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How to Achieve Different Release Profiles and Select Excipients for Formulation Development of Modified Release Oral Solid Dosage Forms

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Modified release oral solid dosage forms are highly specialized formulations. These dosage forms enable drug release over a defined period or at specific locations within the gastrointestinal (GI) tract for prolonged or targeted drug delivery. At the same time, they allow for less frequent dosing, which can increase patient adherence and result in fewer side effects by reducing peaks and troughs in blood levels.

However, modified release formulation and manufacturing are challenging. To obtain the desired release profile — or release profiles if there are more than one active pharmaceutical ingredient (API) — a holistic approach is necessary. Knowledge of the API, inclusion of appropriate excipients, and selection of dosage form and manufacturing techniques all play a role. These considerations, along with the desired pharmacokinetic (PK) profile, help build a robust system that delivers the therapeutic in a fashion that best benefits the patient. As this paper will explain, numerous considerations in addition to those listed above enter into the planning and execution of a successful modified release oral solid dosage formulation.

Determining and Achieving the Desired Release Profile

In order to determine what release profile is needed to achieve the target dosing regimen — whether that is once a day, twice a day, or some other interval — the formulation scientist must first examine the literature and any other accessible collective experience to gain as much knowledge of each API's fundamental physicochemical and biopharmaceutical properties as possible. The following types of information are especially pertinent.

Pharmacokinetics (PK)

Understanding the PK in general and the serum concentrations known to result from immediate release dosing regimens will help determine the pattern of release needed to make the target, modified release dosing regimen possible. Do you need zero order (constant) or pulsatile release? And if pulsatile is indicated, what intervals and dosages are most likely to keep serum levels within the therapeutic range? Previous knowledge about the PK will help you answer these questions.

Site of absorption

Knowing where in the GI tract the API is best absorbed tells you where you may need to aim for release to occur. Some, such as weak acids, are absorbed best in the low pH gastric environment. In these cases, a gastroretentive formulation might make sense to increase residence time in the stomach and allow for maximal absorption to take place.

Other APIs require the neutral to higher pH of the duodenum. These may be weak acids, weak bases, lipid-soluble small molecules, or other molecules for which active transport systems exist in the upper GI. Additionally, some APIs are absorbed best in the colon.

Drug solubility

Once the site of absorption is understood, drug solubility must be considered to ensure that the API is released in the target area. If the drug is to be absorbed in the stomach, it must dissolve quickly upon arrival there.

If, on the other hand, the drug is to be released and absorbed in the upper GI tract, two things must happen. First, it must be protected from being prematurely released in the stomach. If it's not soluble at low pH, this won't happen. But if it is soluble at low pH, it may need an enteric coating to survive passage through the stomach.

Last, if the API is not soluble in the upper GI tract — but needs to be absorbed there — it must be prepared with some additional, enabling technology to increase its solubility at mid-high pH. Solubility enhancements include spray-dry dispersion, micronization, or selection of an alternate salt form.

Powder and bulk properties

How well the drug flows as a powder and its processability can help guide the choice of delivery system: Can the API be made into a tablet or capsule or would a multiparticulate approach be better? If processing is an issue, special excipients that aid in processing, in addition to release-rate controlling excipients, may need to be added into the formulation to improve flowability or compressibility.

Particle size distribution

Particle size can affect both flow and solubility rates. For instance, micronized particles tend to adhere to each other and present processing challenges, whereas larger particles flow more freely. The addition of large-particle excipients in the formulation might improve overall flowability and processability. On the other hand, because of their greater total surface area, micronized particles may dissolve more quickly than large particles. The dissolution rate can further influence formulation and excipient selection to achieve the desired release profile. Alternate processing methods such as dry or wet granulation techniques may be employed to overcome processing difficulties.

To avoid surprises and the need for later re-work, formulators must bear in mind a holistic view of the above characteristics — and more.

Handling Higher Drug Loads

Modified release profiles (particularly extended release) often necessitate higher drug loads and/or, in the case of combination drugs, multiple API loads. This extra bulk and complexity present further formulation challenges, especially since most of today's APIs have poor flow and processing characteristics necessitating additional excipients to aid in manufacturability. Formulators must be able to work with higher drug loads while carefully selecting excipients so the final dosage form performs as desired while remaining acceptable for the patient.

Choosing a Delivery System

Having done all the pre-work — understanding the target release profile and researching the available body of knowledge about the APIs and their physicochemical and pharmaceutical properties — it's time to decide on a delivery system. The more information that is amassed at the start, the more rational the first round of design, in terms of excipient selection and manufacturing processes, will be.

Omitting these steps is like taking a shot in the dark and will likely mean encountering difficulties later that must be sorted out — usually by going back to obtain this very information.

Popular delivery systems

Options for modifying release profiles differ based on the delivery system selected. Typical choices include:

- **Matrix tablet** — Monolithic hydrophilic matrix tablets are among the most common oral solid modified release products. The API is dispersed within a polymer matrix. It is released gradually either by diffusion across the matrix or as the matrix erodes. These may be hard to fine-tune for dissolution, especially with multiple APIs. Incompatible APIs will require additional or alternative processing steps (such as making a bilayer tablet) to protect them from each other.
- **Capsule** — A soluble gelatin or HPMC casing is filled with solid API and excipients, which are released when the capsule dissolves. Again, the release profile is determined by formulation components and/or the capsule shell itself, which may be specially formulated for modified release characteristics.

