ejpmr, 2018,5(9), 225-236

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SOLID LIPID NANOPARTICLE: A POTENTIAL APPROACH IN DRUG DELIVERY SYSTEM

Prashant Pandey*[1], Prakash Chandra Gupta[1], Sanjay Yadav[1]

[1]University Institute of Pharmacy, Chhatrapati Shahu Ji Maharaj University, Kanpur 208024, Uttar Pradesh, India.

***Corresponding Author: Prashant Pandey**

University Institute of Pharmacy, Chhatrapati Shahu Ji Maharaj University, Kanpur 208024, Uttar Pradesh, India.

Article Received on 12/07/2018 **Article Revised on 01/08/2018** **Article Accepted on 22/08/2018**

ABSTRACT

To improve the solubility and bioavailability solid lipid nanoparticles (SLNs) are the new approach in drug delivery system. Since a decade, a lot of research works are performed to utilize solid lipid nanoparticles as alternative drug delivery system to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles. SLNs offer great promise to controlled drug delivery and site specific and gene delivery. Nanostructured lipid carrier, lipid drug conjugates, polymer lipid hybrid nanoparticles are the new emerging drug delivery system. This review concentrated on drug incorporation models, advancement in lipid nanoparticles, method of preparation, secondary production steps, characterization, application and future of SLNs. This review presents a broad treatment of solid lipid nanoparticles discussing their advantages, limitations.

KEYWORDS: Solid lipid nanoparticles (SLNs), Polymer lipid hybrid nanoparticles (PLNs), Acoustic method**,** Membrane Contractor technique.

INTRODUCTION

Targeted delivery of a drug molecule is a challenge and a wide area for pharmaceutical research scientist. Development of colloidal delivery systems such as nanoparticles, liposomes, and micelles are the new approach for improving drug delivery. A nanoparticle is the most fundamental component in the fabrication of a nanostructure, and is far smaller than the world of everyday objects that are described by Newton's laws of motion, but bigger than an atom or a simple molecule that are governed by quantum mechanics.[1] Drug and gene delivery, production of improved biocompatible materials and *in vitro* and *in vivo* diagnostics are examples of nanotechnology application.[2] Penetrability through several anatomical barriers, sustained release of their contents and their stability in nanometer size are the dependent barriers for the successful implementation of nanoparticles for drug delivery. As the regulatory approval and high cast of the polymers have limited the use of nanoparticles to clinical medicine. To overcome these, lipids are used as an alternative carrier, particularly for lipophilic drugs. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs) [Figure1]. Since a decade, trials are being made to utilize solid lipid nanoparticles as alternative drug delivery system to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles. SLN combines the advantages of different colloidal carriers and also avoids some of their disadvantages.[3] SLNs have ability to incorporate drugs into nanocarriers and promise for attaining the bioavailability enhancement along with controlled and site specific drug delivery. SLN's are considered too well tolerated in general, because of their similar composition to physiological lipids.

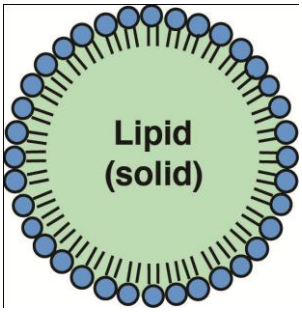


Fig. 1: A typical structure of SLN.

A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decreases the danger of acute and chronic toxicity.[4,5] In SLNs as compared to other colloidal carriers liquid lipid is replaced by solid lipid. The use of solid lipid as a matrix material for drug delivery is well known from lipid pellets for oral drug delivery (e.g. Mucosolvan® retard capsules).[5,6] Solid lipid nanoparticle may be a promising sustained release and drug targeting system for lipophilic CNS antitumor drugs.[7] The lipid core is stabilized by surfactants (emulsifiers) [Table1]. The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), diglycerides, monoglycerides

(e.g. glycerolmonostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently.[8] SLNs as an advanced drug and gene delivery nanosystems present significant opportunities for improving medical therapeutics.[9]

Table 1: List of excipients used in SLN preparation.[5, 12]

Lipids	Surfactants
Triglycerides	**Phospholipids**
Tricaprin	Soy lecithin (LipoidÒ S 75, LipoidÒ S 100)
Trilaurin	Egg lecithin (Lipoid E 80)
Trimyristin (Dynasan 114)	Phosphatidylcholine (Epikuron 170, Epikuron 200)
Tripalmitin (Dynasan 116)	**Ethylene oxide/propylene oxide copolymers**
Tristearin (Dynasan 118)	Poloxamer 188
Hydrogenated coco-glycerides	Poloxamer 182
(SoftisanÒ 142)	Poloxamer 407
Hard fat types	Poloxamine 908
WitepsolÒ W 35	**Sorbitan ethylene oxide/propylene oxide copolymers**
WitepsolÒ H 35	Polysorbate 20
WitepsolÒ H 45	Polysorbate 60
WitepsolÒ E 85	Polysorbate 80
Acyl glycerols	**Alkylaryl polyether alcohol polymers**
Glyceryl monostearate (ImwitorÒ900)	Tyloxapol
Glyceryl distearate (Precirol)	**Bile salts**
Glyceryl monooleate (Peceol)	Sodium cholate
Glyceryl behenate (CompritolÒ 888 ATO)	Sodium glycocholate
Glyceryl palmitostearate (PrecirolÒ ATO 5)	Sodium taurocholate
Waxes	Sodium taurodeoxycholate
Cetyl palmitate	**Alcohols**
Fatty Acids	Ethanol
Stearic acid	ButanoL
Palmitic acid	Butyric acid
Decanoic acid	Dioctyl sodium sulfosuccinate
Behenic acid	Monooctylphosphoric acid sodium
Acidan N12	
Cyclic complexes	
Cyclodextrin	
para-acyl-calix-arenes	

ADVANTAGES OF SLNs

1. Easy manipulation of particle size and surface characteristics of nanoparticle to achieve both passive and active drug targeting after parenteral administration.
2. Site-specific targeting achieved by attaching targeting ligands to surface of particles.
3. Magnetic guidance can be used for targeting.
4. Drug loading is relatively high.
5. Controlled release and particle degradation characteristics can be changed by changing matrix constituents.
6. SLNs used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.
7. Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods[10]
8. Increased bioavailability of poorly water soluble molecule[11]
9. Lyophilisation can be done.
10. Avoidance of organic solvents.

