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Solid Lipid Nanoparticles: A Review

Mobina Begum and Naseeb Basha Shaik *

Department of Pharmaceutics, G.Pulla Reddy College of Pharmacy, Osmania University, Hyderabad-500028, Telangana, India

Address for Correspondence: Naseeb Basha Shaik, naseebgprcp@gmail.com

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ABSTRACT: Nanotechnology is one of the pharmaceutical fields which is gaining interest and emerging rapidly as it is providing various advantages like targeted drug delivery, programmed drug release, protection of drug from harsh environment etc. Nanoparticles are produced by employing nanotechnology. SLN come under the category of nanoparticles. These are sub-micron colloidal lipidic particles having size in nanoscale i.e., 50-200 nm. Various advantages by formulating SLN are Enhanced bioavailability, Targeted release, Easy scale up, Sterility, and Controlled release. This article gives review on materials employed for preparation of SLN, various preparation methods with their advantages and disadvantages, characterization techniques, different routes of administrations through which SLN can be given and various applications of SLN in different fields.

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INTRODUCTION

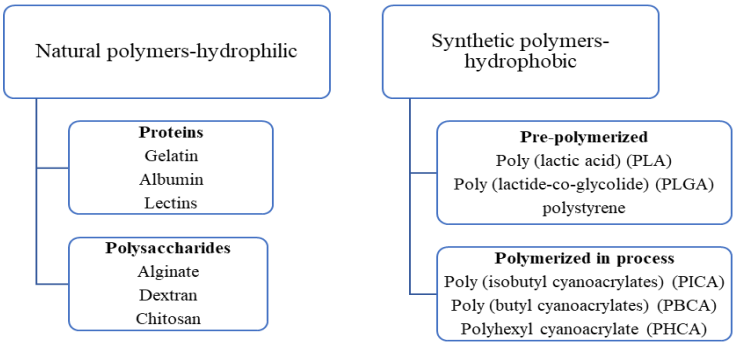
Nanotechnology is one of the pharmaceutical fields which is gaining interest and emerging rapidly as it is providing various advantages like targeted drug delivery, programmed drug release, protection of drug from harsh environment etc., nanoparticles are produced by employing nanotechnology. Nanoparticles mainly composed of polymers which can be from different origins like natural, semi synthetic or synthetic. First nanoparticles was formulated using non-biodegradable polymers like polyacrylamide, polymethylmethacrylate, polystyrene etc.,[1,2] but due to their toxicity and unsuitability for systemic administration later they were replaced by biodegradable polymeric system. From then nanoparticles are produced using biodegradable polymers like poly(cyanoacrylate)[3].

1. POLYMERS USED IN NANOPARTICLE PREPARATION

1.1. Natural Polymers

These are widely used as they are biodegradable, biocompatible and immunomodulators but they also have certain drawbacks like immunological response leading to antigenicity, variation from batch to batch and biodegradability in certain conditions. These are classified as proteins and polysaccharides.

Alginate polymer can be used for oral, ophthalmic, intravenous formulation[4]. Dextran, albumin and gelatin are not suitable for parenteral administration and chitosan should be restricted to use outside the body only.



1.2. Synthetic Polymers

Pre-polymerized polymers are accepted for human use, whereas alkyl cyanoacrylate polymers show toxicity[5].

Nanoparticles are of two types: i) Polymeric nanoparticles and ii) Lipidic nanoparticles. In Polymeric nanoparticles polymers which are listed above are used for nanoparticles formation whereas in Lipid nanoparticles lipids which are solid at room temperature are used for nanoparticles formation and this are novel carriers. Further, lipid nanoparticles are of two types i.e., SLN (Solid Lipid Nanoparticles) and NLC (Nano Lipid Carriers). SLN are sub-micron colloidal lipidic particles having size in nanoscale i.e., 10-1000 nm. SLN was first formulated in 1991[6]. SLN combine the advantages of emulsions like easy large-scale production and stability along

with advantages of solid nanoparticles formulations like protection of drug, controlled release etc. SLN are nothing but dispersion of physiological lipids into aqueous phase of water or surfactant.

