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Review Article

Improving oral drug bioavailability with polycations?

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ABSTRACT

The administration of drugs *via* the oral route is challenging due to the (bio)chemical aggressivity of the digestive system and to the presence of barriers that hinder cell uptake and access to the bloodstream. Indeed, the gastrointestinal tract is characterized by large variations of pH, the presence of enzymes and surfactants, and by absorption barriers such as mucus and the epithelium. Thus, many compounds such as proteins and nucleic acids do not reach the systemic circulation due to their premature degradation and/or large size. Among the different strategies that have been investigated to address these challenges, polycations have been explored to improve the oral absorption of many types of drugs. Because of their multiple positive charges and repetitive structure, polycations can protect sensitive drugs against rapid degradation and interact with the gastrointestinal mucosa. Moreover, cationic polymers promote drug transfer across intestinal barriers through various mechanisms, including the opening of the tight junctions, and change in uptake pathway. This contribution provides an overview of the most common polycations currently investigated as absorption enhancers for the oral route, and discusses the manner in which they are employed (co-administration, micro- and nanoparticles, conjugation) to improve the oral drug delivery of different classes of therapeutics.

1. Introduction

Drug administration *via* the oral route is widely used, and is preferred due to its convenience and low associated costs. However, the oral delivery of compounds which are sensitive to degradation, poorly water soluble, or poorly membrane-permeable remains challenging. For example, biomacromolecular drugs such as proteins and polynucleotides can easily undergo denaturation or degradation in the gastrointestinal (GI) tract due to pH fluctuations, and the presence of surfactants (*e.g.*, bile salts) and enzymes [1,2]. Furthermore, their high molecular weight and polarity lead to inefficient permeation through mucus and the epithelium. Among the different strategies that have been investigated to address this challenge, formulating drugs with polycations has been shown to increase their solubility, protect labile compounds from pH changes and digestive enzymes, and serve as permeation enhancers. In addition, polycations are particularly interesting for oral drug delivery because of their mucoadhesive properties, which increase the retention time of drugs in the GI tract, and their ability to promote the absorption process by a variety of mechanisms [3,4]. Even though polycations can destabilize cell membranes and exhibit toxicity, compared to the parenteral route, the systemic exposure to polycations delivered orally is assumed to be low, and therefore better tolerance is expected [5,6]. This contribution will begin by providing an overview of the intrinsic mechanisms by which the most widely investigated polycations (*e.g.*, chitosan, poly(amido amine) (PAMAM), poly(L-lysine)) in pharmaceutical sciences can increase oral bioavailability or induce toxicity when co-administered alongside drugs. Thereafter, aspects of the formulation of drugs with polycations into nano/microparticles and bioconjugates are reviewed, including a presentation of the performance of such systems *in vivo*. This manuscript will not cover buccal delivery [7] as well as the use of polycations in the preparation of tablets [8–10], or polycations complexed with polyanions in layer-by-layer assembling systems [11,12].

2. Free polycations

Because of its simplicity, co-administration of polycations with drugs in solution (Fig. 1A) is the most convenient and widely investigated manner to affect the oral bioavailability of therapeutic agents. This section introduces several polycations that have been orally co-administered with drugs, and discusses their toxicity and the mechanism by which they increase bioavailability.

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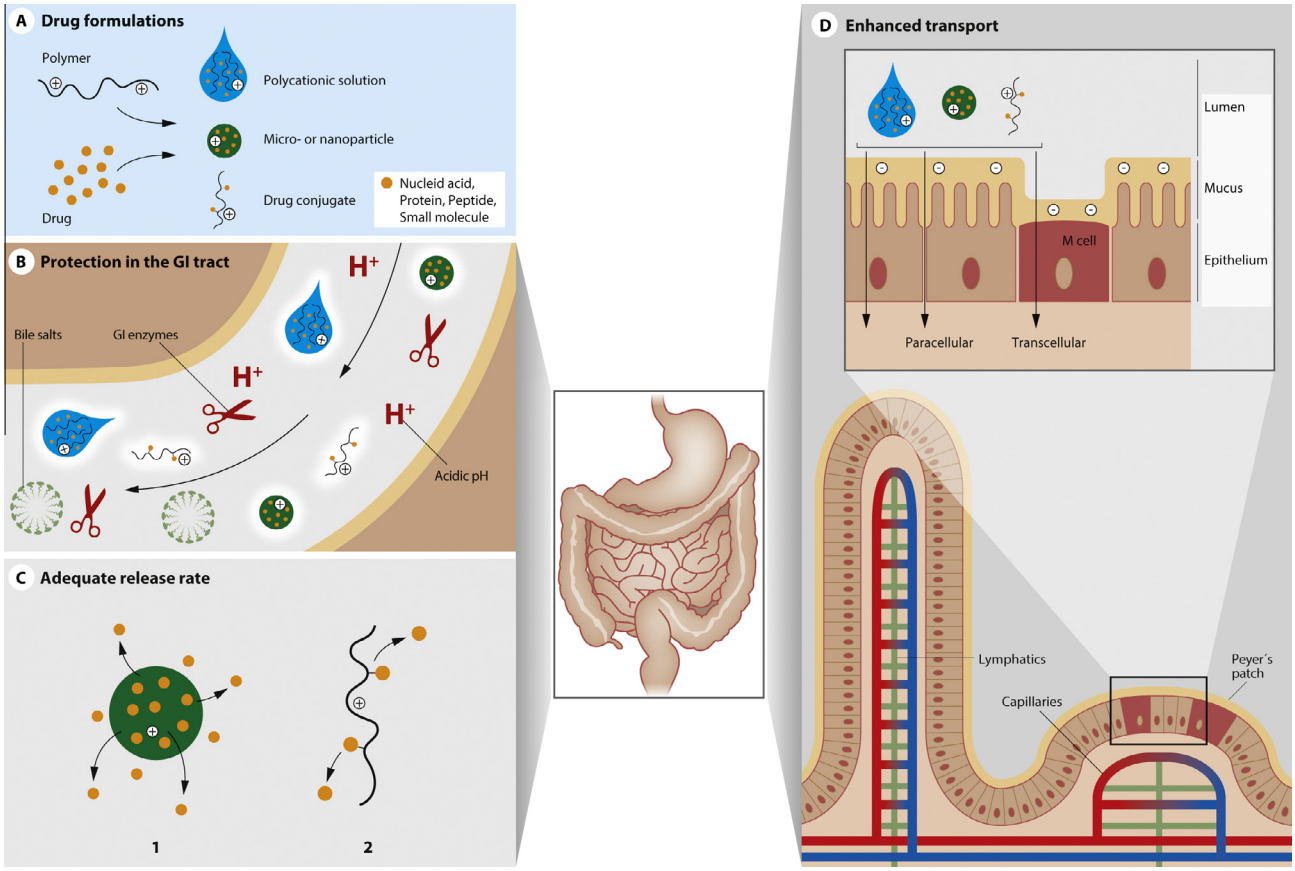

