IPP

Innovations in Pharmaceuticals and Pharmacotherapy

www.innpharmacotherapy.com

eISSN: 2321–323X

Original Article

Solid Lipid Nanoparticles: A Lipid Based Drug Delivery

Sarika Nikam, Mayura Chavan, Padmini. H. Sharma *

*****Department of Pharmaceutics, Padmashree Dr. D.Y. Patil College of Pharmacy, Akurdi, Pune, Maharashtra. India

Abstract

Solid Lipid Nanoparticles is one of the new types of colloidal drug carrier system. SLN consist spherical particles of nanometer range dispersed in water or aqueous surfactant solution. Due to biodegradable and bioacceptable nature of SLN these are less toxic than polymeric nanoparticles and it also overcomes some disadvantage of traditional colloidal drug carrier system. Preparation methods of SLN like hot & cold homogenisation, ultrasonication, emulsification, supercritical fluid technique are described. Aspect of solid lipid nanoparticles their uptake, route of administration, applications, list of different lipid, surfactant are incorporated. Characterisation of SLN by appropriate method like photon correlation spectroscopy, scanning electron microscopy, differential scanning colorimetry is highlighted.

Keywords: Solid lipid nanoparticles, SLN, Colloidal drug carrier, Nanotechnology

***Corresponding Author: Dr.Mrs.P. H. Sharma,** Dr. D. Y. Patil Educational Complex, Sector No- 29, Akurdi, Pune Email-id:pharmabrain20@yahoo.co.in

1. NANOTECHNOLOGY [1-3][5]

It comprises nanotechnological development on the nanometer scale, usually 0.1 to 100 nm. Nanotechnology is the science of small. Nano Derives from the Greek word “Nanos”, which means dwarf or extremely small. Nanoscience deals with the study of molecular & atomic particles.

Applications of nanotechnology in pharmaceutical field areas

- Nanosuspensions– They are colloidal dispersion of nanosized drug particles that are produced by suitable method & stabilized by stabilizer.
- Nanoparticles – they are solid colloidal particles size range from 30-100 nm.
- Nanosphere- polymer matrices in which drug is dispersed or dissolved.
- Nanocapsules- Membrane wall structure with an oil core containing drug.

2. NANOPARTICLES

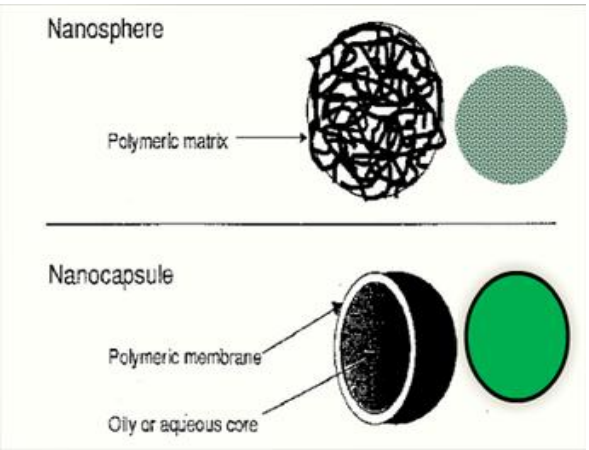
Nanoparticles are solid colloidal particles ranging from 1 nm to 1000 nm in size, active ingredients (drug or biologically active material) is dissolved or encapsulated in polymeric material.

Mainly two types of nanoparticles are shown in Fig 1

1) Nanospheres - It is matrix Type structure in which a drug is dispersed in polymer matrix.

2) Nanocapsule - In this drug is encapsulated within central volume surrounded by continuous polymeric sheath.

Fig 1: Types of nanoparticle



There are following two approaches for the formation of nanoparticles.

1) The "Top Down" approach, shown in Fig 2 which involves the breaking down of large pieces of material to generate the required nanostructures from them.

Fig 2: Top down approach

2) The "Bottom Up" approach, which implies assembling single atoms and molecules into larger nanostructures.

