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Review article

Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients

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ABSTRACT

Biopharmaceutics is routinely used in the design and development of medicines to generate science based evidence to predict in vivo performance; the application of this knowledge specifically to paediatric medicines development is yet to be explored. The aim of this review is to present the current status of available biopharmaceutical tools and tests including solubility, permeability and dissolution that may be appropriate for use in the development of immediate release oral paediatric medicines. The existing tools used in adults are discussed together with any limitations for their use within paediatric populations. The results of this review highlight several knowledge gaps in current methodologies in paediatric biopharmaceutics. The authors provide recommendations based on existing knowledge to adapt tests to better represent paediatric patient populations and also provide suggestions for future research that may lead to better tools to evaluate paediatric medicines.

1. Introduction

Biopharmaceutics is defined as the study of the factors (physicochemical properties, dosage form, and biological parameters) influencing the bioavailability (and therefore pharmacokinetic profile) of a drug in man and the use of this information to optimise pharmacologic or therapeutic activity of drug products in clinical applications [1]. Biopharmaceutical science and tools are used widely in the design and development of pharmaceutical formulations to predict and optimise their clinical performance.

Drug solubility and permeability are key measurements that underpin biopharmaceutical inputs for orally administered medicines with these properties being used to derive secondary measures that include biopharmaceutics classification system (BCS) and the maximum absorbable dose (MAD). These biopharmaceutical inputs are used in drug development in terms of risk assessing the 'developability' and optimisation of a drug formulation design [2,3], such that critical absorption factors are identified early to maximise the bioavailability of successful products [4]. For example, Kawabata et al. reported on how biopharmaceutical knowledge was used to assist in the formulation design of poorly water soluble drugs leading to more efficient development of appropriate medicines [5]. Biopharmaceutical measures also provide weight in regulatory submissions in terms of eligibility for biowaiver status based on the BCS [6,7].

Biopharmaceutical inputs are critical in the design and development of biologically relevant in vitro tests used to predict the performance of a drug and/or medicine. However, it is essential that the in vitro tools developed are known to be robust and reliable. Dissolution testing that results in an in vitro in vivo relationship (IVIVR) has the potential to negate the need for future clinical bioequivalence testing [8].

Bridging of formulations (demonstrating bioequivalence between two alternative formulations) is of interest both in drug development and within clinical practice. If the commercial formulation is not available for pivotal clinical studies during

Abbreviations: BCS, Biopharmaceutics classification system; EMA, European Medicines Agency; FaSSIF, Fasted state simulated intestinal fluid; FDA, (United States) Food and Drug Administration; FeSSIF, Fed state simulated intestinal fluid; GI, Gastrointestinal; IVIVR, In vitro in vivo relationship; MAD, Maximum absorbable dose; PBPK, Physiologically based pharmacokinetic; P-gp, P-Glycoprotein; PK, Pharmacokinetic; SGF, Simulated gastric fluid; USP, United States pharmacopoeia.

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development, a bioequivalence study is likely to be required prior to launch. Biopharmaceutical knowledge, particularly the BCS [9], provides justification in specific cases for a biowaiver in place of a clinical bioequivalence study [4,10,11]. This application of biopharmaceutics has helped to avoid additional in vivo studies with a significant reduction in the cost and time of developing drug products. Biowaiver monographs are available for over 30 drugs with more in preparation (http://www.fip.org/bcs_monographs); this equates to reduced clinical trials although the exact number of clinical trials avoided due to the use of biopharmaceutics is difficult to determine accurately. A reduction in clinical studies is of particular significance for the paediatric population where ethical and logistical constraints limit recruitment of children into clinical trials.

In silico physiology based pharmacokinetic (PBPK) modelling is now used routinely in risk assessment for formulation changes within an industrial setting [4]; the input parameters for these models are directly derived from biopharmaceutical measurements. The use of PBPK modelling, especially when used in conjunction with other biopharmaceutical tools (such as in vitro predictive tests), offers further opportunity to minimise clinical testing [12].

The aim of this review is to present the current status of biopharmaceutical tools and tests that may be appropriate for use in the development and introduction of oral immediate release age appropriate medicines. The existing tools are discussed together with any limitations for use within paediatric populations. The authors provide recommendations based on existing knowledge to adapt tests to better represent paediatric patient populations and also provide suggestions for future research to drive paediatric formulation development and minimise the number of clinical studies required.

