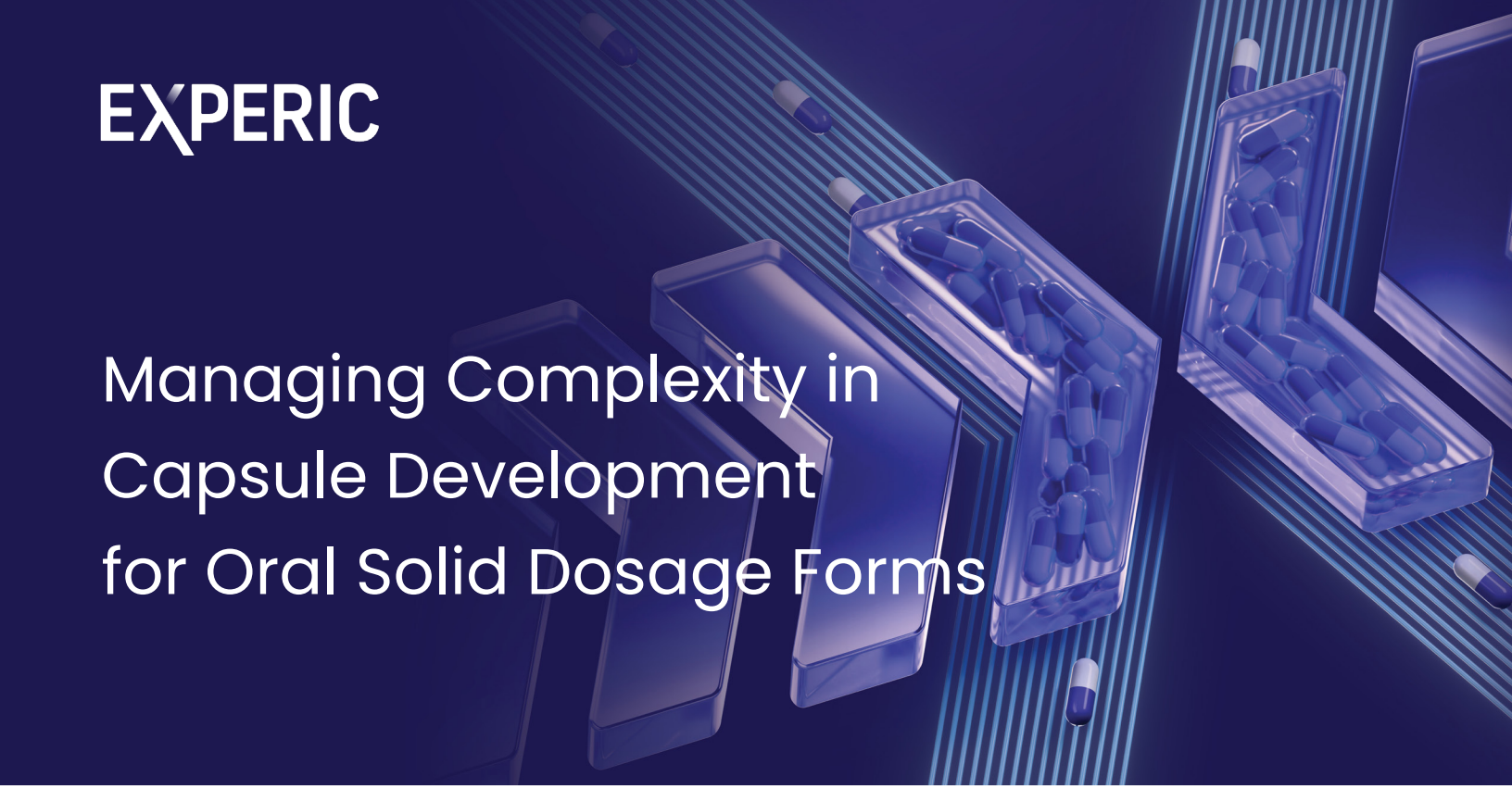
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Managing Complexity in Capsule Development for Oral Solid Dosage Forms

The Hidden Complexity of Capsule Development

Capsule development for oral solid dose (OSD) is often considered a relatively simple process. In practice, however, capsule-based drug products present a wide variety of complex formulation, manufacturing, and supply challenges. This complexity often does not arise from the capsule itself, but from the interactions between formulation properties, manufacturing requirements, material availability, packaging, and the clinical supply demands that must be managed throughout development.

As small molecule pipelines shift toward ever more complex, potent, and sensitive active pharmaceutical ingredients (APIs), these development steps can no longer be seen as sequential, linear phases. Instead, success increasingly relies on an intentional and integrated approach. Integrating formulation development, specialized capsule filling, manufacturing, packaging, and clinical supply helps to inform capsule development as it progresses, minimizing downstream risks, reducing avoidable material loss and delays, and providing more predictable pathways to clinic.

Formulation Affects Flowability and Cohesion

Formulation decisions are the first critical stage of capsule development. While formulation is often seen in isolation, and formulation decisions are rarely seen as the purview of clinical supply, combining analytical methods at this stage enables smarter decisions to select formulations that streamline manufacturing, scaling, packaging and clinical development. For this reason, a significant amount of the development timeline is devoted to the formulation phase of an OSD development program, typically 6–12 weeks out of the total average of 20–30 weeks.

