SAGE Open Medicine
Volume 12: 1–11

DOI: 10.1177/20503121231225319
journals.sagepub.com/home/smo
Sage

A review on oral novel delivery systems of insulin through the novel delivery system formulations: A review

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Abstract

Parenteral administration of insulin remains the most common route of administration, causing local hypertrophy at the injection sites because of multiple daily injections. Because of this, there is an interest and effort in oral insulin administration that is convenient and mimics the physiology of endogenous insulin secreted in the liver. However, oral insulin encountered different challenges due to abundant enzyme degradation, the presence of a mucus layer, and the underlying intestinal epithelial membrane barrier in the gastrointestinal tract. This narrative review reviewed the literature dealing with novel oral insulin delivery approaches. Various pieces of literature were searched, filtered, and reviewed from different sources, and the information obtained was organized, formulated, and finalized. Oral insulin has been formulated and extensively studied in various novel delivery approaches, such as nanoparticles, microspheres, mucoadhesive patches, encapsulations, hydrogels, ionic liquids, liposomes, and complexation. The efficiency of these formulations demonstrated improved efficiency and potency compared to free oral insulin delivery, but none of them have greater or equivalent potency to subcutaneous insulin. Future studies regarding dose-dependent therapeutic efficacy and the development of new novel formulations to produce comparable oral insulin to subcutaneous insulin are warranted to further support the suitability of the current platform for oral insulin delivery.

Keywords

Diabetes mellitus, insulin, drug delivery, oral insulin delivery, in vitro release

Date received: 26 July 2023; accepted: 16 December 2023

Introduction

Diabetes mellitus (DM) is one of the most widespread fatal diseases, responsible for more than 4 million deaths each year worldwide.[1] To date, the most common route of administration remains parenteral delivery of insulin, which causes local hypertrophy and fatty deposits at injection sites, and this pathway is unable to mimic the physiological hypoglycemic mechanism of insulin.[2,3] Because of this, there is an interest and effort in other routes of administration, including pulmonary, nasal, and oral. In particular, oral administration of insulin mimics the physiology of endogenous insulin secreted in the liver after gastrointestinal (GI) absorption and is expected to protect pancreatic cells from autoimmune destruction. Moreover, oral insulin delivery reduces patient suffering and increases the convenience of drug administration, although insulin must maintain its conformation intact through the gastrointestinal tract (GIT).[4] The critical challenges of successful oral insulin delivery are enzyme degradation, the presence of a mucus layer, and the underlying intestinal epithelial membrane barrier in the GIT.[1,5]

The primary source of insulin, a dipeptide hormone that regulates blood glucose levels, is the pancreatic β cells. It is made up of 51 amino acids with two chains: the A-chain, which has 21 amino acids, and the B-chain, which has 30 amino acids. Two covalent disulfide connections, CysA7 to CysB7 and CysA20 to CysB19, join these two chains. Furthermore, an intra-chain disulfide bond exists in the A-chain between CysA6 and CysA11.[6] Insulin can be susceptible to GI proteolytic enzymes such as pepsin, trypsin,

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Table 1. The physiological barriers of oral insulin administration and the mechanisms.

Physiological barriers	Constitution	Mechanisms to overcome	References
Digestive enzyme degradation	Chymotrypsin, carboxypeptidase, elastase, trypsin, and pepsin	Hydrophobic effect, shielding effect, and using a gastro-resistant framework	13–15
Degradation caused by stomach acid	pH 1–2 gastric acid	Coated by acid-resistant polymer, and pH responsiveness	11,16–18
Retention by the barriers of the mucus layer	Electrolytes, glycoproteins, lipids, proteins, and water	The mucus-inert electroneutral surface and charge-reversing	12,19
Intestinal epithelial cell layer retardation	Apical endocytosis, basolateral to the circulation, degradation of lysosomes, and tight junction	Enhancer of permeation, raise the level of active transportation	20,21

chymotrypsin, and carboxypeptidases. Efforts have focused on the development of novel oral insulin formulations that can overcome these barriers and maximize oral insulin bioavailability. Some approaches involve co-administration with known absorption enhancers such as fatty acids and protease inhibitors (PI), while others involve the use of smart polymers or carrier systems that can protect insulin from proteolytic digestion and mediate its absorption through the GIT epithelium.[7] The use of submicron colloidal carriers has also been suggested as a promising approach to overcome the aforementioned barriers.[8]

Modification of the structure of insulin was also explored to confer resistance to degradation by GI acids and enzymes and/or to improve permeability through the gut wall by converting it into enteric-coated carriers or other novel types.[9] Mucoadhesive intestinal patches were made using a special combination of mucoadhesive polymers and coated with a waterproof backing that improved intestinal permeability by adhering strongly to the intestinal mucosa. Additionally, the patches prevented enzymatic degradation and resulted in site-specific delivery to the gut. To further improve the effectiveness of the patches, intestinal iontophoresis was used to facilitate the permeation of insulin through the gut.[10] This study aimed to review the literature dealing with novel oral insulin delivery approaches.

