Recent Advances in Solid Lipid Nanoparticle Based Drug Delivery Systems

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Abstract:
Delivering the drug accurately and safely to its target site at the precise time period to have a controlled release and attain the maximum therapeut effect remains a benchmark in the design and development of newer drug delivery systems. In this review, the latest research developments of the Solid lipid nanoparticles (SLNs) according to the recent relevant literatures were focussed. This paper highlights various production techniques for SLNs as well as their advantages and disadvantages. Analytical techniques for characterization of SLNs like electron microscopy, dynamic light scattering, atomic force microscopy, differential scanning calorimetry, X-ray diffraction, nuclear magnetic resonance and electron spin resonance are discussed. Aspects of principles of drug release and different administration routes of SLNs were described. These SLNs have been claimed to overcome the shortcomings of other colloidal drug delivery systems.

Keywords: Solid lipid nanoparticles, Colloidal carriers, Production techniques, Administration routes

INTRODUCTION:
Nanoparticles are colloidal particles ranging from 10 to 1000 nm (1.0 µm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and/or to which the active principle is adsorbed or attached (1). Recently, significant effort has been taken to develop nanotechnology for drug delivery, as it offers a suitable means of delivering low molecular weight drugs, as well as macromolecules such as peptides, proteins or genes to cells and tissue. Nanoparticles can be used to provide targeted delivery of many drugs, to sustain the drug effect in target tissue, to improve oral bioavailability and to enhance the stability of therapeutic agents against enzymatic degradation (2).

Now a days nanotechnology, as applied to medicine, brought significant advances in the diagnosis and treatment of disease. The desired applications in medicine include drug delivery, nutraceuticals, both in vitro and in vivo diagnostics and production of improved biocompatible materials (3-6). Nanoparticles are emerging as a class of therapeutics for cancer and can show improved efficacy, while simultaneously decreasing side effects, owing to properties such as more targeted localization in tumors and active cellular uptake (7). Engineered nanoparticles are one of the important tool to realize a number of these applications. The reason why these nanoparticles are attractive for medical purposes is based on their important and unique features, such as their surface to mass ratio that is much larger than that of other colloidal particles, their ability to adsorb and carry other compounds and their quantum properties. These nanoparticles have a relatively large surface which is able to bind, adsorb and carry other compounds such as drugs, probes and proteins. However, many other challenges must be overcome to realize the anticipated improved understanding of the patho physiological basis of disease, bring more sophisticated diagnostic opportunities, and yield improved therapies.

The important goals for research of nanotechnologies in drug delivery include:

a) Decrease in toxicity while maintaining therapeutic effects,
b) Specific drug targeting and delivery,
c) Biocompatible and greater safety, and
d) Development of safe medicines.

SLNs were developed at the beginning of the 1990s as an alternative novel carrier system to liposomes, emulsions and polymeric nanoparticles. SLNs are produced by replacing the liquid lipid (oil) of an o/w emulsion by a solid lipid or a blend of solid
lipids, i.e. the lipid particle matrix being solid at both room and body temperature. (8) SLNs offer unique properties such as smaller size, larger surface area, interaction of phases at the interfaces, and these are attractive for their ability to improve performance of nutraceuticals, pharmaceuticals and other materials.

Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). For pharmaceutical applications, all formulation excipients must have Generally Recognized as Safe (GRAS) status. (9). To achieve and maintain a solid lipid particle upon administration, the lipid nanoparticle’s melting point must exceed body temperature (37 °C). High melting point lipids investigated include triacylglycerols (triglycerides), acylglycerols, fatty acids, steroids, waxes, and combinations thereof. Surfactants that are investigated include bile salts such as sodium taurocholate, biological membrane lipids such as lecithin, biocompatible nonionics such as ethylene oxide/propylene oxide copolymers, sorbitan esters, fatty acid ethoxylates, and mixtures thereof. An overview of lipids and surfactants used for preparation of SLNs is provided in Table 1.

Advantages of SLNs over polymeric nanoparticles:
SLNs combine the advantages of other colloidal particles like polymeric nanoparticles, fat emulsions and liposomes while simultaneously avoiding their disadvantages (10). The advantages of SLNs include the following such as:
1. SLNs particularly those in the range of 120–200 nm are not taken up readily by the cells present in the RES (Reticulo Endothelial System) and thus bypass liver and spleen filtration (11).
2. In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
3. It is easy to manufacture than bipolymeric nanoparticles.
4. Controlled and targeted release of the incorporated drug can be achieved.
5. Increased scope of drug targeting can be achieved by coating with or attaching ligands to SLNs
6. Enhanced drug stability. SLNs stable for three years have been developed. This is of more importance compared to the other colloidal carrier systems (12,13).
8. SLNs can be enhancing the bioavailability of entrapped bioactive.
9. Excellent reproducibility with use of different methods as the preparation procedure (10).
10. The feasibility of incorporating both hydrophilic and hydrophobic drugs (14-16).
11. The carrier lipids are biodegradable and hence safe (17-19).
13. Feasible large scale production and sterilization (21).

