Expert Opinion

Systems for region selective drug delivery in the gastrointestinal tract: biopharmaceutical considerations

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Background: The design of a proper region-specific oral drug delivery system has to take into consideration the differences in anatomy, physiology and absorption characteristics that exist between segments within the gastrointestinal (GI) tract, as well as transit kinetics of the dosage form and the site of drug release within the GI tract. *Objective*: The aim of this review is to examine the various biopharmaceutical aspects of region-specific drug delivery in the GI tract. *Methods*: This review is mainly focused on pharmacokinetic and pharmacodynamic aspects of region-selective drug delivery with special emphasis on drug absorption pathways (para- and transcellular, absorption and efflux transporters, lymphatic uptake etc.). It includes a discussion of gastroretentive systems, colonic delivery, and lipid-based formulations. The review also addresses targeted therapy of local diseases within the GI tract. *Conclusions*: The advances in pharmaceutical technology allow for the development of a variety of region-specific drug delivery systems for oral administration to optimize local and systemic therapy.

Keywords: absorption pathways, colonic drug delivery, controlled release, drug absorption transporters, gastroretentive dosage form, peptide delivery

Expert Opin. Drug Deliv. (2008) 5(6):681-692

1. Introduction

The oral route is the most convenient and preferable way to administer drugs. For drugs with high solubility and high permeability (BCS class 1) clinical effectiveness can be achieved by relatively simple immediate or controlled release formulations. However, these formulations can be insufficient for drugs characterized by low systemic absorption following oral administration. The poor bioavailability of pharmacologically active compounds prevents the development of otherwise promising drug candidates and therefore is a major challenge for the pharmaceutical industry. The design of a proper delivery system can modify this unfavorable pharmacokinetic profile and lead to improved bioavailability together with controlled absorption properties.

There are several processes that may occur following drug release from a dosage form in the gastrointestinal (GI) tract, including precipitation, chemical/enzymatic/bacterial degradation in the lumen, absorption (passive and/or carrier mediated), efflux by *P*-glycoprotein pump, and metabolism in the intestinal wall. The GI tract is not a uniform structure; it is composed of several regions differing in anatomy, biochemical environment, pH, microbial flora, expression of transporters, and absorption characteristics (**Table 1**). For drugs that have region-specific absorption properties, transit kinetics of the dosage form (and of the released

10.1517/17425240802182281 © 2008 Informa UK Ltd ISSN 1742-5247

Table 1. Parameters of various segments of the gastrointestinal tract [1,3,42,100,113].

Parameter	Stomach	Small intestine	Colon
Length (cm)	20	350 – 700	90 – 150
pH	1.5 – 2 fast, 3 – 6 fed	6 – 7	5.5 – 7
Bacterial count (CFU/ml)	10^2 – 10^4	10^3 – 10^4	10^{11} – 10^{12}
Absolute surface area (m^2)	0.053	200	0.35
Transit time (h)	0 – 2 fast	3 ± 1	> 20

Table 2. Drugs compounded in gastroretentive dosage forms.

Captopril [114]	Atenolol [115]
Acyclovir [44]	Cinnarizine [116]
Cisapride [117]	Ciprofloxacin [71]
Calcium [118]	Furosemide [24,70,119]
Ketoprofen [120]	Levodopa [26,121]
Metformin [11,122]	Misoprostol [14]
Sotalol [123]	Tetracycline [124]
Verapamil [125]	Diltiazem [126]
Ofloxacin [127]	Bisphosphonates [128]

drug) within the GI tract significantly affect the absorption. The amount of time needed for a dosage form to leave the stomach is highly variable (ranging from several minutes to several hours) [1]. The transit time of the dosage form through the small intestine is relatively constant (3 ± 1 h) and unaffected by food [2,3]. Most of the transit time of a non-disintegrating dosage form in the GI tract is in the large intestine, where it may stay for an extremely long period of time (up to several days) [4]. The pharmacokinetic and pharmacodynamic profiles of the drug may be influenced not only by the physicochemical properties of the drug molecule but also by its delivery site. Successful targeting to an appropriate GI region can lead to enhanced therapy. Local therapy of ailments of the alimentary canal itself (e.g., inflammatory bowel disease [IBD], irritable bowel syndrome, colorectal cancer, and peptic ulcers) is another important reason for targeting a drug to a specific region within the GI tract.

This review focuses mainly on pharmacokinetic and pharmacodynamic aspects of region-selective drug delivery. A brief review of the available technologies and references for more comprehensive technological discussion are also provided. To simplify the discussion we used the term 'conventional' in all cases where the dosage forms were not specially designed to release their payload at a specific region of the GI tract and compared them with targeted drug delivery systems.

