In this edition of *Eye on Excipients*, researchers present the results of a study that examined how isomalt can be used as a carrier for liquid APIs in solid oral dosage forms.

Many active pharmaceutical ingredients (APIs) can be formulated into either liquid or solid oral dosage forms. A major advantage of liquid dosage forms is that the API is already dissolved and generally absorbs more quickly *in vivo*. Solid dosage forms, on the other hand, have the advantage of not requiring preservatives and are generally more stable and easier to handle. A liquisolid is a tablet or powder with a liquid API absorbed into a solid carrier excipient in an effort to combine the advantages of both liquid and solid dosage forms.

Companies have successfully formulated liquisolids to enhance the bioavailability of poorly soluble APIs such as carbamazepine [1], fenofibrate [2], and hydrochlorothiazide [3]. To create the liquisolid, the API is dissolved or suspended in a suitable non-volatile liquid and then blended with porous excipients to create a free-flowing, compactable dry powder [4]. The resulting liquisolid system has an enhanced dissolution profile due to the increased surface area, increased aqueous solubility, and improved wettability compared to a dry formulation of the same API.

However, formulating a liquisolid system presents certain challenges. Compared to the solid carrier, the liquid is virtually non-compressible, so the carrier must be able to absorb a sufficient amount of the liquid while retaining compactability and flowability. In addition, the liquid absorption must be strong enough to prevent leaking during tableting or stability testing but not so strong as to prevent adequate dissolution.

Companies frequently use dibasic calcium phosphates, magnesium aluminometasilicates, and silicon dioxide to convert liquid APIs into free-flowing powders because the porous structure of these excipients provides a large specific surface area.

<table>
<thead>
<tr>
<th>Material</th>
<th>Dynamic viscosity (cP)</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linseed oil</td>
<td>30</td>
<td>Mühle Schlingemann</td>
</tr>
<tr>
<td>Simethicone G7-2243 LVA</td>
<td>440</td>
<td>Dow Corning</td>
</tr>
<tr>
<td>Simethicone antifoam C100EP</td>
<td>2,450</td>
<td>KCC Europe</td>
</tr>
<tr>
<td>galenIQ 721 (Isomalt EP, USP-NF, JP)</td>
<td>NA</td>
<td>Beneo-Palatinit</td>
</tr>
</tbody>
</table>

**Figure 1**
Crystal shapes of isomalt constituents
a. GPS crystal
b. GPM crystal

**Table 1**
Materials

*Oliver Luhn and Joerg Bernard
Suedzucker*

*Michael Black and Maj-Britt Cepok
Beneo-Palatinit*
for API absorption. However, these materials are not readily water soluble, and for many solid dosage forms, fast dissolution in aqueous media is a decisive requirement. For example, with chewable or compressed lozenge tablets, where taste and texture play an important role, a water-soluble filler-binder with pleasant organoleptic properties is the excipient of choice.

Isomalt is a common example of such a filler-binder. In comparison to other polyols, isomalt offers a remarkable sensorial profile, including a sugar-like sweet taste and a pleasant mouth feel. It is non-cariogenic and has a low glycemic index. Companies frequently use isomalt to manufacture powder sachets, compressed lozenges, and chewable and effervescent tablets due to its high compactability and ease of use [5]. The study described here evaluated a direct compression type of isomalt to determine its suitability as a solid absorbent for liquisolid formulations.

Materials and methods

The materials used in the study are listed in Table 1. Chewable tablets were manufactured by blending the isomalt with 7 percent by weight (w/w) of each liquid component using a high-shear granulator and then the whole quantity of liquid was added in one step to the powder bed. The mixture was blended at 250 rpm for 180 seconds to create a homogeneous blend.

Tableting. Tablets were produced immediately after the blending step on a full-scale and fully instrumented, 24-station tablet press (Fette type P1200iG) using a 12-millimeter concave punch. The press speed was adjusted to produce 30,000 tablets per hour. No pre-compression step was used. Tablet hardness was adjusted in two steps between 60 and 110 newtons. The target tablet weight was 600 milligrams.

