International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

"Recent Prospective of Emerging Colloidal Solid Lipid Nano Drug Delivery Systems"

Vishal Dhokale[1], Ajay Shinde[2], Suvarna Sonawane[3]
SVPM College of Pharmacy, Malegaon(Bk.), Savitribai Phule Pune University, Pune India -413115

Submitted: 01-04-2022 Accepted: 11-04-2022

ABSTRACT:
Solid lipid nanoparticles provide benefits over other colloidal carriers such as liposomes, polymeric nanoparticles, and emulsions, such as controlled drug release and targeted drug delivery with greater stability. Solid lipid nanoparticles are spherical nanometersized particles that are submerged in water or an aqueous surfactant solution and are either lipophilic or hydrophilic drugs. Even improving the solubility and bioavailability of poorly soluble medications should be done with biodegradable and bio-acceptable polymers that can overcome the harmful effects of standard drug carriers. By encapsulating the problems associated with conventional chemotherapy as SLN, they may be largely addressed.This review focuses on drug candidate selection, benefits, and preparation techniques such as highpressurehomogenization, ultrasonication/high speed homogenization, solvent evaporation/emulsification, supercritical fluid method, microemulsion based approach, and spray drying method. Photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry, and other suitable analytical methods for the characterization of solid lipid nanoparticles are presented. Oral, parenteral, topical, pulmonary, and other modes of delivery are all thoroughly discussed.

KEYWORDS: Colloidal Drug delivery, Enhance Solubility, Solid lipid Nanoparticles, Lipid Matrix.

I. INTRODUCTION:

The profound understanding achieved in many domains of Biotechnology, Biomedical Engineering, and Nano-technology, the field of Novel Drug Delivery System is growing at an exponential rate.[1] The fact that the bulk of novel chemical entities (more than 60% of medications) originate from synthesis are poorly soluble is widely recognised. As a result, several of these drugs have issues with bioavailability following oral administration. The use of cyclodextrin microemulsions, such as cyclosporine A (CycA)loaded microemulsions sold as a commercial product, as well as microparticles and nanoparticles based on synthetic polymers or natural macromolecules, are common techniques to improve solubility and, as a result, oral absorption. To circumvent the limitations of classic formulations, lipid-based drug delivery methods have been proposed. Solutions, suspensions, emulsions, microemulsions, self-emulsifying drug delivery systems (SEDDS), dry emulsions, and solid lipid nanoparticles are just a few of the possibilities available[(1)].Solid lipid nanoparticles (SLN) have been studied as an alternate drug delivery technique to colloidal drug delivery systems such lipid emulsions, liposomes, and polymeric nanoparticles for over a decade. SLN combines the benefits of many colloidal carriers while avoiding some of their drawbacks. SLN can be used to increase the bioavailability of medications like cyclosporine A and to provide lipophilic pharmaceuticals like camptothecin a longer half-life. Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions with solid biodegradable lipids as the matrix. SLNs combine the benefits of numerous colloidal carriers in their class while avoiding the disadvantages, such as physical stability, protection of integrated labile medicines from degradation, controlled release, and great tolerability. In vitro and in vivo testing of SLN formulations for several delivery routes (parenteral, oral, dermal, ophthalmic, pulmonar, rectal) has been completed[(2,3)].Solid lipid nanoparticles are unique possible colloidal carrier system as an alternative to polymers. They are similar to an oil in water emulsion for parenteral nutrition, but the liquid lipid has been replaced with a solid lipid as seen in Fig. 1.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

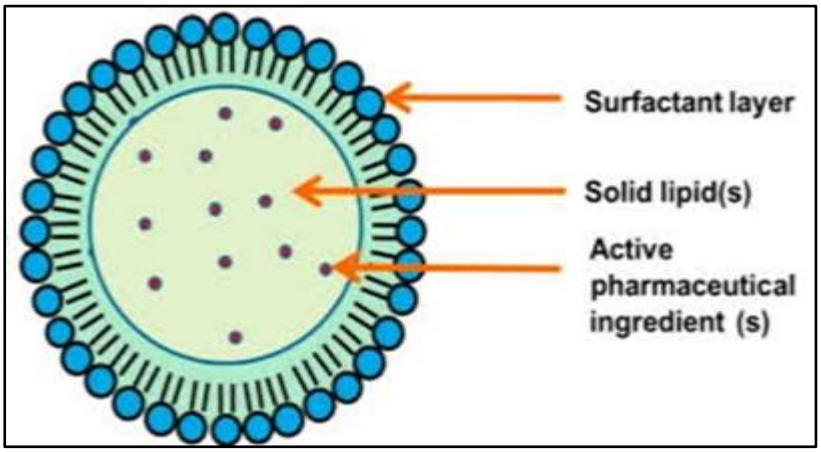

FIG. 1: STRUCTURE OF SOLID LIPID NANOPARTICLES(SLN)[4]

They offer several benefits, including superior biocompatibility, minimal toxicity, and improved delivery of lipophilic medicines via solid lipid nanoparticles, as well as a physically stable system[4].Since their introduction in the early 1990s, solid lipid nanoparticles (SLNs) have been regarded the most effective lipidbased colloidal carriers. This is one of the most used methods for increasing the oral bioavailability of medicines that are poorly water soluble. SLNs are made up of physiologically acceptable lipid components that are solid at room temperature and are in the submicron size range of 10-1000nm. Figure 2 shows a schematic illustration of various particulate drug carriers such as emulsions and liposomes, as well as their benefits, in comparison to SLNs. All of the benefits of polymeric nanoparticles, fat emulsions, and liposomes are combined in SLNs[5].

