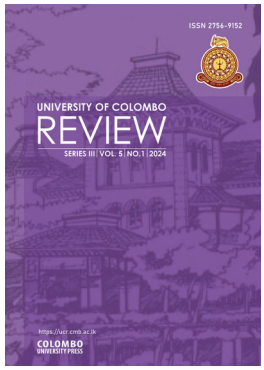

DOI: https://doi.org/10.4038/ucr.v5i1.134

University of Colombo Review (Series III),
Vol.5, No.1, 2024

Recent advancements in lipid nanoparticle technology for oral insulin delivery

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ABSTRACT

Nanotechnology is important in many industries, particularly in drug delivery and administration. This technology has been used to create nanocarriers for enteral drug delivery. There are different types of nanocarriers including polysaccharide-based and lipid-based nanocarriers. Lipid nanoparticles have recently been developed for loading and administering insulin via the enteral route to treat diabetes mellitus. Insulin cannot be administered orally due to its low bioavailability, extreme gastrointestinal conditions, and instability. When insulin is loaded onto these nanocarriers, it increases bioavailability, stability, drug release pattern control, and protects insulin from extreme conditions. This review article aims to discuss recent applications as well as novel methods and approaches for oral insulin delivery using liposomes, solid lipid nanoparticles, and nanostructured lipid carriers.

KEYWORDS:

Insulin, Diabetes mellitus, Liposome, Solid lipid nanoparticles, Nanostructured lipid carriers

Suggested Citation: Welengodage, I. & Katuwavila, N.P (2024). Recent advancements in lipid nanoparticle technology for oral insulin delivery. *University of Colombo Review* (New Series III), 5(1), 130- 144

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Introduction

Insulin was first identified by Frederick G. Banting and Charles H. Best with the help of Macleod and Collip in 1921 (Pratt, 1954). Insulin is a globular protein that contains 51 amino acid residues in two chains, of which 21 are in the A chain and 30 are in the B chain. These two chains are linked together by sulfur atoms (Hu and Luo, 2018). This natural hormone is secreted by beta cells of the islets of Langerhans in the pancreas of the human body (Aldous et al., 2023). The main purpose of this circulating insulin is to decrease the elevated levels of blood glucose to the physiological level by the uptake of glucose to cells. Adipose tissue, the liver, and muscles are the main locations in the human body where the uptake of glucose occurs (Fazakerley et al., 2019). In the event of autoimmune disorders, the body's own immune cells attack the beta cells in the pancreas and alter or stop the production of insulin. If a sufficient amount of insulin is not in circulation after food consumption, the mechanism of glucose uptake to the cells does not occur normally, which causes a rise in the blood glucose level. This condition is known as type 1 diabetes mellitus (Sharma et al., 2015). In type 2 diabetes mellitus, insulin cannot bind and cause glucose uptake to the cells due to a resistance of insulin receptors (Lee et al., 2022). Therefore, elevated blood glucose levels can be observed. The other main type of diabetes mellitus is gestational diabetes which only occurs during pregnancy (Sarría-Santamera et al., 2020). According to recent studies, five main clusters were identified in diabetes mellitus; namely, severe autoimmune diabetes related to type 1 diabetes, severe insulin deficient diabetes, severe insulin resistant diabetes, mild obesity-related diabetes, and mild age-related diabetes which are related to type 2 diabetes (Ahlqvist et al., 2020;; Sarría-Santamera et al., 2020).

Subcutaneous injections are the most commonly used method of insulin delivery to treat hyperglycemic conditions (Shah et al., 2016). Pharmacokinetic activities of insulin can be categorized into four groups: short acting, middle acting, long acting (glargine, Levemir), and rapid acting (lispro, aspart). It can also be classified based on the types of insulin utilized in insulin therapy, including biosimilar, analog, and human insulin (Sarkar et al., 2021).