Tablet mass uniformity and friability

The mass uniformity of the tablets was characterized according to European Pharmacopoeia (Ph. Eur.) 2.9.5. Friability was analyzed according to Ph. Eur. 2.9.7.

Results and discussion

Surface characteristics. Isomalt is a blend of the diastereomers 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (GPM) and 6-O-α-D-glucopyranosyl-D-sorbitol (GPS). Each of these two components has a distinct crystal shape, as shown in the SEM images in Figure 1. The material consists of agglomerated primary particles with an average particle size of 1 micron that contain crystallites with a median particle size of 0.1 micron [6].

The SEM image of direct-compression-grade isomalt in Figure 2 reveals a sponge-like structure with a multitude of cavities. Also, the GPM and GPS crystals don’t interlock seamlessly, which creates additional void space. Liquid APIs can be absorbed onto the surface and into these cavities and void space.

Compactability. Tablet hardness increased gradually with increased compression force, as shown in Figure 3. The compression forces applied were well below the punch limit of 54 kilonewtons. Neither capping nor adherence to the tablet punches were observed.

Tablet friability and mass uniformity. Tablet mass uniformity and tablet friability complied with pharmacopoeial requirements, as evidenced by the data in Table 2.
Conclusion

This study demonstrated isomalt to be a convenient carrier for liquid APIs in the manufacture of direct-compression chewable tablets. Linseed oil and two simethicone fluids with different viscosities were each loaded at 7 percent w/w onto a direct compression type of isomalt in a simple blending process. The loaded isomalt showed suitable flow properties for tableting in an industrial-scale rotary tablet press equipped with a force feeder. The tablet hardness yield was excellent. Both tablet mass uniformity and friability complied well with pharmacopoeial standards.

Formulators must be aware that limitations in blend flowability and compactability will quickly arise once the liquid component in the liquoriskid exceeds a certain concentration. In such cases, it’s recommended that the isomalt be blended with one of the more porous carrier excipients mentioned in this article’s introduction.

This will allow the tablet to maintain the excellent sensorial properties of the isomalt but improve absorption. T&EC

References


Oliver Lubn is head of pharmaceutical technology and Joerg Bernard is head of food and non-food technology at Suedzucker AG, Wormser Strasse 11, 67283 Obrigheim (Pfalz), Germany (www.suedzucker.de, 49 621 421 0). Michael Black is head of sales for pharma and Maj-Britt Cepok is product manager for pharma at Beneo-Palatinit GmbH, Maximilianstrasse 10, 68165 Mannheim, Germany (www.beneo.com, 49 621 421 150).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mean tablet hardness (newtons)</th>
<th>Tablet friability (percentage) n=25</th>
<th>Tablet mass (milligrams) n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>galenIQ 721 + 7 percent linseed oil</td>
<td>66</td>
<td>0.5</td>
<td>Mean = 600 Minimum = 591 Maximum = 609</td>
</tr>
<tr>
<td></td>
<td>108</td>
<td>0.3</td>
<td>Mean = 599 Minimum = 576 Maximum = 612</td>
</tr>
<tr>
<td>galenIQ 721 + 7 percent simethicone Q7 L2243 LVA</td>
<td>72</td>
<td>0.5</td>
<td>Mean = 604 Minimum = 585 Maximum = 605</td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>0.4</td>
<td>Mean = 603 Minimum = 590 Maximum = 609</td>
</tr>
<tr>
<td>galenIQ 721 + 7 percent simethicone antifoam C100EP</td>
<td>60</td>
<td>0.5</td>
<td>Mean = 599 Minimum = 591 Maximum = 606</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>0.4</td>
<td>Mean = 598 Minimum = 590 Maximum = 605</td>
</tr>
</tbody>
</table>