2. Stomach and upper small intestine

2.1 Technological principles and evaluation

Targeted and controlled delivery of drugs to the upper part of the GI tract can be accomplished by a gastroretentive dosage form (GRDF). Gastric retentivity is achieved by delaying the evacuation of the dosage form from the stomach. The principal challenge in the development of a GRDF is to overcome the normal tendency of the stomach to clear its content (either by continuous propulsive forces in the fed state or by the 'housekeeper waves' occurring every 1 – 2 h in the fasted state). Gastric residence time of the dosage form is variable, and depends on many physiological, pathological and pharmaceutical factors. For example, body posture, age, gender, osmolarity and pH of food are capable of influencing the gastric emptying [1,5].

Several approaches have been employed (with varying degrees of success) to achieve gastric retentivity, including: bioadhesion to gastric mucosa, buoyancy over gastric content, high-density units, administration with pharmacological agents that slow gastric motility, expansion to large dimensions following oral administration, and utilization of an extracorporeal magnet. A detailed appraisal of the various technologies is beyond the scope of this paper and may be found elsewhere [6-10]. Examples of drugs that have been compounded into GRDFs can be found in **Table 2**.

Administration of the dosage form with high-calorie food is a relatively simple way to attain some degree of gastric retention for a large single non-disintegrating unit [11,12]. These dosage forms are treated by the stomach as indigestible solids and, therefore, their evacuation from the stomach is delayed by repulsive forces in the pyloric region. Hence, a caloric load of the meal (and especially fat content) will dictate the extension of duration of the fed state and thereby gastric retentivity. Providing reproducible gastric retentivity at the fast state is much more complicated and has not yet been achieved [13-15]. The emptying of a multiparticulate dosage form was shown to be less dependent on the presence or absence of food in the stomach [16], and bears the advantage of not being an all-or-nothing system.

When developing region-selective drug delivery systems (such as GRDFs), it is very important to accurately ascertain that the drug release occurs at the desired part of the

GI tract. Therefore, methods to track the transit of the dosage forms in the GI tract are needed. The state-of-the-art technique used for evaluation of the dosage form's performance is gamma scintigraphy [17,18]. This method provides high precision while being relatively safe. A small amount of radioisotopes can be incorporated into the final dosage form without interfering with other components. The direct follow-up on the location of the dosage form provided by gamma scintigraphy can be used for establishing a correlation between GI transit and pharmacokinetic data. Utilization of several isotopes, when one is incorporated into the dosage form and the other is mixed with food, allows for simultaneous determination of the relationship between the dosage form and the food transit time in the GI tract; this may be necessary for the safety evaluation of large gastroretentive devices [19]. Other more accessible methods are X-ray and MRI. MRI is an advantageous imaging technique because it lacks ionizing radiation and therefore allows the researcher to perform experiments in a crossover design [20,21]. One disadvantage is that a relatively large amount of contrast agent may be required to be incorporated into the dosage form to allow detection, which may preclude simultaneous compounding of an active ingredient.

In recent years the development of GRDFs mainly focused on expandable [6,7] and floating techniques [22,23]. Whitehead *et al.* [15] showed in humans that a multiple unit floating system was significantly more gastroretentive (over 5.5 h) in comparison to non-floating beads in the fed state. A floating tablet of furosemide stayed for 6 h in the stomach of human volunteers [24]. The major limitation of the floating approach is the requirement to maintain a sufficient stomach content to allow an effective separation between the dosage form and the pyloric region [15]. In addition, the gastric retentivity of such dosage forms was shown to be very susceptible to body position [5,25]. We have recently reported that the expanding-unfolding GRDF demonstrated a significant gastric retention (up to 10.5 h in 75% of subjects) when administered with a low-calorie breakfast to healthy volunteers [20]. For this type of GRDF it was demonstrated that the combination of elasticity and geometric properties is a key for ensuring proper gastric retention [26,27]. The major requirements for the expandable devices are an initial small size to be readily swallowed with a rapid size increase in the stomach (to prevent premature emptying), a sufficient final size and strength to withstand stomach contraction, and ultimate biodegradation following the end of drug release. In the development of this type of dosage form safety issues must be taken into consideration, such as possible occlusion of esophagus or pylorus. Moreover, an excessive gastric retention of more than 24 h may result in the accumulation of several dosage units in the stomach. Consequently, the performance of GRDF should be evaluated with various imaging techniques to rule out any possible safety problems.

