



RECENT DEVELOPMENT IN COMPLEX TABLET FORMULATION DESIGN FOR VERSATILE APPLICATIONS

In this article, Mathieu Degomme, PharmD, Pharmaceutical Development Project Manager, and Aline Moulin, PhD, Pharmaceutical Development Director, both of Skyepharma, outline three case studies from recent early-stage development programmes to illustrate what kind of complex tablets can be developed to meet specific target dissolution profiles for versatile applications.

Recent research in pharmaceutical science has mainly been concentrated on improving the administration of drugs that are already recognised as offering therapeutic advantages rather than on developing new pharmacologically active molecules – because such an approach requires less investment, reduces the time to market and produces results that are nearly always valuable.¹

Indeed, to have the targeted therapeutic impact, a drug must be biologically available and reach the circulatory system in effective concentrations. Such concentrations must be maintained – if possible, without excessive fluctuation – for long enough to allow the drug to be distributed to all target tissues and organs before it is eliminated.^{2,3}

Modified-release (MR) drug delivery systems are developed to modulate the apparent absorption and/or alter the site of release of drugs, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms.^{4,5} Possible therapeutic benefits of a properly designed

MR dosage form include improved efficacy and reduced adverse events, increased convenience and patient compliance, optimised performance, and a greater selectivity of activity or new indications. A clinically successful MR product with enhanced medical benefits also offers commercial advantages, such as product differentiation and/or line extension, maximised drug potential and market expansion, and increased cost effectiveness.

The bioavailability of a drug depends on the quantity and the rate at which it reaches the systemic circulation. If there are no problems with its absorption – or if there is no accumulation of the drug – then its bioavailability can be regulated by controlling the release kinetics from the dosage form.

With the use of drug delivery systems, it is possible to modulate the drug release rate so as to control the following factors:

- The rate of uptake through the gastro-intestinal (GI) tract into the bloodstream
- The plasma concentration
- The maintenance of plasma concentration levels, hence efficacy and duration of action.

Thus, depending on the duration of action required, controlled drug delivery systems can convey greater quantities of drugs than conventional pharmaceutical dosage forms for prolonged therapeutic efficacy.

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Dr Mathieu Degomme

Pharmaceutical Development
Project Manager

T: +33 4 74 95 20 18

E: m.degomme@skyepharma.fr



Dr Aline Moulin

Pharmaceutical Development Director

T: +33 4 74 95 21 15

E: a.moulin@skyepharma.fr

Skyepharma Production SAS

55 Rue du Montmurier
38070 Saint-Quentin-Fallavier
France

www.skyepharma.fr

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Different case studies from recent early-stage development programmes will be reported in this section to illustrate what kind of complex tablets can be developed to meet specific target dissolution profiles for versatile applications.

CASE STUDY ONE

The target product profile defined with our partner for this first case study was to maintain the plasmatic concentration of the API above a defined target over a 12-hour period, to limit the tablet intake to two per day.

We used Geomatrix® tablet technology. The tablets are made of three layers that have specific functionalities:

- The fast-release layer will behave similarly to an immediate-release tablet
- The slow-release layer will delay the release of the amount of API it contains through a swelling effect
- The dissolution profile of the slow-release layer is also controlled by a third layer – the inactive layer which reduces slow-release layer exposure to the dissolution media.

This technology allows us to target a wide range of drug-release profiles and plasmatic concentration to be maintained as needed. For this project, the targeted *in vitro* dissolution profile – Geomatrix® sustained release – was defined as shown in Figure 1.

