Polymeric Nanoparticle Technologies for Oral Drug Delivery

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Abstract

Biologics are being increasingly used for the treatment of many diseases. These treatments typically require repeated doses administered by injection. Alternate routes of administration, particularly oral, are considered favorable because of improved convenience and compliance by patients, but physiological barriers such as extreme pH, enzyme degradation, and poor intestinal epithelium permeability limit absorption. Encapsulating biologics in drug delivery systems such as polymeric nanoparticles (NPs) prevents inactivation and degradation caused by low pH and enzymes of the gastrointestinal (GI) tract. However, transport across the intestinal epithelium remains the most critical barrier to overcome for efficient oral delivery. This review focuses on recent advances in polymeric NPs being developed to overcome transport barriers and their potential for translation into clinical use.

Technology Primer

The revolution in biomedical research that has occurred over the last half-century has resulted in an unprecedented understanding of the biological processes associated with many diseases. With this knowledge, exciting new therapies are being developed that could have a significant impact on the treatment of numerous diseases. Many of these new therapies are biological in nature, such as peptide hormones, antibodies, growth factors, enzymes, vaccines, and nucleic acids, and are known as biologics[1]. However, the impact of biologics may be limited to a narrow set of indications because administration is currently restricted to parenteral methods. Many diseases that would benefit from biologics are chronic, requiring frequent treatments over a prolonged period of time.

Injection-based therapies can suffer from poor patient compliance and reduced efficacy due to the pain and inconvenience associated with treatment regimens[2,3]. Therefore, alternate routes of administration are under investigation. Of these routes, oral is considered the most desirable because of the convenience and improved compliance[4].

Polymeric NPs are one technology that is currently being studied for oral delivery applications[5,6]. NPs are particles with a diameter on the order of 100 nanometers (nm), comparable in size to many viruses[7]. For drug delivery applications, most NPs are formed from biodegradable or biocompatible polymers that are approved for human use by the US Food and Drug Administration (FDA)[8,9]. Polymeric NPs are usually formed through a self-assembly process during which therapeutics such as small molecule drugs and biologics are encapsulated within the core of the NP[10,11]. The choice of polymer and self-assembly conditions provide considerable design flexibility by enabling modulation of physicochemical parameters (size, surface charge, hydrophobicity) and drug release properties (controlled or triggered)[12]. The surface properties of NPs can be modified by using different polymer end groups or attaching polymers to the NP surface[13]. Targeting ligands such as antibodies, peptides, or small molecules can also be attached to the NP surface to allow specific interactions with tissue components or cellular receptors[14]. Finally, because of their small size, NPs have large specific surface areas for interaction with epithelial surfaces.

Findings

Challenges of Oral Delivery

The challenges associated with oral delivery are due to the number of barriers that must be overcome in the GI tract before a therapeutic is absorbed and enters the bloodstream (Figure 1A). The first barrier is the harsh pH environment of the stomach and small intestine and enzymes secreted for digestion[15]. The pH environments in the GI tract can range from 1 in the stomach to 8 in parts of the intestine[16], which can cause pH-induced oxidation, deamidation or hydrolysis of protein therapeutics, leading to loss of activity[17]. Enzymatic degradation is due to proteases, nucleases, and lipases secreted to digest biological molecules prior to absorption. GI proteases generally digest 94–98% of orally administered proteins[18]. From the lumen of the small intestine, a therapeutic must reach the mucosal barrier for absorption. The intestinal mucosal barrier can be divided into extrinsic and intrinsic barriers[19]. The extrinsic barrier consists of the microenvironment overlying the epithelial cells, in particular the mucus layer. The role of mucus is to protect epithelial surfaces by trapping pathogens and foreign particulates and rapidly clearing them[20,21]. Penetration of this mucus barrier is necessary in order to reach the absorptive epithelial cells of the intestine. The intrinsic barrier consists of the epithelial cell monolayer, representing the major restrictive barrier to passive diffusion of material from the lumen to the lamina propria. The cells maintain this barrier through the formation of tight junctions, which are fusions between lateral membranes of adjacent cells that regulate the permeability of the monolayer[22].

There are several pathways used by molecules to cross the epithelial cell barrier, which include transcellular (transport through the cell, with crossing of the cell membranes),

paracellular (transport between adjacent cells), and transcytosis transport pathways[15]. Because of the size and charge of biologics, most are restricted to the transcytosis pathway, which is an active transport pathway that relies on receptors to bind and guide material in endosomes through the cell without entering a degradation pathway[23]. Once past the mucosal barrier, the biologics must diffuse through the lamina propria and enter the bloodstream through the capillaries or the lacteals. Biologics entering the capillaries are transported through blood vessels from the intestines through the portal system where they are also susceptible to first-pass metabolism.

