

Review Article

INSIGHT ON SOLID LIPID NANOPARTICLES: CHARACTERIZATION AND APPLICATION IN DIABETES MELLITUS

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ABSTRACT

Solid lipid nanoparticles (SLNp) are a new class of alternative colloidal carriers developed at the beginning of the 1990s with the particle size ranging from 50 to 1000 nm. The SLNp consists of the drug molecule, surfactants, and solid lipid core suitable for incorporation of lipophilic, hydrophilic, and poorly water-soluble molecules. Diabetes mellitus (DM), is a prototype multifactorial complex diseases that regarded as one as one of the leading causes of morbidity and mortality in the world. DM caused by inadequate secretion of insulin or by the damaged cells of Islet of Langerhans of the pancreas. The present review provides information about the suitable choice of lipid, amount of surfactants was used for SLNp preparation, characterization, and various route of administration to increase the relative oral bioavailability in diabetic animals. Moreover, limitations associated with nanocarrier system for insulin delivery have also been discussed. Solid lipid Nanoparticulate system might be efficiently overcome peripheral hyper insulinemia, lipo-hyper-atrophy and improves the life quality of diabetic patients in the near future.

Keywords: Diabetes mellitus, Palmitic acid, Nanocarrier system, Microscopy

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INTRODUCTION

The desirable action of drug molecules depends on the absorption, distribution, metabolism, and elimination process. Sometimes negative response from the subjects has been observed in clinical trials. Because newly developed drug molecules showed poor absorption, increase in metabolism that leads to rapid elimination before entered into the target site. Low solubility and fluctuation of drug concentration in the plasma have been observed after oral administration [1]. Controlled release is defined as delivering the precise amount of drug molecules into a target site in estimated time using a carrier. Bioavailability is the proportion of a compound that is available for utilization in the metabolic process. Solid lipid nanoparticles are a new class of alternative colloidal carriers developed at the beginning of the 1990s with the particle size ranging from 50 to 1000 nm. The SLNp made from lipids that remain as a solid state at room temperature and body temperature [2]. SLNp consisting of physiological and biodegradable lipids are suitable for incorporation of lipophilic, hydrophilic, and poorly water-soluble drugs within the lipid matrix [3]. The SLNp enhancing the oral bioavailability of weakly soluble agent by incorporating the drug molecules into biodegradable solid lipid nanoparticles which allow the controlled drug release due to their solid matrix [4]. SLNp carriers also protect the loaded drug molecules from premature degradation; increase their attraction within the internal environment and penetration [5]. The reasons for the increasing interest in the lipid-based system includes small size, a relatively narrow distribution which provide biological opportunities for site-specific drug delivery, controlled release of active drug over a long period, and protection of incorporated drug against the chemical degradation, lipids enhance oral bioavailability and reduce plasma profile variability [6, 7]. The absence of organic solvents during the preparation of SLNp is also another advantage [8]. SLNp has been proven a better alternative carrier system than conventional oil emulsion method. Then compared to polymeric nanoparticles, SLNp is less toxic, excipient inexpensive, large scale production by high-pressure homogenization and use of biological lipids. In comparison with liposomes, SLNp offers better protection to drug against chemical degradation. Depending on the nature of the drug higher payload might be achieved [9, 1].

Lipids and surfactants for SLNp preparation

Many biodegradable lipids are solid at room temperature, can be achieved in high purity, inexpensive, and are generally recognized as

safe. Notably, the Triacylglycerol (Trilaurin, Trimyristin, Tripalmitin and Tristearin), Acylglycerols (Glycerol monostearate, Glycerol benzoate and Glycerol palmitostearate), fatty acids (Benzoic acid, Decanoic acid, Palmitic acid, and Stearic acid), Cetyl palmitate, and Cyclodextrin (Sodium taurocholate and para-acyl-calixarenes) are used as lipid carriers for the SLNp preparation in a safe, quality and cost-effective manner. Surfactants are utilized to control the stability of a system by decreasing the surface tension. Some common surfactants used in the SLNp formation are Phospholipids (Phosphatidylcholine, Soy lecithin and Egg lecithin), Poloxamer, alkyl aryl polyether alcohol polymers, pluronic F127, bile salts (Sodium cholate, Sodium glycocholate and Sodium taurocholate), Tween80 and polyvinyl alcohol [10, 11]. Nano and microparticles made up of these lipids and suspended in the water offer an option for formulating both Biopharmaceutical Classification System (BCS) class II and IV which might reduce the side effects. Nanoparticles of these lipids made by using a template synthesis from a microemulsion of the molten lipid in aqueous surfactants, by precipitation of the wax from a solution in a non-ionic surfactant on addition of water, or by emulsifying the molten lipid into a hot aqueous surfactant solution with high-shear mixing to obtain the desired submicron particle size [12]. Small molecules can be entrapped within the lipid matrix of the nanoparticles by dissolving or dispersing the material in the molten lipid prior to particle formation. More than hundred APIs using SLNp had been encapsulated [13]. Table 1 shows the lipid and surfactants used for SLNp preparation.

