Orally disintegrating tablets (ODT) are relatively novel solid dosage form that involves rapid disintegration or dissolution in the mouth without necessity of drinking water. They are also known as fast disintegrating, fast melt or fast dissolving tablets. Formulation of ODT was originally developed to address swallowing difficulties of conventional solid dosage forms (tablets and capsules) experienced by wide range of patient population, especially children and old age patients (1-3). ODT can be manufactured by different methods such as lyophilization, moulding, sublimation or direct compression. The direct compression is a relatively simple and cost-effective process, but it is directly influenced by the properties of the excipients, which have to be carefully selected based on their characteristics and desired functionalities - particle size distribution, good flowability, enhanced compactability or disintegration properties (4-7).

In ODT preparation, mannitol is widely used as a diluent because of its sweet taste and cooling sensation in the oral cavity. However, untreated mannitol powder is characterized by poor flowability and poor compactibility. For this reason, the current trend is to use multifunctional co-processed mixtures with mannitol. Co-processed excipients possess advantages that cannot be achievable by the simple physical mixtures of their components (8-11). Various co-processed ready-to-use mannitol based mixtures for fast disintegrating oral preparations are commercially available (12-14). Parteck® ODT is a combination of two components: mannitol and croscarmellose sodium (13), whereas Ludiflash® consists of mannitol, crospovidone, polyvinyl acetate and small amounts of povidone (14).

Our preliminary studies have shown that placebo ODT prepared with Ludiflash® or Parteck® ODT and addition of 3% crospovidones as disintegrant.
with Parteck® ODT and Ludiflash®, therefore, the objective of the present work was to evaluate the suitability of these mixtures to formulate ODT with loratadine. Loratadine is a potent long acting, non-sedating tricyclic antihistamine with selective peripheral histamine H1 receptor antagonistic activity. It is characterized by an acceptable taste, it does not require taste masking and it is a good candidate for fast disintegrating oral preparations (16). Orally disintegrating loratadine tablets might provide a dosage form which is easy to administer and provide immediate release of drug. Designed ODT were evaluated for weight variation, hardness, friability, thickness, wetting and disintegration time and pore structure. Additionally, possible interactions between the components of tablet mass were evaluated by differential scanning calorimetry.

EXPERIMENTAL

Materials

Ludiflash® and crospovidones (Kollidon® CL-F - standard fine, Kollidon® CL-SF - superfine) were obtained from BASF, Ludwigshafen, Germany. Parteck® ODT was purchased from Merck, Darmstadt, Germany. Magnesium stearate was a product of POCh, Piekary Śląskie, Poland. AcDiSol® was purchased from FMC Biopolymer, Brussels, Belgium and loratadine was obtained from Hasco, Wrocław, Poland.

METHODS

Evaluation of flow properties of the powder blends

Compressibility

A tapping apparatus (Electrolab EDT – 1020, Mumbai, India) was used for the compressibility studies. The weight powder was poured into a measuring cylinder. Tapping was carried out until no further change in powder volume was achieved. The bulk (d_b) and tapped (d_t) densities were calculated as quotients of the weight of the powder to its volumes occupied before (V_0) and after tapping (V_ta), respectively (17). The compressibility - Carr’s index (C) and Hausner ratio (HR) were calculated by equations (1) and (2) and expressed as median (n = 3).

\[ C = \frac{V_0 - V_{ta}}{V_0} \]  
\[ HR = \frac{d_t}{d_b} \]

Flowability

The angle of repose (AR) was determined to indicate the flowability of the powders. An appropriate amount of powder was poured through a glass funnel in a controlled manner onto a platform until a stable and height-fixed heap was formed (n = 3). AR was measured as the angle made by the inclined plane of the heap with the horizontal (17) and expressed as median.

Preparation of tablets

Different ODT formulations (Table 1), each weighing 180 mg, were prepared by direct compression method using a single punch tablet machine (EP1 Erweka, Heusenstamm, Germany) equipped with 8 mm diameter flat-faced punches. Different adjustments of the machine settings were tested. The adjustment which gave the highest possible hardness value with the shortest disintegration time was selected and applied to all tablet formulations.

