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# Development of Direct Compressed Loratadine Minitablets

GULNUR YELEKEN[1*], HANNA KOTŁOWSKA[2], MAŁGORZATA SZNITOWSKA[2], EWA GOLENIA[2], GULBARAM USTENOVA[1]

[1] *Department of pharmaceutical Disciplines, Asfendiyarov Kazakh National Medical University, Kazakhstan, 050000, Almaty, Tole - Bi Street, 94*
[2] *Department of Pharmaceutical Technology, Medical University of Gdańsk, J. Hallera 107, 80-416 Gdańsk, Poland*

**Abstract**

Loratadine is commonly used in paediatric pharmacotherapy of allergic rhinitis and urticaria. Syrup is an available dosage form for children, although it contains co-solvents and sweeteners with potential risk of adverse effects. The aim of the study was to develop loratadine minitablets as an alternative dosage form. Seven formulations with a loratadine dose of 0.5 or 1 mg per one minitablet were proposed and compression process parameters were optimised for 2 and 3 mm minitablets and for 5 mm tablets using a single punch Gamlen Tablet Press. The optimised process parameters were used in manufacturing minitablets using a laboratory rotary press. Scale-up was successful and minitablets obtained in both apparatus disintegrated within 90 sec and released 80% of loratadine within 5 min.

**Key words:** minitablets, direct compression, loratadine, paediatric dosage form

## INTRODUCTION

Recently, WHO and EMA initiated a few programmes for paediatric dosage forms development. They are directed especially to pharmaceutical manufacturers to encourage them to formulate medicines appropriate for children [1, 2]. These considerations should be primarily focused on solid dosage forms. They exhibit better physical, chemical and microbiological stability in comparison with liquids, which are considered as standard form in paediatric pharmacotherapy. Nevertheless, they often required use of co-solvents like propylene glycol and glycerol or sweeteners like sucrose, for example loratadine syrup available commercially. These excipients are listed as generally recognised as save (GRAS) but special attention has to be taken when their higher content is included in paediatric formulations. There are reports that propylene glycol may act as central nervous system depressant, especially in children less than 4-years-old due to immature metabolism [3]. Glycerol used in higher concentrations may cause stomach mucositis or diarrhoea because of its osmotic properties [4]. To increase palatability of liquids sucrose in concentration up to 35% is often added, although long-term use of these formulations may cause dental problems [5]. So far tablets have been approved for application only for children from 6 or even 12 years of age. It is due to limited number of relevant studies of children swallowing ability and risk of choking [6].

Minitablets, with size of 3 mm and less, are one of the solid oral dosage forms that could be successfully administered to children, even under six years old. They can be produced by conventional eccentric or rotary tablet presses [7]. Because of small sizes they can be easily swallowed by preschool-aged children or even infants and toddlers. Thomson et al. [8] showed that 86% of 5 years old children swallowed easily single 3 mm minitablet. In other study acceptability of four oral formulations (4 mm tablet, powder, suspension and syrup) in 1-4 years children was compared and small tablets were the most acceptable oral dosage form [9]. The swallowing ability of 2 mm minitablet in 6-months infants was confirmed by Spomer et al.[10] and Klingmann et al. [11]. However, small size of minitablet (5-20 mg) may result in insufficient active substance therapeutic dose capacity in one unit. Therefore, minitablets have to be considered as multiple unit dosage form. In one clinical study it was proven that five and ten 2 mm and 3 mm minitablets can be safely administered to preschool-aged children (2 and 3 years old) when mixed with jelly food on a spoon. 75% of 2-year-old children and 93% of 3-year-olds swallowed ten 3 mm minitablets. None of children choked but some of them chewed minitablets before swallowing [12].

Dosage flexibility is an additional advantage of minitablets. To ensure the appropriate dose of active ingredient, the adequate number of units according to body mass/age can be administered. Dosing by multiplication is more accurate than common practice - a tablet subdivision [13]. Counting the right number of small units could be a real difficulty for patients or caregivers, thus there is a necessity to design dosing device that could measure a defined number of minitablets. A few suitable electronic tablet dispensers have been already launched to the market [14].

The aim of the research was to develop composition of direct compressed loratadine 2 and 3 mm minitablets as an alternative to liquid form. Minitablets should release the active substance quickly, disintegrating fast, however appropriate mechanical strength should be granted. Using the same composition compression process parameters were compared for two laboratory tableting machines – Gamlen Tablet Press and rotary press for three different sizes of units: 2, 3 mm minitablets and 5 mm tablets. This was performed to indicate potential problems in further scale-up step.

