

Accelerating development of enabled formulations for poorly soluble drugs

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Efficacy issues due to inadequate gastrointestinal (GI) absorption caused by insufficient aqueous solubility are encountered in up to 70% of new drugs in development.¹ Typically, *in vitro* analysis and preclinical studies are used to predict the behaviour of the drug *in vivo*. These methods are notoriously poor at predicting drug behaviour in humans however, meaning that solubility issues are often only discovered when the drug is first administered in clinical trials. The drug substance and/or formulation must then be reworked and the process started again. The cost and time expended in this process can be considerable. Importantly, the selection of formulation prototypes to overcome a solubility issue using these tools also carries a significant risk of non-resolution in subsequent clinical testing.

Quotient Clinical has developed an innovative approach to identify and overcome these solubility challenges, which enables formulations to be designed, manufactured and clinically evaluated rapidly within a single organisation. Data from the early stages of the clinical evaluation can be fed back into the process, allowing formulations to be modified, manufactured and passed straight into the clinic again. This unique approach means that formulation issues can be detected,

corrected and clinically validated more quickly, with typical product development cost savings in excess of £500,000. Quotient has named this approach RapidFACT® (Rapid Formulation and Clinical Testing).

The benefits of this approach in terms of drug performance and clinical decision making are described henceforth, and case studies where significant time and cost savings have been made are outlined.



Impact of solubility on drug performance

Drug solubility has a significant impact on bioavailability, therefore selecting and optimising an appropriate drug formulation is imperative to the success of the program; moreover there is currently a very high prevalence of low solubility drugs in development (70%). Although solubility can be estimated through *in vitro* dissolution studies, and performance predicted through *in silico* modelling tools, the full impact can only be truly assessed once the drug has been administered to humans in a clinical trial. Solubility issues may manifest themselves clinically as low or variable bioavailability, an extended C_{max} , non-linear pharmacokinetics (PK) or a susceptibility to food effects. Although formulation technologies are available that can help reduce the impact of solubility challenges on bioavailability, until now processes that provide the ability to screen prototype formulations rapidly in humans have been unavailable.

Formulation approaches to solubility challenges

The various approaches to improving drug solubility fall broadly into two categories: drug substance modification and drug product (formulation) modification. In modifying the drug substance, the chemical form of the drug can be changed by generating a new polymorph or salt, and the physical form of the drug can be amended by reducing the particle size or crystallinity. In each case, the dissolution rate and/or solubility of the drug may be enhanced. However, if these approaches prove unsuccessful, formulations can also be designed to improve solubility. Examples of these include cyclodextrin complexes, lipid-based formulations, suspensions and nanosuspensions, and spray dried dispersions; all of which contain solubility-enhancing excipients appropriate for the particular drug substance.

Once the drug substance and/or formulation has been modified, it must be evaluated to see whether the solubility has improved. The traditional route is to assess solubility via *in vitro* dissolution methods followed by preclinical studies. Only if both of these give a positive indication of drug solubility will the drug or formulation then progress into human clinical studies.

Preclinical evaluation – high cost, high risk, low correlation

The entire process of re-formulation, *in vitro* analysis and preclinical assessment can take at least 12 months and cost more than £1 million. Not only is this a time-consuming and costly process, but it is generally accepted that preclinical models do not provide good correlation to human bioavailability and thus solubility^{2,3}. This is illustrated in Figure 1.

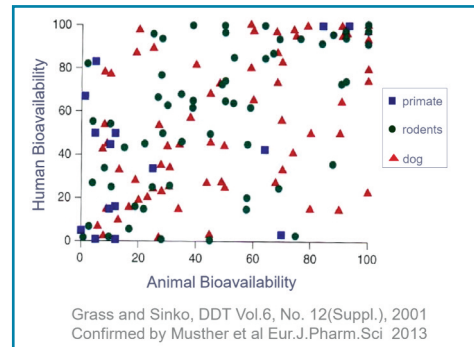


Figure 1. Graphical representation of the lack of correlation between human bioavailability and that of dog, primate and rodent species^{2,3}.

