SOLID LIPID NANOPARTICLES - A REVIEW

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ABSTRACT

Lipid nanoparticles can manage drug release and target delivery, they were created in the early 1990s as a different carrier such as liposomes, polymeric nanoparticles, and emulsions. This article provides an overview of the potential merits and demerits of lipids nanoparticles, excipients, and all the various techniques used in the production of nanoparticles. Factors affecting the stability of SLN, include the effects of various excipients used in its manufacture and other secondary factors (such as freeze-drying and spray-drying) that affect stability. Issues related to SLN production and the technology used are discussed in depth. Particular attention is onto patterns of drug use in the SLNs and patterns of release from the SLNs. A detailed discussion of the analyses that go into evaluating SLNs and their primary use, which is mostly for targeted delivery.

Keywords: *High-pressure homogenization (HPH), Solid lipid nanoparticle (SLN), Photon correlation spectroscopy (PCS), Nuclear magnetic resonance (NMR), Dynamic light scattering (DLS), Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Generally Recognized as Safe (GRAS), Laser diffraction (LD).*

1. INTRODUCTION

Numerous recent expression approaches use nanotechnology, which is the medication of nano-sized structures containing the API [1-2]. Nanoparticles can be formulated to target specific cells or tissues, allowing for precision in drug delivery. Surface modifications and functionalization of nanoparticles can enable them to recognize and interact with particular cells, minimizing the impact on healthy tissues and reducing side effects. Through the use of targeted and controlled drug delivery, nanotechnology seeks to identify conditions as precisely and promptly as feasible and to treat them without causing side effects as soon as possible. [3]. Using the principles of nanotechnology, several essential drug delivery systems have been created, including solid lipid nanoparticles, nanoparticles, nano-suspensions, nano-emulsions, nanocrystals, etc. [4].

Lipid-based nanoparticle drug delivery systems are of two types Vesicular shape and Particular shape. Vesicular shape has four types liposomes, nanoparticles, deformable liposomes, and ethosomes also Particular shape has two types solid lipid nanoparticles and nano-structured lipids.

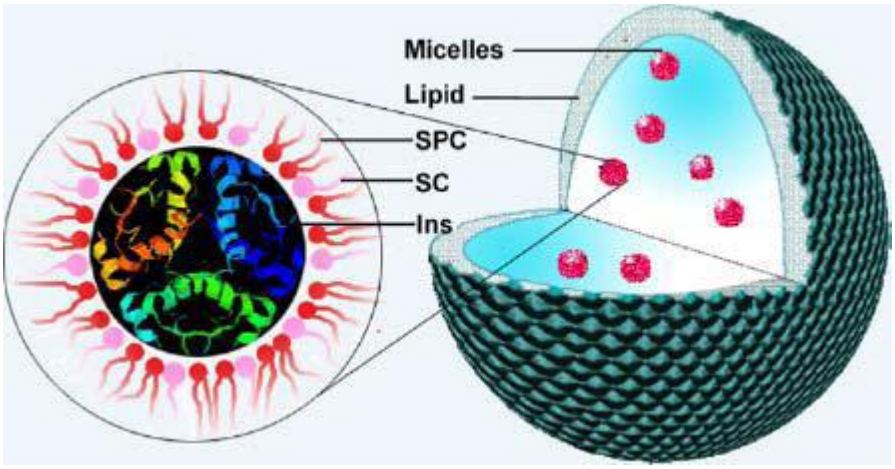

Fig no. 1 Demonstrates the solid lipid nanoparticle's structure. [5]

SLN introduced in 1991 represents a carrier system for emulsions, liposomes, and colloidal carriers like micro and nanoparticles. SLNs are made up of solid lipids, active ingredients (typically drugs) surfactants used to stabilize the nanoparticles (emulsifier), and co-surfactants (water/solvent) [6,7].

The lipids used are triglycerides, semi-glycerides, fatty acids, steroids, and waxes [8]. The range in size (approximately 10 to 200nm) of SLNs allows them to penetrate the blood-brain barrier composed of endothelial cells. It evades the reticulo-endothelial system and circumvents the liver. These carriers exhibit a superior capability to encapsulate drugs, enhancing the stability of the drug within their lipid matrix. Furthermore, they enable a controlled release that extends over several weeks. [9].

