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Recent Advances in Polymeric Nanoparticles for Oral Delivery of Biologics: A Pharmaceutics Perspective

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Abstract

Oral administration of biologics such as peptides, proteins, vaccines, and nucleic acids is one of the most significant challenges because of enzymatic breakdown, acidic gastric environment, and low absorption in the intestines. Polymeric nanoparticle has become a potential solution to surmount these obstacles, as it provides protection of biologics, controlled release as well as increased mucosal uptake. This review will present a pharmaceutics-oriented overview of recent developments in polymeric nanoparticle-based oral delivery systems with particular emphasis on preclinical animal studies. The significant advances in natural and synthetic polymers, surface modification techniques including mucoadhesion, conjugation of ligands and pH- sensitive coatings and the applications in different classes of biologics are also critically examined. The animal studies show enhanced oral bioavailability, prolonged therapeutic effect and improved immune response, showing the potential of the systems as less invasive methods of administration compared to the conventional administration. Although some of these advances have been made, issues of formulation complexity, reproducibility, large-scale production and long-term safety have yet to be resolved. This review highlights the existing gaps and suggests future research to enable translation of polymeric nanoparticles in oral biologic delivery into clinical practice.

Key Words:

Polymeric Nanoparticles, Oral Delivery, Biologics, Peptides, Proteins, Vaccines, Nucleic Acids

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1. INTRODUCTION

Oral route is well known as a most convenient and preferable method of drug administration, so its benefits include better patient compliance, convenience and non-invasive administration. Nevertheless, oral delivery of biologics, such as peptides, proteins, vaccines, and nucleic acids, is a challenging task in pharmaceutics[1]. Biologics are inherently labile molecules, which are vulnerable to enzymatic degradation by the gastrointestinal (GI) tract, chemical hydrolysis in the acidic stomach environment, and poor absorption across the intestinal epithelium[2]. These obstacles greatly diminish bioavailability and efficacy, and may require parenteral administration, which is painful, inconvenient, and correlates with poor patient compliance.

1.1. Background information and context

Over the past years, polymeric nanoparticles have become a paradigm-shifting platform in oral delivery of biologics[3]. The nanoscale carriers have several benefits such as they provide protection of biologics against harsh GI environment, they also have a controlled and sustained release, they are also more mucoadhesive and they also have targeted transports across intestinal barriers[4]. Natural polymers (including chitosan and alginate) as well as synthetic polymers (poly(lactic-co-glycolic acid) (PLGA) and PEGylated systems) have been widely investigated in preclinical animal models showing significant enhancement in oral absorption and therapeutic effect. Further optimization of nanoparticle performance with respect to biologic delivery has also been achieved with improvements in surface modification strategies such as ligand conjugation, mucoadhesive coating, and pH-sensitive encapsulation[5].

1.2. Objectives of the Review

The primary objective of this review is to provide a pharmaceutics-centered analysis of recent advances in polymeric nanoparticles for oral delivery of biologics, with a focus on animal-based preclinical studies. Specifically, this review aims to:

1. Examine recent developments in natural and synthetic polymeric nanoparticle systems.
2. Evaluate the impact of surface modification and targeting strategies on oral bioavailability.
3. Summarize the application of polymeric nanoparticles across various biologic classes, including peptides, proteins, vaccines, and nucleic acids.
4. Identify current limitations, translational challenges, and future research directions in this rapidly evolving field.

1.3. Importance of the Topic

Improving oral delivery of biologics is of tremendous clinical and pharmaceutical importance. The non-invasive oral formulations have the ability to enhance patient compliance, eliminate the need of frequent injections, and increase the availability of important medicines like insulin, vaccines and gene therapeutics[6]. Moreover, polymeric nanoparticle platforms provide a flexibility to adjust drug delivery and enhance therapeutic efficacy as well as reduce the systemic side effects. This review offers an in-depth view on the current state-of-the-art, challenges, and opportunities of polymeric nanoparticle-mediated oral delivery of biologics due to the consolidation of evidence available in preclinical animal studies[7].

