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Recent advances in oral delivery of macromolecular drugs and benefits of polymer conjugation

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ABSTRACT

Oral administration of drugs is a two-edged sword – on one hand it is a non-invasive and easy-to-handle administration of drugs, on the other hand macromolecular pharmaceutical compounds cannot easily cross the epithelial barrier to reach systemic circulation or they could be inactivated in the gastrointestinal tract. Due the latter's nature with pH variations and proteolytic enzymes which digest and degrade external compounds, in particular peptides and proteins, oral delivery of macromolecular substances is an ongoing challenge in the field of pharmaceutical research. Several avenues of overcoming these drawbacks have been evaluated in the past, among them the promising approach of conjugation to natural and synthetic polymers. Polymers provide protection under harsh gastrointestinal conditions, may further enhance macromolecular drug absorption and pharmacological activity, and thus augment therapeutic efficiency. This short review highlights state-of-the-art developments in the field of oral macromolecule delivery and the benefit of polymer conjugation. We focus on a main review period from 2012 to 2017, and critically discuss latest developments for macromolecule engineering.

1. Introduction

The modification of therapeutic entities with synthetic polymers is gaining increasing interest in the field of pharmaceutical sciences. New classes of macromolecular drugs such as peptides and proteins displaying high therapeutic potential but also often moderate stability and short biological half-lives are intensively investigated and can strongly benefit from polymer modification [1]. Indeed, the clinical value of polymer conjugation has been proven since the early 1990s when the first poly(ethylene glycol) (PEG)–protein conjugates were approved for systemic therapies [2]. Since then, nine PEG formulations are currently marketed and many more are under clinical evaluation [3••]. Nevertheless, most studies analysing polymer modification of macromolecules focus on the systemic application route [4] while considerably little work has been conducted to improve the stability of therapeutic macromolecules after oral administration. Here we give a concise overview of opportunities and challenges associated with oral administration of larger drug molecules. We highlight very recent approaches for their chemical modification with natural and synthetic polymers and outline future prospects for the field.

Drug administration *via* the oral route is simple, non-invasive, painless, and thus often associated with improved compliance, *i.e.*, degree to which a patient correctly follows drug scheme, and therapeutic outcome. Moreover, oral pharmaceutical preparations do not require sterility during production and can be obtained with relatively simple and cost-effective equipment. Nevertheless, when it comes to oral delivery of macromolecule drugs such as peptides, proteins or enzymes this route of application becomes challenging from a pharmaceutical point of view. When administering macromolecules orally, one may distinguish between those that aim at having an effect directly in the GI lumen and those that are supposed to be absorbed in the gastrointestinal (GI) system, most likely in the small intestine, to reach systemic circulation. For the latter ones it is not be sufficient to simply survive the GI transit but they additionally need to cross the intestinal barrier and reach the blood stream in an intact conformation which displays another difficult challenge (Fig. 1).

The human GI system is equipped with pH variations, digestive enzymes and other components which assemble an environment designed to digest and inactivate macromolecular compounds [5]. The GI system is generally sectioned into stomach, small and large intestine (Fig. 1). Digestion of peptides/proteins is initiated in the stomach where pepsin is an efficient enzyme to cleave hydrophobic amide bonds. This degradation is particularly effective in combination with the low stomach pH and constitutes the major obstacle for successful oral application of intact macromolecules. Once entering the small and later the large intestine, drugs are exposed to various pancreatic peptidases, lipases, *etc.* that – in combination with bile salts, microbiota and a slightly alkaline pH – complete “nature's toolset” for denaturation of

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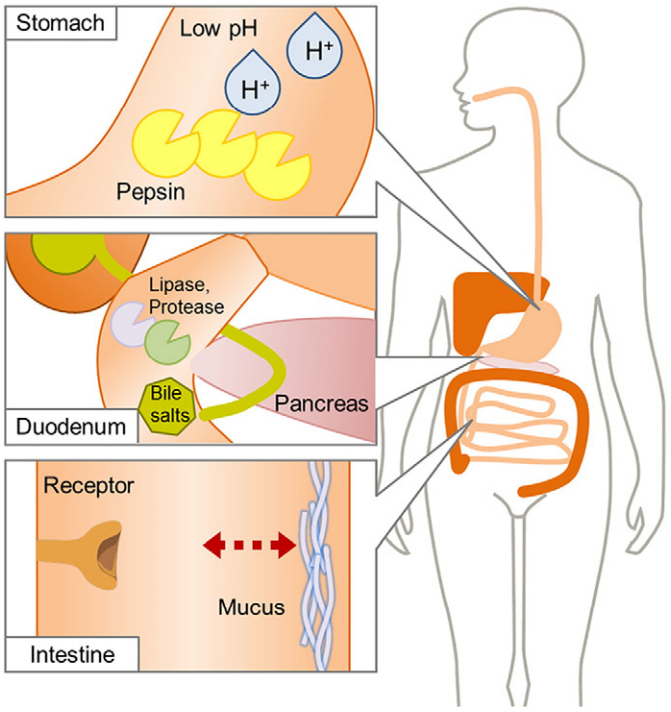

