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Solid lipid Nanoparticles for Oral delivery of Poorly Soluble Drugs

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Abstract
Solid Lipid nanoparticles show interesting features concerning therapeutic purposes. Their main characteristic is the fact that they are prepared with physiologically well-tolerated lipids. Different substances have been entrapped into lipid Nano-particles, ranging from lipophilic and hydrophilic molecules, including labile compounds, such as proteins and peptides. Solid lipid nanoparticles are with a size in nanometre range can protect the drug against in vitro and in vivo degradation, it release the drug in controlled manner and also offers the possibility of drug targeting. The use of solid lipid drug nanoparticles is an universal approach to increase the therapeutic performance of poor soluble drugs in oral route of administration. The present review discusses the physico-chemical properties of solid lipid nanoparticles, Lymphatic mechanism, production methods, invio fate of lipids and potential therapeutic applications.
Keywords: Lipids, Nanoparticles, Oral Delivery, Lymphatic uptake, Poor soluble drugs.

INTRODUCTION

The gastrointestinal (GI) tract acts as a physiological and chemical barrier setting several challenges for oral drug delivery systems (DDS). The development of composite formulation methods helps to improve bioavailability, and the potential of this emerging field is promising. In this context, increased knowledge on lipids makes them more and more interesting for the formulation of poorly water-soluble drugs and the formation of solubilized phases from. **(Constanze Setzer et al., 2010)** Lipid Matrices have been used for a long time as a carrier for lipophilic drugs to enhance their oral bioavailability. Various lipid particulate carriers have been developed and studied for many years.

Phospholipids have a special amphiphilic character, which absorption may occur when placed in water, they form various structures depending on their specific properties. Mostly, they form micelles or are organized as lipid bi-layers with the hydrophobic tails lined up against one another and the hydrophilic head-group facing the water on both sides. These unique features make phospholipids most suitable to be used as excipients for poorly water soluble drugs. Thereby, it has to be kept in mind that the enhanced solubility of lipophilic drugs from lipid-based systems will not necessarily arise directly from the administered lipid, but most likely from the intra-luminal processing, to which it is subjected before it gets absorbed. **(Constanze Setzer et al., 2010)**

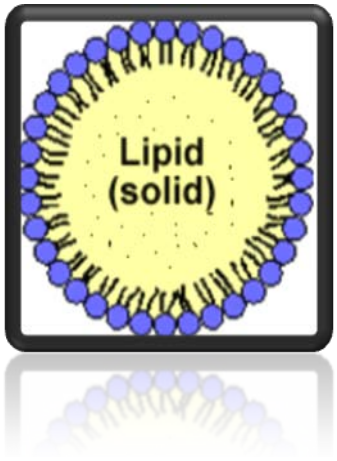
Lipid-based drug delivery systems may contain a broad range of oils, surfactants, and co-solvents. They represent one of the most popular approaches to overcome the absorption barriers and to improve the bioavailability of poorly water-soluble drugs. Furthermore, among the factors affecting the bioavailability of the drug from lipid-based formulations are the digestion of lipid, the mean emulsion droplet diameter, the lipophilicity of the drug and the type of lipids. Lipid formulations can reduce the inherent limitation of slow and incomplete dissolution of poorly water-soluble drugs and facilitate formation of solubilized phases from which absorption may occur. The solubilized phases most likely arise from intral aminal processing after lipid absorption. The co-administration of lipids with drugs can also impact their absorption pathway although most orally administered compounds gain access to the systemic circulation via the portal vein, some highly lipophilic drugs are transported directly to the systemic circulation via intestinal lymphatic's, which improves oral bioavailability of API.

SOLID LIPID NANO-PARTICLES

The first approach of using lipid micro particles was described by (**Eldem et al.,**) reporting the production by high-speed stirring of a melted lipid phase in a hot surfactant solution obtaining an emulsion. Solid micro particles are formed when this emulsion is cooled to room temperature, and the lipid recrystallizes. The obtained products were called "lipid nanopellets", and they have been developed for oral administration. Lipospheres were described by Domb applying a sonication process. To overcome the drawbacks associated to the traditional colloidal systems such as emulsions, Liposomes, and polymeric nanoparticles solid lipid nanoparticles (SLN) have been developed for similar purposes.