Table no. 1: Lipids and Surfactants used for preparation of SLNs

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Surfactants</th>
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<tbody>
<tr>
<td><strong>Triacylglycerols:</strong></td>
<td><strong>Phospholipids:</strong></td>
</tr>
<tr>
<td>Tricaprin</td>
<td>Soy lecithin</td>
</tr>
<tr>
<td>Trilaurin</td>
<td>Egg lecithin</td>
</tr>
<tr>
<td>Trimyristin</td>
<td>Phosphatidylcholine</td>
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<td>Tripalmitin</td>
<td></td>
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<tr>
<td>Tristearin</td>
<td></td>
</tr>
<tr>
<td><strong>Acylglycerols:</strong></td>
<td><strong>Ethylene oxide/propylene oxide</strong></td>
</tr>
<tr>
<td>Glycerol monostearate</td>
<td>copolymers:</td>
</tr>
<tr>
<td>Glycerol behenate</td>
<td>Poloxamer 188</td>
</tr>
<tr>
<td>Glycerol palmitostearate</td>
<td>Poloxamer 182</td>
</tr>
<tr>
<td></td>
<td>Poloxamer 407</td>
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<tr>
<td></td>
<td>Poloxamine 908</td>
</tr>
<tr>
<td><strong>Fatty acids:</strong></td>
<td><strong>Sorbitan ethylene oxide/propylene oxide</strong></td>
</tr>
<tr>
<td>Stearic acid</td>
<td>copolymers:</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>Polysorbate 20</td>
</tr>
<tr>
<td>Decanoic acid</td>
<td>Polysorbate 60</td>
</tr>
<tr>
<td>Behenic acid</td>
<td>Polysorbate 80</td>
</tr>
<tr>
<td><strong>Waxes:</strong></td>
<td><strong>Alkylaryl polyether alcohol</strong></td>
</tr>
<tr>
<td>Cetyl palmitate</td>
<td>polymers:</td>
</tr>
<tr>
<td></td>
<td>Tyloxapol</td>
</tr>
<tr>
<td><strong>Cyclic complexes:</strong></td>
<td><strong>Bile salts:</strong></td>
</tr>
<tr>
<td>Cyclodextrin</td>
<td>Sodium cholate</td>
</tr>
<tr>
<td></td>
<td>Sodium glycocholate</td>
</tr>
<tr>
<td></td>
<td>Sodium taurocholate</td>
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<tr>
<td></td>
<td>Sodium taurodeoxycholate</td>
</tr>
<tr>
<td><strong>Hard fat types:</strong></td>
<td><strong>Alcohols:</strong></td>
</tr>
<tr>
<td>Witepsol W 35</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Witepsol H 35</td>
<td>Butanol</td>
</tr>
</tbody>
</table>
Disadvantages:
1. Poor drug loading capacity (22).
2. Drug expulsion after polymeric transition during storage.
3. Relatively high water content of the dispersions (70-99.9%) (23).
4. The low capacity to load water soluble drugs due to partitioning effects during the production process.

Nanostructured lipid carriers (NLC):
A new generation of NLCs consisting of a lipid matrix with a special nanostructure has been developed (24-25). This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%. Carrier system. However, the NLC system minimizes or avoids some potential problems associated with SLN (26).
1. Payload for a number of drugs too low
2. Drug expulsion during storage of formulations
3. High water content of formulated SLN dispersions.

The NLC are produced successfully by the high pressure homogenization method and it is possible to obtain particle dispersions with a solid content of 50 or 60%. The particle dispersions thus produced have a high consistency with a cream-like or almost solid appearance. NLC were introduced to overcome the potential difficulties with SLNs (27-29). The goal to develop NLC was to increase the drug loading and to prevent drug expulsion. This could be seen in three ways. In the first model, spatially different lipids composed of different fatty acids are mixed which leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal. The highest drug load could be achieved and maintained by mixing solid lipids with small amounts of liquid lipids (oils) which is called imperfect type NLC. Drugs which shows higher solubility in oils than in solid lipids can be dissolved in the oil and yet be protected from degradation by the surrounding solid lipids which is called as multiple types NLC, and are analogous to w/o/w emulsions since it is an oil-insolid lipid-in-water dispersion. Because of their properties and advantages, NLC may find extensive application in topical drug delivery, oral and parenteral administration of cosmetic and pharmaceutical actives. The NLCs have been investigated in the topical and dermatological preparations (30), in the delivery of clotrimazole (31), ketoconazole (32) and other antifungal imidazoles (33). The NLCs were also prepared to investigate whether the duration of brain targeting and accumulation of drugs in the brain can be enhanced by intravenous delivery. Apomorphine as a model drug has been targeted, through certain vessels, to selected brain regions by in vivo real-time bioluminescence imaging of the rat brain (34).

Lipid drug conjugates (LDC):
LDC nanoparticles can be termed as a special form of nanoparticles consisting of 100% LDC or a mixture of LDC with suitable lipids. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix (35). In order to overcome this problem, the so called LDC nanoparticles with improved drug loading capacities have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by covalent linking or by salt formation. The obtained LDC is then processed with an aqueous surfactant solution to a nanoparticle formulation using high pressure homogenization technique. Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections (36).

PREPARATION METHOD OF SLNs:
1. High shear homogenization technique:
High shear homogenization techniques were initially used for the production of solid lipid nanodispersions (37). This technique is easy to handle. Dispersion quality is often compromised by the presence of micro particles (38). β-carotene loaded solid lipid nanoparticles formulated by high shear homogenization process had been investigated on size distribution, stability, drug loading, and drug release (39). Different process parameters like stirring rate and cooling condition on the particle size and zeta
potential, emulsification time are investigated. Lipids used in this study are tripalmitin, mixture of mono, di, triglycerides (WitepsolW35) with glycerol behenate and poloxamer 188 used as steric stabilizers (0.5% w/w). Higher stirring rates did not significantly affect the particle size, but slightly increased the polydispersity index.