2.2 Local treatment in the stomach

Continuous delivery of therapeutic agents to the stomach can be used for treatment and prevention of local ailments, such as gastro-esophageal reflux disorder and peptic ulcer. *Helicobacter pylori* is one of the most prevalent bacterial pathogens and is associated with a variety of disorders (peptic ulcer, gastric cancer, mucosa-associated lymphoma etc.) [28]. Infection by *H. pylori* usually occurs in early childhood, and unless treated, colonization of the gastric mucosa persists for life [28,29]. The treatment of *H. pylori* associated peptic ulcer is usually based on a combination of several antimicrobial agents with proton pump inhibitors or H_2 blockers; this complex regimen can result in poor compliance. The bacteria reside mainly in the surface layers (mucus and mucosa) of the antral region of the stomach [29,30], and adequately high local antibiotic concentrations are required for successful treatment [31]. The relatively short residence time of conventional dosage forms in the stomach is usually given as the reason that complete eradication of *H. pylori* is not achieved. It is still unclear whether antimicrobial drugs exert their activity by a local or systemic action following oral delivery [32]. Diffusion from the systemic circulation into the gastric mucosa following intravenous administration was demonstrated in man for several antibiotics, including for example, amoxicillin, metronidazole, and clarithromycin [33]. Despite the controversy, it has been proposed that continuous local delivery could be beneficial for *H. pylori* therapy. For this reason, several GRDFs that enhance local delivery were evaluated with variable degrees of success. Shah *et al.* [34] proposed porous chitosan microspheres loaded with amoxicillin and metronidazole. However, they showed a too rapid *in vitro* release rate. Wang *et al.* [35] developed positively charged gelatin microspheres of amoxicillin that were mucoadhesive in the isolated rat stomach model. Murata *et al.* [36] reported that floating alginate gel beads containing chitosan resulted in increased drug concentration in the gastric mucosa compared with metronidazole solution. Rajinikanth and Mishra [37] proposed a floating *in situ* gelling system of clarithromycin and sucralfate that was found superior to clarithromycin suspension in clearing *H. pylori in vivo* in Mongolian gerbils. Comprehensive reviews on various drug delivery systems targeted for the treatment of *H. pylori* can be found elsewhere [29,38].

In general, several points should be taken into consideration when developing a gastroretentive system targeted for the treatment of *H. pylori* associated ulcers. It seems that expandable large dimension systems may be inadequate and pose some safety problems in cases of mucosal inflammation or ulcer. A multiparticulate system, however, could be advantageous. Moreover, a combination of approaches (like low density and mucoadhesion) can lead to longer retention and improved reproducibility. The major obstacles for mucoadhesive systems are the high turnover rate of gastric mucus and unspecific binding to various intestinal contents.

Still, this type of delivery appears promising for the treatment of *H. pylori* when close contact with the mucus layer may significantly increase the local antibiotic concentrations. In addition, it is important to note that drugs that significantly elevate gastric pH are usually implemented in *H. pylori* treatment and utilization of any technology that relies on acidic environment will probably fail to work.

2.3 Gastroretentive dosage form and systemic absorption

Following oral administration most drugs have to be absorbed into the blood to produce therapeutic action. The region-specific absorption of certain drugs (sometimes called 'absorption window') may be for various reasons, such as poor solubility at different pH values, poor stability in some GI regions, presence or absence of absorptive or efflux transporters, and presystemic metabolism in the gut wall [39]. The three main absorption mechanisms are transcellular, paracellular, and carrier-mediated transport. For passively transcellularly absorbed drugs no significant variation in the intestinal permeability is expected in the various segments of the alimentary canal. The two other permeation pathways, however, clearly demonstrate regional variability, and these differences are discussed below.

2.3.1 *Paracellular absorption route*

Small polar molecules are too hydrophilic to penetrate through the cell membrane and therefore are mainly absorbed by the paracellular passive diffusion mechanism. The pore size of epithelial junctions was shown to decrease aboral in the intestine [40-42]. Hydrophilic drugs (e.g., atenolol, acyclovir, metformin) have a higher permeability in the upper GI tract in comparison to lower regions [43]. If such drugs are compounded in a conventional controlled release dosage form, a considerable part of the drug is released in the distal intestine where permeability is limited and thus the bioavailability is impaired. Alternatively, if the drug is slowly released from the GRDF in the upper GI the extent of absorption will be similar to an immediate release formulation. The bioavailability of acyclovir from a magnetic controlled release tablet was reported to be higher when it was positioned in the stomach, with the aid of an external magnet, in comparison to the group without a magnet [44]. We have recently demonstrated in the rat model, that continuous gastric infusion of atenolol results in bioavailability very similar to that of gastric bolus administration (of the same dose), while colonic delivery leads to about a fourfold decrease in the extent of absorption [45]. In summary, the controlled release gastroretentive approach can accomplish prolonged release for hydrophilic drugs without a decrease in bioavailability that occurs with a conventional controlled release formulation.

