formulation

Developing oral controlled-release drug products

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This article describes the various types of oral controlled-release (OCR) dosage forms and discusses the factors to consider when developing an OCR drug product.

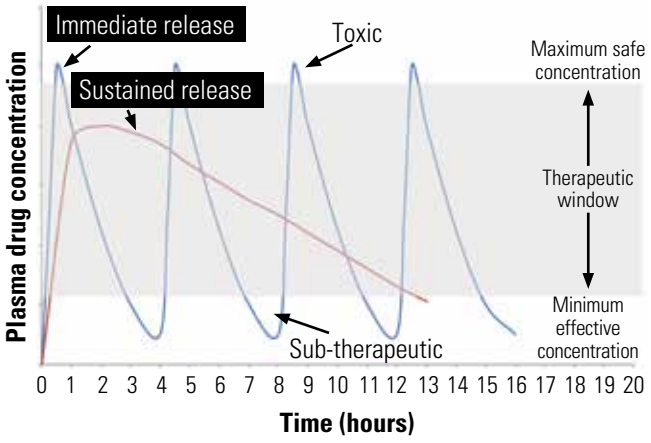
Oral controlled-release (OCR) drug products release the active pharmaceutical ingredient (API) into the patient's gastrointestinal (GI) tract either slowly or after a delay. This results in much of the API being released in an area of higher pH, over a wider range of GI location, and over time. The peak concentration (C_{max}) of API in the blood plasma for an OCR dosage form will typically be lower and delayed and will rise and fall more slowly than for an immediate-release dosage form, as shown in Figure 1.

Companies develop OCR dosage forms for a number of reasons, including:

- If an API is prone to degradation in acid, an OCR formulation will protect the API as it passes through the stomach.
- If an API causes local irritation, an OCR formulation can spread it over a wider area, lowering the local concentration and minimizing the irritation.
- If an API causes side effects at high plasma concentrations, the lower C_{max} can help prevent them from occurring (Figure 1).
- If there is a lack of effect as the API's plasma concentration drops below a certain threshold, an OCR product can help keep the plasma concentration within the desired range for longer, extending the duration of therapeutic effect. This allows less frequent dosing, making it easier for patients to stay on schedule and avoid periods of lack of effect (Figure 1).

Figure 1

Immediate versus sustained release profiles



While these are the most common patient benefits of OCR dosage forms, not all benefits will be relevant to every product, and in some cases, these attributes are not beneficial. To determine the right mix of attributes to offer the best benefit profile for OCR products, carefully and holistically consider each API's pharmacokinetics, pharmacodynamics, side effects, therapeutic window, metabolism, absorption, and physicochemical behavior.

In OCR product development, decisions made at the outset determine success. Selecting the final dosage form, developing the approach to formulation and processing, and avoiding common roadblocks are key. While a surprisingly wide variety of OCR formulations are possible, faulty planning for development and manufacturing can cost time and money and can potentially end a whole project.

Diverse dosage forms offer a range of advantages and disadvantages for OCR medications. Tablets are faster, easier, and more economical to produce but limit the ability to fine-tune release profiles or dosages. Multiparticulate capsules allow for complex, timed delivery of multiple APIs and mid-clinical-phase dose adjustments but are costly and time-intensive to develop and manufacture. The following guidance can help formulators make informed decisions.

Types of OCR formulations

OCR product types vary widely and can be characterized by functionality or composition. Examples of possible OCR dosage forms are:

- **Matrix:** The API is dispersed within a polymer matrix.
- **Reservoir:** The API in solution resides in a permeable polymer shell as a monolith or multiparticulate. Note that premature coating failure in monolithic reservoirs can cause APIs to be released all at once, possibly leading to toxic blood levels and short durations of effect.
- **Diffusion:** The API diffuses across a polymer membrane, such as in a reservoir system or through a gelled matrix.
- **Erosion:** Only dissolution of the matrix or coating releases the API.
- **Monolith:** The product is a single entity.
- **Multiparticulate:** Small beads containing the API and excipients are placed in a capsule, preparing the beads by various methods, including spray coating or powder layering the API onto a core, such as a sugar sphere. API-loaded beads can also be coated with polymers to modify the API release rate, and multiple populations of beads can be included to create combination products or different drug-release profiles.
- **Ion exchange:** A drug-resin complex releases the API in the presence of a specific pH.
- **Osmotic:** A semipermeable polymer coats a core containing the API and an osmotic agent. As water penetrates the polymer, the API dissolves and exits through the coating via osmotic pressure.
- **Hybrids and new developments:** Combination formats, novel materials and processes, and innovative add-on technologies are constantly expanding the possibilities.