Potential routes of SLNp administration

A drug molecule entered into our body by a different route (oral/topical/inhalation/injection) of administration. Ordered applications of SLNp under *in vivo* conditions depend on the following factors (i) Route of administration. (ii) Absorption and desorption of drug molecules, and (iii) Depend on the lipase and esterase enzymatic action. Reports are available in the aspects of possible route of SLNp administration such as parenteral (polysorbate loaded SLNp), per oral (Camptothecin-loaded SLNp for antitumour activity, rutin loaded SLNp for type 2 diabetes mellitus), transdermal (Nano ointment from Rutin loaded solid lipid nanoparticle for diabetic wound) and pulmonary route of administration (supercritical fluid extraction based emulsions) [38-41]. Briefly, the drug loaded SLNp passing through the oral cavity, intestinal lumen, apical mucous layer, water layer, epithelial cells of intestine, basement membrane and finally reached inside into blood vessels (fig. 1).

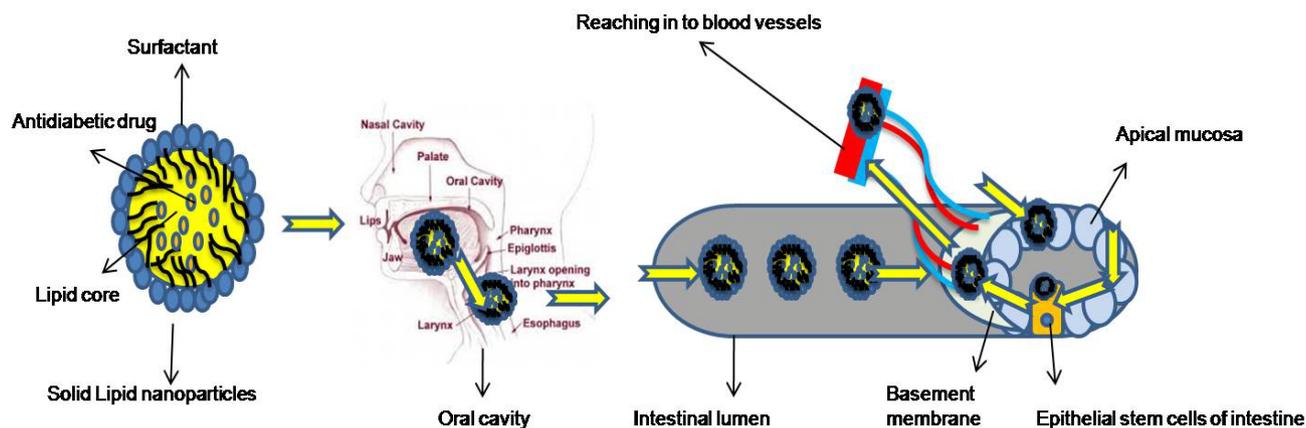


Fig. 1:

