European Journal of Pharmaceutics and Biopharmaceutics 130 (2018) 247–259

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

Preclinical models for colonic absorption, application to controlled release formulation development

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ARTICLE INFO

Keywords:
Controlled release formulations
Colon
Colonic permeability
Drug absorption
Oral route

ABSTRACT

Oral controlled release (CR) formulations have many benefits and have become a valuable resource for the local and systemic administration of drugs. The most important characteristic of these pharmaceutical products is that drug absorption occurs mainly in the colon. Therefore, this review analyses the physiological and physicochemical features that may affect an orally administered CR product, as well as the different strategies to develop a CR dosage form and the methods used to evaluate the formulation efficacy. The models available to study the intestinal permeability and their applicability to colonic permeability determinations are also discussed.

1. Introduction

The oral route is the most physiological way to administer drugs, having several advantages for the patients. Controlled Release (CR) formulations for the oral route have gained importance during the last decades. A CR system is able to provide therapeutic control, as it delivers the drug at a determined velocity and/or at a determined site, according to the needs meant to be covered. This review focuses on oral CR formulations targeting the colon and colonic drug absorption, since the absorption in this segment of the gastrointestinal tract is of great relevance for oral CR formulations.

1.1. The colon as targeted absorption site

The colon is one of the sites where local and systemic delivery of drugs can take place. Both, local and systemic treatment, when targeting to the colonic region, can offer considerable therapeutic benefits to patients. Colonic drug delivery is of interest in the treatment of colonic diseases like ulcerative colitis, Crohn's disease, colon cancer and local infections. Thereby, a direct treatment at the affected area will be ensured, so that patients require a lower dose, causing fewer systemic side effects [1–3].

In addition to local therapy, the colon can also be used as a targeted window for introducing drugs into systemic circulation in order to reduce gastric irritation or first pass metabolism of orally ingested drugs [4]. Evidence suggest that a lower activity of cytochrome P450 3A (CYP3A) in colon than in the small intestine, so that a delivery of a CYP3A substrate in the colon may be reflected in higher plasma levels and enhanced oral bioavailability [2,5,6]. Other drugs such as peptides and proteins are degraded in the stomach and the small intestine, therefore, oral delivery of this type of compounds is possible as the colon provides a more suitable environment than the upper gastrointestinal tract [7,8]. This approach is very interesting for drugs such as insulin [9,10].

Colon CR formulations can be employed when a delay or a modification in the absorption is required, but, being at the same time, a drug with high permeability and good absorption through the small intestine. CR products can be beneficial for drugs with a short elimination half-life, side effects associated to the peak plasma concentration and multiple daily doses [11,12]. The objective of developing a CR formulation with this type of drugs is to achieve constant concentrations for prolonged periods of time; thus, it may be feasible to increase the effect duration, reach a once daily dose, avoid fluctuations of the plasmatic concentration and reduce adverse effects. Whether CR is for local or systemic therapy, the main goal of CR products is to improve patient compliance and, therefore, treatment efficiency [11–13].

Moreover, recently it has been demonstrated that the Biopharmaceutic Classification System (BCS) employed to classify drugs according to their solubility and permeability in the small intestine [14], can be applied to colon absorption [15]. In addition,

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https://doi.org/10.1016/j.ejpb.2018.07.008
Received 15 May 2018; Received in revised form 4 July 2018; Accepted 5 July 2018
Available online 06 July 2018
0939-6411/

several studies have shown that many drugs have a significant absorption in the colon, which is crucial in the development of CR formulations with systemic effects [15–19].

1.2. Factors affecting drug absorption

There are several factors and variables that affect the absorption process of a drug and the behaviour of the pharmaceutical formulation after oral administration [20–22]. The most important are the anatomical and physiological features of the gastrointestinal segment at which the drug is targeted and, the physicochemical properties of the active pharmaceutical ingredient.

1.3. Anatomical and physiological characteristics of the colon

Traditionally, Immediate Release (IR) forms have been designed to release the drug in the upper regions of the gastrointestinal tract, as only the small intestine is structured to provide a maximum absorption, due to its higher available absorption surface and its higher transporter protein abundance [23]. An orally administered dosage form takes about 3 h to travel through the small intestine to the beginning of colon [4], and a CR formulation is designed to release the drug within 12–24 h [24]. Therefore, to obtain a successful CR product, it is necessary to take into account the specific characteristics of the colon, which will affect the design and development of the CR formulation [25]; Table 1 shows a comparison of features between the human colon and the human small intestine [4,13,20,23,26–36]. Moreover, the total time for transit along the colon tends to be highly variable and influenced by several factors such as diet, mobility, stress, diseases and drugs [4]; this fact can also have an impact on the CR final effect of the CR product.

