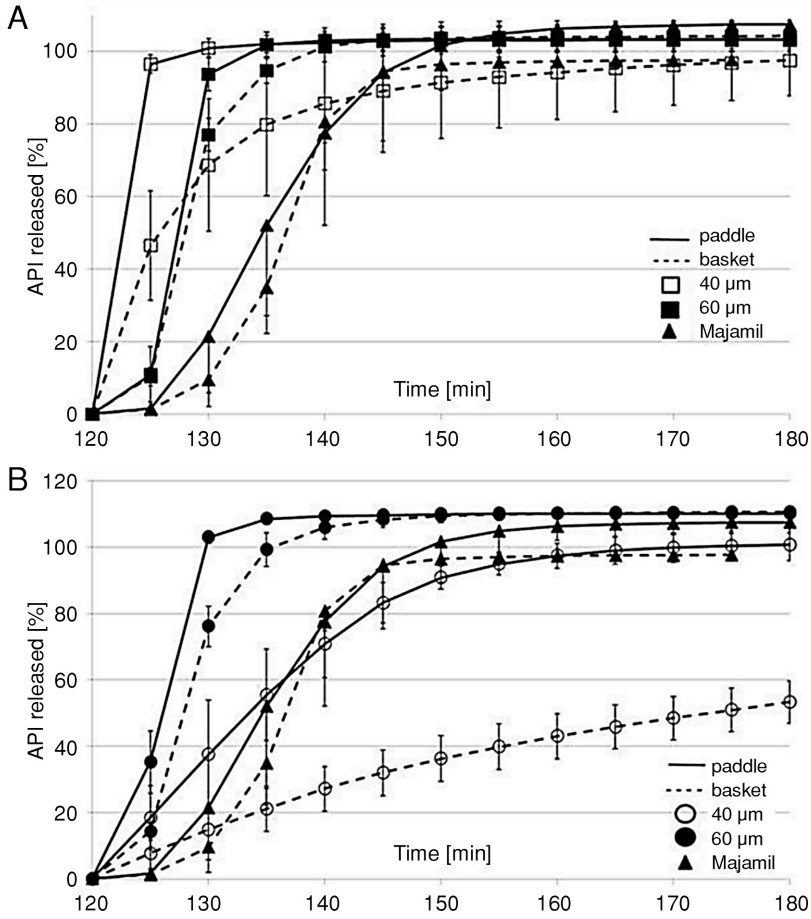

Figure 2. Release rate of diclofenac from loose MT 2 mm (A) and loose MT 3 mm (B) coated with 40 µm or 60 µm film thickness, in comparison with Majamil commercial tablets – the test performed in a paddle (solid line) and basket (dotted line) apparatus. These profiles were recorded in a buffer phase pH 6.8 following the acid phase.

less than 1 h. The acid phase limits were met in all cases; therefore, all graphs are presented only for a buffer phase, after MT were exposed to the acid phase of the dissolution test. Loose MT and MT in gel carriers or in a capsule were tested. The larger number of MT in one vessel (20 or 8 units) may cause mutual rubbing of the cores and consequently abrasion of the functional coating leading to the loss of gastro-resistance. This phenomenon was not observed, however, in any conditions of the dissolution tests.

MT were tested in both, paddle and basket apparatus, with the aim to compare the effect of the apparatus on the diclofenac dissolution profile (Figure 2), especially considering the different size of the units and thickness of the coating layer. This stage of the experiment was performed for the loose MT.

None of the examined MT formulations released diclofenac in the acid phase up to 2 hours. Figure 2 presents the dissolution profiles observed in the buffer stage. Although the faster release of diclofenac occurs in a paddle apparatus than in basket apparatus ($p < 0.05$), the difference is especially large only for MT coated with a thinner polymer layer. Two sizes of MT cores (3 and 2 mm) with a 60 µm film thickness did not show any differences in release rates of diclofenac. After 10 min almost 100% of API in a paddle apparatus and around 80% in a basket apparatus were released. The release of diclofenac was always faster from MT than from the reference tablet, which released around 80% of API only after 20 min, independent of the used apparatus.

In contrast to MT coated with a film of 60 µm, MT with a thinner film, i.e. 40 µm, demonstrated unexpected dissolution profiles. Besides the above mentioned large delay of the release observed in the basket apparatus, the most significant was the effect of the size of MT. The fast release of API from MT coated with the thinner film was observed only in

2 mm MT. Thinner film applied to the cores MT 3 mm resulted in a surprising effect – drug release was spectacularly slower than observed for MT with 60 µm film coating. In order to explain the reason for this phenomenon, the MT after the acid stage were examined visually (Figure 3). During the acid phase, significant swelling of MT 3 mm/40 µm was noted and this effect did not occur in three other types of MT. This means that the 40 µm film layer was an insufficient protective barrier for a larger size of MT, even if the release of diclofenac was not observed.