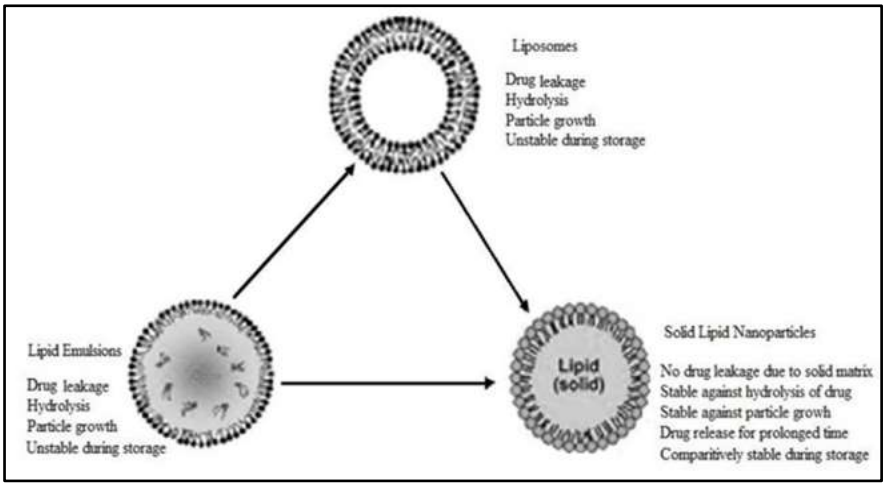

FIG. 2: A DIAGRAMMATIC REPRESENTATION ON SLN OVER EMULSIONS AND LIPOSOMES[5]

Advantages[4,5]

1) Control and/or target the release of a medication.
2) Outstanding biocompatibility.
3) Make medications more stable.
4) Extensive and improved medication content.
5) Scalable and sterilizable.
6) Encapsulated chemical release kinetics can be better controlled.
7) Bioavailability of entrapped bioactive substances is improved.
8) Chemical protection for integrated labile chemicals
9) Biopolymeric nanoparticles are far more difficult to make.
10) There is no need for a specific solvent.
11) Emulsions can be made using traditional procedures.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

12) Commercial sterilisation treatments are possible.

Disadvantages[4,5]

1) Particle expansion.
2) Gelation propensity that is unpredictable.
3) Polymeric transitions have unexpected kinetics.

BASIC GOALS OF SOLID LIPID NANOPARTICLES FOR FORMULATION AND DEVELOPMENT[5]

- Possibility of drug release under supervision.
- The drug's stability has improved.
- A large medication payload
- The carrier has no biotoxicity.
- Organic solvents should be avoided.
- Drugs that are lipophilic and hydrophilic are included.

CHOICE OF DRUG CANDIDATES:

The Biopharmaceutical Classification System (BCS) can be used as a starting point for selecting candidates for SLNs (Fig No. 3). Chemical compounds are split into four classes based on this categorization, with class II having high solubility and low permeability and class IV having low solubility and low permeability.

As a result, molecules from classes II and IV are most likely the best options for making solid lipid nanoparticles[6].

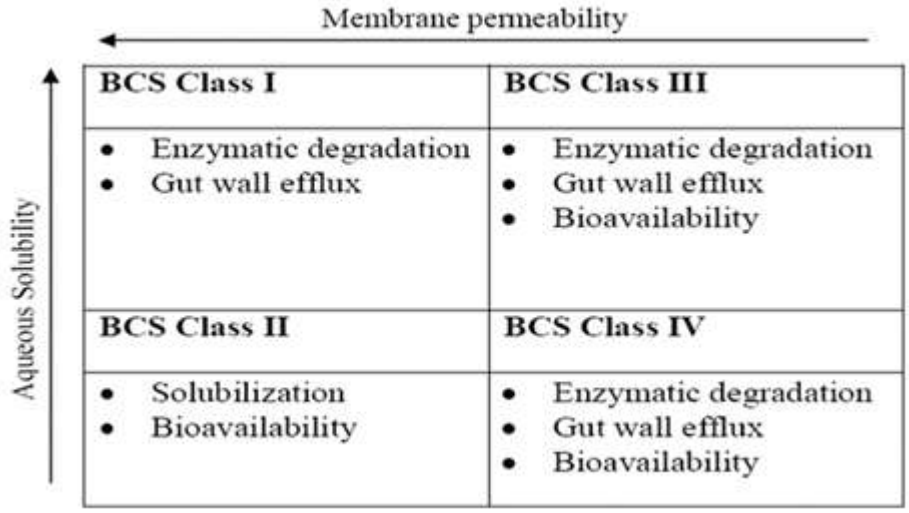

FIG 3: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)[6]

FACTORS TO BE CONSIDERED IN THE FORMULATION OF SLN[5,6,7,8]

Lipids (matrix materials), emulsifiers, co-emulsifiers, and water are all common constituents in the formation of SLNs. To fulfil the criteria of stability and targeting, charge modifiers, stealth agents that boost extended circulation duration and targeting ability, are also utilised. Table 1 lists the various excipients utilised in the formulation of SLNs.