Disadvantage of SLNs

1. Particle-particle aggregation due to small size and large surface area.
2. Difficult in physical handling
3. Limited drug loading and burst release.
4. Unexpected polymeric transitions dynamics

DRUG INCORPORATION MODELS

Solubility of drug and drug loading capacity are inversely proportional. Thus enhanced solubility results in reduced entrapment efficacy. To overcome this, Müller et al reported a cold homogenization technique which is performed at room temperature or below (0° C).[13]

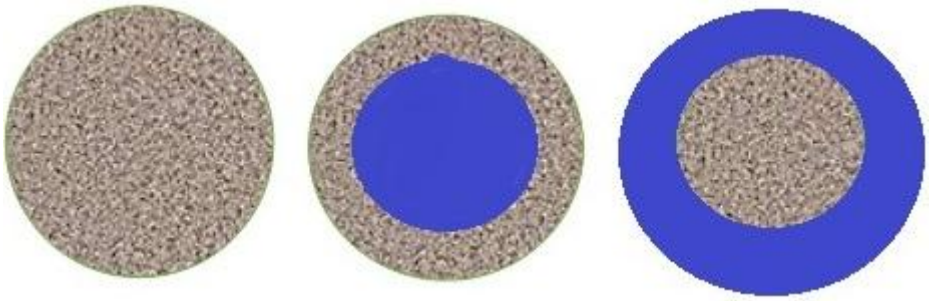
Factors affecting loading capacity of a drug in lipid are:[14]

- solubility of drug in lipid melt,
- miscibility of drug melt and lipid melt,

- chemical and physical structure of solid matrix lipid,
- polymorphic state of lipid material
- Solubility

There are three models of drug incorporation: [Figure2]

- Solid lipid solution
- Drug enriched shell
- Drug enriched core



Solid solution Drug enriched shell Drug enriched core

Fig. 2: Models of drug incorporation.

Solid solution

In the case of the solid solution model, the drug is molecularly dispersed in the lipid matrix when the particles are produced by the cold homogenization technique and using no surfactant or no drug-solubilizing surfactant. The drug has strongly pronounced interactions with the lipid.[15, 16]

Drug enriched shell

According to the drug-enriched shell model of drug incorporation, a solid lipid core forms when the recrystallization temperature of the lipid is reached. On reducing the temperature of the dispersion, the drug concentrates in the still liquid outer shell of the SLN.[16, 17, 18]

Drug enriched core

According to the drug-enriched core model of drug incorporation, cooling the nanoemulsion leads to a super saturation of the drug which is dissolved in the lipid melt at or close to its saturation solubility and the drug precipitates prior to lipid recrystallization. Further cooling finally leads to the recrystallization of the lipid surrounding the drug as a membrane.[13, 16]

ADVANCEMENT IN SLNS

As SLNs have several advantages of controlled and targeted drug delivery but have some limitations i.e.

- Limitation of drug load by the solubility of the drug in the solid lipid.
- Drug expulsion phenomenon when lipid crystallizes to the stable β-form.
- Particle concentration in the aqueous dispersions ranging from about 1% to a maximum of only 30%.

It was observed that drug was expelled out of SLN during storage due to highly ordered crystalline lipid matrix which was leaving very little space for drug molecules. To overcome these limitations of SLNs, Lipid Drug Conjugates (LDCs), Nanostructured Lipid Carriers (NLCs) and Polymer lipid hybrid nanoparticles (PLNs) are introduced.[19]

Lipid drug conjugates (LDCs)

A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix.[20] LDCs are spherical in shape and lipid drug core are stabilized by a surfactant interfacial region. Fatty acids, acylglycerols, waxes and mixture of these are utilized as core lipids. Surface stabilizers includes bile salts, cholesterol, phospholipids, sphingomyelins. Use of ligands promote tissue targeting. LDC enables the incorporation of both hydrophilic (e.g., doxorubicin and tobramycin) and lipophilic (e.g., progesterone and cyclosporine A) drugs.[19]

Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers (NLCs), formulated with biocompatible solid and liquid lipids, are an improved generation of solid lipid nanoparticles (SLNs), providing a delivery system for various active drugs with controlled-release characteristic.[21, 22] Addition of a liquid lipid to a solid lipid leads in a less ordered crystal lattice and increased imperfection that results in high drug entrapment and stability during storage. A comparison among Triptolide, TP-SLNs and TP-NLCs were made by *Cong Zhang et. al.* i.e. Fatty degeneration in the hepatocytes, dead cells in the macrophages manifested as a starry sky appearance in the spleen, and obvious kidney proximal tubular dilation were seen, which were also observed in male mice after oral administration of TP. However, in the TP-NLCs group at the same dose, no apparent changes were found.[22]

Three models of NLCs were proposed: [Figure 3]

1. Imperfect type NLCs were prepared from a lipid mixture of spatially different lipids composed of different fatty acids. This provide a larger distances between the fatty acid chains of glycerides and

general imperfection of the crystal lattice. This provide more space for guest molecule in molecular or amorphous form.

