Choosing a Formulation and Process Approach to Oral Controlled Release Products

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Do you want to develop an oral controlled release (OCR) product? If so, you'll quickly realize there are a lot of questions to answer. What do you want the final dosage form to do? What formulation and process approach are you going to use? What traps and roadblocks might you encounter? Understanding the options and their ramifications is the first step toward devising a plan.

Introduction

Choosing the wrong approach to developing and manufacturing your extended release (ER) product can leave you in a blind alley. With no path forward, will you have the money and time to start over? Or will your product simply fall by the wayside?

This white paper alone cannot solve this complex problem. What it can do is offer some considerations, a framework and some guiding questions to help you make informed decisions as you work toward a solution.

In 1952, the first U.S. market approval for a time-release pharmaceutical product was granted to Smith, Kline & French for its Dexedrine Spansule. Since then, many varied and successful approaches to creating OCR medications have been developed. Today, more than 65 years later, a surprisingly wide variety of controlled release formulations are possible. However, developing them may require more time, funds and effort than expected. Enlisting the help of an experienced OCR formulator can quicken the process and ensure your project’s success, especially for complicated formulations requiring multiple active pharmaceutical ingredients (APIs) or complex release patterns.

Choosing the best technology and approach for your product can save a lot of frustration and cost on the road to approval.

Learning from two failed products

What happens if you choose the wrong path for your product?

Imagine your company makes an ER tablet with five dosage strengths. The product is on the long tail of decline — it has gone generic — but is still making millions of dollars and matters to your small company. The original site of manufacture is closing, and the product must be transferred. Here’s the problem: The five dosage strengths are not dose proportionate, which means you can’t qualify for a biowaiver. If you transfer production, you’ll have to conduct separate bioequivalence assessments for each strength. You’ll also have to conduct stability studies separately so there’s no chance of reducing the effort by bracketing. All of these evaluations are costly, and if some strengths pass and others fail, you’ll end up with an incomplete product offering.

Now imagine a different product: a multi-particulate ER capsule in Phase II development. There are five coating layers on the beads: a seal coat on the substrate, the first drug layer, another seal coat, the ER polymer layer and an outer immediate release drug coat. Your developer used uncommon equipment to develop the product. The process and formulation are robust and efficient and achieve exactly the clinical profile desired. So what’s the problem? Your development partner doesn’t do commercial manufacturing. Now you need to find a commercial manufacturing site with the exact expertise, equipment, capacity and interest to take on your production.
Feasibility matters for development, scalability and transfer

Products can run into trouble in a myriad of ways. The product may be too expensive to make relative to competing products. The time required to manufacture might be too lengthy and costly relative to the competition. The approach could be technically unsuitable for the desired functionality. Patients might not like the product or be unable to take it. The original manufacturing plan could fall through with few options for backup manufacturing. The production scale may not keep up with demand.

At a minimum, remediating problems like these costs time and money you won’t want to spend. At worst, the solutions are economically or technically unfeasible and the product never sees the light of day.

Development feasibility is one of the uppermost concerns for pharmaceutical developers considering an OCR project. Less obvious is that scale-up, scale-down and transfer feasibility should also be considered at this stage. To make the right choices to produce a viable formulation, not just for approval but for the whole product lifespan, understanding the options for design and formulation is critical.

Making informed decisions from the beginning will save time, money and frustration. The complexity of the proposed product, the likely clinical strategy and the degree of market competition surrounding it should all factor into the plan.

Background: types of OCR formulations

Broadly speaking, OCR products can be characterized by their functionality or composition. Briefly, some possible OCR dosage forms include:

- **Matrix** — API is dispersed within a polymer matrix
- **Reservoir** — API is contained within a polymer shell as either a monolith or multiparticulate
- **Diffusion** — API gradually diffuses across a polymer membrane, as in a reservoir system, or through a gelled matrix
- **Erosion** — API is released only as the matrix or coating dissolves
- **Monolith** — the finished product is a single piece
- **Multiparticulate** — the finished product contains a population of beads
- **Ion exchange** — API is released from drug-resin complex in the presence of a specific pH
- **Osmotic** — the product core contains API and an osmotic agent, coated with a semipermeable polymer; as water penetrates, drug dissolves and is pushed out a hole in the coating by osmotic pressure
- **Hybrids** — combinations of formats

Over the years, the pros and cons of each type from a performance point of view have become clear, but the various formulation types come with a host of other potentially important considerations as well. Characteristics to consider that may or may not be important for your proposed formulation include:

- Stability
- Cost
- Ease of change to batch scale
- Ease of tech transfer
- Availability of expertise
- Availability of equipment capacity
- Manufacturing cycle time
- API interactions with other components of the product
- Complex release profiles
- Applicability of add-on technology (e.g., solubility, bioavailability enhancement, taste-masking)
- Dosage strength flexibility
- Special population considerations: pediatric, geriatric, dysphagia, polypharmacy
- Abuse/misuse potential
- Alcohol co-administration effect
- Counterfeiting potential
- Ease of dose ranging, titration or tapering in clinical studies
- Dose-proportionate fill/biowaiver applicability
- Drug load/dosage form size
Will a tablet or a capsule work best for your OCR application?

