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STRATEGIES FOR STREAMLINING THE DEVELOPMENT OF COMPLEX ORAL DRUG PRODUCTS

Here, Aruna Railkar, PhD, Senior Drug Development Consultant at Quotient Sciences, presents three case studies to illustrate the formulation challenges in complex drug programmes.

Drug development programmes, regardless of dosage form or molecule type, are challenging, given the many stages a lead drug candidate or new chemical entity (NCE) must progress through to achieve regulatory approval and demonstrate efficacy in patients. For complex drug programmes requiring specialised formulation development expertise – such as solubility enhancement, modified release or paediatric dosage forms – the challenges in achieving both clinical and commercial success are even greater.

For drug developers with challenging molecules, establishing a suitable formulation and technology strategy early in the development process will help to decide whether or not the desired target product profile (TPP) can be achieved and reduce time to clinic. Overall, an integrated approach to drug development that combines drug substance, drug product and clinical testing activities can remove white space, minimise risks and accelerate development timelines.

For formulation design, an integrated approach offers the ability to screen a range of technologies and dosage forms using biorelevant *in vitro* screening tools and physiologically based *in silico* models, providing a significant advantage for flagging early developability problems before transitioning drug candidates into human pharmacokinetic (PK) studies to understand a molecule's full potential.

This article presents three case studies that explore how Quotient Sciences' integrated drug development platform, Translational Pharmaceutics® – which incorporates drug substance, drug product and clinical testing – has been applied to overcome formulation challenges in complex drug programmes, helping to reduce timelines and, ultimately, get new treatments to patients faster.

SOLUBILITY-ENHANCEMENT CASE STUDY

Formulation Development and Screening of Solubility-Enhancing Formulations Using an Integrated Drug Development Approach

Poor aqueous solubility, leading to solubility-limited exposure, has been recognised as a major challenge in the development and evaluation of NCEs during early discovery, preclinical and clinical development stages (Phase I and II). There are various formulation strategies to improve solubility, all with the primary goal of improving oral bioavailability.

Quotient Sciences' approach to solubility enhancement is based on understanding a molecule's physicochemical properties, using the Developability Classification System (DCS) to choose the most appropriate formulation approach and technology for each molecule. By understanding the drivers of poor exposure

Dr Aruna Railkar
Senior Drug Development Consultant
E: aruna.railkar@quotientsciences.com

Quotient Sciences
Mere Way
Ruddington
Nottingham
NG11 6JS
United Kingdom

www.quotientsciences.com

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for a drug, formulation efforts can be focused on appropriate techniques to provide meaningful improvements for *in vivo* performance.

The company has the capability to evaluate chemical modifications, such as salt and polymorph screening, and physical modifications, such as particle size reduction, complexation, solubilisation using a lipid-based approach and stabilisation using amorphous forms. With its integrated Translational Pharmaceutics platform, from drug substance to clinic, solubility enhancement can be addressed early in the drug substance stage or downstream in the drug product stage.

In this case study, a poorly soluble NCE facing challenges of low oral exposure, non-linear PK, high variability and a large positive food effect was assessed.[1] These issues, which were observed in the first-in-human (FIH) study, were preventing the customer advancing their programme into patient clinical studies.

To overcome these challenges, a two-part Translational Pharmaceutics study was conducted for the client. Drug products based on three solubility-enhancing formulation platforms were developed:

- A micronised formulation using particle-size reduction of the API
- A self-emulsifying drug delivery system using a lipid-based formulation
- An amorphous formulation using a spray-dried dispersion (SDD).

Drug products were produced on a small scale for fast clinical assessment in human subjects without the need to conduct larger-scale, cost-prohibitive process development and lengthy stability programmes for multiple technologies.

In part one, the Translational Pharmaceutics platform enabled integration of real-time adaptive clinical manufacturing and dosing of drug product in healthy volunteers using a six-period crossover design to obtain comparative human PK data from the three enabling formulations. In part two, higher doses were administered to healthy volunteers to establish safety margins for patient clinical studies and dose linearity was determined based on the area under the curve (AUC).