Barriers for oral absorption of insulin

The GIT presents insulin with a series of oral absorption hurdles, primarily enzymatic, physical, and chemical. Oral medications pass through the GIT, stick to the mucous layer, pass past the intestinal epithelium, and then go into the bloodstream. However, because of its instability in the GIT and limited epithelial penetration, insulin has a very low oral bioavailability (less than 1%). The chemical barrier to the insulin taken orally is built by the amazing shift in pH values from 1.0 to 2.5 in the stomach to 7.5 in the terminal ileum. Pepsin in the stomach, pancreatin in the small intestine (including trypsin, chymotrypsin, and elastase), aminopeptidases in the brush border membrane, and certain enzymes in the cytosol are the primary enzymes involved in the breakdown of proteins in the GIT. Furthermore, if any insulin manages to withstand the aforementioned proteases, it will most likely be broken down by the liver's enzymes. Furthermore, the transport of insulin molecules across the mucus layer, which is known to be negatively charged, is hampered by their negative charge in the small intestine.[11,12] The physiological barriers to oral insulin administration and the mechanisms to overcome them are summarized in Table 1.

Oral insulin delivery approaches

Orally administered insulin maintains a large surface area available for absorption in the gut and can easily mimic the physiological fate of insulin in the body, achieving better glucose homeostasis.[22,23] GIT consists of tightly connected epithelial cells that can limit the absorption of proteins such as insulin through the oral route.[24] Although many attempts have been made to deliver insulin by oral administration, it has been difficult to affect its pharmacological action and stability. Much work has attempted to use nanoparticles (NPs), hydrogels, liposomes, and microspheres to manufacture oral insulin.[25] Chitosan (CS) micro- and nanospheres have emerged as potentially effective formulations for mucosal transport of insulin.[26] Different novel oral insulin delivery approaches were summarized in Figure 1.

Insulin and nano substrate interaction forces

There are humidity ranges on the other polymer surfaces where the pull-off forces are significantly higher. The insulin-polymer adhesion forces were identical for all polymers at 80% relative humidity, most likely as a result of surface hydration effects and static charge mitigation predominating.[27] Because they have a detrimental effect on the in vivo fate of NPs systems, protein corona formation and nano-protein interactions have received a lot of interest. On the other hand, these interactions can also be leveraged to develop sophisticated medication delivery systems.[11]

The CS polymers stabilized insulin's natural structure. The impact of the modified CS's cholesterol moieties was also investigated, and the findings suggested that the

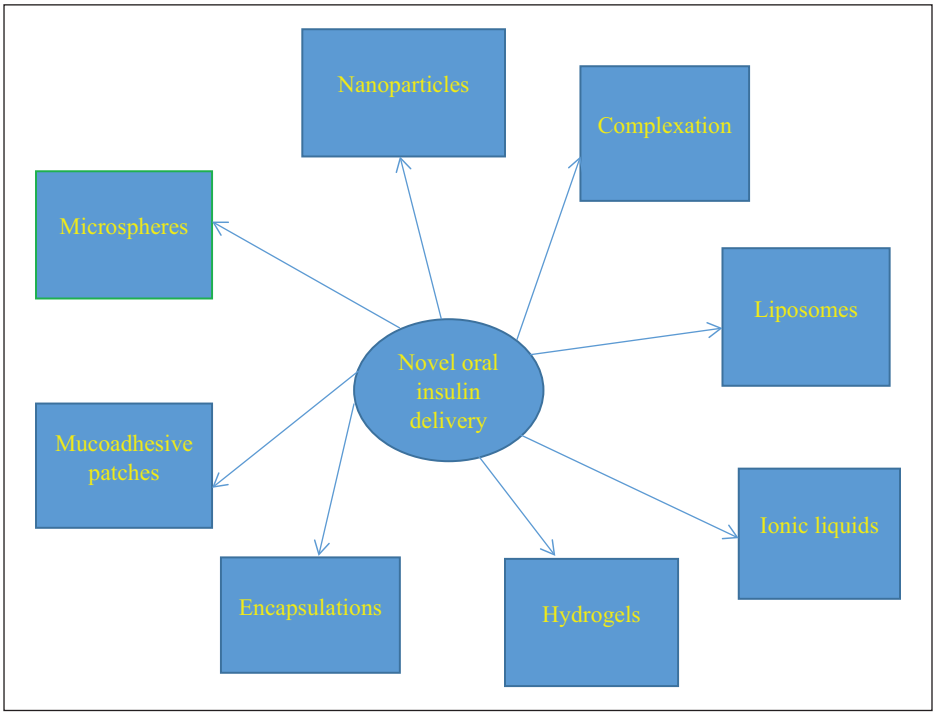

Figure 1. Novel oral insulin delivery approaches.

cholesterol components would lessen the CS polymers' affinity for human insulin. Subsequent investigations revealed that the tyrosine, phenylalanine, and acidic residues interact with one another Intramolecularly to produce the insulin-polymer complexes. An additional intriguing discovery is that the encapsulation process is significantly influenced by van der Waals, electrostatic, and CH-π interactions.[14]