There are certain complications that can arise in intravenous (IV) insulin therapy. It can cause hypoglycemia, skin bulges, pain at the injection site, and local allergic reactions (Mukhopadhyay et al., 2012). Insulin should also not be injected during certain time periods depending on the patient's blood glucose level. Hence, to enhance the acceptability of insulin to patients and to reduce the pain caused by injections, scientists and researchers have attempted to develop noninvasive insulin administration methods. Oral administration is the most suitable and acceptable drug delivery method in medicine (Alqahtani et al., 2021). Oral administration of insulin is the safest method because it does not cause hypoglycemia or any complications at the administration site (Arbit and Kidron, 2017). However, low bioavailability,

harsh gastrointestinal environments, and poor stability due to proteolytic enzyme degradation by trypsin, pepsin, and chymotrypsin makes it challenging to administer insulin orally (Lin et al., 2007). Nanoparticles are widely being researched as drug-delivery vehicles to be used in medicinal applications due to their strong adaptability, small size, high stability, high carrier capacity, incorporation of both hydrophilic and hydrophobic substances, and feasibility of absorption by enterocytes in the small intestine (Wang et al., 2022). Despite their benefits, nanoparticles have certain drawbacks including low stability, a tendency to agglomerate, the possibility of causing allergic reactions, and the high cost of large-scale production (Desai, 2012). However, due to high patient acceptance, researchers have developed a variety of insulin-loaded nanoparticles for oral administration including chitosan, alginate, polymeric micelles, polysaccharide-based nanoparticles, and lipid nanoparticles (Hariyadi and Islam, 2020; Seyam et al., 2020).

This review aims to discuss these recent advances and applications of lipid nanoparticles in oral insulin delivery.

Lipid nanoparticles

The ability of liposomes, solid lipid nanoparticles, and nanostructured lipid carriers to transport both hydrophilic and hydrophobic compounds has made them a popular choice for oral insulin delivery. Additionally, they are more suitable for oral insulin delivery due to the ease of scaling up production, very low or no toxicity, extended half-life and modified drug release pattern, increased time of action, biocompatibility and biodegradability, as well as their ability to maintain a more constant serum level of a drug (Ghasemiyeh and Mohammadi-samani, 2018).

Recently, lipid nanoparticles were developed to avoid recognition by immune cells in the body. Nanoparticles that are sensitive to pH have also been developed, which allows them to remain stable in gastric acidity and release the active drug on reaching the intestine (Plaza-Oliver et al., 2021). Despite these advantages, there are certain disadvantages such as the burst release of drugs by an erosion mechanism, the expulsion of drugs, low drug-loading efficiency, and the lack of extensive clinical studies (Ghasemiyeh and Mohammadi-samani, 2018). To overcome these disadvantages, certain special development methods were used such as improving entrapment efficiency using viscosity enhancing agents, protecting and controlling the release of insulin from solid lipid nanoparticles by coating them with a cationic polysaccharide called chitosan Witepsol 85E, and increasing the stability of lipid nanoparticles using surfactants and bile salts (Boushra et al., 2016).

Liposomes

Liposomes are widely used as drug carriers mainly because of the composition of the liposome membrane, its encapsulating efficiency, stability, rate of drug release,

and the ability to distribute throughout the body after administration (Liu et al., 2022; Nsairat et al., 2022). Supporting factors that make liposomes effective drug carriers include liposome size, surface charge, size distribution, and drug type administered (Sercombe et al., 2015).

When insulin was liposome-trapped and given orally in the late 1970s to investigate the prospect of oral insulin delivery, tests showed that a small, yet considerable amount of insulin entered the circulation. These insulin-loaded liposomes have been developed by andar methods. Insulin concentration (I), lecithin (L), cholesterol (C), and tween-80 (T) variables are used for these two main insulin-liposome development methods. The efficiency of liposomes for oral insulin administration will vary depending on the composition of these variables. According to studies, the most effective liposomes contain L 100 mg, C 20 mg, I 150 units, and T 1 percent v/v, and these liposomes have been prepared using the solvent spherule evaporation method. (Guanabara et al., 1994).

Polyelectrolyte complexation is one of the methods used for making chitosan nanocarriers and it is associated with lecithin liposomes. This complex has been discovered as a new nanocarrier for oral insulin delivery. Studies have shown that when this liposomal preparation is administered orally to streptozotocin-diabetic rats, blood glucose levels are reduced (Al-Remawi et al., 2017).

