Orally dispersible powders, dry syrups and dry suspension formulations are entering the pharmaceutical market more and more these days. In most cases, these dosage forms are formulated within the life-cycle management of an existing active pharmaceutical ingredient (API), but they are also becoming an attractive option for new chemical entities (NCEs).

Consumers and patients appreciate the benefits of such formulations – notably packaging convenience, taste and ease of use. Moreover, direct orally dispersible powders represent an alternative to liquid formulations, for example in paediatric and geriatric patient groups. With a total sachet weight of usually between 1 and 1.8 grams, dispersible powders or dry suspensions provide ample volume for the API, together with a drug carrier bulk excipient and flavouring components; this is in contrast to tablets which are limited in their size and weight – and thus more difficult to formulate.

Another reason for the rapidly growing market for powder formulations is the availability of new filler excipients that act as the ideal drug carrier for this dosage form and enable the formulation to be developed and produced more easily. Isomalt, a sugar alcohol (disaccharide alcohol) derived from sugar beet, is one such excipient. It has been widely used for more than 20 years as a bulk sweetener in sugar-free cough drops, confectionery and nutraceutical products. With physical and chemical modifications, a tailor-made pharmaceutical isomalt (galenIQ™) has been developed for applications in the field of oral solid-dosage forms.

While agglomerated isomalt is known for its excellent compactability and very low hygroscopicity, other important properties make it a highly functional filler-binder for use in almost all drug formulation processes such as direct compression, wet granulation, fluid bed agglomeration, roller compaction and extrusion. However, the most favoured way of preparing a drug formulation is dry blending of all ingredients without further processing: this method results in considerable time-savings and is very cost-effective. Dry blends may be used for compression or compaction processes, or used directly in the form of sachets of powder. This ‘sachet’ trend can already be noticed in the market, since line extensions of well-established brands are often formulated as sachets and stick packs. Sachets thus represent both a convenient and fashionable form of drug delivery.

The Ideal Bulk Excipient
When developing a dry powder formulation for oral application, a bulk excipient should ideally fulfil the following requirements:

- Excellent flowability
- High physical stability during the process of mixing
- High dilution potential and content uniformity
- Specific morphology to prevent segregation
- Chemical stability
- Low hygroscopicity
- Pleasant, sweet taste
- Suitability for all patients
- Economical to manufacture

The development of a tailor-made isomalt as a pharmaceutical excipient has opened up the market for dry powder blend formulations.
In addition, the bulk excipient should ideally also be directly compressible. This would enable the use of the same dry powder in the formulation of orally dispersible powders or tablets (for example, chewables) without any major changes in the formulation. All in all, the bulk excipient should allow line extensions of a drug product to be easily developed without changing the major components.

In the following, pharmaceutical-grade isomalt (gelenIQ™) will be discussed in terms of each of the above-mentioned requirements. The product range includes different qualities suitable for various solid dosage forms; however, the discussion will focus on agglomerated grades, which are suitable for direct dry blending.

**Powder Characteristics and Flowability**
Looking at excipients from a manufacturing point of view, it is important to have particle sizes fulfilling specific requirements that are essential for the production process. For example, there should be only a minimum of dusting within the production area as this may hamper proper sealing of the package and thus cause a loss of product. Furthermore, flowability and homogeneity have to be correct at all stages of manufacture. Agglomerated grades provide very good flowability with low dust formation and a morphology that helps to ensure homogeneity, as well as preventing segregation.

Agglomerated isomalt is a white, odourless and water-soluble material. In tests, different grades of isomalt have shown excellent flowability and powder characteristics, differing only in terms of solubility (see Table 1).

**High Dilution Potential and Content Uniformity**
Maybe the biggest challenge for all dry blends is homogeneity. Since different qualities of excipient show different morphologies, they differ in their behaviour with respect to content uniformity and segregation. To achieve good results with dry blends, excipients should have a large and possibly rough surface structure; this helps to prevent segregation when blended with APIs having a large particle size. Cavities on the surface provide the possibility to hold and carry micronised APIs. Ideally, the formulation of powder blends with different

| Table 1: Typical powder characteristic values measured for galenIQ™ 720 and 721 |
|-------------------------------|-------------------------------|
| Solubility in water at 20°C (g/100g) | 25 | 42 |
| Bulk density (g/l) | 420 | 420 |
| Tapped density (g/l) | 470 | 470 |
| Hausner factor | 1.12 | 1.12 |
| Carr index | 10 | 10 |
| Angle of repose | 33° | 31° |
| Flowability (s/100g) (orifice d = 6mm) | 55 | 57 |

**Excipients for pharmaceutical applications**
Tereos Syral is applying a new quality system of product identification for its range of excipients and setting up extended documentation, in conformity to the Ph. Eur. and the USP-NF monographs.

- MERITENA® PHARMA maize starch
- MYLOSE® PHARMA glucose syrup
- MALDEX® PHARMA maltodextrin
- MERITOSE® PHARMA glucose monohydrate and anhydrous
- MERITAB® PHARMA DC-dextrose
- MERITOL® PHARMA sorbitol liquid
- MERISORB® PHARMA sorbitol powder
- MALTILITE® PHARMA maltitol liquid and powder

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API particle sizes should be facilitated – be it 100 mesh or 10µm, or both at the same time.