2. POLYMERIC SYSTEMS FOR ORAL DELIVERY OF BIOLOGICS

Polymeric nanoparticle has become a promising multifunctional platform of oral biologics delivery due to its capacity to encapsulate macromolecules, protect them against gastrointestinal (GI) degradation, and increase the absorption across the epithelium. Polymers, both natural and synthetic, enable nanoparticles to be tuned in terms of size, surface charge and degradation kinetics, which are considered to promote oral bioavailability. This section expounds on natural polymer-based systems and synthetic polymer-based systems that are supported by animal-based preclinical evidence[8].

2.1. Natural Polymers

a) Chitosan Nanoparticles

Chitosan is a cationic polysaccharide obtained by deacetylation of chitin and is well-known to possess mucoadhesive characteristics and the capability of temporarily opening intestinal epithelial tight junctions. This improves the paracellular biologics transportation.

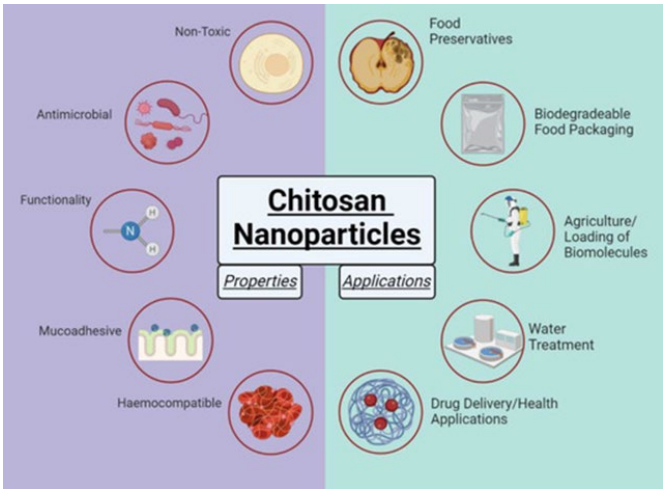

Figure 1: Chitosan Nanoparticles[9]

- In diabetic rat models, insulin-loaded chitosan nanoparticles orally delivered resulted in a remarkable, long-lasting hypoglycemic effect, whereas free insulin produced a slight effect (insignificant) when administered orally. Chitosan has a positive charge that enhances the electrostatic interaction with mucosal surfaces that are negatively charged, increasing the retention time.
- Further modifications of derivatives, e.g. thiolated chitosan, increase mucoadhesion and enzyme resistance.

b) Alginate Nanoparticles

Alginate, an anionic polysaccharide derived by extraction of brown algae, is applicable to pH-sensitive delivery. It expands in the neutral/basic intestinal conditions, and it releases biologics in the absorption site[10].

- In murine models, oral vaccine antigens encapsulated in alginate nanoparticles demonstrated both increased mucosal and systemic immune responses, which indicates the possible use of this technology in non-invasive vaccination.
- Additional stabilization of alginate nanoparticles by coating with polycations, e.g. chitosan, enhances encapsulation efficiency and intestinal residence time.

Strengths: Biocompatibility, Biodegradability, Mucoadhesion and Low Toxicity.

Weaknesses: Batch-to-batch inconsistency in polymer purity, comparatively poor mechanical stability, and a lack of control over the release kinetics.

2.2. Synthetic Polymers

- **Poly(lactic-co-glycolic acid) (PLGA) Nanoparticles:**

PLGA is a synthetic polymer approved by the FDA that has found wide application in drug delivery because it is biocompatible and its degradation rates can be varied[11].

- Oral insulin in PLG encapsulated form in rat models
- A nanoparticle exhibited a long-lasting hypoglycemic effect of up to 12 hours compared with unencapsulated insulin, which was dissolved quickly in gastric fluid.
- The hydrophobic property of PLGA ensures that biologics are not subjected to enzyme hydrolysis and that the degradation products (lactic acid and glycolic acid) are metabolically acceptable.

➢ **PEGylated Systems**

Modification of nanoparticles with polyethylene glycol (PEG) enhances their dispersal in the systemic circulation and gives them a stealth effect with reduced recognition by opsonins.