SLN are biocompatible and biodegradable and have been used for controlled drug delivery and specific targeting. These colloidal carriers consist of a lipid matrix that should be solid at both room and body temperatures, having a mean particle size between 50 nm and 1000nm.which are dispersed in water or aqueous surfactant solution. They are made up of solid hydrophobic core having a monolayer of phospholipid coating. Solid core contains the drug

dispersed or dissolved in lipid matrix. They have potential to carry lipophilic or hydrophilic drugs. **(Patricia Severino et al., 2011)**



Structure of SLNs

A clear advantage of the use of lipid particles as drug carrier systems is the fact that the matrix is composed of physiological components, that is, excipients with generally Recognized as safe (GRAS) status for oral and topical administration, which decreases the cytotoxicity.

SLN prepared up to concentrations of 2.5% lipid do not exhibit any cytotoxic.

Effects *in vitro.* Even concentrations higher than 10% of lipid have been shown a viability of 80% in culture of human granulocytes. In contrast, some polymeric nanoparticles showed complete cell death at concentrations of 0.5%.

SLN can be obtained by exchanging the liquid lipid (oil) of the o/w Nano-emulsions by a solid lipid. In general, a solid core offers many advantages in comparison to a liquid core. Emulsions and Liposomes usually show lack of protection of encapsulated drugs, and drug release as a burst (emulsions) or Non controlled (from Liposomes). SLN possess a solid lipid matrix identical to polymeric nanoparticles. In addition, SLN are of low cost, the excipients and production lines are relatively cheap, and the production costs are not much higher than those established for the production of parenteral emulsions.

Advantages of SLNs over polymeric nanoparticles: (Rahul Nair et al.,2011)

SLNs combine the advantages of other colloidal particles like polymeric Nanoparticles, fat emulsions and Liposomes while simultaneously avoiding their Disadvantages. The advantages of SLNs include the following such as:

1. SLNs particularly those in the range of 120–200 nm are not taken up readily by the Cells present in the RES (Reticulo Endothelial System) and thus bypass liver and spleenFiltration.
2. In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
3. It is easy to manufacture than bi-polymeric nanoparticles.
4. Controlled and targeted release of the incorporated drug can be achieved.
5. Increased scope of drug targeting can be achieved by coating with or attaching ligands to SLNs.
6. Enhanced drug stability. SLNs stable for three years have been developed. This is of more importance compared to the other colloidal carrier systems.
7. Better control over release kinetics of encapsulated compound.
8. SLNs can be enhancing the bioavailability of entrapped bioactive.
9. Excellent reproducibility with use of different methods as the preparation Procedure.
10. The feasibility of incorporating both hydrophilic and hydrophobic drugs.
11. The carrier lipids are biodegradable and hence safe.
12. Avoidance of organic solvents.
13. Feasible large scale production and sterilization.
14. Chemical protection of labile incorporated compound.

Disadvantages:

1. Poor drug loading capacity.
2. Drug expulsion after polymeric transition during storage.
3. Relatively high water content of the dispersions (70-99.9%).
4. The low capacity to load water soluble drugs due to partitioning effects during the Production process.

Lipid Materials for Oral Administration.

The term lipid is used here in a broader sense and includes triglycerides, partial glycerides, fatty acids, steroids, and waxes. However, it is required that matrix maintains the solid state at room temperature, and for this purpose, the selection of lipids is based on the evaluation of their polymorphic, crystallinity, miscibility, and physicochemical structure .

Furthermore, the use of mono- and di-glycerides as lipid matrix composition might increase drug solubility compared to highly pure lipids, such as monoacid triglycerides. Naturally occurring oils and fats comprise mixtures of mono-, di-, and triglycerides, containing fatty acids of varying chain length and degree of unsaturation. The melting point of these lipids increases with the length of the fatty acid chain and decreases with the degree of unsaturation. The chemical nature of the lipid is also important, because lipids which form highly crystalline particles with a perfect lattice (e.g., monoacid triglycerides) lead to drug expulsion during storage time. Physico-chemically stable lipid nanoparticles will be obtained only when the right surfactant and adjusted concentration have been employed. **(Patricia Severino et al., 2011)**

