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Review Article

A REVIEW ON CLASSIFICATION, METHOD OF PREPARATION, CHARACTERIZATION OF SOLID LIPID NANOPARTICLES AND THEIR APPLICATION

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ABSTRACT

Nanotechnology is a rapidly expanding research area, encompassing the development of human-made materials in the nanometer size range. Nanoparticles attracted scientists across many disciplines to engineer many desired properties that might otherwise be incompatible on a single device. Formulation scientists are facing challenges such as poor solubility and bioavailability of the newly invented drugs. One of the approaches to face the poor solubility and bioavailability of the drugs is to develop the particulate carrier system. Solid lipid nanoparticles or liposphere or nanosphere system is the most feasible particulate carrier system which is an alternative to nanoemulsions, liposomes, and polymeric nanoparticles. This carrier system offers added advantages in comparison to other related particulate drug delivery systems. Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine, and research, as well as in other varied sciences. This carrier system offers added advantages in comparison to other related particulate drug delivery systems. This review presents state-of-the-art information on various basic and applied aspects of solid lipid nanoparticles viz. SLNs structure and morphology of SLNs, Classification, advantages, limitations, Composition, Method of preparation and post-manufacturing process of SLNs. It also focuses on the Drug release from SLNs and factors affecting drug release from SLNs. Appropriate analytical techniques for the characterization of SLNs, Different routes of administration, Applications of SLNs and market scenario including the patents to exploit these SLNs in the pharmaceutical market also discussed.

KEYWORDS: *Nanoparticles, Solid Lipid Nanoparticles, Method of preparation, Evaluation, Application.*

INTRODUCTION

Nanotechnology is defined as the understanding and control of matter at dimensions between 1 and 100 nm where unique phenomena enable novel applications [1]. The term Nano originated from the Greek Nanos which means 'dwarf'. It is one billionth of a meter [2]. Nanoparticles can bedefined as particulate dispersions or solid particles with asize in the range of 10-1000nm [3].

The lipid nanoparticles may be considered as derivatives of o/w emulsions, wherein the liquid lipids of oil droplets are replaced by lipids that exist in the solid form at body temperature. The solid lipid matrix of the lipid nanoparticles not only provides a controlled release pattern, but also protects chemically labile drugs against degradation, thus simulating the matrix effect of polymericnanoparticles. Based on their morphological and structural differences, lipid nanoparticles can be categorized into two categories: SLNs and NLCs. The SLNs are considered first generation lipid nanoparticles while NLCs constitute the second generation [4].

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1. Introduction to SLNs:

Lipids have been used as an alternative carrier for polymeric nanoparticles, particularly for lipophilic pharmaceuticals and lipid nanoparticles are known as solid lipid nanoparticles (SLNs) (fig.1) [5].

SLNs introduced in 1991 represent an alternative and suitable system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. As represented in Table 2.

The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. SLN are made of solid hydrophobic core having a monolayer of phospholipids coating. The hydrophobic chains of phospholipids incorporated in the fat matrix and have the potential to carry lipophilic or hydrophilic drugs or diagnostics [6].

2. Type/Classification of SLNs & Drug Incorporation Models:

SLNs are broadly classified into three types, depending on nature and type of lipids, chemical nature and structure of drug, solubility of active ingredient in the lipid, type and concentration of surfactant, temperature during production, and production method used [7].

SLNs are spherical, highly ordered crystalline particles formed of pure solid lipids or an admixture of two or more solid lipids. Based on the morphological differences and variance in drug incorporation, three models are proposed for SLNs viz. drug-enriched shell model, drug-enriched core model, and solid solution model/homogeneous matrix model [8].

The drug release pattern is defined by the drug incorporation models of SLNs, which have been categorized as follows (fig.2) [5].

Table No. 1: Type/Classification of SLNs & Drug Incorporation Models

Solid solution Model	Drug –enriched Shell Model	Drug –enriched Core Model
• Formation of this model in cold homogenization technique • Using no drug solubilizing surfactant • Drug dispersed in lipid matrix • There is a strong interaction between lipid and drug	• Formation of this model in hot homogenization technique • Formation of lipid core at recrystallization temperature of lipid • Cooling of the obtained dispersion leads to re partitioning of the drug to the lipid phase • Concentration of drug in surrounding membrane	• Dispersion cooling leads to a supersaturation of the drug which is dissolved in the lipid. • Precipitation of drug in melted lipid • Finally, further cooling lead to recrystallization of the lipid • Formation of drug-enriched core

2.1. SLNs. Type I or homogenous matrix model: [7, 9, 10]

Type I SLNs are prepared by cold homogenization method.In this method, solid drug is dispersed in melted solid lipid. After cooling, solidification of the lipid drug combination takes place.This solidified complex is grounded in its solid state to provide uniform drug distribution in SLNs [7].