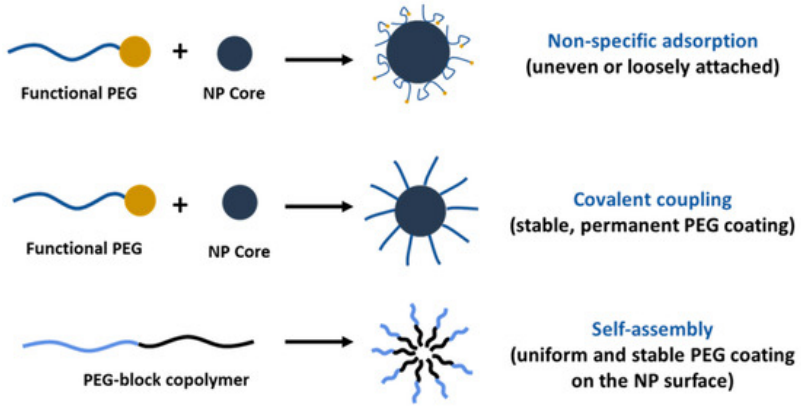

Figure 2: Comparison of PEGylation strategies for nanoparticle surface modification[12]

- PEGylated PLGA nanoparticles in rat models increased the systemic insulin half-life as compared to non-PEGylated PLGA nanoparticles.
- The approach minimises premature clearance, which enhances the bioavailability of orally administered biologics.

➢ **Other Synthetic Polymers**

Poly(e-caprolactone) (PCL) and polymethacrylates (Eudragit) have been used as well in animal studies due to their slow degradation and pH-sensitive release respectively. As an example, Eudragit-coated nanoparticles were used to cover the insulin against gastric acid and the release was more in the intestine, the plasma insulin in the rats was higher than the uncoated systems[13].

Strength: Low degradation rates can be controlled, mechanical strength is high, the response is reproducible, and encapsulation is high.

Weaknesses: Possible toxicity of residual monomers, comparatively high price and scale-up difficulties in reproducibility.

2.3. Comparative Insights

To bring some clarity to the benefits and limitations of various systems, the following table compares natural vs. synthetic polymeric nanoparticles with respect to the use of oral biologics delivery.

Table 1: Comparison of Natural and Synthetic Polymeric Nanoparticles in Oral Delivery of Biologics (Based on Animal Studies)[14]

Polymer Type	Examples	Mechanism/Properties	Representative Animal Study Outcome	Strengths	Weaknesses
Natural Polymers	Chitosan, Alginate	Mucoadhesion, transient opening of tight junctions, pH-sensitive swelling	Chitosan–insulin NPs: sustained hypoglycemia in diabetic rats; Alginate–antigen NPs: enhanced mucosal immune response in mice	Biodegradable, biocompatible, enhances mucosal uptake	Poor reproducibility, weaker mechanical stability
Synthetic Polymers	PLGA, PEGylated PLGA, PCL, Eudragit	Protection from enzymatic degradation, sustained release, PEGylation prolongs systemic circulation	PLGA–insulin NPs: prolonged glucose reduction in rats; Eudragit-coated NPs: improved intestinal release in rat models	Controlled release, reproducible, tunable degradation rates	Scale-up limitations, cost, potential toxicity from monomers

3. SURFACE MODIFICATION AND TARGETING STRATEGIES

Although polymeric nanoparticles provide inherent protection to biologics against enzymatic and acidic degradation, surface modification approaches have been particularly successful in improving their oral delivery. Engineering nanoparticle surfaces has enhanced mucosal adhesion, epithelial transport, stability in the gastrointestinal tract, and site specific release. Such strategies are of essence to oral biologics that are prone to get degraded and have low intestinal permeability[15].

There are three broad categories of surface modification strategies that are commonly used, namely mucoadhesive coating strategies, ligand-based targeting strategies and pH-sensitive strategies. Table 2 provides a comparative overview of some representative animal studies that used these methods.

3.1. Mucoadhesive Coatings

Enhancement of residence time at the intestinal mucosa is one of the best strategies to improve the bioavailability of orally administered biologics. Mucoadhesive coverings enhance exposure of nanoparticles to the intestinal tissue further by prolonging their interaction with the tissue, which enhances their probability of absorption[16].

- The thiolated chitosan nanoparticles have gained much attention in the research as they are able to disulfide link with the cysteine-rich regions of the mucus glycoproteins. Thiolated

chitosan nanoparticle-insulin conjugates exhibited a much higher hypoglycemic effect in rats than unmodified chitosan nanoparticle-insulin conjugates.