Solid lipids are advantageous because they have been shown to enhance the stability of lipophilic chemical products and the controlled release kinetics of encapsulated substances. There are several physicochemical properties related to the lipid phase's physical state that may contribute to these possible advantages. Firstly, in a solid matrix, the molecules or ions of the active reagents are bound within the structure of the solid material.

This can restrict their movement and diffusion, making it more difficult for them to come into contact with other reactants or participate in chemical reactions. The primary mechanism governing particle mobility in a solid is diffusion through the solid matrix. This diffusion is often slower than molecular motion in a liquid, which can lead to a retardation in the rate of chemical degradation reactions. Second, it is possible to regulate the microphase separation between the API and carrier lipids in the liquid particles, which avoids the buildup of API compounds on lipid particles, which are often the site of chemical breakdown reactions. Thirdly, adding bioactive compounds to SLN improves their poor absorption.

Due to diverse research endeavors, it has been demonstrated that employing a solid matrix, as opposed to a liquid one, can decelerate lipid digestion, and encapsulated substances facilitate prolonged release. Another significant component of SLNs is surfactants, predominantly of the aqueous type. These surfactants primarily function as emulsifiers, facilitating the formation of oil-in-water emulsions, and as stabilizers for dispersion in SLNs. Mainly selection of surfactants is largely contingent on the chosen route of administration. These usually comprise a solid hydrophobic core with the medication either dissolved or distributed throughout [10].

Khan, M.F.A., et al conducted a study on Hydrogel Containing SLN filled with Simvastatin and Argon oil. With the aid of argan oil and NP-containing, we were able to synthesize biodegradable and biocompatible components for cutaneous distribution. Under laboratory conditions, the drug release, higher retention time, increased permeability, and excellent encapsulation efficiency were all proven by SIM-SLNs with a spherical morphology and homogenous particle size distribution. Because argan oil has antihyperlipidemic qualities, transdermal delivery of SIM-SLNs using hydrogels based on the oil may improve bioavailability and provide promising nanocarriers with therapeutic potential.

2. Solid lipid nanoparticle formulation

The primary obstacle to the commercialization of SLN is the utilization of excipients without recognized status. SLN cosmetics, all products currently used in cosmetics and dermatological applications are valid. In the context of administering SLN orally, all materials commonly used in oral form are tablets, pills, and capsules can be used. Even surfactants with cell membrane potential are used in oral products that are used and are accepted as excipients by the regulatory authorities. Moreover, materials that have been approved for GRAS status may be utilized. Since lipids (o/w emulsions for IV administration, delayed release oil-based injectables for administration) are not digested parenterally like liquid lipids are, the circumstances are different for parenteral administration. Nevertheless, substances (glycerol, and fatty acids) present in the glycerides utilized in SLN formulation are also present in parenteral emulsions [11].

The definition of “lipid” is those compounds that are soluble in non-polar organic solvents and include semi-glycerides, triglycerides, fatty acids, steroids, and waxes. Every category of emulsifiers (based on cost and weight of the molecular structure) has been used to control lipid dispersions. Study finds a better combination of emulsifiers to prevent particle aggregation.[12]

2.1 LIPIDS

The main component of solid lipid nanocarriers, the lipid(s) affects the stability, drug encapsulation, and controlled release pattern of the lipid dispersion. Biocompatible/biodegradable lipid components, such as fatty acids, glycerides, and waxes, can be used to manufacture SLN dispersion. There have been reports of SLN uses in the food, cosmetics, and pharmaceutical nanotechnology sectors. It is well acknowledged that the lipids utilized in solid lipid dispersion are affordable, physiologically well-tolerated, and safe (GRAS). [13-15]

