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Oral Insulin Delivery by Utilizing Nanotechnology

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Abstract:
Diabetes is a chronic metabolic condition defined by a shortage of insulin in the body, resulting in blood glucose regulation failure. Diabetes patients typically require frequent insulin injections to maintain normal blood glucose levels, which can be an unpleasant method of administration. Long-term medication injection places a significant physical and psychological strain on diabetes patients. The creation of oral insulin formulations is currently a hot and difficult topic in the world of medicine and pharmacy in order to increase patients' adaptability to insulin use and lessen the pain caused by injection. Thus, oral insulin administration is a promising and convenient means of relieving patients. However, because insulin is a peptide medication, it is easily destroyed by stomach enzymes. Furthermore, insulin has a high hydrophilicity, a big molecular weight, and a very limited oral bioavailability. To address these issues in clinical practice, oral insulin delivery nano-systems were devised and built using a rational combination of various nanomaterials and nanotechnology. Such oral nano-systems offer the benefits of high flexibility, small size, simple processing, long-lasting pharmacological activity, and drug controlled-release, which can effectively improve insulin oral bioavailability and efficacy. This study highlights the basic principles and recent accomplishments in oral insulin delivery nano-systems, including the physiological absorption barrier of oral insulin and the development of materials to nanostructures for oral insulin delivery nano-systems.

***Index Terms*:** oral insulin, absorption barrier, nanodrug delivery system, bioavailability

Introduction:
Diabetes is one of the top 10 diseases affecting human health worldwide, and it is also one of the 21st century's fastest-growing global health issues. Diabetes morbidity accounted for 9.63% of all patients worldwide in 2019, and diabetes kills about 4.6 million people each year [1,2]. Diabetes is classified as Type I (autoimmune reaction-induced) or Type II (insulin resistance-induced) [3]. Patients with T1DM almost totally lose their insulin secretion function, necessitating the use of exogenous insulin. Patients with T2DM are insulin resistant, which means their blood glucose levels are not sensitive to insulin [4,5]. Patients in the early stages of T2DM can be managed with a sensible diet, physical exercise, and oral hypoglycemic medications like as metformin and -glucosidase inhibitors. However, in the late stages of T2DM, blood glucose levels can only be regulated by direct insulin administration [6]