2. COMPOSITION OF SLN

SLN mainly consists of lipids which are solid at room temperature and emulsifying agents which are used to disperse lipids in aqueous phase[7].

2.1. Lipids

This form main component of lipid carrier and influences the drug loading capacity and stability. Selection of lipid depends on route of administration. Lipid content more than 5% results in particles with larger size distribution[8,9,10].

Examples:
Triacylglycerols: Trimyristin, Tripalmitin and Tristearin
Acylglycerols: Glycerol monostearate and Glycerol behenate
Fatty acids: Stearic acid and Palmitic acid
Waxes: Cetyl palmitate
Cyclic complexes: Cyclodextrin
Hard fat types: Witepsol W 35.

2.2. Emulsifier and Co-Emulsifier

During high pressure homogenization particle size will be reduced i.e., new surface is formed which may form agglomerates by contacting another new surface leading to instability, to prevent this process emulsifiers are added. Emulsifier will cover the surface of new particles formed thereby aiding in stability [8,9,10]. Sometimes, due to lower mobility of the phospholipid molecules, sudden lack of emulsifier on the surface of the particle i.e., emulsifier will not sufficiently cover the newer surface this leads to particle aggregation. To avoid this process co-emulsifiers are added which acts by reducing the surface tension and properly covering lipidic surface.

Examples:
Lipoids: Lipon E 80S, Lipon S75, Lipon S100, Phospholipon 80H and Phospholipon 90H
Ethylene oxide/ Propylene oxide copolymers: Poloxamer 188 and Poloxamer 407
Spans and Tweens: Polysorbate 20 and Polysorbate 60
Alkyl aryl polyether alcohol polymers: Tyloxapol
Bile salts: Sodium cholate, Sodium glycocholate and Sodium taurocholate
Alcohols: Ethanol and Butanol

2.3. Cryoprotectants

This are used to protect the formulation from damage due to freezing[11].

Examples: Trehalose, mannitol and Polyvinyl pyrrolidone

2.4. Charge Modifiers

They are used to modify release and stability[11].

Examples: Stearyl amine, DPPC (Dipalmitoyl Phosphatidyl Choline) and DMPG (Dimyristoyl Phosphatidyl Glycerol).

2.5 Stealthing Agents

These agents are used for improving circulation time[11] .

Examples: Poloxamer and polyethylene glycol

3. ADVANTAGES AND DISADVANTAGES OF SLN

SLN are having advantages of emulsion along with polymeric formulation[12,13]. Some of the main advantages and disadvantages of SLN are listed in **Table 1**.

4. DRUG LOADING AND RELEASE OF DRUG FROM SLN

4.1 Drug loading

Drug loading process is classified into three types, they are[14,15]:

i. **Homogenous matrix model:** In this model the drug will be homogenously dispersed in the lipid matrix. This type of drug loading is seen with hot homogenization of highly lipophilic drugs and cold homogenization. Drug release from this model is by diffusion.
   e.g. prednisolone can release drug up to 1 week[14,15]

ii. **Drug-enriched shell model:** Drug will be present at the outer shell. Drug free lipid core will be present in this model. This model is formed due to phase separation which occurs during cooling process where lipid precipitates leaving drug free lipid core.
   e.g. coenzyme Q10 releases fastly[14,15]

iii. **Drug-enriched core model:** This model is obtained when the lipids in shell precipitates. Drug release follows ficks law of diffusion.

5. PRINCIPLE OF DRUG RELEASE FROM SLN

5.1. Particle size: Drug release is affected by particle size, where tiny particles have larger surface area, therefore, most of the drug associated would be at or close to the particle surface, leading to quick drug release. Whereas, larger particles have large cores which allow additional drug to be encapsulated and step by step diffuse out. It is a challenge to formulate nanoparticles with the tiniest size attainable and with most stability[14,15].

5.2. Surface area: Larger surface area due to smaller particle size in nanometric range gives high drug release. When the drug is homogenously dispersed in the lipid matrix, slower drug release can be achieved. It depends on kind of drug enclosing model of SLN[14,15].

5.3. Partition coefficient: There is an inverse relationship between drug release and the partition coefficient of the drug[14,15].

