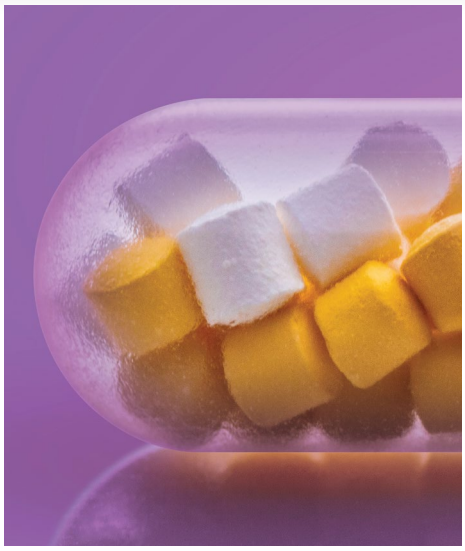
**ARTICLE** | Nathan Dormer, PhD • Director of Drug Development

ADARE® PHARMA SOLUTIONS

# CUSTOMIZED RELEASE THROUGH DISPERSED DOSAGE FORMATS DRIVING PATIENT ACCEPTANCE AND THERAPEUTIC PERFORMANCE



**Pharmaceutical development is as much an art as it is a science, with experts working to find the best solutions and then formulating them in a manner that is universally accessible, efficacious, and sustainable. This is doubly true for drug delivery. On one hand, drug developers must navigate what is physically possible in terms of dose or modified release of the drug itself; on the other hand, factors such as patient compliance, market need, and (unfortunately) payor acceptance can also impart moderate influence.**

**Typically, dosage format is a practical decision based on the target product profile: how the developer envisions the product best addressing a clinical indication by maintaining population-wide efficacy. Once the preferred format is identified, "fit" is considered. Sometimes, slight compromises must be made during formulation development simply due to technical challenges with achieving the necessary dose and duration. Ideally, technical appropriateness aligns with patient-centricity to satisfy all product criteria.**

In most cases, drug developers have a general idea of what is technically feasible based on products already on the market or their existing understanding of controlled release technology conventions. Moreover, they generally can provide adequate information for a CDMO partner to efficiently begin development of dosage form prototyping, if not an explicit formulary.

For example, a developer may request their product provide a 12-hour release, with half of the drug deployed in the first three hours, because their research and/or modeling indicates that such release supports the pharmacokinetic profile or provides a fast-acting effect.

With a modest set of target product profile "wants" and "needs" like these, the formulation development process for solid oral dosage forms typically becomes straightforward.

But moderate challenges arise when considerations about patient centricity are applied, effectively reducing the degrees of freedom to two or even one. Continuing with the "12-hour release with 50% in the first three hours" example, let's further postulate that the dose is also 500 mg, once daily. Such delivery is no problem for a larger bilayer tablet or another modified release swellable tablet matrix, but what if the patient is not able or willing to swallow pills? What if the drug has a bitter or unpalatable taste? What if this is an indication, such as cancer, where compliance is critical?

These sound like steep challenges to overcome, but the reality is that solutions exist in the dispersed dosage format space (e.g. powders, granules) that can meet these requirements while achieving the same modified release and/or taste-masked capability as complex tablet dosage forms.

## Does "modified" or "controlled" release always mean "delayed"?

No. Controlled or modified release simply indicates that the entire drug release is not immediate (i.e., 85% in 30 minutes or less). Drug release profiles can be immediate, delayed immediate, sustained, or delayed sustained; dispersed formats also exist that can achieve each profile (Fig. 1). Even within sustained release, diffusion- and erosion-based systems can approximate asymptotic- and linear/zero-order-profiles, respectively. "Loading" doses are sometimes used to get therapeutics onboard immediately, while the rest is sustained or delayed.

Thus, specific release profiles are accomplished by applying purpose-built technologies and different combinations of materials in specific configurations; this can be done for dispersed dosage formats just as well as tablets.

