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Current Opinion in Pharmacology

Intestinal patch systems for oral drug delivery

Amrita Banerjee[1] and Samir Mitragotri[1,2]

Intestinal patches provide a unique platform for oral delivery of drugs which possess poor oral bioavailability, necessitating their administration by injections. Intestinal patch based devices prevent drug degradation in the gastrointestinal tract, facilitate their intestinal absorption through forming a localized drug depot at the delivery site and provide unidirectional, controlled drug release while preventing luminal drug loss. Consequently, intestinal patch-based devices are being developed for oral delivery of several drugs such as insulin, exenatide, calcitonin, interferon-α, erythropoietin and human granulocyte colony-stimulating factor for the treatment of diabetes, osteoporosis, hepatitis or for chemotherapy. This technology shows promise as a needle-free alternative to injectable drugs that would improve the quality of lives of millions of people requiring chronic administration of injectable drugs.

Addresses
[1] Department of Chemical Engineering, University of California, Santa Barbara, CA 93106, USA
[2] School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA

Corresponding author: Mitragotri, Samir (mitragotri@seas.harvard.edu)

Current Opinion in Pharmacology 2017, **36**:58–65

This review comes from a themed issue on **New technologies**

Edited by **Barry Hirst** and **David Brayden**

http://dx.doi.org/10.1016/j.coph.2017.08.005

Oral drug delivery — potential and challenges

Oral drug delivery is one of the preferred routes of drug administration due to its non-invasive nature and ease of use. It eliminates pain, anxiety and expertise required for self-administration of injectable formulations, and is therefore especially useful for chronic diseases that require frequent drug dosing. According to a report by the World Health Organization, the adherence to medication regimen for chronic diseases such as hypertension and diabetes in developed countries is only 50% or less [1–4]. This level of non-compliance leads to increased complications, co-morbidities, deaths and approximately $100 billion in incurred costs [2]. Amongst patients with type 2 diabetes mellitus, reluctance to start insulin therapy is commonly observed and needle phobia is cited as the second most common reason (13%) for failure to start insulin treatment [1]. Further, adherence to injectable regimen was found to be notably lower than oral medications amongst diabetes patients [1].

Aside from higher patient compliance, oral formulations can be designed in multitude different ways and cost of production is comparatively lower than injectable formulations [5]. Therefore, not surprisingly, development of candidate drugs into oral products is preferred. Globally, the oral delivery market in 2013 was $64.3 billion and is predicted to be about $100.8 billion by 2018 [6]. However, currently many newly discovered drugs possess poor aqueous solubility and membrane permeability [7,8]. Use of high throughput screening and other pharmaceutical profiling has resulted in a shift in the discovery of lead compounds such that 50–60% of pipeline drugs are biopharmaceutical classification system category II drugs with poor aqueous solubility and high membrane permeability [9]. Oral drug delivery is contingent upon, drug release from the formulation in the gastrointestinal tract (GIT), solubilization in the GI fluids, transport across the gastric/intestinal membrane and absorption into systemic circulation in its active form after hepatic metabolism [9]. Different strategies can be utilized to surmount challenges related to low solubility and/or low permeability of small molecule drugs such as using surfactants, weak acids-bases, prodrugs, bile salts, chelators, fatty acids, modulating pH and solvent system, micronization and complexation [10]. However, many of these strategies cannot be applied to large molecule drugs such as peptides, proteins and nucleic acids, which demonstrate poor permeability across intestinal membrane due to their large size. In addition, these molecules are susceptible to rapid acidic/proteolytic degradation in the GIT and can lose their active secondary/tertiary/quaternary conformation with change in formulation conditions such as pH, temperature, solvent, chemical modifications and agitation during processing [11,12]. Consequently, most therapeutic macromolecules have insignificant oral bioavailability (proportion of drug that reaches systemic circulation in its intact/unchanged form upon oral administration) and therefore require parenteral administration (through injections) to achieve a clinical response [13]. However, short half-lives and rapid renal elimination of peptide/protein drugs entails frequent injections, which becomes especially cumbersome and significantly hampers the quality of life of patients suffering from chronic diseases such as diabetes, osteoporosis and cancer. Oral delivery of short half-life protein/peptide drugs such as glucagon like peptide-1 (GLP-1) and interferon-γ

(half-lives of ~2 and 1.1 minutes respectively) [14,15] is especially challenging because in addition to GI degradation and low intestinal permeability, these drugs need to travel through hepatic portal system to undergo first-pass metabolism before reaching systemic circulation to demonstrate bioactivity, which is a longer process compared to parenteral administration and may further reduce bioavailability. On the other hand, protein drugs with long half-life such as semaglutide, a GLP-1 receptor agonist with a half-life of 160 hours, being developed by Novo Nordisk for the treatment of type 2 diabetes, have recently shown great promise for oral delivery [14]. The different approaches that can be undertaken to improve oral bioavailability of large molecule drugs have been briefly discussed in the following sections.