Self-assembling NPs occur spontaneously when cationic CS and anionic polymers, such as insulin, combine electrostatically. Numerous researchers were drawn to this straightforward method because it may be completed rapidly in mild circumstances and does not require any hazardous solvents like chemical cross-linkers or surfactants that could damage the structure of insulin. Because of mucoadhesion and reversible tight junction opening, the manufactured CS-NPs enhance paracellular intestinal uptake from the enterocytes and shield the core insulin from enzymatic destruction in the digestive system.[28]

Release and uptake of insulin from novel formulations

Drug release from polymeric nanocarriers is affected by several factors, including the type of composition, the ratio of composition, the physical or chemical interaction between components, and manufacturing methods. Depending on the mechanism of drug release from the vehicles, it can be divided into four categories, including diffusion, solvent, chemical interaction, and stimulated release.[29] Diffusion-controlled drug release occurs in capsule-like systems where the drug is dissolved or dispersed in a core. It was released via diffusion through inert water-insoluble polymeric membranes (reservoir systems) or polymeric matrices (monolithic systems).[30] Transport of a solvent into drug delivery systems may affect drug release behavior from the delivery carriers. Solvent-controlled release includes osmotic and swelling-controlled release. Osmotic controlled release occurs in a carrier that is packed with a semipermeable polymer membrane, and water flows from the carrier with a low concentration of drug to the center of the carrier with a high drug concentration. A swelling-controlled system is mainly composed of polymer material having a three-dimensional cross-linked network structure, such as a hydrogel, in which mesh size controls drug-release behavior.[31] Smart polymeric drug delivery systems are able to release entrapped drugs at the appropriate time and site of action in response to specific physiological triggers. These polymers exhibit a response to a small stimulus, leading to a macroscopic alteration in their structure and properties.[32,33] Some stimuli (e.g., pH or enzyme) can also be exploited by means of carriers made of labile bonds, which are broken under the action of the stimulus.[34]

Insulin absorption was time-dependent and occurred by endocytosis. The intracellular traffic led to a basolateral exocytosis of NPs. Confocal microscopy revealed that insulin-loaded NPs were adsorbed on the surface of Caco-2 cells, and the majority were internalized. Intracellular or even

nuclear localizations of NPs in Caco-2 cells have been reported in the literature.[35] Different transcellular pathways, such as receptor, caveolae, micropinocytosis, and microtubular-mediated endocytosis, were implemented in the cellular internalization of insulin-loaded NPs.[36]

Nanoparticles

The development of NPs-based insulin delivery systems can shield insulin from chemical and enzymatic breakdown when it is encapsulated in NPs. Additionally, polymeric NPs have the ability to greatly increase absorption through the paracellular pathway and enhance uptake by small intestinal epithelial cells.[11] Most NPs designed as drug delivery systems have sizes ranging from 70 to 300 nm, or around 1 µm for the largest.[37] The NPs loaded with 10 IU/mL insulin were found to have an average particle size of 551.67 nm.[38] The development of an oral insulin platform based on glucose-responsive polymeric NPs have the following benefits: they bypass intestinal epithelial barriers, protect the integrity and bioavailability of loaded insulin against the GIT, and release insulin only when blood glucose levels are met, thereby preventing hypo and hyperglycemia.[39]

One of the smart/intelligent systems in site-specific drug delivery is stimulus-sensitive NPs due to their ability to respond to environmental stimuli and deliver bioactive materials to a specific site in the human body when needed.[1,40] Polymeric NPs have been used as drug carriers as their properties include biocompatibility, biodegradability, and the ability to protect insulin from degradation.[4] The NPs prepared from CS and its modifications, such as aminated CS, arginine CS, carboxymethyl CS, glycolic CS, mannosylated CS, succinyl CS, and thiolated CS, are promising, as are other polymeric vehicles that allow the encapsulation of insulin for oral administration purposes.[1,41] Optimized drug delivery, high stability, high carrier capacity, and the ability to incorporate both hydrophilic and hydrophobic substances are some of the key technological advantages of using NPs as drug carriers.[42] However, there are some disadvantages as well, including toxicity, cost, and regulatory challenges.[43]

Among the various carriers, solid lipid nanoparticles (SLN) represent a major class of NPs that are widely used in oral protein delivery. They were prepared by a w/o/w double emulsion strategy. Evaluation of the colloidal stability of SLNs in simulated gastric juice (SGF, pH 2) revealed an aggregation of SLNs, while SLNs remained unchanged in neutralized simulated gastric fluid (SGF). Various SLNs showed no significant aggregation or disintegration in the simulated intestinal fluid (SIF, pH 6.8) with or without trypsin. The in vitro insulin release profile showed approximately 40% insulin released from INS HA2-O-SLNs (an aqueous core loaded with insulin) within 2 h. The release profile of insulin from INS HA2-W-SLNs was more sustained compared to that of INS HA2-O-SLNs and INS SLNs (SLNs without HA2 peptide). After 12 h of incubation, approximately 55% and 35% of the encapsulated insulin were released from the INS HA2-W-SLNs in pH 6.8 and pH 5.5 buffers, respectively, which was significantly less than the INS SLNs and INS HA2-O-SLNs (70% and 50%).[44]

