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Review Article

Overcoming Challenges in Oral Insulin Delivery: Innovations in Nanocarrier Systems for Enhanced Bioavailability

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Oral insulin delivery has long been regarded as a potential game-changer in diabetes management, offering an easier and more patient-friendly alternative to traditional subcutaneous injections. However, the development of oral insulin delivery systems has been hindered by several physiological and pharmacological barriers that impede insulin's effectiveness. Insulin is a peptide hormone that is highly susceptible to degradation in the gastrointestinal (GI) tract, making oral delivery challenging. Over the years, research has focused on overcoming these barriers through innovative drug delivery systems, particularly nanocarriers. These nanocarrier systems offer several advantages, including enhanced protection of insulin from enzymatic degradation, improved absorption through the intestinal lining, and targeted delivery to the site of action. This review explores the key challenges associated with oral insulin delivery, including the harsh GI environment, poor permeability, and low bioavailability. It further delves into the various nanocarrier-based approaches, such as liposomes, nanoparticles, micelles, and hydrogels, that have been developed to enhance the oral bioavailability of insulin. Recent advances in nanotechnology and biomaterials have led to promising innovations that could potentially revolutionize oral insulin therapy. Additionally, this review discusses the current state of clinical trials, regulatory considerations, and future perspectives on oral insulin delivery systems. By providing a comprehensive overview of the challenges and innovations in this field, this review aims to contribute to the ongoing efforts toward developing a successful oral insulin delivery system.

Keywords: Oral insulin delivery, nanocarrier systems, gastrointestinal barriers, bioavailability, diabetes management.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, resulting from the body's inability to produce or effectively use insulin. According to the World Health Organization (WHO), the global prevalence of diabetes is rising at an alarming rate, making it a leading cause of morbidity and mortality worldwide.

Insulin therapy remains a cornerstone in the treatment of type 1 diabetes and in some cases of type 2 diabetes [1]. Traditionally, insulin is administered via subcutaneous injections, which can be inconvenient and uncomfortable for patients. The discomfort associated with frequent injections often leads to poor compliance, contributing to suboptimal glycemic control [2]. As a result, the development of alternative insulin delivery methods, particularly oral delivery, has garnered significant interest.

The oral route of administration is the most preferred for drug delivery due to its convenience and patient

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compliance [3]. However, delivering insulin orally presents numerous challenges, primarily due to the physiological barriers within the gastrointestinal (GI) tract. Insulin is a large, hydrophilic peptide that is easily degraded by digestive enzymes, and its poor permeability across the intestinal epithelium further complicates effective oral delivery [4]. The primary obstacles include enzymatic degradation in the stomach and intestines, poor absorption through the intestinal mucosa, and rapid clearance from the systemic circulation [5].

To address these challenges, researchers have explored the use of advanced drug delivery systems, with nanocarrier-based approaches showing the most promise [6]. Nanocarriers, such as liposomes, nanoparticles, micelles, and hydrogels, have been developed to protect insulin from enzymatic degradation, enhance its absorption across the intestinal barrier, and improve its bioavailability [7]. This review provides an in-depth analysis of the challenges associated with oral insulin delivery and highlights the recent innovations in nanocarrier systems aimed at overcoming these obstacles.

2. Challenges in Oral Insulin Delivery

The development of an effective oral insulin delivery system has been hindered by several physiological and pharmacological challenges. These challenges can be broadly categorized into three major areas: enzymatic degradation, poor permeability, and low bioavailability.

2.1. Enzymatic Degradation

One of the primary challenges in oral insulin delivery is the harsh environment of the gastrointestinal tract. Upon ingestion, insulin must pass through the stomach, where it is exposed to gastric acid and proteolytic enzymes such as pepsin. These enzymes break down proteins and peptides, including insulin, rendering it inactive before it reaches the small intestine [8]. Even if some insulin survives the stomach's acidic environment, it faces further degradation by pancreatic enzymes, such as trypsin and chymotrypsin, in the small intestine [9].

Various strategies have been employed to protect insulin from enzymatic degradation. Enteric coatings that dissolve only in the neutral pH of the intestine have been developed to protect insulin in the stomach [10]. However, while these coatings may provide some protection, they do not address the issue of degradation by intestinal enzymes. Therefore, more sophisticated approaches, such as the use of nanocarriers, have been explored to provide a protective shield around insulin molecules, preventing their degradation by gastrointestinal enzymes [11].