In the first model, the drug is molecularly and homogeneously dispersed in the lipid matrix of the particles. Hence, drug release occurs via diffusion from the solid lipid matrix and/or by degradation of lipid matrix. As consequence of their structure, this type of SLN can show controlled release properties [9].

SLN type I or the homogenous matrix of solid solution, in which the drug is molecularly dispersed in the particle matrix [10].

2.2. SLNs.Type II or drug-enriched shell model: [7, 9, 10]

Type II SLNs are produced by hot homogenization method.The lipid is melted by increasing the temperature of the system and drug is dispersed in the melted lipid. During the cooling of hot o/w nanoemulsion system, lipid is solidified first and deposited on the outer layer of shell.This concentrated outer layer of shell shows a burst effect on drug release. Concentrations of drug on outer shell can be modified as per requirements [7].

In case of the second model (drug-enriched shell), the drug is concentrated on the outer shell of the nanoparticles. An outer shell enriched with active compound can be obtained when phase separation occurs during the cooling process from the liquid oil droplet to the formation of a SLN, since the lipid precipitates first forming a practically compound-free lipid core. This model is not suitable for prolonged drug release; nonetheless it may be used to obtain a burst release of the drug [9].

SLN type II or the drug enriched shell andwhere the drug is concentrated in the particle shell [10].

2.3. SLNs.Type III or drug-enriched core model: [7, 9, 10]

Type III SLNs are those in which active pharmaceutical ingredient is concentrated in the center of SLNs. Drug concentration is very high and near to its saturation in the lipid melt. When this highly concentrated lipid cooled down, solubility of drug in lipid melt will be reduced and deposited on the center of the SLN leads to formation of drug enriched core [7].

In contrast to drug-enriched shell model, drug-enriched core model is formed when precipitation of the drug is faster than lipid during cooling of the nanoemulsion. Generally, prolonged drug release is observed from these SLN [9].

SLN type III or drug enriched core models, where the drug is concentrated in the particle core [10].

3. Advantages and Disadvantages of SLNs: [11-15]

Advantages of SLNs:

- Broad range of course of organization
- Good physical solidness
- Protection from debasement of fused labile medications
- Modulated (quick or continued) arrival of the medication is conceivable
- Targeted tranquilize conveyance
- No utilization of natural solvents amid readiness
- Ease of scale-up
- Excellent biocompatibility
- No need of exceptional solvents
- Conventional emulsion creation systems could be utilized
- Raw materials utilized in the creation of emulsions could be utilized
- Use of biodegradable physiological lipids decreases both acute and chronic toxicity.
- SLNs possess better stability and are able to control release of incorporated drug in comparison with polymeric nanoparticles and liposomes.
- Improves solubility and bioavailability of poorly soluble drug molecules.
- SLNs have better stability compared to liposomes.

- High concentration of functional compound can be achieved.

Disadvantages of SLNs:

- Particle development
- Gelation propensity
- Unexpected polymorphic changes
- Thermal debasement of warmth labile medications
- Sophisticated hardware
- Unpredictable gelation inclination.
- Coexistences of a few colloidal animal groups.
- Drug removal after polymeric progress amid capacity.

4. Composition Profile of SLNs: [4, 5, 16]

SLN are prepared by a combination of lipids, Surfactants/Emulsifier, co-surfactants and other ingredients (fig 3).

4.1. Lipids:

The lipid, the main ingredient of lipid nanoparticles that influence their drug loading capacity, their stability and the sustained release behavior of the formulations

Ex: Fatty acid, fatty alcohol, triglycerides, mixture of mono-diglycerides wax

Selection criteria for lipids:

Important point to be considered in the selection of drug carrier system (lipid) is its loading capacity and also the intended use.