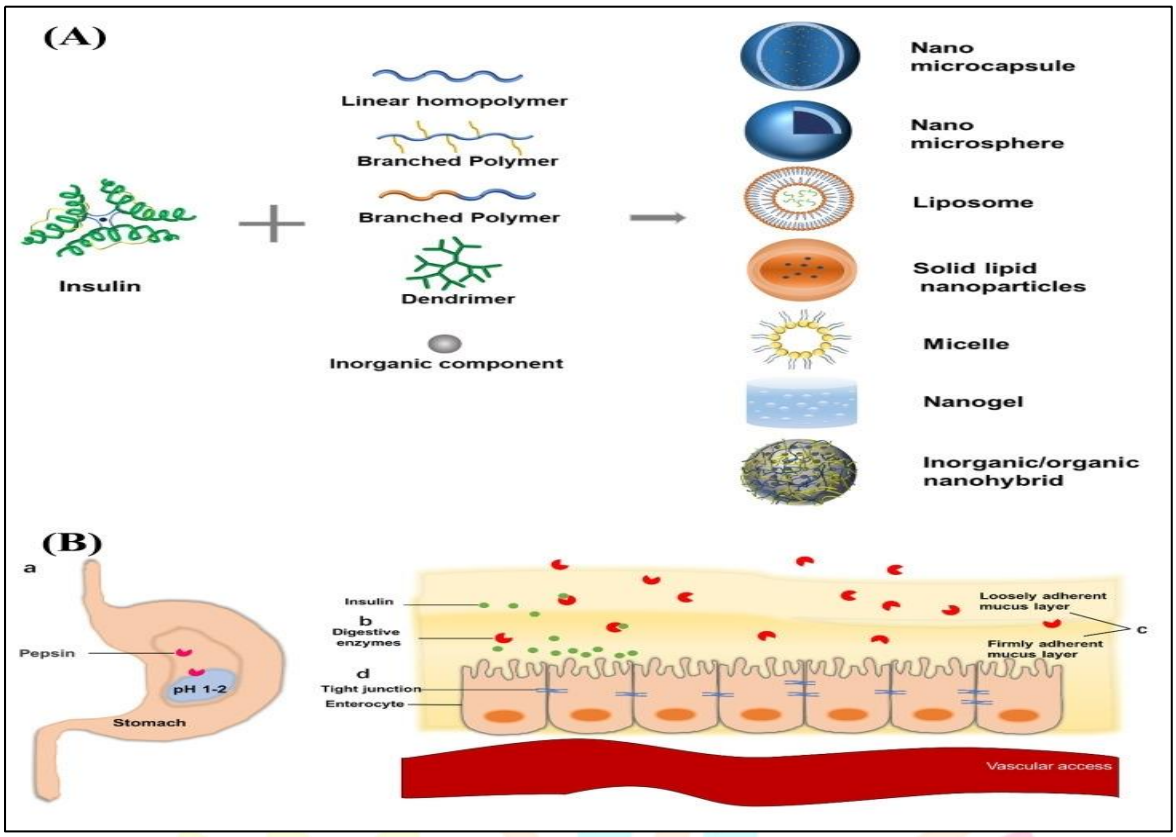


Figure 1
(**A**) Materials and nanostructures of oral insulin delivery systems. (**B**) The physiological absorption barrier of oral administration of insulin.

Currently, the Food and Drug Administration (FDA) in the United States has approved more than 100 insulin products for clinical use in the treatment of diabetes. However, because all of these medicines are injections, the difficulties in operation brought on by injections will place a significant psychological strain on diabetics. More seriously, injections expose patients to a variety of physiological risks, including hypoglycemia responses, lipoatrophy, fat hypertrophy at the injection site, local allergic reactions, erythema, itching, abscesses, and induration [7,8,9]

The development of noninvasive insulin delivery has become a research objective for many medical and pharmaceutical researchers in order to improve patient adaptability and lessen pain caused by injection. A great number of researchers have developed noninvasive insulin administration methods in recent years, including perinasal [10,11,12] sublingual [13,14] trans-ocular [15,16,17,18,19], pulmonary [20,21,22] and rectum [23,24]. However, achieving the intended therapeutic effects remains difficult because to low bioavailability, inability to match the concentration gradient of normal human insulin, additive safety, and low therapeutic activity. [25,26]

As the most accepted form of delivery, oral administration is also the safest and most convenient mode of insulin administration. Its primary benefit is that it avoids problems and hypoglycemia at the administration site [27,28]

However, due to its high molecular weight, strong hydrophilicity, poor stability, and low tolerance against hydrolysis by proteases, oral insulin treatment has a bioavailability of less than 2% [29,30,31,32] Furthermore, oral insulin can only play its role after passing through the gastrointestinal tract's physiological absorption barrier, which has become a challenge in the development of oral insulin [33,34]. To boost the formulation's oral bioavailability, enzyme inhibitors, permeability enhancers, and pH regulators have been added. The most notable example was ORMD-0801, manufactured by the Oramed pharmaceutical business and included permeability enhancers, a soybean trypsin inhibitor, and a calcium chelating agent. It is currently in clinical phase III and has a bioavailability of 5-8%; however, the safety and efficacy of its additions are still unknown.[35].

Oral administration of macromolecular pharmaceuticals has become a possibility in the last 20 years as a result of the convergence of nanotechnology and pharmaceutics [36,37,38], and oral insulin is another potential study area in this area. [39,40] In this paper, we highlight the physiological hurdles to oral insulin absorption and talk about the various materials used to create nano-drug delivery systems (Figure 1). Insulin delivery nano-systems are being built using a variety of ways to increase their bioavailability when taken orally. Finally, the trend in future research toward enhancing bioavailability is discussed.

Physiological Absorption Barrier of Oral Insulin

For diabetics who receive insulin injections, there are several physiological side effects in addition to a significant psychological load. The preferred method of insulin administration is orally. It is consistent with the physiological mechanism of insulin action and has the qualities of being painless and having strong adaptability. The very poor absorption of oral insulin, however, presents a dilemma. The explanation is that oral insulin must get past a lot of gastrointestinal environment-related barriers before it can have the desired therapeutic effects [41,42]. To overcome these physiological hurdles, delivery devices with various functions and structures must be developed for oral insulin delivery nano-systems. Table below provides a summary of the components of these obstacles as well as the primary strategies for overcoming them.

The physiological barriers of oral insulin administration and the mechanisms.

