Department of Pharmaceutical Technology, Faculty of Pharmacy, Medical University of Gdansk, Poland

Comparison of the coating process and *in vitro* dissolution of 3 mm gastro-resistant minitablets and 5 mm gastro-resistant tablets with pantoprazole

M. Szczepanska, M. Sznitowska*

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**Corresponding author: Malgorzata Sznitowska, Department of Pharmaceutical Technology, Faculty of Pharmacy, Medical University of Gdansk, 81-416 Gdansk, Poland*
msznito@gumed.edu.pl

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Minitablets are solid oral forms, which, due to their size (1-3 mm), may be easily swallowed by children. The administration of minitablets in a certain number of units allows for flexible dosing for a broad age group of paediatric patients, which is particularly important for modified-release drugs. In this study, enteric-coated minitablets (3 mm) with pantoprazole were developed and compared to conventional tablets (5 mm). Eudragit L 30D 55® and Acryl Eze II® films, which were 50 and 80 µm thick, respectively, were applied using two different fluid bed systems. The increase in the pantoprazole release rate occurred not only due to the application of a thinner film but also due to the reduction in the size of the core independent of the coating apparatus that was used. In contrast to minitablets, the thin film's thickness was insufficient for 5 mm tablets and a loss of gastro-resistance was observed. The insertion of minitablets into a hard gelatine capsule did not affect drug release from the minitablets under *in vitro* conditions.

1. Introduction

The size of the standard tablets and capsules that are available on the market is commonly unsuitable for small children and some adult patients, such as people with dysphagia (Liu et al. 2016). In addition, these traditional forms are indivisible or divisible in only two or four parts, and thus, the desired lower paediatric dose often cannot be obtained. The division of the modified-release tablets is particularly problematic.

Tablets with a 1-3 mm diameter are commonly called minitablets (MT) (Lennartz and Mielck 1998; Aleksovski et al. 2015) and, due to their small size, are easy to swallow and are accepted by children of practically all ages (Klingmann et al. 2018; Kluk et al. 2015). An important advantage is that administration of a variable number of MT units allows for flexible dose adjustments for the paediatric population. MT can also be considered in a multiparticulate form, which are popularly known as sprinkles (Lopez et al. 2016). In addition, MT allow for a wide range of possibilities for obtaining modified-release forms, as in the case of tablets and pellets, by coating the cores with functional films. Until now, modified-release oral forms with flexible doses for paediatric patients have not been developed. Therefore, the development of oral solid dosage forms that allow for flexible dose adjustments for patients of different age groups can be achieved with MT (Mohamed et al. 2010). The need to develop more personalized and patient-friendly paediatric solid oral forms is indicated by the EMA (European Medicines Agency 2009).

Proton pump inhibitors (PPIs) represent an example of drugs that pose difficulties for determining appropriate paediatric dosages. They require a gastro-resistant form, which is achieved in medicinal products for adults by coating the tablets or pellets. If the dose adjustment for a child is necessary, in pharmaceutical compounding practice, enteric capsules for adults are emptied and the dose for a paediatric patient is prepared by weighing or counting the appropriate number of coated pellets. Unfortunately, it is frequent practice to crush pellets into powder, which disrupts the structure of the functional film and causes a loss of gastro-resistance.

MT provide the opportunity to obtain modified-release units using coatings. Through coating, delayed-release forms can be produced in the form of conventional tablets, and prolonged-release forms can be developed in the form of pellets, which means that there is a wider use of coating process in comparison to tablets. The coating process of MT is still an attractive research topic. Although several publications are already available (Bodea and Napoca 2010; Gaber et al. 2015; Souza et al. 2013), there is still little knowledge about the key process parameters and the quality control of coated MT compared to tablets or pellets. More research will allow for one to determine the occurrence of possible similarities and differences between the coating processes of different size cores and will allow for the better prediction of the changes in the release rate when the size of the core changes. Compared to granules, pellets and microspheres, MT cores have some additional advantages. They have more uniform sizes, shapes, and porosities, which can assure a final product with better uniformity and provide a more reproducible coating process (Aleksovski et al. 2015). Furthermore, MT have a smaller total surface area than do pellets, and therefore, a smaller amount of coating mixture is needed to achieve the same film thickness, which significantly reduces the coating time (Czajkowska et al. 2015). Similarly to pellets, MT can be coated in a fluidized bed apparatus, but this technique is generally unsuitable for bigger tablets. Conversely, MT coating in a perforated pan, as that used for tablets, is another option, although it was shown to be suitable for MT not smaller than 2 mm and the drum was modified using a mesh insert to prevent MT cores from falling through the perforation (Vuong et al. 2008).

