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Review article

Polyelectrolyte complexes as prospective carriers for the oral delivery of protein therapeutics

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ABSTRACT

The oral administration of protein therapeutics is hindered by the multitude of barriers confronted by these molecules along the gastrointestinal tract (i.e., acidic environment, proteolytic degradation, mucosal barrier, etc.). Their unique properties (e.g., high molecular weight, hydrophilicity, charge, etc.) and labile structure are mainly responsible for their instability in the harsh conditions along the gastrointestinal tract (GIT) and dictate the employment of alternative routes for their administration (e.g., parenteral). The association of proteins with colloidal carriers represents an interesting approach to overcome the aforementioned issues. However, certain requirements, such as stability in the GIT, stimuli-responsiveness, protection of the encapsulated biomolecule from enzymatic degradation and permeability of the mucosa, have to be met in order to efficiently deliver the sensitive payload to the intended site of action, thus resulting in enhanced bioavailability. The formation of colloidal polyelectrolyte complexes (PECs) seems to be a promising strategy towards this direction, and the present review aims to provide an insight into PECs (e.g., preparation methods, characteristics) along with their advantages and drawbacks as drug delivery vehicles for the oral administration of protein-based therapeutics.

Contents

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1. Introduction

Therapeutic biomolecules (i.e., proteins, peptides, enzymes, nucleic acids, hormones, etc.) have only recently become readily available, owing to the advances in biotechnology, which enabled their large-scale manufacturing [1,2]. Their increasing availability has improved the treatment options in many areas of biomedicine and their use for the therapy of several diseases is now a well-established clinical practice. In addition, the exceptional therapeutic efficacy and high selectivity of macromolecules as compared to conventional drugs has radically advanced the pharmaceutical industry, especially since the commercial launch of the recombinant human insulin [3–6].

However, despite their potential advantages, the lability and structural complexity of biomolecules both restrict their delivery via other than parenteral routes and lead inevitably to the quest for novel approaches in order to treat or prevent various diseases [3,4]. For example, the development of oral formulations of therapeutic proteins faces several hurdles along the GIT, rendering such molecules less appealing as drug candidates. More specifically, despite the convenience and non-invasive nature of the oral route, orally administered macromolecular drugs undergo severe presystemic degradation, and several issues (e.g., poor solubility and stability in the gastric environment, low intestinal permeability, etc.) need to be simultaneously addressed in order to exert their therapeutic effects [1,4,7]. Consequently, the development of galenic formulations providing robust clinical results is severely impeded.

Since the properties of the nanoscale entities are completely different from those of the bulk materials, the evolution of nanomedicine has become a key component for the future research in medical intervention [8,9]. Formulation into nanoscale drug delivery vehicles has long been proposed as a means to facilitate the delivery of macromolecules to specific tissues or cells since the nanoscale dimensions offer high surface-to-volume ratio and allow interactions with biological systems at their structural size level [10,11]. Accordingly, the formation of colloidal PECs is an interesting approach in this direction [11].

Polyelectrolyte complexes are spontaneously formed upon mixing oppositely charged polyelectrolytes (PEs) under certain conditions and have the unique ability to combine physicochemical properties of at least two PEs, along with a facile preparation procedure and responsiveness to various stimuli. Additionally, PECs can be formed in water, eliminating this way the use of organic solvents and attracting the interest of the pharmaceutical industry for oral drug delivery purposes [12,13]. Since several macromolecules of high pharmaceutical importance are PEs, their association with PECs has been thoroughly investigated as a means to overcome the current limitations in their oral delivery. The present review article aims to provide an insight into the principles and mechanisms governing the interactions between PEs and summarizes the recent advances in the development of PECs as prospective carriers for the oral delivery of macromolecules.

2. The oral administration route

Various routes (i.e., nasal, oral, pulmonary, etc.) have been investigated and assessed for their potency as ideal administration pathways for macromolecular drugs, and among them, the oral route is the most extensively studied, [14] mainly due to its accessibility and non-invasive nature (i.e., high patient compliance) [15] as well as the potential benefits regarding safety and economical aspects [16]. The oral drug pathway utilizes the GIT for medication delivery and represents a systemic route of administration, underlining that systemic effects are expected to be elicited. It consists of the swallowing of the appropriate dosage form and the subsequent intestinal absorption of the therapeutic compound after it has successfully crossed the various chemical (i.e., pH, enzymes) and penetration related (i.e., mucus layer, absorption membrane) barriers [16,17]. Apart from the aforementioned barriers, the physiology of the GIT and the digestion process itself could lead to limited absorption of many therapeutic entities, and therefore, the influence of feeding and temporal patterns on gastrointestinal transit and absorption should be also taken into account in the development of formulation technologies for oral drug delivery application. Due to the above, the oral pathway continues to be extremely challenging and requires additional efforts to represent a viable administration route for the majority of therapeutic entities [18,19].

2.1. Barriers to the oral delivery of proteins/peptides

The labile structure and high molecular mass of biomolecules preclude their intestinal absorption, resulting inevitably to reduced oral bioavailabilities and diminished therapeutic efficacy compared to parenteral routes [3,4,6,11,20]. Other factors influencing the intestinal absorption of orally administered macromolecules include their short plasma half-lives, their hydrophilicity and susceptibility to proteolysis, their poor solubility and stability in gastrointestinal conditions, their interactions with food or gastric acid, as well as the variations in gastric emptying and intestinal transit times [5,16,21]. It becomes therefore obvious, why only a small fraction of the orally administered dose can reach the systemic circulation intact [6,20].

An overview of the barriers encountered by orally administered macromolecules is provided below, along with proposed strategies to overcome them and increase the therapeutic efficacy. Thorough understanding of the physiology of each barrier would lead to the identification of the exact mechanisms governing each of the aforementioned presystemic elimination steps, thus enabling the development and optimization of galenic formulations appropriate for oral drug delivery applications.

2.1.1. The chemical barrier

Significant pH variations can be observed alongside the GIT with respect to species, location, exact organ function and metabolic state [22]. In particular, the pH in the oral cavity ranges from 6.5 to 6.9 [23], while a harsh acidic environment is observed in the stomach, with pH ranging from 1 to 3 [2], serving various functions, such as protein denaturation, activation of pepsin, as well as inhibition of bacterial growth [23]. As approaching the duodenum, the pH is partially neutralized, ranging between 6.0 and 6.5 [24] to obtain a final value of 7–8 in the colon and rectum [2,22].

The majority of proteins exhibit a pH-dependent charge density and are mostly ampholytic, carrying both negatively and positively charged side chains [25,26]. Therefore, electrostatics mainly govern the attractive and repulsive interactions between their