Physiological Barriers	Constitution	Mechanisms to Overcome	References
Destruction by gastric acid	Gastric acid, pH 1.0–2.0	pH responsiveness	[43,44,45,46,47]
Degradation by digestive enzymes	Pepsin, trypsin, chymotrypsin, elastase, and carboxypeptidase	Shielding effect, hydrophobic effect	[48,49,50,51]
Retention by the mucus layer barriers	Water, glycoproteins, proteins, electrolytes and lipids	Charge-reversing, "Mucus-inert" electroneutral surface	[52,53,54,55]
Retardation by intestinal epithelial cell layer	Tight junction, apical endocytosis, degradation of lysosomes, and basolateral to the circulation	Permeation enhancer, increase the active transportation	[31,42,56,57,58]

The Structures of Oral Insulin Delivery Nano-systems

Liposomes, polymeric micelles, solid liposomal nanoparticles, organic nano-microspheres/microcapsules, nanogels, and inorganic/organic nanohybrids are some of the structural subtypes of oral insulin delivery nano-systems. In order to increase the structures' solubility, permeability, release qualities, targeting, and protective effects, different functional components might be added with them. Here, we have a summary of the nano-systems for oral insulin delivery.

Liposomes

Liposomes are water-containing cored bilayer vesicles with phospholipid bilayer membranes that range in size from 25 nm to 2.5 um (Figure 3A and Table 3). The benefits of liposomes include low toxicity, great biocompatibility, excellent non-immunogenicity, good biodegradability, and simplicity of scaling.[109] The liposomes will be viewed as an exogenous substance to activate the body's immune system once they have entered the body. The reticuloendothelial system will phagocytose them after that, focusing enrichment in organs like the liver, spleen, lung, and bone marrow while lowering toxicity to the heart and kidneys. However, bile salts and trypsin lipase are known to degrade liposomes, and liposomes can cluster in the stomach environment.[110] Liposomes have a weak physical stability, making them susceptible to corruption and the production of laxatives. Injection, ultrasonic dispersion, melting, thin film dispersion, and reverse evaporation are a few of the frequently utilized lipid manufacturing techniques. [111]
Using cholesterol, egg yolk lecithin (EPC), and the cationic lipid DOTAP as carrier materials, Wang et al. synthesized cationic liposomes (CLs) via thin film hydration. [112]

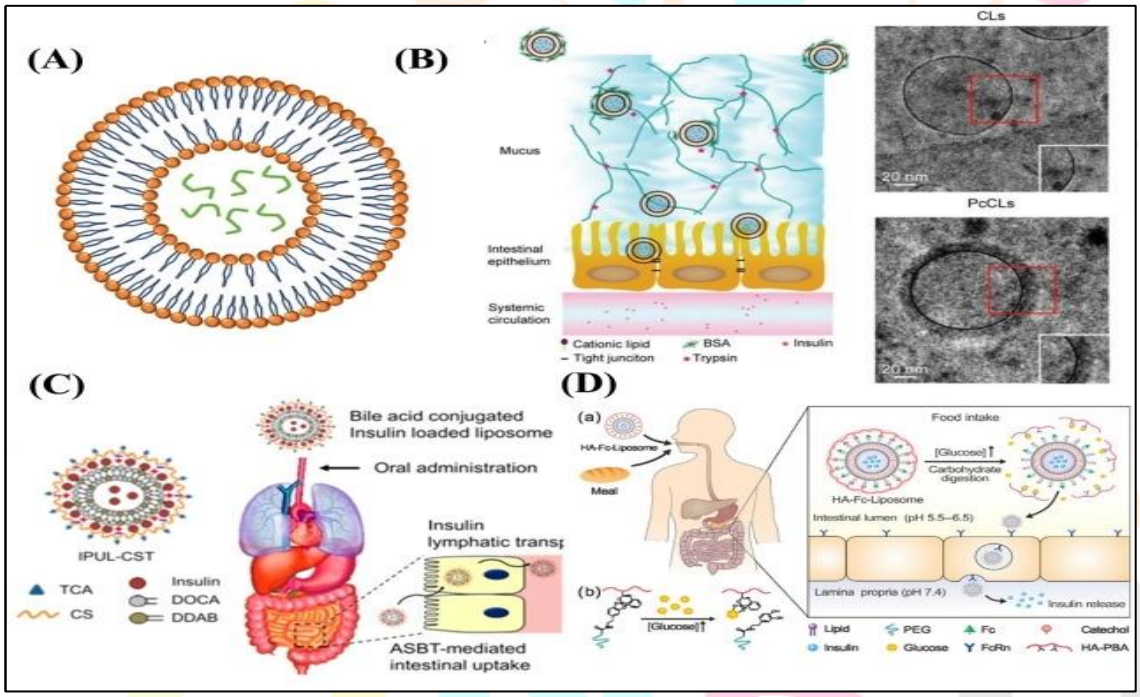
In order to create cationic liposomes with neutral charge and hydrophilic surfaces that could cross mucus and epithelial barriers, bovine serum albumin (BSA) was adsorbed onto them (Figure 3B). The oral bioavailability of insulin may be enhanced by PcCLs. Experimental studies conducted in vitro and in vivo have revealed that PcCL absorption and trans-