The aim of this research was to determine how the manufacturing parameters (such as the selection of a coating mixture or fluid bed system), film thickness and core size affect the quality parameters of enteric-coated MT with pantoprazole sodium as the active pharmaceutical ingredient (API). Therefore, two coating mixtures and two different fluid bed systems were used to assess their effects on the gastro-resistance of the obtained products. The difference between MT 3 mm and 5 mm tablets (T) that are coated under the same conditions was evaluated. Moreover, the effects of the core size and film thickness on the release rate of pantoprazole were determined *in vitro*. The obtained enteric-coated products were compared

with a reference drug product commonly available on the market (Controloc®). In addition, the effect of hard gelatine capsules on the release rate of pantoprazole from MT was investigated to prepare this form as an alternative for capsules filled with pellets.

2. Investigations, results and discussion

2.1. Physical evaluation of the minitablets and tablets prepared for coating

Minitablets (MT 3 mm) and tablets (T 5 mm) containing 25 % w/w pantoprazole were produced using a compression pressure of 100 MPa, which means that the employed compression force for MT or T was 0.7 kN or 2.0 kN, respectively. During the direct compression in a rotary tablet press and after the wet granulation (with water), the tablet mass was sticking to the tools. Since pantoprazole is highly sensitive to heat, light, moisture and acid, which causes difficulties in the direct compression of API, it is necessary to stabilize the process by granulating the API using alkaline salts. Therefore, pantoprazole was granulated using sodium carbonate solution (25 % w/w), and no subsequent difficulties were observed (Choudhry et al. 2012).

Both types of cores (MT and T) met the Ph.Eur. requirements for mass uniformity and demonstrated good mechanical properties. The mean hardness was found to be 15.4 ±1.24 N for MT 3 mm and 52.4±5.82 N for T 5 mm. The friability for all batches was below 0.3 %. The satisfactory mechanical strength of the cores was particularly important for the proper fluid bed coating process.

2.2. Enteric coating

MT and T were successfully coated in both A (Aircoater 025®) and B (4M8-Trix®) fluid bed systems using Eudragit L 30D 55® or Acryl Eze II®. However, T needed a modification of the coating system. A Wurster insert was removed from apparatus B because otherwise the 5 mm tablets would be wedged due to their size. Eudragit L (dispersion) and Acryl Eze II (powder) are enteric coating mixtures based on the pH-sensitive methacrylic acid – ethyl acrylate copolymer (1:1) that is soluble at pH > 5.5. The coating mixtures with the same polymer but from different suppliers were chosen to better characterize the differences in the processing and gastro-resistance of the products. For the same reason, two fluid bed systems were used. Enteric forms with two different film thicknesses of 50 and 80 µm were prepared to evaluate the influence of film thickness on API release. Since enteric polymers contain acid groups, interaction with the acid-sensitive API may occur (Dangel et al. 2000). To protect the pantoprazole, a sub-coating with a 10 % solution of HPMC with PEG was performed.

2.3. In vitro dissolution test

The release test of pantoprazole from MT and T was performed in a Ph.Eur. basket apparatus. One T or five MT units (containing 20 mg pantoprazole) were placed in each vessel. The effect of five MT units enclosed in hard gelatine capsules was also examined. In the acid phase, no release of the API was observed, which meant that all tested products (both the 50 and 80 µm coatings) met the Ph.Eur. requirements.

