Journal of Pharmaceutical Sciences 105 (2016) 476–483

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

Literature Review of Gastrointestinal Physiology in the Elderly, in Pediatric Patients, and in Patients with Gastrointestinal Diseases

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ARTICLE INFO

Article history:
Received 28 June 2015
Revised 16 September 2015
Accepted 30 September 2015
Available online 5 November 2015

Keywords:
paracellular transport
passive transport disease effects
pediatric
gastrointestinal transit
permeabiltiy
elderly
CYP enzymes
transporters
metabolism
solubility

ABSTRACT

Oral bioavailability studies during the development of new medical entities or generic drugs are typically performed in healthy volunteers. Approved drug products are, however, used by patients with diverse disease backgrounds, and by pediatric and elderly patients. To provide the knowledge base for assessing the potential effects of age or co-morbidity on the *in vivo* performance of an orally absorbed, systemically active drug product, the literature regarding the gastrointestinal (GI) physiological characteristics (pH, permeability, and transit time) in children, in the elderly, and in patients with GI diseases (irritable bowel syndrome, ulcerative colitis, and Crohn's disease) is reviewed herein, with the knowledge gaps highlighted.

Introduction

Oral formulations developed for achieving the desired pharmacokinetic characteristics and clinical efficacy of individual drugs include immediate release (IR), extended release, modified release, and delayed release formulations. When designing an oral drug product, regardless of a new chemical entity or a generic drug, many factors would be considered, including its absorption, disposition, metabolism, and elimination profile, its stability in the stomach, its physicochemical properties (p*K*a, lipophilicity, solubility), its dose, the local site of delivery, and gastrointestinal (GI) physiology. GI physiology plays an important role in affecting the *in vivo* performance of a drug product and in the extent of its oral pharmacokinetic variability in its target disease population.

The first-in-man study and early clinical pharmacology studies are in general conducted in healthy adults; as are the bioequivalence studies for generic drugs. To translate and predict the bioavailability results from healthy volunteers to the pediatric patients, to the elderly patients, and to the disease population, understanding of the GI physiological characteristics across all age groups and across subpopulations with local GI diseases is important. Notably, the intestinal mucosal surface area increases from approximately 3320 cm^2 in infants to 17,700 cm^2 in adults,[1] Adults aged 65 and older constituted 12.9% of the US population in 2009 and will constitute approximately 19% of the US population by 2030.[2] GI physiological characteristics with respect to drug absorption may differ among healthy adults, adult patients, elderly patients, pediatric patients, and patients with GI diseases. Conceivably, the interaction between individual patients' GI physiological profiles and the formulation characteristics of a drug product could cause significant inter-subject differences in the *in vivo* performance (AUC and C_{max}) of an active pharmaceutical ingredient (API).

In addition to age, GI diseases are another factor that could potentially impact *in vivo* performance of an API as a result of

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http://dx.doi.org/10.1002/jps.24696
0022-3549/

physiological changes. Among the non-cancerous GI diseases, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are very common. IBS affects 25-45 million people in the US and 9%-14% of populations worldwide[3]; IBD affects 1.4 million people in the US and 396 per 100,000 persons worldwide.[4] Considering the sizes of elderly and pediatric populations and the prevalence of IBS and IBD, we reviewed the literature for GI physiology and function in these patient populations and compared their GI characteristics. We reviewed herein the literature regarding the factors that could affect oral bioavailability or local delivery of an oral product, and highlighted the emerging knowledge gaps.

Factors Controlling Oral Absorption

The form of an API (i.e., whether a crystalline or amorphous solid state or a salt) as well as the specific formulation used could influence its *in vivo* release, and consequently its rate and extent of absorption. Additionally, GI physiology also significantly affects oral bioavailability.[5-7] Oral absorption of a drug is determined by its intestinal membrane permeability (including paracellular permeability, passive transcellular permeability, and/or carrier-mediated transport); luminal concentration or maximal luminal concentration (solubility) of the non-ionized form; available GI absorption surface area; and GI transit time.[8] Three of these parameters—permeability, luminal concentration of the dissolved, un-ionized drug after release from the formulation, and total transit time of the formulated drug—can be used to mathematically calculate oral absorption of a drug as follows:

$$\begin{aligned}\iint J\mathrm{d}s\mathrm{d}t &= \iint \left(J_{\text{passive}} + J_{\text{carrier-mediated}}\right)\mathrm{d}s\mathrm{d}t \\ &= \iint (P_{\text{w}}C + P_{\text{carrier-mediated}}C)\mathrm{d}s\mathrm{d}t \end{aligned} \quad (1)$$