As slow-release layer behaviour is impacted by the tablet design (size, shape), excipients (type, amounts, viscosity grades) and process parameter, a wide range of parameters have been studied as well as their impact on dissolution profiles. Different profiles were obtained, thus demonstrating the versatility of the Geomatrix® technology for the obtention

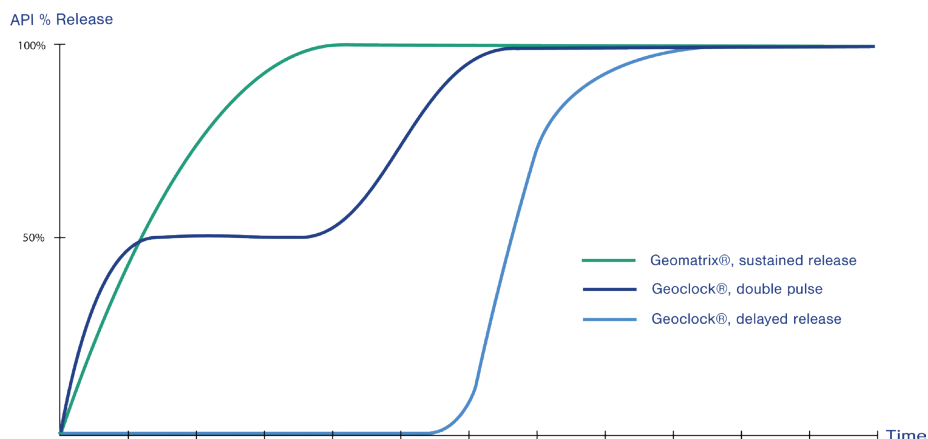


Figure 1: Examples of dissolution profiles obtained with Geomatrix® and Geoclock® technologies.

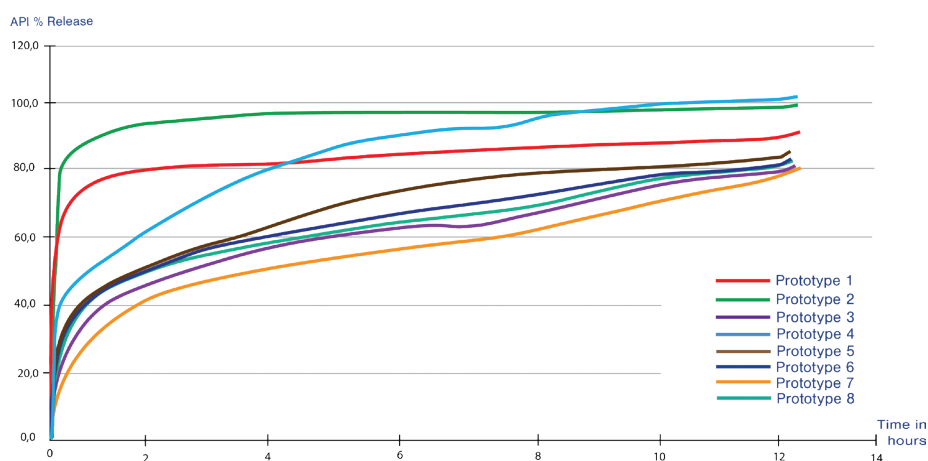


Figure 2: Dissolution profiles obtained for the different Geomatrix® prototypes.

of sustained-release profiles, as illustrated in Figure 2. In this particular case study, our partner chose three prototypes with significantly different profiles for further preliminary clinical evaluation.

Slow-release layer behaviour can also be impacted by pH conditions. Specific pH dependent excipients can thus be chosen to reduce pH impact on drug-release profiles, and Geomatrix® tablets can, at the end, be film coated to target a specific GI area and enable potential API absorption.

CASE STUDY TWO

The target product profile defined for this project was to block the API release during three hours after the tablet intake, and release the API as fast as possible after this lag time (dissolution profile similar to an immediate-release tablet as soon as the API release begins). For this project, we decided to use Geoclock® simple pulse tablets.

Geoclock® simple pulse tablets are made from a core tablet containing the API, and

an inactive layer applied by press coating. The inactive surrounding layer will provide a delayed-release effect by delaying the core water intake and the drug release during an appropriate time (from one to 10 hours). Once the water reaches the core, the swelling of this core induces outer shell breaks and the core acts as an immediate-release tablet. This phenomenon is independent from pH conditions (location in the GI tract and fed/fasted conditions). This technology is particularly appropriate for the development of tablets with APIs used in chronotherapy approaches.