It is established that silica coating is chemically inert, biocompatible, hydrophilic, and inexpensive. Researchers have prepared liposomes having layers of silica to enhance the stability of the formulation (Li et al., 2012). These silica-coated liposomes improve the stability of the complex and enhance the effectiveness of encapsulation by inhibiting the leaking of insulin through the silica coating. At pH 2.5, fluidic phosphatidylcholine lipid vesicles were produced by thin film hydration, and an upper layer of silica was created by acid catalysis. Insulin was loaded within these fluidic phosphatidylcholine lipid vesicles (Bellare et al., 2010).

Protein corona liposomes (PcCLs) were made by adsorbing bovine serum albumin to cationic liposomes (Wang et al., 2018, p.12). The primary goal of using this PcCL is to overcome small intestine barriers such as mucus and epithelium. According to studies, the hydrophilic surface and neutral surface charge of PcCLs, as well as the enzyme hydrolyzing nature of bovine serum corona, increase the velocity of penetration through the mucus (Wang et al., 2018, p.12). The interaction of the cationic liposome nanocore and the underlying epithelium improves transepithelial transport. PcCLs were administered intravenously to type 1 diabetic rats, and the results showed a significant reduction in glucose and increased oral bioavailability up to 11.9% (Wang et al., 2018).

As per the findings of Hu et al., bile salts such as sodium glycocholate-coated liposomes improve the preservation of insulin from enzymatic degradation because they have improved permeability through the gastrointestinal epithelium, low toxicity,

and protease inhibition (Hu et al., 2013). The studies aim to develop recombinant human insulin (rhINS) loaded glycocholate liposomes using the reversed-phase evaporation method following homogenization (Niu et al.,2011).. Particle size and the efficiency of entrapment of the liposome particle can be adjusted by changing homogenization parameters. In vitro studies show that sodium glycocholate protects insulin from pepsin, trypsin and alpha chymotrypsin and that, even under increased stress levels, the stability of rhINSs was preserved (Niu et al.,2011).

To decrease the development of macro and microvascular complications in postprandial glucose levels, an oral insulin administering method was developed by Fc receptor (FcRn)-target liposomes with a glucose-sensitive hyaluronic acid (HA) shell (Yu et al., 2019). These studies were based on the principle that immunoglobulin G (IgG) binds with the Fc portion of the liposome and that this specific binding is dependent on pH. The HA shell detached and released insulin because of the high concentration of intestinal glucose caused by the binding of glucose with the conjugate system of phenylboronic acid groups and HA. This transportation of protein into circulation occurs primarily across the apical side of duodenal enterocytes (Yu et al., 2019).

Recent studies show that folic acid (FA) stabilizes and increases bioavailability of insulin-loaded liposomes in oral administration (Yazdi et al., 2020). The liposomes were stabilized by coating them with several layers of polyelectrolytes such as a negatively charged poly (acrylic acid) (PAA) and positively charged poly (allyl amine) hydrochloride conjugate. This final liposome structure is identified as a 'layersome'. This layersome structure is important in vesicular systems where it increases drug load as well as in particulate systems where it enhances robustness and storage stability. Finally, pharmacodynamics and pharmacokinetics studies revealed almost double hypoglycemia and a 20% increase in bioavailability compared to the standard insulin solution administered subcutaneously (Agrawal et al., 2013).

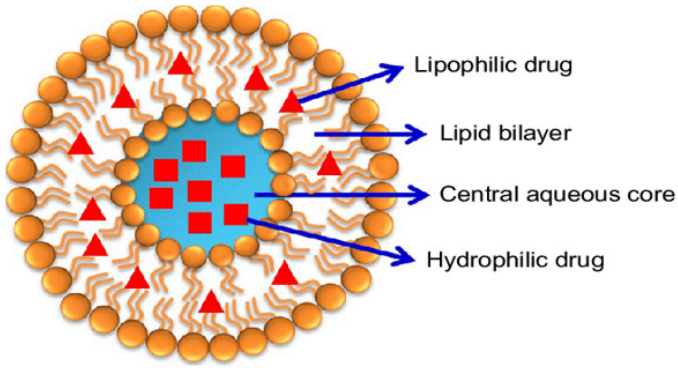

Figure 1: An illustration of a liposome (Din et al., 2017)

Solid Lipid Nanoparticles (SLN)