Evaluation of tablet properties

Uniformity of weight and thickness

Uniformity of tablet weight and thickness was carried out according to the specifications of European Pharmacopoeia (17). The thickness was measured using calibrated digital caliper (Beta 1651 DGT, Milan, Italy). Obtained data were calculated

<table>
<thead>
<tr>
<th>Ingredient (mg/tablet)</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L1</td>
</tr>
<tr>
<td>Ludiflash®</td>
<td>162.8</td>
</tr>
<tr>
<td>Parteck® ODT</td>
<td>–</td>
</tr>
<tr>
<td>Loratadine</td>
<td>10.0</td>
</tr>
<tr>
<td>Kollidon® CL-SF</td>
<td>5.4</td>
</tr>
<tr>
<td>Kollidon® CL-F</td>
<td>–</td>
</tr>
<tr>
<td>AcDiSol®</td>
<td>–</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.8</td>
</tr>
</tbody>
</table>
from n = 20 and presented as the mean ± standard deviation.

**Mechanical properties**

The crushing strength of the tablets (n = 20) was measured using a Pharmaton hardness tester (5Y, Pharmaton AG, Thun, Switzerland) and presented as the mean ± standard deviation. Friability (n = 3) was determined using a friabiator tester (EF-1 W, Electrolab, Mumbai, India) (17) and presented as median.

**Drug content**

Ten tablets from each formulation were crushed into powder and accurately weighed. Hundred milligrams of the crushed tablet mass was dissolved in the medium. After filtration through 0.45 μm cellulose acetate filters (Millipore, Bilerica, MA, USA), concentration of loratadine was determined by the HPLC system Agilent Technologies 1200 equipped with a G1312A binary pump, a G1316A thermostat, a G1379B degasser and a G1315B diode array detector (Agilent, Waldbronn, Germany). Mobile phase was 0.025 M sodium phosphate buffer pH 3.7 and acetonitrile (1 : 4; v/v), the flow rate was 1.0 mL/min and UV detection was performed at a wavelength of 247 nm (18-20). The column temperature was maintained at 25 ± 0.5°C. For injection into the HPLC system, 20 μL of sample was used. The retention time of loratadine was 3.5 min. Standard calibration curve was linear over the range of 1–100 μg/mL with the correlation coefficient (R²) 0.999. Data are presented as median (n = 3).

**Wetting time**

The measurements were carried out according to the method described by Bi et al. (21). The tablet was put on twice folded filter paper (12 × 10.75 cm) placed in the middle of a Petri dish (7 cm in diameter) containing 7 mL of 0.05% red dye aqueous solution. The time necessary to the complete wetting of the outer surface of the tablet was detected by stopwatch. The measurements (n = 6) were performed at 25 ± 0.5°C. Data are presented as median.

**Sensory evaluation of tablets**

Sensory evaluation of roughness and taste of tablets was carried out by six healthy volunteers (Research Ethics Committee at the Medical
University of Białystok approval number R-J-002/460/2013). A numerical scale was used with the following values: 0 – pleasure/no roughness; 1 - slight pleasure/ slight roughness; and 2 – unpleasant/roughness.

**Evaluation of disintegration time**

**In vivo**

Disintegration time of the tablets in the oral cavity was evaluated by six healthy volunteers (Research Ethics Committee at the Medical University of Białystok approval number R-J-002/460/2013). After the mouth was rinsed with purified water, one tablet was hold in the mouth without chewing until the tablet disintegrated, and the mouth was rinsed again. The end point for disintegration time was the time when the tablet placed on the tongue disintegrated until no lumps remained (n = 6). Data are presented as median.

**In conventional disintegration apparatus**

Disintegration time of tablets (n = 6) was measured using pharmacopoeical apparatus (Erweka ED-2L, Heusenstamm, Germany). The test was performed at 37 ± 0.5°C (17). Distilled water was used as a disintegration medium. Data are presented as median.

**On wire cloth**

Disintegration time was determined by placing tablets (n = 6) on a wire cloth (diameter 2 mm) and dropping water on it at a rate of 4 mL/min. The time required for a tablet to completely pass through the wire cloth was noted as disintegration time (22). Data are presented as median.

**On Petri dish**

Petri dish having a diameter of 7 cm was filled with 10 mL of water and the tablet (n = 6) was carefully put in the center. Time for the tablet to completely disintegrate into fine particles was measured (23). Data are presented as median.

**Determination of the specific surface area**

The surface area of the tablet (n = 3) was determined by nitrogen adsorption using porosimeter

---

Figure 1. Bimodal pore size distribution in ODT formulations: L1-L3 (A), P1-P3 (B)
Gemini VII (Micromeritics, Norcross, USA). Prior to the analysis, the samples were degassed on SmartPrep apparatus (Micromeritics, Norcross, USA) for 24 h at a temperature of 80 ± 0.5°C using helium as purge gas. Data were evaluated using the Brunauer-Emmet-Teller (BET) equation, while the calculation of the pore size and pore distribution was performed following the scheme of Barett-Joyner-Halenda (BJH) (17). Data are presented as median.