- Lipids that form highly crystalline particles with a perfect lattice cause drug expulsion.
- More complex lipids containing fatty acids of different chain length form less perfect crystals with many imperfections. These imperfections provide the space to accommodate the drugs.

Factors affecting selection of lipids:

- Drug solubility in the lipids
- Drug-loading capacity
- Stability of drugs in the lipids
- Drug release pattern
- Lipid crystallization
- Lipid polymorphism

It has been reported that, with an increase in the lipid content by 5%_10% there is increase in viscosity of the lipid melt, which results in larger particle size and a broader particle size distribution of the obtained SLNs.

The crystallization characteristics, hydrophilicity of lipids, and shape of lipid crystals are specific for each of the lipids. The lipid matrix plays a decisive role while considering drug release kinetics, drug-loading capacity, and other physicochemical properties of the nanoparticulate system**.**

4.2. Surfactants/Emulsifiers:

Poloxamer 188, Poloxamer 407, Tween 20, Tween 60, Tween 80,Span 20, polyvinyl alcohol, cremophor EL, Lecithin, sodium dodecyl sulphate, sodium glycolate.

4.3. Co surfactants:

Benzalkonium chloride, butanol, glycerol, sorbitol, and glycerol tristearate, 1-butanol Low molecular weight PEG , diethylene glycol monoethyl ether ,propylene glycol, ethanol, and sorbitan monostearate

4.4. Other Ingredients:

Some of the other important ingredients used in the formulation of SLNs. As represented in Table 3.

Manufacturing Technique of SLNs: [4, 17]

The methods used for the preparation of SLNs/NLCs are broadly divided into three main categories: Classification of methods of preparation of SLNs are as below (Fig. 4).

1. High Energy Input Methods
2. Low Energy Input Methods
3. Miscellaneous Methods

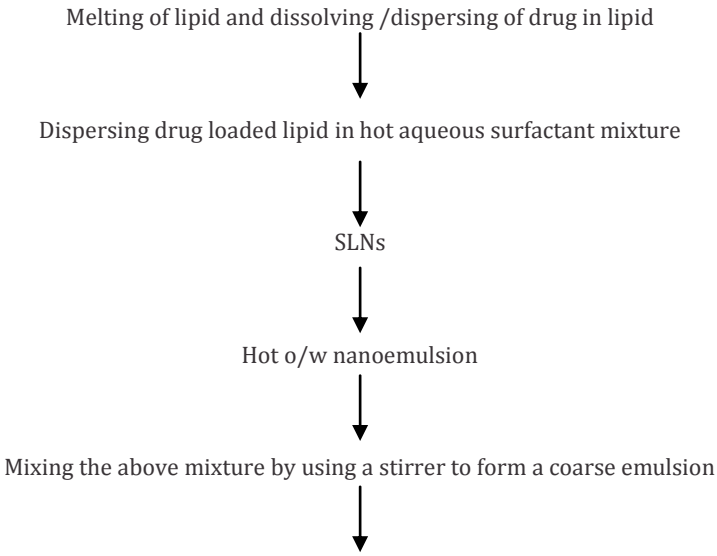
1. High Energy Input Methods:

1.1. High pressure homogenization technique:

A. Hot HPH technique

B. Cold HPH technique

A. Hot HPH technique:



Emulsion is homogenized by using high pressure homogenization above the melting point of lipid

↓

Solidification of nanoemulsion by cooling down at room temperature

B. Cold HPH technique:

Melting of lipids and dissolving /dispersing of drug in lipid

↓

Solidification of drug loaded lipid in liquid nitrogen or dry ice

↓

Grinding in a powder mill (50-100µm)

↓

Dispersing the powder in aqueous surfactant dispersion medium

↓

Mixture is homogenized by using high pressure

↓

Homogenization at room temperature

↓

SLNs

1.2 High shear homogenization technique:

Chamber with a rotor-stator homogenizer

↓

Placing the lipid ingredients and the water phase into the homogenize

↓ Applying high shear mixing (5 000 – 25000 rpm)at temperatures above the melting temperatures of the lipids

After homogenization, the formed hot microemulsion is cooled to form SLN.

1.3. Ultrasonication technique:

Pre-emulsion from melted lipid and hot surfactant solution is first prepared

↓ Ultrasound (20kHz.) is applied with a sonotrode that is in contact with the liquid

The cavitation causes disintegration of the lipid phase into smaller droplets

↓

The obtained hot micro emulsion is then cooled to form the SLN.