1. **Selection of lipids:** Recently, the argument for using lipid components in the development of oral medicinal dosage forms was examined. The following features should be present in lipid matrices used to make SLNs for I.V. administration.

1) They must be able to produce tiny particles (in the nanometer range) with a low micro particle content (>5 m).
2) They should be able to load lipophilic and perhaps hydrophilic medicines with appropriate capacity.
3) They should be able to be autoclaved for sterilisation.
4) They should be stable in aqueous dispersions and can be lyophilized or spray dried for long-term storage.
5) Toxicologically, they should be acceptable.
6) They should decompose easily.

When compared to SLNs made with highly ordered crystal packing lipids like beeswax, cetylpalmitate, tripalmitate, and solid paraffin, SLNs made with less ordered crystal lattice lipids like glyceryl monostearate and glyceryl behenate promote effective drug inclusion. Their long-term stability, however, is vastly different. Within glycerides, tripalmitate had the highest physical stability, followed by tribehenin, which is owing to

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

the existence of 15% monoglycerides in tribehenin that had surfactant capabilities. Glyceryl monostearate, on the other hand, is exceedingly unstable, and significant particle development occurs within a few days of production. This is due to the presence of 50% monoglycerides in glyceryl monostearate, which are responsible for the physical instability of the product. The loading capacity of the drug carrier system, as well as the intended usage, are important factors to consider. For example, complex glycerides, such as hard fats, are not suitable for controlled release applications because they melt at body temperature. The average particle size of SLN dispersion is affected by the lipid's melting point. With higher melting point lipids, the average particle size of SLNs synthesised by high-pressure homogenization increased. The purity of the lipids is critical for producing high-quality SLNs.

2. Selection of emulsifier: Emulsifiers should be nontoxic, compatible with other excipients, capable of creating acceptable size with a little amount of material, and offer enough stability to SLNs by covering their surface. Another factor to consider when choosing an emulsifier is the emulsifier's in vivo destiny; for example, the poloxamer series gives SLNs long-circulating capabilities by limiting RES absorption, allowing passive targeting, whereas polysorbate 80 coated SLNs increased drug delivery to brain targeting.

Particle aggregation occurs when the amount of emulsifier used is reduced, resulting in an increase in particle size. Excessive emulsifier usage, on the other hand, should be avoided to avoid decreased entrapment effectiveness, burst release (as seen in SLN release experiments), and hazardous effects associated with surfactants[4]. Surfactant mixes (Lipoid S 75/poloxamer 188 or tyloxapol/lecithin) stabilised SLNs had smaller particles and better storage stability. Trotta et al. tested the effect of emulsifiers on the size of SLNs by employing a variety of emulsifiers to make SLNs using glyceryl monostearate. Epikuron 200: cholic acid sodium salt as emulsifier produced the lowest SLNs (160 nm).

SLNs dispersions stabilised with non-ionic surfactants have higher particle sizes than those stabilised with ionic surfactants. The use of non-ionic surfactants in conjunction with lecithin resulted in larger particles. When two or more emulsifying agents are used together, mixed surfactant films develop at the interface. These combined surfactants effectively cover the surface and provide enough viscosity to support stability.

3. Selection of co-emulsifier: The phospholipids employed to make SLNs are not soluble in continuous phase and do not form highly dynamic micelles. During the homogenization process, surplus phospholipid molecules form tiny, mostly unilamellar vesicles. However, phospholipid molecules linked to vesicles have limited mobility. As a result, they are unable to cover the newly formed surfaces during solid lipid recrystallization. Because phospholipid molecules have a poor mobility, a sudden loss of emulsifier on the particle's surface causes particle aggregation and an increase in the particle size of SLNs. Co-emulsifiers such as glycocholate (ionic) and tyloxapol (non-ionic polymer) are used to avoid this. Micelles can be formed by these water-soluble emulsifiers.

Material	Examples
Lipid Matrices	Beeswax Behenic acid Cholesterol Glyceryl trilaurate (Dynsan 112) Glyceryl trimyristate (Dynsan 114) Glyceryl monostearate Glyceryl tristearate (Dynsan 118) Glyceryl behenate (Compritol) Glyceryl monostearate (Imvitor 900) Solid paraffin Stearic acid
Emulsifiers	Soy lecithin Egg lecithin (Lipoid E 80) Poloxamer 188 (Pluronic F 68) Poloxamer 407