2.2 Screening of lipids

Lipid carrier-based formulations have as their main goal the distribution of lipophobic/lipophilic medicines to interested areas. To increase lipophilic moiety solubility, phospholipids are employed to improve permeability. It is possible to increase the restricted permeability of hydrophilic medicines through bio-membranes by inserting the active moiety into the lipid core. As a result, medications that are both lipophilic and hydrophilic can be enclosed in lipid carriers.[10] Delivery of lipid carriers can reduce the instability of peptides and proteins in the GIT at varying pH levels. Rapid clearance, immunological response, inadequate localization, drug accumulation at the action location, and diffusion and redistribution in tumor cells are the drawbacks of site-specific/targeted administration. The selection of appropriate lipid carriers can reduce these issues.[16]

2.3 The lipid selection standards for solid lipid nanoparticles. [17-23]

- The primary criterion mentioned for choosing lipid carriers is the partition coefficient.
- Drug compatibility with the lipid carrier(s)
- To reduce stability issues, the lipid carrier's melting point should be higher than 45°C.
- Core materials should have an HLB value of less than 2. Compared to hydrophilic materials, they are more hydrophobic and contain greater potential to create solid matrices.
- The ability of the lipid carrier to stabilize the integrated medicine or drugs is desirable.
- Drug breakdown and ejection will result from higher and lower crystalline lipid matrices.
- Density of lipid packing and thermodynamic stability
- Topical preparation's occlusive property is contingent upon the degree of lipid crystallinity.

2.4 Surfactants

Numerous researchers have looked at the different ways to prepare SLNs, how to choose lipids for optimal entrapment effectiveness, and how to stabilize and lyophilize them over the past few years. Stabilizing agents, or surfactants, are crucial for producing a solid lipid colloidal system out of all those factors. In the nanoparticle preparation process, colloidal stability is important, they lessen the in-between surface tension of lipophilic and lipophobic phases of the colloidal dispersion and make the process of developing nanoparticles easier. [24] The hydrophilic and lipophilic moieties that make up the head and tail of surfactant's natures are lipophilic and lipophobic. To create a stable lipid colloidal system, surfactants are utilized. A typical view of ionic and non-ionic surfactants is that they result in steric repulsion stability and electrostatic stability, respectively. By using modest amounts of non-ionic surfactants to assume genuine steric stability, the Gibbs-Marangoni effect causes instability. The functional groups of zwitterionic or amphoteric surfactants are negatively and positively charged.

To create colloidal lipid nanoparticles, amphoteric surfactants such as phospholipids and phosphatidylcholines are utilized. At both high and low pH states, they demonstrated the characteristics of cationic and anionic surfactants.[25,26]

2.5 Surfactant and Co-surfactant Selection Criteria for SLNs [27-29]

To increase the stability of lipid dispersion during the storage period, the right choice of surfactants and cosurfactants should be made.

Ionic surfactants are suggested because they generate less toxicity and irritation. They have the following benefits, which increase the bioavailability of poorly soluble medications:

- Non-ionic surfactants are better at solubilizing poorly soluble medications because they are more hydrophobic.
- They don't harm or irritate biological membranes.

2.6 Merits of SLN [30]

Some have argued that SLN avoids the drawbacks of other colloidal carriers while combining their advantages. Proposed advantages include-

 Targeting drugs and controlling their release.
 Increase the stability of the drug.
 High payload of drugs.
 Introduction of hydrophilic and hydrophobic drugs.
 Absence of carrier bio-toxicity.
 No problems with sterilization and large-scale production.
 Trapped bioactive molecules will become more bioavailable.

2.7 Demerits of SLN

 Particle expansion by aggregation.
 Unstable tendency toward gelation
 Unpredictable changes in polymeric structure
 In a few cases burst release

2.8 List of Lipids and Surfactants used for the preparation of SLNs

Lipids	**Surfactants**
Triglycerides	**Phospholipids**
Acyl glycerols	Soy lecithin
Glyceryl monostearate	Egg lecithin
Glyceryl behenate	**Ethylene oxide/propylene oxide copolymers**
Glyceryl palmitostearate	Polysorbate 60

Waxes	Polysorbate 80
Stearic acid	**Alcohol**
Palmitic acid	Butanol
Tristearin	Butyric acid
Fatty Acids	Ethanol
	Propylene oxide copolymers/Ethylene oxide
	Poloxamer 182
	Poloxamer 188
	Poloxamine 908