2. Hot homogenization technique:
Hot homogenization can be carried out by high intensity ultrasound or high pressure homogenizers. It is carried out at temperature above the melting point of the lipid and it is similar to homogenization of emulsion. The aqueous emulsifier phase and the pre-emulsion of the drug loaded lipid melt maintained at same temperature is obtained by high-shear mixing device. Above the lipid melting point high pressure homogenization of the pre-emulsion is maintained. The quality of the final product depends on the quality of the pre-emulsion to a great extent. Lower particle sizes are produced at higher processing temperatures due to lower viscosity of the lipid phase (40) and this leads to accelerate drug and carrier degradation. Good product is obtained due to several passes through the high-pressure homogenizer, typically 3-5 passes. Increasing the homogenization may leads to an increase of the particle size due to particle coalescence which occurs because of the high kinetic energy of the particles. Aqueous dispersions of lipid nanoparticles-flurbiprofen solid lipid nanoparticles and flurbiprofen nanostructured lipid carriers were prepared by hot homogenization followed by sonication technique. Then aqueous dispersions of lipid nanoparticles were incorporated into the freshly prepared hydrogels for transdermal delivery. (41)

3. Cold homogenization:
The problems of the hot homogenization technique have been overcome by developing Cold homogenization technique. Indecisive polymorphic transitions of the lipid due to complexity of the crystallization step of the nanoemulsion lead to several modifications and/or super cooled melts. A hydrophilic and temperature-induced degradation drug, vinorelbine bitartrate loaded solid lipid nanoparticles were prepared by a cold homogenization technique (42). First step in between cold and hot homogenization is same but they are differing from next steps. The melt containing drug is refrigerated rapidly using ice or liquid nitrogen for distribution of drug in the lipid matrix where particles in the size range of 50-100 microns are obtained. Bigger particle sizes and a broader size distribution are typical of cold homogenized samples compared to hot homogenization technique (43).

4. Ultrasonication or high speed homogenization: SLNs were successfully prepared by an ultrasonic and high speed homogenization method to improve the oral bioavailability of the poorly water-soluble drug cryptotanshinone. The incorporation of cryptotanshinone in SLNs had markedly changed the metabolism behavior and absorption is enhanced significantly by employing SLN formulations (44). SLNs can also be produce by sonication or high speed stirring (45). It is very simple and it can be advantageous over other method like hot and cold homogenization because the equipment used in this technique is very common in every lab. Disadvantage is like it distributes larger particle size ranging between micrometer range lead to physical instability like particle growth upon storage and also metal contamination due to ultrasonication.

5. Micro emulsion technique: Gasco and coworkers develop a new technique for production of SLNs based on the dilution of micro emulsions (46). They are prepared by stirring an optically transparent mixture at 65-700 which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooylphosphate) and water. The hot micro emulsion is dispersed in cold water (2-30) under stirring. Typical volume ratios of the hot micro emulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the micro emulsion. According to the literature (47), the droplet structure is already contained in the micro emulsion and therefore, no energy is required to achieve submicron particle sizes. Cationic solid lipid nanoparticles could carry saquinavir for the
improved medication of individuals infected by human immunodeficiency viruses fabricated by microemulsion method (48). Different methods for preparation of SLNs were summarised in table 2.

6. Solvent emulsification-evaporation technique: In solvent emulsification-evaporation technique, the hydrophobic drug and lipophilic material 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 (49,50). 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. Here the mean particle size depends on the concentration of lipid in organic phase. Very small particle size could be obtained with low lipid load (5%) related to organic solvent. The big advantage of this method is the avoidance of any thermal stress, which makes it appropriate for the incorporation of highly thermolabile drugs. A clear disadvantage is the use of organic solvent which may interact with drug molecules and limited the solubility of the lipid in the organic solvent. Solid lipid nanoparticle delivery systems of oridonin have been formed using stearic acid, soybean lecithin and pluronic by emulsion evaporation–solidification at low temperature (51). The SLN formulation of risperidone was formulated using response surface methodology of design of experiment. The SLN was prepared by solvent evaporation method and characterized by non-destructive methods of analysis (52).

7. 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 (53-55). Cyclosporine solid lipid nanoparticles prepared by emulsification-diffusion method will improve absorption and bioavailability (56). Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid (57). When heating is required to solubilize 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 (58). Throughout the process constant stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilization (59). Doxorubicin SLN were prepared by solvent emulsification-diffusion method using Glyceryl caprate (Capmul®MCM C10) as lipid core, and curdlan as the shell material. (60)

This technique has advantages over the other methods, namely: (a) high reproducibility and narrow size distribution (b) easy implementation and scaling up (no need for high energy sources). (c) it is efficient and versatile. (d) less physical stress (e) it is not necessary to dissolve the drug in the melted lipid. Drawbacks associated with this method are (a) drug diffusion into aqueous phase occurred easily , which leads to low entrapment of drugs in SLN (61). (b) the need to clean up and concentrate the SLN dispersion.

8. Melting dispersion technique: In melting dispersion technique drug and solid lipid were melted in an organic solvent which is regarded as oil phase and simultaneously water phase was also heated to same temperature as oil phase. Then the oil phase is added slowly in to a small volume of water phase with continuous stirring at higher rpm for few hrs. Then it was cooled down to room temperature to give SLNs. Reproducibility
was more than ultrasonication method but less than that of solvent emulsification-evaporation method (62,63).

9. **Double emulsion technique:** In double emulsion technique the drug 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. Thereafter, the double emulsion was stirred and was isolated by filtration (64). The zidovudine loaded SLNs were prepared with stearic acid by process of w/o/w double-emulsion solvent-evaporation method using 3(2) factorial design and different triglycerides alone and in different combinations, with/without stearic acid. Two operating variables, amount of lipid and polyvinyl alcohol concentration were found to have significant effect on the particle size and entrapment efficiency of the SLN (65). 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 (66). This technique is mainly used to encapsulate hydrophilic drug (peptides). A major drawback of this technique is the formation of high percentage of microparticles. Sodium cromoglycate containing SLN was tried to be prepared by this method but the formed colloidal system gave the average particle of micrometer range. Insulin loaded SLN was prepared by a novel reverse micelle-double emulsion technique, using sodium cholate-phosphatidylcholine based mixed micelle (67,68).