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

	Poloxamine 908 Polysorbate 80 Cremophor EL
Co-emulsifiers	Taurocholate sodium salt Sodium dodecyl sulphate Sodium glycocholate Sodium oleate Butanol
Cryoprotectants	Trehalose,Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl pyrolidone (PVP), Polyvinyl alcohol (PVA), Gelatin
Charge modifiers	Stearylamine, Dicetylphosphate Dipalmitoyl phosphatidyl choline (DPPC), Dimyristoylphophatidyl glycerol (DMPG).
Agents for improving circulation time	Polyethyleneglycol, poloxamer
Preservatives	Thiomersal

Table 1: Excipients used in solid lipid nanoparticle (SLN) drug delivery systems[4]

SOLUBILITY OF DRUGS IN LIPIDS:

TheTri, di, and monoglycerides (of various hydrocarbon chain lengths), fatty alcohols, carboxylic fatty acids, and fatty esters are the most often utilised oil solvents in lipid-based medicinal products. Medium-chain glycerides have the best properties for drug solubilization and the generation of microemulsions. Long chain glycerides with higher melting points, on the other hand, are required for the manufacture of SLNs. It is common to find that the amount of medicine that can be dissolved in a lipid formulation exceeds the value calculated from the drug's solubility in lipid alone. Because a drug's solubility throughout the whole formulation is higher, it's possible that it's found not just in the oil phase, but also in the interfacial area of a lipid assembly. The interfacial area provides a unique anisotropic environment capable of supplying hydrophobic groups with a water-poor zone.The drug's solubility in the lipid melt is higher than in the solidified lipid, and this is a key factor in determining entrapment efficiency and loading capacity. Drug solubilization is aided by the presence of mono and di glycerides in the lipid matrix material.Preparing prodrugs improves the drug's solubility in lipids, as seen with the stearic acid derivative of fluoro uracil and azidothymidine palmitate. Complexation of the drug with lipid components and creation of lipid drug conjugates are two further ways to make SLNs for weakly lipid soluble medicines[8,9] .

Solid Lipid Nanoparticle Prepration Methods:

1. Homogenization at high pressure
A. Homogenization in a hot environment
B. Homogenization at a low temperature
2. High-speed homogenization/ultrasonication
3. Evaporation of the solvent
4. Method of solvent emulsification-diffusion
5. The technique of supercritical fluid
6. Method based on microemulsions
7. The procedure of a double emulsion
8. Technique for Solvent Injection
9. Using a Membrane Contractor

1. **High pressure homogenization (HPH):** It's a dependable and strong technology that's being employed for the first time to make SLNs. High-pressure homogenizers force a liquid through a tight gap at high pressure (100–2000 bar) (in the range of a 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 extremely high shear

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

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 the two forms of HPH. In both situations, a preliminary step entails dissolving or dispersing the medication in the lipid melt to incorporate it into the bulk lipid[10]

A. Homogenization in a hot environment: Hot homogenization is carried out at temperatures over the lipid's melting point, and so might be considered emulsion homogenization. A high-shear mixing mechanism creates a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (at the same temperature) (Ultra-Turrax). The quality of the pre-emulsion has a significant impact on the end product's quality, and droplets in the range of a few micrometres are desired. 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. The homogenization process can be repeated as needed. It's important to remember that high-pressure homogenization raises the sample's temperature (about 10°C for 500 bar). 3–5 homogenization cycles at 500–1500 bar are usually adequate. Increasing the homogenization pressure or the number of cycles typically causes particle coalescence, which happens as a result of the particles' high kinetic energy, and the sample may remain as a super cooled melt for several months[9,10].

B. Homogenization at a low temperature: Cold homogenization, on the other hand, is done with solid lipid and so constitutes a high-pressure grinding of a suspension. To guarantee that the lipid does not become molten owing to the increase in temperature during homogenization, effective temperature control and management is required. Cold homogenization was created to address the heat homogenization technique's three major drawbacks.

1. Equipment that may withstand temperature-induced drug deterioration.
2. During homogenization, drug dispersion into the aqueous phase
3. The nano emulsion's crystallisation stage is complicated, which leads to
4. To a variety of changes and/or super-cooled melt pressure.

The first stage is the same as in heat homogenization, and it involves solubilizing or dispersing the medication in the bulk lipid melt. The drug-containing melt is swiftly cooled, ensuring that the drug is distributed uniformly throughout the solid matrix. Low temperatures make the lipid more fragile, resulting in particle comminution. In a cooled emulsifier solution, solid lipid nanoparticles are disseminated. At or below room temperature, the pre-suspension is homogenised under high pressure. Cold homogenised samples, on average, have bigger particle sizes and a broader size dispersion than hot homogenised samples[5,10].

2. **High-speed homogenization/ultrasonication:** Ultrasonication or high-speed homogenization procedures are also used to make SLNs. Smaller particle sizes need 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 experiment[11]
3. **Evaporation of the solvent:** The lipophilic substance is dissolved in a water-insoluble organic solvent (for example, cyclohexane) and emulsified in an aqueous phase. Nanoparticles 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 at decreased pressure (40–60 mbar) was used to remove the organic solvent from the emulsion[11,12].
4. **Method of solvent emulsification-diffusion:** This process may produce particles with typical 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 utilised 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[12,13].
5. **The technique of supercritical fluid:** This is a relatively novel method for producing SLN that has the benefit of not requiring the use of

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

solvents. This platform technology for powder and nanoparticle manufacturing comes in a variety of flavours. The rapid expansion of supercritical carbon dioxide solutions (RESS) technique can be used to make SLN. As a solvent, carbon dioxide (99.99 percent) was an excellent choice[5,6].

