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A Review: Comparison of PEGylation Methods in Efforts to Improve the Bioavailability Profile of Oral Products Based on Insulin, Peptides, and Therapeutic Proteins

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ABSTRACT

Biopharmaceuticals, including insulin, therapeutic proteins, and peptides, have become essential in the treatment of chronic and complex diseases due to their high specificity and favorable safety profiles; however, their oral delivery remains highly challenging because of gastrointestinal instability, enzymatic degradation, mucus entrapment, and limited epithelial permeability, leading to low and variable bioavailability. This review critically evaluates and compares PEGylation-based strategies developed to overcome these barriers and improve the oral bioavailability of biopharmaceutical products. A narrative literature review was conducted using PubMed and ScienceDirect databases, focusing on original research articles published within the last ten years and selected according to predefined inclusion and exclusion criteria. The analyzed studies demonstrate that PEGylation consistently enhances physicochemical stability, solubility, and resistance to proteolytic degradation, while reducing nonspecific interactions with the intestinal mucus layer. Various PEGylation platforms, including PEGylated nanoparticles, liposomes, polymeric carriers, self-emulsifying drug delivery systems, and microfluidic-based lipid nanoparticles, were shown to improve mucus penetration, prolong intestinal residence time, preserve biological activity under simulated gastrointestinal conditions, and facilitate transepithelial transport. Although the extent of bioavailability enhancement varied depending on the molecular characteristics of the active compound and the PEGylation technique employed, the overall findings highlight PEGylation as a robust and adaptable formulation strategy. Collectively, this review emphasizes the importance of rational PEGylation design tailored to specific biological barriers, positioning PEGylation as a key enabling technology for the development of next-generation oral biopharmaceutical delivery systems.

Keywords: *PEGylation, biopharmaceutical, biopharmaceuticals, oral*

INTRODUCTION

Biopharmaceutical products such as therapeutic proteins, peptides, and monoclonal antibodies have great potential in modern therapy due to their ability to work more specifically on certain biological targets, thus generally producing fewer side effects than conventional small molecule drugs. These characteristics make biopharmaceuticals very attractive for the treatment of various chronic and complex diseases, such as cancer, autoimmune diseases, metabolic disorders, and degenerative diseases. However, the success of biopharmaceutical therapy is not only determined by its biological activity, but also depends heavily on the success of its delivery system into the body. In this context, the development of oral formulations for biopharmaceuticals still faces significant challenges, particularly related to unfavourable biopharmaceutical profiles. The gastrointestinal tract is a very hostile environment for biological molecules, due to extreme pH variations, digestive enzyme activity, and limited transit time. The highly acidic pH conditions of the stomach and the presence of proteolytic enzymes such as pepsin, trypsin, and chymotrypsin can cause degradation of the primary, secondary, and tertiary structures

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of biopharmaceutical molecules (Baral & Choi, 2025). Such structural damage has the potential to reduce or even eliminate therapeutic activity before the drug reaches its site of action, resulting in very low clinical efficacy.

In addition to stability issues, biopharmaceuticals also face significant challenges during the absorption phase. Their relatively large molecular size and complex three-dimensional structure make it difficult for these molecules to pass through the intestinal epithelial membrane. Unlike small-molecule drugs that can passively diffuse through lipid membranes, biopharmaceuticals generally do not meet the physicochemical criteria for such mechanisms. Active transport in the intestine also has limitations, as the physiologically available transporter systems are not designed to transport therapeutic proteins or peptides in significant quantities (Baral & Choi, 2025; Ghosh et al., 2018). As a result, only a very small fraction of the oral dose of biopharmaceuticals is able to reach the systemic circulation. The combination of low stability in the gastrointestinal tract and permeability barriers results in very low and inconsistent oral bioavailability of biopharmaceuticals. This explains why, to date, most biopharmaceuticals are still administered via parenteral routes, such as intravenous or subcutaneous injections, even though these routes are less comfortable for patients and may reduce treatment compliance. Therefore, innovative formulation approaches are needed to overcome these barriers and open up opportunities for the development of more effective oral biopharmaceutical formulations.