Polymeric NPs encapsulating biologic molecules are able to overcome several of the barriers to oral delivery. They are stable in the GI environment and can protect encapsulated biologics from the harsh pH and enzyme degradation[24–26]. Modification of the NP surface with poly(ethylene glycol) enables the NPs to penetrate the mucus barrier[20]. However, the remaining hurdle is that intestinal absorption of NPs is highly inefficient because NP properties such as particle size prevent effective transport across the intestinal epithelium. Several strategies are under investigation to overcome this intestinal transport barrier in order to make oral biologics delivery feasible.

Mucoadhesives

Mucoadhesives are materials designed to interact with the intestinal mucus layer in order to increase the residence time and contact of NPs with the epithelium, resulting in an increase in concentration of biologics at the absorption site[27] (Figure 1B). Some examples of mucoadhesives include chitosan[28], polyacrylic acid[29], and poly(fumaric-co-sebacic) anhydride[30]. Many mucoadhesive materials also act as permeation enhancers, reversibly opening tight junctions to enhance paracellular transport[31]. While the NPs are unable to pass through the paracellular pathway because of particle size, many biologics are able to cross through this pathway[32]. One disadvantage of this approach is that the permeation enhancer activity is non-selective, meaning that toxins and other pathogens present in the intestines could potential cross the intestinal barrier once the tight junctions are open[33].

M Cells

Other approaches to oral delivery have focused on taking advantage of natural transcytosis pathways present in the GI tract. One pathway that has been the focus of many studies is the transcytosis pathway used by M cells to transport antigens across the intestinal barrier for immune surveillance[34,35] (Figure 1C). M cells are associated with Peyer's Patches (PP), an organized component of the gut-associated lymphoid tissue (GALT). M cells have several properties that allow for adherence by NPs, such as reduced proteases, lack of mucus secretion, and a sparse glycocalyx[36]. A number of approaches have been used to target NPs to M cells. Studies have shown that larger NPs[37,38] and more hydrophobic polymers[39] improve M cell transport. In addition, targeting ligands conjugated to the NP surface, such as bacterial adhesins[40], IgA antibodies[41], and toxins[42], increase M cell transport. One drawback to this approach is that the M cells are closely associated with immune cells in the lamina propria as part of the PP. Studies with glucan NPs showed that a majority of NPs were endocytosed by dendritic cells after M cell transcytosis, preventing them from reaching the bloodstream[43]. Besides limiting the effectiveness of the delivery system, uptake by

dendritic cells increases the risk that the NPs or biologics induce an immune response[44]. This may limit the use of this approach for long-term oral delivery, but could enable this approach to be used for oral mucosal vaccinations[45].

Vitamin B12 Receptor

More recent approaches have focused on receptor-mediated transcytosis pathways that are not associated with the GALT (Figure 1D). One example is the vitamin B12 receptor. When vitamin B12 is ingested, it is bound by intrinsic factor (IF) in the small intestine and the vitamin B12-IF complex interacts with an IF receptor that traffics vitamin B12 across the intestinal epithelium and allows it to reach the bloodstream[46]. NPs have been designed to target this pathway by conjugating vitamin B12 to the surface of biologic-loaded NPs. Studies with insulin-loaded NPs targeted to the vitamin B12 receptor have demonstrated enhanced absorption of insulin after oral administration[47–49].

Neonatal Fc Receptor

Another receptor targeted by NPs is the neonatal Fc receptor (FcRn), which mediates IgG transport across the intestinal epithelium[50,51]. FcRn is present in the apical region of epithelial cells in the small intestine and colon[52]. FcRn interacts with the Fc portion of IgG in a pH-dependent manner, binding with high affinity in acidic (pH <6.5) but not physiological environments (pH ~7.4)[53]. Therefore, in segments of the intestine that are acidic such as the duodenum and jejunum[54], targeted NPs can interact with FcRn at the apical surface of the epithelial cells and be taken up by receptor-mediated endocystosis. In segments of the intestine that are not acidic, the targeted NPs can still be taken into the cells by fluid-phase pinocytosis and interact with FcRn once inside acidic endosomes[55]. Targeted NPs bound to FcRn in the endosomes are trafficked across the epithelial cells through the FcRn transcytosis pathway and released from the receptor on the basolateral side of the cells at neutral pH. NPs loaded with insulin and surface-modified with IgG Fc demonstrated successful transcytosis across the epithelium and entry into the bloodstream, where the NPs were able to reach the liver, spleen, lungs, and kidneys[56]. The NPs were able to generate a hypoglycemic response for 15 hr with a clinically-relevant dose of only 1.1 U/kg[57], lower than other oral insulin delivery systems that require 10–100 U/kg to generate a glucose response[15].