It is perhaps unsurprising that human and animal bioavailability differ so widely given the vast disparity in anatomical and physiological conditions observed. The differences in gastrointestinal conditions between humans and dogs, shown in Table 1^{4,5}, all have an impact on the dissolution and absorption of drugs. The actual performance of the new formulation only truly becomes clear when the drug is administered to humans in a clinical trial. The need for an alternative approach to assessing novel drug formats is clear, to prevent the need for multiple cycles of lengthy and costly preclinical studies.

	Human	Dog
Intestinal pH	5.5 - 6.8	6.5 - 8
Small intestine transit	Mean 238 min (180 - 300 min)	Mean 111 min (15 - 206 min)
Bile acid concentration (fasted state)	2mM	6mM
Phospholipid concentration (fasted state)	0.2mM	2mM
Neutral lipid concentration	0.1mM	3mM

Table 1. Differences in gastrointestinal conditions between humans and dogs^{4,5}.

Rapid formulation development and clinical testing (RapidFACT)

Through RapidFACT, Quotient Clinical is able to evaluate formulation prototypes directly, flexibly and rapidly in the clinic, negating the need for preclinical PK testing. Prototype formulations are developed and manufactured in the GMP facility before passing directly into the clinical facility, within 24 hours, for immediate evaluation. This is in contrast to the conventional process, where the selected formulation from the *in vitro* and preclinical stage is transferred to a manufacturing facility, the process scaled up, verified and stability data generated. At least three months of stability data must be generated before an Investigational Medicinal Product Dossier (IMPD) is submitted to the regulatory authorities for approval, after which the clinical batch is manufactured, released and shipped to the clinical trial site for dosing. This entire process can take approximately 12 months and involve up to four separate vendors. A comparison between the conventional and RapidFACT approaches to formulation development and clinical assessment is shown in Figure 2.

The RapidFACT approach streamlines the process, removing the need for poorly predictive preclinical studies and multiple stages of technology transfer from development to manufacturing or clinical site. As a result of integrated GMP and GCP processes, a shelf-life of less than seven days can be assigned. This provides ample time for the batch to be released and ready for clinical dosing. Therefore, fewer end product tests and stability data points are required, allowing the IMPD to be submitted and approved earlier in the process. This approach enables the 'lab to clinic' timeline to be significantly shortened. The benefits over separate conventional formulation development and clinical assessment are numerous and are summarised below, and in Table 2 on page 8.