One approach that has been widely developed is the use of PEGylation-based delivery systems. PEGylation is a formulation strategy that aims to improve the stability, solubility, and performance of biopharmaceuticals by attaching polyethylene glycol (PEG) chains to drug molecules or their carriers (Makharadze et al., 2025). In general, PEGylation can be done through direct covalent bonds to protein or peptide functional groups, or through surface coating of carriers such as nanoparticles, liposomes, or emulsion systems. The addition of PEG chains produces a hydrophilic and flexible hydration layer around the drug molecule (Suk et al., 2016; Tenchov et al., 2023). This layer acts as a steric barrier that protects the biopharmaceutical molecule from digestive enzyme attacks and non-specific interactions with other biological components in the gastrointestinal tract. Additionally, the presence of PEG can reduce protein aggregation tendencies and increase molecular solubility, thereby maintaining the physical and chemical stability of the drug during delivery.

Not only does PEGylation provide protection against degradation, but it also plays an important role in increasing the chances of oral absorption of biopharmaceuticals. One of the main obstacles to the absorption of large particles is the intestinal mucus layer, which acts as a protective barrier against foreign objects (Yamazoe et al., 2021). Unmodified particles tend to be trapped or eliminated by mucus before reaching the epithelial surface. The PEG layer creates a surface that is relatively “non-sticky” to mucus, allowing particles to move more freely and approach the intestinal epithelial cells (Pangua et al., 2024). With increased interaction between the delivery system and the epithelium, the chances of absorption also become greater. Through a combination of protection against degradation, increased stability, and facilitation of mucus penetration, PEGylation is a promising approach in the development of oral biopharmaceutical formulations. This strategy is expected to increase oral bioavailability, reduce the need for parenteral administration, and ultimately improve patient comfort and therapeutic success.

METHODS

This study uses a literature review design with a narrative approach to examine the method of PEGylation in improving the bioavailability profile, particularly in oral preparations. A systematic literature search was conducted on two main databases, PubMed and ScienceDirect, using the keywords “pegylated” AND “biopharmaceutical”, “PEGylated insulin oral”, “PEGylated oral”, and combinations of “PEGylated” with “insulin”, “enzyme”, “antibody”, “oral”, ‘protein’, and “peptide”, limited to original research articles published in the last ten years. All search results were combined, duplicates were removed, and selection was performed through title and abstract screening, followed by full-text review according to the inclusion-exclusion criteria. The data used included studies on PEGylation methods, formulation characteristics, in vitro or in vivo test conditions, and reported biopharmaceutical results. All articles that met the criteria were analyzed narratively, and 31 of the 50 research articles were obtained from this process.

RESULTS AND DISCUSSION

Polyethylene Glycol (PEG) is a hydrophilic and biocompatible polymer with high solubility in water. Therefore, adding PEG to a system serves to increase hydration, attract water, and reduce the hydrophobic properties of the carrier material (Patel et al., 2023). PEGylation using PEG-4000, as in the study by Momoh et al. (2021), has been shown to increase microparticle stability, improve zeta potential, narrow polydispersity, and

form new polymer entities that are more homogeneous and hydrated. These factors are known to directly contribute to increased solubility and dispersion of particles in aqueous media (Momoh et al., 2021). This effect of increased solubility is also considered favorable, as reported by another study, namely Homayun et al. (2019), which showed that PEG increases the solubility and dispersion of oral delivery systems, mainly by increasing particle hydrophilicity and neutralizing surface charges. Therefore, particles interact and disperse more easily in an aqueous medium, which directly affects the increase in solubility (Homayun et al., 2019).

In addition to increasing solubility, PEGylation can also increase drug permeability, especially when it has to pass through complex biological barriers such as the blood–brain barrier (BBB). In this process, poly(ethylene glycol) (PEG) chains are added to the drug or its delivery system so that the particle size remains in the nanometer range, reducing interactions with plasma proteins and prolonging circulation time in the blood (Digiacomo et al., 2024). The effectiveness of PEGylation in increasing permeability is demonstrated by a study by Kang et al. (2016), in which PEGylated liposomes conjugated with anti-transferrin receptor antibodies were able to increase the distribution volume up to fourfold and significantly increase BBB surface permeability (PS) compared to liposomes without antibodies. These results confirm that PEGylation not only prolongs the circulation time of drugs, but also helps drugs cross the BBB more efficiently (Kang et al., 2016).