Table 1: Advantages and Disadvantages of SLN

Advantages of SLN	Disadvantages of SLN
Enhanced bioavailability	Formulation with poor drug loading capacity
Formulation with particle size 120-200 nm will pass easily through res system thereby bypasses first pass metabolism	Instability during storage due to polymer transition
Easy scale up and sterility	High water content in the formulation leads to stability problem
Controlled release	Particle growth during storage
Lesser usage of organic solvents	Having lesser capacity to load hydrophilic drugs

Table 2: Various Methods of Preparation and Purification of SLN

Methods of preparation	References	Purification	References
1. High pressure homogenization: A. Hot homogenization B. Cold homogenization	9	1. Freeze drying	22
2. Ultrasonication/high speed homogenization: A. Probe Ultrasonication B. Bath Ultrasonication	9	2. Spray drying	19
3. Solvent evaporation method	19	3. Sterilization	23
4. Solvent emulsification-diffusion method	9		
5. Supercritical fluid method	9		
6. Microemulsion based method	9		
7. Spray drying method	19		
8. Double emulsion method	20		
9. Precipitation technique	19		
10. Film-ultrasound dispersion	9		
11. Melting Dispersion Technique	9		
12. Membrane Contractor	21		

5.4. Crystallinity: Crystallinity behavior of the lipid and high mobility of the drug lead to fast drug release. There is an inverse relationship between crystallization degree and quality of drug[14,15].

5.5. Surfactant: The type of surfactant and its concentration, which will interact with the outer shell and affect its structure, should be noted as the outer factor, which is important, because a low surface-active agent concentration results in a marginal burst and prolonged drug dissociation[14,15].

6. PREPARATION OF SOLID LIPID NANOPARTICLES

There are various methods of preparation of SLNof which commonly used preparation method is High pressure homogenization by hot homogenization[16,17].Various methods of preparation and purification of SLN are listed in **Table 2**.

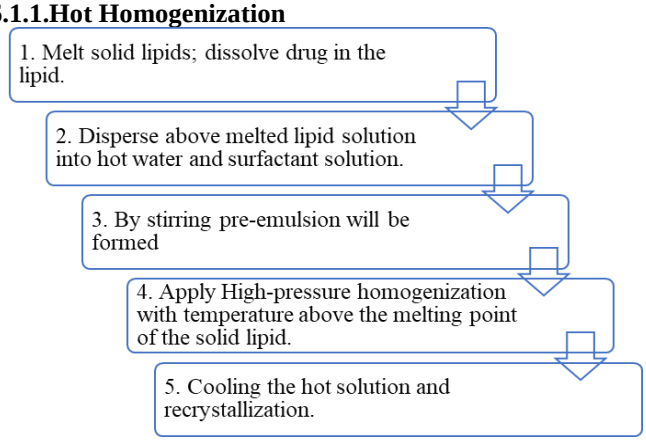
6.1. High pressure homogenization

It is commonly used reliable and effective method of SLN preparation. At the beginning this method was used to prepare solid lipid Nano emulsion but now is also used to prepare SLN [9].

Principle involved in this procedure is the liquid content will be pushed with high pressure by the homogenizer for short distance then due to high shear stress the particles will be broken down leading to formation of nanoparticles. Two approaches in this process are:

In Hot homogenization, homogenization is done by melting the lipid at temperatures where the lipid can melt whereas in Cold homogenization high temperatures are avoided [9]. The steps involved are

