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REVIEW ON SOLID LIPID NANOPARTICLE FOR MUCOSAL DRUG DELIVERY SYSTEM

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ABSTRACT

Solid lipid nanoparticles (SLN) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. SLNs are solid core lipid nanocarriers, which can hold both hydrophilic and hydrophobic drugs. They can be made up of biocompatible ingredients and therefore are one of the preferred choices for drug delivery. Due to their unique size dependent properties, lipid nanoparticles offer possibility to develop new therapeutics. Mucosal drug delivery involves administration to moist cavities, such as the lining of the mouth, vagina, and bladder. Mucosal drug delivery systems possess additional advantages, such as close contact with the mucosal surface, when compared to other approaches. The MDDS provides a high surface to volume ratio and longer residence time, resulting in effective absorption and increased the bioavailability of the drug. In this review, attention is focused to give regarding solid lipid nanoparticles advantages, disadvantage. Mucosal drug delivery systems advantages, limitation, Physiological Importance of Mucins and Saliva. Methods of preparation of SLNs, influence of various excipients in SLNs, characterization of the SLNs, application of SLNs.

KEYWORDS: - Solid lipid nanoparticles, Mucosal drug delivery systems, Nanostructured lipid carriers, Routes of administration, Influence of excipients.

INTRODUCTION

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.[1]

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to traditional colloidal carriers such as - emulsions, liposomes and polymeric micro – and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carriers for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipids, dispersed in water or in aqueous surfactant solution. SLN offers unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals.[2]

Formulation scientists are facing the challenges in improving the low solubility and bioavailability of the newly invented drugs. One of the approaches to face the above problems is to formulate the new particulate carrier system.[2]

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting the wide attention of formulators worldwide. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes, and polymeric nanoparticles). They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offers unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve the performance of pharmaceuticals, nutraceuticals and other materials.[3]

Advantages of solid lipid nanoparticles[4]

- The use of biodegradable lipids reduces the possibilities of severe and prolonged toxicity.

- Enhancing the bioavailability of low water-soluble active constituents.
- Enhancing the stability of chemically labeled drugs through protection from the external environment.
- SLNs have improved stability in comparison with other drug carriers as liposomes.
- The high entrapment efficiency of the active constituents.
- The possibility of lyophilisation.

Disadvantages of solid lipid nanoparticles[4]

- The drug loading ability is poor.
- Water content in the dispersions is comparatively high (70-99.9%).
- The unpredictable tendency to gelation.
- The unpredicted dynamics of polymeric changes.
- Drug expulsion during storage after a polymeric transition.
- The possibility of particle growth.

Mucosal drug delivery[5]

Oral mucosal drug transport system is subdivided into buccal and sublingual wherein buccal cavity is extensively relevant for drug administration via mucosa in case of sublingual path generally beneficial for quickest onset of motion as with inside the case of Angina pectoris. The buccal mucosa strains the internal cheek, and buccal formulations are located inside the mouth among the top gingivae (gums) and cheek to deal with local and systemic conditions. The buccal path offers one of the capacity routes for usually large, hydrophilic and volatile proteins, oligonucleotides and polysaccharides, in addition to conventional small drug molecules. The oral cavity has been used as a domain for local and systemic drug delivery.

Mucosal drug delivery involves administration to moist cavities, such as the lining of the mouth, vagina, and bladder. This allows for high drug concentration in local treatment of disease with reduced systemic side-effects. The mucosal route can avoid significant drawbacks present for the oral administration of drugs, such as hepatic first-pass metabolism, slow absorption, and drug degradation within the gastrointestinal tract, without the need for painful injectable products.

Whilst mucosal drug delivery offers exciting opportunities for novel therapies, there are several challenges present which require specialist expertise to overcome. Importantly, the palatability and irritancy and formulation retention at the site of application need to be considered in the design of such medicines. Robust and validated in vitro and ex vivo methods are essential tools to assess the performance of mucosal drug delivery systems and to predict there in vivo behavior.

