Maximising the Potential of Amorphous Spray-Dried Dispersions to Enhance Clinical Bioavailability

QUOTIENT CLINICAL
The Translational Pharmaceutics Company

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INTRODUCTION

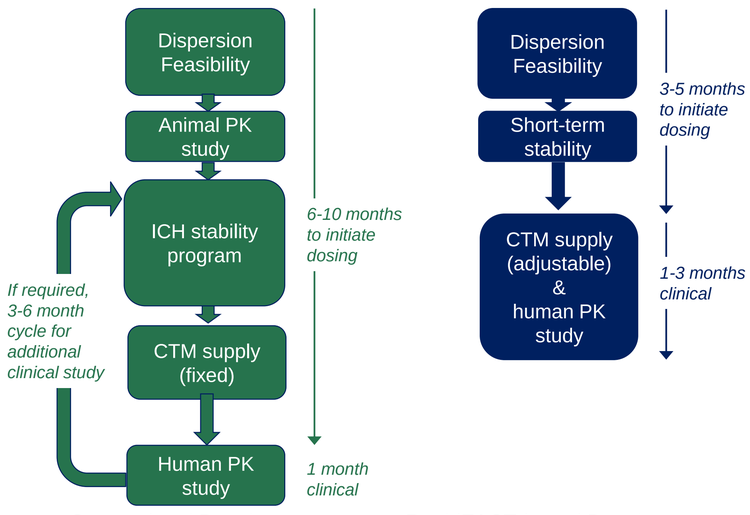
Amorphous Dispersions (ADs) provide an effective approach to oral bioavailability improvement for poorly soluble compounds. Small-scale manufacturing and analytical techniques allow laboratory and preclinical feasibility assessments of AD-based formulations early in development, however, many factors exist that limit the effective transition from these early prototypes to optimal dosage forms for successful clinical dosing.

These constraints are well-documented [1], including:

- CMC requirements to demonstrate long-term physical and chemical stability
- Complex solution behaviour of amorphous systems
- Poor correlation between animal and human pharmacokinetic (PK) data
- Unit dosage forms that often fail to achieve high exposure for high doses of AD

As shown below, the most significant weakness in conventional approaches to developing AD-based products is the extensive time and resource needed to investigate or repeat human PK trials when a target profile is not met.

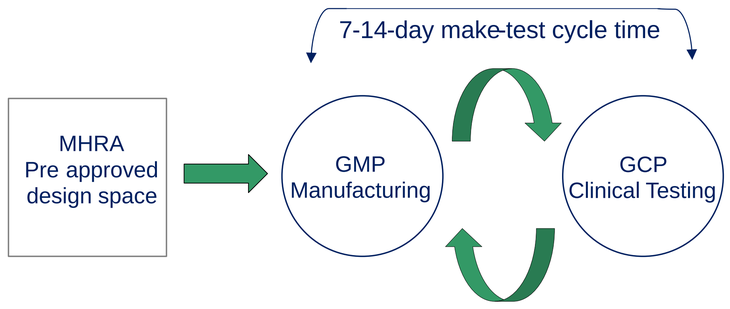
This poster presents an innovative approach to AD formulation screening and optimisation studies called RapidFACT™ (*Rapid F*ormulation Development *A*nd *C*linical *T*esting). RapidFACT uses an integrated GMP manufacturing and clinical testing platform. The main benefits of this model are the streamlined CMC data requirements to support real-time, on-site manufacture and dosing, and the ability to select and adjust product compositions during the clinical study in response to emerging PK data [2].



METHODS

RapidFACT programmes are conducted through either development of formulation prototypes at Quotient, or by technology transfer from a Sponsor or 3rd party.
Key elements for the CMC programme are:

- Decide if investigative products will be fixed-formulations or will utilise a continuous formulation design space.
- Confirm formulations and manufacturing parameters at appropriate scale (typically 200-300 units). This scale is maintained for GMP clinical batches.
- Generate regulatory submission batch release data and short-term stability data (typically 7 or 14 days).
- Submit CMC package and clinical study design to the UK regulatory authority (MHRA).



The schematic above shows the typical cycle time for within-trial manufacture of GMP product. A clinical study may include 5 or 6 dosing periods in an exploratory (12-16) number of subjects. Interim review of PK or other clinical data may be performed between periods to drive selection of the next formulation for dosing.

Whilst this approach can be used for effective and rapid clinical screening of prototypes, an important strategy that creates further formulation flexibility is establishing a formulation design space; whereby CMC data are generated at the extremes of the design space and included in the regulatory submission. Approval of the design space permits within-trial selection and manufacture of any new formulation composition within the design space. The design space unlocks many of the typical constraints for AD-based product optimisation.