1.4. Electro-spray technique:

In this relatively new technique an electrodynamic atomization is used to produce SLN directly in powder form The obtained particles by this method have narrow distribution and size below 1 micrometre. However the method is still under investigation for its applicability in the production of larger quantities of dispersions.

2. Low Energy Input Methods:

Mainly Low Energy Input Methods are divided into 2 way based on Nanoparticle Precipitation from Homogeneous Systems and Solvent-based methods.

2.1. Nanoparticle Precipitation from Homogeneous Systems.
2.2. Solvent-based methods.

2.1 Nanoparticle Precipitation from Homogeneous Systems:

2.1.1 Microemulsion-based techniques:

"Microemulsion is defined as a transparent, optically isotropic, and thermodynamically stable liquid system composed of water, oil and amphiphilic compounds (surfactant and cosurfactant).

A. Hot micro emulsion technique/micro emulsion dilution technique:

Lipophilic drug is dissolved/dispersed in hot lipid melt

↓

Lipid melt is then added slowly under continuous stirring to the hot aqueous surfactant and co surfactant phase

↓

To form a clear o/w microemulsion.

↓

Further dilution of microemulsion using cold

↓

SLN

B. Microemulsion cooling technique:

The emulsifying wax was melted at 37-55Same temperature under minimal stirring.

↓

Adding water phase

↓

O/w microemulsion is formed on addition of suitable polymeric surfactant to the aqueous phase.

↓

Cooling at less than 4^0C.

↓

SLN

C. Microwave-assisted microemulsion technique:

The aqueous phase containing surfactants and cosurfactant is mixed with the lipid meltContinuous stirring with controlled microwave environment

↓

Hot microemulsion.

Cooling of this microemulsion using cold water (at 2-4C^0)

↓

SLN

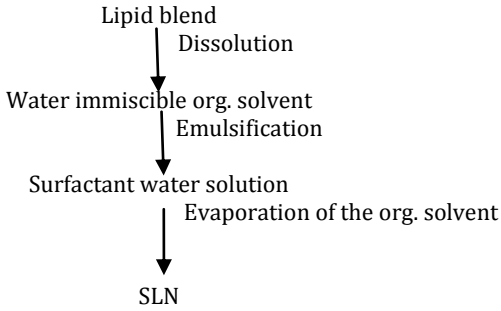
2.1.2 Membrane contactor technique:

This is a well-established method to form emulsions and microemulsions. The method is also used now for the formation of lipid-based nanoparticles

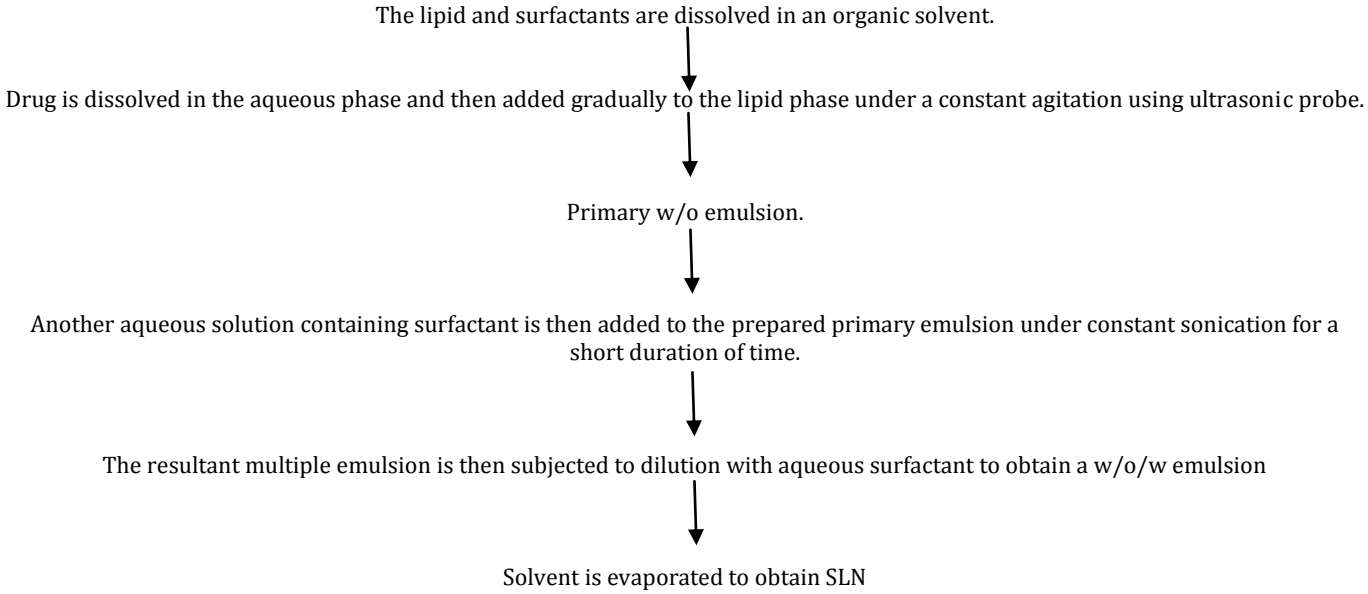
2.2. Solvent-based methods:

