

Added Functionality Excipients: An Answer to Challenging Formulations

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Added functionality excipients **facilitate the development of novel drug delivery methods** and improve processing techniques.

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Tablets and capsules are preferred drug delivery vehicles because they can be precisely dosed, easily manufactured and packaged on a large scale, and can contribute to good patient compliance. Over the years, significant advances in the manufacturing processes of oral solid dosage forms have occurred, including the transition from tablet preparation by wet granulation to direct compression. The development of various added functionality excipients (AFEs), which are used to achieve formulations with desired end-effects, is equally important. The majority of excipients used in the manufacture of solid oral dosage forms have existed for the past two to three decades, many of them continue to be used today for large-scale tablet and capsule manufacturing.

Obtaining regulatory approval for the use of new excipients and breaking the tradition of conventional formulation development have been two major hurdles in convincing formulators to incorporate new excipients into their for-

mulations. Despite these challenges, many new AFEs have been successfully introduced and are used in the pharmaceutical industry to date.

Compared with existing excipients, the improved physical, mechanical, and/or chemical properties of such AFEs have helped solve formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation (1).

The use of conventional tablets is challenging to pediatric, geriatric, and uncooperative patients who may have difficulty swallowing them. Similarly, swallowing tablets is problematic when water is unavailable or when patients have a persistent cough or a gag-reflex.

These problems have been addressed by the recent introduction of orally disintegrating tablets (ODTs), which also are known as fast-melt, quick-dissolving, mouth-dissolving, or orodispersible tablets (2). Upon placement on the tongue, these tablets rapidly absorb saliva and disperse or dissolve within 10–45 s. The dispersed tablet can then be swallowed easily without water. Many bulk excipients commonly used for conventional tablets do not fulfill the development requirements of an ODT, thus necessitating the use of specific excipients and technologies to mask the drug's

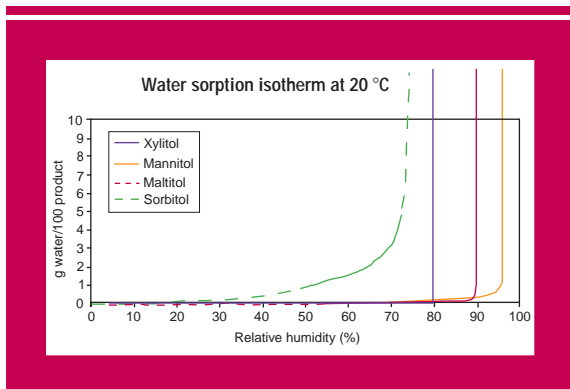


Figure 1: Moisture sorption profiles of various excipients.

unacceptable taste and improve the ODT's overall mouthfeel.

An ideal bulk excipient for ODTs should have the following properties:

- disperses and dissolves in the mouth within a few seconds without leaving any residue
- masks the drug's offensive taste and offers a pleasant mouthfeel
- enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature
- preferably directly compressible and yields sufficiently robust tablets to withstand manufacturing, packaging, and transportation, yet disperses quickly on the surface of the tongue.

ODTs are manufactured using a wide variety of technologies such as lyophilization, direct compression, granulation, spray-drying, molding, and the cotton candy process (1). The quick dispersing effect is generated by the excipient's ability to absorb water quickly, thus enabling the water to be wicked away rapidly to the tablet's core. A tablet's rapid dispersion on the surface of the

tongue also is facilitated by the use of a superdisintegrant such as crospovidone, sodium starch glycolate (SSG), or croscarmellose. Although crospovidone typically is used for ODT formulations, the use of SSG may be advantageous in some ODT technologies and platforms, especially when the final dosage form is small or when wet granulation is used. One advantage of incorporating SSG into the intragranular phase during wet granulation is its ability to act as a binder when wet and regain its superdisintegrant efficacy upon drying the granules.

Most commercial ODTs have been developed using mannitol as the bulk excipient of choice. Mannitol is overwhelmingly preferred over lactose because of its extremely low hygroscopicity (see Figure 1), excellent chemical and physical drug compatibility, good compressibility, better sweetness, and relatively slower dissolution kinetics. Although both excipients have relatively low aqueous solubilities compared with other excipients (see Figure 2) that have acceptable palatabilities, the dispersibility of a bulk excipient is more important than its water solubility for a successful ODT formulation. Many of the initially marketed ODTs were prepared by the wet granulation of mannitol followed by direct compression. However, added functionality mannitols are now available to

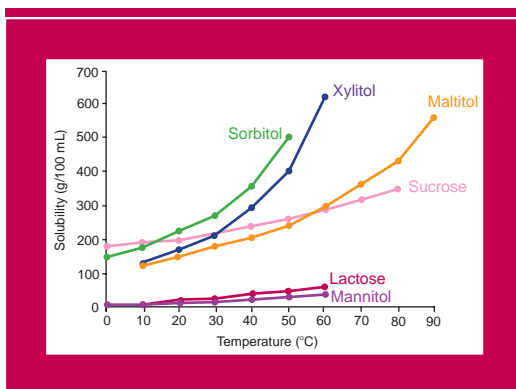


Figure 2: Aqueous solubility profiles for various excipients.

simplify the process of ODT manufacturing by direct compression.