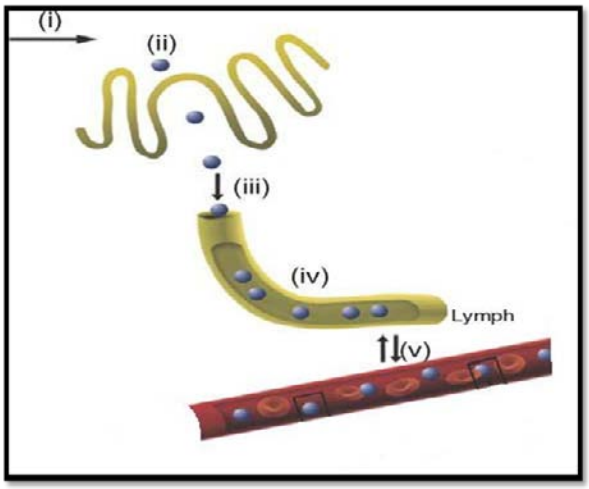
Different Lipids and Surfactants used for preparation of SLNs (Rahul Nair et al., 2011)

Lipids	Surfactants
Triacylglycerols: Tricaprin Trilaurin Trimyristin Tripalmitin Tristearin	**Phospholipids:** Soy lecithin Egg lecithin Phosphatidylcholine
Acylglycerols: Glycerol monostearate Glycerol behenate Glycerol palmitostearate	**Ethylene oxide/propylene oxide copolymers:** Poloxamer 188 Poloxamer 182 Poloxamer 407 Poloxamine 908
Fatty acids: Stearic acid Palmitic acid Decanoic acid Behenic acid	**Sorbitan ethylene oxide/propylene oxide copolymers:** Polysorbate 20 Polysorbate 60 Polysorbate 80
Waxes: Cetyl palmitate	**Alkylaryl polyether alcohol polymers:** Tyloxapol
Cyclic complexes: Cyclodextrin	**Bile salts:** Sodium cholate Sodium glycocholate Sodium taurocholate Sodium taurodeoxycholate
Hard fat types: Witepsol W 35 Witepsol H 35	**Alcohols:** Ethanol Butanol

Lymphatic transport mechanism of SLNs

Use of lipid based drug delivery systems has led to effective development of many such compounds with acceptable oral bioavailability. The ability to efficiently deliver lipophilic drug molecules, especially in combination with lipid based delivery systems has led to renewed interest in intestinal lymphatic drug transport. After absorption into the enterocytes, the vast majorities of orally administered drugs rapidly diffuse across the cell, are absorbed into the capillaries of portal vein and are thereby processed via liver to systemic circulation. Highly lipophilic drug molecules, however, may associate with lymph lipoprotein in the enterocytes and gain access to the mesenteric (intestinal) lymphatic's, effectively bypassing the liver and gaining access to the systemic circulation via the thoracic lymph duct. The extremely high drug concentration attainable in lymph (up to 1000 times higher than the plasma concentration) often drug delivery advantages in addition to reduced first-pass metabolism for lymphatically transported drugs, including specific delivery to lymph resident B and T lymphocytes and opportunity to target the principle pathway of tumor metastasis **(Porter CJH et al., 2001)**.

The unique properties of lipids viz., their physiochemical diversity, biocompatibility and proven ability to enhance oral bioavailability of poorly water soluble, lipophilic drugs through selective lymphatic uptake have made them very attractive candidates as carriers for oral formulations. With the above promises, the emerging field of lipid-based oral drug delivery system. (**Sanjay Singh et al., 2009**)



A diagrammatic representation of uptake of lipids by intestinal lymphatic (Adapted from Florence TA, 2005)

i. **Flow in GIT**
ii. **access and adhesion to M- cells of Peyer's patches or enterocytes;**
iii. **passage into the mesenteric lymph;**
iv. **flow in the lymph vessels**
v. **transport between lymph and blood**

Phospholipids have a special amphiphilic character, which absorption may occur When placed in water, they form various structures depending on their specific properties. Mostly, they form micelles or are organized as lipid bi-layers with the hydrophobic tails lined up against one another and the hydrophilic head-group facing the water on both sides. These unique features make phospholipids most suitable to be used as excipients for poorly water soluble drugs. Thereby, it has to be kept in mind that the enhanced solubility of lipophilic drugs from lipid-based systems will not necessarily arise directly from the administered lipid, but most likely from the intra-luminal processing, to which it is subjected before it gets absorbed. **(Constanze Setzer et al., 2010)**