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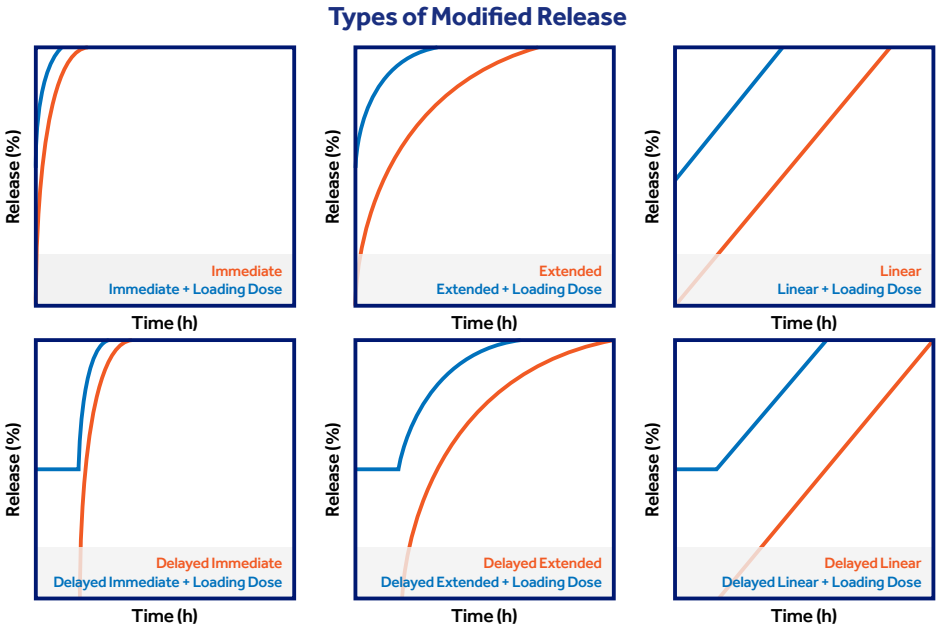


**Fig. 1** – Common types of modified release that are acheivable with tablets and dispersed dosage formats alike.

## Can a dispersed dosage format be made imperceivable to patients?

Yes. One might be quick to think that an oral powder will have a taste, or that it will feel gritty in one's mouth if it is mixed into a drink or sprinkled on food. However, this does not have to be the case. The qualitative threshold for mouthfeel or dosage form perception shifts as a combinatory function of particle size and administration vehicle rheology: the study of a vehicle's deformation response to forces (such as chewing and swallowing) and inherent physical properties (such as viscosity).

For example, for a powder dosed orally without a vehicle, a smaller particle might be most suitable, though it must be large enough to not get caught between teeth. Conversely, if a much larger particle or bead is warranted because of a large dose or a highly customized release, one might consider using a more viscous liquid vehicle for administration, whether co-packaged with the powder or recommended via the label.

## How does Adare Pharma Solutions assess the need for customized drug release?

When partnering with a customer to develop a customized delivery system, Adare scientists sit down with the customer to find out everything we can about their desired outcome.

**1** First, we seek information about the dose and duration: How much total product needs to be delivered after each administration and how does the delivery look in terms of GI location?
**2** Next, we determine the preferred release profile. **(Fig. 1)**
**3** Finally, we consider "softer" parts of the formulation. Can it be a tablet, or does it need to be a powder? If it's a powder, will it dissolve in a vehicle, be sprinkled on food, or be placed within a traditional capsule? These are just two examples of the kinds of questions we partner with the customer to answer.

With this information, we can then recommend the technologies, or combinations of technologies, that best fit the customer's needs. After determining technology and raw material possibilities based on dose and release profile, we triangulate the dose, duration, and format to find the technology candidates most likely to be successful.

## What customized release solutions are offered by Adare Pharma Solutions?

In addition to standard tablet and capsule manufacturing, Adare offers an extensive line of proprietary technology solutions.

