About 90 percent of API molecules in the discovery pipeline are water insoluble, contributing to bioavailability challenges [1]. Pharmaceutical developers use special methodologies—such as spray drying and micronization—to improve the solubility and bioavailability of such poorly soluble APIs. However, successfully formulating a final dosage form and designing an appropriate manufacturing process with APIs prepared using such complex methods can be challenging.

This article provides guidance to help formulators develop solid oral drug products using complex active pharmaceutical ingredients (APIs).
While you may think you’ve analyzed an API’s chemistry, manufacturing, and controls (CMC), the guidelines for new technologies such as spray-dried dispersions (SDDs) are still poorly defined, and you must ensure that your analysis holds up. A robust regulatory strategy and timeline can help prioritize CMC activities. This article discusses the factors you should consider when developing a drug product with a complex API.

**Preformulation studies**

Finite resources combined with a rush to market can tempt developers to eliminate or delay key preformulation studies, but knowing your API candidate’s physicochemical properties from the start can help forestall problems. The studies can help you select the best development approach, minimizing the need to repeat experiments or alter a formulation during later clinical-development phases and helping to avoid process and manufacturing challenges. Also, clinical teams may not appreciate your wish to circle back and perform a physicochemical characterization or modify a process and/or formulation late in development.

Comprehensive preformulation studies can help you identify a more stable API than you otherwise would to achieve your desired drug product attributes. For example, API physical characterization might uncover hydrates, solvates, or polymorphs with variable properties, including those related to solubility and stability. A thorough evaluation of different API forms, pH solubility, pKa, and animal pharmacokinetic data can help you determine if a particular dosage form, such as modified-release, could provide an appropriate dosing strategy and eliminate last-minute surprises during development.

When you have identified the intended dosage form, excipient compatibility studies (ECSs) can ensure that the selected excipients are compatible with the API and won’t affect the product’s potency or produce harmful degradants. Recognizing patterns of incompatibility during early development phases can save you time. For example, to avoid a Maillard reaction, you might want to eliminate reducing sugars from a formulation if the API has a primary amine group. Similarly, you should avoid using povidone with APIs that degrade in the presence of peroxides because chemical manufacturers use hydrogen peroxide as an initiator for povidone manufacturing, and povidone always contains traces of peroxide.

Often, due to budgetary constraints or to accommodate aggressive timelines, pharmaceutical manufacturers overlook ECSs and choose to rely solely on finished-product stability data. This can be costly, and incompatibilities detected during those studies can severely delay the drug development process as well as regulatory submission.

**Stability**

An SDD is a metastable amorphous molecular dispersion of an API in a polymer matrix. Under certain conditions, an SDD may revert from the free amorphous state to the more stable, but less soluble, crystalline state. This affects solubility, bioavailability, and ultimately, drug efficacy.

Throughout downstream processing and storage, you must be cognizant of conditions that help maintain an SDD’s amorphous state. Deviations in temperature, humidity, or light can cause reversions. Also, if you don’t properly understand the drug-degradation pathway, you may select a process that could degrade the API (such as heat, oxygen, or chemical or mechanical stress) or introduce harmful degradants.

The typical drug load of an SDD is about 30 to 50 percent, which limits the excipient amounts a formulation can contain to keep the tablet size acceptable for oral administration. For higher doses, you can achieve a smaller tablet size by densifying the SDD using a roller compaction process if the API is amenable.

The SDD’s particle size distribution must be suitable for downstream processing to avoid segregation in a direct blend process. For a cohesive and poorly flowing SDD, you can improve flow by adding glidants.

You must establish critical process parameters (CPPs) for the manufacturing process as well as critical quality attributes (CQAs) for the product early in the development process. If you don’t give these and other potential
issues proper attention early in the program, downstream problems that were unapparent during early development can materialize during scale-up, potentially requiring a reformulation and undoubtedly causing costly delays. Pay attention to these well-known challenges and remain focused on mitigation strategies throughout development.

Challenges during scale-up

Consider the supply chain for the API and excipients as well as process scale-up early in the drug development process. Make sure to:

1. Design formulations and processes in the lab that are scalable beyond a few hundred grams.
2. Design processes and formulations during R&D with larger-scale equipment in mind for ease of scale-up. For example, if you prepare a binder solution by heating with a magnetic stirrer during development, determine how you will heat, safely handle, and stir 100 to 200 kilograms of solution at commercial scale.
3. Plan for the transition from R&D to commercial production by using equipment trains during development that match the equipment trains you'll be using for the larger-scale batches at the production facility. This will allow you to avoid performing tech transfers from one facility to another, which affects costs and timelines.

Knowledge and broad experience can ensure that your process is feasible, safe, and cost-effective at a commercial scale. A CDMO with the knowledge, expertise, and equipment to successfully formulate and process a variety of complex and challenging APIs into immediate- or modified-release dosage forms can help successfully guide your program from R&D through regulatory filing and commercialization.

References


Neha Shah, PhD, is a scientist at Recro Gainesville, Gainesville, GA (770 531 8800, www.recrogainesville.com). The company provides oral solid dosage form development, regulatory support, clinical and commercial manufacturing, and packaging and logistics services to the global pharmaceutical market, specializing in modified release oral solid dosage forms and DEA-controlled substances.