Figures 1 A and B show the release rate of the active substance in the buffer phase from the MT and T that were coated in the B apparatus. By comparing the tested Eudragit L coated products with the reference product (Fig. 1A), one can observe that the same release rate was obtained from T 80 µm and from Controloc® ($p>0.05$) and finally 80 % of pantoprazole was released after 25 min for both products. However, in contrast to T, MT released API more rapidly (80 % of the pantoprazole was released after 15 min or after 20 min). As one can expect, the MT with a thinner film released API more rapidly. The clear effect of the film thickness could be observed after 10 min of the test when 60 % of the API was released from the MT 50 µm, whereas from the MT 80 µm, the same dose was released after 15 min, and statistical significance was demonstrated within 20 min ($p < 0.05$). The effect of the core sizes could also be observed. The MT 3 mm with the same film thickness as T (50 µm) started to release pantoprazole after 10 min, whereas from the T 5 mm, the process started after a 5 min delay ($p <0.05$ within 10-15 min). Similarly, after 15 min, the release of API from the T 80 µm was not observed, while during this time, 50 % of the API was released from MT despite having the same film thickness ($p < 0.05$ in 10 min).

In Fig. 1B, one can observe that the use of Acryl Eze II, which is another commercial acrylic coating product, did not result in a release rate from the prepared tablets similar to the reference product. All obtained formulations released API more rapidly than those coated with Eudragit L. That is, 80 % of a dose was released after 15 min, while in case of the Eudragit L coating, 80 % of the API was released within 15 to 25 min (except for the MT 50 µm). The observed difference may result from the different compositions of the excipients in the coating mixture. With the Acryl Eze II instead of polysorbate and TEC, other excipients, namely poloxamer, calcium silicate and sodium bicarbonate were present. The difference in the coating layer composition may result in different resistances to the pH 6.8 buffer stage during the dissolution study. However, it is also probable that the difference already occurred in the acidic stage of the test, thus leading to the faster release of pantoprazole when the tablet was transferred to the buffer fluid.

This laboratory-scale study demonstrates the lack of an impact of the used apparatus on the release rate of API in vitro. An asterisk (*) in Figs. 1 A and B represents a statistically significant difference when the A and B fluid bed systems are compared. However, these differences do not affect the discussed correlations. Most of the statistically significant differences between the apparatuses are related to the T 50 µm coated with Eudragit L. In this case, a significant problem with the gastro-resistance after the coating in the A apparatus was observed. After 2 h in the acid phase, a cracked coat and brown spots were visible, although no released API was detected in the dissolution medium. This indicates an