Advantages of oral mucosal drug delivery system[5,6]

- Bypassing the gastrointestinal tract and hepatic portal system, this increases the bioavailability of orally delivered medicines that would otherwise be processed in the liver's first pass. Furthermore, the medication is shielded from destruction by the intermediate gastrointestinal tract's pH and digestive enzymes.
- Increased patient compliance due to the elimination of injection-related pain; administration of pharmaceuticals to patients who are unconscious or incapacitated; and ease of administration when compared to injections or oral medications.
- Sustained drug delivery.
- In comparison to the oral route, a relatively rapid onset of action can be accomplished, and the formulation can be withdrawn if therapy is needed to be discontinued.
- Increased ease of drug administration.
- The buccal mucosa is strongly vascularized, and medicines can be rapidly absorbed into the venous system beneath the mouth mucosa, despite being less permeable than the sublingual area.
- Mucosal surfaces lack a stratum corneum in comparison to TDDS. As a result, in oral mucosal modes of administration, the primary barrier layer to transdermal drug transport is not a factor. As a result, oral mucosal systems have a faster start and stop time than transdermal patches.
- When compared to transdermal patches, oral mucosal administration is less variable amongst patients, resulting in lower inter-subject variability.
- The oral cavity's vast contact surface aids in rapid and thorough medication absorption.

Limitations of oral mucosal drug delivery system[5,6]

Depending on whether local or systemic action is required the challenges faced while delivering drug via oral especially buccal drug delivery can be enumerated as follows.

For local action, rapid drug clearance due to the flushing action of saliva or the intake of foodstuffs may necessitate frequent dosage.

Cos of the non-uniform distribution of medications inside saliva after release from a solid or semisolid delivery device, some parts of the oral cavity may not receive effective doses.

Patient acceptance in terms of flavor, irritancy, and mouth feel' is an issue for both local and systemic intervention. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

Physiological importance of Mucins and Saliva[5,6,7]

The mucosal tissues are in addition included with mucus, that's negatively charged, and incorporates big glycoproteins termed mucins. These are idea to make contributions drastically to the visco-elastic nature of saliva, and keep a pH of 5.8–7.4. Mucin includes a protein core, wealthy in O-glycosylated serine and threonine, containing many helix-breaking proline

residues. The salivary glands secreting mucus additionally synthesize saliva, which gives safety to the smooth tissues from chemical and mechanical abrasions. The common thickness of the salivary move inside the mouth varies between 0.07 and 0.10 mm. Sustained adhesion of the dosage form (tablet, patch) to the mucosa is an essential first step to a hit buccal transport. The mucus performs an essential position at some point of this mucoadhesive manner through buccal drug transport systems. The interplay among the mucus and mucoadhesive polymers normally utilized in maximum dosage paperwork may be defined through theories summarized in the **table 1.**

Table 1: Postulated mechanism for Polymer – Mucosal adhesive properties.

Theory of adhesion	Mechanism of adhesion
Adsorption	Secondary chemical bonds such as van der waals forces, hydrophobic interactions, electrostatic attraction, and hydrogen bonds between mucus and polymer.
Diffusion	Entanglements of the polymer chains into mucus network.
Electronic	Attractive forces across the electrical double layer formed due to electron transfer across polymer and mucus.
Wetting	Analyze the ability of the past to be spared over the biological surface and calculate the interfacial tension between the two. The tension is considered to be proportional to $X^{1/2}$, where X is the polymer –polymer interaction parameter. Low values of these parameters correspond to structural similarities between polymers and an increased miscibility.
Fracture	Relates to the force necessary to separate surfaces to the adhesive bond strength and it is often used to calculate fracture strength of adhesive bonds.

Methods of preparation of solid lipid nanoparticles[8,9,10,11,12]

1. High pressure homogenization.
a. Hot homogenization.
b. Cold homogenization.
2. Ultrasonication / high speed homogenization.
a. Probe Ultrasonication
b. Bath Ultrasonication.
3. Solvent evaporation method.
4. Solvent emulsification-diffusion method.
5. Supercritical fluid method.
6. Microemulsion based method.
7. Spray drying method.
8. Double emulsion method.
9. Precipitation technique.
10. Film-ultrasound dispersion.

1. High Pressure Homogenization (HPH)

For the manufacture of SLNs, it is a dependable and powerful technology. High-pressure homogenizers force a liquid through a tight gap at high pressure (100–2000 bar) (in the range of few microns). The fluid accelerates from a very low velocity to a very high velocity (over 1000 km/h) in a very short distance. The particles are disrupted down to the submicron level by high shear stress and cavitation forces. Generally, a lipid percentage of 5-10% is employed, however up to 40% lipid content has been studied. Hot homogenization and cold homogenization are two common HPH techniques that both functions on the same principle of mixing the medication in a large amount of lipid melt.