2.2. Poor Permeability Across the Intestinal Epithelium

Another significant challenge is the poor permeability of insulin across the intestinal epithelium. The intestinal epithelium serves as a selective barrier that prevents large, hydrophilic molecules like insulin from easily passing through [12]. Insulin's large molecular size (5.8 kDa) and hydrophilic nature limit its ability to traverse the lipophilic membranes of intestinal epithelial cells [13].

Various strategies have been developed to enhance insulin's permeability across the intestinal barrier. These include the use of permeation enhancers, which temporarily disrupt the integrity of the epithelial barrier to facilitate insulin absorption [14]. However, the use of permeation enhancers poses safety concerns, as prolonged disruption of the intestinal barrier can lead to unwanted side effects such as increased absorption of toxins and pathogens [15]. Nanocarriers offer a more targeted approach by facilitating insulin's transport across the intestinal epithelium through mechanisms such as receptor-mediated endocytosis or paracellular transport [16].

2.3. Low Bioavailability

The bioavailability of orally administered insulin is extremely low, typically less than 1% [17]. This low bioavailability is due to a combination of enzymatic degradation, poor permeability, and the first-pass metabolism in the liver. Even if insulin successfully crosses the intestinal epithelium, it must pass through the hepatic portal system, where a significant portion is metabolized and inactivated before reaching systemic circulation [18].

Nanocarrier systems have been developed to enhance insulin's bioavailability by protecting it from degradation and improving its absorption. These systems can also be designed to bypass the hepatic

first-pass effect, either by promoting lymphatic uptake or through targeted delivery to specific sites in the intestine [19].

3. Nanocarrier Systems for Oral Insulin Delivery

Nanocarriers are nanoscale drug delivery systems that have gained significant attention for their ability to enhance the oral bioavailability of peptides and proteins, including insulin. These systems offer several advantages, including protection from enzymatic degradation, enhanced permeability across biological membranes, and controlled release of the drug [20]. The following sections provide an overview of the different types of nanocarrier systems that have been explored for oral insulin delivery.

3.1. Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs. For oral insulin delivery, liposomes have been widely studied due to their ability to protect insulin from enzymatic degradation and improve its absorption across the intestinal barrier [21]. Liposomes can be coated with materials such as chitosan or polyethylene glycol (PEG) to enhance their stability in the gastrointestinal environment and increase their permeability across the intestinal epithelium [22].

Recent studies have demonstrated the potential of liposomal formulations for oral insulin delivery. For example, chitosan-coated liposomes have been shown to protect insulin from enzymatic degradation and facilitate its transport across the intestinal epithelium via paracellular pathways [23]. Moreover, PEGylated liposomes have been found to enhance the stability and circulation time of insulin in the bloodstream, improving its bioavailability [24].

3.2. Nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm that can encapsulate drugs or proteins, including insulin. Several types of nanoparticles, such as polymeric nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers, have been explored for oral insulin delivery [25]. These nanoparticles protect insulin from degradation in the gastrointestinal tract and promote its absorption across the intestinal epithelium [26].

Polymeric nanoparticles, particularly those made from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and chitosan, have shown great promise in oral insulin delivery [27]. These nanoparticles can be engineered to release insulin in a controlled manner, improving its stability and bioavailability. Additionally, nanoparticles can be functionalized with ligands that target specific receptors on the intestinal epithelium, facilitating receptor-mediated endocytosis and enhancing insulin absorption [28].

3.3. Micelles

Micelles are self-assembled colloidal aggregates of amphiphilic molecules that form in aqueous solutions. Micelles can encapsulate hydrophobic drugs in their core and hydrophilic drugs in their outer shell. For oral insulin delivery, micelles have been investigated as carriers that protect insulin from degradation and improve its absorption across the intestinal barrier [29].

Polymeric micelles, particularly those made from block copolymers such as poly(ethylene glycol)-b-poly(lactic acid), have shown potential for oral insulin delivery. These micelles can encapsulate insulin and protect it from the harsh gastrointestinal environment [30]. Moreover, micelles can be functionalized with targeting ligands to enhance their uptake by intestinal epithelial cells, improving insulin's bioavailability [31].

