International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 548-562 www.ijprajournal.com ISSN: 2456-4494

Polymeric Nanoparticles (PNPS) For Oral Insulin Delivery:

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Date of Submission: 15-09-2025 Date of Acceptance: 25-09-2025

ABSTACT:
Successful oral insulin administration can considerably enhance the quality of life (QOL) of diabetes patients who must frequently take insulin injections. However, oral insulin administration is seriously hampered by gastrointestinal enzymes, the wide pH range, and the mucus and mucosal layers, which limit insulin oral bioavailability to ≤2%. Therefore, a large number of technological solutions have been proposed to increase the oral bioavailability of insulin, among which polymeric nanoparticles (PNPs) are highly promising for oral insulin delivery. The search for an effective and reliable oral insulin delivery system has been a major challenge facing pharmaceutical scientists for many decades. Even though innumerable carrier systems that protect insulin from degradation in the gastrointestinal tract with improved membrane permeability and biological activity have been developed, a clinically acceptable device is still not available for human application. Efforts in this direction are continuing at an accelerated speed. One of the preferred systems widely explored is based on polymeric hydrogels that protect insulin from enzymatic degradation in the acidic stomach and deliver it effectively in the intestine. Swelling and deswelling mechanisms of the hydrogel under varying pH conditions control the release of insulin. The micro- and nanoparticle (NP) hydrogel devices based on biopolymers have been widely explored, but their applications in human insulin therapy are still far from satisfactory. The recently published research articles chosen for this review are based on applications of PNPs with strong future potential in oral insulin delivery and do not cover all related work. In this review, we summarize the controlled release mechanisms of oral insulin delivery, the latest oral insulin delivery applications of PNPs nanocarriers, as well as challenges and prospects. This review will serve as a guide to future investigators who wish to engineer and study PNPs and hydrogel-based devices as oral insulin delivery systems.

Keywords: Oral insulin delivery , Diabetes ,Quality of life (QOL) ,Gastrointestinal enzymes. ,pH range ,Mucus barrier ,Mucosal layer , Insulin bioavailability ,Polymeric nanoparticles (PNPs) ,Nanocarriers, Pharmaceutical challenges, Carrier systems, Gastrointestinal tract (GIT).

I. INTRODUCTION :

Diabetes mellitus is a common disease where the body cannot control blood sugar properly. By 2040, it is expected that around 642 million people will have diabetes. People with type 1 diabetes need insulin injections for life to keep their blood sugar normal and avoid serious problems like ketoacidosis. But taking daily injections can cause pain, skin problems, fat loss at the injection site, low blood sugar (hypoglycemia), allergic reactions, and other health issues.[1,2]

Many other ways to deliver insulin without injections have been studied, like oral (by mouth), nasal, lung (pulmonary), rectal, and skin (transdermal) methods. Among these, taking insulin orally (by mouth) is the most convenient and safe because it can work more naturally, like insulin produced by our body.[1,2]

However, oral insulin faces many challenges. It gets broken down quickly by stomach and intestine enzymes, has low absorption because of its large size, and doesn't easily pass through the intestine wall. To solve this, scientists are making new drug delivery systems (DDS) that improve insulin's stability and help it get into the body better.

By putting insulin inside special carriers (like nanoparticles), its absorption, stability, and safety can be improved. These carriers need to be safe, compatible with the body, and break down naturally. So, nanoparticles made from safe materials are being studied for delivering insulin by mouth.

This review talks about new methods for oral insulin delivery and diabetes treatment, including different types of nanoparticles

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(polymeric, lipid-based, and inorganic). It also discusses the clinical trials done so far.

Giving medicine less often and using fewer extra ingredients can make it easier for people—like kids, older folks, or those with long-term illnesses to take their meds properly. Peptides like insulin are hard to take by mouth because they break down in the stomach and don't easily pass through the gut. Shots work, but people don't like getting poked every day, and there's a chance of infection. So, there's a need for better ways to keep these kinds of drugs working in the body for longer.[2,3]

New delivery methods are being made to keep insulin stable, work better in the body, and last longer, so people don't need to take it as often. Since diabetes is a common problem, these systems are mainly tested for it especially with long-acting types of insulin like insulin glargine.

The shape of nanoparticles plays a big role in how they act in the body. Some studies say round particles are better, others say rod or disc shapes get inside cells more easily. In fact, rod-shaped ones with the right size seem to work better than round ones for getting into cells.

In our work, we made special polymer-based nanoparticles in different shapes using a method called crystallization-driven self-assembly. These particles, filled with silver ions, stuck better to cells and killed bacteria. Later, we tested them with insulin and found that these shaped particles helped insulin last longer in the body. The rod-shaped ones worked especially well, even better than the regular insulin or the round particles.[1,2]

Polyelectrolyte complex coacervation is widely used to prepare nanoparticles from ionic polymers, especially for encapsulating charged, water-soluble therapeutics like proteins and nucleic acids. By adjusting polymer properties and assembly conditions, nanoparticles with high encapsulation efficiency and bioactivity can be formed under mild conditions. Chitosan (CS), a natural polycation, forms complexes with nucleic acids and polyanions such as heparin and TPP to entrap active ingredients like insulin. Traditional mixing methods (manual, vortex, drop-wise) lack reproducibility and produce nanoparticles with broad size distributions, limiting scalability.

To overcome this, a flash nanocomplexation (FNC) method was developed, using a confined impinging jet (CIJ) or multi-inlet vortex mixer (MIVM) for rapid, solvent-free mixing of polyelectrolytes. FNC enables continuous production of nanoparticles (30–150 nm) with narrow size distribution. This study explores FNC for encapsulating insulin, a 5.8 kDa polypeptide, using CS/TPP to improve nanoparticle uniformity, stability, encapsulation efficiency, and reproducibility.[1,2]

CS/TPP is promising for oral insulin delivery due to biocompatibility and mucoadhesive properties of CS, which enhance epithelial transport. Unlike conventional drop-wise methods, FNC offers better control and quality. This study optimizes FNC conditions (flow rate, pH, concentrations), characterizes the nanoparticles, and evaluates their insulin delivery efficiency and glucose regulation in a diabetic rat model.[1,3]

