Rapid Formulation Development and Clinical Testing of Gastro-Retentive Controlled Release Technology to Enable Once-Daily Dosing

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Introduction

MK-X is marketed as an oral immediate release (IR) tablet given twice daily (BID). MK-X had demonstrated poor colonic absorption in dogs and conventional matrix based controlled release formulations failed to achieve adequate trough concentrations in a human pharmacokinetic (PK) study to support once daily dosing. Data from IR formulations indicated that the drug was highly absorbed from the upper gastrointestinal (GI) tract and, therefore, a gastroretentive (GR) system was proposed for further development.

A Rapid Formulation Development and Clinical Testing (RapidFACT®) study was designed, incorporating gamma scintigraphic imaging to evaluate the GI transit of prototype monolithic and bi-layered GR tablet formulations and the PK of MK-X in healthy volunteers. Drug products were manufactured immediately prior to clinical dosing. This allowed rapid adjustment of prototype composition in response to emerging clinical data to optimize product performance.

RapidFACT

RapidFACT uses a Translational Pharmaceutics® delivery platform which utilises a co-located GMP production and clinical testing facility (1). 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 (2).

Following initial dosing, the Translational Pharmaceutics platform also allows GMP drug products to be made in real-time in response to interim analysis of clinical data, typically on a 7-14 day cycle

Drug products can be selected from a panel of pre-approved fixed formulation compositions. Alternatively, building upon ICH Q8 Development Pharmaceutics and Quality-by-Design principles(3), products can be selected from any point within a continuous formulation design space (Figure 1). In this scenario, a range of product performance attributes are obtained by varying the quantitative composition of one or more formulation components(4).

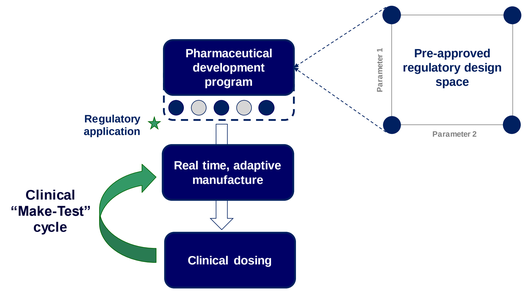

Figure 1: The RapidFACT process

Over 100 formulation optimization programs (RapidFACT) have now been completed with a wide variety of parameters assessed/optimized via a design-space approach. The flexibility to evaluate as many as 5 parameters within a single study has been successfully implemented.

Methods

Two prototype MK-X tablet formulation platforms were developed based on a monolithic swelling matrix tablet and a bilayer tablet containing separate swelling and drug release layers.

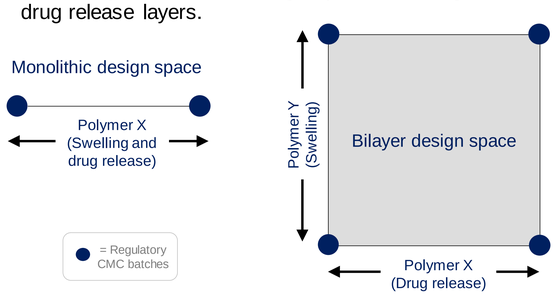

Figure 2. Formulation design spaces for GR formulations

A single dimensional formulation design space was enabled for the monolithic dosage form to allow adjustment of the polymeric content of the tablet matrix to optimize the formulation swelling and drug release rate. A two dimensional formulation design space was generated for the bilayer tablet to allow independent optimization of the swelling and drug release properties of that formulation (Figure 2)

Drug product radiolabelling

The formulations were radiolabelled with indium-111 to allow collection of scintigraphic images. The absence of any interaction between the drug and the radiolabel was confirmed by comparison of dissolution profiles from unlabeled tablets and product containing the radiolabel carrier particle.

Clinical study design

Prototype formulations were evaluated in comparison to IR formulation in 18 healthy volunteers in a 6-period, sequential clinical study. Scintigraphic images and PK samples were taken at regular interval for 48 hours. Routine safety assessments were performed throughout each dosing period.

Interim PK and scintigraphic analyses were performed between each dosing period to assess performance and allow selection of the formulation composition to be studied in the subsequent dosing period from within the pre-approved design space. Scintigraphic data were analysed to determine key parameters including initial and complete tablet disintegration time.

Approval was obtained from the Ethics committee, the administration of radioactive substances advisory committee (ARSAC) and MHRA in 32 days including the time to respond to comments. The approval enabled any composition within the formulation design space to be studied, and decisions regarding which formulation compositions to assess to be made in direct response to emerging clinical data

Results

All formulations were well tolerated. There were no serious or severe AEs reported.

The bilayer GR tablet formulations demonstrated gastroretention of up 16 hours. Monolithic formulations showed approximately 11 hours gastroretention. Gastric emptying times were very consistent between subjects.

Example scintigraphic images are shown in Figure 3, illustrating gastroretention of a bilayer tablet formulation for 16 hours.

Results

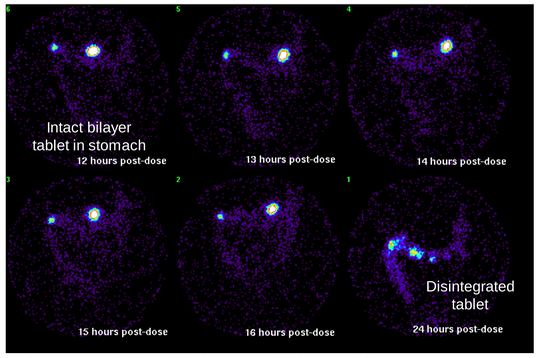

Figure 3. Scintigraphic images of bilayer tablet system showing tablet remaining located in the stomach at 16 hours

Conclusion

An optimised dosage form that provided prolonged gastric retention in the fed state was developed. Rapid formulation and clinical testing strategies allowed the evaluation of a wide range of GR formulation options for MK-X on the basis of pharmacokinetic and gastroretention performance.

The results showed that the bilayer tablet systems performed best overall. The gastroretentive formulation of MK-X was optimised and selected for further development in less than 7 months

References

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