API behavior as a powder is one of the primary physical challenges development teams must address. Central challenges, especially for small molecules, include poor flowability or a high degree of cohesion, which can complicate filling, especially at lower fill weights. Planning for flowability and cohesion issues begins at formulation to avoid loss of yield during capsule filling. Importantly, a formulation issue that may appear manageable during development can ultimately translate into real yield loss and inefficiency once manufacturing advances into a GMP environment.

While it might make sense at small scales to sacrifice throughput to manage bridging, insufficient filling consistency, segregation, and inconsistent flow, this is not sustainable as development scales. Neglecting flowability and cohesion factors can lead to rejected capsules, lower yields, and longer batch times. To avoid these risks, take time during formulation to consider manufacturability alongside API performance.

Capsule Filling Decisions Are Multifaceted

During capsule-filling, powder properties, dose requirements, equipment performance, and environmental conditions must come together to produce a consistent drug product. This is particularly complex for lower-dose targets, which have narrower tolerances and require highly sensitive methods paired with a high degree of executional precision.

Blend uniformity and powder behavior can affect cohesion and flow and, along with equipment inefficiencies, can significantly impact yield and fill performance. The good news is that specialized filling equipment, modified process parameters, and tailored excipient systems can improve consistency and keep a program on track.

Environmental Conditions Affect OSD Stability

Preserving stability of an oral solid dose (OSD) product often requires tightly controlled environments during manufacturing, particularly for moisture- or light-sensitive APIs and formulations. To protect these products' stability, processing is typically conducted under low-humidity conditions. However, this introduces additional challenges, as low-humidity environments can increase static, thereby complicating both powder transfer and fill accuracy.

This means that manufacturers must often balance a complex variety of factors to ensure both product integrity and manufacturing efficiency. Striking this balance is challenging, requiring the manufacturer to navigate not only environmental controls but also material-handling strategies and equipment configurations.

Sometimes the manufacturing environment is dictated not by the physiological nature of the API and/or excipients, but by regulatory necessity. OSD programs often involve un- or under-characterized new chemical entities, potent or highly potent APIs, cytotoxic agents, hormones, or controlled substances, each of which brings specific regulatory requirements for containment, facility design, scheduling, and personnel training.

Clinical Supply Is Complicated

Once a formulation and manufacturing process have been established, the next constraint may seem surprisingly simple: having enough material to continue development. A specially formulated API may need to support a host of activities, including process and analytical method development, preclinical studies, initial clinical supply, stability programs, and shipping qualification. At early stages, API quantities are usually severely limited. This makes material allocation a complex development decision rather than simply a supply-chain exercise, as every failed batch, repeat experiment, additional analytical study, or unnecessary transfer consumes precious supplies.

Determining quantities required for the entire development lifecycle, from formulation through clinical testing, is itself a formidable challenge. Procuring too much can deplete finite resources and strain later development phases, while allocating too little can cause delays when additional formulation material is needed.

Managing the Clinical Supply Cycle

The dynamic nature of modern drug development becomes particularly apparent when the product enters the clinical supply cycle. With fluctuating enrollment rates, expanding cohorts, evolving and adaptive protocols, and shifting timelines, resupply is far from a one-off contingency; it is a series of recurring decisions that feed into the next.

Stability During Packaging and Shipping

Clinical trials can span months or even years across multiple regions and storage conditions. Appropriate packaging is key to protecting the drug product against environmental stresses during clinical stages. Stability during packaging and shipping is important to meet clinical trial needs.

Some common methods to protect stability during packaging include using materials that actively scavenge oxygen or moisture; however, these additions bring their own operational and compatibility challenges. For example, many scavengers require moisture to activate. In dry pharmaceutical packaging, there may not be enough water unless it is deliberately added. These scavengers, which are often iron-based, can also trigger metal detectors during storage and transport. These complications can affect stability and transport times, leading to delays.

Packaging for Blinded Trials

Developing placebos that match the appearance, weight, and other characteristics of the active drug product on trial can be challenging. This often requires parallel development and stability programs that must be carefully orchestrated to meet the time constraints of clinical trials. In low-dose or highly sensitive formulations, the actual API may constitute less than 1% of the overall drug product. This makes both packaging and placebo design harder, as tiny absolute changes in moisture, oxygen, or API distribution can translate into large relative changes in dose, stability, and appearance, and the margin for error is very small.

Applying QbD to Manage Development Risks

Quality by Design (QbD) provides a practical framework for identifying and managing the interdependent needs of capsule development. By discussing formulation and manufacturing concerns with clinical teams, developers can begin development with a quality target product profile (QTPP) and appropriately identify critical quality attributes (CQAs). Together, the QTPP and CQAs provide a cohesive framework that facilitates better decision-making. They also enable better risk management by identifying early factors of concern for capsule development. Furthermore, design-of-experiments (DoE) studies can build confidence by interrogating the relationships among critical material attributes (CMAs), critical process parameters (CPPs), and CQAs to optimize manufacturing robustness, improve supply reliability, and align development with regulatory expectations.

Integration as a Competitive Advantage

For small and medium-sized biopharma companies navigating capsule development - particularly those entering clinical development for the first time - the right CDMO partner can provide more than manufacturing capacity. An experienced CDMO partner that applies QbD principles can help to manage the big picture, from formulation and filling through manufacturing, packaging, and clinical supply.

The earlier formulation and manufacturing decisions are considered together, the more effectively downstream challenges can be anticipated and managed. If you are planning a capsule-based development program, speak with the Experic team about how an integrated approach can help you navigate these challenges from development through clinical supply. Contact us to discuss how we can help support your program.