II. ROLES & POSSIBLE MECHANISM OF NANOCARRIERS IN ORAL DRUG DELIVERY SYSTEM :

Nanocarriers are very helpful in making oral drug delivery better. They help improve how well a drug dissolves, stays stable, passes through the gut wall, and gets into the body. How drugs get absorbed in the stomach and intestines depends on their size. Tiny particles (smaller than 200 nm) can get into cells through a process called endocytosis, while bigger ones (1–10 microns) are taken up by special immune parts like Peyer's patches or gut macrophages. Nanocarriers help protect drugs from being broken down by stomach enzymes or thrown out by proteins like P-glycoprotein, which usually block drug absorption. They also help deliver drugs in a slow and targeted way, including things like proteins, peptides, small drugs, and genetic material.[4,3]

We can also change the surface of nanocarriers by adding ligands (special molecules) so they stick better to target cells and get absorbed more. Materials like chitosan help nanocarriers stick to the gut lining, improving how well they get into the body. Safe and biodegradable materials like PLGA, alginate, and others can make the drug release at the right place (like in the intestine) and protect drugs like insulin from getting destroyed in the stomach. Some ingredients like TPGS and cyclodextrins help keep the drug stable and stop it from being pushed out by the body. Research has shown that using these nanocarriers can keep drugs working longer—like insulin lowering blood sugar for many hours. In short, nanocarriers solve many problems of regular oral drug delivery and make treatments work better.[4]

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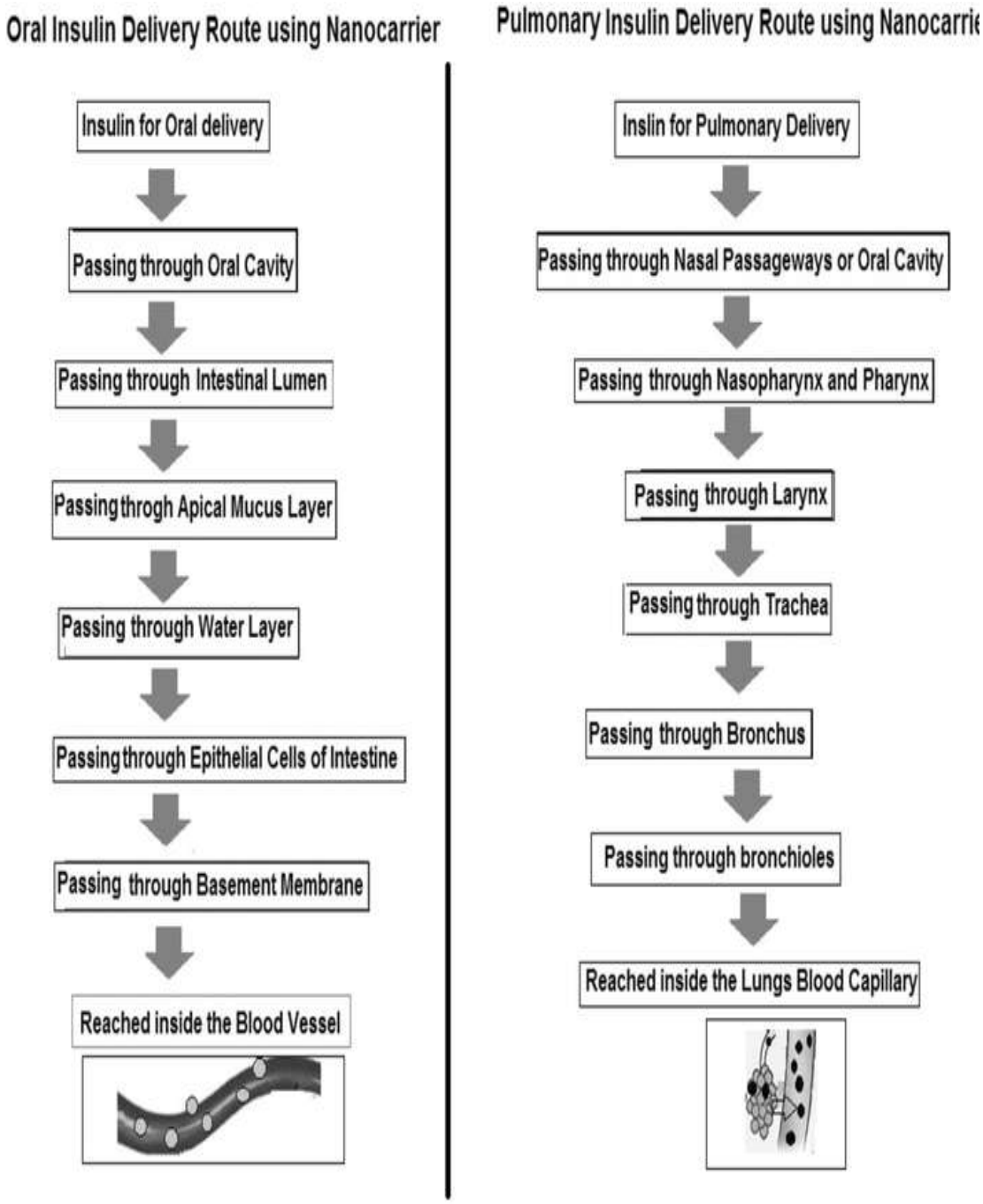

FIGURE: 1: diagram of oral insulin delivery route using nanocarrier and pulmonary insulin delivery route using nanocarrier. [4]

Nanocarriers based insulin delivery:

Due to the drawbacks of conventional injectable insulin, drugs have been modified through nanocarriers with targeting ligands for their selective and targeted delivery meant for oral and pulmonary delivery. Different nanoparticles developed to form stable and efficient insulin delivery system (Fig. 2) are discussed below.[4,5]