10. **Membrane contactor technique:** 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 advantages of this technique are its facility of use, the control of the SLN particle size by suitable choice of process parameters. 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 aqueous and organic phases were placed in the thermostated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase. Vitamin E loaded SLN are prepared using using a membrane contactor technique to allow large scale production and their stability is demonstrated (69).

### Table 2: Different methods for preparation of SLNs

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Lipid</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>High shear homogenization technique</td>
<td>β-carotene</td>
<td>Stearic acid</td>
<td>39</td>
</tr>
<tr>
<td>Hot homogenization</td>
<td>Flurbiprofen</td>
<td>Trimyristin</td>
<td>41</td>
</tr>
<tr>
<td>Cold homogenization</td>
<td>Vinorelbine itartrate</td>
<td>Glycerol monostearate</td>
<td>42</td>
</tr>
<tr>
<td>Ultrasonication or high speed homogenization</td>
<td>Cryptotanshinone</td>
<td>Compritol 888 ATO</td>
<td>44</td>
</tr>
<tr>
<td>Micro emulsion technique</td>
<td>Saquinavir</td>
<td>Stearylamine</td>
<td>48</td>
</tr>
<tr>
<td>Solvent emulsification-evaporation technique</td>
<td>Oridonin</td>
<td>Stearic acid</td>
<td>51</td>
</tr>
<tr>
<td>Solvent emulsification-diffusion technique</td>
<td>Cyclosporine-A</td>
<td>Glycerol behenate</td>
<td>56</td>
</tr>
<tr>
<td>Double emulsion technique</td>
<td>Zidovudine</td>
<td>Tripalmitin</td>
<td>65</td>
</tr>
<tr>
<td>Solvent injection technique</td>
<td>Oxybenzone</td>
<td>Tristearin</td>
<td>72</td>
</tr>
<tr>
<td>Supercritical fluid technology</td>
<td>Indomethacin</td>
<td>Tripalmitin</td>
<td>74</td>
</tr>
</tbody>
</table>
11. **Solvent injection technique:** Solvent injection technique is a new approach to prepare SLN. It has following advantages like use of pharmaceutically 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 organic solvent mixture was slowly injected through an injection needle into stirred aqueous phase with or without surfactant. Then the dispersion was filtered with a filter paper in order to remove any excess lipid. The presence of surfactant within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize the formed SLNs until solvent diffusion was complete by reducing the surface tension. Solvent injection-lyophilization method was used to prepare cinnarizine SLNs, a lipophilic drug. This was found to be an efficient method for preparing stable drug-loaded SLNs. SLNs bearing oxybenzone were prepared by ethanol injection method to improve its effectiveness as sunscreen and were characterized for particle size, polydispersity index, zeta potential and surface morphology. The schematic representation of solvent injection method was shown in figure 1.

![Figure 1: Schematic representation of solvent injection method](image)

12. **Supercritical fluid technology:** The supercritical fluid technology is a new technique and has advantages of solventless processing. It is a new production technique for nanoparticles of water-insoluble drugs in combination with lipids, characterization and development of lipid nanosuspension formulations, and examination of the possibility of delivering the prepared nanosuspensions as aerosols for inhalation using Aradigm's AERx Single Dose Platform with micron-sized nozzles and the all mechanical AERx Essence with sub-micron-sized nozzles. The continuous supercritical fluid extraction of emulsions method was used for particle precipitation of solid lipid nanoparticles. Ketoprofen and indomethacin were used as model compounds in formulation with lipids such as tripalmitin, tristearin and Gelucire 50/13. SLNs can be prepared by the rapid expansion of supercritical carbon dioxide solutions which is called as RESS method.

13. **Spray drying method:** Spray drying method is a cheaper method than lyophilization. This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle. The best result by spray drying method was obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol/water mixtures (10/90 v/v).

**Various characterization methods:**

**Drug incorporation and loading capacity:**

The crucial ingredients for SLNs contain lipids, and a single or a combination of emulsifiers. Depending on the lipid, emulsifier and the method of preparation the particle size, and the surfactant used for the preparation of SLNs is found to vary. Factors that influence the loading capacity of a drug in the lipid are:

1. Drug solubility in the melted lipid.
2. Miscibility of lipid melt and the drug melt.
3. Chemical and physical arrangement of solid lipid matrix.
4. Polymorphic condition of lipid material.

The condition to obtain a adequate loading capacity is a sufficiently high solubility of the drug in the lipid melt. Usually, the solubility...
must be higher in the melted state than that essential in the solid state because the solubility reduces when the melt cools and might even be lesser in the solid lipid. The presence of mono- and di-glycerides in the lipid used as the matrix material also promotes drug solubilization. The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice (e.g. monoacid triglycerides) lead to drug expulsion (76). In broad the conversion is slower for long chain than for short chain triglycerides. A finest SLN carrier can be formed in a controlled way when a definite fraction of β'-form can be created and preserved during the storage time. By doing this ordinary SLN carrier transforms to an intellectual drug delivery system by having a built-in triggering mechanism to set off transformation from β'- to β-forms and accordingly controlled drug release (77).

**Determination of incorporated drug:** It is of primary importance to determine the sum of drug incorporated in SLN, since it influences the release characteristics. The degree of encapsulation can be assessed ultimately by determining the quantity of drug remaining in supernatant after centrifugation of SLN suspension or otherwise by dissolution of the sediment in a suitable solvent and subsequent analysis. Standard analytical techniques such as spectrophotometry, high performance liquid chromatography, or liquid scintillation counting can be used to assay the drug (78).