Equation (1) describes the amount of drug absorbed, where J is flux per unit surface area and unit time and comprises passive and carrier-mediated components; P_{w} is apparent passive permeability; $P_{\text{carrier-mediated}}$ is apparent carrier-mediated permeability; C is the luminal concentration, assuming a sink condition on the other side of the membrane; s is the absorption surface area; and t is transit time. If assuming only the ionized form is absorbed via the carrier-mediated route, the above equation applies to a zwitterion drug and a strong acid drug that is almost completely ionized beyond the duodenum. Drug molecules are a weak acid or base. For a weaker acid with a single pKa value, $P_{\text{carrier-}A-} \times [A-] = P_{\text{carrier-}A-} * \frac{K_a C}{K_a + [H+]}$, so the apparent $P_{\text{carrier-}A-}$ is defined as $P_{\text{carrier-}A-} * K_a/(K_a + [H+])$ and used in Equation (1) as a general form with the total concentration, C. P_{w} is defined as $\frac{DK}{h}$, with D as the diffusion coefficient; K as the partition coefficient, and h as the membrane thickness.

Passive flux is attributed mainly to transmembrane permeation and, to a small extent, paracellular transport. The luminal pH profile along the GI tract and the pKa values of the drug are factors of its un-ionized concentration in the lumen, and thus, its passive flux, as only the un-ionized form can permeate through intestinal epithelium. For a drug primarily absorbed via a carrier-mediated process, once it is dissolved in intestinal fluid, the fraction absorbed is controlled by the level of transporter expression along the intestine and its binding affinity to the transporter. Intestinal epithelium is comprised of villi and microvilli, especially prominent in the small intestine, which increases the surface area available for drug absorption beyond the geometric surface area contributed by intestinal radius and length. Therefore, a specific formulation design rendering a longer resident time, particularly at the site where its absorption takes place, would be used to achieve a higher extent of absorption.[9,10]

The factors highlighted above affect *in vivo* performance of a drug product and, hence, also play a key role in affecting *in vivo* oral bioavailability and efficacy. Individual physiological and disease factors, in addition to aging and developmental factors, impact permeability and transit time and, ultimately, *in vivo* performance of drug products. These factors and their associated impacts are discussed below.

GI Factors Affecting *In Vivo* Performance of Drug Products

The reviews below focus on important GI physiological factors that will provide the basis for future physiologically based absorption modeling case studies evaluating the impacts of age, developmental changes, and GI diseases on the *in vivo* performance of drug products.

GI Dimensions and Capacity

The volume of gastric fluid is normally small ([averaging 28 mL and ranging from 18 to 54 mL])[7]; or [ranging from 20 to 100 mL] in healthy adults,[11] but gastric capacity can range from 2000 to 3000 mL to accommodate food ingestion. Gastric capacities increase with development: neonates (10-100 mL); infants and toddlers (90-500 mL); older children (750-960 mL); and adolescents (1500 mL).[7] Intestinal dimensions increase from 275 cm in length and 1.9 cm in diameter at birth to 600-800 cm in length and 4.5 cm in diameter in adults.[1] Among children, intestinal lengths increase with age: neonates (275 cm), infants and toddlers (380 cm), and older children (450 cm).[7] As developmental changes are multifaceted, singular consideration of absorption surface area in calculating pediatric doses is likely inadequate without considering ontogenic changes in enzymes, transporters, transit time, and luminal pH.

GI Transit

Once swallowed, an oral dosage form disintegrates in the stomach or intestine and drug molecules are dissolved and absorbed. Hence, T_{max} is highly influenced by gastric emptying, especially for IR products, and the bioavailability of acidic drugs that are absorbed primarily in the stomach. Acid-labile drugs that are protected by an enteric or pH-dependent coating dissolve at a pH > 5 only in the duodenum and further along the intestine; therefore, these drugs are subject to the impact of gastric emptying as well. Moreover, upon gastric emptying, oral solid dosage forms (modified-release, delayed-release, extended release) that do not disintegrate and dissolve in the stomach could be subject to the influence of aging and GI diseases on their transit in the GI tract; consequently, so are their delivery profiles.[8]

Impact of Age

Total transit times and transit profiles are similar between children aged 8-14 years[12] and adults aged 18-65 years.[13] Cross-study comparisons of total GI transit or orocecal transit across various age groups of healthy subjects including children (neonates included), adults, and the elderly are summarized in Table 1.[12-18] Upon further examining the results reported by Brogna et al.,[14] though the elderly adults (on average, 75 years of age) and younger adults (on average, 30 years old) had similar total GI transit times as shown in Table 1, they had a significantly slower gastric emptying of radiopaque markers (2×5 mm^2) taken with a meal, than younger adults. From the group of children averaging 5.5 years old (2 months to 12 years old) studied by Corazziari et al.[15] (Table 1), further analysis by dividing the children into two different age groups of 2-3 years old group and 3-12 years old group