excipients

Starter pellets: Materials, manufacturing methods, and applications

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This article summarizes the types of starter pellets available, how they are made, and how they are used in the pharmaceutical industry

A large variety of starter pellets—also called seeds, beads, nonpareils, micro-granules, and starter cores—can be used in tablets and capsules to meet formulation requirements. Usually, the goal of developing the multiparticulate final dosage form is to establish the desired dissolution profile, target a specific release location or time, and/or mask off-tastes. The benefits of multiparticulate formulations include:

- Reducing the intra- and inter-variability of the dosage form,
- Controlling the onset and duration of drug release,
- Delivering the active pharmaceutical ingredient (API) to distal sites within the gastrointestinal (GI) tract,
- Facilitating fixed-dose combinations forms,
- Time-shifting the release of API combinations, e.g., one releasing quickly and the other slowly,
- Using a single, basic pellet formulation and varying the dose by changing the number of pellets the tablet or capsule contains, and

- Adding variety to traditional sold dosage forms, including orally disintegrating tablets (ODTs), multiple-unit pellet system (MUPS) tablets, sachets, stick packs, and drinking straws for pediatric and geriatric use. Coated starter pellets can also be used in oral suspensions.

Pellets—typically 100 to 2,000 microns in diameter—are made by extrusion-spheronization, direct pelletization, prilling, and layering. For use in formulations, the pellets are first subjected to drug layering and coating using well-established techniques, including the Wurster process and other fluid-bed processes, powder layering, and other mechanical processes.

Naturally, the characteristics of the starter pellets determine how they will perform in these preparatory coating processes and in the final dosage form. While some characteristics may not seem critical in small-scale development (e.g., friability), those properties can strongly affect the product's success once it reaches commercial manufacturing. They can also affect the final product's cost structure. Table 1 lists some characteristics and how they affect the product [1].

TABLE 1

Effect of pellet characteristics on formulations [1]

Characteristic	Considerations
Size	Final dosage form, drug load, and processability
Particle size distribution	Dissolution profile, batch-to-batch uniformity
Surface area	Target drug load, film thickness, choice of binder, dissolution profile
Solubility	Processing (process time)
Hardness	Compression into tablets (MUPS)
Friability	Processing (process times and yield)
Inertness	Compatibility with API

In fact, as pellet-based formulations become more complex, the quality aspects of the starter cores and their processability can have a greater impact on the cost of the final product than the base price of the pellets does. For example, if insoluble cores are used, spray rates can be higher and process times shorter. Likewise, opting for low-friability pellets when coating in a fluid-bed process will minimize losses (maximize yields).

In short, it is important to evaluate many different factors when choosing starter pellets. Do not only consider the excipient's price per kilogram; study how your choice will affect costs when production is scaled up. Using off-the-shelf products from the warehouse or simply re-specifying what worked in earlier formulations may be unwise. Rather, evaluate the application carefully to find the best option right from the start because once the project is underway, time pressure and other limitations may make switching difficult.

Types of starter pellets

Pellets can be classified as being neutral substrates or functional ingredients, and both can serve as carriers for subsequent drug layering. They can also be manufactured as API-matrix pellets or pure API pellets.

Neutral starter pellets should be as inert as possible to prevent them from interacting with the API; they should serve only as a carrier to enable API layering, often followed by the application of a coating to mask off-tastes and/or modify API release. Functional starter pellets, however, actively support the formulation, such as by improving API solubility, improving dissolution, and enhancing stability.

API-matrix pellets combine an excipient and an API and can subsequently be coated to achieve the desired dissolution profile. These matrix pellets can comprise as much as 90 percent API. In addition to binders, API-matrix pellets can include functional polymers that control the dissolution profile based on particle size, thereby eliminating the need for an additional functional coating.

In some cases, depending on the API's characteristics and the technology used, it is possible to create pellets of 100 percent API and apply a functional coating to them. A number of manufacturers offer equipment to create these pellets, including ACG, Freund-Vector, and Glatt. A 2011 article described some of the production technologies—aside from extrusion-spheronization—used to create API-matrix and API pellets [1].