2. Amorphous type NLCs are prepared by using special lipids such as hydroxyl octacosanyl, hydroxyl stearate, isopropyl myristate, etc. that avoids the crystallization or transformation upon cooling.
3. Multiple type NLCs are analogous to w/o/w multiple emulsions since these are oil/ solid lipid/ water and prepared for the drugs those shows higher solubility in oils than in solid lipids. Such drugs are dissolved in oil and protected from degradation by the surrounding solid lipids.

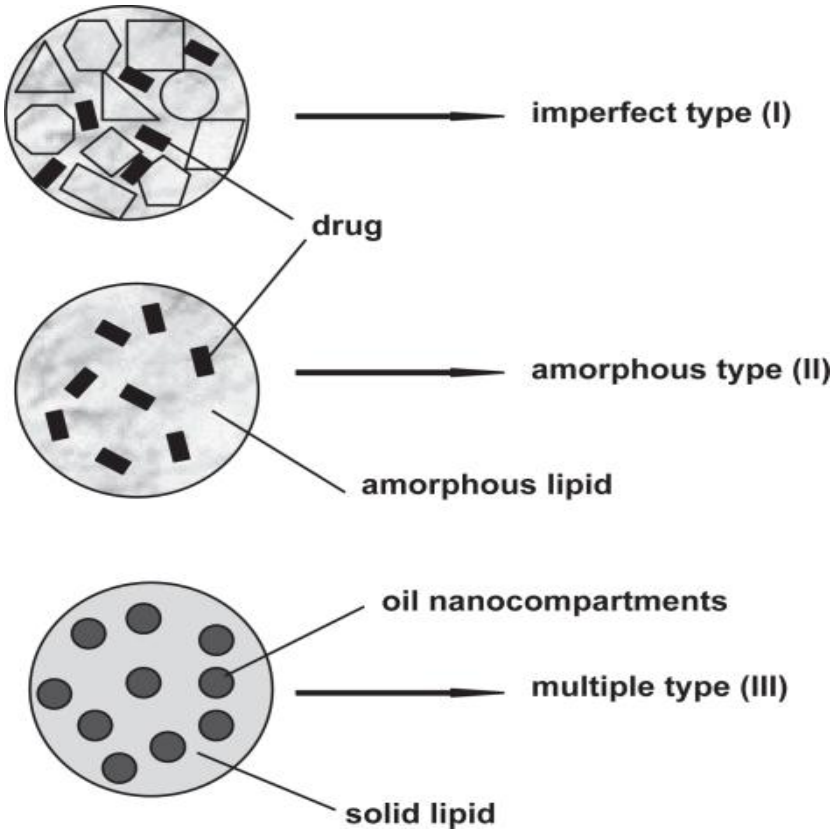


Fig. 3: Three models of NLCs.

Polymer lipid hybrid nanoparticles (PLNs): [Figure 4] PLNs promising as drug delivery in treatment of cancer like breast cancer. PLNs composed of three components first is hydrophobic polymer core to encapsulate poorly water soluble drugs., second is hydrophilic polymeric shell to improve PLN stability and circulation half-life and third is lipid monolayer at core and shell interface that promote drug retention in polymer core. It has been shown in vitro that hybrid NPs possess the ability of carrying poorly water-soluble drugs with high encapsulation and loading yields, tunable and sustained drug release profiles, excellent serum stability, and differential targeting of cells.[23, 24]

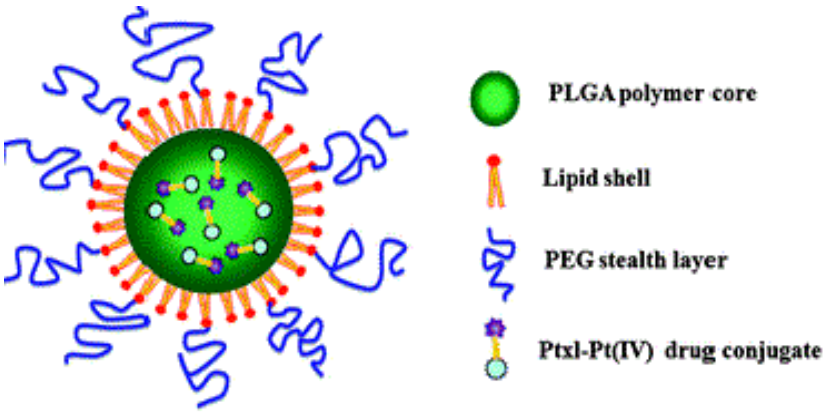


Fig. 3: Three models of NLCs.

SLNs PREPARATION TECHNIQUES (PRIMARY)

1. Emulsification solvent evaporation technique
2. Solvent emulsification-diffusion technique
3. Supercritical fluid technique
4. High pressure homogenization technique
- Hot homogenization technique
- Cold homogenization technique
5. Microemulsion based technique
6. Ultrasonication /high speed homogenization technique
7. Precipitation technique
8. Film-ultrasound dispersion technique
9. Double emulsion technique
10. Solvent Injection Technique
11. Membrane Contractor technique

Emulsification solvent evaporation technique

This technique is based on SLN dispersions by precipitation in oil/water emulsions. The lipophilic compound is dissolved in water immiscible organic solvent such as cyclohexane, which is emulsified in an aqueous phase. SLN dispersion is formed by precipitation of the lipid in the aqueous medium after evaporation of the solvent. The mean diameter of 25 nm with cholesterol acetate as model drug and lecithin/sodium glycocholate mixture as emulsifier has been reported for the prepared SLN. The reproducibility of the result was verified by Siekmann and Westesen, who produced the cholesterol acetate SLN with mean size of 29 nm.[25, 26]