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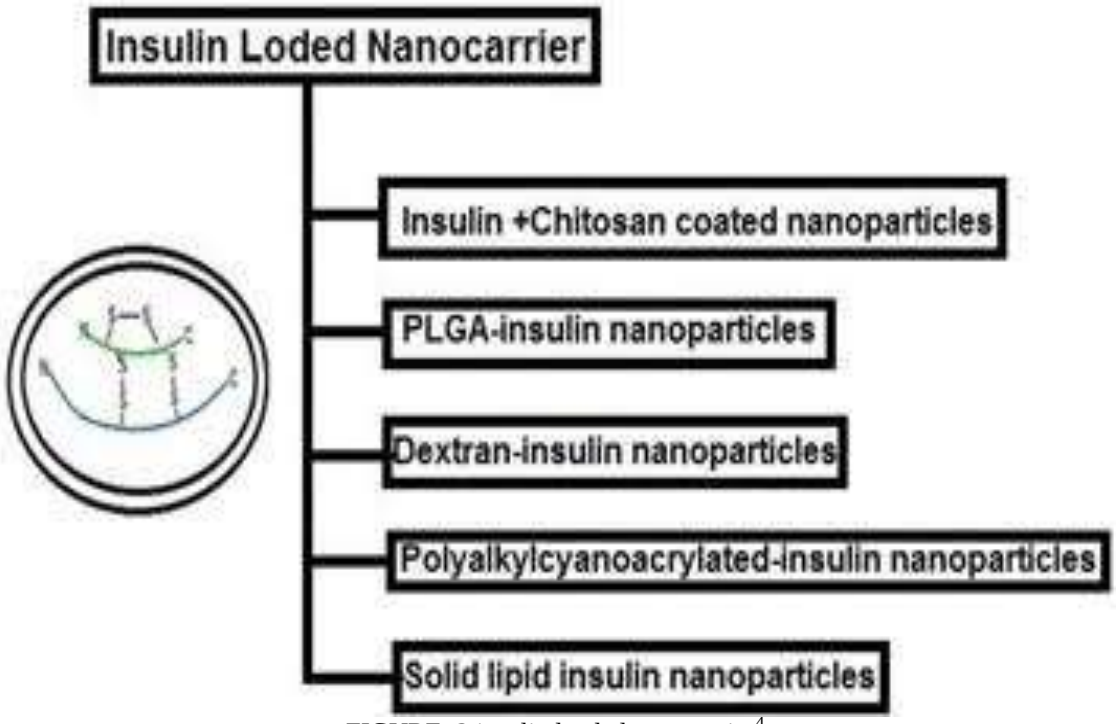

FIGURE: 2 insulin loaded nanocarrier[4]

III. BARRIERS OF INSULIN DELIVERY:

One of the biggest problems with giving insulin by mouth is that it gets destroyed in the digestive system before it can work. The stomach has a very acidic environment, which can damage insulin and make it useless. As insulin moves from the stomach to the intestines, the pH (acidity level) changes, which can also break or change insulin's structure and reduce its effect.

Besides the acid, the digestive system has strong enzymes that break down proteins. In the stomach, an enzyme called pepsin starts this process. In the small intestine, other enzymes like trypsin and chymotrypsin continue breaking insulin down. Chymotrypsin is especially harsh and destroys insulin much faster than trypsin. Bile salts in the intestine can also make insulin break apart into smaller pieces called monomers, which are more easily destroyed.[5]

There are also physical barriers that make it hard for insulin to be absorbed. A thick mucus layer lines the intestines and traps large, water-loving molecules like insulin. Even if insulin gets past the mucus, it still has to pass through tightly packed cells in the intestine. These cells have tight junctions between them, which block large molecules. Because insulin is large and doesn't mix well with fat, it has a hard time passing through or between these cells. That's why only a tiny amount of insulin is able to enter the blood.[5]

Another problem is that even if insulin gets inside the intestinal cells, certain enzymes like cytochrome P450-3A4 can break it down. Other proteins, such as P-glycoproteins, can push insulin back out of the cells. Insulin also changes shape depending on how concentrated it is—sometimes forming single units (monomers), pairs (dimers), or groups of six (hexamers). The single units are the easiest to destroy, which makes it harder to keep insulin stable.

Some scientists are trying a method called receptor-mediated transcytosis. In this method, insulin sticks to special receptors on intestinal cells, gets pulled inside, travels across the cell in a bubble, and is released on the other side into the blood. This method can work but is slow and doesn't absorb much insulin. To improve it, researchers are making tiny carriers called nanoparticles that can help insulin reach the right receptors using special tags like transferrin, lectins, or vitamin B12.[5]

In short, many chemical, enzymatic, and physical barriers make it very hard for insulin to work when taken by mouth. That's why its absorption is less than 1%. Scientists are working on new ways to solve these problems and make oral insulin a better option in the future.[5]

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3(A).**Chemical Barriers**:

The inside of our digestive system (GI tract) has different levels of acidity. The stomach is very acidic (pH 1–3), while the intestines are more neutral or slightly basic (pH 6.5–8). This change in acidity is a big problem for medicines like insulin that are made of proteins. These types of drugs are large and easily damaged. In the stomach, the strong acids (like hydrochloric acid) and salts (like sodium chloride) can break important bonds in insulin, causing it to lose its effect. To solve this problem, scientists have made special protective coatings (encapsulation) that can keep insulin safe from stomach acid and help it stay effective as it moves through the digestive system.[6,5]

3(B).**Enzymatic Barriers:**

Another big problem with giving protein-based medicines like insulin by mouth is that they get broken down by enzymes in the digestive system. This starts in the stomach with enzymes like pepsin and cathepsin, which are very good at cutting up proteins. Then, in the small intestine, more enzymes like chymotrypsin, elastase, and carboxypeptidases continue breaking down the drug. These enzymes make it hard for insulin to stay active and work properly when taken by mouth. [5,7]

Insulin is mostly broken down by trypsin, chymotrypsin, and carboxypeptidases found in the intestines. To stop this from happening, scientists have tested enzyme blockers such as aprotinin, bacitracin, trypsin inhibitors, and camostat mesilate, which help protect insulin. One example is a product from a company called Oramed (ORMD-0801), which uses a special ingredient from soybeans to block the enzyme trypsin.[7,5]

Even though this method shows promise, more research is still needed to make sure it's safe and works well. In recent years, scientists have also used new materials like liposomes, nanoparticles, polymersomes, and metal-organic frameworks to protect insulin from being destroyed so it can safely reach the intestines.[7,5]

3(C).**Physical Barriers:**

Inside the intestine, there is a thick, sticky layer called mucus. This layer has a negative charge and helps the body absorb water, nutrients, and small molecules. At the same time, it blocks harmful things like bacteria and viruses. Since the mucus is always being made and shed, it can trap and remove unwanted substances, including medicines like insulin, before they reach the wall of the intestine. This makes it hard for insulin to be absorbed when taken by mouth.[8,5]

To solve this, scientists have created special carriers that help insulin pass through the mucus. These carriers have neutral charge and are water-loving (hydrophilic), so they don't stick to the mucus. Even though this helps a little, only a small amount of insulin still gets through, and these methods have not yet been tested well in large groups of people.[8,5]

After passing the mucus, insulin faces another barrier: the intestinal lining, which is made of tightly packed cells. Drugs must pass through these cells (transcellular) or between them (paracellular) to enter the blood. Most drugs go through the cells, but this works best for small, fat-friendly drugs under 700 daltons in size. Insulin is big (5800 daltons) and water-based, so it cannot pass easily.