- Nanoparticles coated with poly (ethyleneimine) were demonstrated to enhance mucosal adhesion and penetration of rabbit intestinal models resulting in greater oral bioavailability of encapsulated proteins.

3.2. Ligand-Conjugated Nanoparticles

Ligand targeting of the nanoparticle surface allows receptor mediated endocytosis which increases biologic transport across epithelial cells. This method takes advantage of the normal nutrient absorption routes of the bowel.

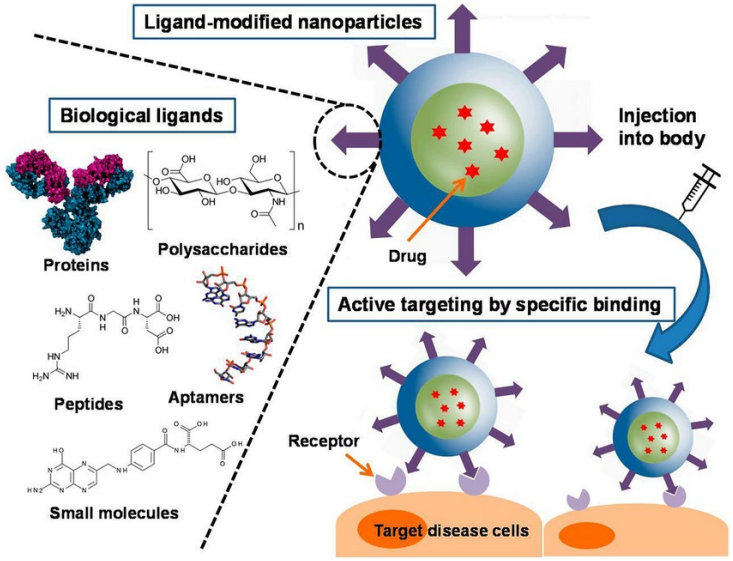

Figure 3: Different types of ligand-conjugated nanoparticles with various active molecules and their targeting mechanisms[17]

- PLGA nanoparticles functionalized with transferrin that carried therapeutic proteins showed better intestinal uptake in mouse models than unmodified PLGA nanoparticles.
- Nanoparticles conjugated to folic acid have also been studied. Folate-modified chitosan nanoparticles-insulin demonstrated greater plasma insulin levels and more hypoglycemic effects than unmodified chitosan nanoparticles in rat studies.

Other ligands that have been investigated in animal models include lectins, aptamers and peptides which are specific to intestinal transporters.

3.3. PH-sensitive Coatings

The gastrointestinal tract has a unique pH environment: extremely acidic in the stomach and around neutral in the intestine. pH sensitive coatings are thus essential in protecting biologics against gastric degradation and release of biologics at intestinal sites of absorption.

- Nanoparticles coated with Eudragit have been well researched. Eudragit-coated nanoparticles enclosing insulin showed a substantial increase in plasma insulin in comparison to uncoated nanoparticles in rat models as a result of targeted release in the intestine.

- On the same note, the use of alginate nanoparticles coated with pH-sensitive polymers showed enhanced antigen release and mice immune responses when orally administered vaccines.

Table 2: Surface Modification Strategies for Polymeric Nanoparticles in Oral Delivery of Biologics (Animal Models)[18]

Strategy	Polymer/ Modification	Animal Model	Biologic Delivered	Key Findings	Strengths	Weaknesses
Mucoadhesive Coatings	Thiolated chitosan	Rats	Insulin	Greater hypoglycemic effect vs. unmodified chitosan NPs	Prolonged mucosal adhesion, tight junction opening	Possible mucosal irritation, limited mobility
	Polyethyleneimine (PEI) coating	Rabbits	Proteins	Improved mucosal adhesion and absorption	Strong cationic interaction	Potential cytotoxicity
Ligand-Conjugated NPs	Transferrin-PLGA	Mice	Proteins	Enhanced intestinal uptake via receptor-mediated endocytosis	High specificity	Complex synthesis, cost
	Folate-chitosan NPs	Rats	Insulin	Higher plasma insulin & improved hypoglycemia	Exploits folate receptor pathway	Risk of immunogenicity
pH-Sensitive Coatings	Eudragit-coated PLGA	Rats	Insulin	Increased plasma insulin due to intestinal release	Protects from gastric degradation, targeted release	Dependence on GI pH variability
	Alginate with pH-sensitive coating	Mice	Antigens (oral vaccine)	Enhanced mucosal immune response	Intestinal antigen release	Incomplete release in altered GI motility