**Table 1. Composition of minitablets with loratadine [% w/w]**

| Excipients | Function | Formulation | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Loratadine** | Active substance | 6.66 | | | | | | |
| **Flowlac 100** | Diluent | 80.0 | - | - | 80.0 | - | - | 62.84 |
| **Vivapur 102** | | - | 80.0 | 75.0 | - | 80.0 | 80.0 | - |
| **Corn starch** | Disintegrant | 12.84 | 12.84 | 7.84 | 7.84 | 7.84 | 7.34 | 30.0 |
| **Ac-Di-Sol** | | - | - | - | 5.0 | 5.0 | 5.0 | - |
| **Starch 1500** | | - | - | 10.0 | - | - | - | - |
| **Magnesium stearate** | Lubricant | 0.5 | | | | | | |
| **Aerosil 200** | Glidant | - | - | - | - | - | 0.5 | - |

## EXPERIMENTAL

### Materials

Loratadine was purchased from the Institute of Hetero Labs Ltd (Hyderabad, India). The proposed formulations contained following excipients: spray-dried lactose – Flowlac 100 (Meggle, Wasserburg, Germany), microcrystalline cellulose – Vivapur 102 (JRS Pharma, Rosenberg, Germany), corn starch (Polpharma SA, Starogard Gdanski, Poland), croscarmellose sodium – Ac-di-sol (FMC Europe, Brussels, Belgium), partially pregelatinized maize starch – Starch 1500 (Colorcon, Dartford, UK), magnesium stearate (Alfa Aesar, Karlsruhe, Germany) and colloidal silicon dioxide – Aerosil 200 (Evonik, Darmstadt, Germany).

Preparation of minitablets and tablets Minitablets with a diameter of 2 mm and weight 7.5 mg and with a diameter 3 mm and mass 15 mg and 5 mm tablets with 75 mg of weight containing 0.5, 1 and 5 mg of loratadine, respectively, were prepared from powder blends (Table 1).

Two laboratory presses were used: Gamlen Tablet Press (Gamlen Tableting, Nottingham, UK) and rotary press Erweka RTP-D8 (Erweka, Heusenstamm, Germany), equipped with single round flat-faced punches (2, 3 and 5 mm). All excipients were sieved (0.315 mm) and afterwards mixed for 15 min, magnesium stearate was added last and the mixing was continued for additional 5 min. Tableting masses were compressed using pressure of 150 and 250 MPa.

### Properties of powder mixtures

Powder flow was characterised using methods proposed by Ph. Eur. 8.0 [15]. Flow rate and angle of repose were determined using Manual Powder Flow Tester (Electrolab, Mumbai, India). Powder sample (100 g) was placed in a funnel with 15 mm orifice and the time needed for the entire sample to flow out was measured [s/100 g]. The angle of repose was measured from the height of the cone formed from test sample poured through the funnel on 10 mm flat base. The bulk density [g/ml] was determined by measuring the volume of 100 g powder sample placed loosely in a graduated cylinder . Subsequently, the sample was tapped for 1250 times using SVM tester (Erweka, Heusenstamm, Germany) to obtain the tapped density. Experimental values were used to calculate Hausner ratio and compressibility index and to assess powder flow character according to pharmacopoeial monograph 3.9.36 [15].

### Minitablets and tablets properties

**Mass and thickness uniformity:** Twenty minitablets were randomly selected and individually weighed. Thickness of minitablets was determined by electronic caliper (Topex, Warsaw, Poland). The average values and relative standard deviations (RSD) were calculated.

**Hardness:** Crushing strength of 5 mm tablets was measured using standard Ph. Eur. hardness tester (Erweka, Heusenstamm, Germany). Whereas hardness of minitablets was determined using a Texture Analyser TA.XT Plus (Stable Micro Systems, Surrey, UK). Ten randomly selected minitablets were tested to check the maximum force needed to crush the tablet by a stainless steel probe moving downwards with a speed of 0.01 mm/s.

**Friability:** Accurately weighed sample (6.5 g of minitablets or tablets) was placed in a drum of a pharmacopoeial apparatus (Erweka, Heusenstamm, Germany) and subjected to 100 rotations. The percentage loss of mass was calculated.