6. **Method based on microemulsions:** Gasco and his colleagues developed SLN preparation procedures based on microemulsion dilution. A low melting fatty acid (stearic acid), an emulsifier (polysorbate20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate), and water are commonly mixed at 65-70°C to produce an optically clear combination. Under stirring, the heated microemulsion is disseminated in cold water (2-3°C). The hot microemulsion to cold water volume ratios are typically in the range of 1:25 to 1:50. The composition of the microemulsion has a significant impact on the dilution process. The droplet structure is already present in the microemulsion, hence no energy is necessary to reach submicron particle sizes, according to the literature. Dilution of polymer solutions in water was used by Fessi to create polymer particles. The velocity of the distribution processes, according to De Labouret et al., is a major determinant of particle size. Only solvents that quickly disperse into the aqueous phase (acetone) were used to make nanoparticles, whereas more lipophilic solvents generated bigger particle sizes. The microemulsion's hydrophilic co-solvents perform a similar function in lipid nanoparticle production as acetone does in polymer nanoparticle formation [5,14,15].
7. **The procedure of a double emulsion:** In two processes, warm w/o/w double microemulsions may 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 cosurfactant in the second stage. Warm micro double emulsions are dispersed in cold and then rinsed with dispersion medium using an ultra filtering system to produce SLNs. Multiple emulsions have intrinsic instabilities owing to the internal aqueous droplets coalescing inside the oil phase, the oil droplets coalescing, and the layer on the surface of the internal droplets rupturing. In the case of SLN production, the duration between the synthesis of transparent double microemulsions and their quenching in cold aqueous medium, which is feasible to achieve must be stable for a few minutes[5].
8. **Technique for Solvent Injection:** It is an unique technique for producing SLN that has several benefits over previous methods, including the use of a pharmacologically acceptable organic solvent, ease of handling, and a quick manufacturing procedure that does not need technologically complicated equipment. It works by precipitating lipids from a dissolved lipid solution. The solid lipid was dissolved in a water miscible solvent (such as ethanol, acetone, or isopropanol) or a water miscible solvent combination in this method. The lipid solvent mixture was then injected into a stirred aqueous phase with or without surfactant using an injection needle. The resulting dispersion was then filtered to eliminate any excess lipid using filter paper. By lowering the surface tension between water and solvent, the presence of an emulsifier in the aqueous phase helps to generate lipid droplets at the injection site and stabilise SLN until solvent diffusion is complete[16,17].
9. **Using a Membrane Contractor:** The current study looks at a novel membrane contactor-based approach for preparing SLN in order to enable for large-scale manufacturing. Figure 3 depicts a schematic diagram of the procedure. The lipid phase is squeezed through the membrane pores at a temperature above the lipid's melting point, resulting in the creation of tiny droplets. Inside the membrane module, the aqueous phase circulates and washes away the droplets that develop at the pore exits. Following the cooling of the preparation to room temperature, SLN are produced. The effect of process factors on SLN size and lipid phase flux (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) is examined. Also created are vitamin E-loaded SLN, which have been shown to be stable[17].

SECONDARY PRODUCTION STEPS:

1. **Sterilization:** Autoclaving, filtration, gamma irradiation, and aseptic manufacture can all be used to sterilise SLNs products for parenteral

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

use. Autoclaving is a frequent and popular method of sterilisation, although it has several drawbacks, including high temperature and coalescence due to the lack of applied shear. The melting of lipid particles and the development of an o/w emulsion will occur as the temperature rises. Because just a slight increase in particle size was observed, Schwarz concluded that lecithin is a good surfactant for steam sterilising[5,6].

2. **Lyophilisation:** A product containing hydrolysable pharmaceuticals or a suitable substance for pre-oral administration can be lyophilized for long-term stability. The Oswald would not ripen and hydrolytic processes would be avoided if it were transformed into a solid state. Due to the existence of aggregates between the nanoparticles, all of the lipid matrices utilised create bigger solid lipid nanoparticles with a broader size dispersion when the product is freeze dried. The circumstances of the freeze drying process, as well as the elimination of water, encourage SLN aggregation. During the freeze drying process, a sufficient quantity of cryoprotectant can prevent the agglomeration of solid lipid nanoparticles[5].
3. **Spray drying:** It's a less expensive and less time-consuming alternative to lyophilization. This suggests using lipids with a melting point greater than 70° 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. The inclusion of carbohydrates and a low lipid content favour colloidal particle size preservation during spray drying. Because cooling leads to tiny and heterogeneous crystals, the lower entry temperatures, melting of the lipid can be avoided by using ethanol–water mixes instead of pure water[6].

CHARACTERIZATION OF SLN:

The SLNs must be characterised in order to ensure their quality. However, due to the colloidal size of the particles and the intricacy and dynamic nature of the delivery system, characterisation of SLN is difficult.