Further experiments were performed only in a paddle apparatus. The release of diclofenac from loose MT and enclosed in a hard gelatin capsule was compared (Figure 4). To avoid floatation the capsules with MT were inserted in sinkers.

For MT 3 mm/60 µm and MT 2 mm/40 µm no statistically significant effect of a capsule shell on the release rate of diclofenac was observed ($p > 0.05$). For MT 2 mm/60 µm statistically significant difference was found only at a point measured after 5 min in the buffer phase ($p < 0.05$), but one can conclude that also in this case the capsule did not cause any delay in the release of API.

To further examine the vehicle effect, MT 2 mm were placed in a hydrogel and the release test was performed. In Figure 5 the dissolution curves for MT (60 µm) dispersed in high viscosity gels: 0.5% carbomer or 2% carmellose sodium are pre-

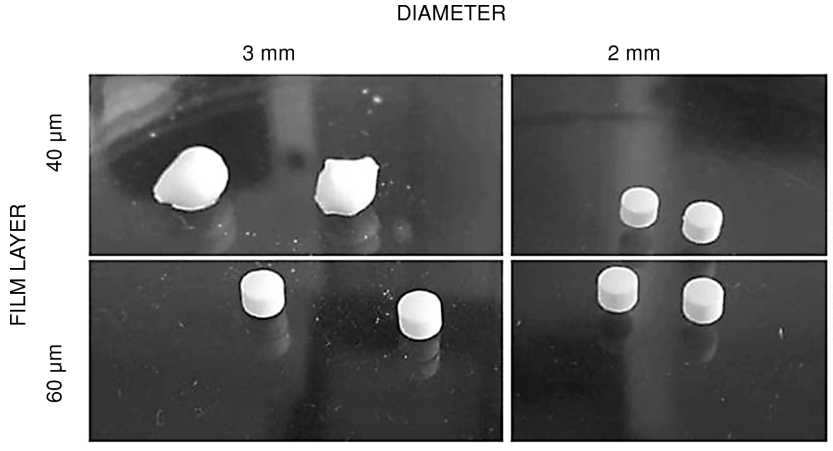

Figure 3. The image of enteric-coated MT after the acid phase of dissolution test (2 h in 0.1 M HCl).

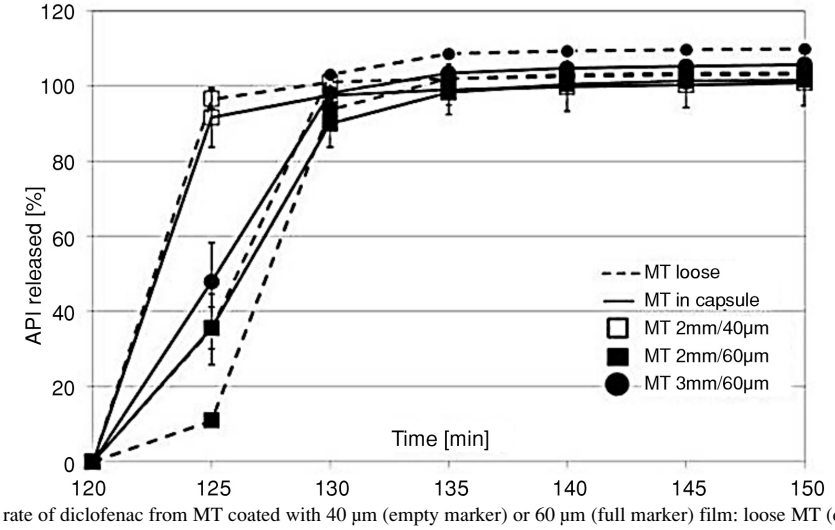

Figure 4. Release rate of diclofenac from MT coated with 40 µm (empty marker) or 60 µm (full marker) film: loose MT (dotted line); MT in a capsule (solid line). These profiles were recorded in a buffer phase pH 6.8 following the acid phase.