Photo 1: Manufacturing monolithic-matrix tablets uses simple equipment and is relatively quick and inexpensive. Delayed release can be achieved by applying a coating that prevents the tablets from immediately dissolving in the stomach.

In addition to evaluating the advantages and disadvantages of each dosage form for the intended product, consider other critical product characteristics, including stability, cost, ease of scale-up and tech transfer, required expertise, equipment capacity, cycle time, API interactions, dosing flexibility, and abuse potential.

Development, scalability, and transfer

Feasibility is a chief concern for pharmaceutical developers considering OCR projects, and poor technology choices or planning can be disastrous. Manufacturing may be too expensive, time-consuming, or technically ineffective, and if scale-up, scale-down, and transfer feasibility aren't considered during planning, the manufacturing plan might fall through with no backup or production scale might not meet demand.

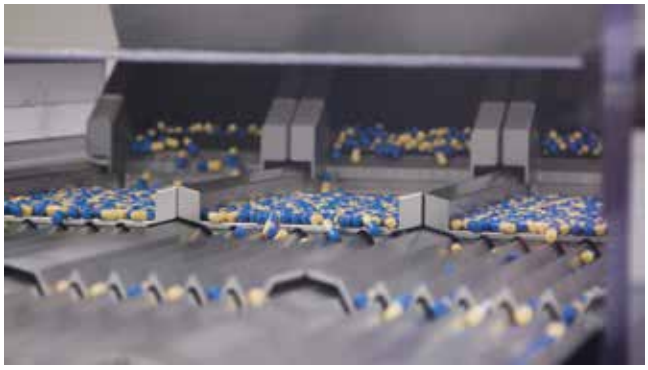


Photo 2: OCR multiparticulate capsules can contain separate populations of beads to keep multiple APIs separate and/or to have them release at different times, achieving complex release patterns.

Understanding the options and their design and formulation ramifications from the beginning is critical and can save time and money and reduce frustration. The nature of the proposed product, the strength of market competition, and likely clinical strategies are all relevant. The right choices will result in a formulation that remains viable from its approval through to the end of the product's lifespan.

Choice of tablet or capsule

To ensure the success of an OCR product, consider the complexity of the performance requirements with respect to the patient, dissolution profiles, and clinical and manufacturing requirements. Also consider the price point needed to compete in the marketplace. For example, tablets may be the best option to limit manufacturing costs for simple products with stiff market competition.

As an exercise to illustrate the types of decisions required, consider two product types: 1) monolithic hydrophilic matrix tablets and 2) two-piece, hard gelatin capsules containing one or more populations of Wurster-coated multiparticulate beads. Each of these common formats has pros and cons with respect to desired performance and from the very different perspectives of formulation, processing, and economics.

Patients. Capsules are generally easier to swallow than tablets. Also, patients or caregivers can open the capsules and sprinkle the contents on food to aid in swallowing, and the API(s) will still release correctly. Tablets, especially if not coated, are more likely to stick in the patient's throat and cause gastric irritation.

Dissolution profiles. Because monolithic tablets have only a single matrix, a tablet that contains multiple APIs will release them simultaneously. Formulators cannot fine tune each API's dissolution profile or prevent the APIs from interacting without additional processing steps.

In contrast, OCR multiparticulate capsules can contain separate populations of beads to keep multiple APIs separate and/or to have them release at different times, achieving complex release patterns. Developing each of the various bead populations is costly and requires its own process step, however, increasing development time and cost, manufacturing cycle times, and testing requirements.