Scientists are now exploring ways to use the body's own transport systems, like the Fc receptor and bile acid transporter, to help insulin pass through the cells. But it's still unclear how safe or effective these methods are, especially since the tight spaces between the cells (called tight junctions) only let very small things through.[5]

To make insulin pass more easily, researchers also use permeation enhancers. These open up the tight junctions temporarily so insulin can enter the bloodstream. But there's a safety concern—if these gaps stay open too long, harmful things like bacteria and toxins might also get in. This could lead to infections, autoimmune diseases, or gut problems like inflammatory bowel disease.[5,8]

IV. TYPES OF POLYMERIC NANOPARTICLES USED IN ORAL INSULIN DELIVERY:

4.1 **natural polymers:**

Natural polymers come from living things and are getting a lot of attention for being eco-friendly. They can break down naturally with the help of tiny organisms and are safe for the human body. Because they are not harmful, they are great for use in drug delivery, especially for insulin. Some common natural polymers include sugars like chitosan, alginate, hyaluronic acid, and dextran, and proteins like gelatin. Chitosan is especially popular because it's easy to find in nature and has many helpful qualities for delivering insulin in the body.[9,10]

4.1.(A) **chitosan:** (CS) is a natural substance made from chitin, which is found in the shells of animals like crabs and shrimp. It is produced through a

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chemical process called alkaline deacetylation. Chitosan has positively charged parts that help it stick to the body's mucous membranes, like those in the nose or stomach. It is biodegradable (breaks down naturally), non-toxic, and low-cost, which makes it a good material for making insulin delivery systems.[9,11]

In one study, Bhumkar and team made tiny particles (nanoparticles) by combining chitosan with gold to deliver insulin through the mouth or nose. These methods are easier than injections but have some problems. For example, oral insulin is often destroyed by stomach acid and enzymes, while nasal insulin faces quick removal from the nose and has trouble passing through the nose lining. Still, their method helped lower blood sugar levels by 30.41% and 20.27%, which is a good result.[10,11]

Another study by Liu and team used chitosan mixed with PEG (a water-loving material) to create insulin carriers. They found that 10% PEG gave the best insulin absorption in the duodenum (part of the small intestine). They also tried mixing it with another material (GMC) and found this improved insulin absorption even more. This showed that making the surface of the particles more water-friendly helps insulin get through the intestine better.

In a separate study, Elsayed and team made insulin-carrying chitosan particles using a method called polyelectrolyte complexation (PEC). These particles protected insulin from being broken down by enzymes and released it slowly for up to 24 hours, helping to keep blood sugar steady.

At NIMS University in India, researchers created a nasal insulin delivery system using chitosan. This system slowly released insulin and kept its level steady in the blood, leading to better control of diabetes.[9,11]

Finally, Kondiah and team used trimethyl chitosan (TMC) to make fast-acting insulin particles. In tests on diabetic rabbits, the system lowered blood sugar by 54.19% within just 4 hours.

All these studies show that chitosan is a powerful material for insulin delivery. It helps protect insulin, stick to the body's tissues, and deliver the medicine without needles—especially useful for oral and nasal routes.[9,11]

4.1.(B). **Alginate**: it is a natural substance taken from seaweed. It is made of two types of sugar units: β-D-mannuronic acid and α-L-guluronic acid. Because of its carboxyl groups, alginate has a negative charge, which makes it useful in systems that respond to electric charges (called polyelectrolyte systems). Like chitosan (CS), alginate is biodegradable (breaks down naturally), non-toxic, sticks to mucus membranes, and causes low immune reactions, making it great for use in insulin delivery.[9,13]

When the environment is acidic or contains certain metal ions (like calcium), alginate can form a gel, which helps in slow and controlled release of insulin.

In one study, Mansourpour and team mixed alginate, chitosan, and β-cyclodextrin to make nanoparticles that could hold insulin. These particles combined the helpful properties of all three materials. The results showed better insulin absorption, but the study was done in a lab (not in animals or humans), so more testing is needed.[9,13]

In another study, a nanocomplex of alginate and chitosan was made for oral insulin delivery. It had an encapsulation efficiency of 63% and a particle size of 748 nm. This result showed that these materials can be useful in helping the body absorb insulin when taken by mouth.

Researchers then improved this system by coating it with calcium chloride, making it into nanoemulsions. These held 47.3% of the insulin and were about 488 nm in size. When tested on diabetic rats, the system helped reduce blood sugar levels over time, showing promise for oral insulin treatment.[9,13]

In another new approach, Verma and colleagues made special layered nanoparticles covered with calcium phosphate and added vitamin B12 to make the particles respond to pH changes in the body. They combined these with chitosan and alginate. When tested in animals, this system improved insulin absorption and kept blood sugar levels down for 12 hours.

Overall, using alginate with chitosan in different forms—like nanoparticles, gel systems, and complex coatings—looks very promising for oral insulin delivery. But more studies in live animals or people are still needed to understand how safe and effective these systems really are.