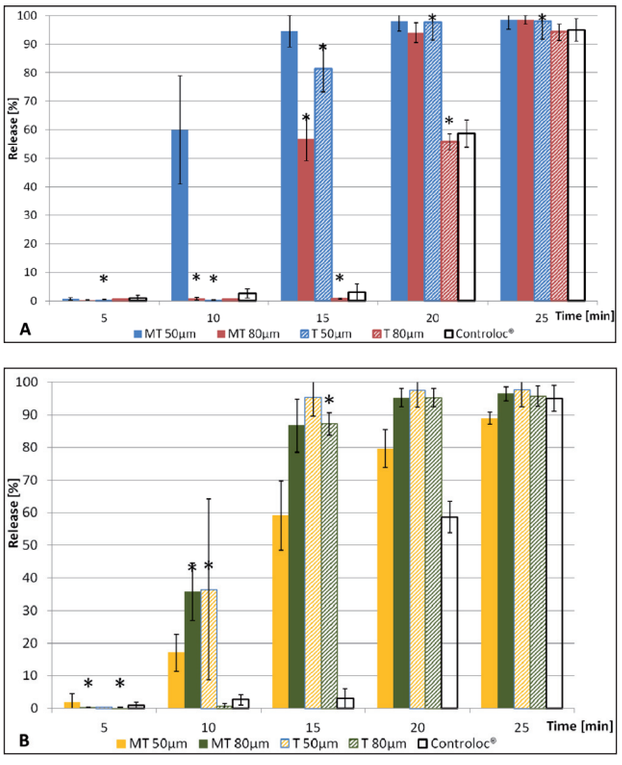

Fig. 1: *In vitro* pantoprazole release in the buffer stage (pH 6.8 phosphate buffer, 900 ml) from MT and T coated in a 4M8-Trix fluid bed system with Eudragit L (A) or with Acryl Eze II (B). Test conditions: basket apparatus, 100 rpm, and temp. 37±0.5 °C. Before the buffer stage, the tested formulations were exposed to an acid dissolution stage (0.1 M HCl, 900 ml for 2 h). The data represent the means ± SD (n=6), and *- indicates a significantly different result compared to the Aircoater 025 fluid bed system.

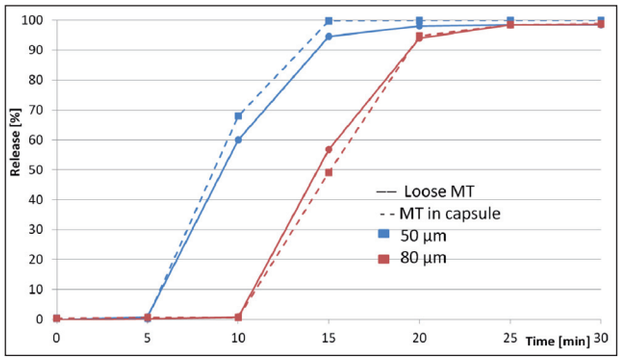

Fig. 2: Comparison of the release of API in the buffer phase (pH 6.8 phosphate buffer, 900 ml) from the loose MT and MT in a gelatine capsule (coating thickness 50 or 80 µm). Test conditions: basket apparatus, 100 rpm, and temp. 37 ± 0.5 °C. Before the buffer stage, the tested formulations were exposed to an acid dissolution stage (0.1 M HCl, 900 ml for 2 h). The data represent the means (n=6).

insufficient film thickness on T and the degradation of the pantoprazole when the coating process was carried out using apparatus A. The difference in both apparatus could be a result of the thin border between the sufficient and insufficient film thickness, which allow for gastro-resistance. Perhaps, the film, which was obtained in apparatus B, was a few micrometres thicker in crucial places, which made it impossible to account for the average film thickness. The acid-sensitivity of pantoprazole is described in the literature (Thanikachalam et al. 2008)

To administer a specific dose to adults who have no swallowing problems, MT could be placed in hard capsules, as is practised for pellets to obtain enteric capsules. Therefore, the release rate of API from the MT that were coated with Eudragit L and placed in hard gelatine capsules was also examined. Five loose MT and five MT that were placed in a gelatine capsule were tested. Figure 2 shows the release profiles of MT coated using the B apparatus. In the acid phase, the gelatine capsules entirely dissolved and no effect on the structure of MT and the release rate of API in the buffer phase was observed. Differences in the API release rates from loose MT and MT in capsules were statistically insignificant for all tested samples ($p > 0.05$).

In summary, it has been demonstrated that gastro-resistant MT 3 mm can be produced with a thinner coating film (50 µm) independent of the coating mixture that was used. In contrast, the use of a 50 µm film with larger cores (T 5 mm) is associated with the risk of gastro-resistance loss. Smaller MT also resulted in a faster release of pantoprazole in the buffer phase. Similar relationships were observed for the MT and T that were coated in two types of fluid bed coating apparatus. The selection of the coating mixture may affect the release rate *in vitro*, but the differences are small. The gelatine capsule had no effect on the release of API from MT *in vitro* under the tested conditions. Therefore, the possibility of administering in hard capsules MT, which were obtained using simple tableting technology, allows for considering this formulation as an alternative to gastro-resistant capsules with pellets.