**Differential scanning calorimetry**

Differential scanning calorimetry (DSC) thermograms of Ludiflash®, Parteck® ODT, loratadine and manufactured formulations were obtained by using automatic thermal analyzer system (DSC TEQ2000, TA Instruments, New Castle, USA). Samples (5 mg) were accurately weighted and hermetically sealed in an aluminum pan (n = 3). An empty pan sealed was used as a reference. Samples were heated from 25 to 250°C at scanning rate of
RESULTS AND DISCUSSION

Useful excipients for direct compression should possess good flow and compression properties. The basic parameter, which allows to evaluate the properties of the tablet mass is the bulk and tapped density. The bulk and tapped density of the designed blends was ranged from 0.51 to 0.54 g/mL and from 0.62 to 0.67 g/mL, respectively (Table 2). Small differences between the bulk and tapped density of the investigated powders proved their good flowability and the lack of interaction between the particles of analyzed mixtures. The Hausner ratio, Carr’s index and angle of repose refer to the packing characteristics of the materials and indicate their flowability. Additionally, angle of repose is a feature associated with internal friction between molecules. A Carr’s index value between 16.0 and 19.4%, a Hausner ratio less than 1.25 and angle of repose between 28.0 and 30.0° indicated that prepared powder blends showed good flow properties and are suitable for direct compression. Good flow properties of designed powder mixtures were also confirmed by the mass uniformity of obtained ODT (Table 3).

The physical evaluation of prepared ODT revealed a uniform thickness and weight for all the formulations. The average weight and thickness were found to be in the range of 180.4 to 183.4 mg and 4.01 to 4.04 mm, respectively (Table 3). Friability and hardness tests indicate if tablets possess a suitable mechanical resistance to avoid crumbling or breaking during the manufacturing process or subsequent packing. All the prepared ODT presented friability < 1% and no tablet was cracked, split or broken in either formula. The hardness of manufactured ODT was in the range of 46.7–67.0 N and the highest values were observed in formulations containing AcDiSol® as disintegrant (L3, P3). The increase in hardness in these formulations might be due to the inter-particle forces between AcDiSol® and other ingredients particles arising during the compression (25, 26). Based on the requirements for loratadine tablets (27), designed ODT were characterized by excellent drug content uniformity (Table 3).

Short disintegration time is one of the most important features of ODT. European Pharmacopoeia recommends disintegrating time for ODT less

---

**Table 4. Disintegration time of manufactured ODT evaluated by four independent methods (n = 6.).**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>In vivo</th>
<th>Conventional apparatus</th>
<th>Petri dish</th>
<th>Wire cloth</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>15.5</td>
<td>13.0</td>
<td>17.0</td>
<td>16.0</td>
</tr>
<tr>
<td>L2</td>
<td>16.0</td>
<td>33.0</td>
<td>14.0</td>
<td>15.0</td>
</tr>
<tr>
<td>L3</td>
<td>37.0</td>
<td>35.0</td>
<td>27.0</td>
<td>27.0</td>
</tr>
<tr>
<td>P1</td>
<td>27.0</td>
<td>18.0</td>
<td>16.0</td>
<td>17.0</td>
</tr>
<tr>
<td>P2</td>
<td>15.5</td>
<td>16.0</td>
<td>17.0</td>
<td>16.0</td>
</tr>
<tr>
<td>P3</td>
<td>34.0</td>
<td>25.0</td>
<td>27.0</td>
<td>27.0</td>
</tr>
</tbody>
</table>

**Table 5. Texture parameters of manufactured ODT (n = 3).**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Total surface area (m²/g)</th>
<th>Average pore radius (Å)</th>
<th>Cumulative volume of pores (cm³/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>0.25</td>
<td>34.01</td>
<td>0.002</td>
</tr>
<tr>
<td>L2</td>
<td>0.38</td>
<td>32.02</td>
<td>0.002</td>
</tr>
<tr>
<td>L3</td>
<td>0.51</td>
<td>48.00</td>
<td>0.001</td>
</tr>
<tr>
<td>P1</td>
<td>4.00</td>
<td>84.01</td>
<td>0.01</td>
</tr>
<tr>
<td>P2</td>
<td>3.00</td>
<td>94.05</td>
<td>0.01</td>
</tr>
<tr>
<td>P3</td>
<td>3.20</td>
<td>94.00</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Preparation and characterization of orally disintegrating loratadine... 459