epithelial permeability were 3.24 and 7.91 times greater than those of free insulin, respectively. Additional research on the behavior of PcCLs revealed that the BSA corona might be shed from the PcCLs system when they crossed the mucus layer, exposing CLs with favorable electrical characteristics to encourage epithelial uptake.

Intra-jejunal injection of PcCLs had significant hypoglycemic effects in Type I diabetic rats, increasing oral bioavailability up to 11.9%. Kim et al. prepared an uncapped positive-charged liposomal nanoparticle (IPUL-CST) with a particle size of approximately 200 nm using a conventional thin film rehydration method[113]. The dimethyloctadecylammonium bromide (DDAB), deoxycholic acid (DOCA), and superparamagnetic iron oxide nanoparticles (SPION) with the diameter of 10 nm were used as materials (Figure 3C). Insulin was loaded by diffusion and electrostatic interaction into this uncapped special structure by dispersing superparamagnetic iron oxide nanoparticles in liposomes, allowing magnetic shear stress to squeeze the liposomal surface and tear it apart and forming open lipid bilayer pores. This allowed insulin to be encapsulated not only on the outside but also on the inside of the liposomes. The encapsulation rate of insulin in such nanoliposomes was significantly increased. The insulin-loaded liposomes were then encapsulated with a chondroitin sulfate-taurocholic acid coupling (CST).

Figure 2

(**A**) The structure of liposomes. (**B**) TEM images of CLs and PcCLs, and schematic diagram for the process of the transport of the PcCLs through the mucus layers and epithelial barrier. (**C**) Schematic diagram of IPUL-CST and its intestinal uptake and lymphatic transport. (**D**) Schematic representation of the glucose-responsive oral insulin delivery liposomes for postprandial glycemic regulation.



The active transport of IPUL-CST utilizing the apical sodium-dependent bile acid transporter-mediated intestinal uptake and lymphatic transport pathways was improved by complexation of the cationic liposomes with the anionic CST. In vivo absorption pathway tests have demonstrated that IPUL-CST absorbed via the distal ileum was transported to the body's circulation via the lymphatic channel. After oral delivery, the apparent bioavailability of an insulin-loaded liposome reached around 34%, and blood sugar levels steadily dropped at least 16 hours later. This work was the first to show how an oral insulin delivery system could easily release insulin when needed by being directly activated by rising postprandial glucose concentrations in the intestine. This work was the first to show how an oral insulin delivery system could easily release insulin when needed by being directly activated by rising postprandial glucose concentrations in the intestine. Gu and his team developed a (Fc Rn)-targeted liposome core-coated phenylboronic acid conjugated hyaluronic acid (HA-PBA) shell glucose-responsive nanoliposome with improved intestinal absorption function (Figure 3D). In order to provide on-demand insulin release and simple administration, this study shows a responsive oral insulin delivery system that is immediately triggered by rising postprandial glucose concentration in the intestine. [40]

Liposomes as an oral insulin delivery nano-system exhibit exceptional biocompatibility, and some nanoliposome pharmaceuticals, such paclitaxel liposomes, have been approved for marketing. Liposomes have a great safety profile and are frequently employed. However, due to the nature of lipid materials, encapsulation efficiency is limited. Nanoliposomes are more suited for the creation of preparations for quick-acting insulin due to liposomes' weak thermodynamic stability and short lifespan.