Solvent emulsification-diffusion technique

SLNs can also be produced by solvent emulsification-diffusion techniques. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during preparation is the most important advantage of this technique. In this method, the lipid matrix is dissolved in a water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure, resulting in a nanoparticulate dispersion formed by precipitation of the lipid in aqueous medium.[27]

Supercritical fluid technique

This is a novel technique which recently applied for the production of SLNs. A fluid is qualified as supercritical when its pressure and temperature exceed their respective critical value. Above the critical temperature, it is not possible to liquefy a gas by increasing the pressure. The supercritical fluid has unique thermo-physical properties. As the pressure is raised, the density of the gas increases without significant increase in viscosity while the ability of the fluid to dissolve compounds also increases. A gas may have little to no ability to dissolve a compound under ambient condition can completely dissolve the compound under high pressure in supercritical range. Therefore, its solvation power is altered by careful control of changes in temperature and pressure. Many gases like, CO_2, ammonia, ethane and CH_2FCF_3 were tried, but CO_2 is the best option for SCF technique because, it is generally regarded as safe, easily accessible critical point (31.5ºC, 75.8 bar), does not causes the oxidation of drug material, leaves no traces behind after the process, is inexpensive, non-inflammable, environmentally acceptable an easy to recycle or to dispose off. In the SCF phase or this technique generally use organic solvents (e.g. DMSO, DMFA) because they are fully miscible in SCF-CO_2. This technology comprises several processes for nanoparticles production such as Rapid Expansion of Supercritical Solution (RESS), Particles from Gas Saturated Solution (PGSS), Gas/Supercritical Anti-solvent (GAS/SAS), Aerosol Solvent Extraction Solvent (ASES), Solution Enhanced Dispersion by Supercritical fluid (SEDS), Supercritical Fluid Extraction of Emulsions (SFEE). Mainly SAS and PGSS were used for SLN preparation.[28]

High pressure homogenization technique

Hot homogenization technique

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also accelerate the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. It should always be kept in mind, that high pressure homogenization increases the temperature of the sample (approximately 10°C for 500 bar). In most cases, 3–5 homogenization cycles at 500–1500 bar are sufficient. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result high kinetic energy of the particles. The primary product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months.[29, 30]

Cold homogenization technique

Cold homogenization method has been carried out to omit the following problems of the hot homogenization technique like temperature mediated drug and carrier degradation acceleration and consequently release of drug into the aqueous phase during homogenization. First stage in cold homogenization is the same with hot homogenization method but the next steps are different. The drug loaded lipid melt is cooled quickly by ice or

liquid nitrogen for distribution of drug in the lipid matrix. The acquired particle sizes are in the range 50-100 microns for this method. Disadvantages of cold homogenized samples are larger particle sizes and a broader size distribution. However, this method reduces the thermal exposure of the sample.[31]

Microemulsion based technique

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the High pressure homogenization based formulations.[32]

Ultrasonication /High speed homogenization technique

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required. It reduces shear stress but has some disadvantages like potential metal contamination, physical instability like particle growth upon storage. In this probe sonicator or bath sonicator is used.[29]

Precipitation technique

The lipid is dissolved in an organic solvent (e.g., chloroform) and the solution is emulsified into an aqueous phase. After evaporation of the organic solvent, the lipid is precipitated, forming nanoparticles.[33]

Film-ultrasound dispersion technique

The lipid and drug are added to suitable organic solutions, and after decompression, rotation and evaporation of the organic solutions, a lipid film is formed. The aqueous solution containing emulsifier is then added to lipid film and, using probe sonication, SLNs are formed. Oleanolic acid SLNs have been produced using soybean phospholipid as a carrier using the film-ultrasound technique.[34]

Double emulsion technique

Double emulsion technique is used mainly for hydrophilic drugs. The drug was dissolved in aqueous medium and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatine, poloxamer-407). Primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). Thereafter, the double emulsion was stirred and was isolated by filtration .After evaporation of organic solvent by rotary, SLNs were recovered by centrifugation at 12000 ×g for 30 min at 4°C.

Solvent Injection Technique

It is a novel approach to prepare SLN, which has following advantages over other production methods like use of pharmacologically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. It is based on lipid precipitation from the dissolved lipid in solution. In this technique the solid lipid was dissolved in water-miscible solvent (e.g. ethanol, acetone, isopropanol) or a water miscible solvent mixture. Then this lipid solvent mixture was injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion was then filtered with a filter paper in order to remove any excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent.[29, 35, 36]

Membrane Contractor technique

It is a novel technique to prepare the SLN. In membrane contactor technique the liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pore swallowing the formation of small droplets as indicated in Figure 2. The aqueous phase was stirred continuously and circulates tangentially inside the membrane module, and sweeps away the droplets being formed at the pore outlets. SLNs were formed by the cooling of the preparation at the room temperature. Here both the phases were placed in the thermostated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase. The influence of various process parameters (aqueous phase cross flow velocity, the lipid phase pressure, aqueous and lipid phase temperature, lipid phase amount and membrane pore size) were studied. The membrane contact or method is also used for the preparation of polymeric nanoparticles, by methods involving a polymerization of dispersed monomers (interfacial polymerization method) or a dispersion of preformed polymers (nanoprecipitation method). The advantages of this process of SLN preparation using a membrane contactor are shown to be its facility of use, the control of the SLN size by an appropriate choice of process parameters and it's scaling up ability.[37]