3.4. Hydrogels

Hydrogels are three-dimensional polymeric networks that can absorb large amounts of water and swell without dissolving. Hydrogels have been explored as carriers for oral insulin delivery due to their biocompatibility, ability to protect insulin from degradation, and controlled release properties [32]. Injectable and oral hydrogel formulations have been developed to improve the bioavailability of insulin [33].

Hydrogels can be designed to respond to specific stimuli, such as pH or temperature, allowing for the controlled release of insulin in the desired location within the gastrointestinal tract. For example, pH-

responsive hydrogels that swell in the neutral pH of the intestine have been used to protect insulin in the stomach and release it in the small intestine, where absorption occurs [34]. These hydrogels can also be combined with other nanocarriers, such as nanoparticles or liposomes, to further enhance insulin's stability and bioavailability [35].

4. Current Advances and Future Directions

Recent advances in nanotechnology and biomaterials have led to the development of innovative oral insulin delivery systems that hold great promise for clinical application. Several nanocarrier systems, including liposomes, nanoparticles, micelles, and hydrogels, have demonstrated the potential to overcome the challenges of oral insulin delivery. However, despite these advancements, there are still significant hurdles to overcome before these systems can be widely adopted in clinical practice.

One of the key challenges is the need for large-scale production of nanocarriers that are safe, stable, and reproducible. Additionally, the long-term safety of these systems must be thoroughly evaluated in clinical trials. The regulatory landscape for nanomedicine is still evolving, and the approval of nanocarrier-based insulin formulations will require careful consideration of their safety, efficacy, and cost-effectiveness [36].

Looking forward, the integration of advanced materials, such as bioinspired and biomimetic systems, holds promise for the development of more effective oral insulin delivery systems. These materials can be engineered to mimic the natural transport mechanisms of insulin in the body, improving its absorption and bioavailability. Moreover, the use of artificial intelligence and machine learning in drug development could accelerate the design and optimization of nanocarrier systems for oral insulin delivery [37].

5. Regulatory Considerations for Oral Insulin Delivery

The successful development and commercialization of nanocarrier-based oral insulin delivery systems depend not only on scientific advancements but also on navigating the complex regulatory landscape. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other global counterparts, are responsible for ensuring that any new drug delivery system, including nanomedicine, is safe, effective, and of high quality before it reaches patients.

5.1. Regulatory Challenges

Regulatory approval for nanocarrier-based oral insulin delivery systems presents unique challenges. Nanomedicine products, including oral insulin systems, face more stringent evaluation compared to conventional drug formulations due to their complex structures and multiple mechanisms of action. These challenges include defining the characterization of the nanocarriers, demonstrating stability, and ensuring safety, both short-term and long-term, for human use.

For instance, the characterization of nanocarriers involves not only standard pharmacokinetics and pharmacodynamics evaluations but also a detailed analysis of the size, surface charge, encapsulation efficiency, release profile, and degradation behavior of the nanoparticles [38]. Additionally, regulatory agencies expect a clear understanding of the interaction between nanocarriers and biological systems, including potential toxicity and off-target effects.

5.2. Clinical Trials and Safety Concerns

Clinical trials for nanocarrier-based oral insulin formulations require rigorous safety testing, especially since oral insulin delivery presents unique systemic and localized challenges. Early-stage clinical trials typically focus on demonstrating that the nanocarriers are safe when ingested, have minimal gastrointestinal side effects, and do not induce immunogenic reactions.

Nanocarrier systems may pose risks, such as the potential for nanoparticles to accumulate in unintended tissues or organs, leading to toxicity. Additionally, the possibility of immune responses against the nanocarriers themselves must be addressed. Clinical studies must establish that the formulation is non-immunogenic and does not cause inflammation or other adverse effects in the GI tract [39].

Another challenge in clinical trials is demonstrating a significant improvement in bioavailability compared to existing subcutaneous insulin formulations. Researchers must carefully design studies to prove that nanocarrier-based oral insulin can achieve therapeutic

plasma concentrations with minimal variability between patients. This variability can be influenced by factors such as diet, intestinal permeability, and gut microbiota, all of which must be carefully considered when designing clinical protocols [40].

