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Review

Pre-systemic metabolism of orally administered drugs and strategies to overcome it

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ABSTRACT

The oral bioavailability of numerous drugs is not only limited by poor solubility and/or poor membrane permeability as addressed by the biopharmaceutical classification system (BCS) but also by a pre-systemic metabolism taking place to a high extent in the intestine. Enzymes responsible for metabolic reactions in the intestine include cytochromes P450 (CYP450), transferases, peptidases and proteases. Furthermore, in the gut nucleases, lipases as well as glycosidases influence the metabolic pathway of drugs and nutrients. A crucial role is also played by the intestinal microflora able to metabolize a wide broad of pharmaceutical compounds. Strategies to provide a protective effect towards an intestinal pre-systemic metabolism are based on the co-administration of enzyme inhibitor being optimally immobilized on unabsorbable and undegradable polymeric excipients in order to keep them concentrated there where an inhibitory effect is needed. Furthermore, certain polymeric excipients such as polyacrylates exhibit per se enzyme inhibitory properties. In addition, by incorporating drugs in cyclodextrines, in self-emulsifying drug delivery systems (SEDDS) or liposomes a protective effect towards an intestinal enzymatic attack can be achieved. Being aware of the important role of this pre-systemic metabolism by integrating it in the BCS as third dimension and keeping strategies to overcome this enzymatic barrier in mind, the therapeutic efficacy of many orally given drugs can certainly be substantially improved.

Contents

1. Introduction

Oral dosage forms are by the most favored ones and are therefore always the first choice. Only when other routes of administration offer

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a clear advantage or the development of oral dosage forms is not feasible, alternative delivery systems are of interest. Reason for the failure in the development of oral formulations is primarily a too low oral bioavailability that is according to the biopharmaceutical classification system (BCS) based on poor drug solubility and/or poor membrane permeability. As there are numerous reviews available focusing on drug solubility and permeability [1–4], these challenges are not reviewed within this article. The BCS, however, does not address another major challenge at all, namely poor gastrointestinal stability, which has in fact a huge impact on the oral bioavailability of many drugs. According to this, the BCS should also address poor and high gastrointestinal drug stability or should at least include the specification unstable and stable. Although certainly of great importance for the design of oral drug delivery systems, there is no comprehensive review about this topic available in the literature.

It is therefore the aim of this review to provide an overview on the pre-systemic metabolism of orally administered drugs taking place in the gastrointestinal tract. Furthermore, detailed information about strategies in order to overcome an intestinal drug metabolism is provided.

2. Pre-systemic metabolism

Quite often poor intestinal stability is not recognized and assumed as a 'first-pass' effect taking place in the liver once first oral bioavailability data are available. In fact there are four primary systems that affect the first pass effect of a drug including the enzymes of the gastrointestinal lumen, gut wall enzymes, bacterial enzymes, and hepatic enzymes. In particular the first three types of enzymes are from the oral drug delivery point of view of interest, as a pre-systemic metabolism by these enzymes can be strongly reduced or even completely excluded by using appropriate formulations. In the gut drugs can undergo Phase I metabolic reactions, including C-oxidation, hydroxylation, dealkylation, N and S-oxidation, desulfuration, reduction and hydrolysis followed by Phase II conjugation reactions [5,6]. The enzymes responsible for metabolic reactions in the intestine include cytochromes P450 (CYP450), transferases, peptidases, proteases and the enzymes of the intestinal microflora (Table 1) [7]. Furthermore, in the gut nucleases, lipases as well as glycosidases influence the metabolic pathway of drugs and nutrients. A crucial role is also played by the intestinal microflora able to metabolize a wide broad of pharmaceutical compounds.

Metabolizing enzymes are distributed all over the GI-tract with high concentration in the duodenum and jejunum. As data from humans are unfortunately not available, the distribution of metabolizing enzymes in the GI-tract of rats is illustrated in Fig. 1 [5]. This heterogeneous expression of metabolic enzyme is also observed in human intestine with higher levels of CYP450 and glucuronosyltransferase in the proximal region of the small intestine, decreasing distally. Moreover, in the intestinal villi the expression of metabolic enzymes is also not-uniform, with the highest levels in mature enterocytes lining the villus tips [8].

Another characteristic that gives to intestine a predominant role in pre-systemic metabolism compared to the liver is the relatively low blood flow of the intestinal mucosa leading to a higher residence time of drugs in enterocytes in comparison to hepatocyte. This phenomenon makes the metabolic enzymes more effective in the intestine then in the liver [8].