As the outer shell layer behaviour – responsible for the lag time – is impacted by the tablet design (size, outer shell thickness), excipients (type, amounts, hydrophobic power) and process parameter, a wide range of parameters have been studied and their impact on dissolution profiles studied. From the different dissolution profiles obtained during the development, one was chosen as it matched the target product profile (Figure 3).

API % Release

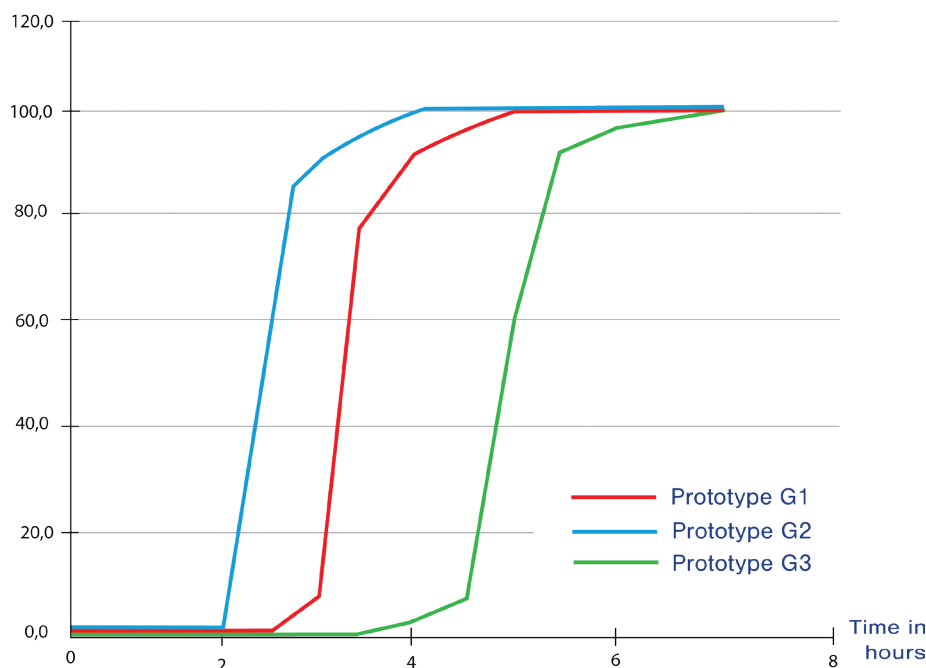


Figure 3: Dissolution profiles obtained for the different Geoclock® prototypes.

Three prototypes which allowed us to obtain the above-described dissolution profiles were selected and registered in the product NDA. Further development led to product industrial development and commercialisation in the US market.

CASE STUDY THREE

The target product profile for the third case study consisted of providing two different behaviours to a single API in one tablet. One fraction of the API needed to be released quickly, as for an immediate-release tablet. The release of the second fraction of the API needed to be delayed. This would lead to a plasmatic concentration above a defined target during 12 hours. One approach for this development was to use the Geoclock® double pulse tablets.

Geoclock® double pulse tablets are made of one core containing one API, an inactive layer applied by press coating and an immediate-release layer containing another, or the same, API, applied at the top of the press-coated tablet. This technology is appropriate in cases where the plasmatic concentration has to be maintained over time above a target by a single administration.

In vitro dissolution profiles obtained demonstrate that two pulses of API release are obtained (Figure 4). The lag time between the two pulses of release and the ratio of API between the immediate-release

part and the delayed-release part can be adjusted to bring the dissolution profile to the target product profile.

Another application can be the management of two APIs in the same tablet with two different drug-release profiles. A recent development consisted of adding natural plant extracts (immediate-release profile) to a Geoclock® tablet containing another API in the core to be delayed released.

