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DRUG DELIVERY—ORAL ROUTE

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INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.

However, the potential for oral dosage form development is sometimes limited for therapeutic agents that are poorly absorbed in the gastrointestinal (GI) tract and unstable to various enzymes, in particular, to proteolytic enzymes, such as peptide and protein drugs. The overall process of oral delivery is frequently impaired by several physiological and pharmaceutical challenges that are associated with the inherent physicochemical nature of the drugs and/or the variability in GI conditions, such as pH, presence of food, transit times, expression of *P*-Glycoprotein (*P*-Gp) and CYP3A, as well as enzymatic activity in the alimentary canal. Manipulation of these problems and challenges is considered an important strategy for improving oral drug delivery, and requires thorough understanding and appropriate integration of physicochemical principles, GI physiology and biochemistry, polymer science, pharmacokinetics, and pharmacodynamics. Over the last 3 decades, much research effort has been made in this area to address various biological and technological issues. Research has opened many novel avenues for the more effective, sustained, or rate-controlled oral delivery of both existing and new therapeutic agents, including peptide and protein drugs emerging from the biotechnology arena.

Furthermore, the oral route offers an attractive approach of drug targeting at the specific sites within GI tract for the treatment of certain pathological conditions, such as gastroesophageal reflux disorder, gastroduodenal ulcers, inflammatory bowel disease, and stomach and colon cancers. Oral drug delivery systems (DDS) can be classified into three categories: immediate-release (IR) preparations, controlled-release (CR) preparations, and targeted-release preparations. This chapter describes the recent technological advances in oral drug delivery and various physicochemical and biological barriers, and also provides some insight on future strategies to improve oral drug delivery.

ANATOMICAL AND PHYSIOLOGICAL CHARACTERISTICS OF THE GI TRACT

Mechanisms and Pathways of Drug Absorption

Orally administered drugs are mainly absorbed in the small intestine (duodenum, jejunum, and ileum) and in the large intestine (colon); however, other regions, such as buccal cavity, stomach, and rectum, also can be considered potential sites for drug absorption. The various anatomical and physiological characteristics of each segment are briefly described in Table 1.

Once at the surface of intestinal epithelium, a drug can be absorbed across by one or a combination of the following mechanisms: passive transcellular, passive paracellular, and carrier- and receptor-mediated transport systems. Paracellular transport involves the passage of drug molecules through aqueous pores created by epithelial tight junctions, and is the most likely route for polar, hydrophilic drugs since they exhibit poor membrane partitioning. In the human small intestine, the average size of these water-filled pores is approximately 7–9 Å for jejunum and 3–4 Å for ileum (2). In the colon, the estimated pore radii are about 8–9 Å, albeit this value was obtained from rat colon (3). Nevertheless, the extent of paracellular transport is limited as tight junctions comprise only about 0.01% of the total absorptive surface area of the intestine (villi) (4). Transcellular absorption involves the transport of drugs through the intestinal epithelial cells (enterocytes) and requires partitioning of drugs across both the apical and the basolateral membranes. Obviously, this route is mainly limited to the transport of relatively low molecular weight lipophilic drugs. Furthermore, studies in

Table 1 Anatomical and physiological characteristics of human GI tract

Region	Length (m)	Absorbing surface area (m^2)	Absorption pathways	Transit (or residence) time of solids (h)	pH		Enzymes and others	Microorganism (counts/g content)
					Fasted	Fed		
Stomach	0.2	0.1	P, C, A (?)	1–3	1.5–3	2–5	Pepsin, lipases, rennin, HCl, Cathepsin	10^2
Small intestine	7	12.0		3–5				
Duodenum	0.3	0.1	P, C, A, F, I, E		5.5	5.0	Bile acids, trypsin, α-chymotrypsin and other peptidases, amylase, maltase, proteases, lipases, nucleases	10^2
Jejunum	3.0	60	P, C, A, F, I, E		6.1	No change	Erepsin, amylase, maltase, lactase, sucrase, peptidases, lipases	10^5
Ileum	4.0	60	P, C, A, F, I, E		7–8	No change	Enteropeptidase (enterokinase) and other peptidases, lipases, nucleases, nucleotidases	10^7
Large intestine	1.5	0.3		4–16		No change		10^{11}
Cecum	0.06–0.07	0.05	P, C, A, E		5.7			
Colon	1.35	0.25	P, C, E		8.0		Reductases, esterases, glycosidases, amidases, sulfatase	10^{11}
Rectum	0.12				7.0			

P = Passive transport; C = Convective transport; A = Active transport; F = Facilitated transport; I = Ion pair transport; E = Endocytosis.
(From Ref. 1.)

humans have demonstrated that absorption by the transcellular route decreases significantly in the colon (small intestine > ascending colon > transverse colon), which has implications for delayed or sustained release formulations, whereas no such gradient exists for the paracellular route (5).