These methods do not require high temperature for processing; accordingly, they are suitable for encapsulation of thermosensitive drugs. The main disadvantage faced by these methods is the toxicological concern raised by the residual solvents

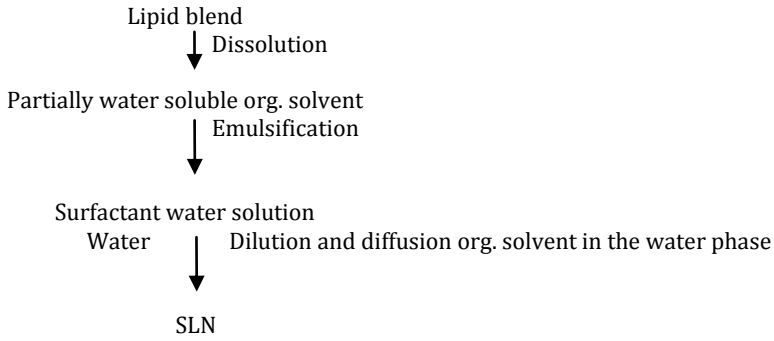
2.2.1. Emulsification-solvent evaporation technique:



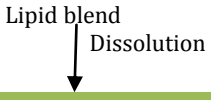
2.2.2. Double emulsion technique:

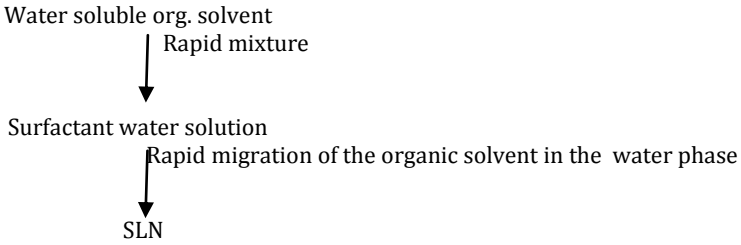


2.2.3. Emulsification-solvent diffusion technique



2.2.4. Solvent injection technique:





2.2.5 Supercritical fluid (SCF)-based methods:

Supercritical fluid (SCF)-based methods are cover various types of techniques like Supercritical fluid nucleation technique/Rapid expansion of supercritical solutions (RESS),Particles from gas-saturated solutions/suspensions (PGSS),Supercritical fluid extraction of emulsions (SFEE),Supercritical fluid based coating technique Supercritical fluid co injection process.

3. Miscellaneous Methods:

3.1. Film ultrasonication dispersion technique:

This strategy includes the development of a thin film of lipid phase containing drug (broke up/scattered), trailed by its drying and ultrasonication within the sight of a watery surfactant arrangement at lifted temperature. This prompts the development of an emulsion containing drug. Resulting cooling of this emulsion shapes the nanoparticles.

Drug release from SLNs: [18]

The arrival of the captured medication from the SLNs is administered by the accompanying standards:

- An opposite relationship exists between the arrival of the medication and the segment coefficient of the medication [19].
- Smaller molecule estimate advances higher surface region, subsequently prompting higher medication discharge [19].
- Homogeneous scattering of the medication in the lipid network causes moderate arrival of the medication. It depends on the type and the drug entrapment model of SLN
- Lipid crystallinity and high medication portability prompt quick arrival of the medication from the SLNs [20].