Table 1: Lipid and surfactants used for SLNp preparation

Drug	Lipid	Surfactants/Stabilizer (%)	References
Insulin	Soya lecithin	Polyvinyl alcohol (0.5, 1 and 2%)	[14]
	Sodium cholate and soybean phosphatidylcholine	Poloxamer188 (0.1 to 5%)	[15]
	Cetyl palmitate	Poloxamer 407 (2%)	[16], [17]
Rutin	Palmitic acid	Polyvinyl alcohol (1%)	[18,19]
Berberine	Glycerol tripalmitate: soybean phospholipid	Pluronic F-68(1%)	[20]
Metformin	Stearic acid and polysorbate 20	Surfactant water system	[21]
Repaglinide	Cephalin, lecithin	Tween 80	[22]
Metformin hydrochloride	Soya lecithin	Polymethacrylic acid (1%)	[23]
Morphine	Compritol	Poloxamer 188(2.5%)	[24]
Silver sulfadiazine	Compritol® 888	Poloxamer 188 (4.5%)	[25]
Talinum portulacifolium	Lipids	Tween-80	[26]
Silymarin	Compritol 888 ATO, soybean lecithin	Poloxamer 188	[27]
Quercetin	Compritol® 888 ATO (glyceryl dibehenate) or Precirol® ATO 5 (glyceryl palmitostearate)	SDS (0.1 to 2.5%); Dioctyl sodium sulfosuccinate (0.1 to 2.5%); Poloxamer 188(2.5%) Tween 20 and 80 (2.5%)	[28]
	Lecithin	TPGS, D-α-tocopheryl polyethylene glycol 1000 succinate (1 to 2.5%)	[29]
	Lecithin	Tween-80 and PEG 400 (1.5 to 4%)	[30]
Umbelliferone (7-hydroxycoumarin)	Lecithin	polyethylene glycol sorbitan monostearate	[31]
Enrofloxacin	Tetradecanoic acid, Palmitic acid, Stearic acid	1% PVA	[32]
Tretinoin, retinol and retinyl palmitate SLNp formulation	Glyceryl behenate, tripalmitate, cetyl palmitate and solid paraffin	-	[33]
	Glycerol monostearate or tripalmitin or stearic acid	Lecithin S75, Polysorbate 80 surfactant (0.1%–0.3%)	[34]
Curcumin	Poly(lactic-co-glycolic acid)	polyvinyl alcohol (PVA), Pluronic F-68, Vitamin ETGPS and Cetyl trimethylammonium bromide (CTAB) 1% w/v	[35]
Hesperetin	Glycerol Monostearate, Stearic acid, Compritol, Oleic acid and Estasan hesperetin	Tween 80 (2 %)	[36]
Cisplatin	Stearic acid and lecithin	Sodium glycolate	[37]

Characterization of SLNp

In order to develop a drug product of high quality, a precise physicochemical characterization of the SLNp is necessary. Commonly used techniques involved in the nanoparticle size, shape, and morphology and distribution characterization are Atomic force microscopy, scanning electron microscopy, SEM combined with energy-dispersive X-RAY spectrometry, scanned probe microscopy, transmission electron microscopy, Photon correlation spectroscopy (PCS) or dynamic light scattering (DLS), laser diffraction, and Fraunhofer diffraction. Among these, the most widely used techniques are PCS and electron microscopy methods [42-44]. Additionally the structure and liquid oil domains of SLNp analyzed

by nuclear magnetic resonance (NMR) and ¹H-NMR. The solid state of the particles is of major importance, as it reduces the mobility of incorporated drugs and preventing the leakage of drug molecules from the SLNp carrier. The thermal physicochemical nature of SLNp analyzed by differential thermal analysis (DTA) or differential scanning calorimeter (DSC) or X-ray diffraction [45].

The functional groups involved in the encapsulation of SLNp evaluated by Fourier transform infrared spectroscopy (FTIR). Zeta potential (ZP) of SLNp determined by its electrophoretic mobility using a Particle Size Analyzer by Helmholtz-smolu chowski equation

$$ZP = E(4\pi\eta/\epsilon)$$

Where E is Electrophoretic mobility; η is defined as the viscosity of the dispersion medium and ϵ is defined as solvent dielectric constant [46]. The amount of drug entrapped within SLNp is measured by UV spectrophotometer or by HPLC. Loading capacity is defined as the ratio between drug and lipid phase. Entrapment efficiency is defined as the ratio between encapsulated drug and total drug added into the system

$$\text{Entrapment efficiency (\%)} = \left\{ \frac{\text{Weight of drug in SLNp}}{\text{Weight of drug added}} \right\} \times 100$$

$$\text{Loading capacity (\%)} = \left\{ \frac{\text{Weight of drug in SLNp}}{\text{Weight of SLNp}} \right\} \times 100$$

