This edition of Eye on Excipients discusses orodispersible minitablets as an alternative dosage form for pediatric patients and others who have difficulty swallowing traditional tablets. The column also describes a study conducted to determine the suitability of agglomerated isomalt as a filler-binder for direct-compression orodispersible minitablets with a low drug load.

Oral drug delivery by tablet is the most convenient route of administration for a medicine. However, some patient groups have difficulty swallowing (dysphagia) or have format, taste, and texture preferences that require alternative administration methods. For this reason, formulators are striving to develop new tablet formulations that promote improved patient compliance and convenience. These include orodispersible tablets (ODTs), minitablets, and orodispersible minitablets (ODMTs).

ODTs are solid-unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing or taking water. ODTs are particularly advantageous for pediatric and geriatric populations, who have difficulty swallowing conventional tablets and capsules. The European Pharmacopoeia has defined the term orodispersible tablet as a tablet that disintegrates readily and within 3 minutes in the mouth before swallowing [1].

The US FDA defines an ODT as a “solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue” [2]. Based on the original product rationale and FDA experience, we recommend that, in addition to the original definition, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or an alternative.

There is no universal definition for minitablets, but they are generally accepted to be compressed tablets with a diameter of 2 to 3 millimeters, as shown in Photo 1. Acceptance studies have shown that minitablets are suitable for use as a single dose and as multiparticulates for pediatrics [3]. Minitablets could also be a suitable administration form for other patient groups with dysphagia and the elderly.

Minitablets can be manufactured on regular rotary tablet presses with a few minor adjustments and the use of appropriate multi-tip punches (Photo 2). Due to their small size, minitablet formulations can present challenges with respect to blend uniformity, flow properties, and mass uniformity.

Therefore, the choice of filler-binder in a minitablet formulation is important. The filler-binder should have powder and compression characteristics that promote both high content uniformity and relatively high tablet hardness at low compression force.

The following study was conducted to evaluate the use of agglomerated isomalt as the filler-binder in a pediatric ODMT formulation containing enalapril maleate as the low-dose active pharmaceutical ingredient (API) [4].

Photo 1: Minitablets are generally accepted to be compressed tablets with a diameter of 2 to 3 millimeters.

Photo 2: Minitablets are manufactured on regular rotary tablet presses using multi-tip punches (center).
**ODMT formulation and tableting process**

Enalapril is a member of the drug class angiotensin converting enzyme (ACE) inhibitors and is used for various treatments, including heart failure, high blood pressure, and hypertensive emergency. It is listed as an essential medicine, emphasizing the need for a suitable dosage therapy for children [5].

Isomalt is a polyol manufactured from sucrose and comprised of two mutually diastereomeric disaccharide alcohols called 6-O-α-D-glucopyranoside-D-sorbitol (GPS) and 1-O-α-D-glucopyranoside-D-mannitol-dihydrate (GPM). Agglomerated isomalt is widely used as a filler-binder for direct-compression tableting due to its high compressibility, flowability, and workability.

It is manufactured from milled isomalt using a fluid-bed process followed by a sieving operation.

The ratio of GPS to GPM can influence isomalt’s water solubility. Isomalt with a ratio of 1:1 GPS to GPM has an aqueous solubility of 25 grams in 100 grams at 20°C, while isomalt with a ratio of 3:1 GPS to GPM has an aqueous solubility of 42 grams. Table 1 shows the typical powder characteristics of each grade.

Figure 1 shows the porous structure and spherical particle shape of each grade, characteristics that promote good mixing and high content uniformity in a powder mixture. To develop the ODMTs for this study, the higher-solubility agglomerate form (3:1 GPS:GPM) was used.

A prerequisite of the therapeutic success of low-dose dosage forms is high content uniformity (CU) and low mass variation (MV). The ability to achieve CU by direct compression is linked to the physical and morphological properties of the API and excipients, their amounts in the formulation, the resulting flowability, the mixing process, and the tableting process.