Factor Affecting Drug Release from SLNs:

Factors contributing to a fast release are the large surfacearea, a high diffusion co- efficient due to small molecular size, lowviscosity in the matrix and a short diffusion distance for the drug [20].

Characterization Technique of SLNs: [4, 5, 16]

Characterization of Solid Lipid Nanoparticles, as represented in Table 4.

1. Routes of Administration of SLNs:

Controlled drug delivery, enhancement of bioavailability of entrapped drugs via modification of dissolution rate [21] and/or improvement of tissue distribution and targeting of drugs [22] by using SLN have been reported in various application routes.

2. Oral administration:

The Formation of SLNs preparation which are given by oral route are aqueous dispersions. SLNs loaded dosage form such as tablets, pellets and capsule. The microclimate of the stomach favours particle aggregation due to the acidity and high ionic strength. It is to be expected that food will have a large impact on SLN performance [23].

3. Parenteral administration:

SLN generally administered intravenously to animals. Distribution of SLN was found to have higher drug concentrations in lung, spleen and brain, while the solution led to more distribution into liver and kidneys. SLN showed higher blood levels in comparison to a commercial drug solution after intravenous [24].

4. Transdermal application:

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Disadvantages of dermal administration are low concentration of the dispersed lipid and the low Viscosity. The incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the Skin [25].

Marketed Product & Patents of SLNs: [26]

The commercial feasibility of any delivery system is governed by the availability of a large scale production method, yielding a product of a quality that is acceptable by the regulatory authorities (e.g., Food & drug administration) and cost of the material. Considering these facts, the scenario is promising in the case of SLNs. As SLNs require easily available and reasonably priced triglyceride lipids, the material cost is much less than carriers like Poly Lactic Glycolic Acid (PLGA), Poly Lactic Acid (PLA), Polycaprolactone (PCL), or phospholipids.

Moreover, SLNs are mainly manufactured by using high-pressure homogenizers which have been in use for the manufacturing of parenteral nutrition products for many years. They may be used even without any modification (e.g., for production of SLNs by hot homogenization technique). Scale-up and manufacturing are also possible when microemulsions are used as templates for SLNs production. Various patents are available on SLNs and some of them are elaborated in Table.

Applications of SLNs:

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 some of which are given below.

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 acid. The lipid nuclic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible

organic solvent where both lipid and DNA are separately dissolved byremoving the organic solvent, stable and homogeneously sized lipid-nuclic 17 acinano particle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

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, vitamine 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 are used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin. Production of the flurbiprofen-loaded SLN gel for topical application after a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Polyacrylamide, glycerol and water were used for the preparation of this type of SLNgel.

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.

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 pesticide. The SLN were prepared here by using compritol 888 ATO as lipid andpoloxamer188 or Miranol UltraC32as surfactant.

SLNs as a targeted carrier for anticancer drug to solid tumors:

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.

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.

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 anti tubercular drug loaded solid lipid nanoparticles are prepared the nebulizationin animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.

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.

Table No. 2: Comparative properties of solid lipid nanoparticles, Polymeric nanoparticles, Liposomes, Lipid emulsions [6]

Sr. No.	Property	SLN	Polymer Nano Particle	Liposoms	Lipid Emulsions
1	Systemic toxicity	Low	> or = to SLN	Low	Low
2	Cytotoxicity	Low	> = to SLN	Low	Low
3	Residues from organic Solvents	No	Yes	May or may not	No
4	Large scale production	Yes	No	Yes	Yes
5	Sterilization by autoclaving	Yes	No	No	Yes
6	Sustained release	Yes	Yes	< or = to SLN	No
7	Avoidance of RES	Depend on size and coating	No	Yes	Yes

Table No. 3: other ingredient used in formulation of SLNs [4, 5, 16]

