

eye on excipients

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In this edition of the column, Hans Huttinga of Kerry Bioscience - Sheffield Pharma Ingredients discusses how excipient manufacturers can help their customers prosper despite the shrinking pipeline of APIs and other unfavorable trends. His company's products serve as examples of the valuable roles excipients can play.

In June, PricewaterhouseCoopers published the latest in a series of industry discussion papers, *Pharma 2020: Virtual R&D—Which path will you take?* [1] It cited several broad trends and challenges facing the pharmaceutical industry. It also repeated an oft-cited concern: New molecules have been in scarce supply for many years. In 2007, for example, the FDA approved only 19 new molecular entities and biologics—fewer than in any year since 1983 [2].

Meanwhile, the patents protecting blockbuster molecules developed during the 1980s and 1990s are expiring, permitting generic manufacturers to cash in on the innovators' research. US research firm Sanford C. Bernstein estimates that, because of competition from generics, the top ten pharmaceutical companies will lose between 2 and 40 percent of their revenue between 2008 and 2012 [2].

At the same time, the cost of developing new molecules has soared. At the 2006 Drug Discovery Technology Conference, it was estimated that the cost of producing a successful new drug could now exceed \$2 billion [3].

A diverging response

In response to these trends, pharmaceutical companies are radically adapting their businesses to survive. Two different markets are emerging: one valuing partnership and innovation, the other seeking competitive prices coupled with consistent supply. In both markets, however, the players realize that they need to market their products more precisely, addressing niches for specialist treatment, establishing clear points of differentiation, and taking closer notice of end-user preferences such as appearance, ease of consumption, and novel convenience functionality.

Imparting these kinds of characteristics to drug products relies not on active pharmaceutical ingredients (APIs), but increasingly on creative and sophisticated use of excipients, whose active role in modern drug products has moved beyond their traditional role as fillers and binders.

Excipients have the potential to extend the functionality of oral solid dosage formulations (OSDFs) through, for example, modified release and controlled absorption, facilitated by tablet coatings. Excipients can also enable manufacturers to produce more attractive and acceptable OSDFs. Orally disintegrating tablets (ODTs) or special coatings, for example, ease swallowing.

When direct-tabletting lactose was invented in the 1960s, it ushered in a new era of effective direct-compression (DC) manufacturing. Since then,

other DC excipients have played a role in controlling manufacturing costs because DC eliminates several process steps. Today, compared to wet granulation, DC costs 50 percent less in labor and up to 18 percent less in excipient materials. Plus, DC formulations use only half as much processing equipment, which means less cleaning and validating. My company has manufactured pharma-grade lactose for many years and holds the original patent for an anhydrous direct-tabletting excipient.

Today, more and more customers are seeking ways to extend patent protection for novel molecules by improving existing dosage formulations or by creating new formulations. That means sustained interest in excipient systems for creating custom fast-dissolving tablets, such as ODTs. Our approach centers on a free-flowing lactose-based functional powder that is DC-ready. Customers only need to add the API and a flavor (or a taste-masked API), plus a lubricant (magnesium stearate), to begin making ODT tablets using standard DC techniques [4]. Two other systems [5, 6] are for making fast-dissolving hard tablets.

Why ODTs?

ODTs provide several benefits to pharmaceutical manufacturers and end-users. ODTs are easy to manufacture and cost effective for pharmaceutical manufacturers. Creating an ODT formulation can be very

straightforward if you use a pre-formulated ODT excipient medium that requires only minimal processing. With a pre-formulation, there are fewer raw materials to buy and test. Plus, if the ODT ingredients are already resident in the relevant monograph and the overall product is itemized in the Drug Master Files, the regulatory process can be faster, meaning the product reaches the market faster. And, crucially, it's likely that pharmaceutical ODT manufacturers can proceed without entering into formal partnerships or getting licenses.

End-users also benefit. ODTs do not need to be swallowed with fluids and are easy to ingest. That makes them an ideal delivery system for people who can't or won't swallow conventional tablets. ODTs can make the API available fast and confer a smooth mouth-feel without a gritty texture. They can improve compliance among, for example, the mentally ill or physically disabled.

Finally, ODTs can reduce packaging costs. Generally poor tablet friability necessitates blister packaging, a significant additional expense. However, ODTs can be made with excellent hardness and friability that makes them suitable for less expensive packages.