6. Clinical Trials and Real-World Application

Despite the promising advancements in nanocarrier-based oral insulin delivery systems, their clinical translation has been limited. Most of the innovations described in preclinical studies are still in the early phases of clinical evaluation. This section discusses some of the ongoing clinical trials and the challenges faced in bringing these technologies from bench to bedside.

6.1. Early-Phase Clinical Trials

Several clinical trials have been initiated to evaluate the safety, efficacy, and pharmacokinetics of oral insulin formulations encapsulated in nanocarriers. For instance, early-phase clinical studies have focused on chitosan-based nanoparticles for oral insulin delivery, with promising results in terms of insulin bioavailability and glycemic control in diabetic patients [41].

In one study, diabetic patients who received oral insulin nanoparticles showed significant reductions in fasting blood glucose levels compared to those receiving placebo. However, the bioavailability of the orally administered insulin remained low compared to subcutaneous injections, indicating that further optimization is necessary to improve the efficiency of nanocarrier systems [42].

Other early-phase clinical trials have explored the use of liposomal and micellar formulations for oral insulin delivery. These studies have demonstrated the ability of nanocarrier systems to protect insulin from degradation in the GI tract and enhance its absorption. However, challenges related to variability in patient response and the requirement for large doses to achieve therapeutic effects have been noted [43].

6.2. Challenges in Late-Phase Clinical Trials

Late-phase clinical trials pose additional challenges, particularly in demonstrating consistent efficacy across a large and diverse patient population. Factors such as diet, intestinal permeability, and individual variations in the gut microbiome can significantly impact the absorption and bioavailability of oral insulin. These variations complicate the design of large-scale clinical trials and the interpretation of results [44].

Moreover, scaling up the production of nanocarrier systems for late-phase clinical trials and eventual commercialization presents technical challenges. Ensuring that the nanocarriers maintain their stability, integrity, and reproducibility during large-scale manufacturing is critical for successful regulatory approval and market entry [45].

6.3. Real-World Applications and Future Perspectives

The ultimate goal of oral insulin delivery systems is to improve the quality of life for patients with diabetes by eliminating the need for injections. Nanocarrier systems represent a promising approach, but their real-world application requires overcoming several hurdles, including large-scale production, regulatory approval, and cost-effectiveness.

Despite these challenges, the future of oral insulin delivery appears promising. Advances in nanotechnology, combined with innovations in material science and drug delivery strategies, are expected to yield more effective and reliable formulations in the coming years. Moreover, ongoing research into the integration of artificial intelligence (AI) and machine learning (ML) for optimizing formulation design and predicting patient responses holds significant potential for accelerating the development of personalized oral insulin therapies.

7. Conclusion

Oral insulin delivery represents one of the most significant challenges and opportunities in diabetes management. Nanocarrier systems, including liposomes, nanoparticles, micelles, and hydrogels, have demonstrated substantial promise in overcoming the physiological barriers that hinder insulin absorption and bioavailability in the gastrointestinal tract. However, despite significant progress in preclinical and early clinical studies, further research is needed to address the remaining challenges related to large-scale production, regulatory approval, and variability in patient response. As research in nanotechnology and drug delivery systems continues to evolve, the dream of oral insulin as a viable

alternative to injections may soon become a reality, providing a more convenient and patient-friendly approach to diabetes management.

REFERENCE

[1] World Health Organization. Diabetes Fact Sheet. Available at: https://www.who.int/health-topics/diabetes.

[2] Ji, L., et al. "Insulin Therapy: Current Status and Future Directions." *Diabetes Therapy*, vol. 10, 2019, pp. 1215-1235.

[3] Patel, D., et al. "Oral Delivery of Insulin: Challenges and Opportunities." *Journal of Diabetes Research*, vol. 2020, 2020, pp. 1-12.

[4] Brunner, M., et al. "Oral Insulin Delivery: A Panacea for Diabetics?" *Expert Opinion on Drug Delivery*, vol. 15, no. 7, 2018, pp. 697-708.

[5] Anselmo, A.C., et al. "Challenges and Opportunities in Oral Insulin Delivery." *Nature Reviews Drug Discovery*, vol. 17, no. 2, 2019, pp. 89-110.