Clinical development. Clinical development often calls for alterations in dose or release pattern. Furthermore, the product might require a range of dosages for titration or tapering. Unfortunately, after a tablet's release profile is customized, any change in the formula may necessitate complete redevelopment. This may require re-evaluating polymer selection, tablet size, and API content. In contrast, because multiparticulate capsules package APIs as beads that behave independently, the dose or component release profile can be easily adjusted without affecting other product attributes.

Patient-to-patient variation in gastric emptying rate is another important consideration. Differences are more likely to affect a tablet's performance, because the entire tablet moves as a unit. The API resides either in the stomach or beyond, unlike capsule beads that move gradually along the digestive tract. This continuous stomach emptying often results in lower patient-to-patient pharmacokinetic variability.

Manufacturing. Manufacturing monolithic-matrix tablets uses simple equipment and is relatively quick and inexpensive. This uncomplicated process facilitates technology transfer and keeps in-process testing and cycle times to a minimum. A batch, which might weigh thousands of kilograms, can be produced in a few hours. If needed, a granulation step can improve the formulation's uniformity and flow for more efficient tablet compression. Newly available excipients can ease manufacturing further, allowing faster batch production, better release, and lower cost.

Manufacturing multiparticulate capsules, on the other hand, is more complicated and requires building a population of beads for each API by adding the API to a core, such as a sugar particle, and then coating it with a release-controlling polymer film. After the beads are formed, they must be mixed in the desired proportion and placed into the capsules. The less-common equipment and more complex processes required complicate technology transfer and scale-up.

The multistep, labor-intensive processing required for multiparticulate capsules limits batch sizes to the hundreds of kilograms and takes up to 24 hours per coating step. As a result, multiparticulate OCR products are frequently more expensive and time-consuming to manufacture than tablets.

TABLE 1

Tablets versus capsules for OCR formulations

Matrix tablets	Multiparticulate capsules
More common	Less common
Lower cost, simpler to manufacture	More expensive to manufacture
More difficult to adjust the dose and/or dissolution release profile without impacting other aspects of the product	Easier to adjust the dose and/or dissolution release profile without impacting other aspects of the product
Better for straightforward products • Commonly single API • Basic release pattern	Better for complex products • Multiple APIs • Complicated release pattern
Often easier to tech transfer	Often more difficult to tech transfer
Significant market competition	Less competition due to greater differentiation

Solutions for drug-delivery conundrums

While tablets are typically less costly and time-consuming to manufacture, multiparticulate formulations are often the best—or the only—choice to achieve a specific dissolution profile. Formulators can combine immediate- and delayed-release granular components to achieve the desired performance.

To illustrate, imagine a drug product with two APIs that must be dosed together. Each API tends to induce tolerance, a state in which the patient requires higher and higher doses to achieve a therapeutic effect. A typical slow-release formulation exposes cells to the drug continuously, causing progressive alterations in their ability to respond. In contrast, sequential administration of immediate- or short-release doses tends not to induce tolerance because the drug level in the patient's bloodstream dips between doses, allowing cell receptors to normalize before their next exposure to the drug. By mimicking this pattern that allows drug levels to drop periodically, formulators can create a once-a-day delivery system that maintains a therapeutic effect without inducing tolerance. This can be accomplished by combining immediate-release and delayed-release bead populations for each API, delivering two to three separate pulses of each API from a single capsule.

Delayed release is another means of achieving useful chronotherapeutic effects. This strategy can be used to delay release of an evening dose of the calcium channel blocker verapamil until early morning, the most frequent time for heart attacks, or release of an arthritis medication can be delayed until overnight to prevent the morning stiffness typical of that disease. Similarly, 12- to 24-hour, sustained-release pain medications can smooth out blood levels to diminish side effects and maintain efficacy.

Summary

The major differences between matrix tablets and multiparticulate capsules for OCR formulations are listed in Table 1.

Solid OCR drug product development is far from straightforward, which is why many companies look to an outsourcing partner with extensive experience in solid OCR formulation, especially for products with complex release patterns or multiple APIs. Such a partner can help streamline the process, eliminate missteps, shorten timelines, and prevent unnecessary expenditures, ensuring the OCR development project's success. *T&C*

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