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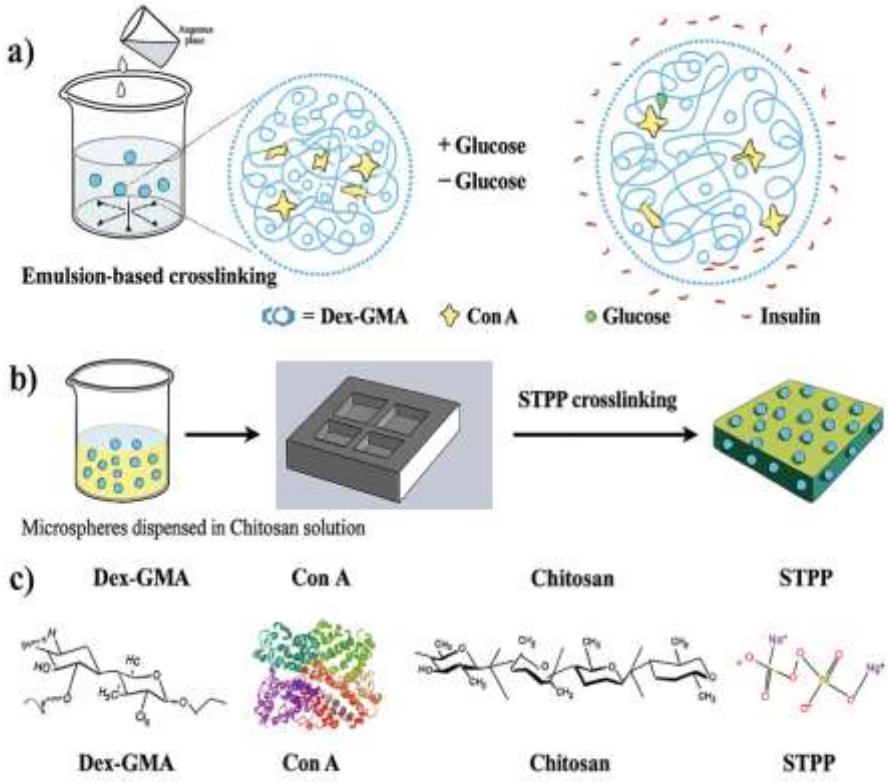

Figure 3.Schematic process of (a) fabricating ConA microspheres via w/o emulsion-based crosslinking, (b) preparation of the chitosan-based scaffolds for insulin delivery, and (c) chemical structures of dextran glycidyl methacrylate (Dex-GMA), concanavalin-A (ConA), chitosan, and sodium tripolyphosphate (STPP).[12,13]

4.1.(C)**Hyaluronic acid (HA):** it is also called hyaluronan, is a natural substance made from two sugar units: N-acetyl-D-glucosamine and glucuronic acid. These sugars are linked together in a straight chain using two types of bonds (β-1→3 and β-1→4). Unlike some other natural materials like chondroitin sulfate and alginate, HA has a negative charge and is very stable due to its structure. Because it comes from natural sources, HA is safe for the body, can break down naturally, and rarely causes immune reactions. This makes it a good choice for use in drug delivery systems (DDSs).[14]

In one study, researchers led by Liu made tiny carriers using calcium carbonate and coated them with HA to deliver insulin by mouth. When tested in diabetic rats, this method helped lower blood sugar levels effectively, almost like insulin injections. Another team, led by Han, created HA nanoparticles that respond to pH changes. These particles protect insulin from being destroyed in the stomach and gut. The particles were about 182 nanometers in size and could hold 95% of the insulin. Tests showed that these HA particles helped insulin pass into the body and reduce blood sugar levels.[9,14]

These studies show that HA could be a useful material for delivering insulin by mouth. However, more research is still needed—both in labs and in live animals—before HA can be considered better or equal to other materials like chitosan and alginate.[14]

4.1.(D)**Dextran**: it is a water-soluble polysaccharide produced by certain bacteria. It is a complex sugar molecule made mostly of α-D-(1→6) glucose units, with some branching at the 1,3 position. Because dextran is both biodegradable and biocompatible, and contains –OH (hydroxyl) groups, it can undergo various chemical modifications. Its hydrophilic (water-attracting) nature and compatibility with the body make it suitable for drug delivery applications, especially in combination with insulin for improving its performance in the body.[9]

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In one study, researchers led by Lopes developed core-shell nanoparticles using dextran. They placed insulin in the center, surrounded by an alginate core and coated it with chitosan (CS) and albumin. The dual coating with CS and albumin helped protect insulin from being broken down by digestive enzymes, and also stabilized the particles across different pH levels. About 70% of insulin stayed inside the nanoparticles when tested in a simulated stomach environment. Moreover, when tested in conditions similar to the intestines, these particles released insulin slowly and helped improve its absorption by interacting with gut cells.[9,16]

Another research team in Iran prepared nanoparticles using a blend of dextran and poly-lactic-co-glycolic acid (PLGA) to deliver insulin orally. By mixing insulin in water with the dextran–PLGA copolymer, self-assembling nanoparticles were formed. These particles showed high insulin loading (about 30%) and an encapsulation efficiency of 90%, using a 10:3 polymer-to-insulin ratio. In lab tests, the insulin-loaded nanoparticles had higher permeability and better bioavailability than free insulin—around 9.77% compared to 0.62% when given at a dose of 100 IU/kg.

In India, Chalasani and colleagues explored a new approach by attaching vitamin B12 (VB12) and intrinsic factor ligands to dextran nanoparticles for oral insulin delivery. They tested various molecular weights of dextran to find the most effective formulation using an emulsion technique. The particles showed insulin entrapment between 45% and 70%, and were able to protect insulin from degradation by 65% to 83%. Dextran with a molecular weight of 70,000 (70K) gave the best results. Further tests in diabetic rats (induced using streptozotocin) showed a significant drop in blood glucose levels—about 70% to 75%. The formulation also showed a strong antidiabetic effect lasting for 54 hours, with a pharmacological bioavailability of 29.4%.,[15,16]

These promising findings suggest that dextran, especially when combined with VB12 and other protective agents, has great potential as a platform for oral insulin delivery.[9]

4.2. **Synthetic polymer:**

Synthetic polymers tend to exhibit hydrophobic characteristics along with superior chemical and mechanical strength when compared to natural (nonsynthetic) polymers. This increased mechanical strength contributes to their slower degradation, making them highly durable as biomaterials [55]. By blending synthetic and natural polymers, researchers can tailor their properties, resulting in more effective insulin delivery systems with improved therapeutic outcomes.[9,17]

4.2.(A) **PLGA**:PLGA (poly(lactic-co-glycolic acid)) is a commonly used material for delivering drugs because it allows for controlled and slow release over time. When it breaks down in the body, it turns into lactic acid and glycolic acid—two natural substances that the body can safely handle. This makes PLGA a safe and biodegradable option for delivering insulin.