6.1.1.Hot Homogenization



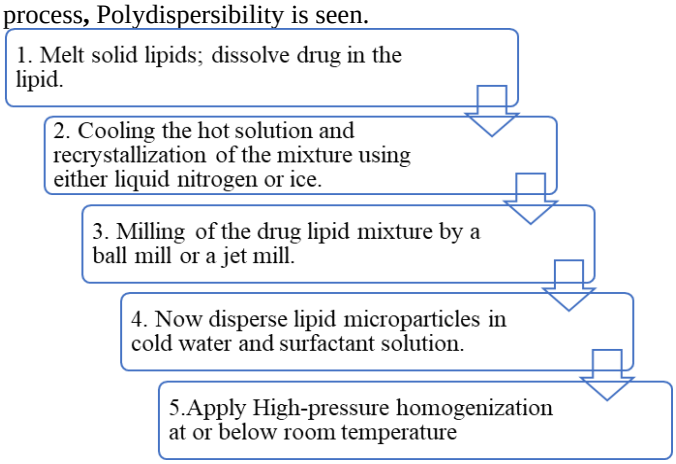
6.1.2. Cold Homogenization

- **Advantages of high-pressure homogenization method**

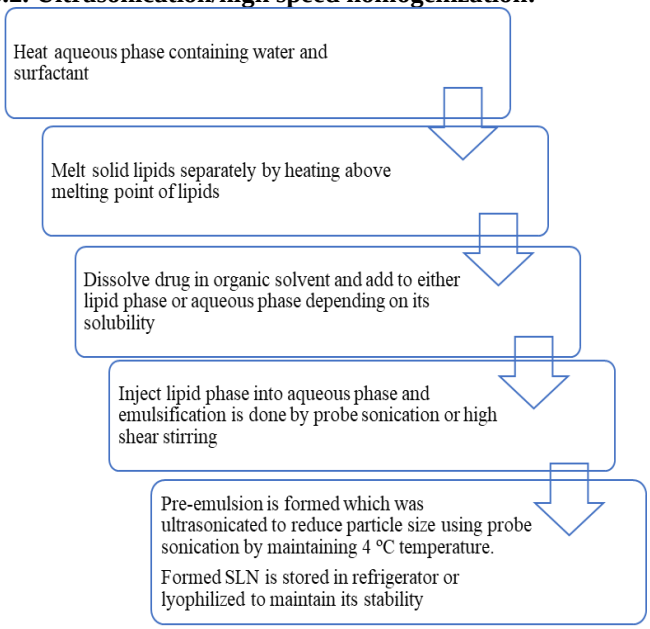
Less cost and reliable process**,** Compatible for lab scale production

- **Disadvantages of high-pressure homogenization method**

Temperature sensitive drug degradation**,** Energy consuming process**,** Polydispersibility is seen.



6.2. Ultrasonication/high speed homogenization:



- **Advantages of ultrasonication method:** Shear stress is less
- **Disadvantage of this method:** Physical instability is seen like particle growth

6.3. Solvent evaporation method

Lipophilic compounds are dissolved in organic water immiscible solvent like cyclohexane. It is then dispersed in the aqueous phase. Solvent evaporation is done under reduced pressure by rotary evaporator, and nanoparticles are formed due to precipitation of lipid molecules in the aqueous medium Siekmann *et al.*[18] prepared 29nm size nanoparticles of cholesterol acetate by this method using lecithin and sodium glycocholate blend as emulsifier

- **Advantages of this method:** Commercial, better technology and scalable process
- **Disadvantages of this method:**Energy consuming, biomolecule degradation and polydisperse distribution

6.4. Solvent emulsification-diffusion method

Partially water miscible organic solvents like benzyl alcohol, isopropyl acetate etc., must be used in this method. Nanoparticles with 30-100nm particle size can be obtained.

Solvent saturated solution and water saturated systems were prepared at temperature where lipids can melt, then lipid and drug mixture were added to solvent saturated system. This organic phase was then dispersed in saturated water phase containing aqueous surfactant. Pre emulsion (o/w) is formed which was further diluted with water to allow solvent diffusion in the continuous water phase due to which lipid aggregation in nanoparticles are obtained

Constant stirring must be maintained throughout the process and the solvent is eliminated by lyophilization process or vacuum distillation[9].

6.5. Supercritical fluid method

It is a novel technique. A Supercritical fluid is a fluid having temperature and pressure more than its critical value by doing so the ability of fluid to dissolve particles will be enhanced. Various process used in this technology for nanoparticle production are Rapid Expansion of Supercritical Solution (RESS), Particles from Gas Saturated Solution (PGSS), Aerosol Solvent Extraction Solvent (ASES) and Supercritical Fluid Extraction of Emulsions (SFEE). PGSS is suitable method using carbon dioxide as gas as it is good choice as solvent [9].

