HPAPI Drug Solid Oral Dosage (SOD) Manufacturing – Ensuring Content Uniformity

What techniques should manufacturers employ when working with low-dose drug products?

By Thomas Daggs, MBA, Vice President, Product Development and Quality Control, and Angelo Consalvo, Director of Manufacturing, Enteris BioPharma

Anyone who takes an oral tablet medication – whether prescribed or over-the-counter – does so under the presumption that each tablet in the bottle is, for all intents and purposes, identical and will provide the desired pharmacological effect without any noticeable difference among doses. Each tablet looks the same, therefore each is the same. Anything less would, for most people, be impossible to fathom.

For drug developers, achieving this "pharmaceutical guarantee" is no small task. It requires the precise distribution of the active pharmaceutical ingredient (API) within the drug product batch in a manner that meets industry standards of "content uniformity." Attaining acceptable content uniformity, however, can be a significant technical hurdle for manufacturers of solid oral dosage forms. This is especially the case with highly potent and moisture labile APIs, including most peptides and protein therapeutics.

High potency active pharmaceutical ingredients (HPAPIs) are generally defined as a pharmaceutical that is active at concentrations of 150 micrograms (mcg)per kilogram of body weight or below. They are powerful therapeutics that use a fraction of the drug substance to provide greater potency than a traditional pharmaceutical product.

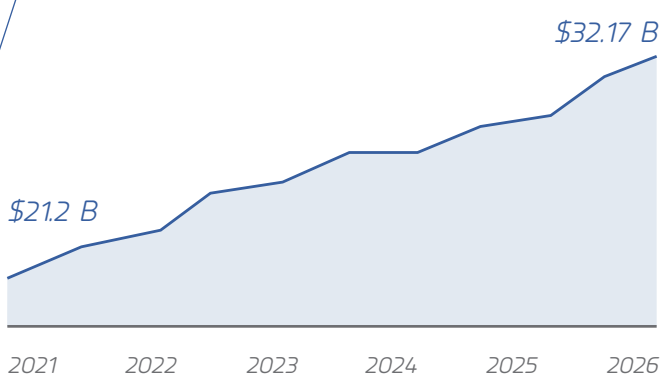
The ability of HPAPIs to achieve efficacy at a lower dose, thereby lowering the cost of goods, has led to an exponential growth in the development and resulting commercialization of HPAPIs. *Estimates suggest that the global HPAPI market is expected to be $21.2 billion in 2021 and $32.17 billion by 2026*, signifying a CAGR of 8.7%[1] compared to an estimated 8% growth in the general pharmaceutical market over the same period. The largest percentage of HPAPIs are used in the formation of anti-cancer drugs, including antibody-drug conjugates or ADCs. Additionally, there are many highly potent compounds developed for other therapeutic applications, such as diabetes, cardiovascular disease and central nervous system and musculoskeletal disorders.

However, with the many benefits that HPAPIs offer, the potency and cytotoxicity of HPAPIs (for those which are amenable to oral delivery, like peptides and small proteins) pose challenges to their manufacture and their low dosages often require specialized formulating technologies when developing solid oral dosage products. Chief amongst these is ensuring content uniformity.

[1]*https://www.marketdataforecast.com/market-reports/high-potency-active-pharmaceutical-ingredients-market*

There are several formulation and process-related variables that impact content uniformity, but dose and ratio of drug substance (percent of the drug composition that is API) are two major determinants of how challenging it will be to achieve optimal content uniformity with an HPAPI.

Estimated Progression of Global HPAPI Market



Consider a 500 mg tablet where 400 mg of that tablet weight is API (a 400 mg dose, 80% ratio of drug substance). As the drug load approaches 100%, the content uniformity is more and more accurately approximated by individual tablet weight. In fact, the United States Pharmacopeia (USP) instructs that the content uniformity of many dosage forms ≥25 mg dose and ≥25% drug substance ratio can be measured using weight variability measurements.