3. Experimental

3.1. Materials

Pantoprazole sodium sesquihydrate was kindly donated by LEK-AM (Ph.Eur. Grade s.PSFP14015, Zakroczym, Poland). The tablet and minitablet cores were composed of microcrystalline cellulose (Vivapur® PH102, JRS Pharma, Rosenberg, Germany), colloidal silicon dioxide (Aerosil® 200, Evonik, Darmstadt, Germany), lactose monohydrate (Flowlac® 100, Meggle, Wasserburg, Germany), sodium stearyl fumarate (PRUV®, FMC BioPolymer, Newark, NJ, USA), crospovidone (Kollidon® CL-F, BASF, Ludwigshafen, Germany) and sodium carbonate (PPH Stanlab, Lublin, Poland).

Hypromellose (Pharmacoat® 606, Shin-Etsu Chemical, Tokyo, Japan) and polietylene glycol 6000 (PEG 6000, Sigma-Aldrich, Steinheim, Germany) were used for the sub-coating. The enteric film was obtained by coating minitablets and tablets with methacrylic acid-methyl methacrylate copolymer: ready-to-use mixture Acryl Eze II® (Colorcon, Dertford, UK) or Eudragit L 30D 55® (Evonik Industries, Darmstadt, Germany) that was mixed with triethyl citrate (TEC, Sigma-Aldrich, Steinheim, Germany) and talc (Luzenac VAL Chisone, Porte, Italy). Controloc® 20 mg (Takeda, Konstanz, Germany) was used as a reference drug product.

3.2. Preparation and evaluation of enteric-coated forms

3.2.1. Preparation of minitablets and tablet cores

Pantoprazole sodium was granulated with a 25 % solution of sodium carbonate using a high shear wet granulation method (Reynolds et al. 2007). Biconvex MT with a diameter of 3 mm (weighing 18 mg and containing 4 mg of pantoprazole) were prepared at a compression pressure of 100 MPa and using a rotary tablet press (RTP-D8, Erweka, Heusenstamm, Germany) with single-tip punches. Additionally, 5.0 mm in diameter biconvex T (weighing 85 mg and containing 20 mg of pantoprazole) was compressed at the same pressure using a rotary tablet press with single punches. Two batches of both types of cores were prepared. The cores were composed of the granulated API (28.5 % w/w), Vivapur 102 (46.5 % w/w), Flowlac 100 (17 % w/w), Kollidon CL-F (4 % w/w), Aerosil 200 (1 % w/w) and PRUV (3 % w/w).

3.2.2. Physical evaluation of minitablets and tablets that were prepared for coating

The hardness of T was tested using a Hardness Tester (TBH 30 MD, Erweka, Heusenstamm, Germany). The crushing resistance of the MT cores (n=10) was evaluated using a texture analyser TA.XT Plus (Stable Micro Systems, Surrey, UK) at a constant speed (0.5 mm/s) of the cylindrical probe. The friability test was carried out according to the Ph.Eur. 9.0 (2.9.7) test for tablets. Previously de-dusted MT or T (6.5 g) were placed in the friability tester (TAR-10, Erweka, Heusenstamm, Germany) and, after 100 rotations, the loss of mass was determined.

3.2.3. Enteric coating

Two apparatus for fluid bed coating were evaluated: apparatus A was an Aircoater 025 (Romaco Innojet, Steinen, Germany) and apparatus B was a 4M8-Trix (ProCepT, Zelzate, Belgium). The latter was tested in two configurations: with a Wurster insert for MT and a bottom spray without a Wurster insert for 5 mm tablets. All process parameters and the differences in the batch size, chamber volume, type of airflow and nozzle spray system are shown in the Table 1. The airflow was increased for the batch and core sizes, respectively.