**Disintegration test:** The test was carried out for six randomly selected units using Ph. Eur. apparatus (Pharma Test, Hainburg, Germany) in 800 ml of water. For testing of minitablets a 1 mm mesh size stainless steel wire cloth was placed on the bottom of the basket. The time needed for minitablets or tablets to disintegrate was measured. Result was given as a time recorded for the last unit out of 6 tested.

**Dissolution study:** The *in vitro* release tests were performed in a paddle dissolution apparatus (Pharma Test, Hainburg, Germany). Number of units equivalent to 5 mg of loratadine (10 units for 2 mm minitablets, 5 units for 3 mm minitablets and one 5 mm tablet) were placed in a vessel filled with 500 ml of 0.1 M HCl. The rotation speed was 50 rpm. At specific time points 5.0 ml samples of the acceptor fluid were analysed spectrophotometrically at 280 nm. The loratadine content was calculated on the basis of the calibration curve (linearity in the range of 2.5-50 µg/ml, $R^2$=0.999)

## RESULTS

The investigation was undertaken to formulate loratadine minitablets by direct compression method and evaluate the novel drug delivery form for paediatric patients. Direct compression requires a careful choice of the excipients, what seems to be especially important in the case of small tablet dies being filled with the powder during manufacturing of minitablets. The recommended dose for

loratadine in children 2–5 years of age is 5 mg given orally once a day. For children form 6 years of age the recommended dose is 10 mg per day or 5 mg every 12 hours [16]. Single dose 5.0 mg of loratadine is contained in 10 units of 2 mm minitablets, 5 units of 3 mm minitablets and one 5 mm tablet obtained in the study. Prepared formulations are presented in Table 1.

The flow characteristics of powder mixtures was assessed using pharmacopoeial tests: flowability, bulk and tapped density, Hausner ratio and compressibility index. Unfortunately, all powder blends were characterised as poorly flowing: angle of repose was greater than 43° and Hausner ratio greater than 1.30. Besides, the powders failed to flow through the funnel with 15 mm orifice. Nevertheless, all of them were used in the pre-tests with Gamlen Tablet Press (GTP).

The 3 mm/15 mg minitablets were prepared in GTP with compression pressure of 150 MPa and 250 MPa. Stability of compression force was not an issue when using GTP because the exact compression force was programmed during the process. This press allows to make one tablet at a time. 15 mg of powder was put in the die using powder pipette GamPette (Gamlen Tableting, Nottingham, UK) with very good precision (RSD ≤ 3.5%). The diameter of the pipette was 3.5 mm and the precise powder dosing proved that even the poor flowability could not necessary exclude uniform filling of the rotary tablet press dies.

## DISCUSSIONS

During tableting in GTP ejection forces were analysed (Table 2). For 3 mm minitablets prepared from mixtures F1, F4 and F7 ejection values were relatively high (> 60 N). Moreover, these minitablets demonstrated very low crushing strength: less than 10 N when compression was 150 MPa (Table 3). Hence, these formulations were not investigated further.

Other blends were based on microcrystalline cellulose (Vivapur 102) and the friction during ejection was considerably lower: 10-56 N (Table 2). Only during compression of 3 mm minitablets from the powder blend F3 larger deviations in ejection force were noted: RSD 29% was observed while for other Vivapur based compositions RSD was about 10%. This is presented in Table 2. It could have been connected with the presence of pregelatinised starch in this formulation.

**Table 2. Ejection force values [N] during compression in GTP of minitablets and tablets - mean value (RSD- %)**

| Compression pressure | 150 MPa | 250 MPa | | |
|---|---|---|---|---|
| Formulation | Minitablets 3 mm | Minitablets 2 mm | Minitablets 3 mm | Tablets 5 mm |
| F1 | 85.74 (6.69) | | 118.41 (10.11) | |
| F2 | 17.56 (8.69) | 22.17 (9.95) | 8.63 (8.2) | 45.52 (9.39) |
| F3 | 14.03 (10.28) | | 12.95 (29.13) | 45.71 (3.75) |
| F4 | 62.29 (19.72) | | | |
| F5 | 15.01 (17.15) | 18.34 (4.45) | 10.20 (10.29) | 45.42 (4.32) |
| F6 | | 17.76 (5.95) | 30.41 (11.15) | 56.31 (8.52) |
| F7 | | | 75.73 (5.34) | |