- **Advantages of this method:**No solvents are used, dry powder formulation is obtained instead of suspension, less temperature and pressure exposure.
- **Disadvantage of this method:**Costly process.

6.6. Microemulsion based method

Lipids with low melting point are heated at temperature above their melting point to form lipidic solution. Aqueous phase containing water, surfactant and co-surfactant is also heated to same temperature as that of lipidic phase. Then the aqueous

phase is dispersed into the lipid phase to get transparent microemulsion of o/w type. This microemulsion is then poured into cold water with 2ºC temperature with constant stirring. Ratio of hot microemulsion to cold water are critical and can be used in ratio of 1:25 to 1:50. If solvent used is having aqueous property like acetone then we can get smaller particles and with lipophilic solvents larger particles are formed, which is not desired. Formed SLN dispersion can be used as granulating fluid for preparing tablets or pellets by granulation method. However, SLN dispersion with less particle content need higher water content to be removed[9].

- **Advantages of this method:** higher stability
- **Disadvantages:** laborious and low nanoparticle content

6.7. Spray drying method

This method is used as an alternative to lyophilization technique. Lipid with melting point >70°C are used in this method. According to Freitas*et al.*[19] best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (1:9).

- **Advantages of this method:** cost effective method
- **Disadvantages of this method:** due to high temperature and sheer forces, particle aggregation and partial melting of lipids.

6.8. Double emulsion method

Double emulsion here is w/o/w type prepared in two steps, in first step aqueous phase containing drug is added to lipid phase containing lipid, surfactant and co-surfactant by heating above melting point of lipids to obtain clear solution. Formed microemulsion is added to aqueous phase containing surfactant and cosurfactant. This method is used for hydrophilic drugs. Principle observed in this process is emulsification then evaporation. Drug and emulsifier are encapsulated in the inner aqueous phase of double emulsion and its partitioning during solvent evaporation into outer aqueous phase is prevented by adding stabilizer. Larger size particles are formed due to which these are termed as lipospheres. Li *et al.*[20]formulated solid lipid nanoparticles of bovine serum albumin (BSA) using double emulsion method.

6.9. Precipitation technique

Lipids used in this method are glycerides, these are dissolved in organic phase, this lipid phase is then emulsified into aqueous phase then the solvent is evaporated which leads to precipitation of lipids and formation of nanoparticles [18].

6.10. Film-ultrasound dispersion

In this method the lipids are dissolved in organic solvent. Organic solvent is removed by evaporation to get lipid film. To this, aqueous phase containing surfactant and co-surfactant is added. Then ultrasound using probe sonicator is applied to get SLN with smaller and even particle size [9].

6.11. Melting Dispersion Technique

Drug and solid lipids are melted in organic solvent then this oil phase is added to small quantity of preheated aqueous phase with constant stirring for about an hour to get SLN. This method is having better reproducibility than ultrasonication method but not as good as solvent emulsification-evaporation method [9].

6.12. Membrane Contractor

Solid lipids are melted, and the liquid phase is passed through the pores of the membrane to get fine droplets. Along with this aqueous phase is poured tangentially to the membrane contractor which sweeps away the droplets formed near the pores. Then cooling the formulation to room temperature gives SLN. Charcosset *et al.* [21] prepared vitamin-E loaded SLN by this method.