Oral drug delivery systems for protein drugs

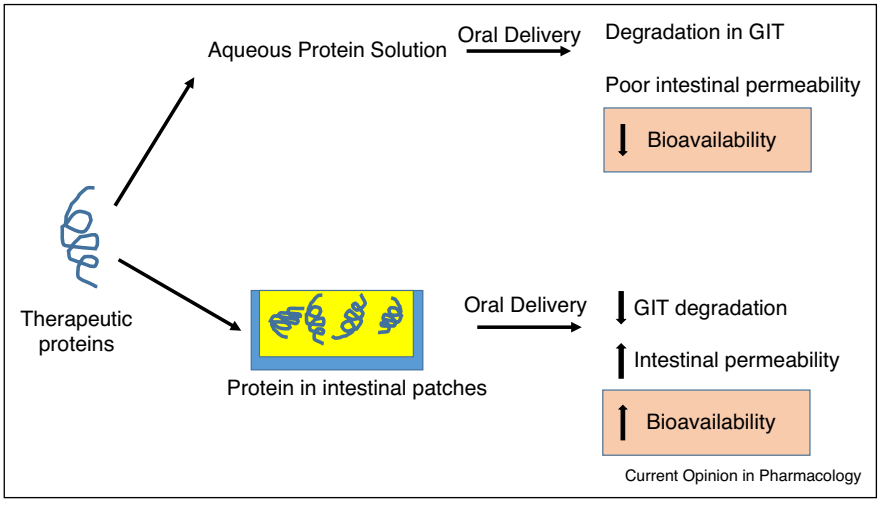
An effective oral delivery system for macromolecular drugs should first, protect drugs from acidic and enzymatic degradation in GIT, second, improve intestinal permeation, third, provide site-specific controlled delivery, fourth, retain active drug conformation in formulation and finally, is non-toxic to intestinal tissue [16]. Selected strategies to prevent drug degradation in the gut include chemical modification of the protein/peptide, coating with acid resistant polymers, use of specific and non-specific enzyme inhibitors, and encapsulation in liposomes, microspheres, nanoparticles and emulsions [17]. An example of chemical modification is Atazanavir®, an oral HIV protease inhibitor where the alpha carbon of its amino acid sequence is substituted with a nitrogen to impart stability against proteolytic degradation [18,19]. Acid resistant polymers such as polymethacrylates, D-amino acids, polyethylene glycol (PEG) can be used to prevent acidic degradation in gut [20]. Specific enzyme inhibitors include trypsin, chymotrypsin, pepsin or aminopeptidase inhibitors such as soybean trypsin inhibitor, aprotinin, FT-448, bacitracin, sodium glycocholate, camostat mesilate and N-acetylcysteine [21–23]. Permeability across the intestinal membrane can be improved by using mucoadhesive polymers, permeation enhancers, cell penetrating peptides, lectins and fatty acids [20]. Although all these strategies show promise in improving oral bioavailability of macromolecular drugs, they may cause adverse effects and do not adequately address all problems associated with oral delivery [24]. For example, chronic use of proteolytic inhibitors can modulate absorption of other proteins as well and cause severe adverse effects [16]. Conversely, particle or solution-based formulations do not provide tight control over site of drug release, causing significant drug loss in the intestinal lumen.

Intestinal patch based devices, on the other hand, have several appealing features and can greatly improve oral bioavailability of drugs (Figure 1).

Intestinal patch-based devices

Intestinal patches are inspired by transdermal patches, which in spite of similar conceptual design, operate in very different physiological environments [25]. Transdermal patches are developed for drug delivery through the skin, are larger in size (inches) and include an adhesive layer to stick to skin, a drug reservoir and a water impermeable backing layer. On the other hand, intestinal patches are mostly millimeter sized and have a pH sensitive layer, mucoadhesive drug reservoir layer and a backing layer. Drug release from transdermal patches can occur over long periods of time for up to a week while that from intestinal patches is expected to occur over a time frame of hours.

Figure 1



Intestinal patches for oral delivery of protein/peptide therapeutics.