3.4. Critical Evaluation

The surface modification techniques also offer significant advantages compared to unmodified nanoparticles as it allows an increase in intestinal adhesion, receptor-mediated uptake, and controlled release. When such strategies are used, animal studies (summarized in Table 2) indicate

consistently higher levels of plasma, and better therapeutic outcomes. Nevertheless, problems that include complexity of formulation, increased manufacturing costs, and possible immunogenicity on repeated dosing should be resolved prior to widespread use[19].

4. APPLICATION OF POLYMERIC NANOPARTICLES IN ORAL DELIVERY OF SPECIFIC BIOLOGICS

Oral administration of biologics is one of the most problematic fields in pharmaceutics because of the obstacles of enzymatic degradation, low gastric pH, and restricted intestinal permeability. Polymeric nanoparticle provides a flexible approach of overcoming these barriers by offering protection, controlled release, and specific uptake in the gastrointestinal tract. Their efficacy in a wide range of biologics, such as peptides and proteins, vaccines, and nucleic acids, is demonstrated in preclinical animal studies[20].

4.1. Peptides and Proteins

The most widely examined group of oral biologics delivery is peptides and proteins, and insulin is the main paradigm therapeutic. The use of polymers, including PLGA and chitosan, to formulate polymeric nanoparticles has shown significant enhancement of oral bioavailability in preclinical studies[21].

- In rat and rabbit experiments, insulin-loaded nanoparticles administered orally achieved a large and prolonged hypoglycemic effect of several hours, which closely resembles physiological insulin secretion.
- The efficacy observed is due to several mechanisms that include: Nanoparticles can preserve insulin against enzyme degradation by the GI tract, increase drug retention at the intestinal mucosa through mucoadhesive interactions, and provide controlled and sustained drug release[22].
- All these features enhance systemic absorption and decrease the variability of conventional oral insulin formulations that are quickly degraded and not well absorbed.

4.2. Oral Vaccines

Oral vaccines encapsulated in polymeric nanoparticles have shown enhanced immunogenicity in preclinical animal studies.

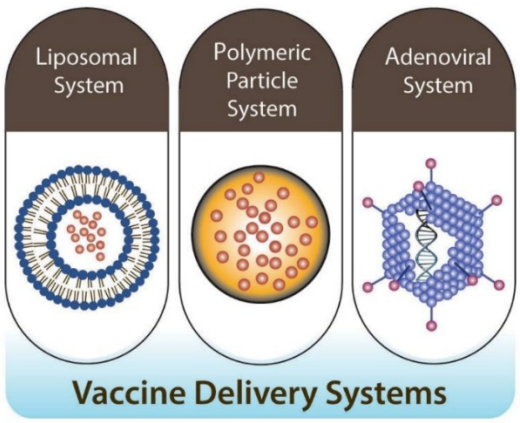

Figure 4: Vaccine Delivery Systems[23]

- Nanoparticles consisting of biodegradable polymer and loaded with antigens induced more mucosal and systematic immune responses in mice than free antigens.
- This enhanced efficacy can be largely attributed to efficient uptake by M cells in Peyer patches which are major antigen-sampling sites in the intestine, and a longer residence time at the mucosal surface, permitting more prolonged exposure to immune cells.
- These observations suggest the possible use of polymeric nanoparticle as a non-invasive oral vaccine delivery system particularly against antigens that are prone to degradation or those that need to be delivered at specific mucosal immune-inductive sites.

4.3. Nucleic Acids

Nucleic acids, including siRNA and DNA plasmids, are not delivered well by mouth because of nucleases and intestinal absorption. To overcome these barriers, polymeric nanoparticles such as PLGA and chitosan-based formulations have been used[24].