Added functionality mannitols for ODTs

ODT formulators prefer to use a directly compressible mannitol, which enables the preparation of robust tablets that can withstand processing and transportation. Specially textured, directly compressible, spray-dried, or granulated mannitol excipients have been designed to meet these needs. Processing these excipients under defined manufacturing conditions gives them a highly porous and friable exterior structure (see Figure 3). Upon compression, the structure crumbles into finer particles, which fill the interstitial spaces between larger porous particles. Textured excipients also provide a satisfactory mouthfeel and are suitable for use in the preparation of harder ODTs by direct compression at low pressure.

One major drawback of most currently marketed ODTs is their requirement for specialized and expensive packaging to protect them

during transportation and handling. Furthermore, the consumer must follow specific instructions to remove fragile tablets from specialized blister packs. For example, the consumer is instructed to peel off the blister pack's aluminum foil gently and not to push the tablet through for removal. Sometimes the entire blister pack is sealed in a plastic pouch for added protection and to ensure that the tablets retain their quick dispersibility even after expo-

sure to unfavorable humidity and temperature conditions. In addition, the high friability of these tablets does not allow them to be packaged and dispensed in regular bottles. These challenges could be addressed by using a compression binder such as a cellulose derivative in addition to the mannitol powder. Another option is the development and optimization of coprocessed mannitols that exhibit a similar flowability and compressibility to the directly compressible mannitols and impart low friabilities to the final dosage forms. Thus, the need for specialized packaging is eliminated.

Coprocessing mannitol with a



Figure 3: SEM micrographs of textured mannitols.

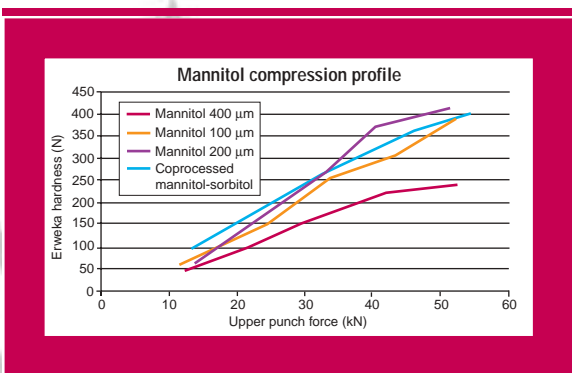


Figure 4: Tableting compression profile for mannitol.

small amount of other polyols is one way to create such an excipient. In the case of sorbitols, the presence of interlocking crystals that are generated using specific manufacturing conditions enable strong binding and result in a more robust tablet at low compression forces. In addition, the mannitol provides the required dispersibility and mouthfeel for a successful ODT formulation. The tableting compression profile depicts the tablet hardness generated using textured mannitols of various mean particle sizes and the coprocessed excipients (see Figure 4). The friability versus compression force profile indicates that the

tablets exhibit significantly low friability, even at a low compression force (see Figure 5). In addition to contributing to the robustness of tablets, the sorbitol also imparts a sweet taste and a unique texture to the mannitol, thereby improving the ODT formulation's mouthfeel. The low level of sorbitol required to obtain an added functionality mannitol does not affect its pharmaceutical conformity to *USP-NF* standards, thus offering an advantage with respect to the regulatory requirements.

The market for ODTs is projected to increase from \$400 million in 2000 to \$1 billion before 2005 (3). A major focus for future ODT development will be improving their cost-effectiveness. Although mannitol will continue to be used as an excipient of choice, AFEs can help greatly when developing more-robust and less-friable ODTs. Dispensing these tablets into conventional bottles will eliminate the need for specialized packaging, thus providing significant cost savings.

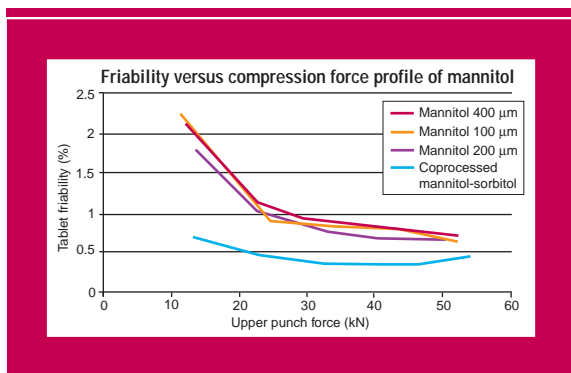


Figure 5: Friability versus compression profile for mannitol.

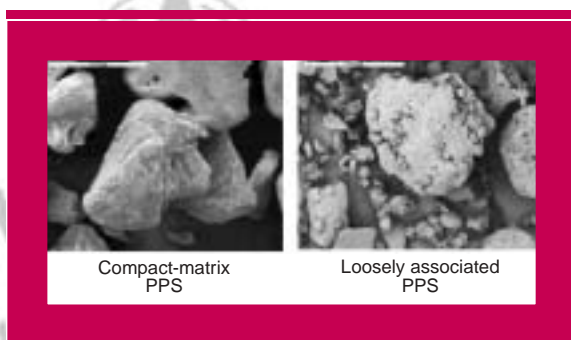


Figure 6: SEM micrographs of pregelatinized starches.