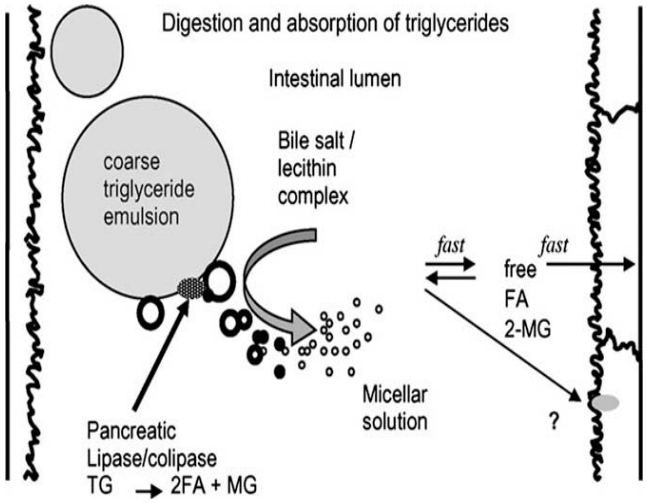
In vivo fate of lipid in human body

An adult digestive system is powerful enough to hydrolyze approximately 100–140 g of lipid everyday. The solubilization of drug in the GI tract and its bioavailability depend predominantly on the intraluminal processing to which lipids are subjected prior to absorption. Therefore, knowledge of the journey of lipids from the GI lumen to the circulatory system in the presence of a powerful digestive system is of great significance for interpretation of the biopharmaceutical properties of oral lipid-based formulations and successful product development Therefore, the focus of this section is to simplify the understanding of the entire process by dividing it into three distinct phases: **(Sanjay Singh et al., 2009)**

(1) Digestive phase, (2) absorption phase, (3) circulatory uptake

Digestive phase

The digestive phase initiates with the physical breakdown of lipid formulation into a coarse emulsion (lipid droplets _0.5 lm) of high surface area due to shear produced by antral contraction, retropulsion and gastric emptying. This is accompanied with hydrolysis of the fatty acid glyceryl esters by gastric lipase secreted from chief cells in the stomach (capable of functioning in an acidic environment) which act at the oil/water interface. The enzymatic hydrolysis reduces the TGs into its more polar products monoglycerides (MGs) and FAs. Lipase cleaves the two ester bonds of the TG molecule, producing a molecule of diglyceride and one free FA first, and then two molecules of free FAs and one molecule of MG (Fig. 2). The dispersed lipid digestion products along with the undigested lipids then empty into the duodenum. In the presence of FAs, cholecystokinin is released into the portal circulation which additionally stimulates the pancreas to release TG lipase and co-lipase required to facilitate the TGs digestion within emulsified particles. Thus, the lipolysis is an autocatalytic process capable of enhancing the emulsification when lipolytic products are produced. Both enzymes being water soluble act at the water/lipid interface of the particles and hydrolyze TGs to MGs and FAs



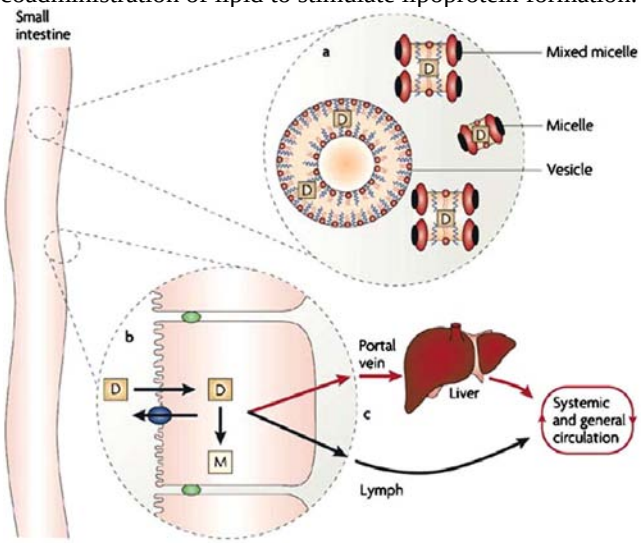
A schematic representation of the role of lipase/co-lipase and mixed bile salt micelles in digestion of triglycerides and solubilization of the digestion products. Each triglyceride molecule is digested to generate two molecules of fatty acid and one molecule of monoglyceride which is solubilized in the lumen of the gut