2.3.2 *Carrier-mediated absorption*

Drug absorption pathways are not limited to passive permeability, either trans- or paracellular. There are many carrier-mediated processes controlling the absorption of various compounds in the intestine (amino acids, nucleosides, small peptides, organic cations and anions, phosphates etc.) These transporters are also exploited for absorption of drugs [46-48]. While some of these carriers were shown to be relatively equally distributed throughout the intestine (i.e., organic anion and cation transporters [49]) others clearly exhibited site-specific distribution. For instance, the dipeptide transporter PEPT1, which is involved in the absorption of β-lactam antibiotics and ACE inhibitors, is present almost exclusively in the small intestine [49]. The activity of CNT (nucleoside transporter) was demonstrated to be higher in the proximal intestine in comparison to distal regions [50]. A controlled release gastroretentive mode of administration can considerably alter the pharmacokinetics of drugs absorbed by a carrier-mediated mechanism that is localized in the upper intestine. The impact of this mode of administration depends on the relative capacity of the carriers.

The most prominent effect of GRDFs is expected in drugs that are mainly absorbed from the upper GI tract by a low-capacity carrier. For these drugs a significant increase in bioavailability can be achieved by prolonged delivery to the upper regions of the GI tract in comparison to immediate release formulation. Riboflavin (a water soluble vitamin) is a good model for such drugs [51,52] and is frequently used as a marker compound in the development of GRDFs due to its safety. Several works have demonstrated that prolonged gastric retention can increase the bioavailability of riboflavin by its continuous delivery to the absorbing region at concentrations that are below the level of saturation of the absorption transporters (**Figure 1**) [20,27,53,54]. Gabapentin, used for treatment of epilepsy and neuropathic pain, is another example. It is absorbed only from the proximal gut by a capacity limited L-amino acid transport system and hence shows dose-dependant bioavailability [55-57]. Development of a controlled-release GRDF led to improvement of dose proportionality [58] and an increase in bioavailability at higher doses [59]. It is of interest that the development of XP13512 (a novel prodrug of gabapentin, engineered to be absorbed by a more equally distributed transporter MCT1) also resulted in enhanced absorption [60].

In contrast to compounds absorbed by saturable carriers, for drugs that are absorbed by high-capacity transporters (localized mainly in the upper intestine) a significant increase in bioavailability following administration by controlled release GRDF should not be expected. We have recently demonstrated that continuous intragastric delivery of valacyclovir (acyclovir prodrug targeted to PEPT1 transporter) allows plasma concentrations to be maintained for a prolonged time in comparison to a high peak followed by rapid elimination after gastric bolus dosing. This concentration profile cannot be attained by a conventional controlled release delivery since the drug is not absorbed from the colon [45]. However, the bioavailability following both gastric bolus and gastric infusion was very similar. In other

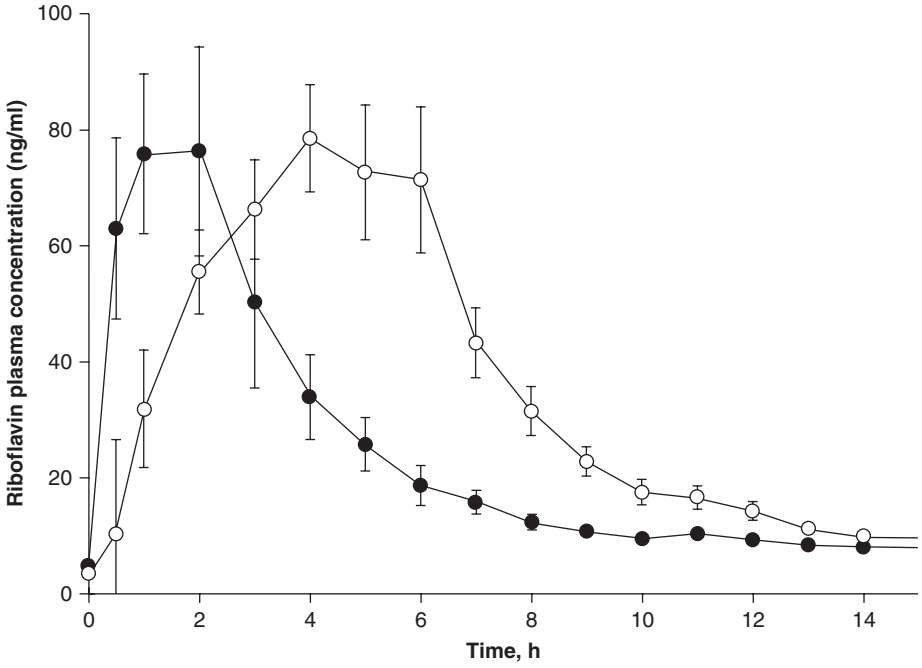

Figure 1. Plasma concentration (mean ± SEM) versus time profile of riboflavin. Plasma concentration following administration of the gastroretentive dosage form (GRDF) (○) or the immediate release capsule (●) to human volunteers (n = 7). Administration of the GRDF resulted in approximately 1.6-fold increase in bioavailability [20].