Trimethyl CS (TMCS) glucosidase inhibitory activity, absorption-enhancing ability, and pH-responsive properties made it superior to CS. In vitro insulin release from TMCS-NPs/Fucoidan-NPs (FD-NPs) and CS/FD-NPs showed rapid insulin release in simulated body fluid (SBF) (76.5% vs 94.2%) compared to SGF insulin release (39.8% vs 46%, 55%). These results demonstrated the effective protection of insulin from harsh acidic conditions. In SIF and SBF, CS/FD-NPs were unstable, releasing almost 90% of the encapsulated insulin. TMC/FD-NPs showed higher insulin protection compared to CS/FD-NPs (57.8% vs 38.9%) after 0.5 h of digestion.[41]

Other delivery systems developed from dextran sulfate and CS-NPs with zinc as a stabilizer also demonstrated promising result. This was developed by the esterification of dextran by acryloylation using acrylic acid polymerized by free radical chain reaction in the presence of ammonium persulfate. Acryloyl cross-linked dextran dialdehyde was converted into NPs by solvent evaporation to develop an efficient cross-linked nanocarrier drug delivery system. The insulin release profile showed a controlled release of about 70% under phosphate-buffered saline (PBS) conditions for 24 h, which increased up to 90% in the presence of 4 mg/mL glucose.[40]

CS-NPs were prepared using polystyrene sulfonate (PSS) as a crosslinker and stabilizer for CS and functionalized using polyglutamic acid (PGA) as a targeting ligand. Ch-PSS-PGA NPs, which are far more stable than Ch-PGA NPs by taking advantage of PSS as a stabilizer were found to be effective. Controlled release of insulin was observed from both Ch-PSS-NPs and Ch-PSS-PGA-NPs in SIF and PBS. In PBS, Ch-PGA-NPs experienced more than 50% insulin release in 4 h, while Ch-PSS-NPs and Ch-PSS-PGA-NPs released the same amount of insulin in 8 h.[45]

Co-modified colon-specific cell penetrating peptide NPs (CS-CPP-NPs) were developed with amphipathic CS derivatives (ACS) and CPPs as vehicles. In vitro release of both ACS-modified NPs (N-trimethyl-N-octyl CS (TOCS-NPs), N-trimethyl-N-dodecyl CS (TDCS-NPs), and N-trimethyl-N-palmitoyl CS (TPCS-NPs)) and CPPs-modified NPs, Tat-co-modified poly lactic-co-glycolic acid (PLGA) (TDCS-Tat-NPs), R8-co-modified PLGA-poly (lactic-co-glycolic acid) (TDCS-R8-NPs), and Penetratin-co-modified PLGA (TDCS-Pen-NPs) exerted little influence on the drug-release behavior of the NPs in SGF (20% cumulative release after 6 h). It is also observed that poly vinyl alcohol (PVA)-NPs showed a significant burst release, reaching 40% after 0.5 h. ACS-modified NPs showed approximately 20% cumulative drug release in SIF with no significant difference. However, PVA-NPs showed a clear burst release, reaching 50% after 1 h and over 80% after 48 h. CPP-modified NPs showed no clear burst release, with a 20% cumulative release after 48 h.[46]

NPs were also formulated by adding a CS solution dropwise into an insulin-containing acetylated cashew gum (ACG) aqueous solution. Polyelectrolyte complex NPs were formed through the interaction of opposite charges in ACG. In vitro insulin release from NP to SGF at 2 h was 34%. Insulin release from NP occurs mostly within 2 h in SIF, followed by slow release up to 24 h, where 51% insulin was released.[47]

The biological behavior of the biopolymer lipid nanocarriers (BLNs) strategy improved the efficiency of insulin entrapment by 2.5-fold (50% vs 20%) over standard w/o/w-SLN while maintaining insulin chemical stability and biological activity. Similar protection was obtained against the degradation of chymotrypsin, where BLN could protect about 25% of the entrapped insulin after 30 min of incubation at pH 7.4, compared to only 2% in the case of free insulin.[8]

Insulin NPs for oral administration based on prosochit have also been developed and characterized. The w/o/w double emulsion-freeze drying approach was used to produce insulin-loaded NPs. Three different varieties of prosochit, prosopis gum (PRG), and CS were used as independent emulsifiers for the outer emulsion. The formulations including PRG, prosochit 201, prosochit 101, prosochit 102, and CS had maximum drug release values of 66.2%, 61.5%, 65.3%, 61.3%, and 58.2%, and maximum permeation values of 49.8%, 53.8%, 49.1%, 54.9%, and 57.6% in phosphate buffer pH 6.8, respectively.[20]

Acid-resistant metal-organic framework NPs (UiO-68-NH2) were used to encapsulate enough insulin and decorate the outside with targeting proteins (transferrin). The transferrin-coated NPs achieved effective transport across the intestinal epithelium and regulated insulin release under physiological settings through a receptor-mediated transcellular pathway, resulting in a high oral bioavailability of 29.6%.[17] Insulin was injected between the layers of stacked nanosheets to create gastro-resistant imine-linked-covalent organic framework (nCOF) NPs. The insulin-loaded nCOF demonstrated both glucose-responsive release and insulin protection in digestive fluids in vitro.[15]