**Determination of particle size:** Particle size and size distribution are the essential characteristics of nanoparticle systems. They decide the in vivo distribution, biological fate and the targeting capability of nanoparticle drug delivery systems. In addition, they can also control the drug loading, drug release and stability of nanoparticles. Many studies have confirmed that nanoparticles of sub-micron size have a numerous advantages over microparticles as a drug delivery system.

**Electron microscopy:** Scanning electron microscopy and transmission electron microscopy offer a way to directly observe nanoparticles and physical characterization of nanoparticles. Transmission electron microscopy has a smaller size limit of detection, is a good validation for other methods and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles (79). Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties (80). Lipidic nanoparticles containing cyclosporine were prepared by the emulsification-diffusion method and their physicochemical stability was characterized by evaluating particle size.

It was observed that SLNs, variations in size were greater and particle size also increased over time in all batches; this effect may have been caused by a probable expulsion of the drug due to the lipid's partial rearrangement.

**Dynamic Light Scattering (DLS):** DLS or quasi-elastic light scattering records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of brownian motion and is quantified by compilation of an autocorrelation function. This function is fit to an exponential, or some combination or modification thereof, with the corresponding decay constant(s) being related to the diffusion coefficient. The advantages of the process are the speed of analysis, lack of requisite calibration, and sensitivity to submicrometer particles (79).

**Entrapment efficiency:** The entrapment efficiency of the drug is determined by measuring the concentration of free drug in the dispersion medium. Ultracentrifugation was carried out using Centrisart, which consist of filter membrane (molecular weight cutoff 20,000 Da) at the base of the sample recovery chamber. The SLNs along with encapsulated drug remain in the outer chamber and aqueous phase moves into the sample recovery chamber. The amount of the drug present in the aqueous phase is determined by HPLC or UV spectrophotometer (81).
Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD): Among the large number of analytical techniques engaged for that purpose, DSC and XRD play a important role because they are able to afford structural information on the dispersed particles. DSC and XRD are renowned typical techniques in the area of pharmaceutics and since data evaluation from these methods is usually straightforward. In addition to XRD, the associated techniques of small angle X-ray and neutron scattering can give very attractive added information on the structure of the systems. Most popular applications are the identification of crystal structures, particle sizes and shapes as well as quantitative phase analysis and determination of crystallinity indices. Structural modifications of materials are accompanied by heat exchanges, e.g., uptake of heat during melting or emission of heat during crystallization. DSC is planned to measure these heat exchanges at some stage in controlled temperature programs and allows to draw conclusions on the structural properties of a sample. DSC and X-ray/neutron diffraction and scattering techniques are crucial tools for SLN characterization and offer many possibilities to gain information on the properties of the dispersed particles (82).

Atomic force microscopy: In this method, a probe tip with atomic scale sharpness is rastered across a taster 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 or allowed to hover just above, with the exact nature of the particular force employed helping to differentiate among the subtechniques (83). That ultrahigh resolution is available with this approach, which along with the capability to map a sample according to properties in addition to size, e.g., colloidal attraction or conflict to deformation, makes atomic force microscopy a valuable tool.

Nuclear Magnetic Resonance (NMR) and Electron Spin Resonance (ESR): NMR and ESR are dominant tools for investigating dynamic phenomena of nanocompartments in colloidal drug delivery systems. Due to the different chemical shifts it is likely to feature the NMR signals to particular molecules or their segments. Simple NMR spectroscopy allows an simple and rapid detection of supercooled melts due to the low line widths of the lipid protons (84). This technique is based on the different proton relaxation times in the liquid and solid state. Protons in the liquid state provide sharp signals with high signal amplitudes, while solid protons give weak and broad NMR signals under these conditions. It also allows for the characterization of liquid nanocompartments in recently developed lipid particles, which are made from blends of solid and liquid lipids (85). The great prospective of NMR with its mixture of different approaches has scarcely been used in the SLN field, although it will provide unique insights into the structure and dynamics of SLN dispersions.

ESR allows the straight, repeatable and non-invasive characterization of the distribution of the spin probe among the aqueous and the lipid phase. Investigational results reveal that storage-induced crystallization of SLN leads to an exclusion of the probe out of the lipid into the aqueous phase (86). Using an ascorbic acid reduction assay it is likely to observe the time scale of the replace between the aqueous and the lipid phase. The progress of low-frequency ESR allows noninvasive measurements on small mammals.

In-vitro drug release: The SLNs dispersion is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed alongside a appropriate dissolution medium at room temperature, the samples are withdrawn at suitable intervals from the dissolution medium, centrifuged and analyzed for drug content using a appropriate analytical method. This method however suffers from the disadvantage of a lack of direct dilution of the SLNs by the dissolution medium. The drug release of camptothecin SLN using a dynamic dialysis method in phosphate buffered saline has been reported (87). Secondly, in reverse dialysis technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN dispersion. The direct dilution of the SLNs is attainable with this process; however the fast release cannot be quantified with this technique (88).
Principles of drug release from SLN:
Drug release is affected by particle size, where tiny particles have larger surface area, therefore, the majority of the drug associated would be at or close to the particle surface, leading to quick drug release. Whereas, larger particles have bulky cores which permit more drug to be encapsulated and gradually diffuse out. It is a challenge to formulate nanoparticles with the smallest size possible and with maximum stability. The common ideology of drug release from lipid nanoparticles is as follows (89, 90)
– There is an opposite association between drug release and the partition coefficient of the drug.
– 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 type of drug entrapment model of SLN.