API % Release

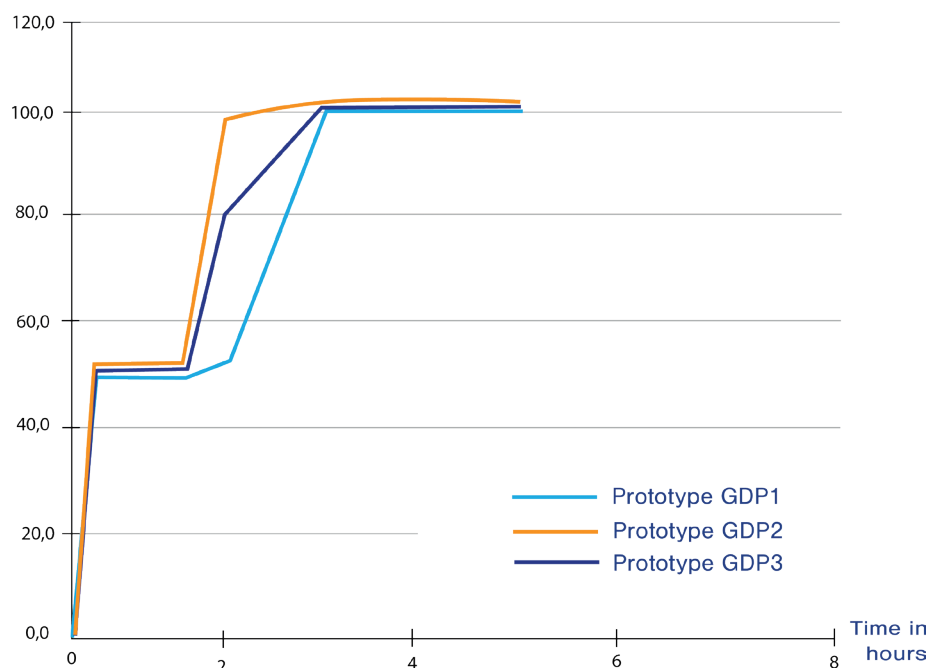


Figure 4: Dissolution profiles obtained for the different Geoclock® double pulse prototypes.

"We were able, by playing with different types of complex tablets, to target with success a wide range of target product profiles."

CONCLUSION

The case studies presented above demonstrate that it was possible, by playing with different types of complex tablets, to target with success a wide range of target product profiles. Note that the multilayer tablets and press-coated tablets presented here are technologies that are already industrialised and manufactured currently at large scale on Skyepharma's GMP site for the European, Brazilian and US markets.

ABOUT THE COMPANY

Skyepharma is a centre of excellence for complex oral solid dosage forms. It provides solutions bringing value to its clients at any stage of a product development lifecycle, from early-stage development up to commercial manufacturing and packaging activities. Skyepharma's value proposition includes services tailored to clients' requirements, supporting them up to market for their solid dosage form projects.

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ABOUT THE AUTHORS

Mathieu Degomme graduated from the University of Limoges (France) in 2009 and, the same year, received his MSc in Development and Production of Pharmaceutical Products from the University of Lyon (France). He then achieved his PharmD, also in 2009, as an apprentice in the validation department at Boiron (France). Again, in 2009, Dr Degomme joined Advanced Accelerator Applications and worked in the production, control and release of radiopharmaceutical sterile products. He joined Skyepharma in 2013 as Quality Assurance Manager and Qualified Person, and was appointed Project Manager at the New Product Introduction Department in 2017.

Aline Moulin graduated from the National Graduate Chemistry School of Montpellier (France) and received her MSc in Biomolecular Chemistry from the University of Montpellier in 2004. She then achieved her PhD at the Institut des Biomolécules Max Mousseron in Montpellier. She was appointed Medicinal Chemistry Research Scientist in 2007 at Sanofi Research Center (Vitry sur Seine, France). She joined the Flamel Technologies (now Avadel Pharmaceuticals, Venissieux, France) R&D team in 2009 to work on the design, development and industrialisation of drug delivery systems. In 2018, Dr Moulin joined Skyepharma as Senior Project Manager and was appointed Pharmaceutical Development Director in 2020.

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