Development of a Paediatric Oral Suspension of a Novel Drug for the Treatment of Kidney Disease

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INTRODUCTION

The aim of this development programme was to develop an aqueous, multi-dose oral suspension formulation of a novel drug candidate at a concentration of 20 mg/ml that would be appropriate for the treatment of kidney disease in paediatric patients aged 2 years and older. A liquid formulation was favoured over a coated granule formulation as it enables flexible dosing by varying the dose volume according to age and/or body weight and was considered more appropriate for the target age group. The API has a molecular weight just below 600 and is a bitter tasting, odourless, white crystalline powder with a particle size (D50) of 30 µm and 0.008 mg/mL intrinsic solubility. It is stable under normal heat and light conditions and is unstable at basic pH. A Quality Target Product Profile (QTPP) for the paediatric liquid is detailed in Table 1.

Table 1: QTPP for Pediatric Oral Suspension

Quality Attribute	Target
Dosage form	Multi-dose oral suspension (aqueous, sugar-free)
Active ingredient concentration	20 mg/ml
pH	Less than pH 6.0
Flavour	Appropriate flavour to mask bitterness
Assay	Release: 95.0% - 105.0%
Shelf-life	24 months
Microbiological Limits	Meets pharmacopoeial acceptance criteria

MATERIALS AND METHODS

The design of the formulation and selection of excipients took into consideration the guidance provided by the European Medicines Agency (EMA)1,2 for paediatric formulations. Additionally, the levels of excipients used were also guided by the EC Notice to Applicants Guideline3. Formulations with alternative combinations of flavours, sweeteners and pH modifiers were assessed and a further aim was to develop a formulation with a minimal number of excipients necessary and to minimise the level of each excipient in the formulation Citric acid was evaluated as a pH modifier to optimise preservation. Citric acid also worked well in combination with the proprietary flavour and sweetener as an important component of the flavor system to improve palatability. Various viscosity modifiers and suspending agents were also evaluated during the development process.

MATERIALS AND METHODS

Centrifugation and dispersion studies were used to evaluate the sedimentation characteristics of the suspension prototypes. As a result, xanthan gum was selected and optimised at an appropriate minimal level to ensure satisfactory resuspendability and homogeneity of the API. Formulation prototypes containing quantities of sodium benzoate ranging from 0.02% w/v to 0.23%w/v were evaluated in a 12-week elevated storage study. The preservative assay and efficacy were monitored with other aspects on the QTTP to identify the lowest level of inclusion of sodium benzoate at the target pH. The level of sodium benzoate was selected on the basis of preservative efficacy testing, the proposed posology of the product and a literature review of acceptable daily intake in the target population. The lead candidate formulation will be scaled-up for clinical testing and palatability assessment.

RESULTS

The output of the development programme resulted in an age-appropriate, oral suspension formulation in line with the QTPP and containing only six excipients. No crystal growth or particle agglomeration was observed during storage at accelerated conditions and the formulations demonstrated consistent homogeneity and content uniformity. The formulations demonstrated complete dissolution of the API using a USP II dissolution apparatus, with >90% dissolution occurring at 5 minutes.

CONCLUSION

There was a specific need for the development of a paediatric formulation of a novel drug for the treatment of kidney disease in children. Based on the knowledge of the physicochemical properties of the drug substance, consideration of regulatory guidance and the selection of appropriate excipients, including flavours and sweeteners, it was possible to design a suspension formulation with a minimum number of excipients that would provide flexibility of dosing to children aged 2 years and older.

REFERENCES:
1.EMA Reflection paper: formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005)
2.EMA Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)
3.EC Notice to Applicants Guideline: Excipients in the label and package leaflet of medicinal products for human use (SANTE-2017-11668)