Water miscible solvents	acetone, acetonitrile, benzyl alcohol, butyl lactate, dichloromethane, ethanol, ethyl acetate, hexane, isobutyric acid, isopropylalcohol, methanol
Cryoprotectants	D-sorbitol, D-glucose, D-fructose, gelatin, glycine, mannose, maltose, sucrose, lactose monohydrate, trehalose, mannitol
stealth molecules	poloxamers, poloxamines, polysorbates, polyacrylamides (PAA) and PVA, stearic acid-PEG-2000 (SA-PEG2000), α-methoxy-PEG-2000-carboxylic acid-α-lipoamino acids (mPEG2000- C-LAA18)
surface charge modifiers	stearylamine, cetylpyridinium chloride, dicetyl phosphate, N,N-di-(beta stearoyl)
Preservatives	Parabens, thiomersal, imidazolidinyl urea, chloromethylisothiazolinone, methylisothiazolinone 1,2-benzisothiazolin-3-one

Table No. 4: Characterizations of SLNs [4, 5, 16]

S. No.	Evaluation Parameter	Method used	Importance
1	Particle size and shape	1. Photon correlation spectroscopy (PCS) 2. Scanning electron microscopy (SEM) 3. Transmission electron microscopy (TEM) 4. Atomic force microscopy (AFM)	Determine skin penetration
2	Zeta potential	Zeta meter	Stability of vesicles
3	Entrapment efficiency	1. Mini column centrifugation method 2. Ultracentrifugation 3. Filtration or gel permeation chromatography	Suitability of method
4	Degree of crystallinity and lipid modification	1. Differential scanning calorimetry (DSC) 2. X-ray scattering 3. Infrared and Raman spectroscopy	Investigating structural properties of lipids
5	Surface charge	Acoustic spectroscopy	Movement of vesicle
6	In vitro drug release study	1.Franz diffusion cell 2. Reverse dialysis 3. Dialysis bag diffusion	Determine the drug release rate from vesicle
7	Drug content	UV, HPLC	Important in deciding the amount of nanoparticles preparation to be used
8	Thermal Stability	Differential Scanning Calorimetry (DSC) (Thermal behavior is analysed)	For stability purpose
9	Molecular Weight & Surface Element Analysis	X-ray photoelectron spectroscopy for chemical analysis (ESCA); Laser Doppler anaemomo-metry; X-ray Diffraction. Gel Chromatography and Static Secondary-ion mass spectroscopy (SSIMS)	for surface element analysis and To know the molecular weight of naoaparticle.

Table No. 5: List of patents on SLNs

Patent no.	Title of patent	Inventor/applicant	Filing year
EP0167825	Lipid nanopellets for oral administration	Speiser Peter	1985
US5250236	Method for producing solid lipid microspheres having a narrow size distribution	Maria R. Gasco	1991
US5667800	Topical preparation containing a suspension of solid lipid particles	Tom De Vringer	1991
WO9305768	Medication vehicles made of solid lipid particles	Stefan Lucks, Rainer Müller	1992
US 5785976	Solid lipid particles, particles of bioactive agents and methods for the manufacture and use	Kirsten Westesen, Britta Siekmann	1994
DE19825856	New topical formulation which includes active agent as liquid lipid nanoparticles in an oil-inwater emulsion	Labtec Gmbh	1998
US6551619	Pharmaceutical cyclosporine formulation with improved biopharmaceutical properties, improved	Lawrence John Penkler, Rainer Helmut Müller, Stephan Anton Runge,	1999

	physical quality and greater stability, and method for producing said formulation	Vittorino Ravelli	
WO0006120	Lipid emulsion and solid lipid nanoparticle as a gene or drug carrier	Seo Young Jeong, Ick Chan Kwon, Hesson Chung	1999
DE19952410 B4	Sunscreen preparations comprising SLNs	Hansen Peter, Heppner Andrea, Schumann Christ of	1999
US6770299	Lipid matrix–drug conjugates particle for controlled release of active ingredient	Rainer H. Muller, Carsten Olbrich	2000
US6814959	UV radiation reflecting or absorbing agents, protecting against harmful UV radiation and reinforcing the natural skin barrier	Rainer H. Muller, Wissing Sylvia, Mader Karsten	2000
US7153525	Microemulsions as precursors to solid nanoparticles	Russell John Mumper, Michael Jay	2001
CA2524589	Compositions for the targeted release of fragrances and aromas	Gerd Dahms, Andreas Jung, Holger Seidel	2003
US2006024374	Pharmaceutical compositions suitable for the treatment of ophthalmic diseases	Maria Gasco, Marco Saettone, Gian Zara	2003
US7147841	Formulation of UV absorbers by incorporation in SLNs	Bernd Herzog	2003
US2006222716	Colloidal solid lipid vehicle for pharmaceutical use	Joseph Schwarz, Michael Weisspapir	2005
US2006008531	Method for producing solid lipid composite drug particles	Boris Shekunov, Pratibhash Chattopadhyay, Robert Huff	2005
US20080311214A1	Polymerized SLNs for oral or mucosal delivery of therapeutic proteins and peptides	Kollipara Koteswara Rao	2006
US11921634	Use of SLNs comprising cholesteryl propionate and cholesteryl butyrate	Maria Rosa Gasco	2006
EP2413918A1	SLNs encapsulating minoxidil, and aqueous suspension containing same	Karine Padois, Fabrice Pirot, Françoise Falson	2010
EP2549977A2	Lipid nanoparticle capsules	Petit Josep LLuis Viladot, González Raquel Delgado, Botello Alfonso Fernández	2011