On the other hand, consider a tablet manufactured with a HPAPI whereby the total tablet weight remains 500 mg, but is intended to deliver an active dose of just 0.10 mg. The drug substance ratio in this case is 0.02%. This can lead to considerable challenges when mass producing the drug. For instance, manufacturing a batch of several hundred thousand units or more of a tablet, where the API content of each 500 mg unit stamped out (about the size of an Advil) cannot vary by more than 0.025 mg (what's left on your finger after a pinch of salt), requires the latest advances in biopharmaceutical and genetic engineering to ensure that each dose contains the precise amount of drug substance.

Wet Granulation Versus Dry Production

One of the simplest processing techniques for achieving content uniformity of low-dose drugs is the use of wet-granulation. Wet granulation is done by creating a wet mass of powders with a granulation liquid. The granulation liquid may be water, organic or a hydro-organic mixture, and often includes a binder, and in the case of low-dose manufacturing, may also include the API. The wet mash is then mixed, dried and milled before blending and final tablet compression. This is a tried-and-true technique, and a highly effective way to obtain a uniform distribution of low-dose API.

Wet granulation can work very well for many HPAPIs. However, it is considerably less functional – and, in fact, potentially detrimental – in the production of solid oral dose (SOD) labile APIs such as many peptides and proteins. This is because liquids can facilitate chemical interactions with other excipients and the residual moisture that is a byproduct of the wet granulation process can be detrimental to long term stability of the drug product. Additionally, the high temperatures often required for drying can cause the degradation of the peptide or protein.

Thus, the manufacture of many SOD peptides and proteins necessitates the incorporation of dry production techniques.

While these are substantially more challenging and require a highly experienced team skilled in dry production, with the ability to identify the best formulation approach needed to achieve optimal content uniformity, such methods can result in excellent content uniformity of low-dose tablets while avoiding the problems inherent to wet granulation.

There are several steps that must be observed when conducting the dry production of HPAPI tablets. Some of these traits are universal to all HPAPI product SOD manufacturing needs, while others, depend on the specific properties of the HPAPI.

1 Understand the Drug Substance – In most cases, the peptide and small protein APIs are an amorphous lyophisate with poorly controlled (or uncontrolled) particle size and particle shape. The lack of control of these basic powder characteristics creates challenges to the process developer who is counting on reproducible flow properties for distribution of the API among other powders and bulk solids. Put simply, the uniform low-dose distribution of a lyophilized API cannot be achieved by a simple dry-blend process. Alternately, some peptides APIs are isolated by means other than lyophilization (spray-drying for example) with uniform powder characteristics that are more amenable to simple blending of dry components.

2 Select the Right Matrix – Especially the Filler – While it can be easy to find excipients engineered specifically for direct compression operations, selecting the right combination of filler, binder, disintegrant and lubricant is key. The filler, in particular, must be precisely matched with the production need and drug product. Ideally the filler should be good flowing particle with a porous surface that provides strong adsorption sites for fine particles of drug substance, and, most importantly, is not reactive with the API. The first two properties are generally achieved with lactose, mannitol or microcrystalline cellulose or dibasic calcium phosphate. During the testing process, it is highly recommended that the production team selects the optimal filler via binary mixture excipient compatibility studies to address ensure there is no reactivity with the API.

3 Disperse the Active Amongst the Filler and Blend – The magic happens in the cone mill. Particle size of the API plays an important role in content uniformity, where smaller particles correspond to better uniformity. However, many milling techniques generate heat, which can degrade certain APIs, and will result in cohesive, poorly flowing powders – powders which will not be efficiently and uniformly distributed among other bulk solids by dry blending.

These risks can be avoided by pre-blending the API with the selected filler and then passing that blend through a cone mill. The mill efficiently deagglomerates the API and takes advantage of the resulting cohesiveness by "sticking" the API particles to the porous filler. The filler of engineered particle size and good flow characteristics can be blended with the remaining tablet components and distributed uniformly by dry blending. Furthermore, this design of mill does not expose the API to excessive heat. After dispersion of the API by co-milling it with the filler, it is blended in with other components which are selected for good flow, compactibility and processability (e.g., binder, disintegrant, flow aid and lubricant). Screen size and mill speed are typically optimized during process development.