1. **Measurement of Particle Size and Zeta Potential:** SLNs' physical stability is determined by their size. The most successful approaches for determining particle size are photon correlation spectroscopy (PCS) and laser diffraction (LD). PCS, also known as dynamic light scattering, is a technique that detects changes in the intensity of scattered light caused by particle movement. Photon correlation spectroscopy (PCS) detects particle sizes ranging from 3 nm to 3 m, whereas laser diffraction detects sizes ranging from 100 nm to 180 m. Although PCS is an excellent tool for characterising nanoparticles, it may also identify bigger microparticles. The zeta potential is measured with a zeta potential analyzer, also known as a zetameter.For size determination and zeta potential measurement, SLN dispersions are diluted 50 times using the original dispersion preparation media. In the absence of any complicating elements such as hydrophilic surface appendages or steric stabilisers, a high zeta potential might lead to particle deaggregation. Storage stability of colloidal dispersions can be predicted using zeta potential measurements[18,19].
2. **Measurement of Crystallinity and Lipid Modifications: X-ray Diffraction and Differential Scanning Calorimetry (DSC):**

The geometric scattering of radiation from crystal planes inside a solid may be used to detect the existence or absence of the latter, allowing the degree of crystallinity to be calculated. Through the measurement of glass and melting point temperature, DSC may be used to assess the type and speciation of crystallinity inside nanoparticles. Due to the rise, thermodynamic stability, lipid packing density, and measurement are all becoming more difficult, whereas drug incorporation rates are decreasing in the following order:

Super cooled melt < α-modification < β9-modification < β-modification[5].

3. **Co-existence of Additional Structures:**

Nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are strong instruments for studying dynamic processes and nano-compartments in colloidal lipid dispersions. Dilution of the initial SLN dispersion with water may result in the loss of surfactant molecules from the particle surface, resulting in additional alterations such as lipid modification crystallisation changes.[5,6]

4. **Entrapment Efficiency:**

The concentration of free drug in the dispersion medium is used to determine the drug's entrapment efficiency. Centrisart, which consists of a filter membrane (molecular weight cutoff 20,000 Da) at the bottom of the sample recovery chamber, was used for ultracentrifugation. The SLNs and encapsulated medication are kept in the outer chamber, while the aqueous phase is transferred to the sample recovery chamber. HPLC or a UV

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

spectrophotometer are used to determine the quantity of medication contained in the aqueous phase[21,22].

$$\text{Entrapment Efficiency} = \frac{\text{Initial drug weight- Weight of Free drug}}{\text{Weight of initial drug}} \times 100$$

5. In-vitro drug release:

In-vitro drug release investigations are utilised for both quality control and the prediction of in-vivo kinetics. The release rate recorded in vivo in this SLN might differ substantially from the release rate measured in buffer solution due to the relatively tiny size of the particles. As a result, in vitro release studies are still relevant for quality control and evaluating the impact of process factors on active component release rates.

a. Dialysis Tubing: Dialysis tubing might be used to achieve in vitro medication release. The SLNs dispersions are inserted in a dialysis tube that has been prewashed and may be hermetically sealed 30. The dialysis sac is then dialyzed at room temperature against a suitable dissolving media; samples are collected from the medium at appropriate intervals, centrifuged, and drug content evaluated using a suitable technique (U.V. spectroscopy, HPLC etc). It is critical to keep the condition of the sink in good working order[23].

b. Reverse Dialysis:A number of Small dialysis sacs holding 1 ml of dissolving liquid are inserted in SLN dispersion in this procedure. After that, the SLNs are put in the dissolving medium. This approach allows for direct dilution of SLNs, however it does not allow for the quantification of fast release[6].

c. Franz Diffusion Cell: The SLNs dispersion is put in a Franz diffusion cell with a cellophane membrane in the donor chamber. The dispersion is then dialyzed at room temperature against a suitable dissolving media; samples are collected from the dissolution medium at appropriate intervals and drug concentration is determined using a suitable technique (U.V. spectroscopy, HPLC etc). It is critical to keep the condition of the sink in good working order[5].

d. Other Parameter for Characterization:

a. Nuclear Magnetic Resonance (NMR): Nanoparticles size and qualitative nature may be determined using NMR.

b. **Atomic Force Microscopy (AFM):** A probing tip with atomic-scale sharpness is restarted over a sample to generate a topological map based on forces acting on the tip and the surface.

c. **Electron Microscopy:**Nanoparticles may be seen directly using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). SEM, on the other hand, is excellent for morphological analysis. The detection limit of TEM is rather tiny.

d. **Dynamic Light Scattering (DLS):**On a microsecond time frame, DLS, also known as PCS, captures the fluctuation in the intensity of dispersed light.

e. **Static Light Scattering (SLS):**SLS is an ensemble approach that collects and fits the scattered light from a solution of particles into a basic main variable.

f. **Acoustic Methods:**It uses the attenuation of dispersed sound waves to determine size by fitting physically appropriate equations to the data.