The drug incorporation model of SLN is critical to the drug release outline. It is related to the composition and production method of SLN as explained above. Drug release is expanded over more than a few weeks since mobility of the drug molecularly dispersed in colloidal particles is very inadequate (91).
Rapid initial drug release exists in the first few minutes in the drug-enriched shell model as a result of the outer layer of the particles due to the bigger surface area of drug deposition on the particle surface (91, 92). The burst release is reduced with increasing particle size and prolonged release could be obtained when the particles were sufficiently large, ie, lipid microparticles (93). The type of surfactant and its concentration, which will interact with the outer shell and affect its structure, should be noted as the other important factor, because a low surfactant concentration leads to a minimal burst and prolonged drug release. The praziquantel loaded hydrogenated castor oil SLNs were formulated to enhance the bioavailability and prolong the systemic circulation of the drug. In vitro release of praziquantel loaded hydrogenated castor oil SLNs exhibited an initial burst release followed by a sustained release (94). In the case of the new generation SLN, the lipid content of the particles dissolves the drug and combines controlled release character with high drug loading capacity (95).
The particle dimension that affects drug release rate directly depends on a variety of parameters such as composition of SLN formulation such as surfactant/surfactant mixture, amount of drug incorporated, structural properties of lipid and drug, production methods and conditions. All those parameters have been broadly investigated and information have been reported in the literature for years (96-100).

Administration routes of SLNs:

Oral administration:
Significant parameters have been broadly overlooked in the design of new and well-organized colloidal drug carrier systems for oral use: I) their firmness upon contact with gastrointestinal (GI) fluids since they are poised of biodegradable materials and particle size in nanorange maximizes the surface area for enzymatic degradation (101), II) particle aggregation due to environmental circumstances of the GI tract leading decline in the interaction capability of particles with the intestinal mucosa (102). Controlled release behaviour of these systems bypass the gastric and enables intestinal degradation of the encapsulated drug (103), and their possible transport through the intestinal mucosa (104). However, the estimation of the stability of colloidal carriers in GI fluids is necessary in order to calculate their appropriateness for oral administration. The machines used for large-scale production often yield an even better product quality than the lab-scale types (105-106). The adhesive properties of nanoparticles are reported to increase bioavailability and reduce or minimize erratic absorption (107). The adhesive properties of nanoparticles are reported to increase bioavailability and reduce or minimize erratic absorption (107). SLN powders or granulates can be placed into capsules, compressed into tablets or integrated into pellets. The conversion of the liquid dispersion into a dry product by lyophilization or spray-drying is useful or often necessary (108). Antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were entrapped into polyvinyl alcohol coated SLN and following a single oral administration to mice,
therapeutic drug concentrations were maintained in the plasma for 8 days and in the organs (lungs, liver and spleen) for 10 days. Suitable adsorbent was employed with free flowing characteristics for improving the physical properties and stability of solid lipid nanoparticles for oral administration. The adsorbent technology would be useful in imparting additional features to the SLNs for pharmaceutical application which would simplify the handling of formulations by patients, ease the process of capsule filling at industrial scale, and can considerably improve the shelf life of the manufactured goods for a longer period of time as compared to liquid formulations (109). Various companies are paying attention in solid lipid nanotechnology for oral drug delivery. Pharmatec (Italy) developed a cyclosporine SLN formulation for oral administration (110). Avoidance of high plasma peak and low variability in plasma profile were provided in this case. AlphaRx have also rifampicin- loaded SLN under preclinical phase (RifamsolinTM). Rifampicin used in treatment of tuberculosis, requires long-term treatment due to poor cellular antibiotic penetration.

Parenteral administration: SLNs are very appropriate for systemic delivery because they consist of physiologically well-tolerated ingredients and have fine storage capabilities after lyophilization. Cationic SLN has been confirmed to attach genes directly via electrostatic interactions, and to have probable benefits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules (111-113). Moreover, coating of SLN with PEG increases steadiness and plasma half life of SLN in order to decline phagocytic uptake, and therefore improves the bioavailability of drugs. Wissing et al (114) intensively reviewed parenteral use of SLN. Peptide and protein drugs are usually obtainable for parenteral use in the market.

SLN products of several pharmaceutical companies can be given as follows: cationic SLN for gene transfer namely TransoPlexR was produced by PharmaSol DDS (Germany) (115). AlphaRx (USA) is developing vancomycin and gentamicin products with VansolinTM and ZysolinTM trade names (www.alpharx.com). They are very efficient in treatment of life-threatening contagious disease such as pneumonia. SkyPharma (UK) has formulations of nanoparticulate technology which includes SLNs and nanosuspensions under preclinical development (116).

Rectal administration: Conventional rectal delivery of drugs is very frequently used for pediatric patients due to easy application. When speedy pharmacological effect is required, in some conditions, parenteral or rectal administration is preferred. The plasma levels and therapeutic effectiveness of rectally administered drugs were reported to be superior compared with those given orally or intramuscularly in the similar dose (117). A few reports are available on the rectal drug administration via SLN in the literature (118). Sznitowska et al. studied the incorporation of diazepam into SLN for rectal administration in order to provide a quick action. They studied that lipid matrix which is solid at body temperature is not an beneficial system for diazepam rectal delivery. They determined to employ lipids which melt around body temperature in their next experiments. PEG coating seems to be a hopeful approach on rectal delivery and consequently, enhancement of bioavailability.

Nasal administration: Approaches such as prodrug derivatization and formulation development have been employed to improve drug absorption through the nasal mucosa. SLN has been anticipated as substitute transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups (119,120). Nasal administration was a capable alternative noninvasive route of administration due to rapid onset of drug action, avoiding degradation of labile drugs in the GI tract and insufficient transport across epithelial cell layers (121). Tobio et al successful reported that the function of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecules (122).