3. Methods of preparation of SLN

3.1 Solvent evaporation method

It combines the emulsion following the evaporation method to prepare SLN. The lipophilic material is primarily dispersed and emulsified in the aqueous phase using organic solvents like cyclohexane. After that solvent is evaporated, lipids precipitate in the water medium, and nanoparticles are formed with an average size of 25 nm, resulting in dispersion. By high-pressure homogenization drug was emulsified in the water phase. Under 40-60 bar pressure, evaporation removed the organic solvent from the emulsion. [31] **Robhash Kusam Subedi et al.** prepared and characterized SLN loaded with doxorubicin. In this study, we successfully prepared doxorubicin SLNs as a model drug by solvent emulsion diffusion method using Capmul®MCM C10 as the lipid core and Cordalan as the shell material. Drug release was observed in in-vitro pH 5 than in pH 7.4. Cytotoxicity results showed that for 1 year at 4°C in storage freeze-dried SLNs were equally effective. These observations suggest an exciting mode of delivery to lipophilic anticancer drugs.

3.2 High-pressure homogenization method

HPH technology is used for SLN production, HPH uses high pressure (100-2000 bar) to push the liquid into void space. Liquids move very fast over long distances (>1000 km/h). Particles are crushed to sub-micron sizes by strong shear pressures and cavitation forces. Typically, 5–10% of the lipid content is utilized.

Nonetheless, research has examined up to 40% of the lipid content. There are two homogenization methods hot and cold homogenization. It works on the principle of mixing a drug into a large amount of lipid solution. Piston gap homogenizers and jet stream homogenizers are the two types of high-pressure homogenizers that are now available. [33-37].

3.3 Hot homogenization method

Lipids melt at temperatures that are roughly 5°C higher than their melting points. During that point, in an aqueous surfactant solution, the medicine is dispersed at the same temperature by the melting lipid that contains the medication. After that, the emulsion is put through a homogenizer for processing. The procedure yields a hot oil/water emulsion, and after the cooling of the emulsion, crystallization of lipid and SLN production occurs. [32,33,34]. **Ekambaram P et al** prepared a formulation and evaluated the SLN of Ramipril. Hot homogenization and ultrasound dispersion effectively incorporated the water-insoluble Ramipril drug. It is conceivable that obtaining particles of a nanoscale size may boost bioavailability. SLN delivers controlled drug release through the use of nanoparticle drug delivery systems. These systems also serve as carriers for lipophilic medications and improve the bioavailability of drugs that aren't very soluble in water.

3.4 Cold homogenization method

The initial step is to incorporate the drug into molten lipids, which are then cooled and solidified. Following the grinding of the solid ingredients in a mortar mill, the lipid nanoparticles that are produced are combined with a cold surfactant formulation at room temperature, or better still, below room temperature. Inhibition capacity does not change during storage of aqueous solid lipid dispersions and allows excellent hot homogenization. Inhibition capacity does not change during storage of aqueous solid lipid dispersions and allows excellent hot homogenization. [35].

3.5 Double emulsion-based method

Prepare water/oil microemulsion by adding melted lipid to surfactant, drug content, and co-surfactant. Then, create a water/oil/water system by adding the formed w/o microemulsion to water solution, surfactant, and co-surfactant. By employing an ultrafiltration system to wash with a dispersion media after dispersing heated micro double emulsions in cold. However, Within the oily phase, internal aqueous droplets coalesce, as do droplets of oil, and there is a disruption in the layer that covers the internal droplet surface, among other intrinsic instabilities that multiple emulsions must contend with. [36]