A functional NP (PG-FAPEP) with a twofold modification was developed to target significant absorption barriers. With a high oral insulin bioavailability of 14.3%, the in vivo investigations further confirmed that PG-FAPEP could penetrate the intestinal epithelium by folate receptor-mediated endocytosis, lysosomal escape, and proton-coupled oligopeptide transporter-mediated exocytosis.[48]

Microspheres

Microspheres are characterized by a uniform dispersion of drugs throughout the polymer matrix. Insulin is usually dissolved in the polymer solution before being processed into microspheres.[3] The particle size of the obtained insulin-loaded microspheres was 5.25 µm.[25] Among the various insulin delivery systems, microspheres could offer many advantages, such as rapid gastric emptying, rapid drug release, and more reproducible absorption due to their increased surface area.[25,49] However, they have their own disadvantages, including instability because of denaturation of proteins, oxidation, aggregation, and bond cleavages in the structure leading to structural changes in the proteins and hence loss of biological activity, which may also result in the initiation of immunogenic responses.[50,51]

The insulin microspheres were successfully prepared by alternately depositing film layers composed of insulin and polyvinyl sulfate potassium on the surface of polylactic acid microspheres. The amount of insulin released from the insulin-loaded microspheres was insignificant in the SGF solution, and the microspheres were relatively stable for 12 h. However, the insulin in the insulin-loaded microspheres was slowly released into the PBS, and the accumulated release rate reached almost 90% after 6 h, which showed that they are promising for oral insulin delivery.[25]

Concanavalin (Con)-sugar affinity-based glucose-responsive microspheres made from glycidyl methacrylate-dextran/con (Dex-GMA/Con A) were used to encapsulate insulin and provide a chemically controlled insulin delivery function. To prepare insulin-loaded glucose-responsive microspheres, a high-speed shear emulsion-based cross-linking method was implemented. Glucose-responsive, insulin-loaded microspheres were firstly prepared via a high-speed shear emulsion-based cross-linking method and then integrated into CS hydrogels to produce a scaffold-based synthetic artificial pancreas. In vitro insulin release from both free microspheres and integrated scaffolds showed a corresponding bolus and basal release rate and amount in response to glucose concentration changes. Therefore, scaffold-based synthetic artificial pancreases show promise in the application of insulin delivery.[49]

By using the solvent evaporation process, microspheres with different mixes of eudragit RL100 and RS100-loaded insulin have developed a stable formulation with good encapsulation efficiency and high bio adhesion. Maximum in vitro release was seen at pH 1.2 and 7.2, with a release of 9% and 87%, respectively.[52]

Using a greener approach, pH-responsive carboxylated cellulose microspheres (CCMs) were developed through the hydrolysis of citric and hydrochloric acid to increase insulin's oral bioavailability. The pH sensitivity of CCMs guarantees the oral bioavailability of insulin. According to in vitro release tests, insulin was released at 48.87% and 85.12% in artificial gastric fluid (AGF) and artificial intestinal fluid (AIF), respectively.[16]

Mucoadhesive patches

Mucoadhesive intestinal patches used a combination of mucoadhesive polymers and coated them with a water-impermeable backing that improved intestinal permeability by increasing adhesion to the intestinal mucosa.[53]

Additionally, these systems prevented the enzymatic breakdown of insulin by preventing the access of gut enzymes to the loaded drugs.[54,55] The optimized mucoadhesive patch had a thickness of 0.4 mm.[56] It extends the dosage form's residence time at the absorption site, increasing the bioavailability, outstanding accessibility, and quick response time. However, mucoadhesive drug delivery systems have some disadvantages, such as the potential for localized ulcer formation, the absence of a reliable model for in vitro screening to find appropriate medications, and low acceptance by the patient in terms of irritancy.[57,58]

Drug efficiency and efficacy in buccal distribution were increased by utilizing hydrophobic polymers, which do not dissolve in saliva, and neutral or positively charged NPs, which exhibit higher adhesion to the negative charges formed by the sialic acid in the mucus. In addition, it appears that unidirectional films and tablets have the maximum bioavailability when compared to alternative buccal delivery vehicles and sprays. This beneficial feature stems from their capacity to reduce the effects of saliva and unintentional GI enzyme digestion, which in turn reduces medication loss.[19]

Intestinal iontophoretic devices, developed by connecting mucoadhesive insulin patches to integrated circuits and on-chip batteries, can be designed and placed into enteric-coated capsules for site-specific delivery of the device in the intestine. The transport of Fluorescein Isothiocyanate (FITC)-insulin by Caco-2 with electric current at the beginning of the study was higher at 15 min but improved significantly from 2 h. When the electric current was applied, about 14.1 g of FITC-insulin was transported through the cells, compared to only about 5.5 g transported in the control group at the end of 5 h.[10]

Encapsulations

Due to the small particle size, the encapsulation in biocompatible nanocarriers promotes the paracellular or transcellular transport of insulin through the intestinal mucosa. Alginate beads, NPs, poly nano capsules, and collagen are some of the materials that have been investigated for use as insulin encapsulation and delivery systems.[14,59] The encapsulated NPs insulin has a mean diameter of 180 nm.[60] Drug encapsulation techniques are essential for delivering toxic, fragile, or poorly soluble substances. A greater therapeutic effect and fewer side effects can be obtained by improving a drug's encapsulation efficiency in drug carrier particles.[61] However, compared to standard formulations, the cost of the ingredients and the formulation process may be higher, they are less reproducible, and significant differences exist in how the polymers react with heat, hydrolysis, and biological agents.[62,63]

