Accelerated PK Screening Study of Formulation Design Space in Early Drug Development

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Abstract

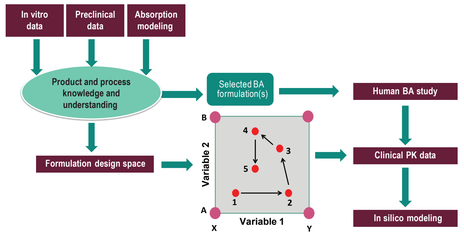
A key element of new drug product development is to achieve desirable formulation bioavailability (BA) to meet the pharmacokinetic target. The BA of a drug product formulation can be impacted by critical quality attributes (CQA), critical material attributes (CMA), and critical processing parameters (CPP). A nonconventional approach to BA study can apply a formulation design space rather than specific formulations during drug product development, where a quantitative range of variables expected to have in vivo impact on exposure, including formulation composition, API/excipient attributes, and process parameters, will be evaluated.

There have been recent efforts in rapid formulation development and clinical testing (RapidFACT) to exploit the benefits of translational pharmaceutics in the clinical screening and optimization of drug products.[1] Merck successfully conducted a formulation design space study in the United Kingdom for development of Compound B in 2016 following the consultation with MHRA.

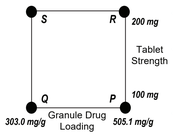
Merck Compound A is in early-phase clinical development. As a crystalline freebase and BCS class II compound, the pH-dependent solubility of Merck Compound A presents an increased risk of drug–drug interactions with proton pump inhibitors (PPIs). The project team leveraged the innovative approach of "spring and parachute" to design the drug product to improve the exposure of prototype tablets under achlorhydric condition.

To understand the clinical relevance of the tablet drug loading and citric acid level, an adaptive clinical study is proposed that includes a formulation design space covering a specified range of drug load and citric acid levels. "Real-time" decisions will be based on emerging human PK data to inform the next clinical formulation, which will be manufactured in time to enable an expedited dosing cycle of every 2 weeks. This approach will enable a better understanding of the dosage form's biopharmaceutical properties and drive more efficient formulation selection decisions.

ACCELERATED PK STUDY OF FORMULATION DESIGN SPACE



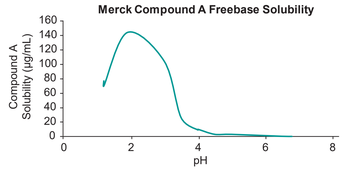
ACCELERATED PK STUDY OF MERCK COMPOUND B



- Accelerated PK screening (APKS) study conducted in UK in 2016 following consultation with MHRA
- Proposed CMC information at the corners of the formulation design space (granule drug loading and tablet strength) is adequate to represent the design space and any formulations contained therein for the proposed study
- Additional regulatory submissions are not needed for **any formulations** within the formulation design space

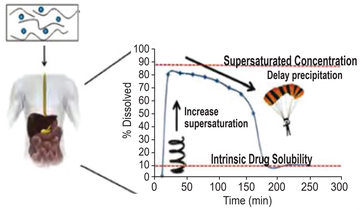
FORMULATION DEVELOPMENT FOR MERCK COMPOUND A

- Merck Compound A is a crystalline weak base with pH-dependent solubility (BCS II)
- Absorption modeling on achlorhydric effect suggested an increasing gastric pH will negatively impact bioperformance with dose dependency >10 mg
- Formulation development focused on increasing exposure in PPI patient

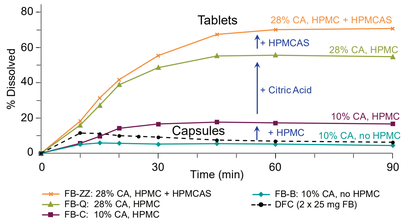


Spring and Parachute Approach

- Acidification to achieve supersaturated state and subsequent inhibition of precipitation
- Spring: acidifier (citric acid)
- Parachute: polymer such as HPMC or HPMCAS



Improvement of In Vitro Dissolution in pH 4.5 Acetate Media by Spring and Parachute

