THE EMERGENCE OF CONTROLLED-RELEASE POWDERS FOR ORAL ADMINISTRATION

Though the number of approved controlled-release powder formats is modest, a rising number of pharmaceutical companies and manufacturing organisations are incorporating controlled-release powder manufacturing to their portfolios to address the growing dosage form problem for paediatric and geriatric patients. Cory Berkland, PhD, and Nathan Dormer, PhD, from Orbis Biosciences look at what this delivery system can offer.

The importance of providing safe and efficacious formularies for populations with dysphagia, such as paediatric and geriatric patients, has been continually cited as an area in need of improvement for pharmaceutical companies and the providers who administer their products.[1-16]

The relative paucity of dispersible format oral products means clinicians and compounding pharmacies have to use alternative solutions to treat their patients that are not always backed by supporting safety, bioavailability and stability studies. Tablets are sometimes administered with improvisatory methods such as crushing the dosage form and mixing with food or drink. These methods not only lead to dosing errors and decreased efficacy, but can perpetuate non-adherence if the active pharmaceutical ingredients (API) are foul-tasting.[17-20]

Due to these issues, The Institute for Safe Medical Practices (ISMP) regularly updates a "Do Not Crush" list, which lists several hundred dosage forms that cannot be compounded due to special controlled-release properties, taste-masking or API protection.[1-6,10-13] The dosage form problem affects over half of the global population (under 18 and over 65 years of age).[17-20] Dosing protocols for populations with dysphagia or resistance to taking traditional capsules or tablets fail to address many formulation design criteria.[21, 22]

MASKING TASTE ISSUES

A number of APIs taste extremely bitter and some granule and tablet-coating techniques can result in an unpleasant feel in the mouth due to irregular surface finishes. It has been estimated that 50% of patients with organoleptic sensitivities are reluctant to take their medicine, with the majority of those reporting poor taste as a large contributor to non-compliance.[12]

> "Recent advances have enabled extended release and taste-masking of orally administered APIs, but the breadth of application currently covers less than 1% of marketed drugs."

Artificial flavours alone are often unable to overcome the extremely unpleasant taste of many active ingredients in syrups and suspensions.[1,10,11] Moreover, efforts to mask flavours using coatings or microencapsulation often result in poorly-controlled, polydisperse particle diameters that result in a sand-like consistency. Ideally, a dosage form would consist of taste-masking with negligible texture while maintaining other extended- or delayed-release properties. The age, weight, surface area and metabolic proclivities of patients may also require substantial dosing considerations that are not linearly scaled.[13]

TABLET SIZE ISSUES

Achieving controlled-release kinetics with tablets is a relatively simple process, as the size and form factor of the dosage form

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lends to using robust coating methods, sometimes with several layers.[17,20] Capsules have the advantage of being injection moulded, extruded or die pressed with gelatines and other controlled-release polymers in a repeatable, high-throughput manner, enabling large doses of medication in a modest form factor. Tablets are simply pressed, then coated with subsequent layers of controlled-release components, which makes translation of specialised controlled release (e.g. delayed or extended) simple.[17,20]

CONTROLLED-RELEASE POWDER FORMATS

Due to the large format of controlled-release pills and capsules, the foul taste of traditional syrups and suspensions, and the lack of controlled-release options for APIs tableted and encapsulated in nearly 85% of marketed drugs,[25,26] many pharmaceutical and contract manufacturing organisations (CMOs) are focusing research and development efforts on controlled-release powder formats, which combine the stability of solid oral dosage forms and dose titration advantages of liquids. These alternatives to tablets address many of the deficiencies discussed earlier, but can still be fraught with inadequacies such as multiple-step manufacturing and inconsistent particle sizes.

> "Micro- and nanoparticulate powders are manufactured with myriad processes, but the primary motivation is integration of controlled-release mechanisms to govern particle disintegration and API dissolution."

The size of such dosage forms, however, renders pills and capsules impractical for patients with swallowing difficulties. Data from current products indicates that the average size of a controlled-release pill is nearly 1.5 cm in length.[23] Physiological studies demonstrate that swallowing becomes difficult when the dimension of the object being ingested is greater than half of the oesophageal diameter, which is 2.0 cm for the prototypical adult.[24] Moreover, the average extended or delayed-release pill may be too large to be swallowed easily.

The merits of tablets are that they contain the volumetric space to:

- Deliver a large payload of API
- Use special controlled-release mechanisms
- Circumvent shelf stability challenges.