Carrier-mediated transport involves interaction of the drug with a specific transporter or carrier, in which drug is transferred across the cell membrane or entire cell and then released from the basal surface of the enterocyte into the circulation (6). The process is saturable and utilized by small hydrophilic molecules (7). Drugs that are shown to be transported by this mechanism include β-Lactam antibiotics, cephalosporins, and ACE inhibitors (7).

Receptor-mediated transport involves internalization of an external substance, which may be a ligand for which there is a surface bound receptor, or a receptor which binds to a surface located ligand (8). During this process, a small region of the cell invaginates and pinches off, forming a vesicle. This process, in general, is known as endocytosis and comprises phagocytosis, pinocytosis, receptor-mediated endocytosis (clathrin-mediated), and potocytosis (nonclathrin mediated) (9).

After a drug is absorbed in the GI tract, it can gain access to the systemic circulation via two separate and functionally distinct absorption pathways—portal blood and the intestinal lymphatics. The relative proportion of drug absorbed via these two pathways is largely dictated by physicochemical and metabolic features of the drug, and the characteristics of the formulation (10).

The portal blood represents the major pathway for the majority of orally administered drugs as it has higher capacity to transport both water soluble and poorly water soluble compounds (10). During this process, hydrophilic molecules are carried to the liver via the hepatic portal vein, and then by the hepatic artery gain across to the systemic circulation for subsequent delivery to their sites of action. On the other hand, highly lipophilic drugs (log P > 5) that cross the same epithelial barrier are transported to the intestinal lymphatics, which directly delivers them to the vena cava, thereby bypassing the hepatic first-pass metabolism (10).

Gastrointestinal Motility

The process of GI motility occurs both during fasted and fed states; however, the pattern differs markedly in the two states. In the fasted (interdigestive) state, the pattern is characterized by a series of motor activities known as interdigestive myoelectric cycle or migrating motor complex (MMC), which usually occurs every 80–120 min. Each cycle consists of four consecutive phases (11, 12). Phase I (basal state) is a quiescent period of about 45–60 min without any contractions, except for rare occasions. Phase II (preburst state) is a period of similar duration (30–45 min) that consists of intermittent peristaltic contractions that gradually increase in intensity and frequency. Phase III (burst state) is a short period that consists of large, intense peristaltic contractions, lasting about 5–15 min. This phase serves to sweep the undigested materials out of the stomach and for this reason, phase III contractions are known as "housekeeper" waves.

As phase III of one cycle reaches the end of the distal ileum (ileocecal junction), phase I of the next cycle begins in the stomach (proximal) or esophagus (lower esophageal sphincter). However, sometimes MMC may originate in the duodenum or jejunum and some MMC may not have action potentials strong enough to traverse through the entire small intestine (12). Phase IV is a brief transitional phase (0–5 min) that occurs between phase III and phase I of two consecutive cycles.

In the fed state, the onset of MMC is delayed. In other words, feeding results into delayed gastric emptying. The duration of this delay is mainly dependent on the size (light or heavy) and composition (fatty or fibrous) of the meals. Consequently, the fate of pharmaceutical dosage forms is mainly subject to the pattern of GI motility in fasted (or fed) state at the time of dosage administration.

PROBLEMS AND BARRIERS TO ORAL DRUG DELIVERY

The biggest problem in oral drug delivery is low and erratic bioavailability, which mainly results from one or more factors such as poor aqueous solubility, slow dissolution rate, low intestinal permeability, instability in GI milieu, high first-pass metabolism through liver and/or intestine variable GI transit, and P-gp mediated efflux. This, in turn, may lead to unreproducible clinical response or a therapeutic failure in some cases due to subtherapeutic plasma drug levels. Indeed, the incomplete and variable oral bioavailability will have its most serious impact for drugs with a narrow "therapeutic window" (13) (e.g., theophylline, carbamazepine, quinidine, etc.) From an economic point of view, low oral bioavailability results in the wasting of a large portion of an oral dose, and adds to the cost of drug therapy, especially when the drug is an expensive one (14). It is, therefore, extremely important that these issues be considered and a suitable technique (or an animal model) be used while estimating the contributions from each factor responsible for low and/or variable bioavailability.

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