(A) Hot homogenization

Hot homogenization is carried out at temperatures over the lipid's melting point, and so might be considered emulsion homogenization. A high-shear mixing device is used to create a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (at the same temperature). HPH of the pre-emulsion is done at temperatures over the lipid's melting point. Higher temperatures cause the inner phase's viscosity to drop, resulting in smaller particle sizes. High temperatures, on the other hand, hasten the deterioration of both the medicine and the carrier. Due to the high kinetic energy of the particles, increasing the homogenization pressure or the number of cycles frequently results in an increase in particle size.

(B) Cold homogenization

Cold homogenization was developed to address a number of issues associated with hot homogenization, including temperature induced drug degradation, drug distribution into the aqueous phase during homogenization, and the complexity of the nano emulsion crystallisation step, which leads to multiple modifications and/or super cooled melts. This method involves cooling a drug containing lipid melt, grinding the solid lipid into lipid microparticles, and dispersing the lipid microparticles in a cold surfactant solution to produce a pre-suspension. Then, at or below room temperature, the pre-suspension is homogenised, and the gravitational force is powerful enough to shatter the lipid microparticles directly into solid lipid nanoparticles.

2. Ultra Sonication and High speed homogenization

Ultrasonication or high-speed homogenization procedures are also used to make SLNs. Smaller particle sizes necessitate a mix of ultrasonication and high-speed homogenization. It decreases shear stress, but it has several drawbacks, including the possibility of metal contamination and physical instability, such as particle development during storage. A probe sonicator or a bath sonicator is utilised in this procedure.

Advantages
- Reduced shear stress.

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

3. Solvent evaporation

Solvent evaporation can also be used to make SLNs. The lipophilic substance is dissolved in a water-insoluble organic solvent (for example, cyclohexane) and emulsified in an aqueous phase. Nanoparticle dispersion is created by precipitation of the lipid in the aqueous medium following the evaporation of the solvent, yielding nanoparticles with a mean size of 25 nm. High pressure homogenization was used to emulsify the solution in an aqueous phase. Evaporation under decreased pressure (40–60 mbar) was used to remove the organic solvent from the emulsion.

Advantages
- Scalable.
- Mature technology.
- Continuous process.
- Commercially demonstrated.
- Disadvantages:
- Extremely energy intensive process.
- Polydisperse distributions.
- Bio molecule damage.

4. Solvent Emulsification-Diffusion Method

This process may produce particles with average sizes of 30-100 nm. The most significant benefit of this procedure is the absence of heat throughout the preparation. Lipid is dissolved in the organic phase in a water bath at 50 °C, and an acidic aqueous phase is utilized to alter the zeta potential to generate coacervation of SLN, followed by simple separation by centrifugation. The SLN suspension was made promptly. After centrifugation, the entire dispersed system can be re-suspended in distilled water.

5. Supercritical fluid method

This is a relatively novel method for producing SLN that has the advantage of not requiring the use of solvents. This platform technology for powder and nanoparticle manufacturing comes in a variety of flavors. The rapid expansion of supercritical carbon dioxide solutions (RESS) methods can be used to make SLN. As a solvent, carbon dioxide (99.99 percent) was an excellent choice.

Advantages
- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is a good choice as a solvent for this method.

6. Microemulsion based method

The dilution of microemulsions is used in this approach. Micro-emulsions (e.g. o/w microemulsions) are two-phase systems with an inner and outer phase. They're manufactured by stirring a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol), and water in an optically transparent mixture at 65-70°C. Under stirring, the hot microemulsion is disseminated in cold water (2-3°C). The SLN dispersion can be used as a granulation fluid for moving solid products (tablets, pellets) through the granulation process, however too much water must be eliminated in the case of low particle content. Rapid lipid crystallisation and aggregation are aided by high-temperature gradients. When compared to HPH-based formulations, achievable lipid levels are significantly lower due to the dilution stage.

Advantages
- Low mechanical energy input.
- Theoretical stability.
- Disadvantages:
- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticle concentrations.