2.1. Cytochromes P450

CYP450 are a superfamily of hemeprotein that catalyze the oxidation of drugs, mainly via a monooxygenase reaction. One of the most important CYP450 is the subtype 3A that accounts for more than 80% of the overall amount of CYP450, followed by the subtype 2C9 accounting for approximately 14%. A schematic illustration of the different CYP450 in human intestine is provided in Fig. 2. From the subfamily CYP3A one of the enzymes more involved in drug metabolism is the subtype 3A4 that represents nearly 70% of the total CYP450 in the intestine. CYP4503A4 recognizes substructures presenting one hydrogen bond donor, two hydrogen bond acceptors and one hydrophobic region. It is also reported that the hydrogen bond acceptor should be distant 5.5 to 7.8 Å from the metabolism site and 3 Å from the heme associated oxygen [9]. In addition, the subtypes 3A5, more commonly expressed in human intestine than in liver, is entangled in the pre-systemic drug metabolism. The two subtypes differ significantly in catalytic activity [10,11]. CYP3A4 for instance is induced by rifampicin and dexamethasone, whereas 3A5 is not [6]. CYP3A4 metabolizes 25 to 51% of cyclosporine in the small intestine. This metabolism was confirmed by measuring the level of cyclosporine metabolites in the hepatic portal vein and systemic circulation during liver transplantation in patients. Data show that two thirds of cyclosporine metabolism occurs in the gut, while the liver is responsible for only one third of this metabolism [6,12]. Extensive pre-systemic metabolism by CYP3A was also demonstrated for midazolam in a study based on twenty healthy volunteers showing that the intestinal metabolism is 44 $\pm$ 14% and hepatic first pass extraction is 43 $\pm$ 0.4% with an overall oral bioavailability of 30% [13]. Moreover, CYP3A catalyzes biotransformation of fluorazepam, ethinyl estradiol, erythromycin, tacrolimus and saquinavir and for all these drugs the extent of intestinal metabolism is greater compared to the hepatic metabolism [6]. The second more abundant intestinal metabolic enzyme is CYP2C9 recognizing substrates presenting a hydroxylation site, an anionic site distant 7.8 Å and between them a hydrophobic site [9]. A study carried out in healthy male volunteers to which 100 mg of sodium diclofenac was administered with and without an inhibitor of CYP2C9 determined the role of this enzyme in the metabolism of diclofenac. In fact, the AUC of diclofenac increased by 59.19% when CYP2C9 was inhibited [14]. Recently the role of intestinal CYP3A4, 2C9 as well as uridine-disphosphate glucuronosyl transferase in metabolizing diclofenac in its enterotoxic derivatives was demonstrated [15].

2.2. Transferases

Transferases are a family of enzymes responsible of Phase II conjugation reactions. Several transferases are present in the gut and their major function is to conjugate drugs with polar moieties in order to convert them to more hydrophilic compounds that are easier to be excreted. The most common drug metabolism pathway is catalyzed by uridine-disphosphate glucuronosyl transferase (UGT) an enzyme located in the endoplasmic reticulum that mediates the transfer of glucuronic acid from uridine diphosphate to lipophilic compounds [16]. It is known that UGT interacts with aromatic or aliphatic hydroxyls, carboxylic acid and amines [17]. Moreover, according to an in silico study a glucuronidation feature (nucleophilic site) and two hydrophobic features separated by 3 or 6.2 Å are essential for the UGT pharmacophore [18]. The UGT subtypes expressed in human small intestine are UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4 and UGT2B6. Among them UGT1A8 and UGT1A10 are exclusively expressed in the small intestine [8]. The gut activity of UGT has been reported for estradiol, 17β-estradiol, ethinyl estradiol, acetaminophen, p-nitrophenol, bilirubin, morphine and propofol [6,7]. Furthermore, salicylamide and pentazocine are metabolized in the gut via glucuronide conjugation as demonstrated exploiting *in situ* individual loop preparation in rabbits. By using the same experiment but carried out in rats, a 6.1% of conjugated morphine was detected in the venous effluent from the loops after 30 min when 100 nmol of morphine was administered. Nalorphine undergoes as well conjugation in the intestinal mucosa. In fact its oral bioavailability in rats is only 17% and AUCs analysis demonstrated that 40% of the pre-systemic elimination is taking place in the intestine. The glucuronidation of oestriol was proven by *in situ* gut loops in three patients [19]. Conjugation by UGTs contributes also to the low bioavailability of reloxifen and the intestinal metabolism was shown to be