words, for these drugs the GRDF approach may provide all the advantages of the controlled release delivery (prevent the high peak concentration, reduce the required doses and improve compliance). But, it should be emphasized that as long as no saturable transport is involved in drug absorption, the GRDF is not expected to increase the bioavailability in comparison to an immediate release formulation.

2.3.3 *P-glycoprotein mediated efflux*

P-glycoprotein (Pgp) is a well recognized factor in mammalian tumor cell resistance to various cytotoxic drugs and in drug absorption and distribution. It is a plasma membrane-bound ATP-dependent transporter which is encoded in humans by the MDR1 gene. Pgp is found in a wide range of normal tissues and functions to protect the body against potentially toxic xenobiotics. Its localization in the apical membrane of the enterocytes suggests that it may play a major role in limiting the bioavailability of drugs following oral administration. An increasing number of drugs are reported to be substrates of Pgp. Most of the data were obtained from *in vitro* and *ex vivo* experiments; however the ability of Pgp to affect drugs' pharmacokinetics was also demonstrated in animal and human studies. It has been suggested that Pgp substrate can benefit if targeted to the upper small intestine [61]. For example, it was demonstrated in one human intestinal perfusion study that the area under the concentration–time curve of talinolol (a known Pgp substrate that is not metabolized by Cyp 3A4 enzyme) decreased with increasing distance from the teeth [62]. However, the data regarding regional differences in Pgp function in the intestine are rather controversial. It is usually acknowledged that Pgp exhibits a distribution in the intestine that is the opposite of that demonstrated by the Cyp 3A4 enzyme; that is, the lower intestine demonstrates a higher level of Pgp in comparison to the upper intestine. There are several reports that support this statement with respect to the small intestine [63-65]. Different results were obtained when the large intestine was included in the evaluation. Some works showed the highest Pgp level in the colon [66,67], while others reported that the jejunum is the region with maximal Pgp level [68,69]. The variety of methods utilized in the assessment of intestinal Pgp distribution undoubtedly contributes to the variability of the obtained data. In summary, additional research that compares all intestinal parts under the same experimental conditions is required to evaluate the potential advantages of site-specific delivery of Pgp substrates.

2.4 Pharmacodynamic considerations

With the help of gastroretentive technologies it is possible to provide the general advantages of controlled release even to narrow absorption window drugs: reduced frequency of dosing, reduced fluctuation of drug concentration, extended time over critical (effective) concentration, prevention of peak concentration-associated adverse effects etc. In many cases, the pharmacological action of drugs (when given in a bolus mode) on some physiological functions may lead to a

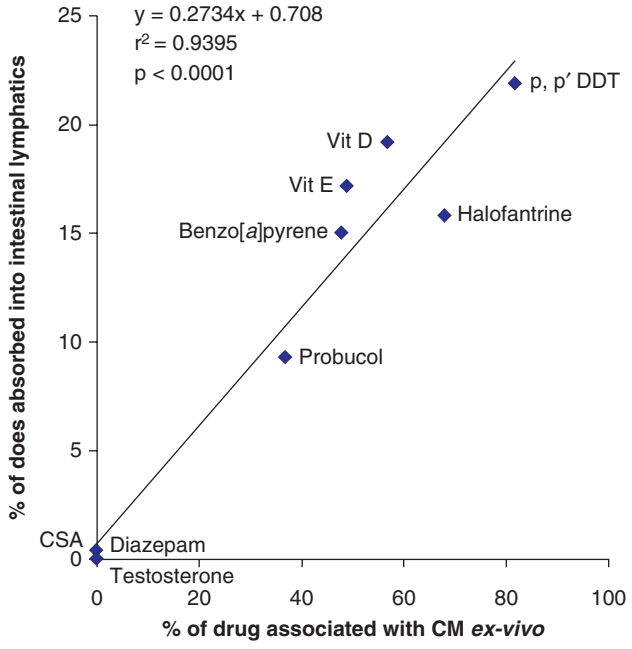

Figure 2. Correlation between the lymphatic availability of tested drugs (% of dose) and degree of association of drugs with isolated chylomicrons in the *ex vivo* model (% of amount).