7. Spray drying method

It's a procedure that's different from lyophilization. This suggests using lipids with a melting point greater than 700°C. The best results were obtained using a 1% SLN concentration in a trehalose in water solution or a 20% trehalose in ethanol-water mixture.

8. Double emulsion based method

In two processes, warm w/o/w double microemulsions can be made. To begin, a clear w/o microemulsion is made by mixing an aqueous solution containing medication with melted lipid, surfactant, and co-surfactant at a temperature slightly over the melting point of lipid. To make a transparent w/o/w system, the generated w/o microemulsion is mixed with water, surfactant, and co-surfactant in the second stage. Warm micro double emulsions are dispersed in cold and then rinsed with dispersion medium using an ultra-filtration system to produce SLNs. Multiple emulsions have intrinsic instabilities due to the internal aqueous droplets coalescing within the oil phase, the oil droplets coalescing, and the layer on the surface of the internal droplets rupturing. In order to produce SLNs, they must be stable for a few minutes, which is the time between the creation of transparent double microemulsions and their quenching in cold aqueous medium.

9. Precipitation technique

Solid lipid nanoparticles can also be produced by a precipitation technique which is characterised by the need for solvents. The glycerides will be dissolved in an organic solvent (such as chloroform) and emulsified in an aqueous phase. The lipid will precipitate when the organic solvent has evaporated, creating nanoparticles.

10. Film-Ultrasound dispersion

The lipid and the drug were placed in suitable organic solutions, and a lipid film was created following decompression, rotation, and evaporation of the organic solutions. The aqueous solution containing the emulsions was then added. Finally, the SLN with the small and uniform particle size is generated using ultrasound with the probe to diffuser.

Influence of various excipients in solid lipid nanoparticle[13,14,15]

1. Particle size

The physical stability, bio destiny of the lipid particles, and release rate of the loaded medicine are all affected by changes in size. As a result, the size of the SLNs must be kept within a suitable range. According to the definition of colloidal particles, well-formulated systems (liposomes, nanospheres, and nanoparticles) should have a narrow particle size distribution in the submicron size range (defined as having a size below 1μm).

2. Influence of the lipids

The average particle size of SLN dispersions has been found to increase with higher melting lipids using heat homogenization. Other crucial factors for nanoparticle production, on the other hand, will vary depending on the lipid. The velocity of lipid crystallization, lipid hydrophilicity (impact on self-emulsifying capabilities), and the morphology of lipid crystals are all examples (and therefore the surface area). Furthermore, in most cases, increasing the lipid content by more than 5%-10% resulted in larger particles (including microparticles) and a broader particle size dispersion.

3. Influence of the emulsifiers

The particle size of lipid nanoparticles is highly influenced by the surfactant/surfactant combination concentration. When a higher surfactant/lipid ratio was used, smaller particle sizes were found in general. During storage, the drop in surfactant content resulted in an increase in particle size. Surfactants reduce the surface tension between the particles' interfaces, producing particle portioning and thereby increasing surface area.

Characterization of the solid lipid nanoparticles

1. Size, zeta Potential and Polydispersity index (PdI) analysis[16,17]

A particle size analyzer is used to measure the average size, zeta potential and PdI of SLNs. All samples are diluted (1:100) with deionized water prior to analysis to ensure a suitable scattering intensity and placed in cuvettes for measurement. Data were generated at 25 °C at a fixed 90 °C light incidence angle. All measurements were acquired by calculating the average of 10 runs for all independent preparation of blank and Drug-loaded SLNs samples (n = 3).

2. Drug Entrapment Efficiency (EE)[18,19,20,21,22]

The concentration of free drug from SLNs is determined by using ultrafiltration-centrifugation technique to calculate the percentage entrapment efficiency (%EE). Three independent preparations of drug-loaded SLNs samples are filtered through centrifugal filter devices and centrifuged at 5000 rpm for 10 min with a fixed 23°C angle rotor. Concentration of drug present in the supernatant (unentrapped) is quantified using a UV spectrophotometer at λ_{max}. The formula adopted for EE calculations was as follows

$$\%EE = \frac{\text{Total amount of drug} - \text{Unentrapped drug}}{\text{Total amount of drug}}$$

Where total amount of drug is the amount of drug added into the lipid phase and non-entrapped drug is the estimated amount of drug present in the aqueous phase of the formulation measure after centrifugation and filtration of the samples.