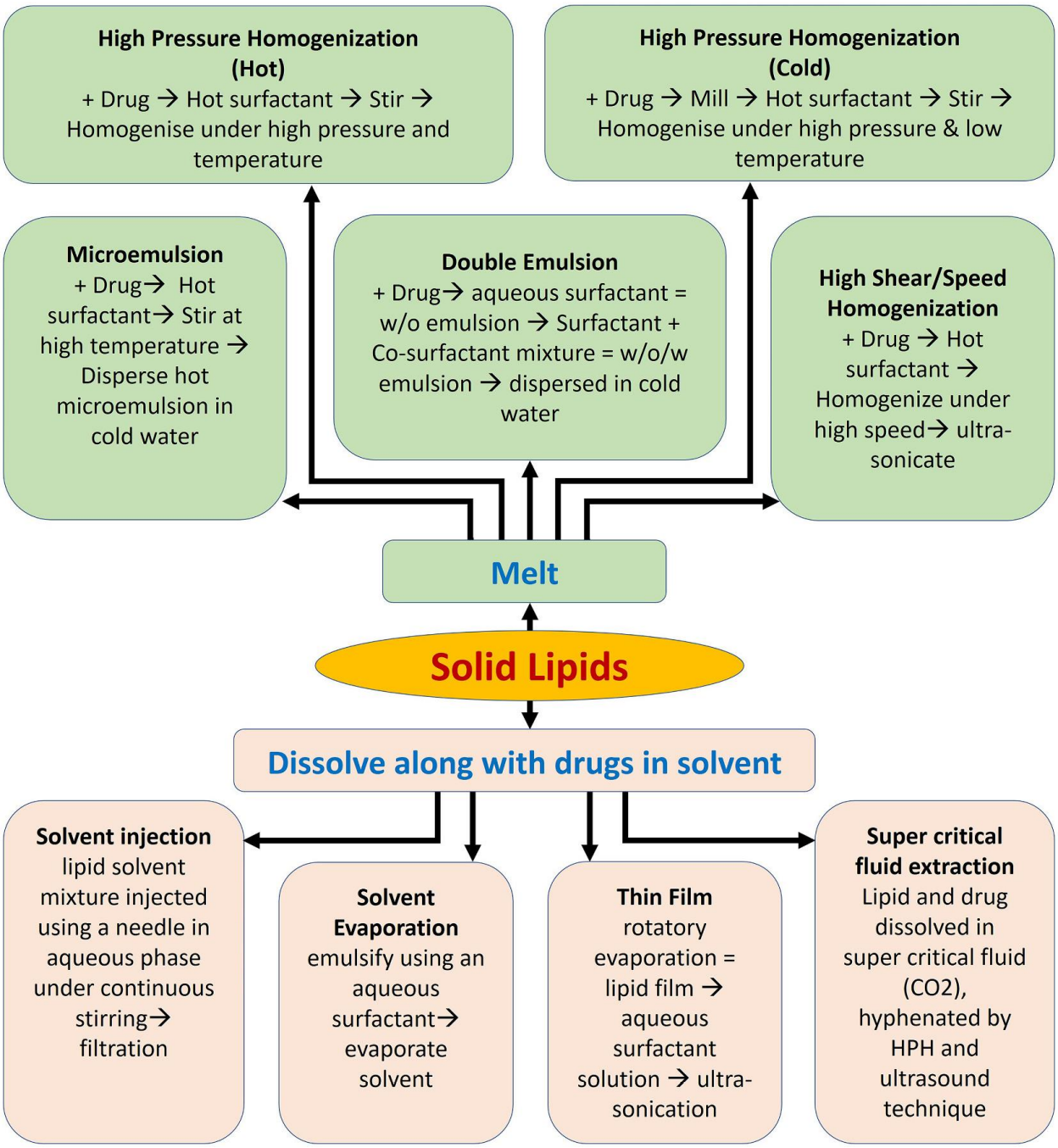

Fig no. 2 Techniques that are frequently employed to create SLNs loaded with drugs. [37]

4. Characterization of SLNs

4.1 Analytical Process of Characterization in SLNs

To accurately describe SLNs, SLN quality must be adequately described. The presence of added structure, zeta potential, crystallinity, dynamic events, lipid modification, particle size, and other parameters all directly affect stability and release kinetics. (38,39)

4.2 Measuring of zeta potential and particle size

Dynamic light scattering, or PCS, is a technique used to quantify variations in scattered light intensity brought on by moving particles and use for measuring particle size. (38,39)