Fig 3: Bottom up approach

Solid Lipid Nanoparticles has been reported as an alternative drug delivery system to traditional polymeric nanoparticles. [6] The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. Generally, they are made of solid hydrophobic core having a monolayer of phospholipids coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics. [7][8] This is one of the most popular approach to improve the oral bioavailability of poorly water soluble drug. [9][10] A clear advantage of solid lipid nanoparticles (SLNs) over polymeric nanoparticles is the fact that the lipid matrix is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity. It is 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 such as physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability.[10] Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids. SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonar, rectal) have been developed and thoroughly characterized in vitro and in vivo.

Table 1: Lipids & Surfactant Used In Solid Lipid Nanoparticles Production.

Lipids	Surfactants
Triglycerols	Phospholipids
Tricaprin	Soy lecithin
Trilaurin	Egg lecithin
Trimyristin	Phosphatidylcholin
Tripalmitin	Ethylene
Tristearin	oxide/Propylene oxide
Acylglycerols	copolymers
Glycerol	Poloxamer 188
monostearate	Poloxamer 182

Glycerol behenate Glycerol palmitosteaate Fatty acids Stearic acid Palmitic acid Decanoic acid Behenic acid Waxes Cetyl palmitate Cyclic complexes Cyclodextrin Para-acyl-calix-arenes	Poloxamer 407 Poloxamine 908 Sorbiton ethylene oxides/propylene oxide copolymer Polysorbate 20 Polysorbate 60 Polysorbate 80 Alkyl aryl polyether alcohol polymer Tyloxapol Bile salts Sodium cholate Sodium glycholate Sodium taurocholate Sodium taurodeoxycholate Alcohol Ethanol Butanol

Advantages of Solid Lipid Nanoparticles [1][5][11-14]

1. SLNs have better stability and easy to produce than liposomes.
2. In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
3. Very high long term stability.
4. It is easy to manufacture than bipolymeric nanoparticles.
5. Better control over release kinetics of encapsulated compound.
6. SLNs can be enhancing the bioavailability of entrapped bioactive.
7. Chemical protection of labile incorporated compound.
8. Raw material which are to be required are same as that of emulsion.
9. Large scale production is possible.
10. High concentration of functional compound can be achieved.
11. Lyophilization possible.

Disadvantage of Solid Lipid Nanoparticles [14-16]

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 hydrophilic drugs due to partitioning effects during the production process.

Aims of Solid Lipid Nanoparticles [11-14]

- Possibility of controlled drug release [10]
- Increased drug stability.
- High drug pay load[10].
- No bio-toxicity of the carrier.
- Avoidance of organic solvents.
- Incorporation of lipophilic and hydrophilic drugs.

Uptake of Solid Lipid Nanoparticles

The majority of orally administered drugs gain access to the systemic circulation by absorption into portal circulation. 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 are suitable candidates for solid lipid nanoparticles, a lipid based 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 longchain TGs lipid core of intestinal lipoproteins formed in the enterocyte after re-esterification of free FAs and MGs. Shortchain TGs are primarily absorbed directly in the portal blood. Hence it is likely that the drug transport via the lymphatic requires co administration of lipid to stimulate lipoprotein formation. [19]

The lymph fluid is emptied (average 3 L per day) via thoracic duct into the subclavian vein, thus protecting the drug from hepatic first-pass metabolism. The drug being transported in the circulatory system, in the form of either micelles or mixed micelles, may then available in its free form, since upon dilution with large volume of lymph/blood, surfactant concentration may reduce below its cmc value & micelles may dissociate into monomers. The drug transported as lipid vesicles may remain

intact for extended period & thereby can result in prolonged release of encapsulated drug. Following fig 4represent the diagrammatic presentation of various mechanisms by which solid lipid nanoparticles enhances the bioavailability drugs. [20]