Fig. 1. Drug–polymer formulations and their advantages. A: Drug formulations prepared with polycations by either simple mixing to obtain a polycation-drug solution, encapsulating the drug in polycationic micro- or nanoparticles, or by synthesizing a covalent drug–conjugate. B: The different formulations should enhance drug stability in the GI tract and shield the drug from the acidic pH, GI enzymes, and bile salts. C: Adequate drug release is required at the targeted site. This is achieved by either releasing the drug from the polymeric particle or by cleavage of the covalent bonds attaching it to the polymer. D: Transport across the intestinal membrane can occur *via* the paracellular and/or transcellular pathway through epithelial or M cells.

2.1. Chitosan

Chitosan is an attractive polymer for biomedical applications due to its biocompatibility, biodegradability, natural origin, and low cost. It is a linear polysaccharide with a molecular weight up to ca. 2000 kDa, obtained by partial *N*-deacetylation of chitin (Fig. 2A) from crustacean shells or mushrooms [13]. Chitosan is composed of 2-amino-2-deoxy-D-glucopyranose and 2-acetamido-2-deoxy-D-glucopyranose units randomly linked together *via* β-(1,4) glycosidic bonds (Fig. 2B). Its charge density, which influences properties such as solubility, permeability, and toxicity, is dependent on the degree of deacetylation (DA) because only the 2-amino-2-deoxy-D-glucopyranose units are ionizable [14]. Chitosan's aqueous solubility is limited by its pK_a of ~5.5–6.5 to acidic solutions, where the polymer possesses a net positive charge. Although chitosan is generally considered as safe, toxicity has been reported to be strongly dependent on the DA. *In vitro*, highly deacetylated chitosan (DA 99%) exhibited toxicity toward monolayers of cultured intestinal epithelial cells (Caco-2), induced morphological changes in the form of a decrease in the number of microvilli, and an alteration in the organization of the terminal web [15]. Conversely, chitosan with a lower degree of DA (⩽65%) produced less morphological changes and generated signs of cytotoxicity only at high concentrations. *In vivo*, rats orally administered a chitosan oligosaccharide (1 kDa) at 2 g/kg/day did not show any significant behavioral changes or altered biochemical marker levels compared to control groups [16]. Because of its relative good safety profile, chitosan is the most widely investigated polycation co-administered alongside drugs in oral delivery systems [17,18]. Its ability to modulate the permeation through Caco-2 cell monolayers was found to depend on pH, molecular weight, and DA of chitosan. At pH 6.2, the transport of mannitol was significantly increased, whereas no effect was observed at pH 7.4 due to polymer insolubility [19,20]. Chitosan, with a DA of 65% and high molecular weight (170 kDa), had a large impact (eight-fold increase) on the mannitol passage through Caco-2 cell monolayers. Inversely, lower molecular weight chitosan with a low DA was not able to affect its transport [15]. However, Caco-2 cells lack the mucus layer which is an important barrier for drug absorption *in vivo*. This became evident as permeation of atenolol, a poorly absorbed hydrophilic drug, through Caco-2 cell monolayers increased significantly during chitosan exposure at concentrations five times lower than those used in the *in situ* rat perfusion model [21]. Indeed, when administered as a solution to rats by single pass intestinal perfusions, chitosan only slightly improved the bioavailability of atenolol. Therefore, the influence of mucus on absorption enhancement by chitosan was tested on a mucin-producing cell line (HT29-H). While the permeation of mannitol was enhanced, a smaller effect was observed than for Caco-2 cell monolayers. Using fluorescently-labeled chitosan, it was shown that the mucus prevented the interaction between chitosan and HT29-H cells. The role of the mucus was further revealed by reducing its thickness and showing that the labeled polymer could then achieve closer contact with the cells [21].

The mechanism by which chitosan enhances mucosal absorption is multi-faceted and not fully understood. Interaction with the cell membrane is an important factor that can facilitate the absorption of drugs in the GI tract. Indeed, chitosan's positive