In pharmaceutical formulation, PEGylation has been proven effective in reducing the toxicity of the formulation. Desai & Shende (2022) reported that PEG modification of neuropeptide Y (NPY) significantly reduced its toxic potential when used as a drug delivery system. In that study, PEGylated NPY in the form of polyplexes did not cause changes in the physical condition of the test animals, including body weight, feed and water consumption, and did not cause mortality during the 14-day observation period, indicating very low toxicity. The protection of the cationic surface charge by PEG was the main factor in reducing these toxic effects (Desai & Shende, 2022). Similar findings were also reported by Sarhadi et al. (2022), who showed that PEG liposomes with vitamin B12 ligands did not cause cytotoxic effects on intestinal epithelial cells in vitro (Sarhadi et al., 2022). Additionally, the use of a PGA-PEG coating on nanocomplexes (ENCPs) was reported to reduce the inherent cytotoxicity of C12-r8 (Niu et al., 2018). Based on this, PEGylation not only improves the pharmacokinetic profile but can also reduce the toxicity of drug formulations.

Various PEGylation strategies have been developed to improve the stability, gastrointestinal resistance, and oral delivery effectiveness of biological molecules, which can be classified based on their samples, namely insulin, therapeutic proteins, and peptides. In insulin formulations, the Polyethylene Glycol–p-Nitrophenyl Carbonate (PEG-NPC) method involves activating PEG into p-nitrophenyl carbonate (PEG-NPC), which is then reacted with insulin through the formation of biologically stable covalent urethane bonds; the result is PEG–insulin that is more resistant to degradation, more stable in the gastrointestinal tract, and has the potential to increase oral bioavailability (Coolich et al., 2023). The Modified Solvent Diffusion–Solvent Evaporation method uses DOCA-PHB-PEG polymer dissolved together with insulin in an organic solvent, which is then poured into an aqueous phase, causing rapid diffusion and the formation of nanoparticles; the result is ultra-small nanoparticles (~10 nm) with a uniform size distribution (PDI 0.299) (Chaturvedi et al., 2015). The PEGylation Snail Cyst–PEG 4000 method is a physical modification that combines snail cyst and PEG-4000 in water until they interact molecularly through stirring and precipitation; the result is stable, hydrophilic composite microparticles with a suitable zeta potential (Momoh et al., 2021).

The Double Emulsion Solvent Evaporation method is based on the formation of a W/O/W double emulsion to encapsulate insulin in protective-coated microparticles; the result is stable microparticles that are resistant to degradation in the stomach and capable of selectively releasing insulin in the intestine, thereby increasing oral bioavailability (Ogbonna et al., 2025). In the emulsification–sonication method, the mucin–PEG mixture in the oil phase is broken down using ultrasonic waves to form microparticles; the result is uniform, stable, acid-resistant Eudragit-coated particles capable of encapsulating insulin without damaging its protein structure (A. Mumuni et al., 2020). The microfluidic mixing method relies on rapid mixing of two phases in microchannels so that PEGylated lipid nanoparticles (LNPs) form spontaneously; the result is LNPs that are stable in the gastrointestinal tract and capable of delivering insulin more effectively (Oyama et al., 2025). The thin film hydration method involves forming a dry lipid layer that is then hydrated to produce folate-targeted PEG-liposomes; the result is liposomes of uniform size that are stable in the gastrointestinal tract and capable of effectively encapsulating and delivering insulin (Yazdi et al., 2020).

The simple incubation PEGylation method is carried out by adding a negatively charged PGA-PEG solution to a positively charged nanocomplex suspension, which is then incubated so that spontaneous electrostatic interactions occur; resulting in PEG-coated nanocomplexes that are stable in intestinal fluid, capable of protecting insulin from degradation, exhibiting effective mucus diffusion, and having high transport ability through the CACO-2 cell monolayer (Niu et al., 2018). The B12–DSPE-PEG 3400-NH_2 conjugation method was performed by dissolving vitamin B12 in dry DMSO, succinylating it using succinyl anhydride and DMAP, activating it with EDC/NHS, and forming an amide bond with the amino group of DSPE-PEG 3400-NH_2 before being incorporated

into insulin-containing liposomes; the result is a liposome formulation that is stable in the gastrointestinal tract, improves insulin absorption and bioavailability, and improves biodistribution, thereby increasing delivery efficacy (Sarhadi et al., 2022). Finally, the PEG-Based SEDDS method involves forming HIP-BIS complexes from insulin glargine, which are then incorporated into PEG-SEDDS to form a stable nanoparticle system of ~40 nm; resulting in oral bioavailability of 1.15% and the ability to deliver insulin glargine orally, although still lower than PG/ZW-SEDDS (Haddadzadegan et al., 2024).