SECONDARY PRODUCTION STEPS

Sterilization

SLNs product should be sterilizes for parenteral application that can be achieved by autoclaving, filtration, gamma irradiation and aseptic production. Sterilization by autoclaving is very common and popular but the problem associated with this is its high temperature and coalescence, as there is no applied

shear. Increased temperature will result in melting of lipid particles and formation of o/w emulsion. Schwarz found that lecithin is a suitable surfactant for steam sterilization, because only a minor increase in particle size was observed.[12, 38]

Lyophilisation

Lyophilisation gives long term stability for a product containing hydrolysable drugs or a suitable product for pre-oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. In case of freeze drying of the product, all the lipid matrices used, form larger solid lipid nanoparticles with a wider size distribution due to presence of aggregates between the nanoparticles. The conditions of the freeze drying process and the removal of water promote the aggregation among SLNs. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process.[5]

Spray drying

It is an alternative and cheaper technique to the lyophilisation process. This recommends the use of lipid with melting point more than 70° C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture. The addition of carbohydrates and low lipid content favour the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol–water mixtures instead of pure water due to cooling leads to small and heterogeneous crystals, the lower inlet temperatures.[29, 39]

CHARECTERIZATION

Particle size and Zeta potential

The physical stability of SLNs depends on their particle size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle movement. The particle size determination by photon correlation spectroscopy (PCS) detects size range of 3nm to 3µm and by laser diffraction in size range of 100 nm to 180 µm. Although PCS is a good tool to characterize nano-particles, but is capable for the detection of larger micro particles.[40] Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement.[41]

Electron microscopy

Electron Microscopy methods such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to measure the overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions. SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample.[43, 44]

Dynamic light scattering (DLS)

DLS also known as PCS records the variation in the intensity of the scattered light on the microsecond time scale. The variation results from interference of light scattered by individual particles under the influence of Brownian motion and quantified by completion of an auto correlation function. The advantage of the method are the lack of required calibration, sensitivity to submicrometer particles and speed of analysis.

Static light scattering (SLS)/Fraunhofer diffraction

In this method the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in size is the primary variable. This method is fast but it requires advanced knowledge of particles optical qualities and more cleanliness than DLS.

Nuclear magnetic resonance (NMR)

The size and the qualitative nature of nanoparticle can be determine by NMR. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool.[44]

Powder X - ray diffraction and Differential Scanning Calorimetry (DSC)

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature. Thermodynamic stability, lipid packing density and quantification are a serious challenge due to

the increase, while drug incorporation rates decrease in the following order:
Super cooled melt < α-modification < β9-modification < β-modification [5]
Due to the small size of the particles and the presence of emulsifiers, lipid crystallization modification changes might be highly retarded. Differential scanning calorimetry (DSC) and X- ray scattering are widely used to investigate the status of the lipid. Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids. Their potential to characterize SLN dispersions has yet to be explored.[45]

Acoustic methods
Acoustic spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge.[43]

IN VITRO DRUG RELEASE

Dialysis tubing
In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.[43]

Reverse dialysis
In this technique a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.[43]

PATENTS

First patent have been granted for solid lipid nanoparticles in 1993 for the claimed method of solid lipid nanoparticles. Various patents of solid lipid nanoparticles are summarized in Table no.2.

Table 2: List of Patents of Solid Lipid Nanoparticle.

S.No.	Name	Patent Number	Filling Date	Publication Date	Inventor	Reference
1	Topical dermal delivery composition using self-assembling nanoparticle with cetylated componants.	US 2014/0234428 A1	15/02/2013	21/08/2014	Barathur RR.	[56]
2	Solid Lipid Nanoparticle entrapping hydrophilic/amphiphilic drug and a process for preparing the same	WO 2013105101 A1	05/3/2012	18/07/2013	Kaur IP.	[57]
3	Formulation of UV absorbers by incorporation in solid lipid nanoparticles	US 7147841 B2	13/06/2003	12/12/2006	Herzog B.	[58]
4	A process for preparing solid lipid sustained release nanoparticles for delivery of vitamins	WO2013105026 A1	09/01/2013	18/07/2013	Kaur IP.	[59]
5	Method for producing solid lipid microspheres having a narrow size distribution	US 5250236	02-08-1991	05-10-1993	Gasco MR.	[60]
6	Medication vehicles made of solid lipid particles (solid lipid nanosphere - sln)	EP 0605497	16-09-1992		Lucks S, Müller R.	[61]
7	Polymerized solid lipid nanoparticles for oral or mucosal delivery of therapeutic proteins and peptides	US 20080311214A1	05-04-2006		Rao KK.	[62]
8	Use of SLN comprising	US 11921634	31-03-2006		Gasco MR.	[63]

	cholesteryl propionate andcholesteryl butyrate					
9	Production of lipid-based nanoparticles using a dual asymmetrical centrifuge	EP1838286 B1	23-12-2005		Massing U.	[64]
10	Solid lipid nanoparticles encapsulating minoxidil, and aqueous suspension containing same	EP2413918 A1	29-03-2010		Falson, Padois P,Fabrice	[65]
11	Lipid nanoparticle capsules	EP2549977 A2	24-03-2011		Josep, Raquel, Alfonso	[66]
12	Solid lipid particles, particles of bioactive agents and methods for the manufacture and use	US 5785976	12-04-1994	28-07-1998	Westesen K. Siekmann B.	[67]

MARKETED PRODUCTS OF SLNs

Lipid based drug delivery system have been used to improve the bioavailability of BCS class 2 drugs. Market survey data show that about 4% of commercial products of oral lipid based formulations are available in the US, UK and Japan market. Marketed products of SLNs are listed in Table no.3.