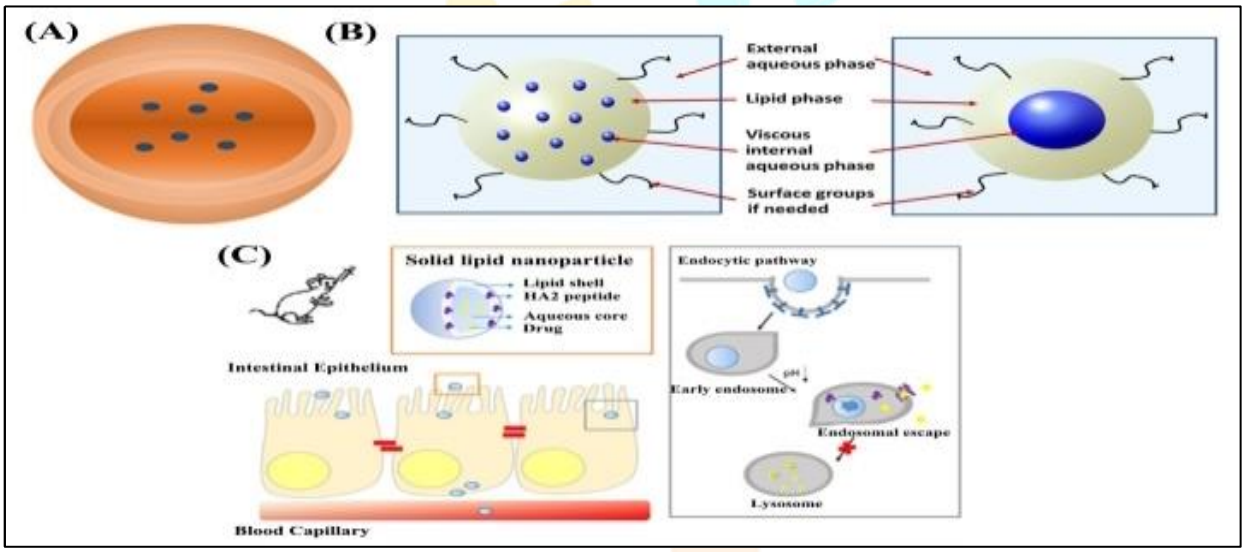


Figure 3
(**A**) Structure of SLNs.
(**B**) Schematic representation of possible structures of VEN.
(**C**) Schematic diagram of SLN and its behavior in intestinal epithelium.

Solid Lipid Nanoparticles (SLNs)

SLNs are solid nanodrug delivery systems composed of solid natural or synthetic lipids such lecithin, fatty acids, fatty alcohols, and other lipid-like materials, with medicines encapsulated or embedded in lipid-like nuclei (Figure 5A and Table 5). SLNs are minimal in toxicity, contain no organic solvents, are biocompatible, and have a high trapping effectiveness for hydrophobic compounds. SLNs, on the other hand, have flaws such as low encapsulation efficiency, short in vivo circulation time, and poor physical stability. Because of drug solubility in lipids and preparation technological restrictions, drug content will be minimal. High-speed homogenization, high-pressure emulsification, solvent emulsification, microemulsion, and ultrasonic dispersion can all be used to create SLNs. Boushra and colleagues synthesize SLN from soy lecithin. [118,119,120,121,122,123,124]

The addition of a hydrophilic viscosity enhancer (VA) to the SLN core resulted in the development of viscosity-enhanced nanocarriers (VEN), which solved the problem of low encapsulation effectiveness of hydrophilic active substances by SLN (Figure 5B) [125]. In fasting rats, oral insulin VEN had a good hypoglycemic effect with a relative bioavailability of 5.1%. Using ultrasonication, Xu et al. created solid nanoliposomes with a shell containing the endosomal escape factor hemagglutinin-2 peptide (HA2), which composed of a soy lecithin solid lipid shell and an aqueous nucleus containing insulin [30]. The HA2-containing shell effectively avoided lysosomal degradation of epithelial cells, insulin accumulation in the basolateral side of epithelial cells was much greater than that of free insulin, and insulin biological activity was maintained to a greater extent during intracellular transport (Figure 5C). When compared to liposomes, SLN has greater stability and a simpler preparation method. The encapsulation efficiency of the hydrophilic medication insulin, however, remains low. The development of oral insulin formulations requires additional research.