In order to encapsulate the insulin, metal-organic framework crystals weighing 2 mg were soaked for 30 min at room temperature in an insulin solution. Insulin NU-1000, the resulting solid composition, was separated by filtering and rinsed with water to get rid of extra insulin. After 60 min, just 10% of the insulin was released using SGF. This may mean that the insulin in NU-1000 is shielded from the stomach's hostile environment. Moreover, when exposed to SIF, the breakdown of NU-1000 starts the release of insulin. After 1 h, insulin NU-1000 released 91% of the encapsulated insulin.[59]

A modified method of double emulsion solvent evaporation was used to develop insulin PLGA NPs. Insulin was enclosed in PLGA combined with polyethylene glycol (PEG), and PVA was present in the exterior aqueous phase of insulin PLGA NPs. The NPs that were produced were mixed with a PI (N-Ethylmaleimide). In comparison to free insulin, insulin NP showed a much greater hypoglycemic impact when mixed with PI.[64]

Comparatively to the other systems, the CS-NP systems interact with insulin more frequently and show a strong preference for peptide hormones. Due to the hydrophobic nature of the cholesterol moieties, CS-NPs may therefore be a better carrier for insulin than CS-NPs treated with cholesterol. The discovery indicated that van der Waals, electrostatic, and CH interactions were the primary determinants of the insulin encapsulation process.[14]

Insulin was also successfully encapsulated using formulations of oil-soluble reversed lipid NPs (ORLN). It has been established that the ORLN system shields insulin molecules from trypsin by preventing direct contact between the two substances by creating phospholipid (PC) vesicles in the intestinal fluid. Moreover, PC was crucial for transcytosis at the intestinal wall. Rats' oral insulin absorption was improved by ORLN-peptide recombinant human insulin (ORLN-PHI), a recombinant human insulin peptide, as opposed to a free PHI solution. Comparing the oral bioavailability of ORLN-PHI to Subcutaneous-administered free PHI, the difference was 28.7%. All things considered, ORLN has promise as a nanocarrier for enhancing insulin absorption through the mouth.[21]

Hydrogels

Hydrogels are hydrophilic polymers made up of three-dimensional viscoelastic networks that inflate in physiological conditions and hold water several times their dry weight. Because of their special qualities, such as their water content, soft, elastic consistency, and low adhesion force with water or biological fluids, hydrogels can be used as biomaterials. Hydrogels have unique physical properties that enable controlled dissolution, shield labile pharmaceuticals from deterioration, and regulate the release of different molecules.[65] Hydrogel has a nanoscale dimension of 10–1000 nm.[66]

CS, cellulose, starch, pectin, and psyllium are examples of naturally occurring polymers that have been employed to create pH-responsive hydrogel carriers for the administration of oral insulin.[67] With their mucoadhesive properties,

hydrogels are regarded as secure drug delivery vehicles for oral administration. This could delay drug release and absorption. The capacity of hydrogels to prevent the inserted pharmaceuticals from enzymatic degradation is another benefit of using them as oral drug delivery vehicles.[68–70]

Hydrogel-based insulin release devices are not lengthy enough to provide the insulin requirements required for clinical application, which is one apparent cause for concern. Insulin can only be released once or twice with the current release mechanisms before it needs to be refilled. Insulin should be released by effective devices at least 10 times before additional administration is required. Another problem is that insulin delivery systems based on hydrogels must expand and contract without experiencing hysteresis. Consistent insulin delivery is difficult due to hysteresis, which allows for a fluctuating variation in insulin delivery. Polyprotein cross-linkers and softer hydrogel materials can both be used to lessen hysteresis.[18,67]

Cellulose nanocrystals (CNCs) were chosen as a biomaterial for hydrogel preparation due to their interesting characteristics, including favorable mechanical properties, low density, hydrophilicity, biodegradability, and high biocompatibility. PH-responsive hydrogel in the form of a semi-interpenetrating polymer network by cross-linking acrylic acid monomers in a CNC suspension was investigated for its drug delivery system.[71,72] Chemical cross-linking consists of the formation of covalent bonds between polymer chains and CNCs, which mandates the surface modification of CNCs with specific functional groups, such as silyl groups, carboxyl groups, or aldehyde groups, to create cross-linking sites. The modification can be achieved by direct surface chemical modification or through the physical interaction or adsorption of molecules to the surface of the CNCs. Combining the advantageous characteristics of both polymers, the resulting hydrogels are expected to have a high degree of crystallinity and favorable mechanical properties.[73] However, the entrapment methods in hydrogel may have potential for drug deactivation due to the covalent binding technique and initial burst release. Moreover, it was reported that unreacted small-molecule cross-linkers have possible toxicities.[69]