APPLICATIONS OF SLN:[5,6,8,10]

1. SLN for Parenteral Application

Because they are made up of physiologically well-tolerated components and have high storage capacities following lyophilization and/or sterilisation, SLN are ideal for systemic distribution. SLN are tiny enough to circulate in the microvascular system and impede macrophage absorption in the case of hydrophilic coating when given intravenously. Cationic SLN has been shown to bind genes directly via electrostatic interactions, suggesting that it might be useful in cancer treatment via targeted gene therapy. The difficulty of powerful medications to cross the blood-brain barrier limits the treatment of central nervous system illnesses such as brain tumours, AIDS, neurological, and psychiatric problems (BBB).

2. SLN for Nasal Application

Due to quick absorption and early commencement of therapeutic activity, nasal administration was a potential alternative non-invasive method of drug administration, avoiding GI tract degradation of labile pharmaceuticals (such as peptides and proteins) and inadequate transport through epithelial cell layers. Approaches including formulation development and prodrug derivatization have been used to increase drug absorption via the nasal mucosa. SLN has been offered by many research groups as an alternate transmucosal delivery route for macromolecular therapeutics and diagnostics. Coating polymeric

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

nanoparticles with PEG as vaccine carriers yielded good results, according to a recent study.

3. SLN for Respiratory Application

By minimising first-pass effects, the lungs provide a large surface area for drug absorption. Because the walls of alveoli in the deep lung are exceedingly thin, rapid drug absorption through aerosolization of medicines (in the 1-3 m size range) occurs. The absorption of particles in the respiratory system is greatly aided by lymphatic drainage. SLN might be used as carriers for anticancer medications or peptide therapeutics to boost their bioavailability in lung cancer treatment. Nebulization of solid lipid particles containing antitubercular medicines was found to improve drug bioavailability and reduce dosage frequency, resulting in improved pulmonary TB therapy.

4. SLN for Ocular Application

SLN delivery of ocular drugs has been recorded on multiple occasions. With the goal of ocular medication targeting, SLN's biocompatibility and mucoadhesive qualities boost their contact with the ocular mucosa and extend the drug's corneal residence duration. In rabbit eyes, SLN was tested as a carrier for ocular administration of tobramycin. As a consequence, SLN increased medication bioavailability in the aqueous humour substantially.

5. SLN for Rectal Application

Diazepam has been included into SLN for rectal delivery to offer a quick response. They did bioavailability 390 experiments on rabbits using SLN dispersions. They discovered that a lipid matrix that is solid at body temperature is ineffective for diazepam rectal administration. In their following trials, they opted to use lipids that melt at body temperature. This region appears to be ripe for research, especially when the advantages of the rectal route are considered.

6. SLN for Topical application

Apart from the properties of a colloidal carrier system, SLN and NLC are particularly appealing colloidal carrier systems for skin applications due to their multiple desired effects on skin. Because they are based on non-irritant and non-toxic lipids, they are ideal for use on injured or irritated skin. Vitamin E, tocopherol acetate retinol, ascorbyl palmitate, clotrimazole, triptolide, phodophyllotoxin, and a nonsteroidal antiandrogen have all been explored for topical use with SLN and NLC. The usage of SLN in sun-protective creams is a completely new, recently found use.

7. SLN in Cancer chemotherapy

Several chemotherapeutic drugs have been encapsulated in SLN and their in vitro and in vivo effectiveness has been studied during the last two decades. Tamoxifen, an anticancer medication, has been added with SLN to extend the time the drug is available for i.v. injection in the breast). In antitubercular chemotherapy, SLN is taken orally. Rifamipcin, isoniazide, and pyrazinamide-loaded SLN systems were able to minimise dose frequency and enhance patient compliance.

FUTURE OF SLNS:[24]

By considering industrial demands such as simple technology, cheap cost, regulatory excipient status, tolerability, scale up, certification, and validation, SLNs can be created as more effective drug delivery in the future. The development of a therapy based on localised medical implants must continue. Efficacy, drug loading, targeting, and toxicity are all factors that should be considered in future study. Implant effectiveness must be evaluated over time while encapsulated and kept, which necessitates research. Implantable devices will enhance disease management therapies and might be used for gene therapy, anticancer therapy, vaccinations, and tissue restoration. In both in vitro and in vivo investigations, further study is needed to understand the structure and behaviour of SLNs at the molecular level.

II. CONCLUSION

The SLN combines the benefits of polymeric nanoparticles, fat emulsions, and liposomes as a colloidal drug carrier. A great deal of study on SLN as a carrier system has solidified the idea that SLN is a nontrivial system. Which might be a colloidal drug carrier system for administering active substances or pharmacologically challenging materials like proteins, peptides, hormones, genes, DNA, RNA, or viral vectors for targeting and exerting their associated effects. In addition to determining the particle size, proper characterisation of complex surfactant/lipid dispersions necessitates the use of numerous analytical procedures.