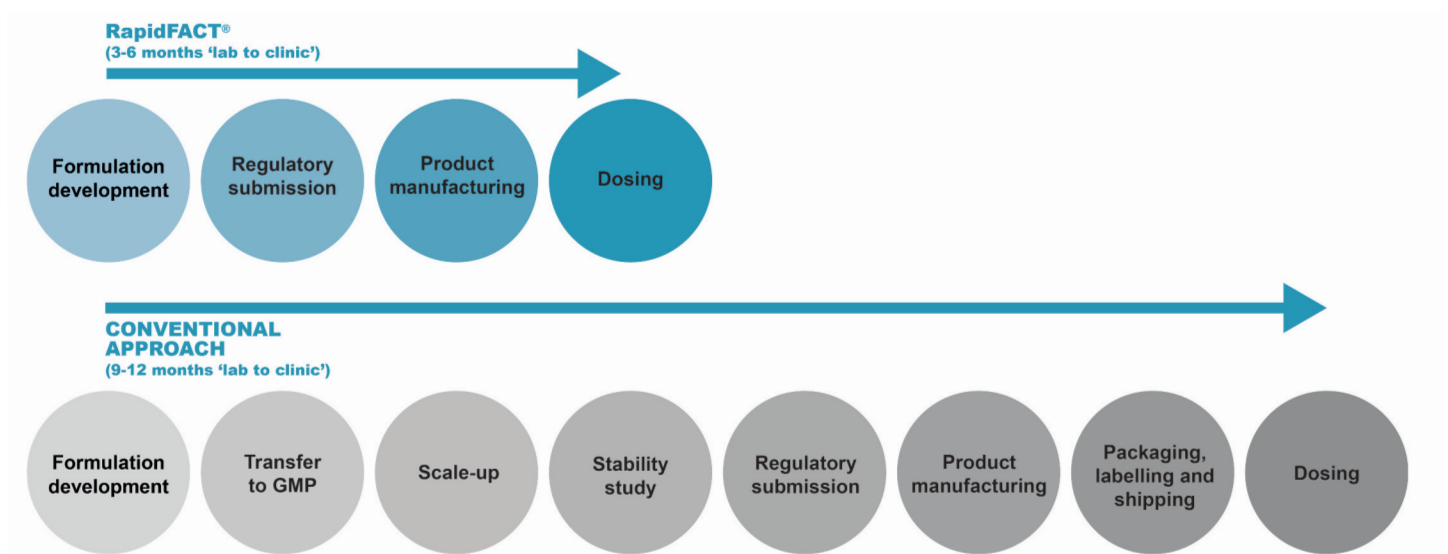


Figure 2. Comparison of conventional vs RapidFACT approaches to formulation development and progression to clinical trial.

RapidFACT significantly reduces:

- **Cost of development.** As preclinical testing and lengthy stability studies are not required, costs of chemistry, manufacturing and control (CMC) and clinical trial manufacture (CTM) can be cut by ~ £500,000;
- **Time to clinic** by at least 6 months;
- **Development risks.** By analysing a number of prototypes rapidly, greater understanding and confidence in the drug and formulation can be obtained at an early stage;
- **Clinical batch size** - removing production scale-up from the critical path and conserving drug substance;
- **Number of vendors** involved in the development/clinical process.

Impact on development and clinical decisions

As well as enabling the seamless, rapid transfer of formulations from manufacture to clinic, the RapidFACT approach also allows flexibility in the design and operation of a clinical protocol. By integrating GMP/GCP processes, clinical data from one dosing period can drive the real-time selection, manufacture and administration of the next dosage form, all within a 10 to 14 day cycle. Prototypes can be rapidly assessed, issues such as solubility can be detected, and selection of the optimal drug formulation completed in a matter of weeks, using the same clinical group of healthy volunteers.

Not only does this dramatically reduce the optimal formulation selection timeline, it also improves the accuracy of the decision making process, as formulations are evaluated based on PK data from the same group of human volunteers rather than preclinical models.

Formulation design space

If development teams are interested in optimising formulation compositions to provide a desired clinical outcome, a formulation design space can be created. This approach, illustrated in Figure 3, builds upon established ICH Q8 principles, and allows products from any point within a continuous composition space to be studied without having to submit multiple amendments to a regulatory authority.

Flexibility and success

The RapidFACT approach is applicable to all classes of small molecule, all routes of delivery, and all therapeutic areas. More than 100 programs have been completed to date, producing and clinically evaluating over 300 formulations. The breadth of solubilisation applications is shown in Figure 4, and the case studies below illustrate the impact RapidFACT has had in successfully resolving solubility challenges over a range of development programs.