Table 1: Differences in the fluid bed systems' characteristics and conditions for MT and T coating

	Aircoater 025 (A)	4M8-Trix (B)
Product temperature [°C]	27	
Spraying pressure [bar]	1.0	
Coating mixture flow rate [g/min]	1.0	
Drying time [min]	30	
Inlet air temperature [°C]	35	38
Exhaust air temperature [°C]	27	28
Inlet airflow rate [m^3/h]	18.5 for MTs 22.5 for Ts	21.6 for MTs 30.0 for Ts
Coating time [min]	30/45 for MTs 50/80 µm 25/40 for Ts 50/80 µm	50/90 for MTs 50/80 µm 40/70 for Ts 50/80 µm
Batch size [g]	50	100
Effective coating process volume [L]	0.15	1
Chamber volume [L]	0.6	19
Type of airflow	Orbital movement (INNOJET ORBITER booster)	Classic Wurster "Expanded bed"
Type of nozzle spraying	Rotary nozzle with horizontal spray (INNOJET ROTOJET spraying nozzles)	Bottom spray with Wurster insert with MTs and without insert with Ts

First, MT and T were sub-coated (film thickness 60 µm) in the A apparatus using a 10 % (w/w) solution of hypromellose with PEG 6000 (in 9:1 ratio). The cores were then coated with aqueous dispersions (20 % of solids) of Acryl Eze II or Eudragit L 30D 55, which are based on the methacrylic acid-ethyl acrylate copolymer (1:1). Eudragit L is a commercial dispersion (30 % w/w) of the polymer with polysorbate 80 and sodium lauryl sulfate in its composition. To obtain the final coating mixture TEC (plasticizer, 1.25 % w/w), talc (glidant, 6.25 % w/w) and water (50.83 % w/w) were added. Acryl Eze II is a ready-to-use powder that, besides the polymer, contains sodium lauryl sulfate, talc, titanium dioxide, poloxamer 407, calcium silicate and sodium bicarbonate. The powder was dispersed in water before coating with no other ingredients added. MT and T were coated until a 50 or 80 µm thick enteric film was achieved (MT 50 µm, MT 80 µm, T 50 µm and T 80 µm formulations were obtained).

The thickness of the film obtained was confirmed using a microscopic method. Cross-sections of MT or T were evaluated using a stereoscopic microscope (type X2000; Opta-Tech, Warszawa, Poland), which was equipped with the computer-controlled image analysis software Opta-View.

3.3. In vitro dissolution test

In vitro dissolution tests were performed using the Ph.Eur. 9.0 basket apparatus (DT 720 Series, Erweka, Heusenstamm, Germany) rotating at 100 rpm at 37±0.5 °C. Five minitablets per basket and one tablet per basket (20 mg of pantoprazole in a vessel) were tested (n=6) in 900 ml of 0.1 M HCl. After 2 h, the dissolution medium was replaced with 900 ml of phosphate buffer for 1 h (pH 6.8, Ph. Eur.). The amount of the released drug was detected in-line using a UV–VIS spectrometer with flow-through spectrophotometric cuvettes (8453, Agilent, Santa Clara, CA, USA) at 305 nm in the acid phase and 288 nm in the buffer phase. The active substance content was calculated on the basis of the calibration curve. The results were compared with the requirements provided in the Ph.Eur. 9.0 (2.9.3). That is, no individual value exceeds 10 % dissolved API after 2 h in the acid phase and at least 80 % of API is released after 45 min in the buffer phase. Our goal was to follow the pharmacopoeial requirements, but with a faster release in the buffer stage (80 % was released within 20 min for MT). The release rate of API from the MT 3 mm placed in a two-colour hard gelatine capsule (size no. 3, Capsugel, Bornem, Belgium) was also investigated under the same conditions as those described above. Additionally, the results of the drug release test were compared with the results for the reference formulation (Controloc® 20 mg, Takeda, Konstanz, Germany). The reference drug is a biconvex oval tablet (9/4.7 mm) that is coated with methacrylic acid-ethyl acrylate copolymer (1:1) (film thickness 80 µm) and sub-coated with hypromellose (film thickness 100 µm).