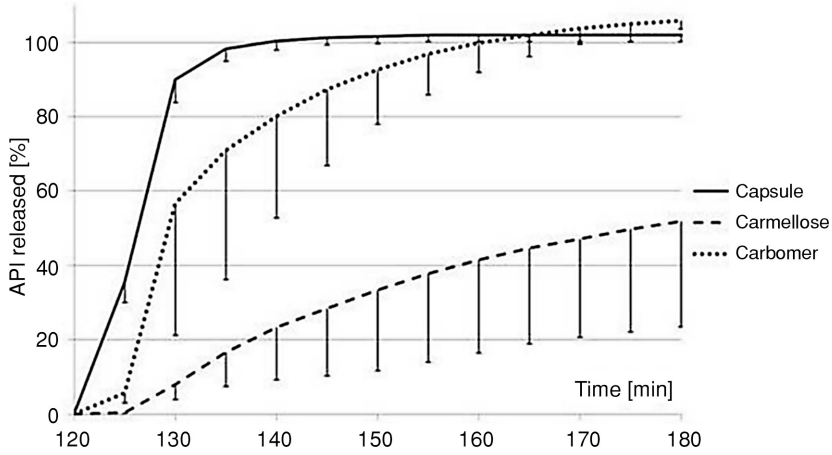

Figure 5. Release rate of diclofenac from MT 2 mm/60 µm inserted in a capsule or suspended in a gel (carmellose or carbomer). These profiles were recorded in a buffer phase pH 6.8 following the acid phase.

sented and compared with the profile observed for MT enclosed in a gelatin capsule.

In the acid phase, gastro-resistance of MT dispersed in the gel vehicles was confirmed. Only in the case of MT mixed with carbomer gel a small release of diclofenac during the acid phase was observed (4.5%), but the Ph.Eur. requirement (<10%) was still met. Carbomer forms a gel structure when the aqueous dispersion is neutralized to pH 6.0 or higher (19). In contact with an acidic environment (first phase of the dissolution test) the gel-sol transition occurs and the lack of the viscous barrier should result in fast drug release in the buffer stage. However, still slower release of diclofenac in a buffer phase was noted. Despite this, the drug release in the buffer stage was still fast (80% of diclofenac released after 10 min), being even faster than from the reference product. In contrast to carbomer, carmellose sodium retained the gel structure during the test, which caused a significant delay in the release process (50% of API released after 180 min). Similar results were obtained for MT 2 mm/40 µm (data not shown). It is important to note that at the tested low stirring speed of the paddle (50 rpm) in the case of both gelly carriers large deviations in the amount of the released API were observed.

DISCUSSION AND CONCLUSIONS

Performed dissolution tests allow observing that different size of MT cores (2 or 3 mm) and the thickness of the coating layer affects the release rate of diclofenac. The goal of the dissolution test was to prove gastro-resistance of the enteric-coated MT and fast release of API in a buffer phase. Accordingly, to the pharmacopoeial (USP) monograph of Diclofenac Delayed-Release Tablets, paddle apparatus is recommended for the dissolution test. The reference product (Majamil enteric tablets) released API faster in a paddle apparatus than in basket apparatus. A similar effect was observed for enteric-coated MT. Therefore, the pharmacopoeial method dedicated to standard size tablets may be considered as also suitable for MT. It is worth to mention, that all tested types of MT released diclofenac faster that the reference tablet of a larger size (7 mm diameter). It may be related to the thicker enteric-film of Majamil (70 µm thickness detected) and larger surface contact of small MT units with dissolution medium.

The applied parameters of the coating process allowed to produce very uniform enteric film measured both in different MT and in different locations in a single MT, which was demonstrated by small deviations in thickness. Moreover, the comparable results of the measured film thickness were obtained with two microscopic techniques, although to achieve good reproducibility in the microscopic analysis of MT cross-sections was not an easy task. The smooth surface of such small cores without artifacts required time-consuming and tedious the sample preparation step. Therefore, some novel methods, like dynamic image analysis (Camsizer XT, Retsch Technology) are worth considering, that allow us to measure film thickness without special sample preparation (20).

Not only the thickness of the functional film on MT but also the size of MT cores had a critical significance for the release of API in the buffer stage. Smaller MT (2 mm) with thinner film thickness (40

μm) released diclofenac quickly and without any problems. However, the same film thickness on the larger cores (MT 3 mm) led to the serious disturbance of its function.

A very slow release of diclofenac in buffer was observed from MT 3 mm/40 μm and this effect was related to the swelling of this formulation at the acidic stage. The film was apparently too thin and the acceptor medium quickly penetrated the MT core, which caused swelling of the starch, without damage to the elastic coat. The swelling was not observed for the smaller cores (MT 2 mm) despite the same film thickness (40 μm), which can be explained by a smaller surface area of a single MT 2 mm which determines the smaller total amount of the fluid that can diffuse to the core.

A few reasons of the subsequent prolonged release of API from MT 3 mm/40 μm in the buffer stage can be taken into considerations: the swollen matrix is a viscous diffusion environment for diclofenac, the coating layer interacts with the matrix gel and does not dissolve fast or diclofenac sodium in MT was changed to the poorly soluble acidic form (21). It is most probable that the observed interesting phenomenon strictly depends on the core composition. It is worth mentioning, however, that in our previous research (7) a thin Eudragit L film layer (50 μm) lost its integrity in acidic medium only in larger tablets (5 mm) while the same thickness applied to MT was sufficient. We conclude that the mass ratio of the coating material to the core is also important since in the problematic formulations the coating weight gain was less than 6%.