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CM: Chylomicrons.

rebound activity of the body that minimizes the therapeutic benefit. Slow input of furosemide (a diuretic drug that has a narrow 'absorption window' in the upper GI tract) from the GRDF has been shown to minimize such counter activity and significantly improve diuretic efficiency of the drug in comparison to an immediate release formulation [70].

Minimization of the local adverse drug effect originating from drug action in the GI tract is also an important issue. A swelling controlled release formulation of ciprofloxacin (designed to deliver its contents over 6 h to the upper GI) demonstrated an antibacterial effectiveness similar to conventional twice daily dosing, while also reducing the incidence of nausea and diarrhea [71]. Retention of the dosage form in the stomach also minimizes the amount of drug that reaches the colon and may reduce adverse effects in it. For example, β-lactam antibiotics are mainly absorbed from the proximal small intestine; the unabsorbed residue can lead to the development of microorganisms' resistance in the large intestine [72].

3. Small intestine

3.1 Lipid-based formulations

About 40% of the novel potential drug candidates are highly lipophilic molecules [73] that usually exhibit low oral bioavailability mainly due to low solubility (BCS class 2). To become orally bioavailable these lipophilic drugs must overcome various barriers. They need to have a sufficient solubility in the aqueous milieu of the GI tract, to penetrate through the unstirred water layer adjacent to the enterocytes, and avoid presystemic metabolism. Dietary fat is absorbed very efficiently in the small intestine, mostly by the lymphatic transport. In order to be absorbed, the dietary lipids need to undergo processing in the GI tract that includes hydrolysis by gastric or pancreatic lipases and emulsification with bile acids and phospholipids (particularly lecithin), which occurs mainly in the upper part of the GI tract. Following oral administration with a high-fat meal or with lipid containing formulation, the lipophilic drug will incorporate into this dietary fat processing mechanism. Administration within lipid-based formulations is a valuable approach to enhance the absorption of lipophilic drugs, and the components of these formulations can enhance bioavailability by several mechanisms.

The lipidic component of the formulation can stimulate biliary secretion of bile salts, phospholipids, and cholesterol, thereby facilitating dissolution. The type of lipidic component has a major influence on the capability of the formulation to enhance absorption. For example, probucol [74] and griseofulvin [75] were better absorbed following administration with medium-chain triglycerides in comparison to long-chain triglycerides. Different lipid-based formulations can be compared using *in vitro* lipolysis models, which were shown to be predictive for *in vivo* situations [75,76].

The lipid-based formulation can also improve the absorption of lipophilic drugs by targeting them to intestinal lymphatic uptake [77]. Both the lymphatic system and the circulatory system drain the intestine. The lymph collected from the intestine empties directly into the systemic circulation. Hence, drugs taken up into the lymph bypass the liver and avoid first-pass hepatic metabolism. Each one of the small intestine villi is drained by central lacteal [78]. The lymphatic capillaries of the large intestine are fewer and smaller than the lacteals of the small intestine and located deeper in the intestinal mucosa [79]. The small intestine seems to play a central role in lymphatic uptake. The association of a drug with chylomicrons in the enterocyte is an essential step in the lymphatic absorption pathway. A model that was developed in our laboratory allows this process to be assessed *ex vivo* and was found to be predictive of the intestinal lymphatic bioavailability potential of lipophilic molecules (**Figure 2**) [80]. It also makes it possible to estimate the impact of the lymphatic transport on the overall bioavailability [81].

The length of the fatty acid chain of the triglyceride formulation has a great impact on the degree of lymphatic transport. It was demonstrated that long-chain (C_{18}) triglycerides lead to a significantly higher lymphatic uptake in comparison to medium-chain (C_{8-10}) triglycerides of halofantrine [82] or phospholipids–valproic acid conjugate [83]. Development of lipidic prodrugs (by covalent binding

of a fatty acid, a glyceride, or a phospholipid) is a promising approach for enhancement of drug bioavailability by targeting to the lymphatic transport. The rationale is to increase the lipophilicity of the prodrugs to affect their absorption pathway (logP of > 5 appears to be necessary for lymphatic transport) [84]. Several experimental *in vivo*, *in vitro*, and *in silico* methodologies for assessment of lymphatic drug transport were recently developed [80,81,85-87].