Example: ODT system

The distinction between ODT and fast dissolution is based on an FDA guidance, which states that ODTs should exhibit an in vitro disintegration time of approximately 30 seconds or less, based on the US Pharmacopeia (USP) disintegration test method or an alternative [7].

Figure 1 shows how disintegration time corresponds to hardness for tablets manufactured using an ODT system. The ODT dissolves faster than starch or microcrystalline cellulose (MCC), making it suitable for use in formulations where those excipients delay dissolution. Figure 2 illustrates that the ODTs are robust enough for bottle packaging. Figure 3 illustrates the particle size distribution, with 150-micron-diameter particles predominating.

FIGURE 1

Tablet hardness vs. disintegration of an ODT system [4]

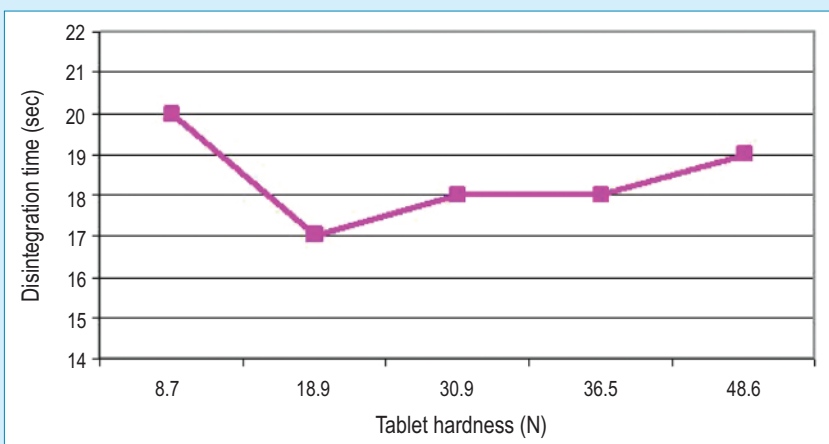


FIGURE 2

Tablet hardness vs. friability of an ODT system [4]

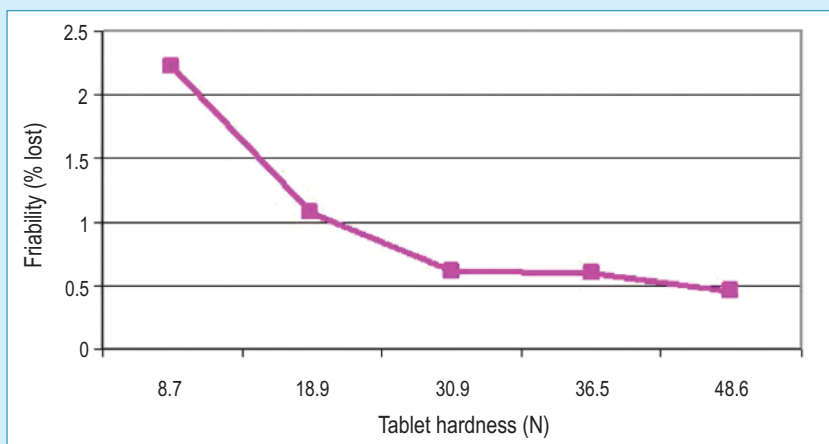
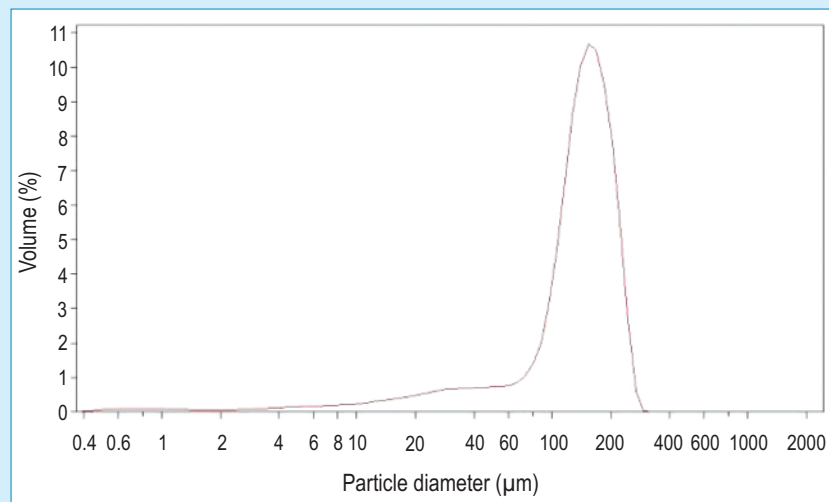