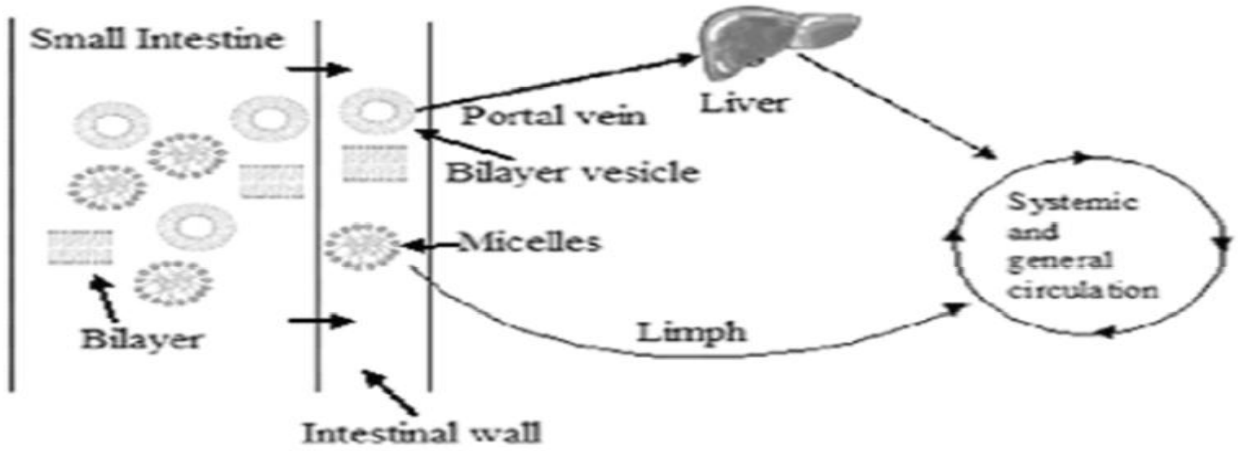


Fig 4 : Various mechanisms of enhancement of drug bioavailability in the presence of lipids.

3. Methods of Preparation of Solid Lipid Nanoparticles: [2][11-16][20-22]

Hot Homogenization Technique: [1]

Melting of the lipid

↓

Dissolution of the drug in the melted lipid

↓

Mixing of the preheated dispersion medium and drug lipid melt

↓

Premix using a stirrer to form a coarse pre-emulsion

↓

High pressure homogenization at a temperature above the lipid melting point

O/W - nano emulsion

↓

Solidification of nanoemulsion by cooling down to room temperature to form SLN

The drug is dissolved or dispersed in melted lipid. In the hot homogenization method the lipid melt containing drug is dispersed in a solution of the hot surfactant at same temperature (5–10^{0}C above the melting point of the *Solid lipid nanoparticle*) by high speed stirring. This pre-emulsion is then passed through a high pressure homogeniser adjust to the same temp generally applying three cycles at 500 bar or two cycles at 800 bars. The hot homogenization technique can be used for lipophilic and insoluble drugs. As the exposure time to high temperature is relatively short, many heat sensitive drugs can be safely processed. The technique is not suitable for incorporation of hydrophilic drugs into SLN because higher portion of drug in water during homogenisation result in low entrapment efficiency.

Cold Homogenization Technique: [1][3]

Melting of the lipid

Dissolution/solubilization of the drug in the melted lipid →Solidification of the drug loaded lipid in liquid nitrogen or dry ice → Grinding in a powder mill (50-100 micrometer particles) → Dispersion of the lipid in the cold aqueous dispersion medium→ Solid lipid nanoparticles.

The first step of preparation is same as hot homogenisation which includes disperse or dissolving or solubilisation of drug in the melted lipid. Then drug lipid mixture is rapidly

cooled with help of liquid nitrogen or dry ice. The drug containing solid lipid is milled by means of mortar or ball mill to micron size (50-100 micron) and these microparticles are dispersed in chilled emulsifier solution yielding a presuspension. Then this presuspension is subjected to high pressure homogenization at room or below room temperature, where the cavitation force is strong enough to break the microparticles to SLNs. This process avoids or minimizes the melting of lipid and therefore minimizing loss of hydrophilic drug to aqueous phase. The cold homogenization only minimizes the thermal exposure of drug, but it does notavoid completely it due to melting of the lipid/drug mixture in the first step of preparation. [7] High pressure homogenization increases the temperature of the sample (e.g. 10-20ºC for each homogenization cycle). In most of the cases, 3-5 homogenization cycles at 500-1500 bar are sufficient to prepare SLN. Increasing the number of homogenization cycle or the homogenization pressure resulted in increase of particle size due to particle coalescence which resulted from high kinetic energy of particles.