In conclusion, SLN are extremely complicated systems with distinct benefits and drawbacks compared to other colloidal carriers. The scientific community is still gathering new dimensions and implications, particularly in nano scalar systems, in order to use these systems as an industrially feasible and economically resilient technology in the field of SLN technology.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1008-1019 www.ijprajournal.com ISSN: 2456-4494

REFERENCES:

[1]. Ramteke K, Joshi S and Dhole S. Solid Lipid Nanoparticles: A Review, International Organisation of Scientific Research and Pharmaceutical Research, 2(6), 2012, 34-44

[2]. Pavankumar AR, Parthiban S (2014) A modern review on solid lipid nanoparticles as novel controlled drug delivery system. International Journal Pharmaceutics and Research 3(4): 313-325.

[3]. Loxley A. Solid Lipid Nanoparticles: A Review, World Journal of Pharmacy and Pharmaceutical Science, 9(8), 2009, 1-10.

[4]. Tekade RK, Maheshwari R, Tekade M, Chougule MB. Chapter 8-solid lipid nanoparticles for targeting and delivery of drugs and genes A2.

[5]. Ekambaram P, Sathali AH, Priyanka K. Solid Lipid Nanoparticles: A Review. Scientific Reviews and Chemical. Communication 2012; 2, 1 :80-102.

[6]. Verma S and Makkar D. Solid Lipid Nanoparticles: a comprehensive review, Journal of Chemical and Pharmaceutical Research, 8(8), 2016, 102-114.

[7]. Saupe A, Gordon KV and Rades T, Structural investigations on nanoemulsions, solid lipid nanoparticles and nanostructured lipid carriers by cryo-field emission scanning electron microscopy and raman spectroscopy, International Journal of Pharmaceutics, 2006, 314(1), 56-62.

[8]. Nasirizadeh, Samira; Malaekeh-Nikouei, Bizhan. "Solid lipid nanoparticles and nanostructured lipid carriers in oral cancer drug delivery". Journal of Drug Delivery Science and Technology, 55(),2020, 101458.

[9]. Vyas S P, Khar R K. Targeted and Controlled Drug Delivery, novel carrier system, CBS Publishers and Distributors, 2012, 15-16, 346-348.

[10]. R. H. Muller, K. Mader, and S. Gohla, "Solid Lipid Nanoparticles ¨ (SLN) for controlled drug delivery—a review of the state of the art," European Journal of Pharmaceutics and Biopharmaceutics, 2000 vol. 50, 1, 161–177.

[11]. Surya kiranVuddisa, Subramanian.S, Sindhu Raavi "Preparation and Characterization of Candesartan Cilexetil Solid Lipid Nanoparticulate Capsules.," International Journal of Pharma Research and Review, 2014, 3(12), 26–31

[12]. Maryam Ghadri, ShobirahFatem, Alireza vatahara."Loading hydrophilic drug in solid lipid materials as nanoparticles" International Journal of Pharmaceutics; 2012 424(4), 128-37.

[13]. Garud A, Singh D and Garud N. Solid Lipid Nanoparticles: Method, Characterization and Applications, International Current Pharmaceutical Journal, 1(11), 2012, 384-393.

[14]. Nikam S, Chawan M and Sharma P. Solid Lipid Nanoparticles: A Lipid Based Drug Delivery, Innovation in Pharmaceutics and Pharmacotherapy, 2(3), 2014, 365-376.

[15]. Jain N K. Advances in Controlled Novel Drug Delivery, CBS Publishers and Distributors, 2011, 408-423.

[16]. Ramteke K, Joshi S and Dhole S. Solid Lipid Nanoparticles: A Review, International Organisation of Scientific Research and Pharmaceutical Research, 2(6), 2012, 34-44.

[17]. Verma S and Makkar D. Solid Lipid Nanoparticles: a comprehensive review, Journal of Chemical and Pharmaceutical Research, 8(8), 2016, 102-114.

[18]. Deshmukh A S. Solid Lipid Nanoparticles, Research Journal of Pharmaceutical Dosage Forms and Technology, 6(4), 2014, 282-285.

[19]. Patil J, Gurav P, Kulkarni R, Jadhav S. Applications of SLN in novel Drug Delivery, British Biomedical bulletin, 1(2), 2013, 103-118.

[20]. Hu L, Tang X and Cui F: Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drug. Journal of Pharmacy and Pharmacology 2004; 56: 1527- 153.

[21]. Anu Mahajan And Satvinder Kaur, **"**Design, Characterization And Pharmacokinetic Studies Of Solid Lipid Nanoparticles Of Antihypertensive Drug Telmisartan", International Journal Of Pharmaceutical Sciences And Research, 8(8) 2017 3402-3412.

[22]. Rohit Mishra, Showkat R Mir, Saima Amin, "Polymeric Nanoparticles For Improved Bioavailability Of Cilnidipine" International Journal of Pharmacy and Pharmaceutical Sciences, 9(4), 2017 129-139.

[23]. Abdul Hasan SathaliA ,Nisha.N ,2015 "Development of Solid lipid Nanoparticles of Rosuvastatin Calcium" Bio Med Rx, 1(5),2015,536-548.

[24]. Shah, V. Shah, U. Upadhyay, solid lipid nanoparticles: a review current pharma research, 1(4), 2011, 351-368
[25]. Priyanka K, Sathali.A,"Preparation and evaluation of montelukast sodium loaded solid lipo nano particles" Journal Young Pharmacist, 4[3], 2012,129-137