FIGURE 3

Particle size distribution of an ODT system [4]



Examples: Two fast-disintegrating systems

Not all APIs are suitable for ODT formulations, but fast-dissolving excipient systems are available for making hard tablets with fast disintegration (i.e., >30 seconds). In this case, specially processed lactose makes it possible to achieve hardness and friability similar to that of pure lactose at a price similar to MCC, but with faster disintegration. The systems can be tailored to suit standard-flow processes or high-velocity processes.

By adjusting the system formulation it is possible to achieve fast disintegration and standard tablet hardness in a standard-flow process using our fast-disintegration system or to achieve faster-than-standard disintegration and harder tablets in a faster-flow process using our high-velocity system. Figure 4 shows the relationship between compression force and hardness for tablets made using the two systems and those made with anhydrous lactose. Figure 5 shows the relationship between tablet hardness and disintegration time for the same three excipients. Figure 6 shows the relationship between friability and hardness for the three excipients. Figure 7 shows the particle size distribution of the fast-disintegration system, which mostly comprises particles with diameters of 200 microns; smaller particles are fairly widespread. Figure 8 shows the particle size distribution of the high-velocity system, which mostly comprises particles with diameters of 150 microns, but has a more exponential fall-off in the smaller particle diameters. Table 1 shows various flowability parameters for the three systems.

Challenges

ODTs and fast-disintegrating tablets aren't the only area where excipient suppliers can use their product expertise and accommodate specific needs to help clients. Another challenge is increased regulation and evolving business practices. One good example is the issue of so-called functional characteristics, which are

FIGURE 4

Tablet hardness vs. compression force

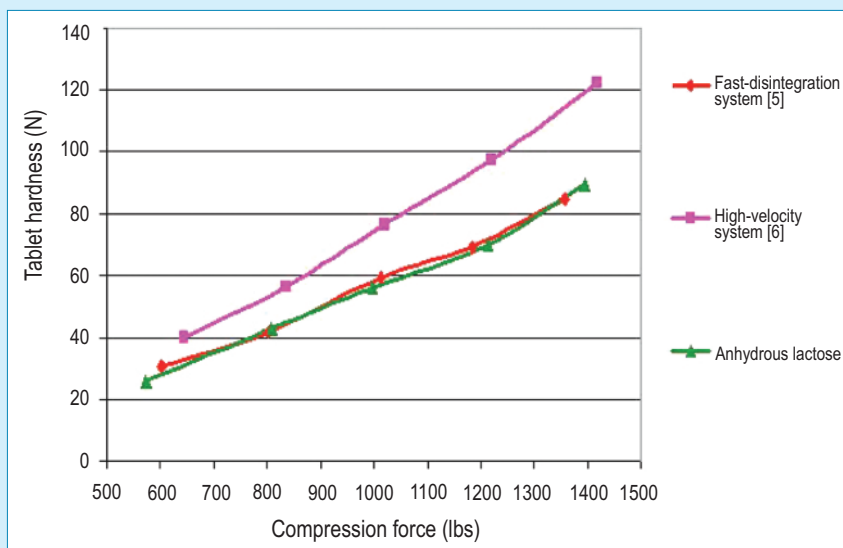
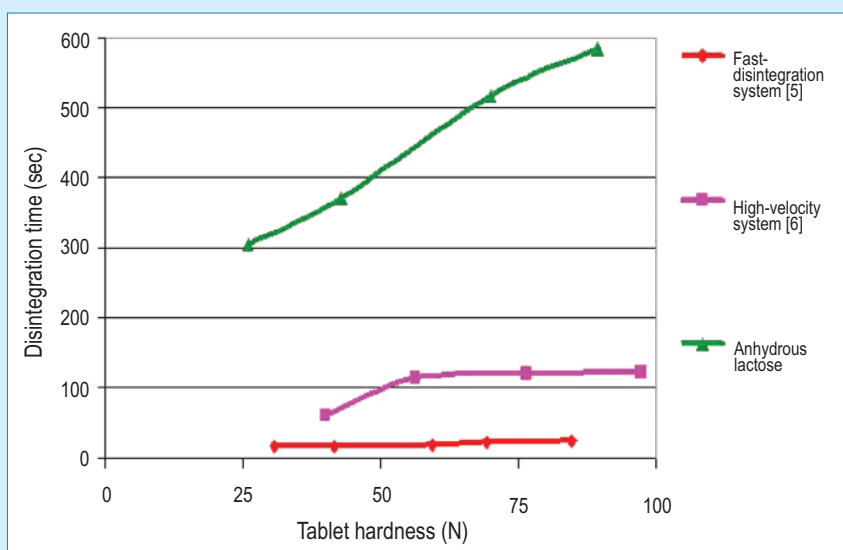