In this article, there isn’t room to address all the possibilities. Instead, as an example, consider hydrophilic matrix tablets and multiparticulate capsules. Tablets and capsules are very different in formulation and process. Each has pros and cons, depending upon the desired effects.

Monolithic hydrophilic matrix tablets are the most common OCR products. Each consists of a polymer matrix that contains the API until it is released via diffusion through or erosion of the matrix.

The most common type of multi-particulate capsule entails one or more populations of Wurster-coated beads in an easily dissolved, two-piece, hard gelatin capsule shell.

What are some of the benefits and constraints of each approach?

From the patients’ point of view
For patients, capsules may be better tolerated. Capsules are often easier to swallow than tablets or caplets (capsule-shaped tablets), though coating the tablet helps. For patients with difficulty swallowing, capsules can be opened and the contents sprinkled on food and still release correctly. Tablets, particularly if uncoated, can be more prone to gastric irritation and sticking in the throat.

From the chemistry, manufacturing and controls (CMC) development aspect
Monolithic tablets are not very customizable. It can be hard to fine-tune their dissolution profiles, especially with more than one API. Because there is only a single matrix, multiple APIs will be released together with little latitude to adjust the dissolution profile of one relative to the other. If they are not compatible, you cannot protect them from each other without additional processing steps such as coating the API particles or resorting to a multilayer tablet.

OCR multiparticulate capsules, on the other hand, can be created with complex dissolution patterns. Separate populations of beads with different release patterns, such as immediate or controlled release, are developed and blended, in desired proportions.

Furthermore, multiple APIs can easily be separated from each other or made to release at different times because they are manufactured as separate beads with distinct dissolution rates. This kind of complex release pattern is impossible with a simple monolithic tablet.

This customizability comes at a cost, though. Each bead type requires its own development efforts, and its own process step, increasing the manufacturing cycle time and in-process testing requirements.

From the point of view of clinical development
Once the new drug product makes its way into clinical development, a different set of considerations comes into play. Often, during this stage, a dose change or a change in release pattern is required. In addition, a range of dosages may be needed for titration or tapering.

It’s easy to assume that changing the dosage strength or altering just one component of a tablet will not affect its release, but that is incorrect. Once you have customized a tablet’s release profile, altering any one of these elements risks altering the dissolution profile and may necessitate repetition of the entire release development process. In a worst case, you may have to reconsider the polymer selection, tablet size and API content, possibly reformulating as if from scratch.

Conversely for multiparticulate capsules, because the APIs are neatly packaged in their own bead populations, each aspect (dose or component release profile) can be altered independently of the other attributes. Because each bead population behaves independently, altering their quantity or composition of one rarely affects the others.

Gastric emptying also affects capsules’ performance much less than it does tablets’. If the dissolution release or drug absorption is affected by gastric emptying, this can be important. The timing of gastric emptying for any individual particle or tablet is variable. At a given moment, a tablet either exits the stomach, or it doesn’t. With a multiparticulate capsule, on the other hand, at any given time, some portion of the beads are likely to exit the stomach while others remain. This statistical population behavior smooths out the capsule performance by turning gastric emptying for the dose from a yes/no instantaneous event to an average time. This often leads to more predictable pharmacokinetic results from patient to patient.
From the manufacturing point of view
Monolithic matrices are simple, quick and relatively inexpensive to manufacture. The equipment involved may be as simple as a blender and a tablet press. Because the process is simple, tech transfer is relatively easy. A batch may be produced in a couple of hours, and batch size is limited only by the capacity of the mixing bin. Batch sizes weighing thousands of kilograms are not uncommon. Thanks to the limited process steps, in-process testing can be kept to a minimum, saving on laboratory time, manufacturing cycle time and ultimately, cost of goods.

In some cases, the powdered raw materials may not flow well. However, adding a granulation step will improve uniformity and flow, making for a more efficient compression process. Using newer, custom formulated excipients can help ease manufacturing further, allowing faster batch production, better release and lower cost.

Making multiparticulate capsules is generally more complex. For each API, a population of beads is built around core particles, such as sugar spheres. After the API is added, each bead is coated with a release-controlling polymer film. The equipment is less common and the processes more complex, making tech transfer and scale-up more difficult. Once all the required populations of beads have been formed, they are mixed in the desired proportions and placed in two-piece hard gelatin capsules.