Ultimately, a new lead formulation was identified for the client in a condensed timeframe of about six months. Overcoming solubility barriers in a short period of time allowed the client to progress the compound into patient clinical studies.

MODIFIED-RELEASE CASE STUDY

Employing an Integrated Approach to Formulation Development and Optimisation of a Modified-Release Dosage Form to Achieve the TPP

There are numerous formulation strategies available for designing modified-release (MR) dosage forms. However, one of the key challenges when developing an MR formulation is to identify the *in vivo* release rate and the dose required to achieve the TPP. While *in vitro* dissolution data are generated to describe drug release, the assumption that this will represent *in vivo* performance is unproven until *in vivo* clinical data are available.

Often, with MR formulations, an overall reduction in exposure is observed when delivering to lower regions in the gastrointestinal (GI) tract, due to reduced absorption. Contributing factors include reduced fluid volumes (for dissolution and solubilisation) and surface area, and differing permeability. Similarly, there are recognised challenges and risks associated with using preclinical animal models to design MR formulations due to significant inter-species anatomical and physiological differences. The use of Translational Pharmaceutics, which combines formulation development, real-time clinical manufacturing and clinical testing in humans, can help identify the optimal platform, dose and release rate to meet the TPP of interest.

In this case study, an NCE in development for the treatment of inflammatory diseases was being dosed twice a day (BID) or three times a day (TID) during early clinical trials due to a short half-life and a slower terminal phase.[2] The customer ideally wanted to develop a once-a-day (QD) product to increase patient compliance and therapeutic outcomes. The TPP was a lower peak-to-trough ratio compared with the immediate-release (IR) product and coverage of the lowest efficacious concentration over the desired duration. A matrix-based MR dosage form was proposed to reduce the dosing regimen frequency.

Quotient Sciences carried out two clinical studies in healthy volunteers to achieve these objectives. In the first study, matrix minitablets in capsules or monolithic matrix tablets were developed and evaluated using *in vitro* dissolution rates of 80% release over eight and 12 hours. While a QD PK profile was achieved in the fasted state with the slower *in vitro* dissolution rate with both types of matrix-based drug products, the formulation was susceptible to a food effect when administered with a high-fat meal. This resulted in most of the exposure occurring within the first 12 hours of dosing, which is not optimal for QD dosing.

The second clinical study was built on the results of the first study and was designed to evaluate a proprietary technology platform, DiffCORE™, from the client, with the overall goal of overcoming the food effect issue. The use of the Translational Pharmaceutics platform enabled evaluation of multiple variables in this two-part adaptive clinical study, including formulation modifications, food effect and dose levels/tablet strengths.

Flexibility was maximised by inclusion of a two-dimensional formulation design space in the regulatory submission, which allowed quantitative changes in the release rate and dosing during the clinical study to achieve the desired PK profile. This integrated Translational Pharmaceutics approach allowed for multiple formulation iterations to be tested in the same healthy volunteers in both the fed and fasted state within a short timeframe, resulting in rapid identification of the optimal formulation to enable QD dosing.

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PEDIATRIC DEVELOPMENT CASE STUDY

An Integrated Paediatric Formulation Development, Taste Assessment and Relative Bioavailability Evaluation Programme

Developing a suitable and palatable formulation is a critical requirement for drug development programmes targeting potential paediatric indications. As young children may have difficulty swallowing tablets and capsules, special dosage forms – for example, liquid formulations such as solutions or suspensions, multiparticulates such as granules (dispersible, dissolvable powders) or mini tablets – may need to be developed, depending on the age of the target population. However, the taste masking of these formulations must be considered to ensure patient compliance.