3.2 Ileo-cecal junction

The ileo-cecal junction (ICJ) is located between the small intestine and the colon. Its main physiological function is to regulate chime entry into the large intestine and to prevent the spread of colonic bacterial flora into the small intestine. Although the ICJ may cause a delay in dosage form emptying into the colon of up to several hours [1,4], the size of the dosage form (in a range of 3 – 12 mm in diameter) does not affect the retention time at the ICJ [88]. Certain substances, like dietary fat and bile acids, were shown to be able to modulate the ileal brake [89]. This activation of the ileal brake was proposed as a method to prolong the small intestine residence time and thereby to enhance bioavailability [90]. Oleic acid can slow down the small intestine transit rate of non-disintegrating tablets. Dobson *et al.* [90] evaluated the effect of oleic acid and monoglycerides on atenolol absorption and reported that only in some volunteers did an increase in small intestine transit time lead to an increase in atenolol absorption. It was also emphasized that the prolongation of residence in the upper small intestine has a greater effect on absorption in comparison to residence at the ICJ. Further research is required to evaluate the utilization of the ileal brake on drug absorption.

4. Colon

The colon is significantly different from the small intestine in many aspects. Its primary functions are water and electrolytes absorption and formation and storage of fecal material. In contrast to the small intestine there are no villi in colonic epithelium and hence the available area for drug absorption is much smaller. In addition, the amount of fluid is relatively low, especially in the distal colon. Therefore, the colon is frequently omitted from drug absorption considerations. However, the successful performance of controlled release formulations shows that for many drugs the colon demonstrates efficient absorption properties (i.e., metoprolol, isosorbide-5-mononitrate, theophylline, nilsodipine) [42,91]. This is in part due to a prolonged residence time of the dosage form in this region and the low enzymatic degradation capacity in comparison to the small intestine. The colonic region can be effectively used for absorption of highly permeable drugs that are absorbed transcellularly. Delayed release dosage form relying on colonic absorption may be beneficial for chronotherapy of asthma, ischemic heart disease or arthritis (diseases that exhibit circadian rhythms).

4.1 Colonic delivery technologies for local treatment of IBD

Specific colonic targeted delivery attracted attention mainly due to local therapy in IBD. IBD is a common name for several chronic inflammatory conditions of the distal intestine. Conventional drug regimens include aminosalicylates, corticosteroids, antibiotics, and immunosuppressive agents. Since IBD treatments are usually chronic, local delivery of therapeutic drug concentration to the infected regions (in the lower intestine) is preferred to minimize systemic side effects.

Three major strategies are usually implemented separately or in combination for local treatment of IBD and for colonic delivery in general: utilization of a pH drop on entry into the colon that is associated with cecal metabolism of polysaccharides (the mean pH in the distal small intestine and the caecum was reported to be 7.5 ± 0.4 and 6.4 ± 0.4, respectively [92]); delayed release dosage forms that rely on GI transit time (usually 5 – 6 h); and utilization of metabolic capabilities of colonic bacterial flora to cleave azo and glycosidic bonds [92]. The last approach can be subdivided into two groups: development of prodrugs for specific molecules or design of more universal carrier systems. For example, several azo-bonded modifications of 5-aminosalicylic acid are commercially available to minimize systemic absorption and to maximize local delivery (mesalazine, sulfasalazine, olsalazine, and balsalazide). Alternatively, delivery systems based on various natural polysaccharides have been proposed, including pectin, guar gum, inulin, chitosan, and others [93]. In analogy to azo-bonded compounds there are other redox-sensitive polymers that have been proposed for colonic drug delivery. The mean redox potential in the proximal small intestine, distal small intestine and the colon is -67 ± 90 mV, -196 ± 97 mV and -415 ± 72 mV, respectively; thus, it can be used as a highly selective mechanism for colonic delivery [94].

All approaches, however, have been only partly successful mainly due to a high intra- and inter-individual variability. The disease state itself may have a major influence on colonic parameters and thereby affect the *in vivo* performance of these delivery technologies. For example, it was demonstrated that metabolic activity of the GI tract flora is reduced, colonic pH is lower, and GI transit rate may vary in IBD patients in comparison to the healthy population [95-97]. A combination of several approaches may lead to a more reproducible dosage form performance [92,98]. An additional benefit can probably be provided by multiparticulate dosage forms that provide a more uniform GI transit and drug release [4,99].

4.2 Systemic absorption from colon

4.2.1 *Peptide and protein delivery*

More recently, the colon has attracted much attention as a promising region for delivery of biopharmaceutics [100-102]. Therapeutic proteins have become a considerable part of the arsenal of clinically used drugs. However, the parenteral route of administration continues to be the main delivery route for these agents due to a poor bioavailability following oral administration. The enzymatic degradation in the gut and poor permeability through the intestinal wall are reasons for this low bioavailability. Many works have demonstrated that the magnitude of the proteolytic activity within the colon is significantly lower than in the small intestine and also different from the proteolytic activity of the small intestine and the stomach [100,101,103]. The upper GI tract is a highly aggressive environment for proteins due to a low pH and pepsin secretion in the stomach. The variety of peptidases secreted from the pancreas lead to a rapid protein degradation in the small intestine. Both luminal [104] and brush border membrane [105] protease activity is lower in the colon in comparison to the small intestine and stomach, which makes the colon a preferred region for delivery of therapeutic peptides. Many peptide drugs are hormones, which are very potent, so even small amounts of the absorbed drug can provide a desired therapeutic response. The colon is also considered to be a superior region for the action of absorption enhancers that facilitate drug permeation through the epithelium [106,107].