FIGURE 5

Tablet hardness vs. disintegration



Test method for the tableting systems

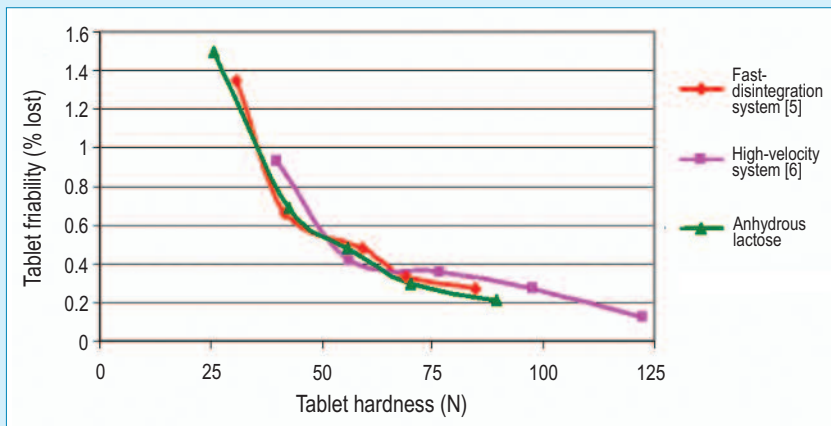
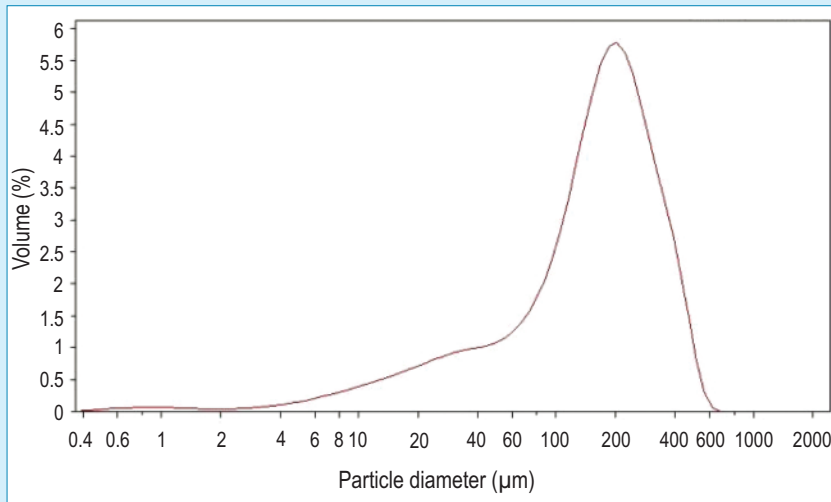
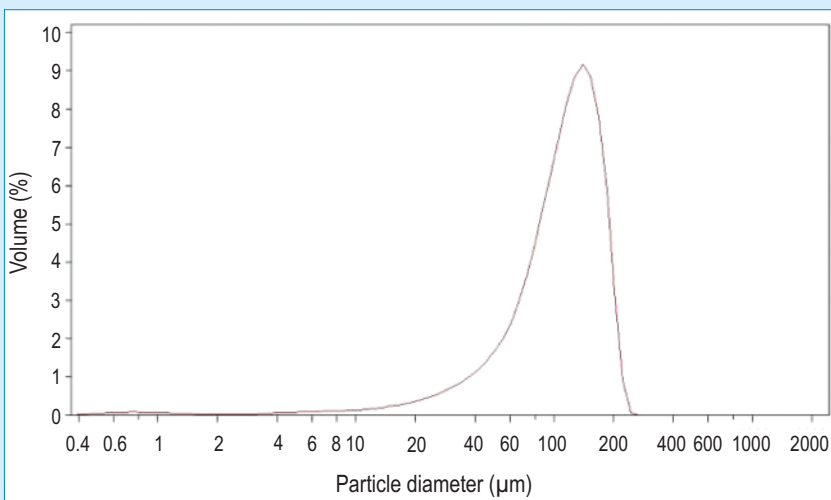
In the compaction stage, the tableting systems were blended for 5 minutes with 1 percent magnesium stearate and compacted on an instrumented ten-station rotary tablet press [9].