The downside of multiparticulate OCR capsule manufacturing is that it is slow, labor-intensive and costly because of the multiple process steps required. The beads are formed via a multi-step, layered coating process. Smaller batch sizes (hundreds of kilograms) and longer processing (sometimes up to 24 hours per coating step) means that manufacturing this kind of product is more expensive and time-consuming than tablet manufacturing.

A note on reservoir formulations
In addition to matrix structures, tablets may also be built as monolithic reservoirs: a permeable shell built around a core containing the API in solution. Should the functional coating fail early, however, the entire drug dose will release at once. This dose dumping typically leads to higher than desired blood levels, side effects, toxicity and short duration of effect. Depending on the API and patient population, this risk may range from clinically insignificant to immediately life threatening. It is essential to get qualified medical input to assess this sort of risk on a product-by-product and indication basis.

Multiparticulate reservoirs, with beads that are structured similarly, albeit on a much smaller scale, mitigate the risk of dose dumping by distributing the dose over a multitude of smaller reservoirs, each of which can retain the drug load independently.

Major differences between matrix tablets and multiparticulate capsules for OCR formulations

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<th>MATRIX TABLETS</th>
<th>MULTIPARTICULATE CAPSULES</th>
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<tr>
<td>More common</td>
<td>Less common</td>
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<td>Lower cost, simpler to manufacture</td>
<td>More expensive to manufacture</td>
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<td>More difficult to adjust dose and/or dissolution release profile without impacting other aspects of the product</td>
<td>Easier to adjust dose and/or dissolution release profile without impacting other aspects of the product</td>
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<td>Better for straightforward products</td>
<td>Better for complex products</td>
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<td>- Commonly single API</td>
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<td>- Basic release pattern</td>
<td>- Complicated release pattern</td>
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<td>Often easier to tech transfer</td>
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<td>Significant market competition</td>
<td>Less competition due to greater differentiation</td>
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New developments
Fundamentally, tablets and capsules are not new. However, utilizing novel materials and processes and combining them with innovative add-on technologies can enable creation of products that were previously not feasible.

Newer technologies include:

- A wide variety of polymers, with varying attributes (hydrophilic, hydrophobic, pH-dependent, swelling/non-swelling) and a range of particle sizes
- Bioavailability/solubility enhancement technologies
- Formulated excipients that simplify development and enable faster processing
- New, faster layering and faster production methods
- Continuous manufacturing methods
Solving controlled release drug delivery puzzles

Examples
Certain situations demand specific dissolution profiles. Such profiles are often achieved by using combinations of immediate and delayed release granular components in multiparticulate capsules.

What if you have a drug that induces tolerance on repeated dosing, but for which abstinence restores sensitivity — and you want to create an OCR formulation of it? Consider a combination drug used to treat vascular disease such as angina, ischemic heart disease and arterial hypertension. Both of its constituents, isosorbide dinitrate and hydralazine, are prone to induce tolerance. The solution is to deliver two to three separate pulses of these APIs from a single, once-a-day capsule. A pulsatile composition produces a plasma profile similar to that obtained by sequential administration of immediate release doses, as in a typical treatment regimen. To achieve this effect, immediate release and delayed release bead populations are created for each API. Combining all of these bead types in a single capsule achieves the required effect.

Useful chronotherapeutic effects can also be achieved through delayed release. Examples of this strategy include: an evening dose of calcium channel blocker verapamil formulated for delayed, early-morning delivery to protect the heart at the most frequent time for heart attacks; and a six- to eight-hour delay, nighttime formulation that releases a rheumatoid arthritis medication in the early morning to prevent the morning stiffness typical of that disease.

Long, sustained release pain medications lasting 12-24 hours may also be formulated. Controlled release eliminates blood-level peaks and their potential for increased side effects, while also reducing blood-level valleys, which carry the risk of poor efficacy from under-dosing.

Conclusion
For oral controlled release medications, the various types of dosage forms offer distinct advantages and disadvantages. Multiparticulate capsules offer more flexibility for sophisticated, timed delivery of multiple APIs and for dose adjustments during clinical trials. However, they are expensive and time-consuming to develop and manufacture. Tablets are faster and more economical to develop and manufacture, though adjusting dosage and release profiles may be more difficult.

In deciding which of the many possible paths to follow, developers should consider how complicated their product is and what its price point must be to compete with other similar products on the market. Simple products are usually best designed as tablets to reduce manufacturing costs that could compromise their success in the marketplace. Finding a partner with as much experience as possible in working with solid oral controlled release formulations will help ensure success in oral controlled release product development.