Insulin was incorporated into the poly (methyl acrylate) (PMA)/salecan/PMA polymer network using a source diffusion technique. Insulin is released into SIF and SGF in vitro from PMA and salecan/PMA hydrogel samples in a pH-dependent manner. For PMA and salecan/PMA hydrogel, the cumulative insulin release at 24 h was 19.7% and 21.5% in SGF and 32.1% and 49.4% in SIF, respectively. When compared to an orally administered free insulin solution, insulin-loaded salecan/PMA hydrogels demonstrated a more than 10-fold increase in bioavailability.[68]

PH-responsive polymeric hydrogels made of cross-linked poly (methacrylic acid) and poly (ethylene glycol) (P (MAA-g-EG)) are used to deliver oral insulin. Due to the cross-linked P (MAA-g-EG) hydrogels' pH-dependent complexing abilities, insulin is released quickly in the gut. Moreover, they have mucoadhesive, enzyme-inhibiting, and high insulin-loading effectiveness without impairing the integrity of the intestinal epithelial membrane. In addition, P (MAA-g-EG) hydrogel microparticles have intestinal mucoadhesive characteristics and block GI proteolytic enzymes. Insulin can be effectively administered orally using CPP with a permeation-stimulating action, and the combination of P (MAA-g-EG) hydrogel carriers helps to provide protection and control drug release.[2]

Ionic liquids

The problems of solubility, bioavailability, permeability, polymorphism, and stability associated with solid-state medications need to be effectively solved. The potential use of ionic liquids (ILs) as liquid therapeutics, reagents, solvents, and anti-solvents in the synthesis and crystallization of drugs, as well as solvents, co-solvents, and emulsifiers in drug formulations, has been investigated in an attempt to address some of these problems.[74] ILs are organic salts that have cations and anions that can be precisely chosen to produce a range of compounds with distinct physicochemical properties and biological activity. ILs are regarded as designer solvents.[75,76] However, they have some disadvantages, such as toxicity and challenges like storage conditions, that is, temperature, pH, and initial burst release rate. Storing of IL, especially at low temperatures, results in shape-transition.[77,78]

ILs, which are composed of organic and inorganic salts with a melting point below 100°C, have been widely used in a number of cutting-edge drug delivery systems. A deep eutectic choline-geranate (CAGE) solvent that was stable at room temperature was remarkably effective at delivering insulin in multiple ways. Insulin was distributed in CAGEs in a single step and remained steady for a very long time.[54] Non-diabetic rats were given oral nasogastric tubes containing 10 U/kg insulin CAGE or its control in enteric-coated oblong capsules. Within 2 h of taking the capsules, the group receiving 10 U/kg of insulin CAGEs saw a rapid 38% drop in blood glucose levels.[22]

Complexations

A complexation approach has been widely investigated to address low aqueous solubility, which subsequently improves the bioavailability of these drugs. Besides improving solubility, drug complexation provides versatile functions like improving stability and reducing the toxicity of drugs.[79] Most insulin complexes were about 80 nm.[80] Insulin interacts electrostatically with the oppositely charged polyelectrolytes of the polymer to spontaneously generate polyelectrolyte complexes in an aqueous solution.[81]

Poly (allylamine) (Paa), paa-thiobutylamidine (TBA), paa-N-acetylcysteine (NAC), quaternized paa (QPaa), and

qpaa-N-acetylcysteine (QPaa-NAC) were all combined with insulin at pH 7.4 to create formulations of polymer-insulin complexes. Tryptic degradation of polymer-insulin complexes revealed that, in contrast to less than 70% for insulin control, >90% of the insulin present in the thiolated complexes was not destroyed after 4 h. After 4 h, it was shown that the QPaa-NAC complex had 10% more undegraded insulin than the QPaa complex, 15% more than the Paa-NAC complex, and 30% more than the insulin control complex.[7]

PH-sensitive polyelectrolyte methyl methacrylate (MMA)/itaconic acid (IA) nanogels are also being tested as carriers to enhance the absorption of orally given insulin. The polyelectrolyte complex method was used to insert insulin into the MMA/IA nanogels (NGs) to create Ins/NGs-PEC. InF12-Tre2 (trahalose) nanogels released 28.71% and 96.53% of their insulin in vitro into SGF and SIF, respectively.[81]

The potential of poly (methacrylic acid)-grafted poly (ethylene glycol) complexation hydrogels (P (MAA-g-EG)) for oral insulin delivery was also explored. The pH-responsive properties of the complexation hydrogels allow inter-polymer complexes to form and dissociate in acidic and neutral/basic conditions, respectively. The hydrogels have mucoadhesive characteristics and calcium-binding capacities that influence the proteolytic activity of calcium-dependent enzymes. They can also incorporate and release insulin quickly in vitro. Insulin-loaded P (MAA-g-EG) effectively increased oral insulin absorption without causing any discernible mucosal injury.[82]

Glycosaminoglycan-(GAG)-binding-enhanced-transduction (GET), a modified CPP platform, was found to be an effective transepithelial delivery vector in vitro and to mediate oral insulin action in diabetic rats. Insulin GET-NCs, or insulin-get-conjugated by electrostatic contact, are a type of nanocomplex. GET enhances insulin uptake, transcytosis, intracellular release, and in vivo activity.[83]