4.2.2 *Absorption of ester prodrugs*

Another example of region-specific metabolic activity of the intestine can be illustrated by esterase activity. Colonic delivery may provide certain advantages for delivery of ester prodrugs. Synthesis of ester prodrugs is a valuable approach to enhance the oral drug absorption of highly hydrophilic drugs. The more lipophilic nature of the prodrugs facilitates transcellular permeability. The active moiety is intended to be released following absorption in the systemic circulation. However, the intestinal wall contains a significant amount of esterase activity [108] and this presystemic hydrolysis [109,110] may limit the utility of this approach. Van Gelder *et al.* [111] evaluated intestinal esterase-mediated degradation of *p*-nitrophenyl acetate and tenofovir disoproxil in several species (rat, man, and pig). They found a significant site-specific difference in esterase activity in all species: duodenum ≥ jejunum > ileum ≥ colon. It was concluded that colonic targeting may be recommended as a potential strategy to reduce esterase-mediated degradation of ester prodrugs.

5. Expert opinion

The technological, physicochemical, and engineering knowledge needed to develop drug delivery systems has now reached the stage that it is possible to provide a wide selection of routes, sites, modes, and rates of administration for a drug. It has previously been established that the development of a drug delivery system should comply with pharmacokinetic considerations, including aspects of absorption, presystemic biotransformation distribution, systemic elimination, and metabolic fate. Pharmacodynamic aspects (including both efficiency and toxicity) that can be influenced by the delivery system should be examined as well.

The drugs that exhibit region-specific absorption properties in the GI tract can benefit from targeted delivery to an appropriate GI segment. For drugs that are highly absorbed but require sustained input function (for example, due to a short half-life), many conventional controlled release technologies can be used. However, for drugs that exhibit poor absorption properties and low bioavailability, more advanced delivery systems are required. These delivery systems can provide a viable solution for low solubility, degradation, and narrow 'absorption window'. The bioavailability, which is an essential issue in oral drug delivery, can be significantly improved in some cases. For drugs that utilize absorption transporters, the proper targeting to the specific region can result in a dramatic change in pharmacokinetic and pharmacodynamic profiles. The pharmaceutical solution of controlled release gastroretentive formulation is still an 'unmet need', and attaining a significant gastric retention is rather difficult. It should be noted that *in vitro* data (e.g., buoyancy or release rate), as well as retentivity data in animal models do not necessarily reflect the *in vivo* conditions in humans. Therefore, the development of gastroretentive devices (for human use) must include the assessment of gastric retentivity properties in human volunteers at relatively early stages of development. The prolongation of the GI residence time provided by GRDFs may be utilized to extend the time available for absorption. This may be an advantage not only for narrow 'absorption window' drugs, but for other drugs as well. The development of the gastroretentive approach for oral administration is very promising and further activity in this area of research is expected.

As a consequence of modern drug discovery techniques (i.e., the introduction of combinatorial chemistry together with advances in *in vitro* screening method) the number of lipophilic drug candidates is constantly increasing. Despite their pharmacological activity, many of these molecules fail to proceed to advanced stages of research and development due to unfavorable properties (e.g., poor water solubility, low bioavailability). The development of a variety of lipid-based formulations provides an opportunity for these drugs to become valuable additions to the arsenal of clinically used drugs. The components of the delivery system can be used to alter not only the absorption process but also the disposition of the lipophilic drugs [112]. It should be taken into consideration that a lipid-based delivery system will be exposed to lipolysis in the GI tract. Thus, there will be a

significant difference between the *in vitro* release data and the *in vivo* performance. In general, the absorption of highly lipophilic drugs will take place in the small intestine, in analogy to dietary fat.

The design of appropriate prodrugs for active moieties that have poor pharmacokinetic and pharmacodynamic profiles is another very fascinating approach. It may be used to alter many drug characteristics (i.e., to widen the 'absorption window', to increase solubility or permeability, to target to the lymphatic transport). However, it should be noted that another important advantage of the drug delivery system approach is that a less complicated regulatory approval is required.

Acknowledgment

A Hoffman is affiliated with the David R Bloom Center for Pharmacy.

Declaration of interest

A Hoffman is scientific founder of Intec Pharma Ltd.

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