3. Differential Scanning Calorimetry (DSC)[22,23]

SLNs dispersions are lyophilized prior to DSC analysis. Solid lipid drug, lipid/drug (7:3) physical mixture and SLNs were subject to DSC analysis. Prior to heating, approximately 3 mg samples are equilibrated in the DSC pan (hermetic crimped aluminum pans) at 45 ^{0}C for 30 min and then heated up to 200 ^{0}C at a scanning rate of 10 ^{0}C/ min under N_2 atmosphere.

4. Fourier Transform-Infrared Studies[24]

The interaction between the lipids and drugs are identified from the Fourier transform -infrared (FT-IR) studies. The FT-IR spectrum of pure drug and combination of drug with lipids are obtained by using a Shimadzu FT-IR Spectrophotometer. The scanning range is 450-4000 cm and the resolution is 4 cm^{-1}. Samples are prepare as KBr pellets.

5. Lyophilization and The recovery rate of solid lipid nanoparticles[24,25]

The SLNs dispersions are fast frozen under -75 ^{0}C in a deep freeze for 5 h in an ultra-low refrigerator and then the samples are moved to the freeze-drier. The drying time is controlled in 72 h and then to get the SLNs powder. The recovery rates of SLNs are calculated from Eq.

$$\text{Recovery (\%)} = \frac{\text{Analyzed weight of SLNs}}{\text{Theoretical weight of SLNs}} \times 100$$

6. Release kinetics[14,26]

In order to understand release kinetics of a drug, the results of *in vitro* drug release studies of nanoparticles are fit to various kinetics equations such as zero order (cumulative % release vs. time), first order (log % drug remaining vs. time), and Higuchi's model (cumulative % drug release vs. square root of time). Values of r^2 and k are calculated for the linear curve obtained by regression analysis of the above plots. The exact mechanism of drug release is determined by the Korse-Meyer–Peppas model (log drug release vs. log time).

7. X-ray Diffraction[27,28,29]

X-ray diffraction (XRD) measurements are carried out by X-ray diffractometer. A Cu Kα radiation at 40 kV and 100 mA are use. Diffractograms are performed from the initial angle 2θ = 3° to the final angle 2θ = 50° with the steps of 0.02°, at a scanning speed of 4°/min (2θ).

8. Stability studies[24,29]

Stability studies are carried out for the formulations having high entrapment efficiency by storing the formulation at two different temperatures 4 ^{0}C and 25 ± 2 ^{o}C and the drug content are estimated every 15 days, to find any change in the entrapment efficiency of the SLNs.

9. *In vitro* drug release studies[22,26,29]

The *in-vitro* releases of drug from different SLN dispersions are determine using the dialysis bag diffusion technique. An accurately weight amount of drug-loaded SLN dispersions containing the drug equivalent to 2.5 mg are transfer to a dialysis bag and seal. The sealed bag are then suspend in a beaker containing 250 ml of phosphate buffer saline pH7.4 and stirred at a constant speed of 50 rpm at 37 ^{o}C ± 0.5 °C. Aliquots are withdrawn at predetermined intervals from the receptor compartment up to 12 hours and the same was replaced with a fresh buffer. Then the drug content is determined spectrophotometrically by measuring the absorbance at λ_{max} using the respective receptor medium as a blank to calculate the amount of drug released from the nanoparticles.

10. *In vivo* studies in rats[22,29,30]

Eighteen Male Wistar Albino rats (body weight 200 ± 50 g) are randomly group into three groups (Control, Standard and Test) of equal size (n = 6): the control group is treat by SLNs without drug, Standard group is treat by marketed formulation and Test group is treat drug loaded SLNs. The animals are kept fasting 12 h prior to the *in vivo* study with water provided ad libitum and no food is allowed after dosing until the end of the study (after 24 h). This study is performing in accordance with CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines. The blood samples are collected in centrifuge tubes containing K_2EDTA (1.8 mg/ml). Blood samples (0.2 ml) are withdrawn from the tail vein at the following time intervals: 0 (predose) 0.25, 0.5, 1, 2, 3, 4, 8, and 24 h after administration. The plasma is separated from the collected blood sample by centrifugation at 4,000 rpm for 15 min and then it is deep-frozen at -70 ^{0}C for further studies.