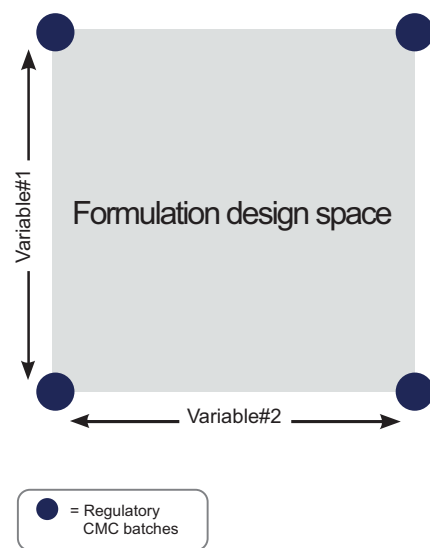


Figure 3. Formulation design space

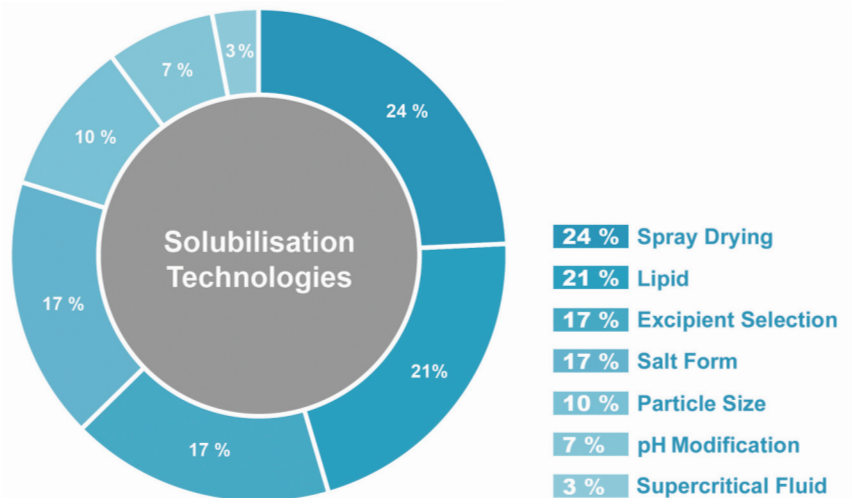


Figure 4. Breadth of RapidFACT technologies and solubilisation technologies



Case study 1:

Lipid-based liquid-filled capsule formulation

Background & need

The client performed a Phase 1 clinical trial on an Immediate Release (IR) formulation of a small molecule which highlighted significant variability in the fasted state, a non-linear PK profile and a pronounced, positive food effect. The objective was to identify an oral formulation that could overcome both the PK variability in the fasted state, and the observed food effect.

Scientific & clinical approach

The formulation strategy selected was to mimic the positive food effect observed during the Phase 1 studies by delivering the drug using a lipid-based, liquid-filled capsule. Formulation prototypes were developed by first analysing the physical and chemical compatibility, and stability of the active pharmaceutical ingredient (API) and excipients. The resulting prototypes were then screened through a discriminatory dissolution test using both the API and the existing IR formulation as references. A series of demonstration batches of candidate formulations were then manufactured to GMP to provide CMC data for submission to the regulatory authorities in the United Kingdom. As a result, approval to commence recruitment for the study was received within 14 days. On commencement of the trial, the newly developed formulations were dosed to 10 healthy individuals in the fasted state versus the existing IR formulation in the fed state. They demonstrated relative bioavailabilities (F_{rel}) of 78-96% upon fasted administration when compared with the IR formulation dosed in the fed state. During a fifth dosing period of the lead formulation, it was confirmed the food effect of the original formulation had been overcome.

Impact

This study delivered an alternative formulation which overcame a specific PK issue with the incumbent IR formulation within a very tight timeline. **Subjects were dosed within 16 weeks of commencement of formulation development, and the total project duration from initiation to completion of the clinical phase was 26 weeks.** This ensured the impact of the formulation program upon the overall development plan was minimised.

Case study 2:

New salt form formulation development – Clovis Oncology



Background & need

Clovis Oncology performed Phase 1 studies on the Free Base (FB) version of their oral epidermal growth factor receptor inhibitor Rociletinib (CO-1686). The outcome of the study showed non-linear systemic exposure and variable PK. Subsequently, a hydrobromide (HBr) salt form was identified as having the potential to substantially improve systemic exposure. A RapidFACT study was implemented to transition Rociletinib into healthy volunteers, comparing the FB and HBr versions of the API and evaluating the inclusion of functional excipients on PK.

Scientific & clinical approach

Three Rociletinib HBr formulation prototypes were identified and manufactured at Quotient's facilities using the same direct compression process. Prototype 2 included a precipitation inhibitor, whilst Prototype 3 included the same inhibitor and an acidic modifier. A formulation design space was also created for the prototypes, to enable dose strengths between 30mg and 80mg to be assessed.

Approval to proceed with the study was granted from the Ethics Committee and MHRA in 29 days. The approval allowed any composition within the design space to be studied and for decisions on this to be made in 'real time' – i.e. in direct response to emerging clinical data.

Impact

Rociletinib HBr exhibited a two-fold increase in relative bioavailability compared with the FB form, as shown in Figure 5, and a greater than two-fold reduction in variability. All of the formulations were well tolerated in the study by the 12 healthy male volunteers. **The entire RapidFACT study took fewer than 5 months from beginning to end, and one of the HBr prototypes was selected for ongoing development.**

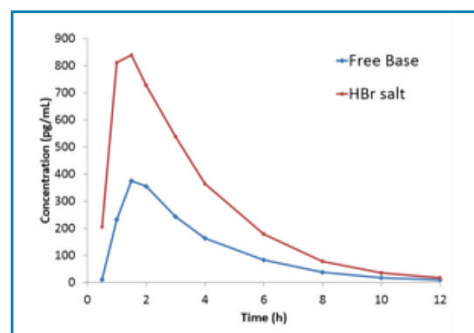


Figure 5. Geometric mean plasma concentrations following oral dosing of Rociletinib free base and HBr salts.