Table 3: List of Marketed Products.

Product Name	Main Active Ingredient	Producer/Distributors
Nano Lipid Restore	Coenzyme Q-10 and Omega unsaturated fatty acids.	Chemisches Laboratorium Dr. Kurt Richter, CLR Berlin
NLC Deep Effect	Coconut oil, tamanu tree extract	Beate Johnen
Intensive Serum Nanorepair Q-10	Q-10, Polypeptide, Mafane Extract (Antiwrinkle effect)	Dr. Rimpler Gmbh

APPLICATION OF SLNs

Topical applications of SLNs have been reported with promising results for therapeutic purposes. It has a potential advantage of direct drug delivery to the site of action, which will generate higher tissue concentrations. Development and evaluation of SLNs of Terbinafine hydrochloride for sustained release and skin targeting has been carried out by Vaghasiya *et al.* Carbopol gels of Aceclofenac SLNs have been prepared by Chawla et al. Pulmonary administration of drugs has some exclusive characteristics as well as large surface area, avoidance of the first-pass effect, high capacity for solute exchange, excellent vascularisation, and ultra-thinness of the alveolar epithelium (0.1-0.5 mm) that can facilitate systemic delivery.[9] Antitubercular drugs like Rifampicin, Isoniazid, Pyrazinamide-loaded SLN systems have been reported for oral administration, which were able to reduce the dose amount and improve patient compliance. Formulation of poor orally bioavailable drug Lopinavir into SLNs were reported using hot self nano-emulsification technique by Negi *et al.* They demonstrated that the oral bioavailability of lopinavir was improved due to higher intestinal lymphatic uptake of Lopinavir-loaded SLNs.[52] Reddy *et al.* studied the influence of the route of administration on tumor uptake and biodistribution of etoposide loaded solid lipid nanoparticles in mice bearing Dalton's lymphoma after subcutaneous, intravenous and intraperitoneal injections. It was observed that subcutaneous injection reduced the biodistribution of SLN to all the tissues studied, whereas intravenous injection resulted in lower levels of etoposide-loaded SLN in RES rich organs compared to free etoposide. SLN experienced significantly higher brain distribution after intraperitoneal injection, indicating its potential application in targeting etoposide to brain tumors.[53] Increasing attention has been paid to the pulmonary route for systemic delivery of peptide and protein drugs, such as insulin. The SLN production is based on solidified emulsion (dispersed phase) technologies. Therefore, due to their hydrophilic nature most of proteins are expected to be poorly microencapsulated into the hydrophobic matrix of SLN, tending to partition in the water phase during the preparation process, which is further enhanced by the use of surfactants as emulsion stabilizers. Therapeutically relevant peptides (e.g. calcitonin, cyclosporine A, somatostatin), protein antigens (e.g. Hepatitis B and malaria antigens) and model protein drugs (e.g. bovine serum albumin and lysozyme) have

been investigated for drug release kinetics, protein stability and *in vivo* performance.[54]

FUTURE OF SLNs

SLNs can be developed as more effective drug delivery in future by taking consideration of industrial needs like simple technology, low cost, regulatory excipient status, tolerability, scale up, qualification and validation. Research must continue to develop a therapy through localized medical implants. Yih *et al.* developed a bio-micro electro mechanical micropumps for controlled release of drug for local action. Factors that should be taken in consideration in future research are efficacy, drug loading, targeting and toxicity. Studies are essential to evaluate the efficacy of implants over time when encapsulated and stored. Implantable devices or nanochips will provide improved therapeutics in disease management and potentially applied as gene therapy, antitumor, vaccines and in repairing damaged tissue, detecting mutated genes or detecting high hormone levels indicative of certain malignance. Further work needs to be carried out to understand the structure and dynamics of SLNs at the molecular level in *in-vitro* and *in-vivo* studies.

CONCLUSION

The SLN are exciting carrier systems for encapsulating bioactive substances and there application. The present review has concentrated on newer approach of nano sized delivery carriers like solid lipid nanoparticle, nanostructured lipid carriers, lipid drug conjugates, Polymer lipid hybrid nanoparticles etc. Implantable devices or nanochips offer an economical system, patient compliance and avoid adverse effects on non-targeted tissues. As SLN have potential of controlled drug delivery to a target tissue, there will be a vast area of investigation in improvement of quality, efficacy and safety of drug in future.