than 3 min (17), whereas FDA guidelines suggest disintegration time less than 30 s (1). However, no special apparatus is mentioned in the pharmacopoeias to test disintegration time of ODT. The conventional test employs a relatively huge volume of medium (900 mL) compared to the volume of saliva present in human buccal cavity, which usually is less than 6 mL (28), so the results obtained in the conventional disintegration test do not reflect the conditions in vivo. Different modifications of disintegrating test have been described in the literature, for example: evaluation of disintegration time using texture analyzer, in wire basket disintegration apparatus or by using charge coupled devices camera applications (21, 29).

In this study, the disintegration time was evaluated by four independent methods – one in vivo and three in vitro. Disintegration time of all obtained ODT was found to be below 37 s (Table 4). Formulations containing AcDiSol® were characterized by the longest disintegration time (above 30 s). ODT with crospovidones disintegrated significantly faster and simultaneously were characterized by the shorter wetting time (Table 3). It might be a result of different disintegration mechanisms evoked by crospovidones and croscarmellose sodium. Crospovidones are water insoluble polymers characterized by easy swelling ability. They absorb water very quickly and subsequently swell without gelling effect. Interestingly, no significant differences in disintegration time of ODT prepared with fine or superfine crospovidones were observed (Table 4).

As texture parameters might have an additional effect on disintegration time, therefore, surface area, pore size and pore distribution in obtained ODT were also evaluated. It was found that the total surface area of ODT performed with Parteck® ODT as a diluent was higher than ODT prepared with Ludiflash® (3.0–4.0 m²/g and 0.25–0.51 m²/g, respectively) (Table 5). The cumulative pore volume in ODT containing Ludiflash® was from 5- to 14-fold lower than in ODT prepared with Parteck® ODT. However, despite different porosity observed in ODT manufactured with Ludiflash® or Parteck® ODT, disintegration time was quite similar. Analysis of pore radius distribution as a function of their volume indicated that in all examined ODT bimodal pore size distribution was observed (Fig. 1).

Organoleptic properties like taste, mouth-feeling and roughness are of considerable importance in ODT design, therefore, the sensory evaluation was also performed. Since the main component in multifunctional mixtures used is spray dried mannitol, all prepared ODT were characterized by very pleasant taste and no lumps was reported (Table 6). Slightly better organoleptic properties possessed ODT with Ludiflash®, but both mixtures could be recommended as excipients for the design of ODT with loratadine.

The physical state of loratadine, Ludiflash®, Parteck® ODT, crospovidones (Kollidon® CL-F, Kollidon® CL-SF), AcDiSol® and manufactured ODT was assessed by thermal analysis. The crystalline form of loratadine has melting point in the range between 132 and 137°C. Mannitol has three polymorphic forms - α, β and δ. The β-crystal form has melting point in the range 155-166°C, it is the most stable and is commonly used in the pharmaceutical formulations (3, 25, 26). DSC thermograms detected the melting peak of loratadine at 137°C and mannitol in its β-form (166°C). No interactions between loratadine, mannitol and other excipients used in the tablet mass were observed (Fig. 2).

**CONCLUSIONS**

The obtained results showed that co-processed mixtures Ludiflash® and Parteck® ODT are suitable...
to form ODT with loratadine by direct compression method. All manufactured ODT complied with the pharmacopoeial requirements. Designed formulations were characterized by suitable physico-mechanical properties, very short disintegration time and pleasant taste and mouth feeling. Short disintegration time of obtained tablets was influenced mainly by the type of the disintegrant used and not by the texture parameters. Disintegration time below 30 s was observed in formulations with crospovidones. Designed ODT are supposed to be a promising alternative for traditional dosage forms with loratadine. However, further investigations with regard to stability of obtained ODT are needed.

Acknowledgments

This study was conducted with the use of equipment purchased by Medical University of Białystok as part of the OP DEP 2007-2013, Priority Axis I.3, contract No. POPW.01.03.00-20-008/09 and supported by Medical University of Białystok grant (143-15781 F). We gratefully acknowledge BASF and Hasco-LEK S.A. for providing the samples of Ludiflash®, Kollidon® CL-SF, Kollidon® CL-F and loratadine.

REFERENCES


Received: 28. 01. 2015