In protein formulation, the Post-Formulation PEG Addition before Lyophilisation method is carried out by adding PEG to the nanocapsule suspension after solidification but before lyophilisation; resulting in increased lysozyme release in SGF through the formation of large pores or, conversely, the formation of a layer that inhibits release (depending on the PEG concentration), protection of enzymes such as trypsin from gastric degradation, increased stability, and controlled release in the small intestine (Abu Abed et al., 2018, 2021). The SpyCatcher–SpyTag Covalent Coupling method utilizes covalent bonds between E. coli-modified SpyCatcher and SpyTag-labeled IL-1Ra in Tris-HCl solution; resulting in significantly higher resistance to GI conditions, stronger mucosal retention and adhesion, increased bioluminescence accumulation, and maintained bacterial and OMV activity (Yao et al., 2025). The mPEG-SPA PEGylation method was performed by adding mPEG-SPA to the phycocyanin solution; the results showed increased stability in GI conditions, maintenance of structure and function, and preservation of anticancer activity (Li et al., 2025).

The covalent coupling method of PEG–chitosan was performed by reacting PEG with chitosan before IFNα was added to the solution; the result was a system with lower permeability and reduced IFNα transport through the intestine compared to encapsulation in CT-NPs alone (Imperiale et al., 2019). The PEG-PLGA nanoprecipitation method uses PEG-PLGA copolymer dissolved in an organic solvent, which is then dripped into water to trigger nanoprecipitation; the result is stable nanoparticles with increased permeability (Feng et al., 2025). The PEG-coated albumin nanoparticle method involves a desolvation process to form albumin nanoparticles before coating them with PEG35; the result is PEG-coated nanoparticles that can penetrate mucus, improve stability, and increase the oral bioavailability of bevacizumab by up to 3.7% (Pangua et al., 2024). The thin film hydration–PEGylation method uses MPEG-DSPE (≥7–10%) to modify liposomes resulting from thin-film hydration; the result is PEG-coated liposomes capable of penetrating mucus and increasing oral absorption of FD4/FD10 with the highest absorption in the PEG-SPM formulation (Yamazoe et al., 2021).

In peptides, the thin film hydration method is performed by hydrating lipids containing TP5 in DMEM medium to produce PEGylated liposomes; the result is an increase in cellular uptake of TP5 without changing its transport rate (Liu et al., 2024). The SEDDS–HIP method is performed by forming a hydrophobic tuftsin–AOT complex through hydrophobic ion pairing before being incorporated into SEDDS to produce a stable nanoemulsion; the result is >90% protection of tuftsin from degradation and a fourfold increase in permeability compared to free tuftsin(Postina et al., 2025). The PEG2000–PEI polyplex method was performed by forming a neuropeptide Y–PEI complex using EDC/NHS and then conjugating it with PEG2000; resulting in a PEG-coated polyplex with 6-month stability, a half-life extension of up to 5.79 hours, and an increase in cancer cell apoptosis of up to 54% compared to free neuropeptide Y (Desai & Shende, 2022). The HA-PEG method in MOFs involves coating the antibody-MOF with hyaluronic acid–PEG to provide mucopenetration and targeting of inflammatory cells; resulting in improved gastrointestinal protection, a reduction in ROS >70%, significant suppression of proinflammatory cytokines, and therapeutic efficacy equivalent to or better than intravenous injection in both acute and chronic colitis models (Feng et al., 2025).

Table 1. Comparison of PEGylation Methods for Insulin, Proteins, and Peptides

Sample	Method	Result
Insulin	Polyethylene Glycol-p-Nitrophenyl Carbonate (PEG-NPC)	Enables precise modification of insulin molecules, improves their stability against enzymatic degradation, and produces PEG-insulin conjugates with better pharmaceutical properties for oral administration.
	Modified Solvent Diffusion-Solvent Evaporation	Produces insulin nanoparticles made from deoxycholic acid conjugated PEGylated polyhydroxybutyrate co-polymeric (DOCA-PHB-PEG) with ultra-small size (±10 nm), stable, and having a narrow particle size distribution (PDI 0.299).
	PEGylation Snail Cyst-PEG 4000	Produces stable, hydrophilic composite microparticles with appropriate zeta potential, and improves encapsulation efficiency, retention, mucoadhesion, protection of insulin from