For efficiency and efficacy reasons, the amount of drug that can be loaded is very important and the loading capacity typically ranges from 1-5% [47]. *In vitro* drug release studies of SLNp are mainly useful for quality control and *in vivo* kinetics measurements by using diffusion technique through dialysis bag or without tubing. The kinetic parameters of drug release determined by using statistical models viz., zero order, first order, Higuchi, Peppas, Hixon-Crowell, square root, Weibull, linear Wagner and log Wagner [11]. During long time storage, the stability of SLNp determined in terms of particle size changes, drug content, viscosity, visual inspection and zeta potential [48,49]. Considerable interest will be carried out during SLNp preparation and characterization process such as the high molecular weight and long chain molecules are not suitable for large scale production using high-pressure homogenization techniques, supercooled melts, lipid crystallization, localization of large amount drug molecules on the surfactants surface, appearance of gelation phenomenon and hydrolyzing of drug molecules in the lipid or water interface [50].

Approaches of SLNp on diabetes mellitus treatment

Type 2 diabetes mellitus (T2DM), is a prototype multifactorial complex diseases that considered as one as one of the leading causes of morbidity and mortality in the world [51]. The pancreas plays a primary role in the metabolism of glucose by secreting the hormones insulin and glucagon. The islets of Langerhans secrete insulin and glucagon directly into the blood [52]. When the blood glucose level falls, glucagon secreted and increased blood glucose concentration partly by breaking down stored glycogen in the liver by glycogenolysis. Gluconeogenesis is the production mechanism of glucose in the liver from the non-carbohydrate precursor, glycogenic amino acids [53]. Several studies were elaborated the risk factors responsible for T2DM including obesity, hypertension, smoking, physical inactivity, low education, dietary patterns, family history and specific gene [54]. Diabetic foot ulcer is the most common, disabling and costly complications of diabetes, such infected ulcers resulting from amputation account for a threefold increased risk of death within 18 mo and associated with severe clinical depression and dramatically increased mortality rates [55]. In India, approximately 45,000 legs are amputated every year, and the numbers are increasing each year. Almost, 75% of these amputations are carried out in neuropathic feet with secondary infection, which is potentially preventable [56]. Commercially available drug for the treatment of DM like metformin, sulphonylurea, Thiazolidinediones causes gastrointestinal disturbances, abdominal pain, metallic taste, hypoglycemic conditions, hepatotoxicity, etc. [57]. Continuous subcutaneous route of insulin administration to type-1 diabetic patients causes allergic conditions, lipodystrophy and severe stomach pain respectively [58]. In order to reduce the risk for patients, the oral route of insulin delivery might be helpful to eliminate the patient's pain, infections and increase the confidential score to diabetes mellitus treatment [59]. However, insulin protein molecules undergo degradation through the intestinal lumen proteolytic enzymes and exhibited lower permeability in the blood stream through lipid bilayer membrane.

Drug carriers system such as liposomes, microsphere, microemulsion, and polymeric nanoparticles is used to enhance the oral delivery of insulin. Gundogdu and Yurdasiper [60] reviewed the transport mechanism of some oral antidiabetic nanoparticulate system. Liposomes have been used to improve the

oral absorption of glucose and make the longer action of insulin by targeting the delivery of insulin into liver hepatocytes. Chono *et al.*, [61] showed the liposomes with phospholipid i.e. palmitoyl phosphatidylcholine, improved pulmonary insulin delivery in experimental rats. The usages of liposome in diabetic treatments are restricted due to (i) their action depend upon suitable lipid molecules, for example liposomes with di lauroyl, dimyristoyl, distearyl or dioleoyl phosphatidylcholine not effective for insulin delivery (ii) intravenous route of administration (iii) minimum amount of insulin in liposome complex and cost-effective [62]. A number of studies have been reported how to encapsulate the protein nature drug molecules into microsphere system to enhance the bioavailability. Ubaidulla *et al.*, [63] reported the chitosan phthalate microspheres containing insulin was prepared by emulsion cross-linking method to deliver the insulin substance orally. The microspheres showed better relative pharmacological efficacy (18.66%). Only a few of them get fruitful results because the outer water phase layer causes failure in the drug development process. Hence, researchers employed solid-in-oil-in-oil emulsion process to encapsulate the insulin in poly (lactic-co-glycolic acid) microspheres system. As a result of the *in vitro* drug release studies, released insulin from the microsphere withstands up to 60 d [64]. Moreover, the microsphere particles sizes are ranges from 1 to 10 μm in diameter; it might be causing defective permeability into the blood barrier system.