Developing formulations for a paediatric population requires special consideration of the excipients because certain excipients that are acceptable in adult dosage forms may not be acceptable in paediatric dosage forms. Depending on the age and indication, some patients, such as neonates, may require enteral feeding by tube, so compatibility with the dosing units is also an important consideration. When a medication is designed to be administered with or sprinkled on food/juices, compatibility and stability with food and taste masking becomes critical, and suitable flavours and sweeteners may need to be a key component of the dosage form strategy.

In this case study, the client wanted to develop an oral paediatric formulation for patients aged three months to 12 years.[3] The goal was to select and identify a suitable novel oral suspension formulation, with an optimal flavour and/or sweetener combination to improve palatability in the target population. Using its Translational Pharmaceutics drug development platform, Quotient Sciences carried out a two-part study to achieve these objectives.

Part one of the study was designed to profile the taste characteristics of the API and identify a suitable flavour system. Five formulations with different flavour and sweetener combinations were compared with the reference drug suspension in healthy volunteers. Taste assessments were performed by administering formulations using the sip-and-spit technique 30 minutes apart, with palate cleansing in between. The clinical trial subjects filled out a questionnaire (immediately after each sip-and-spit part) to rate the overall acceptability and seven key taste characteristics (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness and aftertaste) on a nine-point Likert scale. Statistical analysis of the data enabled selection of the optimal formulation.

Part two of the clinical study enabled a relative bioavailability assessment of the suspension formulation identified in part one, compared with the reference adult formulation, which was an oral tablet.

The integration of formulation development with taste-masking strategies, real-time adaptive GMP manufacturing, taste assessment and PK studies allowed the client to meet the expectations of both regulators and patients. As a result, the client was able to seamlessly enter paediatric patient clinical trials with a palatable drug product in a timely and cost-effective manner.

CONCLUSION

In summary, by integrating drug substance, drug product and clinical testing activities, Translational Pharmaceutics has been proven to accelerate complex molecules through the development pathway. This streamlined approach seamlessly supports Quotient Sciences' customers' programmes across the full development lifecycle, from candidate development to commercial product launch.

Key applications of the integrated approach include:

- Fast-tracking molecules from FIH to proof of concept
- Development and optimisation of clinical formulations, including solubility enhancement, modified release and paediatric drug products
- Lifecycle management of late-stage and commercial products
- Evaluation of novel drug delivery technologies for all routes of administration.

The major benefit of using Translational Pharmaceutics was quantified in a published study by the Tufts Center for the Study of Drug Development (CSDD) as significant time and cost savings in reaching key regulatory and clinical milestones as quickly and efficiently as possible. On average, development timelines are reduced by over a year, delivering financial gains of more than US$200 million (£159 million) per approved new drug through a combination of reduced research and development costs and earlier access to commercial sales. This enables better decision making early on, based on human data, and a more streamlined outsourcing model.

Quotient Sciences offers its clients the ability to develop, manufacture, release and dose drug products within one organisation. This maximises the probability of success and significantly reduces development time and costs for its customers, getting new medicines to patients faster.[4]

ABOUT THE COMPANY

Quotient Sciences is a drug development and manufacturing accelerator, providing integrated programmes and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, the company aims to save precious time and money in getting drugs to patients. Everything it does for its customers is driven by an unswerving belief that ideas need to become solutions, and molecules need to become cures, fast. Because humanity needs solutions, fast.

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ABOUT THE AUTHOR

Aruna Railkar, PhD, has over 25 years of experience in the pharmaceutical industry, working at the discovery–development interface, providing critical input for progressing compounds into clinical development, prodrug evaluation, understanding challenges in absorption/exposure of lead molecules and development of formulation strategies (conventional or enabling) based on compound properties. During her career at Hoffmann-La Roche, Dr Railkar led the group characterising compounds' physicochemical and biopharmaceutic properties to inform NCE selection and provided stage-appropriate formulation development for preclinical and clinical studies, collaborating with discovery and development teams in multiple therapeutic areas. Her area of interest is the development of novel dosage forms for existing drugs. She joined Quotient Sciences in 2019.