		gastrointestinal degradation, modulation of burst release, and prolongation of hypoglycemic effects in in vivo tests.
	Double Emulsion Solvent Evaporation	Produces microparticle structures with a primary coating that improves stability and protects insulin from degradation.
	Sonication Emulsification	Provides resistance to the gastric environment and enters the particle matrix without damaging its protein structure.
	Microfluidic Mixing (Microfluidic-based Nanoprecipitation)	Produces homogeneous reversible charged lipid nanoparticles (LPNs) as oral insulin carriers with a stable structure, making the particles more resistant to the gastrointestinal environment.
	Thin Film Hydration	Produces folate-targeted PEGylated liposomes that carry insulin with uniformly sized liposome vesicles and high purity to eliminate free insulin that is not encapsulated.
	Conjugation of B12 with DSPE-PEG 3400-NH2	Produces stable formulations in the gastrointestinal tract, improves absorption and bioavailability, and enhances biodistribution, resulting in improved insulin delivery efficacy.
	PEG-Based SEDDS	Produces PEG-SEDDS measuring approximately 40 nm that can stably deliver insulin glargine (IG) for oral administration.
	Simple Incubation	Produces stable PGA-PEG-coated nanocomplexes in intestinal fluid that protect insulin from degradation and demonstrate effective diffusion through mucus and good transport across a single layer of CACO-2 cells, resulting in high insulin absorption.
Protein	Post Formulation PEG Addition Before Lyophilisation	Increases lysozyme release, forms large pores that enhance release, creates a layer that inhibits release. Additionally, it effectively protects the enzyme trypsin from gastric degradation, increases stability, and ensures controlled release into the small intestine.
	SpyCatcher-SpyTag Covalent Coupling	Higher stability under GI conditions, stronger intestinal retention and mucosal adhesion, greater bioluminescence accumulation, and maintained activity.
	Pegylation with PEG-SPA	Enhances stability under GI conditions, maintains structure and function, and preserves biological activity.
	Covalent coupling	Lower permeability, reducing IFNα transport through the intestinal epithelium.
	Nanopresipitasi with PEG-PLGA	Forming nanoparticles with a PEG layer on their surface that serves to enhance nanoparticle stability and permeability.
	Thin Film Hydration	PEGylated liposomes penetrate mucus better by increasing oral absorption of FD4/FD10, and the PEG-SPM formulation provides the highest absorption compared to regular liposomes or mucoadhesive GCS-liposomes.
	PEG-coated albumin nanoparticles	Producing PEG-coated albumin nanoparticles that can penetrate mucus more effectively and enhance oral absorption of bevacizumab, with the B-DS-NP-P formulation providing the highest bioavailability (3.7%) compared to free bevacizumab or nanoparticles without HIP complexes.

Peptide	Thin Film Hydration	Enhancing cellular uptake without altering transport rates.
	SEDDS–HIP	Produces stable tuftsin-loaded SEDDS capable of protecting peptides from degradation by intestinal membrane enzymes.
	Polyplex PEG 2000–PEI	Produces PEGylated and stable Neuropeptide Y Polyplex after complexation with PEI, PEGylation, and processing using a microfluidizer.
	HA-PEG on MOF	Improves stability in the gastrointestinal tract and provides anti-inflammatory effects equivalent to or better than intravenous injection, and reduces gastric release by approximately 40% to 40%.

CONCLUSION

PEGylation is a formulation approach that can have a consistent impact on improving biopharmaceutical characteristics, particularly through improved solubility, gastrointestinal stability, permeability, and reduced toxicity. Analysis of various PEGylation methods for insulin, therapeutic proteins, and peptides shows that each method offers different protective mechanisms and functional improvements, but all contribute to the same goal: optimizing the ability of biological molecules to survive and be absorbed via the oral route. This cross-method comparison illustrates that the selection of PEGylation techniques needs to be tailored to the properties of the molecule and the biological challenges faced, so that the formulation can achieve maximum efficiency. Thus, PEGylation serves not only as an additional modification, but as a strategic component in the development of new-generation oral bio-pharmaceutical delivery systems.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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