Fig. 1. Schematic of the human gastrointestinal system and its challenges for oral application of macromolecular drugs. The stomach exhibits an environment with low pH and proteolytic enzymes. Above all, pepsin can efficiently degrade orally administered peptides, proteins, and other susceptible entities leading to their loss of pharmaceutical activity. In the duodenum, other lipases and proteases, and bile salts are secreted by pancreas and liver, respectively. Those biomolecules may further interfere with macromolecular drug stability and absorption. The intestine is the GI part in which most drugs are absorbed. They can interact with local receptors to be taken up actively, or they can be absorbed passively. In both cases, their interaction with the natural mucus layer is crucial as it can act as a barrier and may strongly obstruct macromolecular drug's passage to the systemic circulation.

(therapeutic) macromolecules. Besides this potential inactivation, the oral bioavailability is another key factor for their successful GI delivery. Due to their large size and – in most cases – hydrophilic nature, macromolecular drug diffusion across GI-barriers is hindered and may result in low drug concentration in the systemic circulation [6]. Finally, the epithelial mucus layer provides a viscous and often unsurmountable diffusion barrier for macromolecules [7]. Taken together there are many obstacles to overcome during oral macromolecular delivery and – although favoured by patients and health carers – indicating that this route of application is not as simple as it appears.

2. Polymer conjugation as promising avenue

The challenges in oral macromolecular delivery have to date limited their broad clinical application but several promising avenues are currently investigated as discussed in the following sections. Given the broad number of references in this scientific area, we have specifically focussed on *very recent* approaches – preferentially since 2012 – and seminal papers in order to outline impactful examples that may advance the field in the future.

There are several strategies for improving the oral delivery of macromolecules, ranging from gastric-resistant and gastric-retentive delivery systems [8], to nanoparticle-based approaches [9], cloning of novel biomacromolecules [10], absorption enhancers [11], and covalent surface functionalisation with natural and synthetic polymers (*polymer conjugation*). Bioengineering of macromolecules with polymers features several important advantages as shown in Box 1.

The general underlying principle of delivery improvement by polymer conjugation is increased steric hindrance and shielding of the

Box 1
Oral polymer conjugates of macromolecules.

Key advantages of polymer modification for oral administration
• Steric hindrance and shielding from digestive enzymes and pH variations
• Gastrointestinal transit usually independent from food consumption
• Improved biocompatibility and bioactivity profile of macromolecular drugs
• Provide target-specific interaction in the GI tract and after systemic absorption
• Broad toolset of polymer architectures and chemical coupling techniques available
• Production and upscaling straightforward compared to othercomplex formulations

macromolecule. This creates a “protective zone” around the drug entity and prevents degradation by gastrointestinal enzymes and protection from pH variations [12•]. Polymers offer a broad toolset of potential modifications as they come in many different architectures, length and structures [13]; all of them may impact on the properties of the macromolecule conjugate. Polymer engineering often enhances the lipophilicity of drugs and thus their degree of systemic absorption which in turn may reduce the rate of GI degradation. Conjugation to polymers can also change the pharmacological activity or biocompatibility profile of drugs and – *via* selective interaction with the target cells or tissue – increase their therapeutic efficiency [14•]. In contrast to modification of the chemical structure, the drug can be used in its native conformation and composition which will reduce the impact on its pharmacodynamic profile and activity. Polymer conjugates have an advantageous drug-to-excipient ratio and thus only require relatively small amounts of other additives that potentially induce undesired side effects. Their pharmaceutical production and upscaling process is often less complex than nanoparticle-based systems as they often only require single and simple preparation steps [15•]. Unlike enteric coated tablets or capsules, polymer conjugates' transit through the GI-tract may – due to their small size – be more independent from food consumption, *i.e.*, their absorption is less influenced by presence of nutrients, degree of stomach content, or gastrointestinal emptying leading to reproducible and less variable absorption [16]. These key advantages make polymer conjugation a promising avenue for oral macromolecule delivery as we will further discuss in the next sections. For a detailed evaluation of other oral delivery approaches the reader is referred to recent extensive reviews [3••,6,17]. The selected approaches in this perspective are divided into “smaller” macromolecules (*e.g.*, natural product antibiotics), “larger” macromolecules (*e.g.*, polypeptides and proteins) and enzymes as special type of large proteins. In each section, benefits of engineering with various natural and synthetic polymers are discussed (Fig. 2) and a broad range of pathologies are discussed, including infections, autoimmune and metabolic disorders. Up-and-coming examples of these avenues are given in Table 1.

2.1. Small macromolecules and natural products

Smaller macromolecules, such as natural products are the first group of discussed drugs for which polymer modification may improve their biodistribution, stability or therapeutic efficiency. Antibiotic drugs are an important group of smaller macromolecules that often show suboptimal delivery results due to instability under GI conditions or undesired (systemic) toxicity [28]. Moreover, they suffer from rising susceptibility towards antibiotic resistance. Another major issue is their undesired activity against the benign microflora in the GI tract which is inducing side effects such as diarrhoea and incompatibilities with other