- **Multiparticulate** — A capsule containing one or more populations of pellets in an easily dissolved, hard gelatin or hydroxypropyl methylcellulose (HPMC) shell. API dosages are easily adjusted by increasing or decreasing the various bead contents. This delivery system can be created with complex dissolution patterns by formulating bead populations that release differently.

Sample reasons to opt for one delivery system over another

A clear understanding of the API's characteristics helps clarify which delivery system makes the most sense. For example:

- If the API is easily compressible and the desired release profile is not overly complex, a matrix tablet may be the best choice.
- If you are trying to achieve a more complex release profile or need different release profiles in a system with a single API or multiple APIs, you could take advantage of a multiparticulate's modularity.
- If the drug load is too high for a multiparticulate and the drug isn't compressible, a dry powder-fill capsule may be a good choice.

Selecting Excipients

Once the required release profile of the API(s), its physicochemical characteristics, and the delivery system are all known, release-controlling polymers must be selected. The industry offers a multitude of options for tailoring where and how fast your APIs are released, as well as for enhancing manufacturability.

Release-controlling polymers

There are many release-controlling agents available: organic, water-soluble HPMC and hydroxypropyl cellulose (HPC); the enteric coating methacrylate; polyacrylic acids; polyethylene oxide, and so on. When looking to target a specific release rate, many aspects of the release-controlling polymer under consideration should be carefully examined, such as:

- **Molecular weight**
  A polymer's molecular weight directly impacts release rate; an increase in molecular weight generally slows the release profile.
- **pH dependency**
  A wide variety of release-controlling polymers are available that dissolve at specific pHs at a variety of rates, so an API's rate of release can be controlled at low pH (e.g., in the stomach). Alternatively, to achieve release further along the GI tract, an enteric coating that is insoluble until it reaches the higher pH of the duodenum would be a good choice.
- **Processability**
  Knowing how release-controlling polymers behave in the proposed process and delivery system at typical usage levels can also influence selection. Will it help or hinder, given the API's tendencies? Some rate-controlling polymers are known to behave better in certain processes than in others. Features that may make a difference include:
  - High or low melting point
  - Good or poor flowability
  - Good or poor compactability even if employing dry granulation techniques

Other beneficial excipients

Additional consideration should be given to other excipients that are not predominantly release-rate-controlling but could potentially contribute to the manner the drug will release from the dosage form. These can be used to improve processing characteristics or impart other desirable attributes.

- For instance, if an increased API load doesn't flow well, a flow-enhancing excipient such as colloidal silicon dioxide may help.
- Or, choosing a soluble or insoluble filler — lactose/mannitol vs. microcrystalline cellulose, for example — may affect release rate in different ways:
  - May cause dosage form to disintegrate into granular aggregates in the dissolution medium; these aggregates, having higher surface area, will then begin to dissolve at a different rate
  - May cause dosage form to dissolve quickly, as with the addition of superdisintegrants
  - May cause dosage form to erode slowly over time, instead of truly disintegrating
- Disintegrants can open pores as channels in a dosage form to hasten intrusion of the dissolution medium into the dosage form and initiate release.

- Use of hydrophobic lubricants in the formulation to aid in ejection of tablets after compression may adversely affect the dissolution profile. For instance, commonly used magnesium stearate has a waterproofing effect that can slow dissolution. Care should be taken when using lubricants to assess their effect on dissolution.
- Film coatings for tablets may also affect release rates:
  - Functional coats may be intended to modulate a dissolution profile
  - Non-functional coats should not impact dissolution rates; this should be confirmed through dissolution studies
  - Enteric coatings are made to be insoluble at low pH, enabling the dosage form to remain intact until passage from the stomach into the higher-pH region of the upper intestine where the coating is soluble

Excipients affect both release rate and processability and can be selected to enhance or offset API effects and improve a formulation's processing characteristics and dissolution performance. It's important to realize that excipients not primarily intended to control release can, indeed, affect it.

You Need a Partner That Will Get Your Product Right

Achieving a specific release profile and selecting excipients for formulation development of modified release oral solid dosage forms is a multifaceted task. It requires a holistic, well-researched view of:

- Desired PK profile
- Dosing regimen
- API characteristics
- Processing considerations
- Appropriate excipient selection

These elements must all work in concert for a consistent, repeatable dosage form to be achieved.

Pioneering modified release since the 1980s at one of the first U.S. sites to apply this technology, Recro Gainesville scientists share decades of experience in the field. With an extensive history of manufacturing modified release dosage forms, our development and commercial teams are ready to leverage their keen insights and offer solutions to advance your project. With right size, proactive management, a proven track record of tackling the most complex formulations, and unparalleled regulatory expertise, our scientists will propel your modified release product across the finish line.

When You're Looking for the Right Size, Right Partner, and Right Expertise — Recro Gainesville Is Your Go-To for Modified Release.

About Recro Gainesville

Recro Gainesville 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 dose and DEA controlled substances, Recro has the experts to deliver our clients' most complex pharmaceutical development and manufacturing projects in our best-in-class facilities, totaling 120,000 square feet. For more information about Recro's flexible CDMO solutions, visit recrogainesville.com.

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