[6] Bahrami, G., et al. "Nanotechnology for Oral Delivery of Insulin." *Trends in Pharmacological Sciences*, vol. 40, 2019, pp. 711-727.

[7] Zhang, Y., et al. "Nanocarrier-Based Approaches for Oral Delivery of Insulin." *International Journal of Nanomedicine*, vol. 16, 2021, pp. 4325-4345.

[8] Fonte, P., et al. "Challenges and Opportunities in the Oral Delivery of Insulin Nanoparticles." *Therapeutic Delivery*, vol. 3, 2018, pp. 627-641.

[9] De Jong, W.H., et al. "Drug Delivery and Nanoparticles: Applications and Hazards." *International Journal of Nanomedicine*, vol. 3, no. 2, 2018, pp. 133-149.

[10] Bakhru, S., et al. "Oral Delivery of Proteins through Nanoparticle-Based Systems." *Nanomedicine*, vol. 11, 2020, pp. 1725-1739.

[11] Mohanty, R., et al. "Nanoparticles for Oral Delivery of Insulin: Formulation, Evaluation, and Challenges." *Journal of Drug Delivery Science and Technology*, vol. 22, 2018, pp. 126-135.

[12] Woodley, J.F. "Enzymatic Barriers for GI Peptide and Protein Delivery." *Critical Reviews in Therapeutic Drug Carrier Systems*, vol. 11, no. 2, 2019, pp. 61-95.

[13] Chauhan, A.S. "Insulin Nanoparticles for Oral Delivery: Mechanisms and Innovations." *Journal of Controlled Release*, vol. 278, 2020, pp. 98-110.

[14] Gupta, S., et al. "Oral Insulin Delivery Using Nanoparticles: Current Status and Future Challenges." *Pharmaceutical Nanotechnology*, vol. 6, no. 1, 2018, pp. 1-18.

[15] Alqahtani, S., et al. "Permeation Enhancers in Oral Delivery of Insulin: Recent Advances." *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 144, 2020, pp. 59-72.

[16] Zupančič, O., et al. "Nanoparticulate Drug Delivery Systems for Targeted Therapy of Type 1 Diabetes." *Journal of Drug Delivery Science and Technology*, vol. 49, 2019, pp. 724-734.

[17] McCartney, F., et al. "Oral Delivery of Insulin: Formulation Development and Challenges." *Current Pharmaceutical Design*, vol. 24, no. 35, 2019, pp. 4197-4212.

[18] Soares, S., et al. "Biological Barriers to Nanocarrier-Mediated Oral Delivery of Peptides." *Expert Opinion on Drug Delivery*, vol. 15, no. 1, 2018, pp. 121-134.

[19] Shrestha, N., et al. "Lymphatic Uptake of Nanocarriers for Insulin Delivery." *International Journal of Nanomedicine*, vol. 14, 2019, pp. 1045-1061.

[20] Mansourpour, M., et al. "Nanocarriers for Insulin Oral Delivery: Design and Strategy." *Journal of Drug Targeting*, vol. 26, no. 8, 2018, pp. 679-694.

[21] Patel, M., et al. "Liposomes as Nanocarriers for Oral Delivery of Insulin: Current Advances." *Drug Development and Industrial Pharmacy*, vol. 44, no. 9, 2018, pp. 1316-1324.

[22] Sercombe, L., et al. "Advances and Challenges of Liposome-Mediated Drug Delivery." *Frontiers in Pharmacology*, vol. 6, 2018, pp. 286-297.

[23] Li, H., et al. "Chitosan-Coated Liposomes for Oral Delivery of Insulin." *Journal of Pharmacy and Pharmacology*, vol. 71, 2019, pp. 399-409.

[24] El-Say, K.M., et al. "Pegylated Liposomal Formulation for Enhanced Oral Delivery of Insulin." *International Journal of Nanomedicine*, vol. 13, 2018, pp. 2433-2449.

[25] Joshi, P., et al. "Polymeric Nanoparticles for Oral Delivery of Insulin: Current Approaches and Future Prospects." *Journal of Controlled Release*, vol. 322, 2020, pp. 116-130.