MT can be put into a hard gelatin capsule and such formulation is an alternative to commercial enteric capsules – filled with pellets. The research confirmed that the gelatin capsule shell does not affect the drug release rate. In the course of the two-phase dissolution test, the gelatin capsule dissolves during the first acid phase and no interaction with the enteric coat of MT was observed. Hard gelatin capsule can be regarded as the most universal carrier for enteric-coated MT if the dose requires several minitablets and the patient has no difficulty with swallowing. Enteric-coated MT allows for the treatment of the whole pediatric population according to the recommended dose. According to the summary of Majamil PPH 25 mg product characteristics recommended dosage of diclofenac for children above 1-year-old is 1.5-2 mg/kg in 2 or 3 divided doses. Thus, to obtain the lowest single dose, the number of administered MT (2 mm) can start from 4 units and may be increased with a child age even up to 60 units (in case of MT 3 mm from 2 to 24 units). MT can be placed in a sachet and administered with soft food, although this creates a risk of interactions. Using universal carriers, simple in composition like the proposed hydrogels, may be a more appropriate practice, especially if the lubricating effect of the gel will help to swallow a significant number of minitablets at once. However, the pH value or viscosity of carriers may have an impact on the drug release rate, with possible bioavailability problems. The *in vitro* dissolution tests should be performed to choose the most appropriate vehicle.

Although, both tested gels have neutral pH, which could cause the dissolution of Eudragit L, any disturbance of enteric film function was not observed. The coating barrier was preserved due to the viscous diffusion environment and short time of the contact (5 min mixing time before the test). However, a longer mixing time could cause a loss of gastro-resistance and this should be taken into consideration when a longer time of contact between MT and the gel is required.

As expected, mixing of MT with carmellose gel caused the effect of prolonged-release of diclofenac in the buffer stage. This effect was largely reduced in the case of carbomer gel. Although in our experiments with immediate release MT the use of carbomer gel did not disturb drug release (data not published) but for the enteric-coated MT with diclofenac some reduction of the release rate is evi-

Table 2. Characteristics of the coated minitablets.

	Core surface [mm^2]	Weight gain after coating [%]	Film thickness [μm] mean ± SD	
			Stereoscopic microscopy	SEM
MT 2 mm/40 μm	18.9	9.0	39.7 ± 2.9	38.8 ± 3.6
MT 2 mm/60 μm		16.4	56.4 ± 3.4	56.2 ± 4.0
MT 3 mm/40 μm	32.9	5.7	39.8 ± 3.9	39.5 ± 3.5
MT 3 mm/60 μm		11.2	59.7 ± 2.1	55.4 ± 6.8

dent. This must be related to the two-stage methodology of the dissolution test. In the acidic stage, carbomer gel dissolves but probably the residues of carbomer adsorbed on the surface of MT could re-crosslink after the change of pH at the buffer phase, therefore decreasing the drug release rate.

Such an effect also influenced the reproducibility of results. The large deviations observed can be a problem for the development of such *in vitro* tests for regulatory purposes. However, the stirring speed in the test was low and with more intensive stirring (75-100 rpm) the problem can be reduced. Of course, the *in vivo* examination is necessary to prove that carbomer gel is a first choice carrier for oral delivery of enteric-coated MT, not affecting the bioavailability of API.

To summarize the research one can conclude that the enteric film thickness sufficient to provide gastro-resistant properties of MT with diclofenac was found to be related to the core size. The unpredicted swelling effect observed in MT 3 mm in the acidic environment was overcome by applying a thicker coating. The enteric-coated MT placed in a gelatin capsule may be an interesting alternative to the capsules filled with pellets, especially if the production of MT does not require a special production line. The research creates an interesting opportunity for further investigations of the gel carrier effects, which may verify the obtained *in vitro* results. In contrast to cellulose derivatives, like carmellose, carbomer due to the pH-related sol-gel transformation of its solutions gives the chance to develop a universal neutral gel that can be used to ease the administration of MT in children.

Acknowledgment

The authors gratefully acknowledge Prof. Stane Srčič and Prof. Odon Planinšek (Department of Pharmaceutical Technology, University of Ljubljana, Slovenia) for their valuable advice and technical support with SEM measurements.

This research was financially supported by the Ministry of Science and Higher Education in Poland (MN – 01-0367/08/510). Publication of the article was supported by the project POWR.03.02.00-00-I026/17-00 co-financed by the European Union through the European Social Fund under the Operational Program Knowledge Education Development 2014-2020.

Conflict of interest

The authors declare no conflict of interest.

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