Where large tablets and capsules present swallowing and administration challenges, liquid formats succeed in dose titration most of the time. The advantages beyond ease of dosing are limited in traditional syrups, however. Liquid formats are usually not extended-release, have little-to-no taste-masking and can contain API particles prone to settling and aggregation if not reconstituted properly prior to administration, which have resulted in risks to patient safety.[10,12-16] Recent advances have enabled extended release and taste-masking of orally-administered APIs, but the breadth of application currently covers less than 1% of marketed drugs.

Micro- and nanoparticulate powders are manufactured with myriad processes, but the primary motivation is integration of controlled-release mechanisms to govern particle disintegration and API dissolution.

The requirement of achieving controlled release universally relies on physical sequestration of the API via one or more physicochemical mechanisms, which typically requires multiple steps.

A powder form factor, however, can present unique challenges to achieving controlled release coatings due to:

- The high surface area of particles
- Irregular sizes of particles within the powder
- The number of process steps required to ensure predictable performance and reasonable quality of the final product.

Taste-masking can still be achieved with powders, however, when a coating or other chemical modification is applied.[14,25,26]

Precursor particle method

The most straightforward method for achieving taste-masking and controlled release with powders employs a two-step process in which a precursor particle is manufactured by various means, then coated with one or more layers containing controlled-release materials. Precursor particles can either be:

- Milled API crystals
- API co-mixed with inert bases or controlled-release excipients
- A 100% inert core sans API.

Figure 1: Next-generation powder manufacturing technologies (left) can provide narrow particle size distributions while offering taste-masking and controlled release in a single step, which overcomes limitations provided by traditional powder manufacturing methods (right).

These precursors can be manufactured by any method, which include traditional vibratory methods, congealing/spinning disk atomisation, prilling, hot-melt extrusion (HME) and spheronisation, aqueous dispersions, blending/bulking, electrohydrodynamic spraying (EHDS), or spray drying.[27-34] Material selection for the precursor particle relies on process capabilities, desired end-product controlled-release properties, API thermal and oxidative stability and desired physical properties (surface features, density, friability, hardness, etc).

If taste-masking, delayed-release or stability-enabling properties are required, the precursor particle advances to subsequent traditional layering steps using fluidised beds, Würster coaters, spray/pan coating, or coacervation.[16,35-38] Materials of choice for the secondary coating steps are selected for reasons commensurate with precursor particles (i.e. material compatibility, controlled-release behaviour and stability). The final dosage form, typically granules in the 200–500 µm diameter range, can then be re-suspended, packaged in sachets or sprinkle capsules, placed in dissolving tongue strips, co-lyophilised with other materials for orally-disintegrating tablets (ODTs), or reconstituted in syrup.

Chemical modificiation

The history of manufacturing controlled-release powders by adding one or more coating steps to API-rich cores is very established. These techniques are, however, divergent from state-of-the art techniques that focus on chemical modification of the API and/or substrate using ion exchange resins.[39-41] The main advantages that these methods can yield are liquid stability and deterring abuse of scheduled APIs, such as opiates and amphetamines.

While revolutionary, drug complexation employs a number of manufacturing steps that far surpasses that of simple bead layering, and still usually includes a final coating step.[16,35-38] Indeed, developing controlled-release powders has traditionally employed combinations of manufacturing mechanisms and complex chemistry, which achieve substantial advantages over traditional pill and capsule formats, enabling extended- and delayed-release liquid suspensions and powders, while providing taste-masking as-is, in a liquid constituent, or further compounded.

Precision Particle Fabrication™ technology

The major criticisms of these methods, however, focus on the number of process steps and excipients. Thus, it comes as no surprise that manufacturers are investigating less complex chemistry and single-step manufacturing methods for producing controlled-release powders (Figure 1). One such technology platform, Precision Particle Fabrication™ technology, is a manufacturing scheme that creates oral controlled-release microsphere and microcapsule powders as low as 75 µm in a single step, without the need for secondary coating steps or sieving to remove particles that are too large or too small.[42-47]

CONCLUSION

Though oral dosage forms such as pills and tablets are sufficient for many individuals, a significant fraction of the world's population suffers from swallowing problems, taste sensitivities or an avoidance to taking medication of any format. As these patients are afflicted with acute or chronic illnesses, sometimes a lack of format flexibility and dosage options limits treatment. An emergence in controlled-release powder manufacturing has taken place over the last decade, replacing large tablets with dispersible and dose-flexible alternatives.

The methods for making controlled release powders vary, but typically include forming an API/excipient core precursor then coating with one or more controlled-release layers for a finished product. Contemporary techniques incorporate chemical modification and sequestration of the API, prior to secondary coating steps. Next-generation techniques eliminate the need for multiple steps, achieving even coatings while maintaining monodisperse size distributions and high API content at small overall particle size to enhance palatability.

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