**Table 3. Hardness (H) and disintegration time (D) of minitablets (2 and 3 mm) and tablets (5 mm) with loratadine compressed in GTP**

| Formulation | Compression pressure [MPa] | 2 mm | | 3 mm | | 5 mm | |
|---|---|---|---|---|---|---|---|
| | | H [N] | D [min] | H [N] | D [min] | H [N] | D [min] |
| F1 | 150 | | | 8.94 (15.4) | 00:17 | | |
| | 250 | | | 16.52 (20.4) | 00:20 | | |
| F2 | 150 | | | 37.77 (3.2) | 06:57 | | |
| | 250 | 36.02 (16.9) | 06:25 | 43.31 (3.7) | 07:10 | 106.2 (5.6) | 07:30 |
| F3 | 150 | | | 26.80 (3.1) | 00:22 | | |
| | 250 | | | 32.93 (5.0) | 00:29 | 83.0 (5.1) | 00:40 |
| F4 | 150 | | | 8.05 (10.3) | 00:32 | | |
| | 250 | | | | | | |
| F5 | 150 | | | 34.64 (3.7) | 00:16 | | |
| | 250 | | | | | | |
| F6 | 150 | | | | | | |
| | 250 | 28.69 (5.9) | 01:05 | 32.25 (4.5) | 01:33 | 81.4 (5.5) | 03:24 |
| F7 | 150 | | | | | | |
| | 250 | | | 4.98 (12.53) | 00:20 | | |

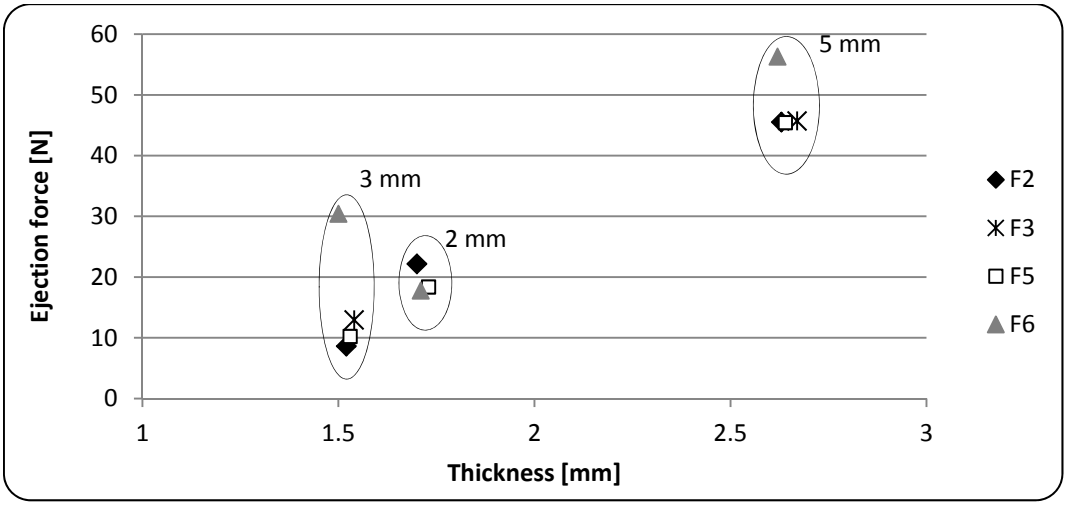


**Figure 1. Ejection force in relation to thickness for microcrystalline cellulose based formulations compressed with pressure of 250 MPa**

In most cases ejection force after compression of 2 mm minitablets was higher than 3 mm (Figure 2). It can be explained by geometry of minitablets (Table 4): 2 mm minitablets had higher thickness (about 1.7 mm) and different thickness to diameter ratio (t/d=0.85) than 3 mm minitablets (thickness 1.5 mm and t/d=0.5). Consequently, thicker 5 mm tablets were prepared with higher ejection force. Finally, for formulations F2, F3 and F5 (Aerosil free) linear relationship was observed between ejection force and thickness, irrespective of the thickness/diameter ratio (Figure 1).