Micro-emulsion drug carrier enclosed in alkyl cyanoacrylates, isopropyl myristate, capryl caproyl macrogol glycerides, polyglycerol oleate and insulin provides enhanced preparation liveness for solubilisation and entrapment of drug molecules [65]. On the other hand, the poly alkyl cyanoacrylate with insulin-loaded drug carrier prepared by microemulsion method using caprylo-caproyl macrogol glycerides and polyglycerol oleate surfactants showed less encapsulation efficiency (32%) and loading capacity [66]. Poly(lactic-co-glycolic acid) (PLGA) is one of the most successfully developed biodegradable polymers suitable for hydrophilic and hydrophobic ligand molecules. Earlier reports showed applications of polymeric nanoparticles in diabetes, especially serum blood glucose reduction. PLGA nanoparticles were prepared by solvent diffusion method, emulsion solvent diffusion method and double emulsion solvent evaporation method was evaluated for their pharmacologic effects via oral administration to experimental diabetic rats and showed a reduction in both the release rate and the total amount of insulin released [67, 68]. Sun *et al.* [68] reported the PLGA nanoparticles with insulin sodium oleate composite reduced 23% of the plasma glucose level and maintained the same condition up to 24h. Because of the anionic sodium oleate, formed complex with positively charged insulin molecules that elevates the liposolubility of the loaded drug candidate such as insulin. Cui and his co-workers [69] prepared polymeric nanoparticles (PLGA, phospholipids) loaded with insulin by the reverse micelle solvent evaporation method shown 90% of encapsulation efficiency, 4% of drug loading capacity, 7% of oral bioavailability with 428 nm of particle size.

Unfortunately, the above-revealed methods are not successful in delivering the insulin because of lower stability, insufficient encapsulation and loading capacity, use of a solvent in drug formulation and toxicity [70, 71]. Then compared to above-mentioned nanocarrier system, SLNp loaded with insulin-mixed micelles exhibited high encapsulation efficiency (97.78%), loading capacity (18.92%), and increased the liposolubility of insulin with stearic acid and palmitic acid [67]. To overcome the stability and permeability problems, a number of research works have been undertaken by using SLNp carrier system. For example, Fonte *et al.*, [72] developed chitosan loaded SLNp to enhance the oral bioavailability of insulin. Lipo-solubility of insulin increases by loading the insulin-mixed micelles into SLNp [38]. Bio-adhesive characters of the suitable lipid molecules carried out the gradient diffusion of lipid molecules into the intestinal body cells [39]. Excoecaria gallocha derived Rutin was used for SLNp preparation with palmitic acid as a lipid matrix and polyvinyl alcohol (PVA) as a capping agent. It exhibited spherically and rod shape, with excellent encapsulation efficiency and stability. Rutin loaded solid

lipid nanoparticles showed a significant anti-diabetic effect in streptozotocin-induced diabetic rats. The solid lipid matrix has enhanced the bioavailability of rutin. Nano-encapsulated ointment from the rutin loaded solid lipid nanoparticles increased the rate of diabetic wound ulcer contraction based on a percentage of wound closure, histopathological scores, hydroxyl proline and antioxidant levels [18]. One of the meglitinide class blood glucose lowering drug molecule is Repaglinide which used for the treatment of T2DM. Notably, it had a short half-life i.e. one hour and exhibited lower bioavailability when entered, a fast and short-acting meglitinide. Repaglinide loaded SLNp delivery into the transdermal patches on diabetic rats showed significant regulation of blood glucose level by its penetration via stratum corneum, epidermis and dermal layer to the blood barrier [11]. The oral administration of cetyl palmitate-loaded SLNp and insulin-octa arginine cell-penetrating peptide loaded SLNp showed a significant hypoglycemic effect in diabetic rats [73, 74].

CONCLUSION

This review gives a suitable choice of lipid and surfactant for the preparation of SLNp to increase the relative oral bioavailability and decrease the hyperglycemic conditions in diabetic long-suffering. In addition to that insulin could be delivered oral as well as pulmonary route using SLNp. Hopefully, the highest encapsulation efficiency, loading capacity, pharmacological bioavailability, protected from the reticuloendothelial system and extended blood occurrence of antidiabetic drug loaded SLNp could replace the subcutaneous insulin injection, diminish physiological stress and improves the life quality of diabetic patients in the near future.

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CONFLICT OF INTERESTS

Declared none

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