Routes of Administration and Their bio distribution[2,15,16,31,32,33]

Distribution processes (adsorption of biological material on the particle surface and desorption of SLN components into the biological environment) and enzymatic processes are examples of SLN interactions with the biological environment. Various administration routes are.

1. Parenteral administration

Peptide and protein medications are commonly accessible in the market for parenteral administration. Because of enzymatic breakdown in the GI system, traditional oral delivery is not viable. With enhanced bioavailability, parenteral administration of SLN minimizes the risk of medication adverse effects. These systems are particularly well suited to drug targeting.

2. Oral administration

The controlled release behavior of SLNs has been shown to allow the encapsulated drug to bypass stomach and intestinal degradation, as well as absorption and transport via the intestinal mucosa. However, in order to forecast colloidal carriers' suitability for oral delivery, the stability of colloidal carriers in GI fluids must be assessed.

3. Rectal administration

In some cases, parenteral or rectal delivery is chosen when a quick pharmacological effect is desired. Because of its simplicity, this method is preferred by pediatric patients.

4. Nasal administration

For its rapid absorption and beginning of drug activity, the nasal route is favored. It also avoids labile drug breakdown in the GIT and insufficient transport through epithelial cell layers.

5. Respiratory delivery

Nebulization of solid lipid particles containing anti-tubercular, anti-asthmatic, and anti-cancer medications was found to improve drug bioavailability and reduce dose frequency, allowing for better pulmonary action management.

6. Ocular administration

With the goal of ocular medication targeting, SLN's biocompatibility and muco-adhesive qualities boost its contact with the ocular mucosa and extend the drug's corneal residence time.

7. Topical administration

SLN are extremely appealing colloidal carrier systems for skin applications because they provide a variety of desirable skin effects in addition to colloidal carrier system properties. Because they are based on non-irritant and non-toxic lipids, they are ideal for use on injured or irritated skin.

Applications of solid lipid nanoparticles[9,15,32,34,35,38,39,40]

1. SLNs as potential new adjuvant for vaccines

Vaccination adjuvants are used to boost the immunological response. The more secure modern subunit vaccines are substantially less effective at

immunizing, necessitating the use of potent adjuvants. Emulsion systems are new breakthroughs in the adjuvant place. These are emulsions of oil and water that break down quickly in the body. The lipid additives in SLNs can be destroyed more slowly in the solid state, giving the immune system a longer period of exposure.

2. SLNs in cancer chemotherapy

Several chemotherapeutic drugs have been encapsulated in SLN for a long time, and their *in-vitro* and *in-vivo* efficacy has been assessed. The findings of that study were shown to improve the efficacy of chemotherapeutic medications while also reducing the negative side effects associated with them. The essential functions of SLN that lead them to an appropriate service for handing over chemotherapeutic drugs are improved drug balance, encapsulation of chemotherapeutic marketers of diverse physico-chemical properties, more suitable drug efficacy, progressed pharmacokinetics, and much less *in-vitro* toxicity.

a. SLNs has targeted carrier for anticancer drug to solid tumor

SLN were supposed to be useful as medication transporters. Tamoxifen is an anticancer medication used in SLN to prolong drug release after IV delivery in patients with breast cancer. The SLN was loaded with drugs like methotrexate and camptothecin to treat the tumor.

b. SLNs in breast Cancer and Lymph node metastases

Mitoxantrone SLN local injections were developed to reduce toxicity while also improving medication protection and bioavailability.

3. SLNs for delivering Peptides and Proteins

As an alternate carrier for therapeutic peptides, proteins, and antigens, solid lipid particulate systems such as solid lipid nanoparticles (SLN), lipid microparticles (LM), and lipospheres were investigated. The research in this field reveals that, under ideal conditions, they may be made to carry hydrophobic or hydrophilic proteins, and that they appear to meet the requirements for an optimal particulate carrier system. Proteins and antigens with healing properties can be added to SLN or adsorbed onto it, and then delivered by parenteral or other routes such oral, nasal, and pulmonary.

Advanced protein stability, proteolysis avoidance, and sustained release of the integrated molecules are all benefits of SLN formulation. Peptides including cyclosporine A, insulin, calcitonin, and somatostatin have been integrated into solid lipid particles and are now being studied. Several local or systemic therapeutic regimens, such as protein antigen vaccination, infectious disease treatment, chronic illness treatment, and most cancer treatment, can be anticipated.

