Pharmaceutical Excipients in Pediatric Formulations

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Introduction

Pharmaceutical excipients are included in formulations for both adult and pediatric patients for a variety of reasons, for example to provide a carrier for the active pharmaceutical ingredient, to improve drug product processability, to facilitate drug solubility or absorption, or to ensure formulation stability and physiological compatibility. While excipients were at one time considered to be 'inactive' ingredients, it is now understood that they can, in certain cases, have an impact on the safety, bioavailability and stability of the drug product as well as patient acceptability. Therefore the presence and quantity of excipients in the formulation need to be justified.

The introduction of the Pediatric Regulation in the European Union (EU) in 2006[1] had a significant influence on the development considerations of drug products for pediatric use. The Regulation outlines the requirements of the *Paediatric Investigation Plan* (PIP) aimed at ensuring necessary data are obtained through studies in children to support the authorisation of medicines for use in children. With regard to pediatric formulations, the PIP should include details of currently available presentations of the drug product and indicate where further formulation development activities are planned to provide an age appropriate dosage form for pediatric use. Within the US, the 2012 *Food and Drug Administration Safety and Innovation Act* (FDASIA)[2] strengthened the laws previously in place to improve the availability of pediatric drugs by making the *Best Pharmaceuticals for Children Act* (BPCA) and the *Pediatric Research Equity Act* (PREA) permanent. The FDASIA also outlined the requirements for the submission of a *Pediatric Study Plan* (PSP) to support earlier pediatric drug development. In support of both the PIP and the PSP, the applicant needs to provide a rationale for the chosen formulation for pediatric administration, along with a justification for the choice of excipients taking into consideration patient safety and the quality of excipients in each formulation.

As intended, the regulations in the EU and US have promoted an increase in the research and development of pediatric-specific dosage forms by both industry and academia, which includes investigation of both the dosage form and excipients to be used.[3,4]

At this time, only the EU and the US have pediatric specific regulation and guidance.

Pediatric Dosage Form Development

When a pediatric product is being developed, consideration needs to be made as to the route of administration and type of dosage form required, as discussed in the European Medicines Agency (EMA) *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*.[5] There are a range of challenges related to pediatric dosage form development, with several reviews available.[6–8] Current regulations require 'age-appropriate' dosage forms, which indicate that a dosage form is required to meet the specific demands of the pediatric population in question including physiological requirements as well as administration challenges. There are many physiological differences between adult and pediatric patients that need to be addressed during the development of a dosage form for pediatric use, for example the pH and residence time in the gastrointestinal tract, and the activity of enzymes and transporters.

A very significant difference between pediatric and adult patients is in the ability to swallow different types of oral dosage forms, with younger children unable to swallow large, monolithic presentations (e.g. tablets and capsules). Multiparticulate dosage forms such as granules, pellets and minitablets, greatly facilitate the administration of solid oral dosage forms in younger children. Liquid oral dosage forms can also be taken by younger children and neonates, providing flexible dosing that can accommodate changes in dose based on adjustments for weight, body surface area, or patient age. The ease of swallowability and dose flexibility have led to a historical dependence on liquid dosage forms for pediatric patients, however they also have some significant drawbacks. Liquids (solutions or suspensions) can have issues with stability, concerns over transport (bulky containers, potential need for refrigeration), potential dosing errors (due to inadequate mixing of suspensions prior to administration), and significant difficulty in masking the unpleasant taste of an active ingredient. There are also concerns with oral powders for reconstitution related to the availability of potable water and appropriate reconstitution.[9] The administration of multiparticulate solid oral dosage forms can overcome some of the challenges associated with liquid presentations.

Development of a pediatric dosage form for oral use should include consideration of multiple dosage forms to address the needs of the pediatric population and the characteristics of the drug, for example a liquid dosage form (solution or suspension, ready made or for reconstitution), a monolithic solid dosage form (tablet or capsule), or a multiparticulate dosage form (for example pellets, granules or mini-tablets). The above considerations would need to be addressed for any dosage form, with age-appropriate delivery required across the target pediatric population, as well as more traditional concerns such as stability, bioperformance, and other factors generally considered for an oral dosage form.[10]

Parenteral dosage forms for children can be the same or similar to the adult dosage form, with the main concern being the availability of appropriate dose strengths and pack sizes to avoid dosing errors. Reasons for accidental misdosing include the requirements for complex dose calculations because of varying pediatric body weights or body surface areas, and complicated formulation dilution steps required to achieve the correct pediatric dose.[11] Factor of 10 errors or decimal place errors are common, especially when drugs are available in several concentrations and when pack sizes deliver multiples of the required pediatric dose.[12] In addition, the total acceptable fluid load for the pediatric patient age group as well as dose accuracy during administration need to be taken into account when developing the drug product. Neonates may only be able to accept very small volumes of medicines in order to avoid volume overload and to allow for the administration of essential fluid nutrition. On the other hand infusions must not be so concentrated that the appropriate dosing rates are not feasible by using standard pump equipment. Pediatric physiology and excipient acceptability should also be evaluated when designing parenteral products.

The Role of Excipients in Pediatric Dosage Forms

The role of excipients in pediatric dosage forms has been outlined in the EMA *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*.[5] Consideration needs to be given to the