- In animal studies, it was demonstrated that these nanoparticles protect nucleic acids against enzymatic degradation, increase intestinal uptake, and intracellular delivery, leading to higher gene expression and therapeutic efficacy.
- Although preclinical results are encouraging, a number of issues are outstanding in clinical translation, such as stability of nanoparticles in physiological environments, manufacturing scalability, and reproducibility between batches.

4.4. Strengths and Limitations

The preclinical data in the peptide, protein, vaccine, and nucleic acid studies show that polymeric nanoparticles have therapeutic potential in oral biologics delivery[25]. Major strengths are:

- GI protective of biologics.
- Increased mucosal and systemic uptake.
- Flexibility in the provision of different classes of molecules.

The limitations however are:

- Poor reproducibility between studies as a result of different methods of nanoparticle preparation and polymer properties.
- Long-term safety uncertainties in animal models.
- Differences in scaling production to clinically relevant levels.

To offer a systematic overview of important results, Table 3 characterizes exemplary animal studies that underline the use of polymeric nanoparticles as vehicle of oral delivery of various classes of biologics, with an additional focus on authorship and methodology strategies.

Table 3: Reference Table

Author(s)	Biologic Class	Nanoparticle System	Method (Animal Study)	Key Findings
Mantaj&Vllasaliu (2020)[26]	Peptides & Proteins	Insulin-loaded chitosan nanoparticles	Oral administration in diabetic rats	Significant hypoglycemic effect; improved absorption due to mucoadhesion and epithelial permeation
Pridgen et al. (2014)[27]	Peptides & Proteins	PLGA insulin nanoparticles	Oral administration in rats and rabbits	Sustained glucose reduction for several hours; improved bioavailability
Pridgen et al. (2015)[28]	Oral Vaccines	Antigen-loaded polymeric nanoparticles	Oral delivery in mice	Stronger mucosal immune response compared to free antigens; uptake by Peyer's patches
Cao et al. (2021)[29]	Oral Vaccines	Biodegradable polymeric nanoparticles	Oral vaccination in mice	Improved antigen stability; prolonged mucosal residence; enhanced systemic and local immune responses
Zhang et al. (2021)[30]	Nucleic Acids	PLGA nanoparticles carrying siRNA	Oral administration in rodent models	Increased intestinal uptake and gene expression; stability issues noted
Morales & Brayden (2017)[31]	Nucleic Acids	Chitosan-DNA plasmid nanoparticles	Oral gavage in rats	Enhanced protection of DNA from enzymatic degradation; moderate gene expression

The use of polymeric nanoparticles in the oral administration of biologics (insulin, vaccines and nucleic acids) has been demonstrated to hold potential in animal studies. These systems have the potential to translate into the future because they are able to shield sensitive molecules and increase intestinal uptake. However, mass reproducibility, stability issues, and long-term animal studies on safety are some of the major issues that need to be studied.

5. DISCUSSION

The present review identifies the great advancements made in the application of polymeric nanoparticles in oral delivery of biologics, on the basis of animal-based preclinical studies only[32].

The results show that natural and synthetic polymers have different benefits when it comes to improving oral bioavailability, biologics protection against enzymatic degradation and controlled release[33]. It is interesting to note that hybrid approaches that combine the advantages of more than one type of polymer (e.g., chitosan-coated PLGA nanoparticles) have been especially promising in addressing the gastrointestinal (GI) barrier.

5.1. Interpretation of Findings

Insulin and peptides in general have repeatedly shown enhanced absorption and therapeutic effect when administered through polymeric nanoparticles[34]. In animal experiments, it was found that it was possible to maintain hypoglycemic effect over many hours, and that the carriers had a potential to reproduce physiological drug release patterns. This is in sharp contrast to free protein delivery which is quickly broken down in the GI tract and has poor absorption[35]. Mucoadhesive properties of natural polymers such as chitosan and protective encapsulation by synthetic polymers such as PLGA are important in improving the systemic uptake.

Nanoparticle-based oral vaccines showed increased mucosal and systemic immune responses in animal models[36]. The results indicate that the delivery of nanoparticles has the potential of surmounting the shortcomings of the traditional oral vaccines, which include degradation in the acidic gastric environment and poor transportation across the intestinal epithelium. Specific uptake by M cells and long-term retention in Peyer patches enhanced antigen uptake and immune stimulation[37].