Advantages

- Low capital cost.

Disadvantages

- Energy intensive process.
- Demonstrated at lab scale bimolecular damage.
- Polydisperse distributions.
- Unproven scalability.

Ultrasonication or High Speed Homogenization: [3]

This ultrasonication technique is a dispersing technique, which is used for the production of solid lipid nanodispersion. Ultrasonication based on the mechanism of cavitation. In first step, the drug was added to previously melt solid lipid. In second step, the heated aqueous phase (heated to same temperature) was added to the melted lipid and emulsified by probe sonication or by using high speed stirrer or aqueous phase added to lipid phase drop by drop followed by magnetic stirring. The obtained pre-emulsion was ultrasonicated using probe sonicator with water bath (at 0ºC). In order to prevent recrystalization during the process, the production temperature kept at least 5ºC above the lipid melting point. The obtained nanoemulsion (o/w) was filtered through a 0.45µm membrane in order to remove impurities carried in during ultrasonication. Then they obtained SLN is stored at 4ºC. To increase testability of the formulation, was lyophilized by a lyophilizer to obtain freeze-dried powder and sometime mannitol (5%) was added into SLNs as cryoprotector.

Solvent Emulsification- Evaporation Technique:

In solvent emulsification-evaporation method, the lipophilic material and hydrophobic drug were dissolved in a water immiscible organic solvent (e.g. cyclohexane, dichloromethane, toluene, chloroform) and then that is emulsified in an aqueous phase using high speed homogenizer. To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the microfluidizer. Thereafter, the organic solvent was evaporated by mechanical stirring at room temperature and reduced pressure (e.g. rotary evaporator) leaving lipid precipitates of SLNs. [9]Here the mean particle size depends on the concentration of lipid in organic phase. Very small particle size could be obtained with low lipidload (5%) related to organic solvent. Drug + lipid are dissolved in H2O immiscible solvent

Emulsification In aqueous phase O/w emulsion →Solvent evaporation at room temperature and reduced pressure SLN

Advantages

- Reduced shear stress.

Disadvantages

- Potential metal contamination.
- Physical instability like particle growth upon storage.

Solvent Emulsification- Diffusion Technique:

In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl

lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid. When heating is required to solubilise the lipid, the saturation step was performed at that temperature. Then the lipid and drug were dissolved in water saturated solvent and this organic phase (internal phase) was emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) using mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. Here the both the phase were maintain at same elevated temperature and the diffusion step was performed either at room temperature or at the temperature under which the lipid was dissolved. Throughout the process constant stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilization.

Solvent + Water are mutually saturated → Add drug and lipid emulsion → O /w emulsion+ Dilution media (water) in the ratio 1:5 - 1:10 Diffusion of solvent to continuous phase→ Solid lipid nanoparticles

Micro Emulsion Based Method: [5]

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 HPH based formulations.

Melting of lipid→Add aqueous solution of drug to melted lipid→Add Surfactant and co-surfactant at a temperature above the melting point of lipid→Formation of clear w/o microemulsion Formed w/o microemulsion is added to a mixture of water, surfactant and co-surfactant under mechanical stirring→Formation of suspension of lipid particles→Wash with dispersion medium by ultrafiltration system →Solid lipid nanoparticles

Advantages

- Low mechanical energy input.
- Theoretical stability.

Disadvantages

- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticle concentrations.

Supercritical Fluid Technology:

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,

CO2, ammonia, ethane and CH2FCF3 were tried, but CO2 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, noninflammable, 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-CO2. This technology comprises several processes for nanoparticles production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution (PGSS), gas/supercritical antisolvent (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.

Gas/Sas:

In this process SCF acts as antisolvent for processing solid that are insoluble in SCF. It exploits the ability of SCF to dissolve in organic solvent and reduce the solvation power of solid in solution, thus causing the solid to precipitate. At first, the near critical or supercritical fluid was introduced in a vessel containing an organic solvent in which the solid material to be crystallized was dissolved which causes the intimate mixing of Solid lipid nanoparticle the fluid and liquid resulting in liquid expansion and particle precipitation. A clear disadvantage of this technique is the lack of control on the particle formation. A modification of SAS technique was used to prepare lysozyme spherical nanoparticles, which combines both the atomization and anti-solvent process, by using water/ethanol solution

Double Emulsion Technique: [5]

In double emulsion technique the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). Thereafter, the double emulsion was stirred and was isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of the incorporation of a lipid/-PEG derivative. Sterical stabilization significantly improved the resistance of these colloidal systems in the gastrointestinal fluids. This technique is mainly used to encapsulate hydrophilic drug (peptides).

