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# Excipients for Formulation Success

Excipients play a crucial role in the manufacturing of solid-dosage forms and the performance of the finished drug product.

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artjazz/shutterstock.comExcipients are typically the major components of a solid dosage form. These non-active substances have well-defined roles in the development of tablets and capsules, and are included for a number of reasons such as to aid the manufacturing process or to add functionality to the formulation.

## Excipients for processing

Excipients can be divided into several broad processing categories for functionality, notes Paul Skultety, vice-president, Pharmaceutical Development Services, Xcelience, a division of Capsugel. Bulking agents such as lactose, dibasic calcium phosphate, or microcrystalline cellulose are used to make the dosage form bigger in size, he says, firstly, so that it is easier to manufacture, and secondly, to achieve a practical tablet weight for patients to handle. The minimum tablet weight is typically approximately 50 mg.

Binders such as pregelatinized starch, microcrystalline cellulose, and various polymers are included to facilitate the granulation step. Binders hold the granules together, making the powders easier to compress. Glidants (e.g., colloidal silica) promote powder flow by reducing interparticulate friction and cohesion, enabling the powder to flow better in the hopper and when filling the tablet or capsule dies. Good bulk powder flowability is essential in high-speed processing and reduces problems associated with content uniformity, which can happen if the powders do not flow uniformly, explains Skultety. Lubricants, such as magnesium stearate or stearic acid, are often used in combination with glidants to reduce the tackiness of the powders. Lubricants prevent sticking of the granules or powders to the dies or punches during compression.

Excipients are also included to protect the API. Antioxidants such as ascorbic acid, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) are used with compounds that may be susceptible to oxidation, says Skultety. In cases where it is necessary to control the pH of the local environment, pH modifiers such as citric acid or sodium acetate can be added. These agents can help if solubility or stability is better in a certain pH range, he explains. Wetting agents such as polysorbates or sodium lauryl sulfate can be added to help wet the API and get it into solution faster.

## Direct compression

In recent years, the term “functional excipient” has been used more often to describe an excipient that can provide an added function or quality over and above the “conventional” excipients, observes Rob Harris, chief technical officer at Juniper Pharma Services. For instance, powder flow for direct compression formulations may be improved with the inclusion of co-processed silicified microcrystalline cellulose, he says.

According to Andrew Bulpin, head of Process Solutions Strategic Marketing and Innovation at MilliporeSigma, an ongoing trend in the industry is toward direct compression for oral solid-dose forms to reduce process complexity. As a result, there are specific requirements regarding the particle structure of the excipient that excipient manufacturers have to address. JRS Pharma’s silicified microcrystalline cellulose (Prosolv SMCC) is a unique combination of microcrystalline cellulose (MCC) and colloidal silicon dioxide (CSD). This functional excipient was developed to address common problems of conventional binders such as low bulk density, poor flow, loss of compatibility, stickiness, and sensitivity to lubricants (1). According to the excipients manufacturer, the production process of Prosolv SMCC leads to homogenous and much finer CSD particle size distribution. Surface area is increased as a result, which enables better flowability and compactibility, and subsequently improves the content uniformity and stability of the formulation. It can be used for direct compression, in which it reduces the number of required excipients and use levels (1).

## Solubility enhancement

Ensuring sufficient API bioavailability is a prevalent challenge for formulators, Bulpin highlights. While there are various solutions available, one approach is to use functional excipients to improve solubility, which will in turn lead to bioavailability enhancement. Inert drug carriers can be used as a vehicle for poorly soluble APIs, he says, and Parteck SLC, a silica carrier with unique pore structure, is well suited for this application.

Mesoporous silica grades, such as MilliporeSigma's Parteck SLC, are a relatively recent addition to the excipient listing, observes Harris. According to him, they are becoming popular in formulations due to their highly porous structure, which can be used to hold liquids (effectively converting liquids into free-flowing solids) or to hold poorly-soluble drugs in the amorphous form, thus enhancing solubility of the drug. Parteck SLC's mesopores provide a surface area of up to 1000 $m^2/g$ for depositing an API, and the API is kept stable. A user-friendly particle size of 5-25 µm and bulk density of 0.32 g/mL allow easy loading, tableting, or capsule creation (2).

Polymers and copolymers--such as cellulosics (e.g., hydroxypropyl methylcellulose [HPMC], hydroxypropyl methylcellulose acetate succinate [HPMCAS]), polyvinylpyrrolidone (PVP), acrylates and methacrylates, polyethylene glycol (PEG), and polyethylene oxide (PEO)--also play a crucial role as solubilizing excipients, particularly in the formulation of amorphous solid dispersions. These polymers are amphiphilic in nature; the hydrophobic and hydrophilic sites enable them to interact favorably with the lipophilic drug and yet disperse and dissolve in aqueous environments such as the gastrointestinal tract. The specific interactions of the polymer with itself, the API, and the aqueous medium can result in a range of solubilizing structures, including micelles, colloids, and ionic complexes (3). Examples of such solubilizers include Soluplus (BASF), Affinisol (Dow), Eudragit E, and Eudragit L 100-55 (Evonik).