These technologies have been specifically designed to maintain the dosage form benefits of larger tablets and capsules (e.g. modified release, taste-masking, high drug loading) while leveraging dispersed or non-standard oral formats. **(Fig. 2)**

potential to turn the "once daily" standard into a "once monthly" or "once yearly" reality, and Unisun® is positioned as a site-specific (i.e. transtympanic) extended release. Our deep expertise and experience with modified release technologies allows Adare scientists to partner with

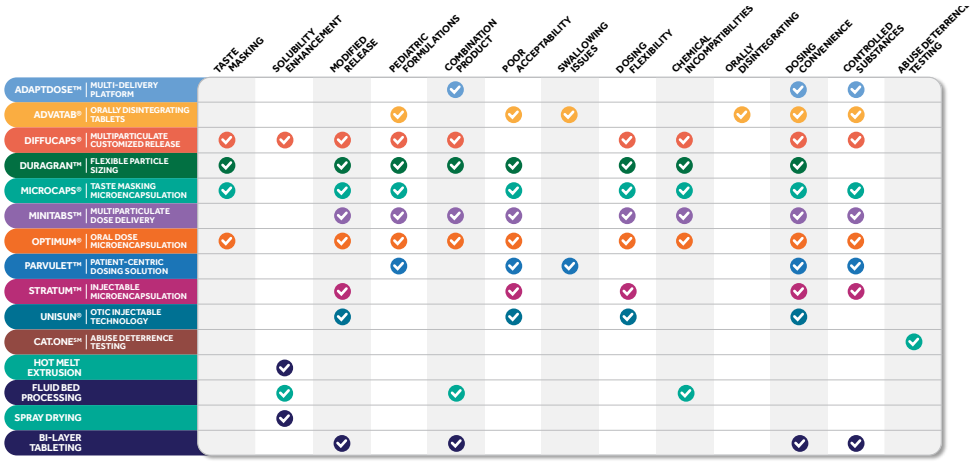


**Fig. 2** – Adare Pharma Solution's suite of non-standard modified release technologies cover multiple target product profile needs.

At Adare, we do not believe drug developers (or, ultimately, patients) should have to choose between performance and dosage format when both are a priority. "Once-a-day" dosing used to be reserved for large bilayer tablets, and that is simply an outdated belief from our perspective.

Our larger modified release tablet options start at Diffutab® and AdvaTab®, and decrease in size from Minitabs™ and Diffucaps® down to sub-200 µm particles in Optimµm® and Microcaps®. These technologies provide a wide reach over product formats, addressing numerous customized release profiles as well as providing liquid-like movement to the digestive tract and ease of dosing. At Adare, our customers have access to cutting edge swellable technologies like Parvulet®, which packs like a powder or tablet and performs like a pudding or apple sauce.

## What does the future hold for Adare's customized release offerings?

We are always assessing ways to provide a greater impact to drug developers, whether they have therapeutics that are already marketed or they're seeking approval for new molecules. We specialize in drug release for extended durations; technologies such as Stratµm® have the

customers in ways that other CDMOs can't. We work hard to ensure that the clinical indication is addressed with as little sacrifice as possible to the ideal drug product format.

At every step in the development process, we maintain constant contact with customers to keep them aware of all influencing factors, from chemistry risks to budget impacts associated with a given course of action. Adare always empowers customers to make informed decisions.

Though other CDMOs possess modified release technologies, Adare is one of the few to specialize in both a wide range of dispersed dosage formats and standard pills. This enables us to suggest solutions that are always in our customers' best interests. With our extensive service offerings, conflict seldom arises between what our customer needs and what Adare can achieve. This flexibility is crucial in helping our customers accomplish their mission to serve patients and improve their quality of life.

**To learn more about Adare's customized release technologies, visit AdarePharmaSolutions.com**

ADARE® PHARMA SOLUTIONS

**Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, customized release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare's seven facilities in the US and Europe have developed and manufactured more than 65 products sold by customers worldwide.**

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COMPLEX DRUG
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# YOUR PARTNER FOR SMALL MOLECULE ORAL SOLID DOSE SUCCESS

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## TRANSFORMING DRUG DELIVERY. TRANSFORMING LIVES.

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