**Table 4 Dimensions of minitablets and tablets**

| Diameter [mm] | Weight [mg] | Thickness [mm] | t/d ratio |
|---|---|---|---|
| 2 | 5 | 1.7 | 0.85 |
| 3 | 15 | 1.5 | 0.50 |
| 5 | 50 | 2.6 | 0.52 |

Minitablets and tablets prepared from powders based on microcrystalline cellulose (F2, F3, F5 and F6) exhibited very good mechanical strength determined with a texture analyser (minitablets) or with a pharmaceopoeial apparatus (tablets). Standard Ph. Eur. apparatus was unsuitable for smaller tablets because the construction did not allow to break a small object and its measuring accuracy was poor for minitablets. Hardness values obtained for 2 and 3 mm minitablets compressed with 250 MPa were about 30 N and 40 N, respectively. Only for 3 mm minitablets prepared from F6 blend hardness was lower (about 32 N), which might been caused by 0.5% of silicon dioxide in this formulation. Hardness of 5 mm tablets was about 80-100 N. Lower hardness of minitablets did not mean low mechanical strength, because friablity of minitablets was very low (data not showed).

Disintegration of F2 minitablets and tablets was greatly slower (6:25-7:30 min) in comparison to formulations F3, F5 and F6 containing pregelatinised starch or croscarmellose sodium as disintegrants. F3 and F5 minitablets disintegrated in about 30 sec, while minitablets prepared from F5 mixture, with silicon dioxide, disintegrated slower – within 1 min. Disintegration time extended largely when tablet size increased and for 5 mm tablets it was from 0:40 to 7:30 min.

Despite these major differences in physical properties of the obtained tablets, dissolution test performed for formulation F6 showed similar release rate of loratadine independently from the geometry and size of tablets (Mann-Whitney U-test, p> 0.5). Dissolution of loratadine in 500 ml of 0.1M HCl was very fast, with at least 80% of the declared dose released within 3 min.

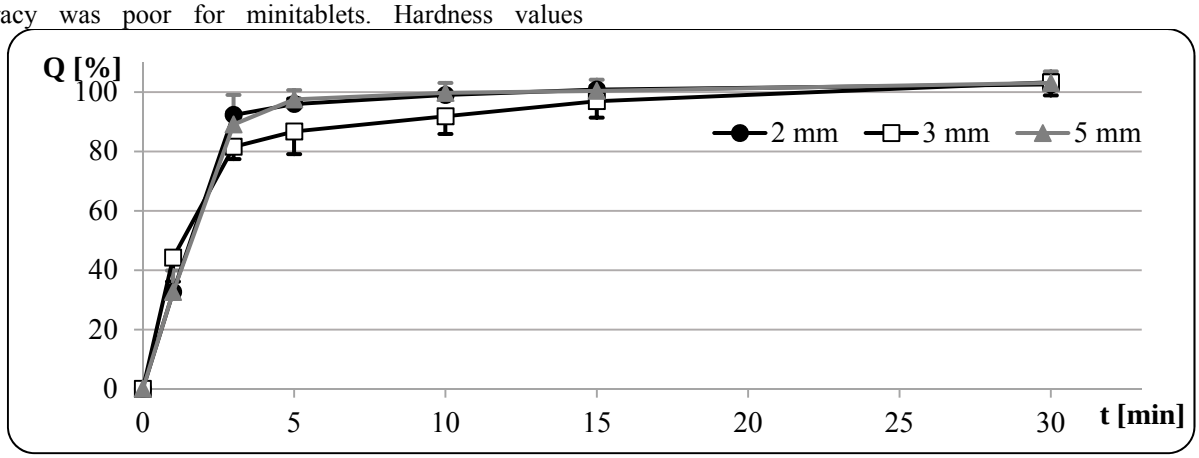


**Figure 2 Dissolution profiles of loratadine from minitablets (2 and 3 mm) and tablets (5 mm) from formulation F6 (n = 6)**

