

Information sheet

Modified-Release Formulation Strategies

The popularity of modified-release (MR) dosage forms continues to rise due to the many therapeutic benefits that they offer for both drug developers and patients. Oral MR formulations are designed to control the rate and/or location of drug release in the gastrointestinal (GI) tract. In contrast to immediate-release (IR) formulations, MR dosage forms can offer:

- **maintenance of drug plasma concentrations over a prolonged period to reduce dosing frequency**
- **attenuation of drug peak-to-trough ratios to reduce peak-related adverse events (AEs) and improve efficacy**
- **drug delivery to targeted regions of the GI tract for localized treatment.**

Although there are many benefits with this type of formulation, there are also several challenges when trying to develop a MR formulation. While moving through the different regions of the GI tract, the formulation must be able to withstand changes in environmental conditions (such as pH, fluid volume, fluid composition, and physical forces) and changes in drug absorption due to active transport mechanisms in the gut epithelium. In addition, the physicochemical and associated biopharmaceutics properties of the active pharmaceutical ingredient (API) must be considered.

A variety of different MR formulation technologies are available, so it is vital that drug developers select a strategy that will provide optimal results in the most efficient and cost-effective manner.

Our experience and expertise

At Quotient Sciences, we have supported more than 100 MR development programs over the past decade across a wide variety of therapeutic areas. Our extensive formulation know-how, coupled with our agile and flexible approach to clinical and commercial manufacturing, makes us the ideal partner to provide an end-to-end solution for the development of MR drug products.



MR formulation technologies

At Quotient Sciences, we recognize that careful selection of appropriate delivery technologies is key to the design of successful MR formulations. We have extensive experience in using a wide variety of formulation technologies to control drug release and delivery, including:

MR format	Objective	Formulation technology
Gastro-retention	<ul style="list-style-type: none"> Keep the formulation in the stomach for an extended period to maximize the duration of absorption or therapeutic activity 	Swellable tablets (monolithic, bilayer, trilayer)
Gastro-resistant	<ul style="list-style-type: none"> Prevent release of the drug in the stomach and/or upper GI tract Overcome first-pass metabolism or gastric irritation 	Enteric-coated tablets or capsules
Sustained or extended release	<ul style="list-style-type: none"> Extend the <i>in-vivo</i> release profile of the drug or enable once-daily dosing 	Matrix tablets, coated tablets, or multiparticulates
Targeted or controlled delivery	<ul style="list-style-type: none"> Release the drug at or near the intended site of absorption or action Have either IR or extended-release characteristics Deliver time-, pH-, or microbially-triggered release 	Tablets, capsules, or multiparticulates
Biphasic release	<ul style="list-style-type: none"> Eliminate the need for repeat dosing Provide rapid therapeutic effect from an IR layer and extended dosing from a sustained-release layer 	Bilayer tablets or multiparticulates
Pulsatile release	<ul style="list-style-type: none"> Release the drug as a pulse after a pre-determined lag time, designed according to the body's circadian rhythm Provide a release mechanism beneficial for drugs where time-dependent dosing is required or those that undergo first-pass metabolism 	Bilayer tablets or multiparticulates

Our unique, integrated approach to accelerate the development of MR dosage forms

Traditional MR development programs follow a rigid, linear process, which relies heavily on using pre-clinical models to predict performance in humans. This can be risky and inefficient, given the poor correlation of bioavailability between pre-clinical species and humans. Repeated cycles of pre-clinical and clinical testing are often needed, which can be costly and time-consuming.

At Quotient Sciences, our unique Translational Pharmaceuticals® platform integrates drug substance, drug product development, real-time adaptive Good Manufacturing Practice (GMP) manufacturing, and clinical testing. Flexible study protocols and rapid 'make-test' cycles

enable optimization of MR formulations in real time based on arising clinical data.

As part of regulatory submissions, we obtain approval to make formulation adjustments within a mapped design space. This means that any formulation within certain defined parameters can be rapidly made and tested to determine the impact on the drug release rate and pharmacokinetic (PK) profile, enabling us to efficiently identify the optimal formulation.

This reduces development risks, maximizes the probability of clinical success, and saves time and costs.



Development of an optimized MR tablet formulation for initial proof-of-concept trials

Background and objectives

SLx-2101, a novel phosphodiesterase-5 (PDE-5) inhibitor, was being developed by Surface Logix as an antihypertensive agent. A Phase II study of an IR tablet determined that a once-daily MR formulation was needed to reduce C_{max} -related AEs and ensure the 24-hour PK profile remained within the therapeutic window.

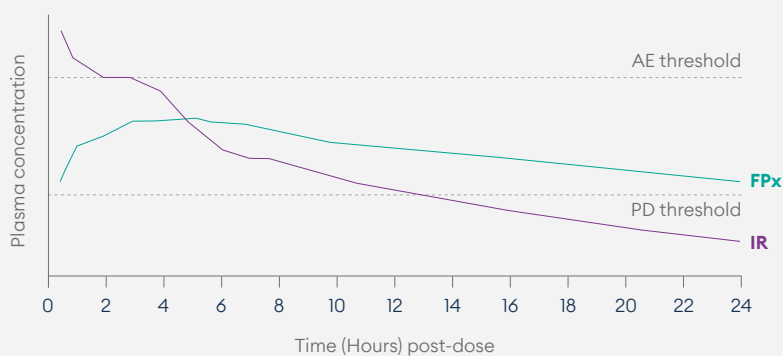
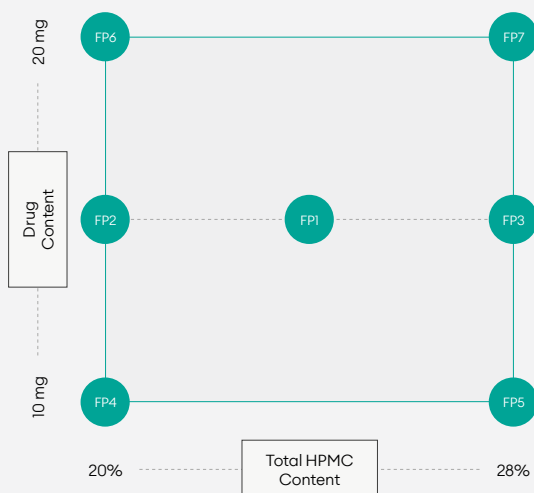
Project scope

Hydroxypropyl methylcellulose (HPMC)-based matrix MR tablets were developed for assessment in an adaptive relative bioavailability Phase I study to optimize the MR tablet formulation based on human clinical data. A two-dimensional formulation design space was established, covering dose strengths between 10 and 20 mg and sustained drug release durations between approximately

12 and 20 hours. The relationship between key formulation variables and formulation performance was investigated. Representative formulations at the extremes and mid-points of the design space were manufactured and characterized to demonstrate that the performance of the formulation can be controlled by varying the levels of drug loading and HPMC in the formulation.

Outcome

SLx-2101 MR tablet formulations within the design space were manufactured in real time and evaluated in a flexible clinical study, avoiding the restriction of only dosing pre-defined formulation compositions. The formulation selection was driven by clinical data from the previous dosing period, and the optimal MR formulation was identified in 6.5 months.



Summary

With over 30 years of formulation expertise and over 100 MR programs developed, the team at Quotient Sciences possess the experience, capabilities, and technologies needed to create a successful MR formulation. Our services for MR programs span the entire development pathway, from candidate development through to commercialization,

reducing development risks and simplifying the supply chain for our customers. By taking a unique, integrated approach that is tailored to each program, we provide optimal results for our customers in the most efficient and cost-effective manner, getting new medicines to patients faster.