Importance

Oral administration is considered a desirable alternative to intravenous administration because of the convenience and improved compliance by patients[2,3,58]. Oral formulations also have advantages for physicians, providing flexibility and adaptability to tune the dosing schedule to individual patients responses based on efficacy and toxicity. Without the intensive demands on staff required by intravenous administrations, oral formulations can also increase the number of patients treated[59] and reductions in the number of hospital or clinic visits could reduce overall costs[60–63].

Translation

Polymeric NPs are currently being studied for administration of a variety of therapeutics, including chemotherapeutics for cancer[64,65], siRNA and small molecule drugs for inflammatory bowel disease[66–68], and insulin for diabetes[47,56]. While these technologies are not yet in clinical trials, they are improving in efficiency to the point of becoming clinically relevant. Recent approaches focused on using natural transcytosis pathways to cross the intestinal barrier also avoid some of the potential safety issues associated with manipulating the integrity of the intestinal barrier through permeation enhancement. Polymeric NP-based therapeutics for other applications, such as treatments for cancer administered intravenously, are currently in clinical trials or have been approved[9,69,70]. This demonstrates that it is possible for polymeric NP technologies to be translated to the clinic and achieve approval by the FDA.

Roadblocks and/or Limitations

There are still challenges that must be overcome before these technologies are used in the clinic. Improved understanding of the differences in the GI tract between animal models and humans would ensure more reliable translation of performance from preclinical to clinical studies. Also, a better understanding of how patient-to-patient variability, diet, fasting states, and disease states affect absorption would help with clinical translation and prediction of performance. Finally, the effects of long-term administration of some therapeutics may need further investigation as some therapeutics can act as growth factors and induce changes in the epithelium, while other therapeutics may be toxic to the intestines[71].

Conclusions

Oral delivery technologies have the potential to have a significant impact on the treatment of many diseases by enabling therapeutics currently limited to parenteral administration to be administered through the oral route. There are currently several different polymeric NP approaches being studied to overcome the barriers of the intestine. Recent studies have demonstrated that polymeric NPs can efficiently deliver therapeutics orally, but further studies are required before these technologies can be translated to the clinic.

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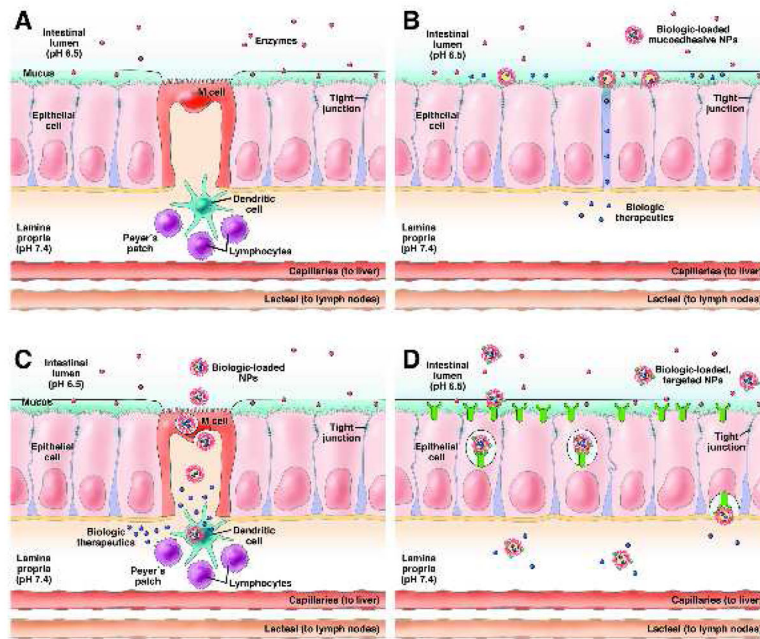
Figure 1.
(A) Schematic illustration of the barriers to oral biologic delivery presented by the GI tract, including acidic pH, enzymatic degradation, a mucus layer above the epithelial cells, the epithelial monolayer with limited permeability due to tight junctions, and immune cells associated with the M cells. (B) Mucoadhesive materials adhere to the mucus layer and release drug at high concentrations near the epithelial cells as well as reversibly open tight junctions to allow for biologic transport across the epithelium through the paracellular pathway. (C) The M cell transcytosis pathway is an approach used to enable NPs to cross the epithelium, but underlying dendritic cells associated with the Peyer's Patches may endocytose NPs in the lamina propria. (D) Receptor-mediated transcytosis pathways such as the vitamin B12 receptor and FcRn can be targeted by NPs to enable transport across the epithelium and release into the lamina propria.