The cyclodextrins form another class of functional excipients that are widely used for solubility enhancement purposes. Cyclodextrins are cyclic oligosaccharides derived from starch that take the shape of a truncated cone consisting of a lipophilic central cavity and an outer hydrophilic shell. The mechanism of solubilization is based on the ability of the cyclodextrin to form water-soluble inclusion complexes with the poorly soluble drug. Besides enhancing solubility, formulation with cyclodextrins has also been shown to improve the physical and chemical stability of some APIs (4). A number of cyclodextrin-based products are already on the market, for example, Takeda's cefotiam-hexetil hydrochloride tablet (Pansporin T), Novartis' nimesulide tablets (Nimedex), and Janssen's itraconazole capsules (Sporanox), to name a few (4).

## Modified-release applications

To increase patient compliance, it is crucial to tailor an API release profile to maximize API efficacy and at the same time reduce side effects, as well as dose frequency, Bulpin points out. Modified-release, functional film-coating systems can be used to delay or extend the drug release from the dosage form, says Pankaj Rege, general manager, Manufactured Excipients, Colorcon. He adds that besides providing product differentiation and branding, film coating can help improve patient compliance by aiding swallowability and taste-masking unpleasant APIs.

The majority of modified-release technologies are based on the use of polymers to encapsulate the API and control its rate of release. Ethylcellulose polymer has long been used as a coating material for such applications. Colorcon's Surelease and FMC Biopolymer's Aquacoat ECD, for example, are aqueous coating systems in which ethylcellulose works as the rate-controlling polymer for drug release. The principle is based on drug diffusion across a water-insoluble membrane. Ethylcellulose aqueous dispersion provides a stable, reproducible, pH-independent drug-release profile with similar dissolution profiles in both fed and fasted states (5). The drug-release profile can be tailored by adjusting three critical formulation attributes--plasticizer, pore former concentration, and film thickness.

According to Kathrin Nollenberger, director of Formulations and Polymers, Evonik, recent developments focus on further improvements of existing excipients, for example, to simplify the use or increase the efficiency of coating systems by easy-to-use or ready-to-use premixes (e.g., Eudragit E PO ReadyMix). Applying such coating systems reduces the risk for failures, as well as saves production and storage costs, she says.

Another focus is to address new challenges such as alcohol-induced dose dumping (ADD) from modified-release formulations, Nollenberger highlights. Dose dumping may occur if the polymer matrix or film coating, which controls drug release, is compromised through dissolution in hydro-alcoholic liquids. Dose dumping is the rapid release of the entire dose or a significant fraction thereof in a short period of time.

One solution to ADD, according to Nollenberger, is to combine the use of existing excipients to novel formulation systems. "An example for such an enabling formulation system is Evonik's technology platform Eudratec ADD, which offers a portfolio of novel coating formulations for extended- and delayed-release formulations using combinations of existing functional polymers for ensuring alcohol-resistant coatings for monolithic and multiparticulate dosage forms," she says. "Reaching this target without any chemical modification of approved and monographed polymers allows an easy and direct application without additional regulatory hurdles."

## Moisture protection

An immediate-release dosage form of a moisture-sensitive API will require measures to protect the drug from humidity, both from the excipients and during processing, Harris highlights. Excipients chosen would either be anhydrous or have low water activity, he says, adding that a “dry” process for manufacture would be required, either by powder blending/direct compression or dry granulation by roller compaction.

According to Rege, formulation development of a moisture-sensitive API requires selecting excipients that mitigate moisture migration as well as applying a moisture-barrier film coating. The low water activity of Starch 1500, a partially pregelatinized maize starch from Colorcon, makes it a good choice as a filler and disintegrant for moisture-sensitive formulations, he notes. Starch 1500 acts as a moisture scavenger, and when used in combination with microcrystalline cellulose, it produces a great mix of good tablet hardness and rapid disintegration, Rege observes. In addition, moisture-barrier film coatings such as Opadry amb II (Colorcon) have been reliably used and are proven to improve the stability of the product in-use and in long-term accelerated stability studies, he says.