In one study, researchers (Sateesh et al.) created a special formula using 1.6% zinc insulin inside PLGA nanoparticles. They also added iron oxide and fumaric anhydride to improve how the insulin works when taken by mouth. This formula worked 11.4% better than insulin injected into the body cavity (intraperitoneal), helping to control blood sugar levels more effectively. The method used to make the nanoparticles—called solvent evaporation—led to 5% drug loading and 75% of the insulin being successfully packed inside. Depending on the method used, the amount of nanoparticles made ranged from 55% to 99%. However, some methods (like the solid o/w technique) caused an early and fast release of insulin, and the particles were smaller (223–243 nm) and held less insulin (only 0.3%–12%).[18]

In another study from China, scientists created PLGA nanoparticles that avoided early insulin release in acidic environments (like the stomach). Instead, insulin was released slowly over 11 days, and tests on animals showed that this helped lower blood sugar levels effectively over time.

Researchers also tested PLGA combined with chitosan (a natural material). The chitosan coating helped the particles stick to the intestines and pass through more easily, thanks to their small size and sticky (mucoadhesive) nature. These particles released insulin based on the pH (acidity level) of the surroundings, which helped improve how well the treatment worked.

At Huazhong University of Science and Technology, scientists developed another system: insulin-loaded PLGA nanoparticles placed inside a PVA (polyvinyl alcohol) gel. This version had 72.6% insulin packed inside, and tests on diabetic mice showed it could lower blood sugar for up to 24 hours.[9,18]

Even though PLGA is a very useful and flexible material that can mix with other natural

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and synthetic substances or metals, scientists still need to carefully study its early-release effects. This is important to make sure it works well as an insulin delieffectively..[18]

4.2.(B) **polyamino acids:**Amino acids are very important in living organisms because they help build proteins and affect how they work. Some synthetic (man-made) polymers include amino acid side chains, which makes them easier to design and useful for medical purposes.[9,19]

One example is the development of chitosan/poly-γ-glutamic acid (CS/gPGA) nanoparticles. These were made by mixing chitosan and polyglutamic acid in a solution with magnesium sulfate ($MgSO_4$) and tripolyphosphate (TPP). These tiny particles were designed to carry insulin through the digestive system. In animal tests, they were able to lower blood sugar for about 10 hours, and 15.1% of the insulin was successfully absorbed.

Another version, called TMC/gPGA nanoparticles (using a modified form of chitosan called N-trimethyl chitosan), may work better for insulin delivery through the entire intestine. This is because their performance matches well with the pH (acidity level) found in different parts of the gut.[19]

In a separate study, Sonaje and colleagues developed a system where insulin-loaded CS/gPGA nanoparticles were coated with gelatin that only breaks down in the intestine. This coating protected the insulin from stomach acids and enzymes. As a result, insulin reached the small intestine safely and lowered blood sugar steadily over time.[9]

Chinese researchers also made a multifunctional chitosan-based nanoparticle that included special chemical groups: carboxyl, phenylboronic acid (PBA), and L-valine (LV). Lab tests showed these nanoparticles were safe (non-toxic) and responded to glucose levels in the body. Animal studies showed that this system improved insulin absorption and helped control blood sugar effectively.[19]

4.2.(C)**pluronics**:

Pluronics, also known as poloxamers, are special types of polymers made up of three connected blocks: two water-loving (hydrophilic) parts on the outside and one water-hating (hydrophobic) part in the middle. Their structure is written as PEO-PPO-PEO, where PEO is polyethylene oxide and PPO is polypropylene oxide. Although they don't dissolve in water, they are amphiphilic, meaning they can interact with both water and fats. They are usually white, waxy granules that have no taste or smell.[9,20]

One special feature of pluronics is that they respond to temperature changes—they can turn into gels when they warm up. This makes them useful for drug delivery, especially for making gels that can be injected and form a solid deposit in the body to slowly release medicine like insulin. Pluronics are also biodegradable, meaning they break down naturally in the body.

They are grouped based on how they look (solid, paste, or liquid) and how heavy their molecules are (molecular weight).

In one study, Shu and colleagues tested a nanoparticle system made from poly(lactic acid) and pluronic to carry insulin. They tested it in the lab and in animals, and it showed good insulin absorption when taken by mouth.[20]

Another study by Xie et al. explored the use of pluronic 85 combined with folic acid and PLGA (a common biodegradable polymer) for oral insulin delivery. They created pluronic F127–grafted PLA nanoparticles and found that insulin was released in two stages (biphasic release). In animal tests, blood sugar levels started to drop about 4.5 to 5 hours after taking the insulin, and the effect lasted for over 18.5 hours.

Because pluronics can easily form gels inside the body, they're useful for making injectable insulin depots. These gels slowly release insulin in a controlled way. Pluronics can also be used to make nanogels, nanoparticles, or nanocarriers, which are tiny systems that can respond to body signals (like temperature or pH) to release insulin over time.[20]

While pluronics look very promising for insulin delivery, many other tiny (nano-sized) systems have also been developed to create the best possible insulin delivery method. These other types of nanosystems will be explained in the following sections.[19,20]

V. RECENT INNOVATION ORAL INSULIN DELIVERY:

With the growing number of people around the world developing diabetes, finding a way to take insulin by mouth (instead of by injection) could make life much easier for many patients. Even though creating a successful oral insulin system has been a major challenge for decades, research in this area continues to grow and move forward.[5,]

In the next sections, we will look at some of the most important and promising technologies

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that have been developed in recent years. We will focus on those that have a strong chance of being tested in humans and discuss ideas for future improvements in oral insulin delivery.[5,21]

5.**A.ionic liquid for oral insulin delivery**: Ionic liquids are special types of salts that stay in liquid form below 100°C. They are made up of an organic positive ion (cation) and an organic or inorganic negative ion (anion). Because of their unique properties—like being thick or thin (viscosity), water-loving or water-hating (hydrophilicity/hydrophobicity), ability to dissolve different substances (solubility), and breaking down safely in the body (biodegradability)—they have become useful in recent years for helping deliver both small and large medicines.[5,21]

Recently, Banerjee and his team created a new type of oral insulin using an ionic liquid made from choline and geranate, called CAGE. The insulin and CAGE mixture can be made in just one simple step and doesn't require any changes to insulin's structure or the use of complicated nanoparticles. Lab studies showed that this insulin-CAGE mixture remained stable for 2 months at room temperature and for at least 4 months in the fridge, without losing its effect.