4 Confirming Uniformity –Typical measures of content uniformity are done in-process by using a thief device to sample the finished powder in the blender at different strata. After the end of production, additional testing is done among 10-30 finished units at product release to confirm the uniformity of content. However, tests during process development can have somewhat limited usefulness as blend uniformity of low-dose powders tends to be riddled with sampling error and finished product testing of a few randomized units does not provide an enhanced understanding of the process or where things might have gone wrong.

An additional measure of uniformity is encouraged where stratified samples of tablets are taken from the press at the beginning, at periodic intervals during the compression run, and at the end of the process. Those units are individually assayed with the results plotted as a function of time. The data can be used to evaluate the suitability of the finished blend, can detect whether the blend is segregating on the press, and will augur finished product uniformity results. Performing this characterization routinely during the early development phase provides a strong data base to anchor scale-up and other process/formulation change activities that will occur during later stages of development.

Choosing the Right Partner in the Development and Manufacture of Solid Oral Dosage, HPAPI Drug Products

Given the increase in the need for outsourcing, pharmaceutical and biotechnology companies face the challenge of identifying the right Contract Development Manufacturing Organization (CDMO) partner that has the capability, knowledge, training, and turnkey readiness to manage the production of HPAPIs drug products. However, not all CDMOs have an expertise in HPAPI drug product manufacturing, making it imperative that companies ask the right questions as they seek the right partner.

In addition to ensuring content uniformity, a considerable challenge in the manufacture of low-dose oral tablets, the following critical parameters covering drug substance development experience and expertise should be considered when choosing a CDMO partner to manage shortened development timelines for HPAPI products.

1 Content Bioavailability: Many of the highly potent compounds, such as peptides, suffer from poor oral bioavailability, so a CDMO that can provide enabling technology can be a major benefit by saving time and money in the development process.

2 Manufacturing Scale: The ability to scale the manufacturing scale to future needs needs is critically important as the program progresses through clinical trials and eventually to commercial readiness. Having a well-constructed "Bench to Market" manufacturing strategy can be the difference between success and failure. Additionally, quality control, quality assurance, and containment strategies are all major factors that need to be considered when it comes to handling highly potent APIs.

3 Safety & Containment: There are number of important safety factors that should be considered before choosing a CDMO, such as assessing the toxicology and potency of the API before handling. However, critically important to ensuring safety is determining the Occupational Exposure Limit (OEL). OEL is defined the maximum airborne concentration of a toxic substance that a worker can be exposed to over a period of time, generally accepted to be an 8-hour period. This must be established at the outset of any HPAPI product manufacturing assignment.

4 Experience: HPAPIs SOD forms are highly complex requiring a highly experienced team skilled in formulation development, with the ability to identify the best formulation approach needed to achieve the target product profile, such as achieving the proper pharmacokinetics. Organizations must ensure that they have readily available access to scientifically trained experts; experts who can actively address specific challenges.

In May 2021, Enteris BioPharma completed the renovation of a state-of-the-art facility in northern New Jersey comprised of industry-leading subject matter experts with robust institutional experience, project management, and rapid problem-solving expertise. The newly designed 32,000-square-foot facility includes 6,000 square feet of cleanroom space with approximately 2,500 square feet dedicated to HPAPI handling/containment and SOD manufacturing.

Complementing its manufacturing capabilities, Enteris' CDMO business delivers expertise in developing immediate- and modified-release SOD forms, including tablets, minitablets and capsules, for non-potent and highly potent APIs. Formulation development capabilities encompass processes for dry blending, dry granulation, wet granulation, tablet compression, capsule filling, and aqueous film coating. Importantly, Enteris has significant experience with HPAPIs and extensive know-how with low-dose formulations achieving excellent content uniformity.

Conclusion

The HPAPI market is an increasingly important segment of the overall pharmaceutical industry. The high capital investment and extensive expertise required for HPAPI and potent drug manufacture is driving the use of contract service providers. However, there are numerous challenges in manufacturing SOD HPAPIs, most importantly, ensuring content uniformity.

Authors

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