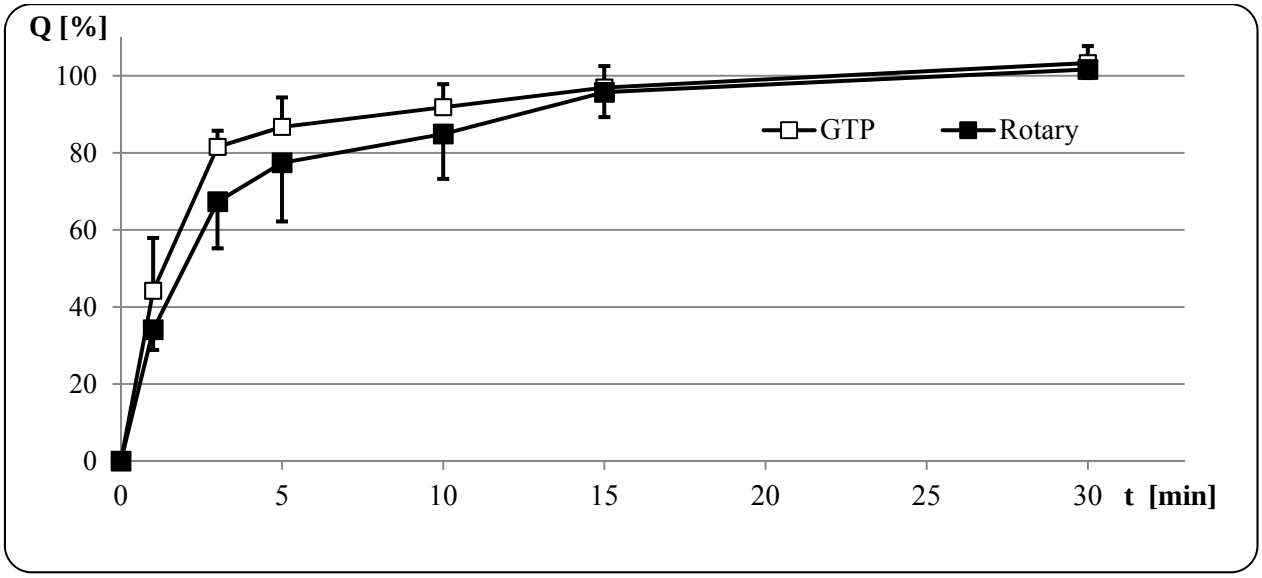


**Figure 3 Dissolution profiles of loratadine from F6 3 mm/15 mg minitablets prepared in GTP and rotary tableting machines (n = 6)**

In the next step formulation F6 was chosen for scale-up using a laboratory rotary tablet press (Erweka RTP-D8). 3 mm flat minitablets were manufactured using single punches (Natoli Engineering, Saint Charles, USA). Tablet press was equipped with four sets of tools. 200 g of the tableting mass was compressed with pressure of 250 MPa, with the turret speed 25 rpm and feeder speed 50 rpm. During the tableting process compression, ejection and pre-compression forces were monitored on-line. Stability of the main compression force was necessary to obtain uniform product in rotary tablet press. Calculated from the applied pressure compression force should be 1.8 kN. However, registered forces varied during the process and were in the range of 1.4-2.3 kN with relative deviation 10.5%. This was not an obstacle, however, to produce 3 mm minitablets with a very good mass uniformity (RSD=1.9%), which was even improved in comparison to the tableting in GTP, where the powder was dispensed with a pipette. Pre-compression force was about 20 N and because it was so small it was neglected. In our earlier studies it was demonstrated that the level of pre-compression force had no influence on minitablets quality. The mean ejection force was lower than during compression in GTP but the recorded deviations were very high (RSD = 60%) as demonstrated in table 5..

**Table 5 Comparison of process parameters and physical properties of 3 mm minitablets (formulation F5) prepared in different tablet presses (compression pressure 250 MPa)**

| Tableting press | Ejection force [N] (RSD) | Hardness [N] (RSD) | Disintegration time [min:sec] |
|---|---|---|---|
| GTP | 30.41 (11.15) | 32.25 (4.49) | 01:33 |
| Rotary | 14.52 (59.79) | 32.50 (7.48) | 01:01 |

Quality parameters, namely hardness and disintegration time, for minitablets prepared in the rotary press were similar to those determined for minitablets obtained from GTP (Student's t test, $p > 0.05$). Very good mechanical strength of minitablets was confirmed also by a very low friability (0.4 %). Also the dissolution rate of loratadine from minitablets (Fig. 3) was comparable irrespectively of the tablet press used (Mann-Whitney U-test, $p > 0.5$).

## CONCLUSIONS

Minitablets with loratadine could be a good alternative dosage form in paediatrics pharmacotherapy because of relatively easy manufacturing process by direct compression and greater stability of the active substance provided by solid dosage forms. Present study has proven also that Gamlen Tablet Press is a useful tool for development of the optimum composition with successful scale-up. By consuming very small amount of active substance one can characterise and optimise process and product parameters.

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