REFERENCES

1. Horikoshi S, Serpone N.: Introduction to Nanoparticles, Microwaves in Nanoparticle Synthesis. Wiley-VCH Verlag GmbH & Co. KGaA, First Edition 2013.
2. Jamali AA, Pourhassan-MM, Dolatabadi JEN et al. Nanomaterials on the road to microRNA detection with optical and electrochemical nanobiosensors. Trac-Trend Anal Chem., 2014; 55: 24-42.
3. Garud A, Singh D, Garud N. Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications. Int Current Pharm J., 2012; 1(11): 384-393.
4. Mandawgade SD, Patravale VB. Development of SLNs from natural lipids: Application to topical delivery of tretinoin. Int J of Pharm., 2008; 363: 132-138.
5. Yadav N, Khatak S,Sara UV.Solid lipid nanoparticles- a review, Int J of App Pharma., 2013; 5(2): 8-18.
6. Müller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery -A review of the state of the art. Eur J of Pharm and Biopharm., 2000; 50:161-177.
7. Muller RH, Maassen S, Schwarz C, Mehnert W. Solid lipid nanoparticles (SLN) as potential carrier for human use: interaction with human granulocytes. J. Countr. Release, 1997; 47: 261-269.
8. Solid lipid nanoparticles. Wikipedia.org. 15 Aug. 2017 http//:en.wikipidea.org/wiki/solid_lipid_nanoparticle (15 Aug. 2017).
9. Dolatabadi ZEN, Valizadeh H, Hamishehkar H. Solid Lipid Nanoparticles as Efficient Drug and Gene Delivery Systems: Recent Breakthrough. Advanced Pharmaceutical Bulletin, 2015; 5(x): x-x.
10. Rupenagunta A, Somasundaram I, Ravichandiram V, Kausalya J, Senthilnathan B. Solid lipid nanoparticles- A versatile carrier system. J Pharm Res., 2011; 4(7): 2069-2075.
11. Fahr A, Liu X. Drug delivery strategies for poorly water soluble drugs, Expert Opinion on Drug Del., 2007; 4(4): 403-416.
12. Mehnert W, Mader K. Solid lipid nanoparticles- Production, characterization and applications. Adv Drug Del Rev., 2001; 47: 165–196.
13. Müller RH, Mehnert W, Lucks JS et al. Solid lipid nanoparticles (SLN) – An alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm., 1995; 41: 62–9.
14. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. Eur J Pharm Biopharm., 2000; 50: 161–77.
15. Schwarz C. Feste Lipidnanopartikel: Herstellung, Charakterisierung, Arzneistoffinkorporation und–freisetzung, Sterilisation und Lyophilisation. PhD thesis, Freie Universität Berlin, 1995.
16. Melike Ü, Gülgün Y. Importance of solid lipid nanoparticles (SLN) in various administration routes and futureperspective. Int J of Nanomedicine, 2007; 2(3): 289-300.
17. Heiati H, Tawashi R, Shivers RR, et al. Solid lipid nanoparticles as drug carriers I. Incorporation and retention of the lipophilic prodrug 3'-azido-3'-deoxythymidine palmitate. Int J Pharm., 1997; 146: 123–31.
18. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev., 2002; 54(1): S131–55.
19. Jaiswal S, Gupta GD. Recent advances in solid lipid nanoparticles and challenge. Indo ame J of Pharm Res., 2013; 3(12): 1601-1611.
20. Morel S, Terreno E, Ugazio E et al. NMR relaxometric investigation of lipid nanoparticles (SLN) containing gadolinium (III) complexes. Eur J Pharm Biopharm., 1998; 45: 157-63.

21. Souza LG, Silva EJ, Martins AL et al. Development of topotecan loaded lipid nanoparticles for chemical stabilization and prolonged release. Eur J Pharm Biopharm., 2011; 79(1): 189-196.
22. Zhang C, Peng F, Jiangling WL et al. Nanostructured lipid carriers as a novel oral delivery system for triptolide: induced changes in pharmacokinetics profile associated with reduced toxicity in male rats. Int J of Nanomedicine, 2014; 9: 1049-1063.
23. Ochekpe NA, Olorunfemi PO, Ngwuluka NC. Nanotechnology and Drug Delivery Part 2: Nanostructures for Drug Delivery. Trop J of Pharm Res., 2009; 8(3): 275-287.
24. Pardeshi CS, Rajput P, Belgamwar V et al. Solid lipid based nanocarriers: An overview. Acta Pharm., 2012; 62: 433-472.
25. Beija M, Salvayre R, Lauth-de Viguerie N et al. Colloidal systems for drug delivery: from design to therapy. Trends Biotechnol., 2012; 30(9): 485-96.
26. Dinda A, Biswal A, Chowdhury Pet al. Formulation Development and Evaluation of Paclitaxel Loaded Solid Lipid Nanoparticles Using Glyceryl Monostearate. J of App Pharm Sci., 2013; 3(08): 133-138.
27. Trotta M, Debernardi F, Caputo O. Preparation of Solid lipid nanoparticles by a solvent emulsification-diffusion technique. Int J of Pharm., 2003; 257: 153-160.
28. Rabinarayan P, Padilama S. Production of Solid Lipid Nanoparticles-Drug Loading and Release Mechanism. Jof Chem and Pharm Res., 2010; 2(1): 211-227.
29. Ekambaram P, Sathali AH, Priyanka K. Solid Lipid Nanoparticles: A Review. Scientific Reviews and Chemical Communication, 2012; 2(1): 80-102.
30. Sinha VR, Srivastava S, Goel H et al. Solid Lipid Nanoparticles (SLN'S) – Trends and Implications in Drug Targeting. Int J of Adv in Pharma Sci., 2010; 1: 212-238.
31. Kamble VA, Jagdale DM, Kadam VJ. Solid lipid nanoparticles as drug delivery system. Int J Pharm Biol Sci., 2010; 1: 1-9.
32. Jain NK. Controlled and Novel Drug Delivery. 1st Edition, CBS Publishers and Distributors, 1997; 3-28.
33. Sinha VR. Solid lipid nanoparticles (SLN'S) – trends and implications in drug targeting. Int J of Adv in Pharm Sci., 2010; 1: 12-238.
34. Kamble MS. Solid lipid nanoparticles and nanostructured lipid carriers - an overview. Int J of Pharm, Chem and Bio Sci., 2012; 2(4): 681-691.
35. Cavalli R, Donalisio M, Civra A et al. Enhanced antiviral activity of Acyclovir loaded into β-cyclodextrin-poly (4-acryloylmorpholine) conjugate nanoparticles. J of Cont Rel., 2009; 137: 116–122.
36. Pandita D, Ahuja A, Velpandian T et al. Characterization and in vitro assessment of paclitaxel loaded lipid nanoparticles formulated using modified solvent injection technique. Pharmazie., 2009; 64: 301–310.
37. Rabinarayan P, Padilama S. Production of Solid Lipid Nanoparticles-Drug Loading and Release Mechanism. J of Chem and Pharm Res., 2010; 2(1): 211-227.
38. Loxley A. "Solid lipid nanoparticles for delivery of pharmaceutical active". Drug Delivery Technology, 2009; 9(8).
39. Freitas C, Muller RH. Spray-drying of solid lipid nanoparticles (SLN-TM). European Journal of Pharm and Biopharm.. 1998; 46: 145–151.
40. Pandey R, Sharma S, Khuller G.K. Oral solid lipid nanoparticle-based antitubercular chemotherapy. Tuberculosis, 2005; 85(5-6): 415-420.
41. Luo Y, Chen D, Ren L et al. Solid lipid nanoparticles for enhancing vinpocetine's oral bioavaila-bility. J Control Rel., 2006; 114(1): 53-59.
42. Kamble VA, Jagadle DM, Kadam VJ. Solid lipid nanoparticles as drug delivery system. Int J of Pharm and Biopharm., 2010; 1(3): 1-9.
43. Ramteke KH, Joshi SA, Dhole SN. Solid Lipid Nanoparticle: A Review. IOSR J of Pharm., 2012; 2(6): 34-44.
44. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles (SLN): A Modern Formulation Approach in Drug Delivery System. Ind J of Pharm Sci., 2009; 71(4): 349-358.
45. Gaumet M, Vargas A, Gurny R et al. Nanoparticles for drug delivery: The need for precision in reporting particle size parameters. Eur J of Pharm and Biopharm., 2008; 69: 1-9.
46. Sharma RK, Sharma N, Rana S et al. Solid lipid nanoparticles as a carrier of metformin for transdermal delivery. Int J of Drug Del., 2013; 5: 137-145.
47. Dinda A, Biswal I, Chowdhury P et al. Formulation Development and Evaluation of Paclitaxel Loaded Solid Lipid Nanoparticles Using Glyceryl Monostearate. J of App Pharm Sci., 2013; 3(08): 133-138.
48. Palei NN, Das MK. Preparation and characterization of lornoxicam loaded solid lipid nanoparticles made from different lipids. Int J Pharm Pharm Sci., 2013; 5(4): 438-442.
49. Kotikalapudi LS, AdepuLN, Ratna JV et al. Formulation and in-vitro characterization of domperidone loaded solid lipidnanoparticles. Int J Pharm Biomed Res., 2012; 3(1): 22-29.
50. You J, Wan F, Cui FD et al. Preparation and characteristic of vinorelbine bitartrate-loaded solid lipid nanoparticles. Int J of Pharm., 2007; 343: 270–276.
51. Khan S, Tiwari T, Tyagi S et al. Preformulation studies and preparation of dithranol loaded solid lipid nanoparticles. Int. J. Res. Dev. Pharm., L. Sci. 2012; 1(4): 183-188.
52. Negi JS, Chattopadhyay P, Sharma AK et al. Development of solid lipid nanoparticles (SLNs) of