The principal role of the colon is to confer a mechanism for the orderly disposal of waste products of digestion [37]. The colon is specialized in keeping the electrolytic and water balance, absorbing Na^+, Cl^- ions and H_2O, and secreting HCO_3^- and K^+ [38]. The most important characteristic of the colon is its long transit time, more than 24 h; whereas the small intestine transit time is shorter, about 2–5 h [28,29]. This long transit time allows drugs to be in contact with the colonic mucosa for a longer period than in the small intestine which compensates the lower surface of the colon for absorption [2]. Nevertheless, not only the colonic characteristics have to be considered when developing a CR formulation, as an orally administered drug also passes through the stomach and the small intestine. Hence, the behaviour of the dosage form will also be affected by the small intestine and the gastric environment [35,39].

1.4. Physicochemical properties of the drug

As has been mentioned, drug absorption through the colon membrane is crucial for CR formulations. All the anatomical and physiological characteristics of the colon, described in the previous section, can influence drug absorption and should be taken into account during CR formulation development. However, there are other factors to consider than biological features: the physicochemical properties of the drug [40].

1.4.1. Drug lipophilicity (distribution coefficient)

Lipophilicity is in general estimated with partition and a distribution coefficient: with a higher distribution coefficient at pH 6.5–6.8 indicating a favourable lipophilicity at small intestinal conditions. Passive diffusion is the main pathway for absorption of orally administered drugs, with the compounds passing through the lipid membrane [38]. Therefore, more lipophilic drugs have a higher permeability. For example, ibuprofen and carbamazepine, with a distribution coefficient of 3.97 and 2.45, respectively, are more lipophilic drugs than ranitidine and amoxicillin, with a distribution coefficient of 0.27 and 0.87, respectively.

1.4.2. Aqueous drug solubility

Aqueous solubility is the major determinant of absorption through the intestinal membrane for poorly soluble and hydrophobic drugs, as intestinal fluids are aqueous. However, for hydrophilic drugs, the rate of drug permeation across the biological membrane is the determining factor for absorption. Therefore, drug solubility and intestinal permeability are closely associated, exhibiting a certain interplay between them. Consequently, efforts to increase drug solubility either by molecular changes or by formulation approaches need to be carefully balanced with the consequences for drug permeability, as depending on the type of solubility-permeability interplay, absorption may decrease, remain unchanged or increase when the solubility is increased [41,42].

1.4.3. pKa (dissociation constant)

The relationship between the drug pKa and the intestinal pH determines the ionization degree of a molecule; only the unionized forms of a drug can be absorbed. The unionized fraction *(f)* can be calculated according to the Henderson-Hasselbach equation: $f = 1/1 + 10^{(pKa-pH)}$ for basic drugs, and $f = 1/1 + 10^{(pH-pKa)}$ for acid drugs. For example, atenolol (pKa = 9.6), a low permeability drug, has a low unionized fraction at pH 7 ($f = 0.25\%$). However, cimetidine (pKa = 6.8) has a bigger unionized fraction at pH 7 ($f = 61\%$), thus its permeability is higher than atenolol permeability at neutral pH.

Yet, *f* is not the only parameter that determines drug absorption, but

Table 1
Human small intestine and human colon characteristics [4,13,20,23,26–36].

		Small intestine	Colon
Length (m)		7	1.5
Absorption surface area (m2)		120	0.3
Absorption surface provided by:		Folds, villi and microvilli	Folds and microvilli
Transit time (h)		2–5	~24
pH		6.0–7.0 (duodenum), 6.0–7.7 (jejunum), 6.5–8.0 (ileum)	5.5–7.5 (ascending colon), 7.0–8.0 (descending colon)
Water volume (mL) (fasting conditions)		130	10 (higher water absorption: contents more viscous)
Microorganism (Organism/g)		10^2 (duodenum), 10^5 (jejunum), 10^7 (ileum)	10^{11}–10^{12} (important role in the gut immune system)
Enzymes[a]		CYP3A family	Enzymes secreted by colonic microflora
Absorption pathway	Passive	Transcellular, paracellular	Transcellular
	Active[b]	PEPT, MRP2, P-gp	MRP3, MRP2, OCTs

CYP3A, cytochrome P450; PEPT, peptide transporter protein, MRP, multidrug-resistance-associated protein; P-gp, P-glycoprotein; OCT, organic cation transporter.
[a] The most important enzymes in small intestine and colon.
[b] The most important transporter protein in small intestine and colon according to Drozdzik et al. [23].