Organic Nanospheres/Nanocapsules

Organic nanospheres and nano-capsules are drug-loaded spherical or enclosed particles having nanoscale dimensions. Nanotechnology was used to prepare them with natural or synthetic polymer materials as carriers. Nano-capsules are made up of a polymer shell and an inner core of liquid (aqueous or oily), with the medicine usually contained in a polymeric membrane. Nanospheres, on the other hand, are homogenous spherical solid drug delivery systems created by combining the drug with a polymeric matrix in some fashion (Figure 6A and Table 6). Organic nanospheres, as opposed to other nanocarriers such as liposomes, micelles, emulsions, nanospheres, or nano-capsules, can provide greater storage and physiological stability to safeguard peptide molecules. They are made through emulsification-evaporation, nanoprecipitation, and self-assembly [105,127,128,129,130,131]. He et al. prepared core-shell structured nanoparticles with controlled particle size, high encapsulation, and high drug loading rate using a transient nanoprecipitation technique (Figure 6B) with a hyaluronic acid-coated insulin/L-penetrating composite nanoparticle as the core and an enteric material hydroxypropyl methylcellulose phthalate (HPMCP) coating as the outer layer, with a particle size of 45-115 n [132]. Sun et al. used the FNC technique to electrostatically complex insulin with a-(2-hydroxy) propyl-3-trimethylammonium chloride modified chitosan (HTCC)/sodium tripolyphosphate (TPP) to form a nanocomplex (NC), followed by a secondary electrostatic complexation to further encapsulate the nanocomplex into the enteric material Eudragit L100-55, and prepared NC-HTCC with improved solubility The results showed that the intestine embedding approach of peptide pharmaceuticals improves drug formulation size controllability, batch reproducibility, and uniform surface coating qualities, as well as dramatically improving insulin oral bioavailability. According to studies, it has a high potential for clinical uses of oral protein therapies.

Using a self-assembled nanoprecipitation process, Wu et al. created virus-like PLGA oral nanoparticles (P-R8-Pho NPs) with a particle size of 81.8 nm.[53] To boost mucus penetration and epithelial cell permeability, the nanoparticles' surfaces were modified using oligoarginine R8 (a cell-penetrating peptide rich in positively charged arginine) and phosphatidylserine. Brush boundary enzymes and intestinal alkaline phosphatase produced by intestinal epithelial cells catalyzed the hydrolysis of phosphatidylserine, exposing positively charged R8, which positively charges the surface of nanoparticles and enhances particle uptake by tiny intestinal epithelial cells (Figure 6D). The nanoparticles' surface charge could be switched for the distinct physiological conditions of mucus and epithelial cell membranes, allowing particle penetration and absorption.

For the organic nanoparticle preparation process, a wide range of materials can be used. Furthermore, most of these materials for nanoparticle preparation contain reactive groups that allow for further functional modifications, such as functional molecules like linker ligands and phenylboronic acids, which allow the systems to achieve functions like pH responsiveness, glucose responsiveness, and ligand-receptor-specific recognition. However, the biocompatibility of these materials must be enhanced before multifunctional insulin delivery nano-systems can be developed.