Solid Lipid Nanoparticles (SLN) are lipids that are solid at room temperature as well as at human body temperature. Surfactants and co-surfactants that stabilize the solid lipid nanoparticle, and active pharmaceutical drugs are the ingredients used to develop SLNs. Triglycerides, partial glycerides, waxes, steroids, and fatty acids are some of the lipids that are used to prepare SLNs (Subroto, Andoyo and Indiarto, 2023). Some of the benefits of using SLNs as a drug carrier include increased drug stability, regulated drug release ability, and proteolytic activity protection (Mishra et al., 2018). The non-toxic nature of the excipients, as well as the advanced engineering materials used to create SLNs, contribute to the physiochemical properties of nanoparticle absorption into the systemic circulation through the portal vein.

Other substances, particularly lipophilic drugs, are transported into the systemic circulation via lymphatics, which increases the oral bioavailability of active pharmaceutical ingredients (Basha et al., 2020). However, SLN's hydrophobic nature explains their low peptide entrapment effectiveness (EE%) (Duong, Nguyen, and Maeng, 2020). Hence, researchers have developed a new formulation named viscosity-enhanced nanocarriers (VEN) by adding a hydrophilic viscosity-enhancing agent (VA) into the SLNs internal aqueous phase of the w/o/w double emulsion system to improve peptide EE% (Boushra et al., 2016). Using human insulin as a model peptide drug, propylene glycol (PG), polyethylene glycol (PEG) 400, and PEG 600 agents were used to assess the effectiveness of the VA. The highest EE% (54.5%) was achieved by 70% w/w PG. These experiments were conducted using fasting rats and achieved a good hypoglycemic response with a 5.1% relative bioavailability. These VENs combine increased viscosity with hydrogen bonding between peptide molecules and VA to promote the stability and trapping of SLNs insulin delivery (Boushraet al., 2016). Other studies show that inserting a hydrophilic polymer called Methocel into SLNs to form Methocel-lipid-nanocarriers (MLNs) also increased insulin EE%. Inserting 2% wt/wt of Methocel A15C doubled the insulin EE% compared to SLNs prepared using the conventional double standard emulsion technique (Boushra et al., 2016). MLNs mainly protect insulin by chymotrypsin degradation in gastrointestinal pH. These findings further demonstrate that MLNs could be extensively absorbed by intestinal epithelial cells due to their low toxicity (Boushra et al., 2016). Methocel A15C's improved drug encapsulation capabilities and capacity to overcome SLNs' other drawbacks make MLN an excellent nanocarrier for the delivery of oral insulin (Boushra et al., 2016).

Further studies were carried out to protect insulin from proteolysis by modifying the SLN with stearic acid-octa arginine (SA-R8) as a carrier for oral insulin administration (SA-R8-Ins-SLNs) (Hui-xia and Press, 2012). Furthermore, these studies show that oral administration increases the stability and bioavailability of insulin. SA-R8 is made using the spontaneous emulsion solvent diffusion method.

Transmission electron microscopy, high-performance liquid chromatography, dynamic light scattering, Caco-2 cell internalization, and in vivo tests on diabetic rats in a hypoglycemic state are then used to evaluate these SLNs modified with SA-R8. It demonstrated that the spherical morphology, positive zeta potential, size, and high loading capacity of insulin in SLNs treated with SA-R8 increase the absorption of oral insulin (Hui-xia and Press, 2012). Another SLN named cationic lipid nanoparticle (cSLN) was developed using the water-in-oil-in-water double emulsion technique to protect insulin from pepsin and trypsin enzymatic activity (Dara et al., 2019). Glyceryl palmitostearate and 1,2-dioleoyl-3-trimethylammonium-propane were used as cationic lipids to develop the lipid matrix of this carrier. According to Dara et al. (2019), biphasic release, initial burst release of the drug during the first 30 minutes, persistent release of the peptide drug, and high loading capacity of insulin are some of the characteristics of cSLNs. Further, these cSLNs enhance the transport of insulin through the monolayer of Caco-2/HT29 cells compared to the free intra-venous insulin solution (Hecq, Amighi and Goole, 2016). New research has been conducted in reverse micelle-double emulsion to produce SLNs loaded with insulin-mixed micelles. The insulin-loaded SLN was created using a stearic acid and palmitic acid combination with the primary goal of extending the shelf life of insulin by preventing drug expulsion during storage and by accommodating additional micelles (Liu et al., 2007). To increase the liposolubility and stability of insulin, sodium cholate (SC) and soybean phosphatidylcholine (SPC) were used. These SLNs' core-shell drug loading patterns were verified by polyacrylamide gel electrophoresis and fluorescence spectra. The drug release behavior was assessed using the Weibull and Higuchi equations, as well as the in situ and external sink methods. For more information on these methods and equations see (Papadopoulou et al., 2006). Drug entrapment efficiency and drug loading capacity were assessed using high performance liquid chromatography. According to the results of these studies, the reverse micelle-double method can overcome all the key limitations of SLNs and it can be a novel approach in oral insulin administration in the near future (Liu et al., 2007).