3.4. Statistical analysis

The statistical analysis of drug release data (% released) was carried out using the Statistica 13.1 software (TIBCO Software Inc, Palo Alto, CA, USA). The non-parametric Mann-Whitney *U*-Test was used to compare the two formulations. A statistical p-value<0.05 was considered as significant.

Conflicts of interest: none declared

References

Aleksovski A, Dreu R, Gašperlin M, Planinšek O (2015) Mini-tablets: a contemporary system for oral drug delivery in targeted patient groups. Expert Opin Drug Deliv 12: 65–84.

Bodea M, Napoca C (2010) Film coating preparation of metoprolol tartrate mini-tablets and in vitro drug release studies. Clujul Med 83: 457–464.

Choudhry P, Patel KS, Jain PK, Arora M, Nagar M, Shinde S, Trivedi P (2012) Design, in vitro evaluation and in vivo studies of novel delayed release tablets of pantoprazole. Int J Biomed Adv Res 3: 828–840.

Czajkowska M, Sznitowska M, Kleinebudde P (2015) Determination of coating thickness of minitablets and pellets by dynamic image analysis. Int J Pharm 495: 347–353.

Dangel C, Kolter K, Reich H, Schepky G (2000) Aqueous enteric coatings with methacrylic acid copolymer type C on acidic and basic drugs in tablets and pellets, Part I: acetylsalicylic acid tablets and crystals. Pharm Technol 24: 64–70.

European Medicines Agency (2009) Guideline on pharmaceutical development of medicines for pediatric use: Better medicines for children. [WWW document]: http://www.ema.europa.eu/docs/en_GB/document_libra

Gaber DM, Nafee N, Abdallah OY (2015) Mini-tablets versus pellets as promising multiparticulate modified release delivery systems for highly soluble drugs. Int J Pharm 488: 86–94.

Klingmann V, Linderskamp H, Meissner T, Mayatepek E, Moeltner A, Breitkreutz J, Bosse HM (2018) Acceptability of multiple uncoated minitablets in infants and toddlers: A randomized controlled trial. J Pediatr 201: 202–207.

Kluk A, Sznitowska M, Brandt A, Sznurkowska K, Plata-Nazar K, Mysliwiec M, Kaminska B, Kotlowska H (2015) Can preschool-aged children swallow several minitablets at a time? Results from a clinical pilot study. Int J Pharm 485: 1–6.

Lennartz P, Mielck JB (1998) Minitabletting: Improving the compactability of paracetamol powder mixtures. Int J Pharm 173: 75–85.

Liu F, Ghaffur A, Bains J, Hamdy S (2016) Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire based observational study. Int J Pharm 512: 374–381.

Lopez FL, Bowles A, Gul MO, Clapham D, Ernest TB, Tuleu C (2016) Effect of formulation variables on oral grittiness and preferences of multiparticulate formulations in adult volunteers. Eur J Pharm Sci 92: 156–162.

Mohamed F, Roberts M, Saleem R (2010) Hydrocortisone mini-tablets for pediatric delivery. J Pharm Pharmacol 62: 1441.

Reynolds GK, Le PK, Nilpawar AM (2007) High shear granulation. In: Salman AD (ed.) Handbook of powder technology. Elsevier, pp. 3–19

Souza DF de, Goebel K, Andreazza IF (2013) Development of enteric coated sustained release minitablets containing mesalamine. Brazilian J Pharm Sci 49: 529–536.

Thanikachalam S, Rajappan M, Kannappan V (2008) Stability-indicating HPLC method for simultaneous determination of pantoprazole and domperidone from their combination drug product. Chromatographia 67: 41–47.

Voung H, Levina M, Rajabi-Siahboomi AR (2008) Investigation of enteric coating of mini-tabs using a perforated pan or a fluid-bed machine. In: Controlled release society annual meeting. New York NY.

Vuong H, Levina M, Rajabi-Siahboomi AR (2008) Evaluation of the enteric performance of lansoprazole mini-tabs coated in a perforated pan. In: AAPS annual meeting and exposition. Atlanta GA.