## Excipient selection

“The selection of excipients is crucial to ensure you end up with components that provide a stable drug product with the desired pharmacokinetic properties,” says Skultety. “For example, if the dosage form is a gelatin capsule, it may be best to avoid excipients that are very hygroscopic as they will have a tendency to adsorb moisture from the capsule shell, which can make the capsule shell brittle.” HPMC capsule shells, which contain much less moisture, can be used as an alternative. According to Skultety, these shells are more flexible and are resistant to crosslinking, which provides a better formulation option for hygroscopic and moisture-sensitive ingredients.

Before starting any design-of-experiments (DOE) work to support the quality-by-design (QbD) approach, Skultety recommends reviewing all the excipients to determine which ones may be critical to the formulation. Upon identification, formulation optimization work and varying the quantities of critical excipients to determine the robustness of the formulation should be performed. “For controlled-release formulations, it is best to do some DOE work around the release-controlling excipients,” he says. “DOE will help to define what the critical parameters are and provide a design space in which the formulation can be successfully manufactured.” Skultety also stresses that the polymer being used to control the release of the active ingredient needs to be consistent so that the drug release from the dosage form will be consistent from lot to lot of polymer used.

Nollenberger points out that the variation of polymer properties is of particular relevance for polymers taken from natural sources such as cellulose derivatives, starch, or carrageenan. “For these naturally derived polymers, small changes in the raw material source can lead to significant changes in the drug product performance,” she explains. “However, for excipients manufactured by fully synthetic processes (such as, the Eudragit polymers), variations of properties are typically much less pronounced, leading to a defined performance and a better control and prediction of their behavior in the formulation.”

As a rule of thumb, Nollenberger asserts that the development of an oral-dosage form should always be based on at least three different batches of the determining excipients, as the performance of the drug product is an interplay between API, excipients, and the manufacturing processes applied. DOE studies are crucial to determine the optimum parameters for ensuring a robust process, she says. During development, each excipient should be selected on a sound justification of its function in the formulation. Control measures to ensure the functionality need to be developed and thoroughly assessed. Also, the selected quantities need to be determined and justified by meaningful DOE studies, says Nollenberger.

## The impact of excipient variability

Today, the industry has a wide variety of excipients compared to past years, notes Anil Kane, global head of Formulation Sciences at Patheon. The excipients used in solid oral-dosage forms are available from various sources and a variety of grades, he says. Although the selection of excipients with the proper functionality and their corresponding levels in the drug product formulation are crucial to drug product performance, a deeper understanding of how variability in the excipients can affect drug product performance and the proposed control strategy is also an important component of improved drug product development (6).

According to Kane, a number of drug product recalls identified excipient variability, and therefore, a lack of an adequate control strategy, as a key contributor to why the drug product failed. This problem further underscores the need for improved excipient variability understanding, he asserts. However, evaluating the impact of excipient variability on drug product performance has presented a greater challenge to date than evaluating API and process impacts on drug product performance. This difficulty is partially due to the pharmaceutical manufacturer having more internal capability to manipulate the API and the manufacturing process for experimental study, he explains.

For excipients, the observed lot-to-lot variability for an individual grade is a function of the control strategy put in place by the excipient supplier, Kane notes. Due to the scales of excipient manufacture and the broader industrial application of many of the materials used as pharmaceutical excipients, it can be difficult for pharmaceutical manufacturers to easily obtain an ideal set of samples to adequately investigate the impact of excipient material properties on drug product performance. Furthermore, the number of excipient material properties combined with the number of excipients in a drug product formulation presents a financial and logistical challenge for executing manageable experimental designs, he says. Risk-based approaches to identify the most impactful excipient material properties have been previously examined as a way to streamline experimental evaluation of excipient variability impacts of drug product performance (7). In addition, Kane believes that a data-based analytical method, which uses quantitative physicochemical property data included in vendor certificates of analysis to further evaluate excipient lot-to-lot variability for a larger number of excipient properties reported by the excipient vendor, could be useful (8).

## References

1. JRS Pharma, Prosolv SMCC [2], accessed Sept. 15, 2016.
2. Merck Millipore, “Merck Millipore Introduces Parteck SLC, Silica-based Excipient for Enhanced Drug Solubility and Bioavailability,” Press Release, Oct. 22, 2013.
3. A. Siew, *Pharm Tech Supp March 2013*, s6-211.
4. M.E. Brewster and T. Loftsson, *Adv Drug Del Rev* 59, 645-666 (2007).
5. S. Muschert et al., *Drug Dev Industrial Pharmacy* 36 (2) 173-179 (2010).
6. C.M.V. Moore, “An FDA Perspective on Drug Development and the Global Regulatory Landscape, presentation at the AAPS Annual Meeting, Washington,” DC (Oct. 12, 2010).
7. J. Kushner et al., *J Pharm Sci* 100 (6) 2222-2239 (2011).
8. J. Kushner, *Pharm Dev Technol* 18 (2) 333-342 (2013).

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