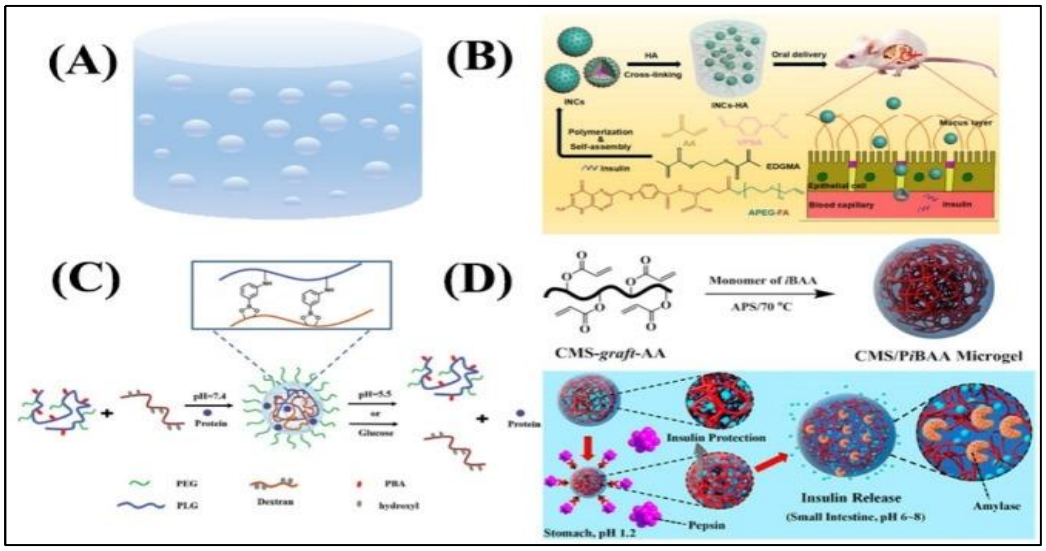


Figure 4
(**A**) Structures of organic nanospheres/nanocapsules. (**B**) Schematic representation of sequential FNC platform for preparation of the CPP/insulin nanoparticles. (**C**) The structure and the preparation process of NC-HTCC. (**D**) The structure of virus -like P-R8-Pho NPs and diagram of P-R8-Pho NPs to sequentially overcome mucus layer and intestinal epithelial cell layer.

Nanogels

Nanogels are nanoparticles with a three-dimensional network structure that are formed by the physical or chemical cross-linking of one or more hydrophilic monomers (Figure 7A and Table 7), which are rich in hydrophilic groups and can be swelled but not dissolved in water. The nanogels can be employed to transport hydrophilic insulin. The nanoparticles exhibit sensitive release to pH, temperature, and glucose after modification of the monomer polymer. [124,125,126] Li et al. employed microemulsion radical polymerization to create smart responsive nanogels of approximately 200 nm using the pH-sensitive monomer ethylene glycol dimethacrylate (EGDMA) and the glucose-sensitive monomer 4-vinylbenzeneboronic acid (VPBA) [134]

Hydrophilic phenylboronic acid-glucose complexes formed as the glucose concentration increased, and the hydrogel size increased. The carboxyl group of acrylic acid lost protons in the pH conditions of the small intestine, resulting in electrostatic repulsion between polymer strands. The nanogel generated a sparse gel structure and eventually released insulin from the nanoscale carrier. Polyethylene glycol-folic acid was added to the system, which targeted the folate receptor on epithelial cells and increased nanogel penetration via receptor-mediated endocytosis. Animal studies confirmed the hypoglycemic impact. Si et al. created a unique nanogel system based on poly (L-glutamic acid)-g-methoxypoly (ethylene glycol)/aminophenylboronic acid (PLG-g-mPEG/PBA) and dextran with a particle size of approximately 44 nm (Figure 7C) [133]. The nanogel was created through the reversible reaction of boron ester linkages between cis-diol on dextran and phenylboronic acid in PLG-g-mPEG/PBA, and insulin was loaded into the cross-linked lattice during the creation process. Because the boron ester link broke at high glucose concentrations and in a weak acid environment, the produced protein-loaded nanogels displayed good stability under normal physiological conditions and could rapidly release insulin in weak acid and high glucose settings. It also had dual pH and glucose sensitivity. Fluorescent imaging using confocal microscope revealed that cells effectively endocytosed the nanogels. Liu et al. prepared nanogels with a particle size of about 400 nm by aqueous dispersion copolymerization and loaded insulin into them through solubilization diffusion using acrylic acid-grafted carboxymethyl starch (CMS-g-AA) and 2-isobutyl acrylate (iBAA) as monomers.[41] The system was pH-sensitive, thanks to an ionization-deionization mutation in the pKa value of iBAA around pH 6.0, which provided pH sensitivity to the material. Figure 7D: Color development responses and morphological changes corroborated amylase's increased breakdown of CMS-containing nanogels, implying that intestine-enriched alpha-amylase might degrade CMS to further accelerate insulin release in the intestine. This type of nanomaterial could promote insulin transmembrane transport into Caco-2 cells and improve insulin oral pharmacological bioavailability.

The nanogels are highly hydrophilic and biocompatible, preventing immune system removal and allowing for long-term circulation. The fundamental downside of hydrogels is their poor storage stability, which renders medication persistence difficult to maintain.