The self-micro-emulsifying drug delivery system (SMEDDS) that is loaded with an insulin-, sodium dodecyl sulfate (SDS) hydrophobic ion pair was developed to take advantage of the hypoglycemic effects of insulin administered orally. Initially, SDS was hydrophobically coupled with insulin to increase its lipophilicity. SMEDDS loaded with an Ins-SDS was successfully optimized. In contrast to insulin and the Ins-SDS complex, the optimized SMEDDS demonstrated significant resistance to GI enzymes.[84] Hydrophobic ion pairing with amphiphilic counterions can significantly boost the lipophilicity of insulin. To improve the loading into the SMEDDS, insulin was complexed with sodium n-octadecyl sulfate prior to optimization. The bulk of insulin remained in oil droplets following release, and the stability of insulin-n-octadecyl sulfate against GI enzymes was significantly improved in the SMEDDS.[85]

Liposomes

Sphere-shaped vesicles called liposomes (Ls) are made of lipid bilayers that PC self-assembles into.[3,86] The best PC/cholesterol ratio prevents insulin from leaking from the Ls core and absorbs the greatest number of insulin molecules. Novel bilosomes contain bile salts, including sodium glycocholate, sodium taurocholate, and sodium deoxycholate, to enhance the stability of Ls taken orally. Spray drying techniques or film dispersion freeze drying can be used to create dried, free-flowing proliposomes. Proliposomes have been utilized to enhance insulin oral bioavailability and GI absorption.[3] Insulin-loaded liposomal formulations are in the size range of 150–210 nm.[87] Site-targeting, sustained or controlled release, protection against drug degradation and clearance, better therapeutic effects, and fewer harmful side effects are just a few of the superior qualities displayed by Ls.[88] However, the high cost of production, drug/molecule fusion and leakage, and the occasional oxidation and hydrolysis-like reaction of the phospholipid are some of the drawbacks of Ls.[89]

Protein coronal Ls (PcCLs) are created when bovine serum albumin (BSA) is adsorbed onto cationic Ls (CLs). The absorption and transepithelial permeability of PcCLs were 3.24 and 7.91 times higher than those of free insulin, respectively. Without trypsin, PcCLs remained stable in the gut buffer, and trypsin could slowly break down the BSA corona, a process that moved much more quickly in mucus than in PBS. At 6 h, 80% of the insulin in SIF had been liberated from CLs. Contrarily, while the amount of insulin released from the PcCLs was 45% less than that from the CLs, it was released at a rate that was noticeably slower. PcCLs had an oral bioavailability of up to 11.9%.[86]

Using the double emulsion technique, a new glucose-responsive multivesicular Ls (MVLs) for self-regulated insulin administration was developed. In vitro, glucose-responsive MVLs have the potential to efficiently control insulin release in response to variations in glucose concentrations.[90]

To produce Ls-in-alginate hydrogels (AINS-Ls-Gel), Ls loaded with arginine-insulin complexes were added to a hydrogel made from cysteine-modified alginate. An ex vivo investigation demonstrates that intestinal penetration of arginine-insulin complexes and AINS-Ls is about two and six times greater than that of free insulin, respectively. The hydrogel improved intestinal mucosal retention and postponed the Ls' early release of insulin.[91]

Limitations of the study

The review has limitations concerning objectivity, the thoroughness of the literature search, and the interpretation of the results. There is only a topic of interest; there is no predefined research question or search strategy. They lack structure and adhere to no set procedure. There are no guidelines or standards for the review. The reviewers will gain knowledge about the issue, but they will not have a thorough grasp of the current state of the science surrounding it.

Future perspectives

DM is one of the most common and fatal chronic diseases and is mostly managed with insulin, particularly when it is

type 1. Due to local hypertrophy and fat deposits brought on by many daily injections, insulin therapy compliance and adherence are currently low. To combat the negative effects of invasive delivery and improve patient compliance, non-invasive alternative strategies have been developed and investigated. However, no formulation has been able to successfully navigate all clinical challenges, and there are no oral insulin medications on the market as of yet. Toxicology, blood insulin levels, and dose-dependent therapeutic efficacy investigations should be conducted in the future to support the viability of the oral insulin delivery system. DM could be spared the discomfort of administering insulin injections if insulin delivery nano systems could overcome the aforementioned difficulties.

Conclusions

Non-invasive alternative strategies have been developed and researched as a means of overcoming injection adverse effects and enhancing patient compliance. The effectiveness of oral insulin in navigating the challenging GI environment, GI membrane permeability, and hypoglycemic effects has been tested in vitro and in vivo. NPs, microspheres, mucoadhesive patches, encapsulations, hydrogels, ILs, liposomes, and complexation were among the methods examined in this study. These methods have enhanced efficiency and potency compared to free oral insulin administration, but not in comparison to SC insulin. Many studies have been conducted on NPs-based oral insulin administration, and CS chose the most well-known polysaccharides to produce NPs. The complex needs of diabetics, high cost, low permeability and bioavailability, instability, and side effects make it difficult to find the ideal insulin delivery method.

Acknowledgements

I want to acknowledge all the authors of the references that I used.

Availability of data and materials

This paper is a review of the previously published data. All data generated during this study was included in this published article.

Consent for publication

Not applicable.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

Not applicable.

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