Another research study was conducted to increase the penetration of insulin through the intestinal mucosal surface and to protect and control the release of insulin by modifying the SLN by coating it with a cationic polysaccharide called chitosan Witepsol 85E (Sharma et al., 2015). The mucoadhesive properties of chitosan increase the drug uptake because the nanoparticle and the intestinal epithelium is in contact for a prolonged period and the penetration of the active drug is increased due to the prolonged concentration gradient through the nanoparticle and the membrane. These Insulin-loaded SLNs were administered to diabetic rats and, after 24 hours, a measurable hypoglycemic effect was observed. The pharmacological bio availability of chitosan SLNs was 17% while that of uncoated SLNs was 8%. Another important

finding is that chitosan protects the SLN from the mononuclear phagocyte system in the intestine. These studies reveal that a chitosan nanoparticle is another optimal carrier for oral insulin delivery (Fonte et al.,2011; Fonte, Andrade and Arau, 2012).

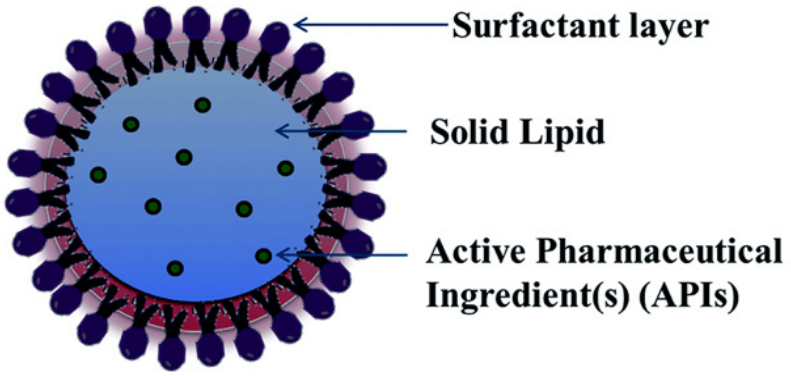

Figure 2: An illustration of solid lipid nanoparticle (Duan et al., 2020)

Nanostructured lipid carriers

Nanostructured lipid carriers (NLC) were designed using a formulation combined with solid and liquid lipids with the aim of enhancing a drug's therapeutic oral bioavailability (Poonia et al., 2016). This new formulation was designed using surfactants, co-surfactants, lipids, and lipophilic counter ions. High entrapment efficiency and drug loading capacity, controlled drug releasing pattern, pH and enzyme breakdown prevention, long shelf-life, p-glycoprotein efflux circumvention, sensory masking, NLCs disposition mechanism through gastrointestinal absorption, and ease of uptake to the lymphatic system by chylomicrons are some of the advantages of NLCs in oral drug delivery (Nguyen et al., 2022).

A novel study was done to identify the impact of protecting against enzymatic degradation by surface decoration with three different surfactants using insulin as a model peptide drug. The lipophilicity of the NLC was increased by ion-pairing with sodium dodecyl sulfate inserted into the NLC (Gamboa et al., 2020; Bashyal et al., 2021). Polyethylene glycol ester (PEG-ester), polyethylene glycol ether (PEG-ether), and polyglycerol ester (PG-ester) are the three different surfactants used to decorate the surface of NLCs. Caco-2 cells were measured via resazurin assay to assess the biocompatibility of these NLCs. Proteolytic studies were done using stimulated gastric acid containing pepsin and stimulated pancreatic juice containing pancreatin. The standard lipid digestion method was used to analyze lipolysis. Cytotoxic studies showed non-cytotoxicity up to a concentration of 0.5%, 0.25%, and 0.125% (w/v) for PG-ester, PEG-ester, and PEG-ether, respectively.