Membrane Contactor 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 pores allowing the formation of small droplets. 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 contactor method is also used for the preparation of polymeric nanoparticles, by methods involving apolymerization of dispersed monomers or a dispersion of preformed polymers. 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.

Solvent Injection Technique:

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 in to stirred aqueous phase with or without surfactant. The resulted 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 resulting in solvent.

Advantages

Use of pharmacologically acceptable organic solvent

- easy handling
- Fast production process without technically sophisticated equipment.

The advantages & drawbacks of existing SLN formulation technique are shown in Table - 2[13]

Table 2: Shows advantages & drawbacks of existing SLN formulation technique

SN	Technique	Advantages	Drawbacks
1.	Microemulsion technique	Low mechanical energy input, thermal stability.	Extremely sensitive to change, labour intensive formulation process.
2.	Contact ultrasonication	Reduced shear stress, effective at lab scale	High metal contamination potential, energy intensive process, unproven scalability.
3.	High pressure homogenization	Scalable, well develop technology, continuous operation, commercially demonstrated.	Extremely energy intensive process, polydispersed distribution, bio molecule damage
4.	Hot homogenization technique	Applicable to lipophilic &insoluble drug, Exposure time to high temperature is short.	Low entrapment efficiency for hydrophilic drug.
5.	Cold Homogenization technique	Best for hydrophilic drug & thermo labile & themosensitive drug	Exposure to heat cannot be completely avoided.
6.	Solvent evaporation technique	No dilution solidification step, monodispersed distribution.	Residual organic solvent

Characterisation of Solid Lipid Nanoparticles [2][3][8][19] [23][31]

Measurement of Particle Size and Zeta Potential:

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for measurements 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. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool for characterize nanoparticles, but it is not able to detect larger micro particles. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion.

Photon Correlation Spectroscopy (PCS):

It is an established method which is based on dynamic scattering of laser light due to Brownian motion of particles in solution/suspension. This method is suitable for the measurement of particles in the range of 3 nm to 3 mm. The PCS device consists of laser source, a sample cell (temperature controlled) and a detector. Photomultiplier is used as detector to detect the scattered light.

The PCS diameter is based on the intensity of the light scattering from the particles.

Electron Microscopy:

Electron Microscopy methods such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to measure the shape and morphological characteristics of lipid nanoparticles. It consist the determination of particle size and distributions. SEM uses electrons transmitted from the surface of the sample and in TEM uses electrons transmitted through the sample.

Atomic Force Microscopy (AFM):

It is an advanced microscopic technique which is used as a new tool to image the original unchanged shape and surface properties of the particles. AFM measures the force acting between surface of the sample and the tip of the probe, when the probe is kept close to the sample which results in a spatial resolution of up to 0.01 nm for imaging.

Determination of Incorporated Drug

Amount of drug incorporated in SLNs affect the release characteristics hence it is very important to measure the amount of incorporated drug. The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium and this separation can be done by ultracentrifugation, centrifugation filtration or gel permeation chromatography and the drug separated can be assayed by standard analytical technique such as HPLC spectrophotometer, spectroflurophotometry etc.

***In- Vitro* Drug Release:**

Dialysis Tubing:

In vitro drug release could be done by using dialysis tubing. The solid lipid nanoparticle dispersions placed in prewashed 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 specific time intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse Dialysis:

In this technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN dispersion. The SLNs are then displaced into the medium.

Rheology:

Rheological measurement of formulation can carried out with help of Brookfield Viscometer, using suitable spindle number. The viscosity depend on dispersed lipid content Increases, The Flow Becomes Nonnewtanion from Newtanion.