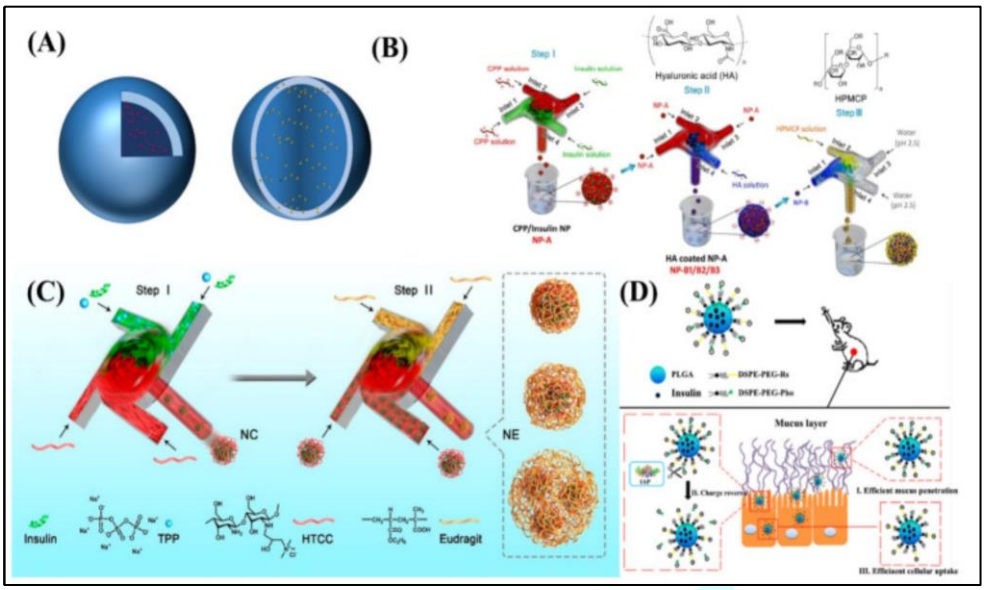


Figure 5 (**A**) Structure of nanogel. (**B**) Schematic representation of insulin-loaded glucose-responsive nanocarriers further encapsulated into hyaluronic acid (HA) hydrogel for oral delivery of insulin. (**C**) Schematic diagram of pH and glucose dual-responsive nanogels for protein delivery. (**D**) Synthetic process and its pH responsiveness of CMS/PiBAA hybrid microgel

Conclusion/Outlook

Oral insulin administration is one of the most effective means of lowering discomfort and improving compliance in diabetic patients. However, due to the physicochemical features of insulin and physiological barriers to absorption in the human gastrointestinal system, the bioavailability of oral insulin remains low, making high efficacy difficult to attain. To boost oral bioavailability, functional factors such as permeability enhancers, enzyme inhibitors, and pH regulators are added to natural insulin formulations; nonetheless, the efficiency and safety of additives remain debatable concerns. Materials with various physical and chemical properties are being investigated as materials science progresses. A variety of insulin-loaded nanostructures have been developed using nanotechnology to improve the bioavailability of oral insulin, laying the groundwork for the creation of oral insulin. Oral insulin delivery nano-systems with a variety of functionalities and delivery mechanisms have been produced by integrating these materials with nanotechnology. These oral insulin delivery nano-systems are intended to improve bioavailability and effectiveness through pH responsiveness, glucose responsiveness, small size, charge modulation, and facilitation of absorption and adherence. Various characterization experiments described in the literature demonstrated that these nano-systems have considerable benefits in avoiding gastric acid, breaking through the retention of the juvenile layer barrier, passing through the intestinal epithelial cell layer, and responsive release. Significant improvements in oral bioavailability were also reported in animal studies. While progress is being made, the shortcomings of the present oral insulin delivery nano-system must also be acknowledged. The safety of the materials utilized to build oral insulin delivery nano-systems needs to be confirmed further, and bioavailability is still suboptimal. Despite a considerable number of nonclinical studies, the clinical progress of oral nano-insulin technology has been hampered by the difficulties of delivering proteins orally. Furthermore, the preparation method for oral insulin remains difficult, which is incompatible with cost-effective commercial production. There is little information available on the storage stability of these preparations.

In general, oral insulin is certainly an active research area because of the large number of diabetics and the disadvantages of insulin injection. The multifunctional delivery nanosystems can effectively improve the oral bioavailability of insulin and provide a promising strategy for oral insulin delivery. However, there is still a long way to go for the transformation of oral insulin delivery nanosystems from laboratory to clinic. In the future studies, more attention should be paid to material safety, precise control of drug dose, feasibility of preparation process, and storage stability. If the insulin delivery nanosystems can overcome these challenges, diabetics could be liberated from the pain of insulin injections.

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