Case study 3:

Using spray drying technology to develop a solid oral dosage form – Idenix Pharmaceuticals

Background & need

Idenix Pharmaceuticals completed a Phase 1 clinical trial of an NSA inhibitor for Hepatitis C (IDX-719) using an oral suspension, but transition to a solid oral dosage form was needed for further development. Additionally, there had been a lack of correlation between the *in vitro* and preclinical models used in the early development of IDX-719, so a RapidFACT program was designed and executed to develop a range of formulation prototypes, and then compare their performance in a rapid and flexible manner in human subjects.

Scientific & clinical approach

Prototype tablet formulations were developed around two Spray Dried Dispersions (SDDs) prepared using two different polymers (P1 and P2). A design space was utilised to permit the optimisation of the extragranular content of surfactant and an acidic modifier during the clinical study as shown in Figure 6. In addition to the formulations within the design space, a solvent-based capsule was also evaluated. Final approval was obtained from the ethics committee and MHRA in 32 days to proceed with the trial. Again, the approval allowed any composition within the design space to be studied, and decisions on this to be made in 'real time' in direct response to emerging clinical data.

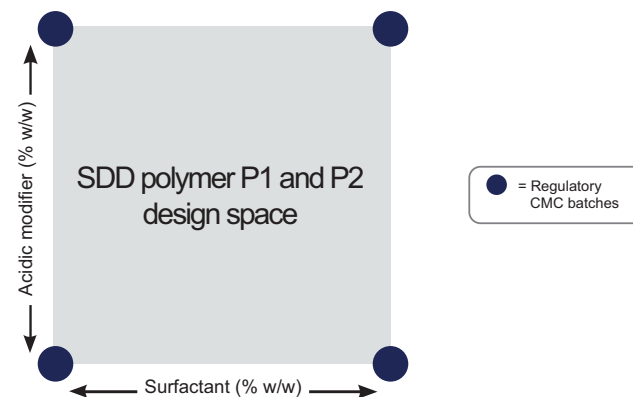


Figure 6. Formulation design space for IDX-719 formulation prototypes.

Impact

Exposures in the range of 38.6% to 97.9% were recorded for P1 SDD based tablets and 22.0% to 29.9% for P2 SDD based tablets, relative to the oral suspension. All of the formulations were well tolerated, so the best performing P1 SDD formulation was selected to support further clinical development. This RapidFACT program allowed evaluation of a wide range of solid oral formulation options, the identification of a suitable candidate for further clinical evaluation and improved confidence in a discriminatory dissolution test.

Summary: benefits of RapidFACT over conventional formulation development and clinical testing

	Convention	RapidFACT
Timeline savings	None	Save > 6 months
Flexibility	Fixed compositions	Adaptive within protocol
Formulation decisions	Based on pre-clinical data	Based on clinical data
API consumption	Standard	Up to 85% reduced
CMC/CTM savings	None	> £500,000
Supply chain	> 4 vendors	Quotient Clinical

Table 2. Benefits of RapidFACT over conventional formulation development and clinical assessment.

References

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5. J. B. Dressman, "Comparison of Canine and Human Gastrointestinal Physiology" *Pharm Res* **3** (3) 123 – 131 (1986).

About Quotient

Quotient Clinical offers unique services – based on its Translational Pharmaceuticals® platform – that integrate formulation development, real-time drug product manufacturing and clinical testing, significantly reducing the time and cost of bringing a drug to market.

For more than 25 years, Quotient Clinical has brought innovation to drug product development programs for pharmaceutical and biotechnology customers worldwide. The company is based in purpose-built, fully integrated facilities, where formulation development, real-time GMP manufacturing and clinical testing are performed in the same facility. Quotient also offer a full range of support services, from study set-up right through to data analysis and reporting.

Contact us to discuss how RapidFACT can accelerate your drug development program.

RapidFACT can be used in any program irrespective of whether the formulation is developed within your organisation, by a third party, or by Quotient. Our experts will work with you to design a bespoke development strategy to deliver your objectives in the most timely and cost efficient way.

For detailed case studies and references, please go to www.quotientclinical.com/resources

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