Mapping the literature to better understand how excipients may affect biopharmaceutics aspects of paediatric drug products – permeability as a case example

Karen Gandham[1,2], Hannah. K. Batchelor[2], Terry. B. Ernest[1]
[1] GlaxoSmithKline, Park Road, Ware, SG12 0DP, UK
[2] School of Pharmacy, Institute of Clinical Sciences, The University of Birmingham, Edgbaston, B15 2TT, UK

Introduction: Excipients have functional roles in paediatric drug product development. Previous research efforts have focused on understanding the safety and toxicity of excipients in paediatric populations (e.g. STEP (Safety & Toxicity of Excipients for Paediatrics) Database and ESNEE project (European Study of Neonateal Exposure to Excipients)). Current understanding of biopharmaceutic risks associated with excipients used in medicines for paediatric populations is limited.

Aim: To map the current literature that describes the biopharmaceutic risks associated with excipients and consider how these may affect drug absorption in paediatric populations.

Methods: A literature search identified indexed publications from the following databases: Scopus, PubMed, and EMBASE using search terms: gastroinstestin* OR gastrointestinal AND excipients. Inclusion criteria were: research studies investigating any biopharmaceutics outcome (pH; solubility; permeability; absorption; bioavailability) related to an excipient. The following data was extracted from each study that met the inclusion criteria: details of excipient, specific methodology used to assess the biopharmaceutics impact of excipient and associated drug. The electronic Medicines Compendium (www.medicines.org.uk/emc) was searched for each excipient identified to note whether that excipient was used within paediatric products to further refine the dataset.

Results: Of the total 160 articles which fulfilled the inclusion criteria, 24 records were identified that highlighted an effect of an excipient on permeability; 6 on GI transit; 78 on solubility and 52 that related to other biopharmaceutic-risks. This other category is used to describe cases where excipients were selected to design formulations intended to increase bioavailability of drugs e.g. self-emulsifying drug delivery systems.

Table 1 shows of the extracted literature data relevant to permeability as an example. The excipients listed in Table 1 were reported to have an inhibitory effect at the P-gP efflux transporter or tight junctions which generally increases drug absorption. However, none of the 24 permeability papers used paediatric-specific models in their methodology. The excipients that are used in paediatric products are shown in bold in table 1.

Excipient classification	**PEGs**	**Polysorbate**	**Polymer**
Excipient name	**PEG 200/ 400***/ **1000**/ 2000/ **6000**	Tween 20, **Tween 80**	Lauroyl polyoxylglyceride combined with PEG 32[a]
			PLLA (Poly(L-Lactic Acid))[b]
			Eudragit L100[c], **Eudragit S100[c]**, Eudragit RL100[c]
			Hypromellose 603[d]
			Poloaxmer[c], Poloaxmer 407[d], Poloaxmer 188[e]
Study model	Rats, Adults*	Rats	[a]in vitro, [b]rats, [c]$CaCo_2$ cells, [d]humans, [e]mice

Table 1. Excipients reported to increase permeability

The range of models used to investigate effects of excipients on permeability included: rats; mice; Caco-2 cells; in vitro tools and healthy adults. None of the models have been developed specifically to understand excipient effects in paeditric populations. Therefore, they may not be suitable to predict permeability effects of excipients in the paediatric population. There is conflict in terms of intestinal P-gp

expression in neonates with Johnson and Thompson (2008) reporting low levels at birth increasing to adult levels by 2 years whereas Fakhoury et al. (2005) reported mature P-gp expression at birth.

Conclusions: Excipients currently used in paediatric products may affect permeability of drugs. However, there are currently no tools that are available to assess the impact of excipients on permeability within a paediatric population. Further work is required to develop age-appropriate models to evaluate permeability in paediatric populations, particularly neonates.

Keywords: Biopharmaceutics, Excipients, Permeability, P-gP

References:

1. T.N. Johnson, M. Thomson. Intestinal metabolism and transport of drugs in children: the effects of age and disease. J. Pediatr. Gastroenterol. Nutr., 47 (2008), pp. 3-10

2. M. Fakhoury, C. Litalien, Y. Medard, H. Cavé, N. Ezzahir, M. Peuchmaur, E. Jacqz-Aigrain. Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. Drug Metab. Dispos., 33 (2005), pp. 1603-1607