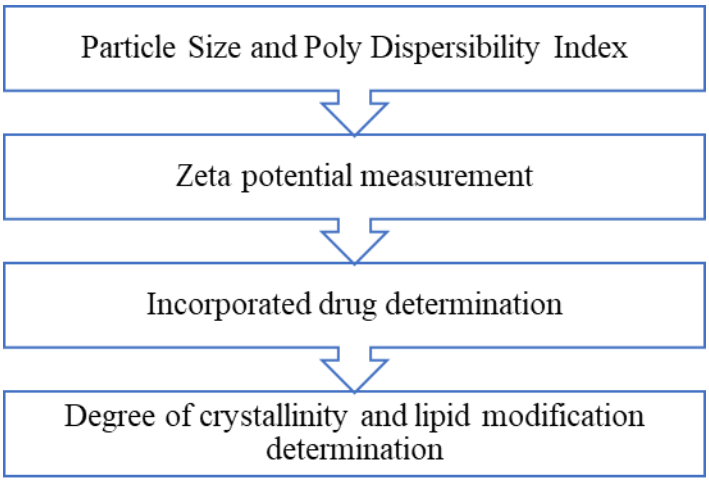
7. PURIFICATION OF SOLID LIPID NANOPARTICLES

7.1. Freeze drying: By lyophilization physical and chemical stability of formulation can be enhanced. Powder formulation is obtained through lyophilization which prevents hydrolytic degradation of drug and Ostwald ripening. Cryoprotectant is added to prevent aggregation of particles [22].

7.2. Spray drying: It is an alternative procedure to lyophilization. This is used for formulation using lipids whose melting point is >70°C [19] .

7.3. Sterilization: This is followed for parenteral formulations. Autoclaving is performed for heat sensitive drugs. Particle size will be increased by sterilization [23].

8. CHARACTERIZATION PARAMETERS OF SLN



8.1. Particle Size and Poly Dispersibility Index (PDI)

Assessing particle size of SLN is important as it will affect the physical stability of formulation[7,17]. It can be done by following technique:

8.1.1. Photon Correlation spectroscopic analysis (PCS): By this technique we can determine particle size ranging from few nanometers up to millimeters. It works on the principle of amount of light scattered by the particles when laser is allowed to pass through it. Scattering of light is due to the

Brownian movement of the particles. The scattered light is detected by photon multiplier[7].

8.1.2. Electron Microscopy: This technique is used to determine the morphology of particles along with size determination. Two techniques come under this category areScanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). SEM employs the principle of detection of electrons transmitted from the surface of particle and TEM employs the principle of detection of electrons transmitted from the particle. TEM can detect even smaller size particles compared with SEM [24].

8.1.3. Atomic Force Microscopy (AFM): It is an advanced technique used to determine particle size. Principle behind this technique is measurement of force acting between the surface of particle and probe[25].

Poly Dispersibility Index (PDI) is the measure of distribution of particles with different sizes. It should be less in value indicating particles are with similar size. PDI value up to 1 is acceptable[26].

8.2. Zeta potential measurement:

Zeta potential assessment for SLN is an essential criterion as it will tell about the stability of formulation by getting information regarding presence of electrostatic repulsions or attractions. For determining zeta potential enough dilution of formulation with deionized water is required. Malvern sizer is employed commonly to determine the zeta potential[27] . Zeta potential canbe used in planning particles with reduced RES uptake. Value ranging from -25 to +25is acceptable and it can be concluded that the particles have enough electrostatic potential [7,17]. Higher the value indicates repulsion forces dominating due to which particle aggregation will be less and formulation can have good stability.

8.3. Incorporated drug determination

Amount of drug that is being incorporated in the particles must be analyzed in order to get accurate results. It can be done by following methods:

8.3.1. Entrapment efficiency: Amount of drug which is encapsulated in the vesicles is determined by separation of the free drug from the encapsulated drug using separation technique like centrifugation or chromatography[6].

$$\mathbf{E.E}\ (\%) = \frac{\text{Total amount of drug in formulation} - \text{Drug present in supernatant}}{\text{Total amount of drug in formulation}} \times 100$$

8.3.2. Percentage Drug Loading: In this method weight amount of formulation was dissolved in organic solution of specified volume then dilution was made with buffer solution. Diluted samples were analyzed [28].

$$\textbf{Drug loading}\ (\%) = \frac{\text{Amount of drug present}}{\text{Total amount of drug used}} \times 100$$

8.4. Degree of crystallinity and lipid modification determination

Modification of lipid structure or crystallinity will affect drug release. The order of drug release due to modification is Super cooled melt < α-modification < β9-modification < β-modification. However, it can be avoided due to smaller size of the particles and due to presence of emulsifier[6].

Analytical techniques used to determine crystallinity are Differential Scanning Calorimetry (DSC) and powder X-Ray Diffraction (XRD). DSC is used to determine crystallinity inside nanoparticles, and it employs the principle of measurement of glass transitions and melting point temperatures and enthalpy. XRD employs the principle of determination of scattering of radiation from the crystal plane present in the nanoparticles[6].

