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Review

Targeting of gastrointestinal tract for amended delivery of protein/peptide therapeutics: Strategies and industrial perspectives

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ABSTRACT

Delivery of proteins/peptides to the gastrointestinal (GI) tract via peroral/oral route involves tremendous challenges due to unfavorable environmental conditions like harsh pH, presence of proteolytic enzymes and absorption barriers. Detailed research is being conducted at the academic and industrial levels to diminish these troubles and various products are under clinical trials. Several approaches have been established to optimize oral delivery of proteins and peptides and can be broadly categorized into chemical and physical strategies. Chemical strategies include site specific mutagenesis, proteinylation, glycosylation, PEGylation and prodrug approaches, whereas physical strategies comprise formulation based approaches including application of absorption enhancers and metabolism modifiers along with delivering them via colloidal carrier systems such as nanoparticles, liposomes, microparticles, and micro- and nano-emulsions. This review stands to accomplish the diverse aspects of oral delivery of proteins/peptides and summarizes the key concepts involved in targeting the biodrugs to specific sites of the GI tract such as the intestine and colon. Furthermore some light has also been shed on the current industrial practices followed in developing oral formulations of such bioactives.

Contents

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1. Introduction

Despite several strides having been taken in the field of medical science, disorders such as hypertension, migraine, neurodegenerative disorders, cancer, diabetes, and infectious diseases have been left untamed. Conventional therapeutic moieties like anti-depressants (ineffective in 20–50% of patients) and beta-blockers (ineffective in 15–35% of patients) underperform regularly [1,2]. Such circumstances have forced researchers to accelerate the development of novel drug delivery systems augmenting therapeutic efficacy focusing on customized medical care by considering the genetic make-up of concerned individuals [3]. It is in these cases, that proteins and peptides have found special utility. Expansion in recombinant DNA technology, solid-phase peptide synthesis, hybridoma technologies and other facets of proteomics–genomics have contributed enormously to the development of promising biological therapeutics [4,5]. These products have added advantages *viz.* high specificity and activity, minimal drug–drug interactions and toxicity. An industrial boom in this sector came with the successful production of therapeutic proteins *viz.* interferons, human insulin, epidermal growth factor, anti-thrombotic agents, erythropoietin, anti-hemophilic factors, anti-hepatitis A and B vaccines, *etc.* Currently, an estimated 400 biologics are undergoing advanced clinical trials, and around 40 peptide–protein drugs are available in the market globally [6,7]. Most of the therapeutic peptide and protein molecules are administrated *via* parenteral route (IM, SC or IV). However chronic diseases such as diabetes, cancer, leishmaniasis *etc.* require frequent invasive administration leading to poor patient compliance. The best accessible alternative then appears to be the oral route perhaps, though the desired bioavailability for proteins–peptides is highly questionable.

The schemata of delivering biotechnologics *via* the oral route comprise the following (i) formulation into a suitable oral delivery system, (ii) protection from the unfavorable environment of GI tract, (iii) enhancing absorption thereby increasing bioavailability, (iv) sustaining therapeutic effect, (v) site specific targeting, and (vi) enhancing stability. Considerable success has already been achieved *via* these strategies (oral desmopressin and cyclosporin A have been developed), however room for massive improvement still exists and it is with this intention that the current review has been compiled. We ponder briefly upon the relevant anatomic sites, absorptive mechanisms and obstructive pathways that regulate systemic trafficking of proteins/peptides. This is followed by a myriad of chemical or formulation assisted site specific and receptor based targeting strategies. The current perspective ends with a short writeup on delivery technologies which have been industrially realized.

2. GI tract: relevant anatomical features

Majorly there are four types of cellular structures which line up end to end forming the cylindrical shaped absorptive framework of the intestine. More than 99% of the intestinal epithelia is covered by enterocytes, a specialized array of columnar epithelial cells, whose apical surface is morphed into multiple projections known as microvilli. Their principal role is absorption of digested nutrients utilizing passive and active processes. Along with maximizing the surface area for absorption; microvilli also subserve digestion by secreting membrane associated hydrolases. The surface of the enterocytes is covered with glycocalyx and mucin (a viscous glycoproteinaceous substance) which is secreted by goblet cells. A third small yet distinct population known as M-cells (making up less than 1% of GI tract coverage) are present in specific regions known as Peyer's patches. The M cells are dedicated cells which have proficiency in absorbing colloidal sized particles (Fig. 1).

Physiologically, they work as immunosurveillants responsible for absorbing various kinds of antigens, macromolecules, microorganisms, and certain types of particles, which are then conveyed to the underlying lymphoid system to induce immune responses. M-cells or microfold cells lack the usual microvilli of enterocytes and exhibit microfolds

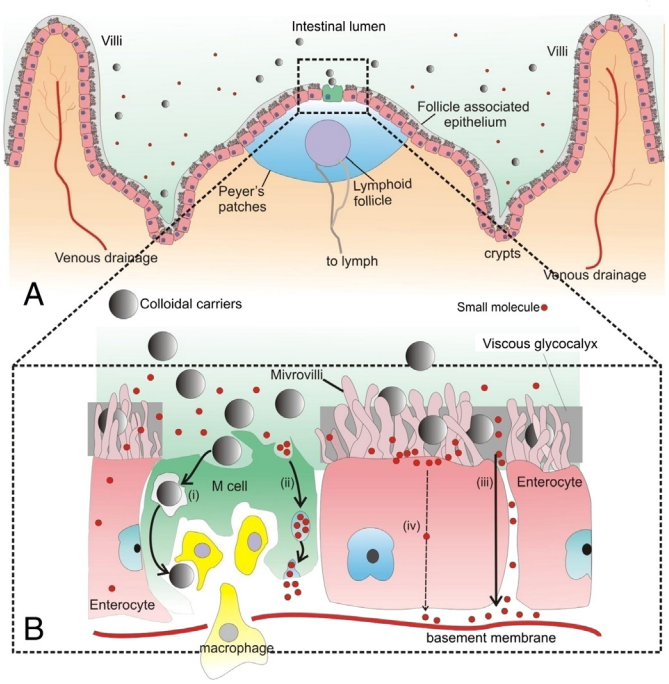

Fig. 1. (A) Cross section of intestinal epithelia showing distribution of M cells and enterocytes along with associated anatomical structures. (B) A magnified view of cells involved in absorptive processes namely (i) phagocytosis, (ii) pinocytosis, (iii) paracellular transport and (iv) transcellular transport. It is evident that colloidal sized entities (proteins, peptides or their carriers) find it difficult to approach apical surfaces of enterocytes due to viscous glycocalyx and microvilli. Therefore, they are more easily up taken by M cells. Smaller molecules are more adept in utilizing transcellular and paracellular transport.

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