2. Clinical studies in paediatric populations

Paediatric oral medicines are often derived from established adult medicinal products (e.g. a liquid, semi-solid or solid based on a tablet formulation). Typically, paediatric clinical studies are conducted following data collection in adults which provides the opportunity to learn about pharmacokinetics (PK) in adults and use this knowledge to predict performance in paediatric patients. Based on United States of America (USA) law, the paediatric study decision tree [13] allows extrapolation from adult data sets if there is sufficient similarity of both (i) disease progression and (ii) response to intervention between source and target population. If the exposure–response relationship of the medicinal product is assumed to be similar, the only clinical studies required are those for dose determination and safety evaluation. This logic is also replicated in European Medicines Agency (EMA) guidance where it is stated that relative bioavailability comparisons of paediatric formulations with the adult oral formulation should typically be conducted in adults, with only dose selection pharmacokinetic studies required in paediatric populations [14].

There may be a need for more than one paediatric formulation from birth to adulthood; therefore, formulation bridging needs to be managed. Formulation bridging often involves undertaking a relative bioavailability study (or in vitro equivalent) in a healthy population to ensure that the pharmacokinetic profile is equivalent for two formulations. For paediatric products, the relative bioavailability study is conducted in adults with subsequent extrapolation to a paediatric population followed by a dose determination/confirmation study. In order to minimise the number of clinical studies conducted in children, the most popular strategy is to use the new paediatric formulation for pivotal efficacy and safety trials conducted within the paediatric population to avoid further clinical bridging studies. Extrapolation can also be used within paediatric populations (up and down age subsets), which reduces the need for additional clinical studies. A recent concept paper by the EMA [15] highlighted the need for scientific validation of the methods used for extrapolation which is of particular importance within paediatric formulation development.

Minimisation of clinical testing in paediatric populations is driven by ethical considerations which limits generation of detailed pharmacokinetic data in paediatric populations. However, Purohit proposed that carefully planned pharmacokinetic sampling in combination with quantitative methods can generate paediatric biopharmaceutics data during development [16]. For example, a formulation switch during the paediatric safety and efficacy study combined with sparse pharmacokinetic (PK) sampling can enable a relative bioavailability assessment [16].

In certain cases, formulations can be bridged in the absence of a clinical study, for example when the drug is defined as biopharmaceutics classification 1 (BCS 1; highly soluble and highly permeable) or where an in vitro in vivo relationship has been established [17]. Polli makes a case for in vitro dissolution studies being better than in vivo clinical studies (in adults) for highly soluble drugs as they (a) reduce costs, (b) more directly assess product performance and (c) offer benefits in terms of ethical considerations [18].

Existing guidance permits a highly soluble, BCS1 drug to be reformulated to target a paediatric population where the first clinical study of the new product is that designed to define the dose within a paediatric population without prior evaluation within an adult population. However, extrapolation of in vitro in vivo relationships or BCS classification in terms of bridging adult and paediatric formulations needs to be undertaken with caution as the criteria for high permeability and solubility need to be relevant for the target paediatric population.

3. Recognised limitations of existing biopharmaceutical tools

The limitations of existing biopharmaceutical tools were highlighted in a meeting on applied biopharmaceutics in 2010 [19]. In terms of prioritisation, it was stated that, "immediate focus should be placed on two key areas for advancing mechanistic understanding: (i) how and where the drug is released from the dosage form in vivo and (ii) the role formulation excipients may play in drug release" [19]. In order to understand these two factors, additional research is required into relevant patient physiology and anatomy to ensure that methods developed reflect the in vivo environment and are therefore more likely to predict performance. It is therefore essential that current biopharmaceutical methods and tools based mainly on adult physiological data are refined and that they reflect the relevant paediatric patient population. These findings also highlight the importance of careful consideration when extrapolating adult biopharmaceutical measurements into paediatric populations. For example, it cannot be assumed that a drug that shows a high dose/solubility ratio in adults will show the same ratio (and therefore risk) in paediatric patients.

It is acknowledged that the absorption process is complex and that predictive methods will always have limitations. The need for validated tests in adults has been recognised with initiatives including the European Union Innovative Medicines Initiative OrBiTo project addressing this need (http://www.imi.europa.eu/content/orbito; accessed 17.12.12). However, as the drug development process has been reformed to address paediatric medicines development in parallel to adult formulations, it is important that paediatric biopharmaceutical models are also developed and validated as a matter of high priority.

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