Absorption phase

The colloidal species produced, in the form of micelles, mixed micelles, vesicles and free FAs as a result of lipid digestion, are taken up by passive diffusion, facilitated diffusion and active transport through the enterocyte membrane. In the cytosol, a fatty acid-binding protein transports them from the apical membrane to the smooth endoplasmic reticulum (ER). In the smooth ER, FAs and MGs are resynthesized into TGs and phospholipids, respectively, which are transferred to the golgi apparatus and stored into secretory vesicles to be released by exocytosis into the extracellular space via basolateral membrane. Another critical step is the association of the absorbed free drug with the intestinal lipoproteins (chylomicrons) within the enterocyte. These chylomicrons are relatively large (<1 lm in diameter) and colloidal in nature which eventually lead to selective intestinal lymphatic transport of the lipophilic compound During the absorption phase, the drug molecules are usually exposed to the activity of major phase I drug metabolizing enzyme, Cytochrome P450 3A4 (CYP 3A4), present at high concentrations in enterocytes located at the villus tip of the small intestine in humans. Studies conducted across different laboratories have accounted the role of these enzymes in increasing the bioavailability of drugs when co-administered with lipid, which is indicative of an additional pathway by which lipids enhance oral drug bioavailability

Circulatory uptake

The majority of orally administered drugs gain access to the systemic circulation by absorption into the portal blood. However, some extremely lipophilic drugs (log P > 5, solubility in TG > 50 mg/ml) gain access to the systemic circulation via lymphatic route, which avoids hepatic first-pass metabolism. Therefore, highly metabolized lipophilic drugs may be potential candidates for lipidbased drug delivery. Compounds showing increased bioavailability in the presence of lipids (dietary or lipid-based formulation) are absorbed via the intestinal lymph as they are generally transported in association with the long-chain TGs lipid core of intestinal lipoproteins formed in the enterocyte after re-esterification of free FAs and MGs. Short-chain TGs are primarily absorbed directly in the portal blood. Drug transport via the lymphatics, therefore, requires coadministration of lipid to stimulate lipoprotein formation.



Various mechanisms of enhancement of drug bioavailability in the presence of lipids: (a) solubilization of drug in the intestinal fluid by formation of colloidal species viz., vesicles, mixed micelles and micelles; (b) interference

with enterocyte-based transport and metabolic processes, thereby potentially changing drug uptake, efflux, disposition and the formation of metabolites (M) within the enterocyte; (c) by selective lymphatic uptake which reduces first-pass drug metabolism as intestinal lymph travels directly to the systemic circulation .

PREPARATION OF SOLID LIPID NANOPARTICLES

SLNs are made up of solid lipid, emulsifier and water/solvent. The lipids used
may be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), and steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently. **(S. mukherjee et al.,)**

The basic production methods for SLNs are as follows-

- Hot homogenization technique.
- Cold homogenization technique.
- micro emulsion technique
- Solvent emulsification-diffusion technique
- Precipitation method
- W/O/W Double emulsion method
- Spray drying method

Schematic representation for the production of solid lipid nanoparticles by the hot and cold homogenization techniques.

Steps	Hot Homogenization Technique	Cold Homogenization Technique
Step 1.	Melt lipid; dissolve or solubilize active ingredients in the lipid.	
Step 2.	Disperse melted lipid in hot aqueous surfactant solution.	Cooling and recrystallization of the active lipid mixture using liquid nitrogen or dry ice.
Step 3.	Preparation of a pre-emulsion by means of a rotor-stator homogenizer.	Milling of the active lipid mixture by means of a ball mill or a jet mill.
Step 4.	High-pressure homogenization above the melting point of the lipid.	Disperse lipid microparticles in cold aqueous surfactant solution.
Step 5.	Cooling and recrystallization.	High-pressure homogenization at or below room temperature.