Nuclear Magnetic Resonance (NMR):

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

X-Ray Diffraction (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 permitting the degree of crystallinity to be assessed. Another method that is little different from its implementation with bulk material, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through measurement of glass & melting point temperature & their associated enthalpies.

Routes of Administration & Their Bio Distribution: [3]

The *in vivo* behaviour of the SLN particles will mainly depend on the following points: Interactions of the SLN with the biological surroundings including: distribution processes & enzymatic processes. Various administration routes are given as follows

Parenteral Administration:

Peptide and proteins drugs are usually available in the form of parenteral formulation

in the market. Since their conventional oral administration is not possible due to enzymatic degradation in GI tract. Parenteral application of SLN reduces the possibility of side effects of drug incorporated with the increased bioavailability. These systems are very suitable for drug targeting.

Oral Administration:
Controlled release behaviour of SLNs is reported to bypass the gastric and intestinal degradation of the encapsulated drug and their possible uptake and transport through the intestinal mucosa. However, the assessment of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration

Rectal Administration:
This Route Is Generally Used For Paediatric Patients Due To Easy Application.

Nasal Administration:
Nasal route is preferred due to the fast absorption and rapid onset of drug action also avoiding degradation of drugs in the GIT due to the enzymes and insufficient transport across epithelial cell layers.

Respiratory Delivery:
Nebulisation of solid lipid particles carrying anti-tubercular drugs, anti-asthmatic drugs and anticancer was observed to be successful in improving drug bioavailability & reducing the dosing frequency for better management of pulmonary action.

Ocular Administration:
Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of drug with aim of ocular drug targeting.

Topical Administration:
SLN are very attractive colloidal carrier systems for skin applications. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

Application [3]
Oral Solid Lipid Nanoparticles in Antitubercular Chemotherapy: [8][24]

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 lipidnanoparticles are prepared.

Solid Lipid Nanoparticles for Topical Use:

SLNs used for topical application for various drug such as anticancer [24], vitamin-A [25] isotretinoin, flurbiprofen[26] .Using glyceryl behenate, vitamineA-loaded nanoparticles can be prepared. This method is useful for the improvement of penetration with sustained release. The isotretinoin loaded lipid nanoparticles were formulated for topical delivery of drug. Production of the flurbiprofen-loaded SLN gel for topical application offer a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations

Solid Lipid Nanoparticles 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. [25] Efficacy of doxorubicin (Dox) has been reported to be enhanced with the help of SLNs. In the methodology the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water and form Dox-loaded solid lipid nanoparticles. The system has enhanced its efficacy and reduced breast cancer cells

Solid Lipid Nanoparticles as a targeted carrier for anticancer drug to solid tumours:

SLNs have been reported to be useful as drug carriers to treat neoplasms. [28] Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate [29] and Camptothecin [29] Tamoxifen an anticancer drug is incorporated in SLN to prolong release of drug after intra venous administration.

Reference:

1. S.P, Vyas, R.k. Khar, Targeted & Controlled Drug Delivery Novel Carrier System, C.B.S. Publication, First Edition, 15-16, 46-348.

2. N.K.Jain, Advances in controlled & novel Drug delivery system, C.B.S. Publication, First Edition, 408-422,

3. S.P.Vyas, Theory & Practice in Novel Drug Delivery System, C.B.S. Publication, First Edition, 299-315.

4. Xiaoling, Bhakara R. Jasti, Design of Control Drug Delivery System, Mc Graw. Hill, 317-377.

5. N.K.Jain, Pharmaceutical Product Development, C.B.S. Publication, First Edition, 445.

6. P. Ekambaram, A. Abdul hasansathali K. Priyanka, solid lipid nanoparticles: a review Scientific Reviews Chemical Communications, 2(1), 2012, 80-102.

7. C. Shah, V. Shah, U. Upadhyay, solid lipid nanoparticles: a review current pharma research, 1(4), 2011, 351-368.

8. Ramteke K.H, Joshi S.A, Dhole S.N.,Solid Lipid Nanoparticle: A Review, IOSR Journal of Pharmacy,2012, 34-44.

9. Waghmare A. S., Grampurohit N.D., Gadhave M.V., Gaikwad D.D., Jadhav S.L, Solid lipid nanoparticles: a promising drug delivery system, International research journal of pharmacy, 2012

10. P. Ekambaram, A. Abdul Hasan Rakhali and K. Priyanka, Solid Lipid Nanoparticle: A Review, Sci. Revs. Chem. Commun, 2012, 80-102.