For compression and ejection force measurements, the press was fitted with load cells and software to automatically measure and record force.

For tablet hardness, an automated tablet tester [10] was used to measure the force required to break the tablet.

For the disintegration time, the apparatus was set according to procedure [701] of the USP/National Formulary XXIV (2006). Six tablets were added to the basket rack assembly. The immersion fluid contained e-pure water held at 36° to 37°C.

Disintegration time was taken at the time when all tablets were fully dissolved.

FIGURE 6**Friability vs. hardness****FIGURE 7****Particle size distribution of a fast-disintegration system [5]****FIGURE 8****Particle size distribution of a high-velocity system [6]**

much more difficult for companies to establish than it is to comply with pharmacopoeial standards.

In fact, identical excipients from different sources may have widely varying success in the manufacture and performance of a new drug formulation that requires specific functional characteristics. Some pharmaceutical manufacturers have sought to formalize functionality within drug product specifications. This is done, for example, in the form of functionality-related characteristics in a number of excipient monographs.

However, specifying functionality could present a significant cost challenge to the excipient industry. If functionality-related characteristics end up in pharmacopoeias, they will become regarded as compulsory tests for specific excipients in all dosage applications, even ones in which the specified parameter is not relevant (e.g., lactose particle size). There is also a risk of attempting to establish functional requirements of excipients that, in fact, are infeasible to produce.

GMP and confirmed provenance

A better solution is to place a greater reliance on current Good Manufacturing Practice (cGMP), which can be characterized as a move away from “inspecting in” quality to guaranteeing quality through manufacturing process design. Elements of cGMP include documentation and traceability; change control and customer notification; and contamination control.

In practice, cGMP is usually manifested as a much stronger line of communication between pharmaceutical manufacturer and excipient supplier. This ensures all expectations are completely understood and, through auditing supplier capabilities, provides control of the manufacturing process and provides confidence that specific functional requirements will be met.

There is a much greater emphasis on provenance in the wake of incidents like the Sudan I food dye crisis of 2003 and the 1996 Haiti tragedy, when more than 80 people died after taking a cough syrup that was contaminated with poor-quality glycerol

TABLE 1

Flowability

Product	Angle of repose (α)	Compressibility (Cair's index)	Flowability (g/sec)
ODT system [4]	31.87	16.84	6.30
Fast-disintegrating system [5]	35.44	28.60	4.10
High-velocity system [6]	26.23	10.75	7.49

[8]. It is no longer sufficient for excipient manufacturers to simply ensure the safety of their product as it leaves the factory. They must be certain the product will not be adversely affected by issues further down the supply chain, ending in possible litigation claims and loss of reputation.

Naturally this places a heavy burden on excipient manufacturers to acquire third-party endorsements. To indicate adherence with cGMP, US manufacturers can demonstrate compliance with CFR parts 210-211 or become an FDA Registered Drug Establishment dedicated to an ingredient such as lactose.

Additionally, for an animal-derived pharmaceutical ingredient, such as lactose, there has been additional scrutiny on provenance since the emergence of transmissible spongiform encephalopathies in the 1990s. Again, the onus lies on the manufacturers to prove they have taken all possible steps to ensure safety. Make sure your supplier of pharmaceutical-grade excipients is taking proper precautions, earning the industry-accepted certifications, and using validated processes to ensure complete traceability. Spec-

ifically for pharma-grade lactose, have makers avoided the use of higher-risk materials, such as rennet, in the whey used for production?

Pharmaceutical manufacturers are seeking partners prepared to share the burden of managing technical development, regulatory approval, and quality assurance within tight cost restrictions. All parties must embrace the market transformation to remain viable businesses. I recommend that you approach today's innovations with a collaborative mindset and a commitment to partnerships of complementary competence. If excipient makers can rise to the challenges that pharmaceutical companies are now presenting, the industry has a bright and exciting future.

T&C

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