4.3 Dynamic light scattering

It is a physics technique that can be used to determine the size of small particles present in the polymers or suspension in solution. In the context of DLS, where energy or photon autocorrelation energy is often used to analyze changes in the body, DLS data changes in scattering using light on a time scale in microseconds. (38,39)

4.4 Fraunhofer diffraction/Static light scattering

SLS is a technique that gathers dispersed light from a particle solution to a fundamental primary variable. (38,39)

4.5 Nuclear magnetic resonance

In nuclear magnetic resonance, atomic nuclei in the steady magnetic field are perturbed by a weakly oscillating magnetic field or near field, and the magnetic field's frequency reacts by producing electromagnetic signal characteristics. NMR is used to measure the size and quality of nanoparticles. (38,39)

4.6 Electron microscopy

TEM and SEM are the methods for measuring nano-particles and evaluating their physical properties, and the first method is used for morphological investigation. TEM detection limit size is small. (38,39)

5. Lipid modifications and Crystallinity measurements

5.1 DSC and Powder X-ray diffraction

To measure the boiling and melting temperatures of nanoparticles, one can ascertain the type and shape of crystallinity present in the particles.

X-ray scattering and DSC are extensively used for checking the lipid condition. An effective method for examining the structural characteristics of lipids is IR spectroscopy. We have not yet investigated their ability to characterize SLN dispersions. [40].

6. Determination of incorporated drug (Loading Efficiency and Entrapment Efficiency)

6.1 Ex vitro and in vivo methods to evaluate drug release from SLNs (41,42,43,)

Many drugs, including highly hydrophilic molecules, are expected to be incorporated into SLNs. Methods for studying drug release in in-vitro include parallel diffusion cells with synthetic or biological membranes.

6.2 Diffusion technique of Dialysis bag

It is a cost-effective technique for molecule separation through diffusion**.** In this method, semi-permeable membranes are used, which transport certain materials depending on their size.

6.3 Reverse dialysis bag technique.

The reverse dialysis capsule method was developed, the nanoparticle system is directly added to the medium released outside the dialysis machine, the medium released in the dialysis capsule is tested at different times, and drug release points are analyzed.

Agitation followed by ultracentrifugation or centrifugal ultrafiltration [44].

7. APPLICATIONS OF SLN

7.1 TOPICAL APPLICATIONS

In terms of regularity, there is no problem with applying cosmetics. The primary advantages of cosmetics are the occlusive effect resulting from the film that SLN generates on the skin and its anti-degradation capabilities against chemically labile substances. [45]

7.2 PULMONARY ADMINISTRATION

Unfortunately, the SLN cannot be placed in the lungs because they are too small in size and shall be expelled. The aqueous SLN dispersion can be aerosolized using a basic technique. SLN mustn't clump during aerosolization. [18]

7.3 ORAL ADMINISTRATION

Aqueous dispersions and traditional dosage forms, like tablets, pills, or capsules, bundled with SLN, are examples of oral forms of SLN. SLNs show promise for sustained release of lipophilic drugs after oral administration. Oral administration of cyclosporine to animals in lipid nano-dispersions results in increased bioavailability and prolonged plasma levels. [35]

7.4 PARENTRAL ADMINISTRATION

Intraperitoneal administration of drug-loaded SLNs will increase the release time. Also, incorporating drugs into the SLN can reduce irritation compared to injected micro-particles. [35]

7.5 TRANSDERMAL APPLICATION

Smaller diameters of SLN dispersions with a reduced lipid content (up to 5%) were noted. Due to low viscosity and low concentration of lipid dispersion, it is not suitable for dermal application on the skin. In general, it is necessary to include SLN dispersions in creams or gels to obtain formulations that shall be applied to the upper part of the skin. Increasing the amount of lipid content in SLN dispersions results in a semi-solid gel. The gel-like system used for direct skin applications and solid lipid content of dispersions results in a semi-solid. [34]