Solvent emulsification/ evaporation:

Nanoparticle dispersions are prepared by precipitation in o/w emulsions. The lipophilic material is dissolved in a water-miscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent nanoparticle dispersion is formed by precipitation of the lipid in aqueous medium. The mean particle size depends on the concentration of the lipid in organic phase. Very small particles can be obtained with low fat loads (5% w/w) related to the organic solvent. The advantage of this method over cold homogenization process is avoidance of any thermal stress. A clear disadvantage is the use of organic solvents **(Mehnert W et al., 2001).** Also, these dispersions are generally quite dilute, because of the limited solubility of lipid in the organic material. Typically, lipid concentrations in the final SLN dispersion range around 0.1 g/L, therefore, the particle concentration has to be increased by means of, e.g. ultra-filtration or evaporation **(Wissing SA et al., 2004).**

Microemulsion method:

This technique is based on the dilution of microemulsions. They are made by stirring an optically transparent mixture at 65-70^{o}C which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3 ^{o}C) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion **(Mukherjee S et al., 2009).**

Experimental factors such as microemulsion composition, dispersing device, temperature and lyophilisation on size and structure of the obtained SLN have been studied intensively. It has to be remarked critically, that the removal of excess water from the prepared SLN dispersion is a difficult task with regard to the particle size. Also, high concentrations of surfactants and co-surfactants (e.g. butanol) are necessary for formulating purposes, however less desirable with respect to regulatory purposes and application **(Wissing S et al., 2004).** The dilution process is critically determined by the composition of microemulsion. According to literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes.

The particle size is critically determined by the velocity of the distribution processes. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (e.g. acetone), while larger particle sizes were obtained with more lipophilic solvents. Due to the dilution step, achievable lipid contents are considerably lower compared with the HPH based formulations **(Mehnert W et al., 2001**

W/O/W Double emulsion method:

Recently, a novel method based on solvent emulsification–evaporation for the preparation of SLN loaded with hydrophilic drugs has been introduced to the scientific community. Here, the hydrophilic drug is encapsulated, along with a stabiliser to prevent drug partitioning to the external water phase during solvent evaporation, in the internal water phase of a w/o/w double emulsion. This technique has been used for the preparation of sodium cromoglycate-containing SLN, however, the average size was in the micrometer range so that the term ‘‘lipospheres’’ in the sense as a term for nanoparticles is not used correctly for these particles **(Cortesi et al., 2002).**

SLN preparation by using supercritical fluid:

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. There are several variations in this platform technology for powder and nanoparticle preparation. SLN can be prepared by the

rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method.

Spray drying method:

It's an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a drug product. It's a cheaper method than lyophilization. This method cause particle aggregation due to high temperature, shear forces and partial melting of the particle. Freitas C et al., recommends the use of lipid with melting point >70^{o}C for spray drying. The best result was obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

Drug Incorporation Models: (Pragati S. et al., 2009)

The types of SLNs depend on the chemical nature of the active ingredient and lipid, the solubility of actives in the melted lipid, nature and concentration of surfactants, type of production and the production temperature. Therefore 3 incorporation models have been proposed for study.

Type I or homogenous matrix model

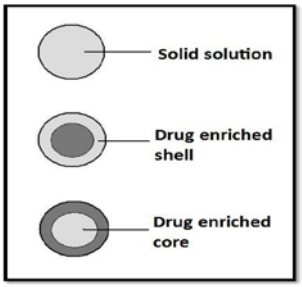
The SLN Type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLN are produced by the cold homogenation method. A lipid blend can be produced containing the active in a molecularly dispersed form. After solidification of this blend, it is ground in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

Type II or drug enriched shell model

It is achieved when SLN are produced by the hot technique, and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w Nano-emulsion the lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model is the incorporation of coenzyme

Type III or drug enriched core model

Core model can take place when the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in the melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core.



Models of drug entrapment

CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

Particle size

- ***Photon correlation spectroscopy*** (technique based on dynamic laser light scattering due to Brownian motion of particles in solution/suspension, suitable for measurement of particles in the range of 3 nm to 3 mm. The Photon correlation spectroscopy (hydrodynamic diameters) diameters are based on the amount of light scattering from the nanoparticles. The nanoparticles are usually polydisperse in nature and polydispersity index (P.I.) gives a measure of size distribution of the nanoparticle population. Theoretically the P.I. for a monodisperse system is zero, for polydisperse systems the P.I. should be less than 0.5 (P.I. greater than 0.5 indicates a very broad size distribution).
- ***Transmission electron microscopy*** (uses electron transmitted through the specimen to determine the overall shape and morphology i.e. both particle size as well as distribution.)
- ***Scanning electron microscopy*** (uses electron transmitted from the specimen to determine the overall shape and morphology i.e. both particle size as well as distribution).
- ***Scanned probe microscopes***
- ***Polarization intensity differential scattering (PIDS)*** (measures the particle size as low to 40 nm)
- ***Field flow fractionation*** (based on the elution of the smaller particles when placed on a parabolic flow profile. All the eluted fractions are analyzed by multi angle light scattering (MALS) where a photometer records the scattering signal of the particles and calculates size weighed radius. MALS allows to measure particle radius from 10 nm–1 μm.)
- ***X-ray diffraction*** (a useful technique to exclude aggregate of more than 1 μm and substantial polymorphic β1 transition form to stable; thus help in characterizing the crystalline nature of the compound and determine the polymorphic shifts present).
- ***Freeze-fracture electron microscopy*** (solid spherical structure with no internal lamellae).