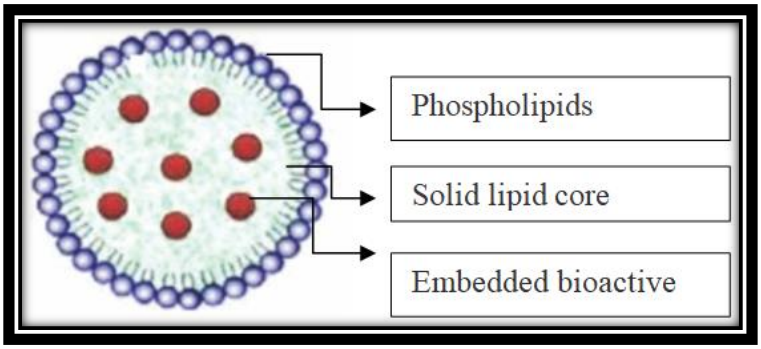


Fig. 1: Structure of SLNs [27]

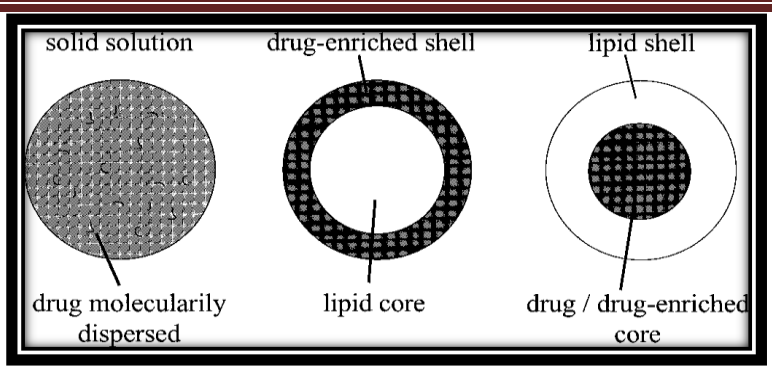


Fig. 2: Type/Classification of SLNs.& Drug Incorporation Models [28]

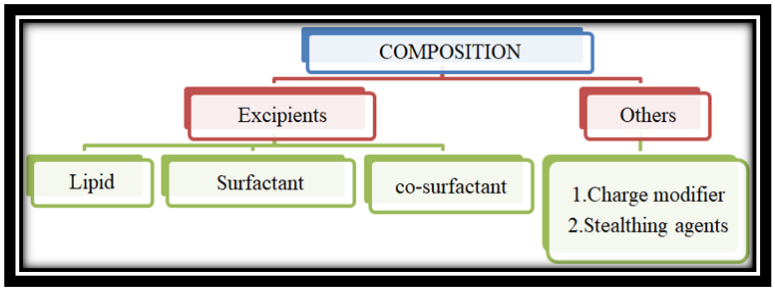


Fig. 3: Composition Profile of SLNs

Fig. 4: Classification of methods of preparation of SLNs [4]

CONCLUSION

SLN are a novel and innovative therapeutic delivery system. Clear advantages include the composition (physiological compounds), the effective production process (especially the possibility of large scale production), avoidance of organic solvents during the production process and the possibility of producing highly concentrated lipid dispersions. SLN are a complex system due to the physical state of the lipid. Appropriate characterization of the formulation requires several analytical methods and will decide over the SLN administration and the most suitable application route. Results obtained with dermal formulations are currently the most

promising and thus will probably be the main application for SLN in the future.

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