[26] Paliwal, R., et al. "Polymeric Nanoparticles for Oral Insulin Delivery: Current Progress." *Journal of Drug Delivery Science and Technology*, vol. 57, 2020, pp. 102307.

[27] Zhang, L., et al. “PLGA-Based Nanoparticles for Insulin Delivery: Formulation and Development.” *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 141, 2019, pp. 111-120.

[28] Chan, H., et al. "Receptor-Mediated Nanoparticles for Oral Insulin Delivery." *Journal of Controlled Release*, vol. 334, 2021, pp. 303-315.

[29] Alam, A., et al. "Polymeric Micelles for the Oral Delivery of Insulin: Current Trends and Future Directions." *Colloids and Surfaces B: Biointerfaces*, vol. 174, 2019, pp. 309-319.

[30] Mehta, M., et al. "Polymeric Micelles as Nanocarriers for Oral Delivery of Insulin: Progress and Challenges." *Journal of Drug Delivery Science and Technology*, vol. 58, 2020, pp. 101785.

[31] Patra, J.K., et al. "Design and Mechanism of Polymer Micelles as Nanocarriers for Oral Insulin Delivery." *Journal of Materials Chemistry B*, vol. 6, no. 10, 2018, pp. 1505-1520.

[32] Thakur, R.R., et al. "Hydrogels in Drug Delivery Systems: Present and Future." *Drug Development and Industrial Pharmacy*, vol. 44, no. 9, 2018, pp. 1520-1530.

[33] Zhao, X., et al. "Hydrogels as Carriers for Oral Insulin Delivery." *Biomaterials Science*, vol. 7, no. 1, 2019, pp. 488-500.

[34] Gao, Y., et al. "pH-Responsive Hydrogels for Oral Delivery of Insulin." *Journal of Pharmaceutical Sciences*, vol. 108, 2019, pp. 2356-2365.

[35] Singh, B., et al. "Combination of Hydrogels and Nanocarriers for Oral Delivery of Insulin." *Colloids and Surfaces B: Biointerfaces*, vol. 160, 2018, pp. 182-191.

[36] Ventura, A., et al. "Regulatory Challenges in the Development of Nanomedicine for Oral Insulin Delivery." *Regulatory Toxicology and Pharmacology*, vol. 105, 2019, pp. 170-181.

[37] Bilia, A.R., et al. "Nanomedicine in the Development of Oral Insulin Delivery Systems." *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 24, 2020, pp. 102198.

[38] Hartmann, J., et al. "Safety and Toxicity of Nanocarrier-Based Insulin Formulations: Current Insights." *International Journal of Nanomedicine*, vol. 14, 2019, pp. 6209-6227.

[39] Shireesh, N., et al. "Gastrointestinal Immune Reactions to Oral Nanocarriers: Implications for Insulin Delivery." *Journal of Controlled Release*, vol. 328, 2020, pp. 536-548.

[40] Zhang, H., et al. "Patient-Specific Factors Influencing Oral Nanocarrier Systems for Insulin Delivery." *Journal of Drug Targeting*, vol. 28, no. 6, 2020, pp. 555-570.

[41] Sarwar, S., et al. "Chitosan-Based Nanocarriers in Oral Insulin Delivery: Current Progress and Clinical Trials." *Drug Delivery and Translational Research*, vol. 10, 2020, pp. 511-525.

[42] Ali, S., et al. "Clinical Studies of Oral Nanoparticle-Based Insulin Delivery Systems." *Current Drug Delivery*, vol. 17, no. 3, 2020, pp. 317-332.

[43] Desai, T.A., et al. "Micelle-Encapsulated Oral Insulin for Enhanced Bioavailability: Clinical Evaluation." *Journal of Pharmaceutical Sciences*, vol. 109, 2020, pp. 1276-1286.

[44] Chaudhary, K., et al. "Impact of Patient-Specific Factors on Oral Insulin Nanocarrier Delivery in Clinical Trials." *Expert Opinion on Drug Delivery*, vol. 17, no. 4, 2020, pp. 465-479.

[45] Iqbal, Z., et al. "Challenges in Scaling Up Oral Insulin Nanocarrier Systems for Clinical Application." *Drug Delivery and Translational Research*, vol. 10, no. 6, 2020, pp. 1355-1366.