Molecular weight

- ***Gel chromatography***
- ***Static secondary-ion mass spectrometry (SSIMS)***
- ***Atomic force microscopy*** (to determine the original unaltered shape and surface properties of the particles)

Surface element analysis

- ***X-ray photoelectron spectroscopy for chemical analysis (ESCA)***
- ***Electrophoresis***
- ***Laser Doppler anaemomometry***
- ***Amplitude-weighted phase structure determination***
- ***X-ray diffraction (XRD)***
- ***Differential scanning calorimetry(DSC)*** (yields information on melting behavior and crystallization

behavior of solid and liquid constituents of the particles).

Density

- ***Helium compression pychnometry***
- ***Contact angle measurement***
- ***Hydrophobic interaction chromatography***

Molecular analysis

- ***H NMR*** (mobility of molecules inside the solid lipid nanoparticles)
- ***Infra red analysis*** (structural property of lipids)

APPLICATIONS OF SOLID LIPID NANOPARTICLES

Solid lipid Nanoparticles possesses a better stability and ease of upgradability to production scale as compared to liposomes. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year. They can deliver drugs to the liver *in vivo* and *in vitro* to cells which are actively phagocytic. There are several potential applications of SLNs **(Mukherjee S et al., 2009)** some of which are given below.

a) SLNs as gene vector carrier

SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids **(Rudolph C et al., 2004)**. The lipid nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nuclic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

b) SLNs for topical use

SLNs and NLCs have been used for topical application for various drugs such as tropolide, imidazole antifungals, anticancers, vitamin A, isotretinoin, ketoconazole, DNA, flurbiprofen and glucocorticoids. The penetration of podophyllotoxin- SLN into stratum corneum along with skin surface lead to the epidermal targeting. By using glyceryl behenate, vitamin A-loaded nanoparticles can be prepared. The methods are useful for the improvement of penetration with sustained release. The isotretinoin-loaded lipid nanoparticles were formulated for topical delivery of drug. The soyabean lecithin and Tween 80 were used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin.

c) SLNs as cosmeceuticals

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The *in vivo* study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream. SLN and NLCs have proved to be controlled release innovative occlusive topicals. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations.

d) SLNs for potential agriculture application

Essential oil extracted from *Artemisia arboreseens* L when incorporated in SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticides. The SLN were prepared here by using compritol 888 ATO as lipid and poloxamer 188 or Miranol Ultra C32 as surfactant.

e) SLNs as a targeted carrier for anticancer drug to solid tumours

SLNs have been reported to be useful as drug carriers to treat neoplasms. Tamoxifen, an anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin.

f) SLNs in breast cancer and lymph node metastases

Mitoxantrone-loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug. Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system is enhanced its efficacy and reduced breast cancer cells.

g) Oral SLNs in antitubercular chemotherapy

Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance. By using the emulsion solvent diffusion technique this antitubercular drug loaded solid lipid nanoparticles were prepared. The nebulization in animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.

h) Stealth nanoparticles

These provide a novel and unique drug-delivery system they evade quick clearance by the immune system. Theoretically, such nanoparticles can target specific cells. Studies with antibody labelled stealth lipobodies have shown increased delivery to the target tissue in accessible sites. Stealth SLNs have been successfully tested in animal models with marker molecules and drugs.

CONCLUSION

Oral drug delivery is continuously looking into newer avenues due to realization of the factors like poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability due to food effect which are playing major role in disappointing in vivo results leading to failure of the conventional delivery system. Since the last decade, the oral drug delivery has taken a new dimension with the increasing application of Solid lipid Nanoparticles as a carrier for the delivery of poorly water soluble, lipophilic drugs.

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