Added functionality partially pregelatinized starches

AFE not only facilitate the development of novel drug delivery technologies such as ODTs, but also help to improve the processing of commonly used excipients such as pregelatinized starches. PGSs are commercially available in fully pregelatinized and partially pregelatinized starch (PPS) grades depending on the degree of starch gelatinization. PPSs are used as fillers in hard gelatin capsules (5–75%), binders in wet granulation tableting (5–20%), disintegrants in tablet formulations (5–10%), and in direct compression tableting (4). However,

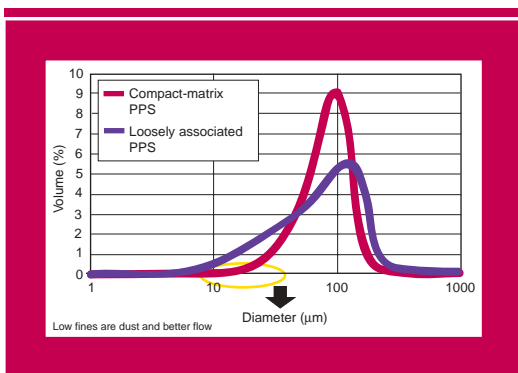


Figure 7: Particle-size distribution of PPSs.

many capsules and tablets that contain currently marketed PPSs as fillers exhibit specific properties that are disadvantageous with respect to increased dust generation during processing and slower drug dissolution.

Altering the composition of the starch and optimizing the gelatinization process can add functionality to PPSs and address some disadvantages of using existing PPSs. SEM micrographs of PPSs with various compositions and methods of manufacturing indicate a significant variation in the matrix structure of the starch grains. PPS particles comprising a compact, embedded matrix are significantly less friable than those made of loosely associated PPS particles (see Figure 6).

Another important processing change for developing an added functionality PPS is to have better control of its particle-size distribution. The decreased friability of a compact-matrix PPS and its relatively narrow particle-size distribution ensures a reduced level of fine particles (see Figure 7). This change ultimately helps reduce dust generation during tableting or capsule filling and imparts improved flow properties (see Table I).

The changes in the composition and particle-size distribution of PPS particles will ultimately influence the dissolution kinetics of the final oral dosage forms. Capsules prepared using a compact-matrix PPS containing a slow-dissolving drug such as acetaminophen exhibit a significantly rapid dissolution of acetaminophen compared with similar capsules prepared using a loosely associated PPS (see Figure 8). Certain changes in the composition of the PPS result in low cold-water solubility and consequently a minimal viscosity increase upon contact with water, and hence a reduced resistance to drug dissolution.

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Table I: Flow properties of PPSs.

Parameter	Compact-matrix PPS	Loosely associated PPS
Mean particle size	100 µm	90 µm
Bulk density	0.64 g/mL	0.61 g/mL
Tap density	0.81 g/mL	0.79 g/mL
Flow (EP method)	5 s	7 s
Angle of repose	35°	41°

Interestingly, the rapid dissolution of acetaminophen in the presence of a compact-matrix PPS occurs in a pH-independent manner. Rapid and pH-independent drug dissolution is advantageous because it may qualify a new formulation for a biowaiver on clinical testing requirements, according to FDA, Center for Drug Evaluation and Research guidelines (5).

A better understanding of the manufacturing variables and market demand has led to the development of specific excipients that enhance the efficiency of pharmaceutical formulations. However, continued globalization in the pharmaceutical industry has increased regulatory concerns that products developed in one market could be used in other parts of the world. To facilitate the global development of new pharmaceutical products, formulators must pay close attention to the multicompendial conformity of excipients.

Various regulatory issues such as genetically modified sources of excipients and their identity-preserved status also are gaining importance. Thanks to the commitment and expertise of excipient manufacturers, AFEs are now playing an important role in addressing the challenges posed by difficult formulations. With the increasing popularity of these ex-

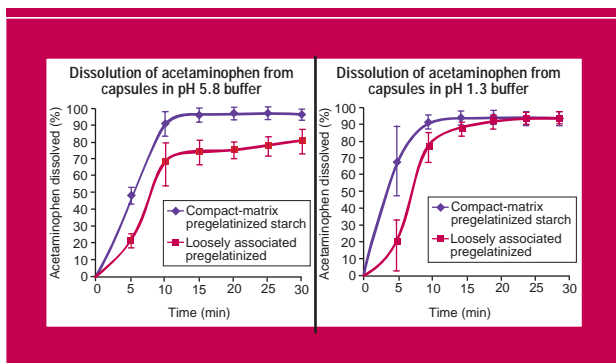


Figure 8: Rapid, pH-independent dissolution of acetaminophen from a compact-matrix pregelatinized starch.

ipients, it is critical that pharmaceutical developers select a reliable excipient supplier with a broad range of products and technical expertise as well as a significant global presence.

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