11. S. Mukherjee, S. Ray and R. S. Thakur, Ind. J. Pharm. Sci., 349-358 (2009).

12. M. R. Mozafari, 41-50 (2006).

13. Rainer H. Muller, Karsten Mader and Sven Gohla, Eur. J. Pharm. Biopharm., 50(1), 161-177 (2000).

14. Wolfgang Mehnart and Karsten Mader, Adv. Drug. Deliv. Rev., 47, 165-196 (2001).

10. Houli Li, Xiaobin Zhao, Yukun Ma and Guangxi Zhai, Ling Bing Li and Hong Xiang, Lou. J. Cont.Release, 133, 238-244 (2009).

15. Melike Uner, Gulgun Yener, Int. J. Nanomedicine, 2(3), 289-300 (2007).

16. Annette Zur Mehlen, Cora Schwarz and Wolfgang Mehnart, Eur. J. Pharm. Biopharm., 45, 149-155(1998).

17. Elena Ugazia, Roberta Cavalli and M. R. Gasco, Int. J. Pharm., 241, 341-344 (2002).

18. Indu Pal Kaur, Rohit Bhandari, Swati Bhandari and Kakkur. J. Cont. Rel., 127, 97-109 (2008).

19. Solid, S. Pragati, S Kuldeep, S Ashok, M.Satheesh, lipid nanoparticles: A Promising drug delivery technology International Journal of Pharmaceutical Sciences & Technology, 2009, 509-516

20. Green PH& Glickman RM, Intestinal Lipoprotein Metabolism, J Lipid Res22,1981, 1153- 17. Antonio J. Almeida and Eliana Souto, Adv. Drug Delivery Rev., 59, 478-490 (2007).1174

21. S. P. Vyas and R. K. Khar, Controlled Drug Delivery - Concepts and Advances, First Edition, Vallabh Prakashan (2002) pp. 38-50.

22. Joseph Robinson and Vincent H. L. Lee, Controlled Drug Delivery - Fundamentals and Applications, 2nd Edition, 4-33.

23. N. K. Jain, Controlled and Novel Drug Delivery 1st Edition, (CBS Publishers and Distributors1997) 3-28.

24. R.Pandey, S. Sharma, G.K. Khuller. Oral SLN Based antitubercular chemotherapy, Tuberculosis (Edinb) 85, 2005, 415-420.

25. H. Chen, X. Chang, D. Du, W. Liu, J. Liu, Podophyllotoxin- loaded solid lipid nanoparticles for epidermal targeting. Journal of Control Release 110, 2006, 296-306.

Solid lipid nanoparticle: a review 44

26. M.C. Santos, W. Mehnert, M. Schaller, Drug targeting by solid lipid nanoparticles for

dermal use. Journal Drug Target, 10, 2002, 489-495.
27. B. Lu, S.B. Xiong, H. Yang, X.D. Yin, R.S. Chao, Solid lipid nanoparticles of mitoxantrone for local injection against breast cancer and its lymphnode metastases. European Journal of Pharm. Sciences, 28, 2006, 86-95.
28. V.S. Shenoy, I.K. Vijay, R.S. Murthy. Tumour targeting: Biological factors and formulation advances in injectable lipid nanoparticles. Journal Pharm Pharmacol, 57, 2005, 411-422.
29. K. Ruckmani, M. Sivakumar, P.A. Ganeshkumar, Methotrexate loaded solid lipid nanoparticles (SLN) for effective treatment of carcinoma. Journal Nano sciences Nanotechnology, 6, 2006, 2991-2995.
30. S.C. Yang,L. F. Lu, Y. CAI, J.B. Zhu, B.W. Liang, Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on brain. Journal of Control Release, 59, 1999, 299-307.
31. Vishwajit Kamble, Deepali Jagdale, Vilasrao Kadam, Solid Lipid Nanoparticle As Drug Dilivery System, International Journal Of Pharma & Bio sciences, sep. 2010