Nuclear Magnetic Resonance (NMR) is used to determine the dimensions and the qualitative nature of nanoparticles. It measures the chemical shifts and comparing with the standard thus providing information on the physicochemical status of components within the nanoparticle[29].

9. *IN-VITRO* DRUG RELEASE STUDIES

Drug release from the formulation can be determined by dissolution or diffusion studies.

9.1. Dialysis bag method: In this method SLN dispersion containing drug was taken in dialysis membrane and the membrane was sealed at both the ends. This sealed bag was kept in required media under controlled temperature. Then samples are withdrawn at regular time intervals and replaced with buffer. Withdrawn samples are analyzed using spectroscopy or chromatography methods to know the amount of drug release [30].

9.2. Reverse dialysis: Little dialysis sacs are prepared in which the buffer solution about 1ml was filled then the sacs were sealed and kept in SLN dispersion. At regular time intervals the sacs are removed and the amount of drug in the buffer solution is analyzed [30].

9.3. Franz Diffusion Cell: SLN formulation is kept on the semipermeable membrane in the donor compartment then the receptor compartment is filled with buffer solution. At regular time intervals samples are withdrawn from receptor compartment and analyzed [31].

10. *EX VIVO* MODEL FOR DETERMINING PERMEABILITY

10.1. Permeability through skin: The animal skin samples with effective area of 3.8 $cm^2$is mounted on Franz-type diffusion cell by placing the stratum corneum side up. SLN dispersion was applied on the skin surface. Receptor compartment contains buffer solution. Then the cell was maintained at 37 ± 0.5°C with stirring speed 600 rpm throughout the experiment. 1 ml sample from receiver medium was withdrawn at predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10 and 12 h) and was replaced with an equivalent volume of buffer solution. Withdrawn samples were filtered through an

aqueous 0.45 m pore size cellulose membrane filter and analyzed by spectroscopy or chromatography [31].

10.2. Permeability through gut: In short, the rat jejunum (20 – 30 cm distal from the pyloric sphincter) or 10 cm long segments of duodenum (1 cm distal to pyloric sphincter); jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum) and colon (2 cm distal to cecum) was excised from the rats immediately after sacrificing the animal used for the study. Intestinal sacs were prepared in which formulation was added and the sacs were kept in the buffer medium. At regular intervals sacs were removed and the sample analysis was done [32].

11. STABILITY AND STORAGE

By stability testing we can come to know the shelf life of the formulation and storage conditions required. Stability data is necessary to get licensing approval from regulatory authorities. Stability testing for SLN need evaluation of properties like drug content or entrapment efficiency, zeta potential, particle size, pH, and appearance as function of time [32].

The most favorable conditions generally used for long term stability are:

• 4°C- Most favorable storage temperature
• 20°C-Long term storage didn't lead to drug loaded SLN aggregation or loss
• 50°C-A rising of particle size was determined

12. ROUTES OF ADMINISTRATION

12.1. Parenteral administration: Through parenteral administration one can achieve 100% bioavailability. Proteins and peptides must be administered through parenteral route only due to their drawback of degradation in mouth due to enzymatic activity. They have shorter half-life due to which it will be necessary for repeated administration which leads to patient incompliance. To overcome this SLN can be formulated and given through parenteral route. SLN is suggested for viral and non-viral gene therapy [33,34].

12.2. Oral administration: Administration of SLN through oral route will provide benefits like lesser variability in plasma level and controlled release as the formulation will bypass the degradation by stomach or intestine. But stability of the formulation in GI fluids is not yet proved [35].

12.3. Rectal administration: By rectal route plasma level and therapeutic efficiency of drugs is high when compared with other route of administrations this can be overcome by formulating as SLN [36]. Sznitowska *et al* [37] formulated diazepam lipospheres for administration into rectum but the lipoid matrix was solid at the body temperature and found it was not advantageous. Sznitowska *et al.*[38] formulated benzodiazepine loaded SLN for administration into rectum of rabbit with lipids which will melt at room temperature and results showed increased availability of drug.