4. SLNs for targeted brain drug delivery

Solid lipid nanoparticles' extremely small particle size, which can be less than 50 nm, is likely advantageous in terms of medication concentration. Smaller carriers are more likely to be taken up by the reticuloendothelial system. Surface modification of solid lipid nanoparticles may allow for drug concentration. SLNs improve a drug's ability to cross the blood-brain barrier, making them a promising drug targeting method for the treatment of central nervous system illnesses. 3',5'-dioctanoyl-5-fluoro-2'deoxyuridine (DO-FUdR) was produced and integrated into solid lipid nanoparticles in a study to overcome the medication 5-fluoro-2'-deoxyuridine (FUdRlimited)'s access to the brain (DOFUdR-SLN).

5. SLNs for parasitic diseases

Parasitic infections (such as malaria, leishmaniasis, and tryanosomiasis) are a major problem all throughout the world. Because such parasitic diseases do not trigger a documented immune response, effective immunization may not be achievable. Antiparasitic chemotherapy is the simplest choice of treatment for those parasitic illnesses. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are a new generation of colloidal carriers that have emerged as a viable alternative to liposomes due to their improved stability, ease of scale and commercialization, and cost effectiveness. Furthermore, due to their particle nature and inherent structure, SLN and NLC are effective in the treatment of parasitic diseases. Recent studies, including our own, have shown that they can be used to a limited extent. However, considerable research on SLN and NLC matrices is urgently needed in order to increase their adaptability in terms of encapsulation and target ability, and to develop a diverse, successful, and relatively inexpensive strategy for anti-parasitic medication delivery.

6. SLNs for ultrasonic Drug and Gene delivery

In recent years, drug delivery research using micelles and nanoparticles has seen a lot of use in ultrasonic medication and gene delivery. The use of these Nano vehicles to deliver large concentrations of cytotoxic medications to sick tissues selectively, reducing the agent's negative effects on the rest of the body, is particularly intriguing. With these nanoparticles, ultrasound, which has historically been utilized in diagnostic medicine, is finding a role in drug delivery. Acoustic waves have been credited in releasing pharmaceutical compounds from nan carriers and making cell membranes more permeable, in addition to being non-invasive and able to be directed on specific tissues. The most common polyether block copolymers used in ultrasonic drug delivery from micelles have been demonstrated to be effective *in vivo* for treating malignancies. Ultrasound causes drugs to be released from micelles, most likely due to shear stress and shock waves caused by cavitation bubbles collapsing.

Ultrasound is utilized to deliver genes *in vitro* and *in vivo* using liquid emulsions and solid nanoparticles. Nanoparticles can be extravagant into tumor tissues due to their tiny packing. Because of the large variety of medications and genes that could be delivered to particular tissues by very non-invasive techniques, ultrasonic drug and gene delivery from nanocarriers offers significant potential.

7. SLNs applications for improved delivery of antiretroviral drugs to the brain

During the early stages of primary infection, the human immunodeficiency virus (HIV) can obtain access to the central nervous system. The virus actively replicates once inside the brain compartment, becoming an autonomous viral reservoir that causes devastating neurological consequences, latent infection, and medication resistance. Antiretroviral medications (ARVs) are typically ineffective in lowering HIV viral load in the brain. This is owing in part to the poor transport of many ARVs, particularly protease inhibitors, over the BBB and the blood-cerebrospinal fluid barrier (BCSBF).

8. SLNs applied to the treatment of malaria

Several nanosized delivery technologies for the treatment and prevention of malaria have previously been proven in animal models. This study discusses a range of ways for delivering antimalarials utilizing nanocarriers, as well as the mechanisms that permit their targeting to Plasmodium spp-infected cells. Because of the unique characteristics of malaria parasites, lipid-based (e.g., liposomes, solid lipid nanoparticles, and nano and microemulsion) and polymer-based nanocarriers are being studied (Nanocapsules and nanospheres).