Later, Palanisamy et al. used computer simulations to study how CAGE interacts with insulin in water. They found that a certain amount of CAGE molecules stick closely to the insulin, pushing water molecules away from its surface, which helps protect it.

In animal experiments, when insulin-CAGE was directly given into the small intestine (jejunum) of healthy rats, it helped the insulin absorb well into the body. When they put insulin-CAGE into special capsules that dissolve in the intestine and gave them orally to rats, it lowered blood sugar levels just as well as injected insulin. Even better, the effect lasted for up to 12 hours. The success of this method came from CAGE's ability to:

Protect insulin from being broken down by enzymes, help it pass through mucus in the intestine, and open tight spaces between cells (tight junctions), allowing insulin to pass through. When researchers checked the rats' intestines after 7 days of daily treatment, they found no harmful changes, showing the method is likely safe. Later, Samir Mitragotri's team developed a gel version of CAGE by combining it with polyvinyl alcohol (PVA) to make a sticky ionogel patch (called a CAGE-patch) that can stick to the intestines and slowly release insulin. Although its full effect in living animals hasn't been tested yet, it shows great promise for future oral insulin delivery[21,22]

5.B.**silica nanoparticles as physiochemical permeation enhancers for oral insulin delivery:** Nanoparticles are tiny particles that can carry drugs like insulin because of their special properties and large surface area. They can hold a lot of medicine and release it in a controlled way. Common types include lipid, polymer, silica, metal-organic, and hybrid nanoparticles.

Inorganic nanoparticles, like mesoporous silica nanoparticles, are strong and stable and have been studied for oral insulin delivery. They can hold a lot of insulin due to their porous structure. However, since they don't break down easily in the body, their long-term safety—especially for people with diabetes who need daily insulin—needs careful study.[23]

Recently, Whitehead et al. discovered that small, negatively charged silica nanoparticles (50 nm) can help insulin pass through the gut by temporarily opening tight junctions between cells. In healthy mice, this method led to 85% insulin absorption, but in diabetic mice using capsules, the effect was much lower (below 30%).[23]

They found that the nanoparticles work by binding to integrins and activating an enzyme called MLCK, which causes the cell structure to relax and open tight junctions, allowing insulin to pass through.

Importantly, no harmful effects or inflammation were seen 24 hours after giving the nanoparticles. However, because silica is not biodegradable, more studies are needed to ensure long-term safety before this method can be used in real treatments.[5,23]

5.C.**zwitterionic nano/micro system for oral insulin delivery:**

Most current methods for improving oral insulin absorption involve opening tight junctions between cells in the intestine. While this helps insulin pass through, it can also cause side effects like infections, inflammation, or even autoimmune diseases. So, scientists are now looking for safer ways that don't involve opening these junctions.[24,25]

Inspired by how viruses move through mucus, researchers developed a zwitterionic micelle system (called DSPE–PCB) that has a special surface like viruses. This allows insulin to pass through mucus and intestinal cells safely, using a natural protein transporter called PAT1, without disturbing tight junctions.[25,26]

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Volume 10, Issue 5 Sept - Oct 2025, pp: 548-562 www.ijprajournal.com ISSN: 2456-4494

This method showed excellent results in diabetic rats, with over 40% insulin absorption, which is much higher than traditional methods (less than 10%). Even after giving the insulin-micelle system twice a day for two weeks, there were no signs of gut damage or leakiness.[25,26]

Other scientists also created similar systems using zwitterion-coated nanoparticles or crosslinked microcapsules, which helped insulin move through mucus and intestinal cells effectively. These methods worked well in animals like mice, rats, and pigs, and may be useful for delivering other protein-based drugs in the future.[24,25,26]

5.D. **Devices for oral insulin delivery**:

In addition to chemical and nanoparticle methods, device-based technologies have been developed to help insulin pass through the digestive system more effectively.[27]

One such device is the LUMI capsule, which contains tiny microneedles that unfold and inject insulin into the small intestine. When the capsule reaches the right pH level (above 5.5), it opens and pushes out the microneedles. Studies in pigs showed that this device delivers insulin quickly (within 15–30 minutes) and safely, without harming the tissue.[28]

Another device, called SOMA, is inspired by the shape of a tortoise. It can self-orient in the stomach and deliver insulin directly through the stomach lining. This makes insulin delivery more predictable than relying on absorption in the intestines. SOMA also worked well in animal tests.

However, both LUMI and SOMA had some issues:

They could only hold small insulin doses (300–700 micrograms).

They had slower or limited insulin release.

The insulin had to survive the harsh digestive fluids before it was injected.

To fix this, scientists made a better version called L-SOMA, which can inject liquid insulin directly into the stomach wall. This version works faster and can deliver larger doses (up to 4 mg) with up to 80% absorption, showing great promise for real use in people.[5,27,28]

VI. NANOMEDICINE TECHNOLOGY ADVANCEMENTS FOR ORAL INSULIN DELIVERY:

New methods for delivering insulin are now being used instead of traditional injections. These new methods are designed to release insulin exactly where it's needed in the body, using special carriers that work in different ways depending on how they're made.

One of the most promising methods uses nanocarriers—tiny particles that can enter cells more easily because of their small size. These nanocarriers have both advantages and disadvantages, depending on their structure, and scientists have created many different types for insulin deliveryIn the next sections, we will explore the different types of nanocarrier systems and how they help in delivering insulin more effectively.[9]