The lipolysis studies revealed the highest release of free fatty acids, which means the highest energy supply for tissues such as the heart and liver during fasting, is in PEG-ester at >90%, and that the lowest is with PEG-ether at 10% (Duncan et al., 2007). Proteolysis results confirm that PEG-ether provides the highest protective effect from enzymatic degradation (Shahzadi et al., 2021). These studies show that NLCs have the highest protective effect from the intestinal enzymatic degradation of peptide drugs, although NLC's are less in biocompatibility (Shahzadi et al., 2021).

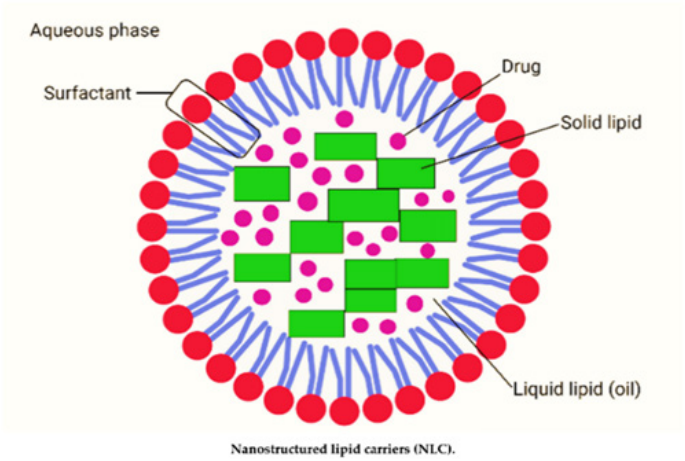

Figure 3: An illustration of nano structured lipid carrier (Azhar et al., 2022)

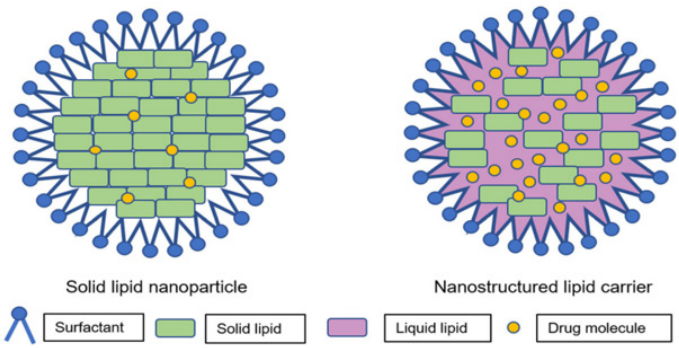

Figure 4: Drug loading capacity of SLNs versus NLCs (Subramaniam et al.,2020)

Conclusion

Insulin-loaded lipid nanoparticles, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers were developed to increase patients' acceptance by giving insulin orally rather than subcutaneously. To ensure effective oral delivery of insulin, researchers continue to work on enhancing the stability and bioavailability of lipid nanoparticles. This includes protecting insulin from enzymatic degradation. Ongoing research aims to design nanoparticles that can target specific sites in the GIT for increased insulin absorption as well as mucoadhesive lipid nanoparticles to prolong the residence time of insulin and thereby facilitate more effective absorption. Incorporation of penetration enhancers into lipid nanoparticles and the addition of co-delivery of other absorption enhancers, such as enzyme inhibitors, are under investigation to enhance the absorption of insulin across the intestinal barrier.

While much of the research on insulin-loaded lipid nanoparticles for oral insulin delivery is still in the preclinical stage, where they have been tested using animal models, certain formulations have progressed to early-phase clinical trials. Continued clinical testing will be essential to demonstrate the efficacy and safety of these formulations, and these studies seek to boost oral route compliance while providing patients with safe and efficient insulin administration.

Conflict of Interest

The authors have no conflict of interest to disclose.

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