Because standard extrusion-spheronization processes produce particles whose sizes vary fairly widely, many pharmaceutical manufacturers often sieve them to narrow the particle size distribution to meet their formulation's requirements. In the case of sugar spheres, the process uses sugar crystals of different sizes, and the target particle size is obtained by using intermediate layered crystals, which prevents large losses to sieving. Usually, the over- and undersize spheres can be used for the next larger or smaller fraction. For the production of some microcrystalline cellulose (MCC) pellets, the same starting material is used for all size grades, and particle size is defined by the parameters of the process, which is followed by a final sieving step. In general, the narrower the particle

Six size grades of Cellets MCC starter pellets: 100 (100 to 200 microns); 200 (200 to 355 microns); 350 (350 to 500 microns); 500 (500 to 710 microns); 700 (700 to 1,000 microns); and 1000 (1,000 to 1,400 microns).

size distribution, greater the requirement for the sieving efforts and therefore the higher the cost for the final product.

In some continuous processes for making starter pellets, sieving is done online, and off-size particles are directly reworked. As a result, the desired particle size comes directly from process, minimizing the amount lost to sieving loss and boosting cost effectiveness.

Neutral starter pellets

A variety of excipients and excipient combinations are used to make neutral starter pellets. They include:

- Sugar
- MCC
- Polyols
- Carnauba wax
- Silica
- Lactose-starch
- Lactose-cellulose

Sugar. Sugar spheres originated in the confectionery industry and entered the pharmaceutical industry more than half a century ago. Today, they are the most common carrier pellet. The product comprises sucrose (maximum of 92 percent), and is made into spheres by layering a sugar crystal with a sucrose-starch syrup or by applying a powder within a coating pan. While the process principles and techniques have changed little over the years, today's coating pans have better controls that allow manufacturers to optimize production. The initial sugar crystal must be completely covered by the sugar-starch coating for it to become a sphere, and thus the size of the crystal is of primary importance with respect to pellet sphericity. Other properties, such us friability, depend largely on the manufacturing process used to create the sugar pellet, which varies from one to another supplier. The most common method uses a coating pan, but each manufacturer can augment or adjust the basic process to achieve different results. Products include Suglets (Colorcon), Non-Pareil Seeds (JRS Pharma), and PaulOrbs (Paulaur.) With, sugar, import duties are sometimes a concern. It depends on the country. In April, India increased its duties on sugar imports from 25 percent to 40 percent in order to protect domestic producers. Thus it often makes sense to source sugar spheres in the country or economic zone in which the drug product will be produced.

MCC. This type of neutral starter pellet is 100 percent microcrystalline cellulose and is usually manufactured by extrusion-spheronization or direct pelletization. With extrusion-spheronization, the hole sizes of the extrusion plate limit the size and sphericity of the pellets. A 500-micron hole is usually the lower limit because the energy input (friction) influences the mass, which may hinder spheronization. The final sphere size of the main fraction is typically close to the hole size of the extrusion plate.

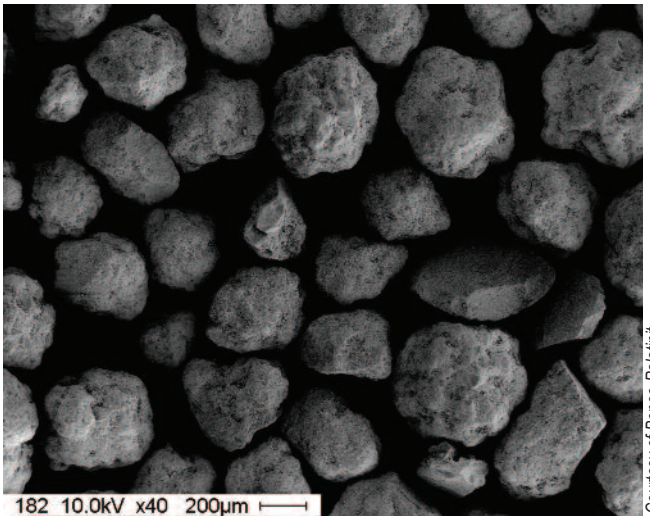
Other processes use a rotor and/or fluid bed to directly pelletize MCC in a single pot, which leads to highly spherical cores of 100 to 1,400 microns. One example is Glatt's "shovel rotor" process that densifies and spheronizes the MCC using an orbital motion to create non-friable pellets suitable for drug layering. The process was described in an article last year [2]. Freund-Vector offers a conical rotor processor that directly agglomerates excipients and/or APIs; it can also apply film coats and layer powders [3]. Brand names of MCC pellets include Cellets (photo), distributed in North America by by Glatt, and Celpheres, offered by Asahi Kasei.