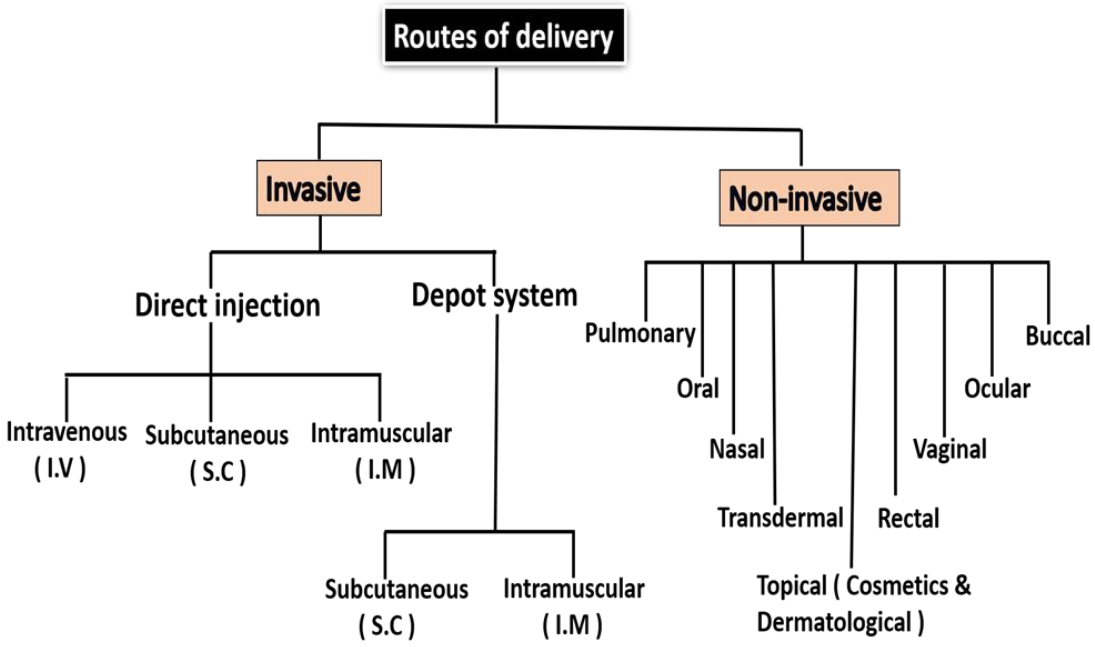

Fig no. 3 Routes of drug delivery for SLNs.

8. Future and Present Developments

The stable and efficient colloidal drug carrier technology known as SLNs can enhance medication delivery therapies. The choice of a safe and efficient structural composition (excipients) is necessary for the creation of SLNs. The excipient is a crucial component in the development of non-invasive, non-toxic, and efficient drug delivery methods. Therefore, the primary attributes that pique the interest of several research organizations worldwide are the physical-chemical properties and composition of lipids and some other components. SLNs' ability to encapsulate pharmacological actives is contingent upon the specific types and combinations of lipids employed. Different structural theories have been proposed to explain the drug and lipid carrier arrangements in SLNs and NLCs. Many researchers have examined the choice of appropriate lipids for lyophilizing and stabilizing agents, as well as for increased entrapment efficiency, in recent years. To create colloidal drug carriers, stabilization is an essential and crucial component. To achieve stability in colloidal throughout the preparation for nanoparticles, these reduce the tension between the surfaces of hydrophilic and lipophilic phases of the dispersion and make the process of forming nanoparticles simpler.[46]

Future studies will advance the efficacy profile, safety profile, and quality of pharmaceutical actives administered in non-invasive and invasive ways.[47]

9. Conclusion

This review has discussed several commonly used traditional methods for preparing SLNs, that are widely used for encapsulating hydrophobic drugs. Lipophilic molecules are intricately associated with the internal aqueous phase, effectively preventing the leakage of drugs into the external water phase during the preparation process. Consequently, it can be inferred that SLNs represent promising and secure lipid nanocarriers, capable of improving both drug entrapment and the pharmacokinetic profile of hydrophobic drugs. The potential for future advancements tests in the optimization of these SLNs loaded with drugs under the quality control standards adhered to by pharmaceutical companies for large-scale production. Thus, research groups around the world are exploring and highlighting the SLN potential in pharmaceutical science, thereby encouraging the pharmaceutical industry to accelerate its development.

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