9. Targeted delivery of SLNs for the treatment of lung diseases

One of the most difficult areas of research in pharmaceutical sciences is the targeted delivery of therapeutic molecules to organs or specific places. A new path for enhancing medication delivery was opened by inventing colloidal delivery methods such as liposomes, micelles, and nanoparticles. Nanoparticles have significant advantages over alternative delivery systems due to their unique qualities such as small particle size, huge surface area, and the capacity to change surface properties. The delivery of targeted nanoparticles to the lungs is becoming more popular.

10. SLNs in tuberculosis disease

SLN have more durability and encapsulation efficiency than liposomes, and unlike polymeric nanoparticles, the manufacturing process uses fewer organic solvents.

Anti-Tubercular Drugs (ATD) have been encapsulated with SLN and have been shown to be effective in experimental tuberculosis. Antitubercular medications such rifampicin, isoniazid, and pyrazinamide SLN systems reduced dosage frequency and improved patient compliance. ATD was co-incorporated into SLN to see if these carriers could be used to treat tuberculosis via the oral route. The findings of this study revealed that SLN has a lot of potential in terms of delivering ATD by reducing dose frequency and enhancing patient compliance through better TB management.

11. SLNs as transfection agent

The same cationic lipid used in liposomal transfection agents is used to make cationic SLNs for gene transfer. The structural and performance differences and similarities between SLN and liposomes were studied. The generated SLNs had a smaller diameter than the comparable liposomes, as revealed by PCS, and AFM confirmed the expected structural differences. Only a small difference in DNA binding was found. The *in vitro* transfection efficacy is governed more by the cationic lipid composition than by the colloidal structure in which it is arranged. As a result, cationic SLN adds to the list of highly powerful non-viral transfection agents by providing one with unique technological features. The use of cationic SLN in conjunction with the nuclear localization signal TAT2 boosted transfection efficiency by a factor of a hundred.

12. SLNs in Cosmetic and Dermatological preparations

Topical applications based on the SLN technology, such as pharmaceutical and cosmetic formulations, have a lot of potential for SLN and have a short time to market. After liposomes, SLN are considered the next generation of delivery systems. Topical treatment of skin disease looks to be preferable due to the lesser likelihood of systemic side effects, yet the stratum corneum prevents xenobiotics from penetrating living skin. Particulate carrier systems could be a way to increase cutaneous penetration. Because epidermal lipids are abundant within the penetration barrier, lipid carriers that bind to the skin surface and facilitate lipid exchange between the stratum corneum's outermost layers and the carrier look to be promising. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been extensively explored in addition to liposomes.

13. SLNs for lymphatic targeting

After intraduodenal injection to rats, solid lipid nanoparticles (SLN) were created and assessed for lymphatic absorption.

14. SLNs for potential agriculture applications

When essential oil produced from *Artemesia arboreseens L* was mixed into SLN, it was able to reduce quick evaporation when compared to emulsions, and the systems were employed in agriculture as safe pesticide carriers.

CONCLUSION

Solid lipid nanoparticles are colloidal dispersions with changed properties of different nanoparticles together with microemulsions, suspensions, liposomes and

polymeric nanoparticles. The foremost issues encountered with nanoparticles may be successively prevented the usage of SLNs, and in the end a chemically stable and physiologically appropriate drug delivery system may be achieved with much less limitations. Only their gelation tendency appears to be the principal problem, however nanostructured lipid carriers are a likely manner to overcome this problem. In addition, the active component, i.e. the drug, can be degraded at some point of their manufacturing primarily based totally on the hot homogenization technique due to the generated heat and stress. Thus, selecting the ideal manufacturing technique is crucial. Several different problems together with particle size, coexistence of various colloidal forms, different shapes and drug ejection from the lipid matrix additionally need to be addressed. The various well-set up strategies for the majority manufacturing of the SLN matrix and its characterization have been discussed. Drugs with physicochemical incompatibility, decreased pharmacokinetic profile, and thermolabile drugs may be introduced to the target site through SLNs. Protein and peptide delivery with a better degree of efficiency and decreased toxicity also can be done with SLNs. Thus, the addition of the theranostics approach with SLNs can take therapeutics and diagnostics in a new direction. Apart from these, the everyday objective of controlled drug delivery is aptly done with SLNs. They are relatively younger drug delivery systems, having acquired primary interest from the early 1990s and future holds top notch promise for its systematic research and exploitation. We can expect many patented dosage forms in the form of SLNs in the future.

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