Polyols. This class of materials includes isomalt (GalenIQ 960 from Beneo-Palatinit), xyiltol (Xylinerts from IPS), and mannitol (Mcell from Pharmatrans Sanaq).

The 960 isomalt (photo) is described by Beneo-Palatinit as a free-flowing isomalt for powder blends and capsule and sachet fillings and an "excellent carrier providing blend uniformity." Its particle size distribution has a D10 of 270 microns, D50 of 380 microns, and D90 of 470 microns.

Xylinert pellets are sugar-free, soluble, and hygroscopic and comprise at least 98 percent xylitol. They are available in nine particle size ranges that span 710 to 1,700 microns. Information about the process used to make them was not available.

Mcell mannitol pellets are also sugar free and offer advantages similar to those of xylitol. They are manufactured by continuous, direct pelletization using a fluid-bed technology that creates pellets directly from a suspension or solution. The process results in robust and spherical



Courtesy of Beneo-Palatinit

Scanning electron micrograph of Beneo-Palatinit's GalenIQ 960 isomalt pellets at 40X magnification.

starter pellets with a narrow particle size distribution that begins at 100 microns.

Wax. Wax-based pellets—often made from carnauba wax—include C-Wax from Pharmatrans Sanaq. They provide a hydrophobic core and are manufactured by prilling, a process that can produce a range of particle sizes. For this material, 850 to 1,250 microns is typical, but smaller sizes are possible. Melting points are 80° to 87°C.

Silicon dioxide. Silica-based pellets contain a minimum of 75 percent colliodial silicon dioxide. The products offered by Idealcures of India are described as hard, low-friability, and free-flowing spheres with uniform particle sizes of 250 to 1,680 microns. Information about the process used to make them was not available.

Functional starter pellets

As mentioned earlier, functional starter pellets are the opposite of neutral starter pellets: They are intended to interact with the API and thereby achieve the targeted drug release profile. It is possible to use acidic or basic carriers, but we'll limit our discussion to tartaric acid pellets. Acid pellets have been used to modulate the microenvironmental pH and thereby enhance API solubility. Examples include verapamil HCl, propiverine HCl, papaverine, and dipyridamole.

Tartaric acid. These pellets are used in sustained-release formulations, where they act as pH-modifiers of weakly basic APIs. Typically, the pellets are layered with the API to improve its solubility in a relatively higher pH environment, such as the lower GI tract. Once there, the highly soluble tartaric acid dissolves, decreasing the pH and facilitating API dissolution.

Tartaric acid pellets can be manufactured using a coating pan or a continuous fluid-bed granulator, and the latter is used to make the TAP pellets offered by Pharmatrans Sanaq. The resulting product is highly spherical and has a narrow particle size distribution between 200 and 800 microns.

Conclusion

The large variety of excipients used to manufacture starter pellets has enabled formualtors to develop new methods of delivery. While sugar spheres remain the standard for multiparticulate formulations, their continued dominance is not a foregone conclusion. In fact, alternatives—including functional cores—are likely to grow as specific and innovative solutions are sought to overcome different formulation challenges. At the same time, process techniques have evolved beyond the well-known extrusion-spheronization and granulation technologies. These newer processes provide a reliable means of manufacturing API-matrix and pure API pellets. *T&C*

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