Agglomerated isomalt provides such a morphology (see Figure 1, page 68). The outer phase of the agglomerate shows a rough surface, and when magnified further, the primary crystals that are used to manufacture the agglomerated grades also show a rough surface and cavities. This is due to the fact that isomalt consists of two components – 1,6-GPS and 1,1-GPM (see below) – which disturb each other during the crystallisation process. The end-result is a non-structured granule; a crystal form, as would occur with other sugars or polyols, is not produced – a significant difference that is important for powder blends.

Determination of Blend Uniformity

In order to determine the blend uniformity of the API, a powder mix using agglomerated isomalt as a carrier was investigated. The disaccharide alcohol was blended with different concentrations of a reference substance (1, 20 and 40 per cent Chinolin/Quinoline yellow; d90 10µm) for 30 minutes in a lab-scale bin blender. In order to measure the homogeneity of the mixture, samples were taken at determined time intervals at different sampling spots and the concentration was measured by spectral photometric analysis. Figure 2 shows the relative standard deviations (rsd) over the time. Blend uniformity was reached after a short time and remained throughout further mixing without segregation.

The very porous and large specific surface areas enable the incorporation of high concentrations of active ingredients, without compromising the flow properties of the final mixture. At the same time, these surface structures prevent segregation even in very low dose blends during the whole process, thus ensuring the homogeneity of the mixture and subsequently the required content uniformity.

The above results have been adopted successfully into formulations with APIs of various particle sizes (for example, low-dose theophylline monohydrate, glibenclamide and high-dose ibuprofen, paracetamol, ascorbic acid).

High Physical Stability During the Mixing Process

Agglomerated isomalt as an excipient exhibits high stability, even if a high shear blending process is used. Table 2 shows that there is no significant change in particle size over blending time, and flowability is not affected.

Chemical Stability and Low Hygroscopicity

Besides mechanical, the chemical stability of the excipient also plays an important role when formulating drugs. Isomalt is manufactured in a two-stage production process. First, sucrose is converted through an enzymatic transglucosidation to the disaccharide 6-O-α-D-glucopyranosyl fructose (isomaltoolose) – a significantly more stable but reducing compound. Second, the hydrogenation of isomaltoolose leads to the stereoisomer disaccharide alcohol 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (1,1-GPM dihydrate) and 6-O-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) in an approximate equimolecular mixture. The ability to shift the ratio between GPM and GPS allows grades with different solubilities. Based on its stable chemical structure, it does not react with other components – for example, with amino acids to form Maillard reaction products. Moreover, having very low hygroscopicity, it provides optimal protection even for moisture-sensitive APIs.

More Than Just a Sweet Taste

Besides the physico-chemical requirements for direct oral applications, the excipients should have a natural, sweet taste with a prolonged release and dissolution kinetics that create a pleasant ‘mouth-feel’ in order to formulate an attractive final product for end-users. Facilitating formulations for direct, orally applicable powders also means that the bulk excipient should help in the design of a taste profile that is acceptable to the patient.

Being derived from pure sugar beet, isomalt has a well-balanced, sugar-like sweet taste. In addition, it has certain capabilities to help suppress the bitter impact of other ingredients. Combined with the right flavours and other masking components, it provides an excellent sweet taste platform. In general, a discussion with specialists in

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**Table 2:** Particle size distribution of galenIQ™ 720 prior to and after 2 and 15 minutes of mixing, utilising a high shear plough share mixer at 120 rpm.

<table>
<thead>
<tr>
<th>Prior to mixing</th>
<th>After 2 minutes of mixing</th>
<th>After 15 minutes of mixing</th>
</tr>
</thead>
<tbody>
<tr>
<td>d5</td>
<td>63µm</td>
<td>43µm</td>
</tr>
<tr>
<td>d50</td>
<td>239µm</td>
<td>224µm</td>
</tr>
<tr>
<td>d95</td>
<td>513µm</td>
<td>501µm</td>
</tr>
</tbody>
</table>

**Figure 2:** Blending of galenIQ™ 720 with colourant (1, 20 and 40 per cent). Relative standard deviations as a function of blend time.
sweeteners and flavours is recommended before formulation work is started.

As the dosage form remains in the mouth during dissolution, the excipient should be non-cariogenic. The US FDA allows manufacturers of sugar-free isomalt-containing products to make the health claim “Does not promote dental caries”, if those products do not reduce plaque pH to less than 5.7 for up to 30 minutes after consumption. Isomalt also shows a very low glycaemic response, making it a highly suitable excipient for formulations taken by diabetics.

**Conclusion**

The development of suitable excipients has enabled pharmaceutical companies to formulate powder blends such as orally dispersible powders or dry syrups. Due to their convenience, these dosage forms have a high level of consumer acceptance. Isomalt fulfils the criteria required of a bulk excipient for use in the formulation of any kind of powder blend: its excellent flowability and mixibility help to maintain homogeneity and content uniformity; its physico-chemical stability supports drug functionality; and its physiological benefits and organoleptic characteristics make it the preferred choice for the formulation of powder dosage forms. Its popularity with companies that manufacture dry powder blends is already reflected in its use in several marketed products.

Bodo Fritzsching graduated as a Nutrition and Equipment Technology Engineer from the University of Applied Sciences, Trier (Germany), in 1992. He subsequently joined Palatinit GmbH, a subsidiary of Südzucker AG, as a Technical Services Manager to advise the food and pharmaceutical industry in Europe about properties and applications of isomalt. Since 2005, Bodo has headed up the Pharma Sales Unit of BENEO-Palatinit GmbH as Sales & Technical Service Manager, Pharma. The Unit is dedicated to the marketing of BENEO-Palatinit’s pharmaceutical grade isomalt product range, galenIQ™.

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