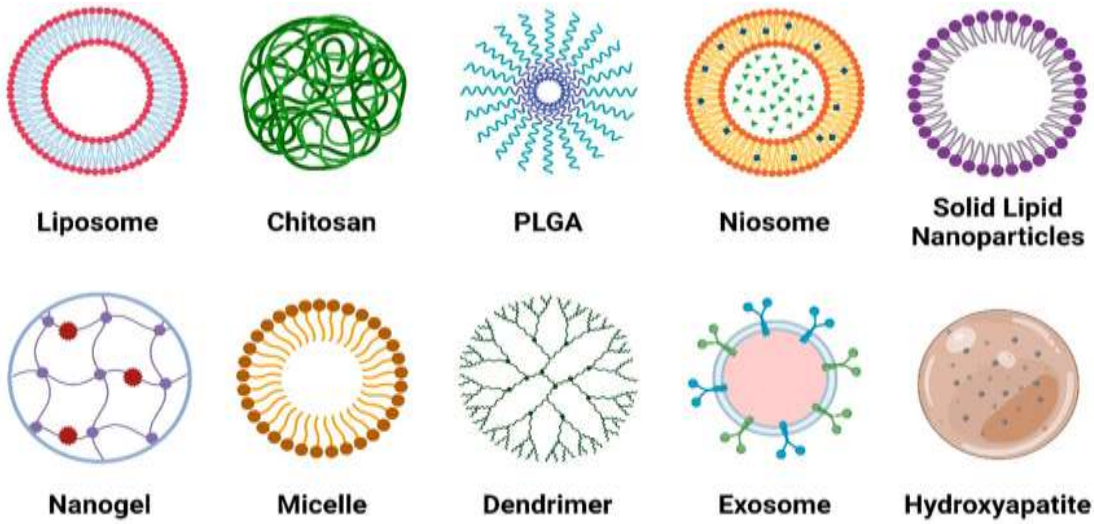

Figure 3 : structural overview of nanocarriers used for insulin delivery: [9]

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Volume 10, Issue 5 Sept - Oct 2025, pp: 548-562 www.ijprajournal.com ISSN: 2456-4494

Table 1 : systems for delivering insulin nanoparticles to treat diabetes mellitus:

Sr.no.	Nanocarriers	Administration route	Effects in vivo	Challenge
1	Liposomes (31)	Oral	-increase hypoglycemic effects. -improved insulin absorption& oral bioavailability	-non uniform coating -lower entrapment efficiency compared to polymeric carries.
2	Chitosan(32)	oral/nasal	-overcome mucus and epithelial barrier -increase bioavailability	-insulin loading efficiency in chitosan nano-formulation. -ensuring stability & controlled release of insulin.
3	PLGA(33)	**Oral**	**-reduction of blood sugar level. --prolonged hypoglycemic effects.**	**-potential lack selectivity in interacting with mucosal surfaces.**
4	**Niosome (36)**	**Oral/mucosal**	**-stabilized again st enzymatic degradation oral and vaginal delivery. --prolonged**	**-low entrapment efficiency. -instability due to alternation in molecular arrangements of surfactants.**
5	**Nanogels (34)**	**Oral**	**-improved hypoglycemic effects -increase bioavailability.**	**-specific size & stability -precise controlled release -tissue penetration -biocompatibility and immunogenicity.**

VII. FUTURE DIRECTION:

Despite significant advancements in the development of polymeric nanoparticle (PNP)-based systems for oral insulin delivery, several challenges persist, particularly in achieving consistent bioavailability, ensuring long-term safety, and scaling up for clinical use. Future research should consider the following directions:

7.1. **Multifunctional Nanocarriers with Responsive Release**

Designing stimuli-responsive nanocarriers (e.g., pH-, enzyme-, glucose-, or temperature-sensitive systems) could enable targeted and controlled insulin release at specific sites within the gastrointestinal tract. Incorporating smart polymers that respond to intestinal pH or glucose levels would improve therapeutic efficacy and reduce systemic side effects.[37]

7.2. **Biodegradable and Biosafe Materials**

Long-term toxicity and accumulation of non-degradable materials remain a concern. Future formulations should prioritize biodegradable and metabolizable nanomaterials, especially for systems using inorganic carriers like silica or metal-based particles.[38]

7.3. **Targeting and Transport Enhancers**

More work is needed to improve transport across intestinal epithelium, such as ligand-functionalized nanoparticles targeting transferrin

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Volume 10, Issue 5 Sept - Oct 2025, pp: 548-562 www.ijprajournal.com ISSN: 2456-4494

receptors, vitamin B12 pathways, or bile acid transporters. This could boost receptor-mediated transcytosis and enhance oral absorption.[39]

7.4. **Clinical Translation and Human Trials**

Most studies remain in preclinical stages. Translating these promising systems into human trials requires overcoming manufacturing, regulatory, and scalability barriers. There is a pressing need to conduct long-term clinical studies focusing on safety, immunogenicity, and pharmacolong-term[40]

7.5. **Device–Nanocarrier Integration**

Integrating ingestible devices (e.g., LUMI or SOMA capsules) with PNPs could enhance delivery precision. These systems can bypass gastrointestinal degradation and deliver insulin directly to the intestinal wall. Such hybrid systems could represent the future of oral protein delivery.[41]

7.6. **Artificial Intelligence for Formulation Optimization**

AI and machine learning can accelerate formulation design, predict pharmacokinetic behavior, and optimize nanoparticle characteristics (e.g., size, charge, composition). This approach could reduce trial-and-error in drug development.[42]

7.7. **Regulatory and Manufacturing Considerations**

Advances in GMP-compliant, scalable manufacturing techniques—such as flash nanoprecipitation or microfluidic systems—are critical to translate lab-scale systems into marketable oral insulin products.[43]

VIII. CONCLUSION:

Oral insulin delivery remains a transformative goal in diabetes care, with the potential to drastically improve patient compliance and quality of life by eliminating the need for frequent injections. Despite numerous physiological and biochemical barriers—including enzymatic degradation, acidic pH, mucus entrapment, and epithelial impermeability—polymeric nanoparticles (PNPs) have emerged as a highly promising strategy to overcome these challenges. Both natural (e.g., chitosan, alginate, hyaluronic acid, dextran) and synthetic polymers (e.g., PLGA, polyamino acids, pluronics) offer unique advantages in protecting insulin, enhancing mucosal adhesion, and enabling controlled release. Recent innovations, such as ligand-targeted nanoparticles, zwitterionic micelles, and hybrid device-nanoparticle systems (e.g., SOMA and LUMI), have demonstrated significant in vivo efficacy, and even human trials are on the horizon. However, key hurdles remain—especially regarding long-term safety, reproducibility, and large-scale manufacturing. Future success will depend on the development of smart, stimuli-responsive, biodegradable carriers combined with precision delivery techniques and AI-driven formulation tools. With sustained interdisciplinary efforts, PNP-based oral insulin therapies may soon become a viable and patient-friendly reality in diabetes management

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