To produce a 1-milligram enalapril maleate ODMT, enalapril maleate (16 percent), 3:1 GPS:GPM agglomerated isomalt (79 percent), and cross-linked polyvinylpyrrolidone (4 percent) as superdisintegrant were mixed together in a Turbula mixer for 15 minutes. Magnesium stearate (1 percent) as lubricant was then added, and the formulation was mixed for an additional 2 minutes. This blend was then compressed on a rotary tablet press into 6.25-milligram round bi-convex tablets using 2-millimeter, 19-tip punches and a compression force of 5 to 6 kilonewtons (71 to 85 megapascals).

**Evaluation of ODMTs**

The tablets were tested to determine disintegration time, rate of dissolution, mass variation, content uniformity, acceptance value, and stability.

The disintegration time was measured using a method developed by Kleinebudde [6]. One ODMT

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**Table 1**

<table>
<thead>
<tr>
<th>Solubility in water at 20°C (g/100 g)</th>
<th>1:1 GPS:GPM</th>
<th>3:1 GPS:GPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density (g/l)</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Tapped density (g/l)</td>
<td>480</td>
<td>480</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>38</td>
<td>37</td>
</tr>
</tbody>
</table>

**Figure 1**

Scanning electron micrograph images of agglomerated isomalt (Philips XL-30 FEG)

a. 1:1 GPS:GPM

b. 3:1 GPS:GPM

Photo 3: A modified test apparatus was used to measure the minitablet dissolution.
was placed into a Plexiglas cylinder, which was then locked with a 710-micron mesh sieve at the top and bottom (Photo 4). The locked cylinder was placed into a conventional disintegration apparatus and weighted with a metal cover. The disintegration time of six minitablets was measured at 37 ± 2°C in demineralized water.

Dissolution studies were performed in a basket apparatus according to USP 39-NF 34 monograph [7]. API release of the ODMTs was measured in a phosphate buffer pH 6.8 stirred at 50 rpm. The wavelength was set to 208 nanometers.

Mass variation was performed according to Ph.Eur. 2.9.5. Twenty minitablets were randomly chosen and weighed on an analytical balance [8]. Content uniformity was determined by a validated method using high performance liquid chromatography (HPLC) with UV-Vis coupling developed by Thabet and Breitkreutz [9]. To determine the acceptance value (AV) of enalapril maleate according to Ph.Eur. 2.9.40, ten minitablets were dissolved in the mobile phase of acetonitrile/phosphate buffer pH 2.2 (50/50) and filtered through a 0.45-micron polypropylene membrane filter before injecting 20 microliters. The investigations were performed in triplicate on a Nucleosil RP-18 column (240 x 4 millimeters, 5-micron pore size) at a temperature of 30°C and a flow rate of 0.7 ml/min. The wavelength to measure the absorption was set to 220 nanometers.

To determine the stability of the enalapril maleate ODMTs, the following critical quality attributes were measured: tensile strength, API release, and disintegration time. The batches were stored in polyethylene bags under ambient conditions, with unprotected samples also tested under accelerated stability conditions of 40°C/75 percent relative humidity following Q1F stability guidelines of WHO [10]. The batches stored under ambient conditions were analyzed after five, six, and seven months, while the samples stored under accelerated conditions were analyzed after one, two, and three months. The tablet properties are shown in Table 2. The dissolution measurements are shown in Figure 2.

The results show that it is possible to obtain sufficiently hard enalapril maleate ODMTs at low compression force. The CU of the ODMTs showed an AV ≤ 15, which is within the specification requirement. The formulation’s mass variation complied with the Ph.Eur.

Over the stability test period, the ODMTs’ disintegration time changed slightly under both storage conditions. However, both initial and post-stability measurements showed that the enalapril maleate minitablets fulfilled both the Ph.Eur. disintegration limit of 180 seconds and the FDA disintegration limit of 30 seconds.

This study demonstrates that low-dose enalapril-maleate orodispersible minitablets can be successfully produced by direct compression using agglomerated isomalt as a filler-binder.

References


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