Respiratory delivery: The respiratory delivery of SLN is a novel and forthcoming area of research. Lymphatic drainage acts
significant role in the uptake of particulates in the respiratory system. The lungs avoid first-pass effects by offering a high surface area for drug absorption. Rapid drug absorption by aerosolization of drugs occurs since the walls of alveoli in the deep lung are extremely thin (123). Epirubicin-loaded SLNs were effectively prepared as an inhalable formulation for treatment of lung cancer. Furthermore the drug concentration in lungs after inhalation of epirubicin-loaded SLNs was much higher than that after administration of epirubicin solution (124). Assessment of inhaled radio-labelled SLN biodistribution has been described and the data showed an important and significant uptake of the radio-labelled SLN into the lymphatics after inhalation (125). Recently, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery (126).

Topical application: SLNs are very attractive colloidal drug delivery systems for skin applications due to their various advantageous effects on skin. They are well suitable for use on inflamed or damaged skin because they are based on non-toxic and non-irritant lipids (127). SLNs and NLC have been studied with compounds such as vitamin E (128), tocopherol acetate (129), retinol (130), ascorbyl palmitate (131,132), clotrimazole, triptolide (133) and a nonsteroidal antiandrogen RU 58841 (134) for topical application. Morphine, morphine-loaded and unloaded SLNs accelerated reepithelialization; acceleration of wound closure, low cytotoxicity and irritation as well as possible prolonged morphine release makes SLN an interesting approach for innovative wound management (135).

Ocular administration: Due to the multiple barriers imposed by the eye against the penetration of drugs, the ocular delivery and targeting are considered difficult to achieve. A major challenge in ocular drug therapy is to improve the poor bioavailability of topically applied ophthalmic drugs by overcoming the severe constraints imposed by the eye on drug absorption. One of the promising strategies nowadays is the use of colloidal carrier systems characterized by a submicron-meter size. Solid lipid nanoparticles and nanostructured lipid carriers represent promising alternatives to conventional and very popular ocular carrier systems, such as the nanoemulsions, liposomes, and polymeric nanoparticles (136). Nevertheless, taking into account the characteristics of the eye, morphometrical properties of the colloidal systems (e.g., average particle size and polydispersion) may represent a limiting factor for topical application without induced corneal irritation, being responsible for the selected system.

Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Colloidal drug delivery systems are considered to enhance the ocular bioavailability of drugs (137,138). Ocular drug administration via SLN has been reported several times (139,140). Cavalli et al (141) evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. Drug concentration in the aqueous humor was determined up to six hours. As a result SLN significantly enhanced the drug bioavailability in the aqueous humor.

Another research group incorporated poorly watersoluble drugs (hydrocortisone, estradiol hemihydrate and pilocarpine base) into SLN and performed in vitro drug permeation study through human organotypical cornea construct. In industrial fields, the incorporation of several antibiotics has been attempted in SLN, due to their broad antimicrobial spectrum. For an instance, OcusolinTM from AlphaRx is a gentamicin loaded-SLN product in the form of ophthalmic solution.

APPLICATION:

Solid lipid nanoparticles for ocular drug delivery: Ocular drug delivery remains demanding because of the composite nature and structure of the eye. It is a necessary to develop novel drug delivery carriers capable of increasing ocular absorption and decreasing both local and systemic cytotoxicity. SLNs are especially useful in ocular drug delivery as they can improve the corneal absorption of
drugs and progress the ocular bioavailability of both hydrophilic and lipophilic drugs. SLNs have another benefit of allowing autoclave sterilization, a essential step towards formulation of ocular preparations. Special consideration has been given to the nature of lipids and surfactants commonly used for SLN production (142).

**SLNs as gene vector carrier:** Cationic solid lipid nanoparticles have established themselves during the past decades. They can well bind DNA directly via ionic interaction and intervene gene transfection. SLN can be used in the gene vector formulation (143). There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids (144). Cationic solid lipid nanoparticles are promising nonviral gene delivery carriers suitable for systemic administration. The relationship between the composition of cationic SLN and their ability to condense plasmid DNA (pDNA) and to transfer it in neuroblastoma cells were investigated (145). The lipid nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It's called genospheres. Mannan-modified DNA-loaded vehicles have great potential for targeted gene delivery (146).

**SLNs as a targeted carrier for solid tumors:** One of the most important challenges in drug delivery is to get the drug at the place it is needed in the body thereby avoiding possible side effects to non diseased organs. The non restricted toxicity of chemotherapeutics thus limits the full use of their therapeutic potential. Local drug delivery or drug targeting results in increased local drug concentrations and provides strategies for more specific therapy. Nanoparticles have specific particles as tools to enable these strategies.SLNs have been reported to be useful as drug carriers to treat neoplasms (147). Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate (148), paclitaxel (149) and camptothecin (150).

**Stealth nanoparticles:** Stealth nanoparticles provide a novel and unique drug-delivery system which can target specific cells. Stealth SLNs have been effectively tested in animal models with marker molecules and drugs. Stealth Tashinone IIA-loaded solid lipid nanoparticles have been prepared by a nanoprecipitation/solvent diffusion method in which Poloxamer 188 was used as a stealth agent. Rhodamine B was successfully incorporated into nanoparticles as a fluorescent marker to view and compare the phagocytic uptake of nanoparticles (151). Antibody labelled stealth lipobodies have shown increased delivery to the target tissue in accessible sites (152).

**SLNs in anti tubercular chemotherapy:** Another prominent example of SLNs-based drug delivery is pulmonary delivery of antimicrobials to treat tuberculosis, a serious lung infection caused by *Mycobacterium tuberculosis*. Antitubercular drugs such as rifampicin, isoniazide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance (153). This antitubercular drug loaded solid lipid nanoparticles were prepared by using the emulsion solvent diffusion technique.

