Rapid formulation development and clinical testing strategies in the development of controlled release products

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ABSTRACT SUMMARY
Rapid formulation development and clinical testing strategies have been developed to respond to the limitations of traditional formulation development strategies. RapidFACT methodology allows the development team to reduce the CMC data package required to obtain clinical results, whilst simultaneously improving the chances of achieving the target product profile (TPP).

The purpose of this abstract is to describe RapidFACT methodology, with reference to case studies in the development of controlled release systems.

INTRODUCTION
The ‘conventional’ process for development of formulations, relies on pre-clinical models to screen prototype formulations and select candidates for clinical evaluation. These candidates must then be scaled up and characterized to provide a package of CMC data supporting a product shelf life of at least three months, prior to proceeding to a human clinical study to establish whether the target product profile (TPP) has been met.

The predictive power of pre-clinical species has been previously reported. As a result of the application of these models, the TPP is frequently not achieved first-time and further cycles of in vitro, pre-clinical and clinical studies are conducted.

In contrast, RapidFACT studies enable screening of new formulations in humans within a co-located GMP manufacturing and clinical research facility, termed ‘Translational Pharmaceutics platform’. Using this platform drug product can be manufactured within 7 days of dosing at reduced scale, removing scale-up and stability package generation from the critical path, to obtaining clinical data on product performance.

The co-located GMP manufacturing and clinical research facility allows clinical data from one study period to be reviewed, and used to select the product to be manufactured and evaluated on the next dosing occasion. Drug products can be selected from either a range of pre-approved fixed formulation compositions. Alternatively, building upon ICH Q8 Development Pharmaceutics and Quality-by-Design principles, products can be selected from any point within a continuous formulation design space (Figure 1) where a range of product performance attributes is obtained by varying the quantitative composition of one or more formulation components.

EXPERIMENTAL METHODS
RapidFACT studies are conducted through either development of formulation technology at Quotient, or by technology transfer from a Sponsor organization or third-party. Demonstration batches of formulations of interest are prepared and characterized for each formulation to generate representative batch release and short-term (typically 7 day) stability data, to cover the time from manufacture to completion of dosing, for inclusion in the regulatory submission.

In the field of oral controlled release it is typical to incorporate flexibility to parameters such as release rate, and drug dose by gaining regulatory approval for a continuous formulation design space. By generating CMC data on formulation prototypes at the extremes of the proposed formulation ranges (Figure 1, Formulation Prototype 1 to 4 (FP1-4)), regulatory approval can be achieved to dose any composition across the space in response to emerging clinical data. This provides the development team with ability to exquisitely control the shape of the plasma concentration: time profile to a TPP.

Formulations are typically evaluated in a sequential 5 or 6 period clinical study in an exploratory (12 to 16) number of subjects. Interim reviews are conducted between each study period to review pharmacokinetic, safety or other data to allow selection of the formulation composition for the subsequent dosing period. This iterative make-test cycle is typically completed within 14 days, and continues until the TPP is achieved, at which point...
other assessments such as food effects may be studied.

RESULTS AND DISCUSSION

To date, 50 RapidFACT programs have been completed, with over 140 different formulations evaluated. These programs have been conducted for a variety of applications (Figure 2) including the development of controlled release systems.

In one case study HPMC based matrix SLx-2101 MR tablets with a 2 dimensional formulation design space covering dose strengths from 10-20 mg and release durations between 12 and 20 hours were developed (Figure 1). The relationship between key formulation variables and formulation performance were investigated and demonstration batches at the extremes 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.

The optimal formulation was identified within three 'make-test' cycles. The total project duration was 28 weeks from commencement of formulation development in the lab to delivery of clinical decision making data.

In a second case study, the goal was to optimize a HPMC matrix formulation to effectively deliver a prodrug to a preferred absorption region of the upper GI tract. A single-dimensional formulation design space was used to allow modification of drug release rate, with pharmacoscintigraphic data used to assess location of drug delivery within the GI tract. The data are shown in Figure 3.

![Figure 2. RapidFACT applications applied in the first 40 programs](image)

**Figure 2.** RapidFACT applications applied in the first 40 programs

![Figure 3. Anatomical location of complete erosion](image)

**Figure 3:** Anatomical location of complete erosion

The combination of formulation design space and pharmacoscintigraphy allowed the efficient investigation of a wide formulation design space and precise optimization of the formulation release rate with few formulation iterations. This study was completed in less than 8 months, including development of the formulation design space at the sponsor.

CONCLUSION

Successful execution of RapidFACT studies for the development of controlled release formulations has been demonstrated. This approach offers great potential to reduce development times, demonstrated on 50 programs, and more than 150 formulations, through the co-location of GMP manufacturing and clinical testing capabilities. In addition, development risk can be significantly reduced by eliminating the need for multiple ‘conventional’ development cycles through the application of innovative and flexible CMC strategies such as formulation design space.

REFERENCES
4. ICH Q8 Development Pharmaceutics (EMEA/CHMP/167068/2004)