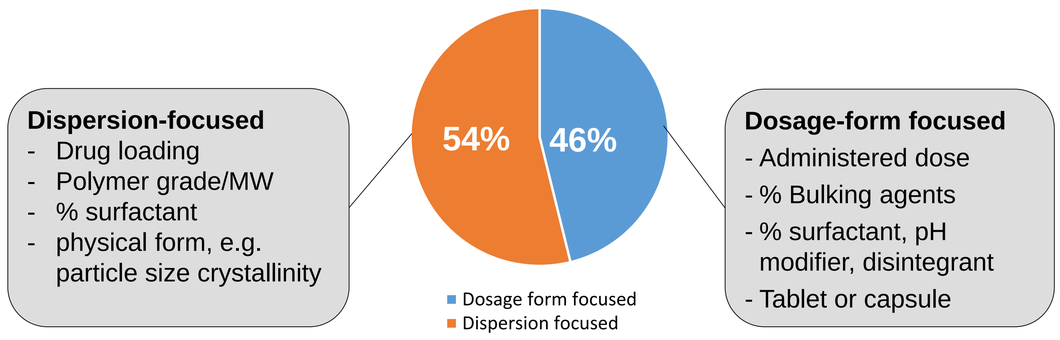
RESULTS

Ten integrated formulation and clinical testing programmes that utilized AD-based drug delivery were reviewed.

The programs can be divided into two categories:

1. Dispersion-focused: dispersion variable(s) evaluated
2. Dosage-form focused: parameters evaluated with a fixed dispersion

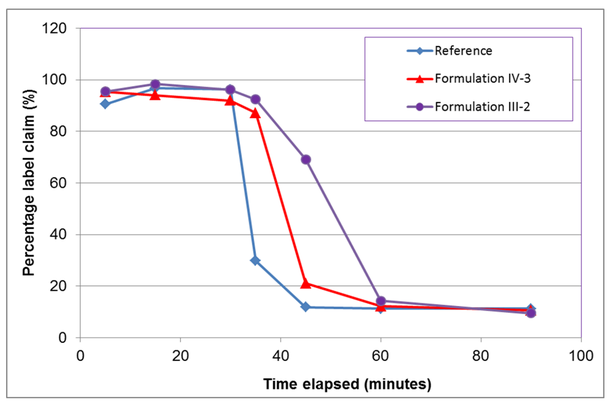
Our analysis of all clinical prototypes generated in these programmes shows a similar frequency in each category:



CASE STUDY (Dispersion focused)

Objective: Rapid development and clinical validation of an improved age-independent formulation, which is simpler and cheaper compared with the reference Phase I suspension, but has comparable PK and improved exposure in the fasted state

Experimental: Formulation prototypes were developed by Quotient Clinical that exhibited different solubility-enhancement and/or precipitation inhibition mechanisms. In vitro characterisation data were generated to reveal the solubility behaviour of lead prototypes, and to support within-trial formulation adjustments.



In vitro test example:

pH switch test in biorelevant media

Goal is to sustain increased solubility at intestinal pH

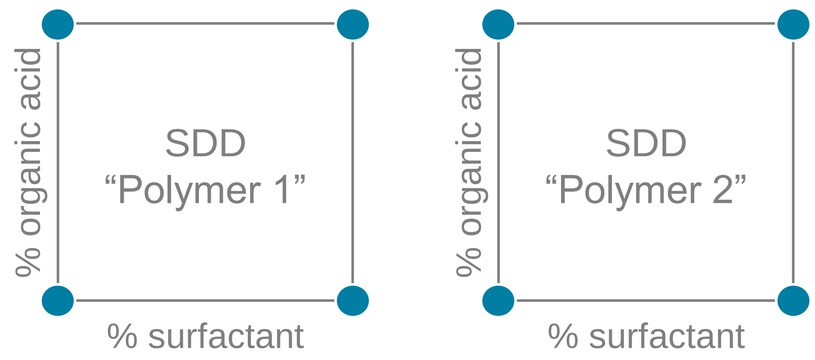
Outcome: Four prototype systems were screened in a 4-way non-randomised crossover design; an AD-based powder-in-bottle dose presentation achieved exposure of reference product with reduced cost of goods

Timing: <7 months from formulation development to PK-driven lead formula selection.

CASE STUDY (Dosage form focused)

Objective: Objective: To transition a BCS Class 2 compound from an oral suspension to a tablet using an adaptive clinical design supported by flexible formulation design spaces. .

Experimental: A spray-dried dispersion (SDD) approach was chosen, but in vitro and animal PK data failed to consistently identify an optimal SDD prototype. Therefore, two SDD prototypes of fixed drug-polymer composition were advanced into a human PK study designed with flexibility to adjust critical tablet parameters. As shown below, both SDD#1 and SDD#2 had 2-parameter design spaces that allowed in-trial formula modifications in response to human PK data.



Outcome: Relative exposure for SDD#1 tablets ranged from 39-98% compared to the suspension reference, whereas relative exposure for SDD#2 tablets remained <30% for all compositions tested. The human PK results did not correlate with animal PK predictions, which validates the use of RapidFACT for this molecule

Timing: 8 months from project initiation to identification of a tablet formula bioequivalent to the suspension [3].

CONCLUSIONS

The design of Amorphous Dispersion products for oral bioavailability enhancement often require intensive human PK assessment, in part due to difficulties in predicting human behaviour and also due to the many product variables that influence performance. To maximise product performance and prevent repetition of development experiments, the RapidFACT approach of integrating product manufacture with clinical assessment provides a time-efficient and data-driven means of AD product optimisation within a single study.

REFERENCES

1. Newman A. *et al.*, J. Pharm. Sci. (2012), 101(4) 1355-1377.
2. McDermott J. & Scholes P., Ther. Deliv. (2015) 6(11) 1269-78.
3. McDermott J *et al.*, Poster #R6178 at: AAPS Annual Meeting 2014