**SLNs in breast cancer:** Photodegradation and low bioavailability are chief hurdles for the therapeutic use of curcumin. Transferrin-mediated SLNs were formulated to increase photostability and enhance its anticancer activity against MCF-7 breast cancer cells. The anticancer activity of curcumin is enhanced with transferrin-mediated SLNs compared to curcumin solubilized surfactant solution and apoptosis is the mechanism underlying the cytotoxicity (154). Mitoxantrone-loaded SLNs local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug (155). Efficacy of doxorubicin has been reported to be enhanced by incorporation in SLNs. Doxorubicin was complexed with soybean-oil-based anionic polymer and dispersed collectively with a lipid in water to form doxorubicin loaded solid lipid nanoparticles. The system has improved its efficacy and reduced breast cancer cells.
SLNs for topical use: Corticosteroids are therapeutic agents generally used in the treatment of skin diseases such as eczema or psoriasis. Topical SLN products show enormous prospective for treating dermatological conditions by targeting corticosteroids to dermal disease sites while decreasing systemic drug absorption (156). Topical application of the drugs at the pathological sites offers possible advantages of delivering the drug directly to the site of action. SLNs are used for topical application of various drug such as vitamin-A (157), isotretinoin, flurbiprofen (158). 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. Miconazole nitrate loaded SLN were prepared by modified solvent injection method and characterized for surface morphology, particle size and drug entrapment (159).

SLNs as cosmeceuticals: Cosmeceuticals is rising as the major application target of these carriers. Carrier systems like SLNs and NLC were formulated with a point of view to meet manufacturing needs like scale up, qualification and validation, simple technology, low cost etc (160). The SLNs have been functional in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers (161). Many features of SLNs are advantageous for dermal application of cosmetic products have been reported, e.g. occlusive properties, increase in skin hydration, modified release, increase of skin penetration and avoidance of systemic uptake. The first two cosmetic products containing lipid nanoparticles were introduced to the market in 2005. Within 3 years after the introduction, of about 30 cosmetic products containing lipid nanoarticles are in the market these days (162).

SLNs for liver targeting: Liver-targeting SLNs with a hepatoprotective drug, cucurbitacin B (Cuc B), using a galactosylated lipid, N-hexadecyl lactobionamide (N-HLBA) were prepared. The galactosyl-lipid N-HLBA was prepared via the lactone form intermediates of lactobionic acid and synthesized by anchoring galactose to hexadecylamine lipid. The Cuc B-loaded galactosylated SLNs and conventional SLNs were successfully prepared by a high-pressure homogenization method. The encapsulation of Cuc B in SLNs resulted in the improvement of cytotoxic activity and galactosyl ligand could further improve the cellular accumulation and cytotoxicity of Cuc B. The incorporation of N-HLBA into SLNs considerably improved the liver targetability of Cuc B-loaded SLNs and galactosylated SLN had a great potential as a drug delivery carrier for improved liver targetability (163). The different drugs incorporated in SLNs for different therapeutic activities were summarised in table 3.

Table 3: A summary of different drugs incorporated in SLNs for different activities.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Doxorubicin, Paclitaxel, Camptothecin, Methotrexate,</td>
<td>14,60, 15, 18, 148</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Rifampicin, Isoniazid</td>
<td>153</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Clotrimazole, Ketoconazole</td>
<td>31, 32</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>Cyclosporin-A</td>
<td>56</td>
</tr>
<tr>
<td>Sunscreen</td>
<td>Oxybenzone, Tocopherol acetate</td>
<td>72, 129</td>
</tr>
<tr>
<td>Antipsycotic</td>
<td>Risperidone, Clozapine</td>
<td>52, 81</td>
</tr>
<tr>
<td>Antiretroviral</td>
<td>Zidovudine, Saquinavir</td>
<td>65, 48</td>
</tr>
<tr>
<td>NSAID</td>
<td>Flurbiprofen</td>
<td>41</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Vitamin-A</td>
<td>157</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>Insulin</td>
<td>53,58</td>
</tr>
<tr>
<td>Anti-parkinsonism</td>
<td>Apomorphine</td>
<td>34</td>
</tr>
</tbody>
</table>

SLN as carriers for peptides and proteins drugs:
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 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. In addition, SLN can present an insufficient loading capacity due to drug expulsion after polymorphic transition during storage, particularly if the lipid matrix consists of similar molecules (164). 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.

**Solid lipid nanoparticles for antimicrobial drug delivery:**

Several unique properties of SLNs make them a promising antimicrobial drug delivery platform. Firstly, SLNs contain occlusive excipients that, upon appliance on skin, readily form a thin film to lessen water evaporation and retain skin moisture. This occlusive property promotes molecule penetrations into the skin. SLNs encapsulated antimicrobial agents such as retinol and retinyl palmitate have shown better drug penetration rate and slower drug expulsion than the free drug counterparts. SLNs can facilitate the delivery of anti-tuberculosis drugs such as rifampin, Isoniazid and pyrazinamide to the lungs as well as to the lymphatic systems. SLNs can provide a sustained release of the carried antimicrobial payloads, which then can effectively eliminate the infectious microbes harbored at these lymphatic sites. Even though the development history of SLN-based antimicrobial drug delivery systems is relatively shorter than other nanoparticle systems such as liposomes and polymeric nanoparticles, SLNs have shown great therapeutic potentials (165).

**CONCLUSION:** Lipid nanoparticle drug delivery technology presents considerable opportunities for improving medical therapeutics, but the technology’s potential remains unrealized. The review has focused on the variety of aspects of SLNs and their applicability in the encapsulation of various drugs. In recent years, number of research works has been successfully carried out in this area. It would result in a simultaneous improvement in the quality, efficacy, and safety profile of drugs.

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