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Nanoparticles for oral delivery: Design, evaluation and state-of-the-art

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ABSTRACT

The oral route is a preferred method of drug administration, though achieving effective drug delivery and minimizing off-target side effects is often challenging. Formulation into nanoparticles can improve drug stability in the harsh gastrointestinal (GI) tract environment, providing opportunities for targeting specific sites in the GI tract, increasing drug solubility and bioavailability, and providing sustained release in the GI tract. However, the unique and diverse physiology throughout the GI tract, including wide variation in pH, mucus that varies in thickness and structure, numerous cell types, and various physiological functions are both a barrier to effective delivery and an opportunity for nanoparticle design. Here, nanoparticle design aspects to improve delivery to particular sites in the GI tract are discussed. We then review new methods for evaluating oral nanoparticle formulations, including a short commentary on data interpretation and translation. Finally, the state-of-the-art in preclinical targeted nanoparticle design is reviewed.

1. Introduction

Oral ingestion remains the preferred mode of delivery for most drugs owing largely to simplicity. The oral route is associated with the greatest degree of patient compliance (especially for chronic conditions) as it ensures convenience, enables self-administration, and offers great flexibility in dosage regimen. Oral products do not require sterile conditions for their manufacture, which reduces production costs. According to the drug delivery market analysis, oral drug products accounted for 38% of the North American drug delivery market in 2012 [1]. The oral drug delivery market was valued at $64.3 billion in 2013 and is expected to cross $100 billion by 2018 [2]. Thus, oral drug delivery will continue to dominate the pharmaceutical market and drug delivery research.

The oral route is also of interest for physiological reasons. The gastrointestinal (GI) tract offers extensive surface area (300–400 m^2) for drug absorption by absorptive epithelial cells (enterocytes) [3–6]. The GI tract contains many other types of cells that may participate in drug absorption, including mucin-secreting goblet cells, endocrine cells, Paneth cells and specialized M cells associated with Peyer's patches that are responsible for antigen transportation through dendritic cells [3–6]. However, many hydrophobic and hydrophilic drugs (taxanes, aminoglycosides, polyene antibiotics *etc.*) have poor bioavailability when administered *via* the oral route due to their inadequate physicochemical (solubility, stability) and/or biopharmaceutical (permeability, metabolic stability) properties [7–9]. Furthermore, a majority of the new chemical entities generated through drug discovery screening exhibit poor aqueous solubility and/or poor permeability. It has been reported that nearly 70% of new chemical entities are dropped during pre-clinical development due to poor oral bioavailability [10]. Oral delivery is even more challenging for biologics (*e.g.* peptides, proteins and nucleic acids) due to their hydrophilicity (leading to low permeability), high molecular weight and poor chemical/enzymatic stability in the GI tract. Fig. 1 summarizes the various challenges/barriers to effective oral drug delivery. The reader is also referred to several excellent reviews discussing the various barriers to developing drugs for effective oral delivery [3–6,11–13].

Numerous studies have shown that nanoparticles can improve the oral bioavailability of hydrophobic, hydrophilic and biologic drugs *via* various mechanisms [3–6,14–16]. In fact, several oral nanosuspension-based products that improve drug dissolution and absorption are on the market [10]. Nanoparticle formulations with more sophisticated design aspects are in preclinical development, including those designed to target a particular region in the GI tract, only diseased regions of the GI tract, or specific cells within the GI tract. Targeting approaches aim to enable better drug absorption and/or localized treatment of various disease conditions, such as gastric ulcers, *Helicobacter pylori* (*H. pylori*) infections and ulcerative colitis. An important aspect of preclinical

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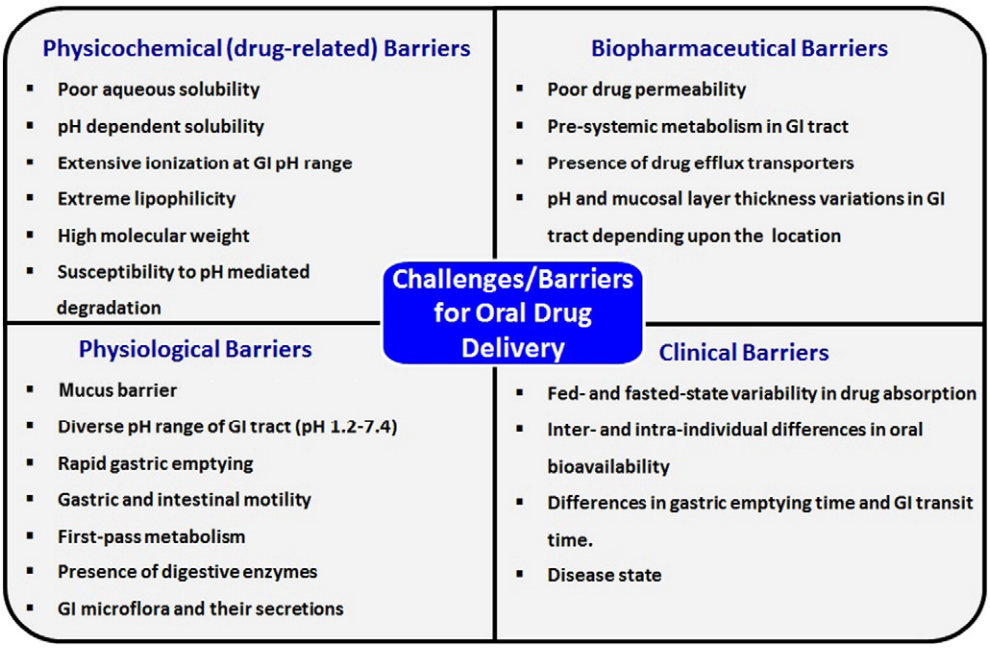

