ACCELERATING AND DE-RISKING THE PRODUCTION
OF PAEDIATRIC ORAL FORMULATIONS

Background & Aim As part of the EU paediatric regulation, the paediatric use marketing authorisation (PUMA) was introduced, with an aim to stimulate research in existing compounds that are off-patent and/or to help transform known off-label use into authorised use. However, success has been limited, with only a few products gaining a PUMA, such as Sianalar 320 micrograms/mL glycopyrronium (equivalent to 400 micrograms/mL glycopyrronium bromide). A distinct challenge to overcome in this area is the development of more ‘age appropriate formulations’, particularly with an excipient composition and load that is suitable for paediatric patients. This project aims to establish an excipient screening platform, supplemented with analytical characterisation of materials, which will act as a decision making tool to accelerate and de-risk the production of age appropriate paediatric medicines.

Method To develop this excipient screening platform, a list of drugs that require an age appropriate formulation was produced using the ‘needs for paediatric medicines’ documents provided by the European medicines agency (EMA), whilst common problematic excipients in paediatrics were identified using an EMA reflection paper. Literature and prescribing data were also reviewed to ensure drugs selected would benefit from an age appropriate formulation. Differential scanning calorimetry (DSC) to determine compatibility of selected drugs with widely used excipients was carried out using a TA DSCQ200 instrument (TA Instruments, New Castle, DE) with TA Instruments Universal Analysis 2000 software. Data was collected under nitrogen atmosphere (50 mL min⁻¹) using pierced flat-bottomed TZero aluminium pans (sample mass about 2 mg) and heating rate of 10 °C min⁻¹ in the range from 50 to 400°C. For samples containing both the drug and an excipient, 1 mg of each was measured out and gently mixed with a spatula for one minute.

Results The most common class of drugs identified as requiring age appropriate formulations were related to cardiovascular disorders and neurology, whilst the majority of drugs identified also exhibit poor aqueous solubilities. Some identified problematic excipients include ethanol, sodium benzoate and sorbitol; however, these excipients may still be used in paediatric formulations, as long as they are below certain concentrations (for example, ethanol concentration should not exceed 0.5% w/v for under 6 years old). Two drugs identified through the initial screening, carvedilol and nifedipine, were analysed by DSC, alone and then alongside starch from corn and starch 1500; the resulting DSC curves showed no changes in peak size, position (peak onset temperatures for nifedipine and carvedilol were observed at 173.2°C and 117.3°C, respectively) and shape, as well as no additional peaks, therefore suggesting compatibility between the tested samples.

Conclusion This first phase of the development of an excipient screening platform will continue to scan several different excipients with selected active pharmaceutical ingredients (APIs) in order to create compatibility profiles. The excipient screening platform generated will accelerate and de-risk the production of age appropriate formulations, as it would allow screening for potential incompatibilities and acceptability, alongside informing formulation of appropriate oral paediatric dosage forms.

REFERENCES

DOES AN INTERDISCIPLINARY APPROACH TO TABLET/ CAPSULE SWALLOWING INCREASE THE UPTAKE OF OR TRANSITION TO SOLID ORAL DOSAGE FORMS IN PAEDIATRIC PATIENTS WITH ALL ACUTE LYMPHOBLASTIC LEUKAEMIA?

Aim Most paediatric formulations produced for children are generally liquids or powders for reconstitution. Palatability of liquid formulations is often cited as a barrier to medication adherence. An alternative to liquid formulations is the conventional solid oral dosage forms, such as tablets or capsules. However, another barrier faced by paediatric patients is the inability to swallow tablets. This presents a number of challenges for children with ALL, as treatment contains a phase of extended ‘maintenance’ therapy to prevent relapse. This involves taking oral chemotherapy daily, ± monthly chemotherapy injections, over 2 years for girls and 3 years for boys. Prior to 2014, paediatric oncology pharmacists would work with children refusing to take or struggling with their liquid medicines. It was a simple approach, where ‘tic-tacs’ were used and swallowin5g these was practiced together. Through education sessions and informal discussions with nursing, medical and play therapists, a culture evolved in 2014 whereby medicine taking was not just the responsibility of pharmacy but of the wider team. Nursing and medical staff were actively involved identifying families that needed support with...