12.4. Nasal administration: This route is normally preferred for its advantages of rapid absorption and avoidance of drug degradation by first pass metabolism. Nasal mucosal adherence can be improved by formulating it as SLN and hence the action can be prolonged [36].

12.5. Respiratory delivery: Nebulization of Solid lipid nanoparticles of target drugs for pulmonary use can help in increased bioavailability and reduces dosing frequency[34,36].

12.6. Ocular administration: By administering SLN through ocular route mucoadhesive property can be enhanced due to which corneal residence time increases and there will be improved action[39]. Cavalli *et al.*[40]formulated SLN of tobramycin, antibiotic for ocular delivery to rabbit. Results have shown that there was increased bioavailability in body. Cavalli *et al.*[41]formulated pilocarpine SLN for glaucoma treatment and got similar results of increased bioavailability.

12.7. Topical administration: Improvement in penetration of drugs and sustained release on skin can be achieved by SLN [42,43].

13. APPLICATIONS OF SLN

13.1. For Targeting Solid Tumors: Anti-tumor drugs comes with various side effects, if not delivered to the site of action, these side effects can be severe. Hence to localize the drug at side of action will minimize various side effects and increases drug concentration at the site of action. SLN was prepared with anti-tumor drugs like Paclitaxel [44] Camptothecin [45] .

13.2. As cosmeceuticals: Various topical drugs like steroids or sunscreen or vit-a can be formulated as SLN for getting localized action in the epidermal layers of skin. Prednisolone was formulated as SLN for getting increased therapeutic action at the site of application [10,46].

13.3. As gene vectors: Various DNA segments can be incorporated into SLN[47].

13.4. Breast cancer and lymph node metastasis: mitoxantrone SLN was prepared to improve the therapeutic effect of drug against breast cancer and its lymph node metastases [48]

13.5. Stealth nanoparticles: Stealth nanoparticles are useful to target dug to immune system as these will not be recognized by immune system and hence can exert their action [49] .

13.6. Liver Targeting: Wang W *et al* [50] prepared cucurbitacin SLN through which increased availability of drug in liver was achieved.

13.7. Anti-tubercular chemotherapy: Various anti-tubercular drugs were formulated as SLN to improve patient compliance and reduce dosing frequency. anti-tubercular drugs formulated as SLN are rifampicin, isoniazid, pyrazinamide [51]

13.8.SLN as potential new adjuvant for Vaccines:
Vaccines can be formulated as SLN due to which we can get enhanced exposure of vaccine to immune system, this is because of solid state of lipid used for formulating SLN [52].

13.9. Skin disease Treatment:
Various skin diseases can be treated by formulating them as SLN due to localized action and minimized systemic side effects provided by the formulation [53] .

13.10. Atopic Dermatitis Treatment
Maia C.S [54] formulated prednicarbate, the topical glucocorticoid used to treat atopic eczema, as SLN for getting localized action and by this fourfold increase was observed compared with that of standard topical formulations.

13.11. Potential agriculture application: From *Artemisia arborescence* oil was extracted and then formulated as SLN in order to minimize evaporation of the oil and used as ecologically safe pesticide [55].

13.12. For treatment of rheumatoid arthritis
Ye J. *et al*[56]prepared SLNs of actarit to minimize side effects of drug like nephrotoxicity and gastrointestinal disorders and to increase therapeutic efficiency. Targeting efficiency of actarit SLN was increased by threefold when compared with normal actarit solution.

13.13. For Diabetes:
Proteins and peptides can be formulated as SLN in order to protect them from degradation due to factors like temperature and pH. Zhang *et al*[57]has formulated insulin as SLN and coated it with a carrier, stearic acid octa arginine as it can help in penetration of peptides into the cells.

CONCLUSION
SLN is the emerging novel drug delivery system because of its localized action and safety provided with the excipients used. Based on drug properties, for getting localized or sustained release drug can be formulated as SLN. Cost effective method for preparation and easy scale up can be achieved with SLN. Hence it can be concluded that SLN acts as good novel drug delivery system for getting effective results.

CONFLICT OF INTEREST
The authors have no conflict of interest.

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DATA AVAILABILITY
Not declared.

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