Fig. 1. Summary of barriers that affect oral drug delivery.

development of oral nanoparticle systems is the choice of experimental models. In this review, we first describe nanoparticle design considerations for targeting particular regions in the GI tract. We then discuss recent advances in *in vitro* and *ex vivo* experimental techniques for the evaluation of oral nanoparticle formulations, as well as a perspective on correlation of preclinical results with clinical translation. Finally, we highlight recent developments in the design and preclinical evaluation of targeted oral nanoparticle formulations.

2. Design considerations for targeting nanoparticles to a specific region of the GI tract

One benefit of nanoparticle formulations is the potential for providing targeted and/or localized drug delivery. Although the term "targeted" brings to mind the vision of nanoparticles that actively seek out their delivery target and selectively accumulate there, "targeting" in the GI tract is generally a more passive process. Here, we use the term "target" to refer to various strategies used for increasing residence time, modulating the relative amount of degradation/drug release that occurs, and/or facilitating interaction of nanoparticle formulations with tissues and cells in a particular section of the GI tract. In the context of the rational design of targeted oral nanoparticle formulations, we discuss diseases and delivery goals that would benefit from targeted delivery, as well as the physiological barriers and targeting opportunities (specific cell types or receptors) associated with various regions of the GI tract. Here, we broadly categorize approaches for stomach targeting, small intestine targeting, intestinal lymphatic targeting, and colon targeting. In Section 4, we further describe recent innovations in nanoparticle platforms designed to target specific regions of the GI tract.

2.1. Design considerations for stomach targeting

Targeting of therapeutic agents to the stomach has received attention for the effective treatment and management of *Helicobacter pylori* (*H. pylori*) infections. *H. pylori* infections affect around 50% of the global population [17–19]. Around 20% of the *H. pylori* infected population develop gastric disorders, such as chronic gastritis and/or gastric ulcers, and around 1–2% of *H. pylori* infected individuals present with gastric cancer [17–19]. Additionally, stomach targeting (and/or gastric retention) can also be useful for: (i) drugs that are primarily absorbed in the stomach (*e.g.* metronidazole), (ii) drugs that are poorly soluble in the intestinal milieu due to pH dependent solubility (*e.g.* verapamil), (iii) drugs with a narrow absorption window in the stomach or in the upper small intestine (*e.g.* furosemide), and (iv) drugs that degrade in the intestinal milieu (*e.g.* captopril) [20]. Gastric retention of the therapeutic agent is of utmost importance, yet is difficult to achieve. For effective stomach targeting, a nanoparticle delivery system must overcome various physiological hurdles, including gastric motility, gastric pH and gastric mucus.

The GI tract is in a state of continuous motility in the fasted and fed states. GI motility is categorized into inter-digestive and digestive motility. During the fasted state, the inter-digestive motility pattern is activated to empty the stomach of the residual contents of the upper GI tract [19–23]. In the inter-digestive mode, motility comprises of four phases (total duration of 4 phases: 90–120 min), and each phase involves cycles of (peristaltic) activity and quiescence. Phase III of the inter-digestive mode involves intense contractions to empty the undigested stomach contents through maximal pyloric opening. Digestive mode is initiated within 5–10 min after the ingestion of food and lasts until the food in the stomach is completely processed [19–23]. Gastric retention of nanoparticles will depend upon the motility phase that is active at the time of ingestion. For effective stomach targeting, nanoparticles should be able to withstand the peristaltic activity of the stomach. Gastric retention of the nanoparticles can also depend upon the fed or fasted state of the individual and also on the type of the ingested food (Fig. 2). Additionally, the pH of stomach is highly acidic, varying between 1 and 3 depending upon the fasted or fed state of the individual [19–23]. Many drugs used for peptic ulcer and antibiotics like clarithromycin that are used for *H. pylori* treatment are susceptible to degradation at an acidic pH and are rendered ineffective in the stomach [24,25]. Similarly, it is important to construct nanoparticles from materials that can provide protection of acid labile therapeutic agents.

Gastric mucus poses a significant barrier to effective stomach targeting of nanoparticles. GI mucus protects the epithelium from exposure to foreign particulates and pathogens, including nanoparticles [3]. Effective gastric mucus penetration may be of particular importance for eradication of *H. pylori* infection, as the bacteria is situated deep inside the gastric mucosa and attaches itself to the gastric epithelial cells with the help of adhesin-like proteins [17–18]. The total thickness of mucus (loosely adherent plus firmly adherent layers) in the human GI