lopinavir using hot self nano-emulsification (SNE) technique. Eur J Pharm Sci., 2013; 48(1-2): 231-9.
53. Reddy LH, Sharma RK, Chuttani K et al. Influence of administration route on tumor uptake and biodistribution of etoposide loaded solid lipid nanoparticles in Dalton's lymphoma tumor bearing mice. J. Control. Rel., 2005; 105: 185–198.
54. Gupta Y, Jain A, Jain SK. Transferrin-conjugated solid lipid nanoparticles for enhanced delivery of quinine dihydrochloride to the brain. J Pharm Pharmacol., 2007; 59: 935–40.
55. Bhattacharya S. Design, development and evaluation of ibuprofen loaded solid lipid nanoparticles. Indo Ame J of Pharm Res., 2013; 4(2): 1402-1419.
56. Barathur RR, Bookout JB. Topical dermal delivery composition using self assembling nanoparticle with cetylated components. US Patent, US 2014/0234428 A1, 2015.
57. Kaur IP. Solid Lipid Nanoparticle entrapping hydrophilic/amphiphilic drug and a process for preparing the same. WO 2013105101 A1, 2013.
58. Herzog B. Formulation of UV Absorbers by incorporation in Solid lipid nanoparticles, Patent No. US 7147841 B2, 2006.
59. Kaur IP. A process for preparing solid lipid sustained release nanoparticles for delivery of vitamins. Patent No. WO2013105026 A1, 2013.
60. Gasco MR. Method for producing solid lipid microsphere having a narrow size distribution, Patent No. 5250236, 1993.
61. Muller RH. Lucks JS. Arzneistofftrager aus festen Lipidteilchen, Feste Lipidnanospharen (SLN), Patent No: EP 0605497, 1996.
62. Rao KK. Polymerized solid lipid nanoparticles for oral or mucosal delivery of therapeutic proteins and peptides, patent no.20080311214A1, 2006.
63. Gasco MR. Use of SLN comprising cholesteryl propionate and cholesteryl butyrate, Patent no. US 11921634, 2006.
64. Massing U. Production of lipid-based nanoparticles using a dual asymmetrical centrifuge, Patent No. EP1838286 B1, 2005.
65. Falson, Padois K, Fabrice. Solid lipid nanoparticles encapsulating minoxidil, and aqueous suspension containing same, Patent No. EP2413918 A1, 2010.
66. Josep, Raquel, Alfonso. Lipid nanoparticle capsules, Patent No. EP2549977 A2, 2011.
67. Westesen K, Siekmann B. Solid lipid particles, particles of bioactive agents and methods for the manufacture and use, Patent No. US 5785976, 1998.