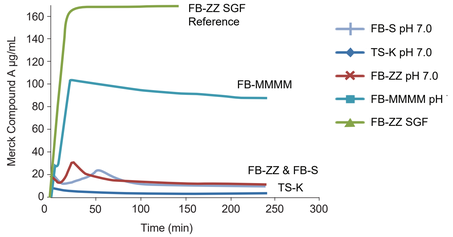


Rapid Formulation Screening

- Online fiberoptic dissolution
- Real-time monitoring of the supersaturation and precipitation
- Rapid, comprehensive DoE characterization

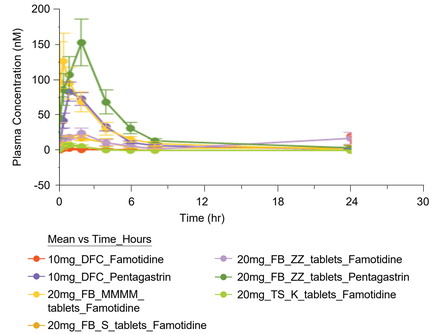
Biorelevant Dissolution Simulating Achlorhydric Condition

- Use media simulating famotidine treatment, pH 7.0
- Improved rank order with dog data and in vitro AUC (0-2 hours or 0-0.5 hours)
- Freebase formulation 4x to 10x higher in vitro AUC compared with tartrate salt (TS-K)

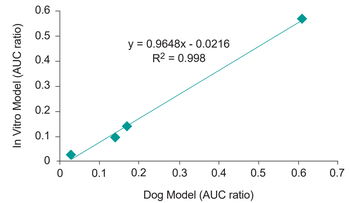


- TS-K – Prototype tablets containing tartrate
- FB-S – Freebase 20% DL, 28% CA, 5%HPMC/2.5% HPMCAS
- FB-ZZ – 20% DL, 28% CA, 2.5% HPMC/2.5% HPMCAS
- FB-MMMM – 10% DL, 28% CA, 1.25% HPMC/1.25% HPMCAS

Canine PK Model of PPI Effect Pentagastrin (pH 1-1.2) vs Famotidine (pH 5.5-7)



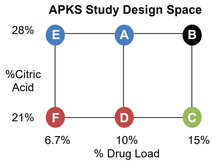
In Vitro/In Vivo Correlation With Famotidine Dog PK Data



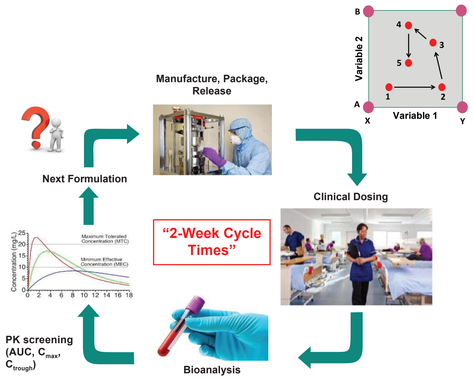
APKS FORMULATION DESIGN SPACE

Explore Formulation Design Space (PPI Conditions)

- Potential variables
  - Citric acid level
  - Drug load/image size
  - Citric acid particle spze
- Inform risk balance between
  - Human PK performance
  - Image size
  - Processability (eg, punch haze)
  - Physical and chemical stability
- In vitro model correlation



Integration of Drug Product Manufacture and Clinical Testing



CONCLUSIONS

- Standard relative bioavailability (BA) studies will take a cycle time of 9 to 12 months if the PK results are less than desired. APKS study will drive better efficiency of relative BA evaluation and reduce the lead time to allow informed formulation selection based on human PK assessment
- Representative drug product stability data from the corner point of formulation design space, brackets the active-to-excipient ratio of the clinical formulations. This approach is analogous to a stability bracketing design strategy following ICH Q1D. Any formulations within the formulation design space are expected to have similar CMC quality and stability as the corner formulations in the design space
- This approach enables any possible formulation within the proposed design space to be manufactured and assessed in the adaptive clinical study. Just-in-time manufacture of clinical formulations, testing, packaging, and dosing will allow rapid PK screening study period within a 14-day cycle. Clinical PK data for each study period will be reviewed in real time and used to guide the formulation to be manufactured for evaluation in the next study period

References

1. McDermott J, et al. *Ther Deliv.* 2015;6(11):1269-1278.

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