Nanoparticle encapsulation also proved useful in protecting fragile nucleic acids such as siRNA and DNA plasmids, and assisting their delivery to the interior of cells[38]. Preclinical data, however, suggest continued issues with stability, reproducibility and long-term gene expression, which are areas that require additional optimization prior to clinical translation.

5.2. Implications and Significance

All of the reviewed studies show that polymeric nanoparticles have wide applicability in various biologic classes[39]. These systems reduce or replace injections and other parenteral administration exposing patients to a non-invasive delivery method that can enhance patient compliance and therapeutic efficacy by the integration of protection, controlled release, and enhanced absorption. Moreover, surface modification techniques, including mucoadhesion, ligand conjugation, pH-sensitive coatings, offer extra possibilities to adjust delivery to a particular intestinal segment, enhance bioavailability and minimize degradation.

These findings are important not only academically. Effective translation of such platforms has the potential to transform oral biologic therapy, and allow oral insulin, vaccines, and oral gene therapies that are not inferior to parenteral therapies. Also, the flexibility of polymeric nanoparticles implies possible use in personalized medicine, with the dosage and release profiles adjusted to the needs of the individual patient.

5.3. Research Gaps and Future Directions

Gaps and Challenges

Although the preclinical evidence is promising, there are a few major gaps[40]:

- **Translational Relevance:** The majority of studies are restricted to small-scale experiments (rats, rabbits, mice) and lack direct extrapolation to humans as a result of the differences in GI physiology, immune response, and enzyme activity.
- **Reproducibility and Scalability:** The composition of the polymer, size of nanoparticle, and encapsulation efficiency vary, which makes reproducibility difficult, especially in large scale production.
- **Long-Term Safety:** There are incomplete safety data in animals, especially on repeated exposure, immunogenicity of the polymers or surface ligands and possible toxicity of degradation by-products.
- **Formulation Complexity:** Surface modifications, conjugation of ligands and hybrid polymer systems work to improve efficacy but add complexity to the formulation, which makes the manufacture costlier and more subject to regulatory issues.
- **Stability of Biologics:** Although the protection is achieved with polymeric nanoparticles, some nucleic acids and sensitive proteins remain unstable, and it is necessary to optimize the encapsulation techniques and excipients.

Future Research Directions

Future studies need to concentrate on:

- **Large-animal studies:** Shifting rodent models to larger animals (e.g., pigs or non-human primates) representing a better model of human GI physiology.
- **Hybrid polymer constructions:** The mixture of natural and synthetic polymers to establish the balance between mucoadhesion, biocompatibility, and controlled release.
- **Better surface engineering:** Exploring novel ligands, biodegradable coatings, stimuli-responsive delivery systems to obtain enhanced targeted delivery and decreased immunogenicity.
- **Scalable production plans:** Devising scalable production processes that are cost effective and that preserve nanoparticle stability and encapsulation efficiency.
- **Complete safety profiling:** Long-term assessment of repeated exposure, immune reaction and toxicity of polymeric products and degradation products.
- **Mechanistic investigations:** The molecular mechanism of intestinal absorption, cellular uptake, and intracellular trafficking of nanoparticles to maximize design and performance.

6. CONCLUSION

Polymeric nanoparticles are a very adaptable and promising delivery vehicle to deliver biologics orally with a high level of protection of the gastrointestinal degradation, controlled release, and intestinal absorption. They are effective in peptides, proteins, vaccines, and nucleic acids in preclinical animal studies and are characterized by long-lasting therapeutic effects, increased bioavailability, and immune response. Natural polymers are very biocompatible and mucoadhesive, whereas synthetic ones offer reproducibility, degradation and release control and

thus, hybrid polymers that combine these advantages are especially promising. Notwithstanding these developments, there are issues of large-scale production, reproducibility, long-term safety and stability of sensitive biologics. This review highlights the significance of future studies using animal-based preclinical models, highlighting new polymer architectures, specific delivery methods, and large-scale production methods. Filling these gaps will be key to bringing polymeric nanoparticle systems to clinical reality as oral bio-therapeutics, with potential to revolutionize patient adherence and response in pharmaceutics.

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