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Comprehensive Review on Solid Lipid Nanoparticles (SLNs)

Mr. Gadkari Viraj Anil[1], Mrs. Maske Deepti N.[2]

YSPM's Yashoda Technical Campus, Faculty of Pharmacy, Wadhe, Satara
Corresponding Author E-mail : virajgadkari222@gmail.com

ABSTRACT:

Lipid nanoparticles (SLNs) represent an advance in pharmaceuticals, possessing unique advantages such as biocompatibility, biodegradability, potential for mass production, and the ability to avoid the use of organic solvents. SLNs provide greater permeability to drugs due to their small particle size and lipid structure. This class of drugs belongs to BCS class III, has poor permeability but good solubility, and is a good candidate for SLN formulation. SLNs facilitate slow and controlled release rates as well as site-specific targeting of drugs. Different mechanisms, management and clinical applications of SLN. This comprehensive review explores the multifaceted aspects of SLNs, including their composition, advantages, limitations, methods of preparation, different characterization techniques of SLNs, and therapeutic applications of SLNs.

INTRODUCTION :

Solid lipid nanoparticles (SLNs) emerged in 1991 to improve the biocompatibility, storage stability, and prevention of degradation of drug compounds. Solid lipid nanoparticles (SLN) have been introduced as water-soluble drugs and systems for drug therapy. Properties and ability to improve drug permeability and bioavailability. SLNs are generally spherical in shape and vary in diameter from 50 to 1000 nm. . Properties of SLN include lipids such as triglycerides, glyceride mixtures, or waxes that remain stable at room and body temperatures.

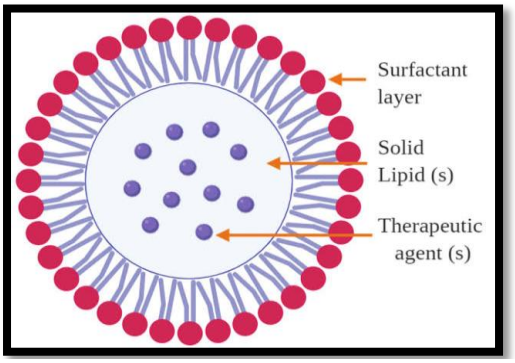

Fig.1 structure of solid lipid nanoparticles

- **ADVANTAGES :**

a. Type of controlled and/or drug release. Improve chemical stability.
b. High drug content and development (compared to other carriers).
c. It can transport lipophilic and hydrophilic drugs.
d. Most lipids are biodegradable and SLN has excellent biocompatibility.
e. Water-based technology (do not use organic solvents).

- **DISADVANTAGES :**

a. Granule growth.
b. Sedation stacks are quite limited.

- **PURPOSE OF SLNs :**

a. SLNs are said to combine the advantages and eliminate the disadvantages of other colloidal carriers. Among the recommendations –
b. Being able to control drug release and drug targeting. Lipophilic and hydrophilic drugs
c. Non-toxic carriers

d. Do not use organic solvents
e. Mass production and sterilization are no problem
f. Increase Encapsulation Bioavailability of bioactive compounds

➢ **APPLICATONS OF SLNs :**

1. Drug delivery: SLN works for drug delivery, increasing the solubility and bioavailability of poorly soluble drugs.
2. By improving the stability and penetration of active ingredients, they provide benefits such as release and better hydration of the skin.
3. Their small size and flexible positioning make them suitable for photographic focus. This increases the efficiency of these agricultural chemicals while reducing environmental impact.
4. They provide a promising platform for nucleic acid delivery and facilitate gene regulation. This may increase the effectiveness of the vaccine.
5. Potential applications for delivering drugs and food to animals by helping to improve performance and reduce side effects are in veterinary medicine.

❖ **METHODS OF SLN'S PREPARATION:**

1) High pressure homegenizer
2) Hot homogenization
3) Cold homogenization
4) Solvent emulsification.
5) By using supercritical fluid.
6) Double emulsion method.

1. High pressure homogenization :

It is a reliable and powerful machine used for the first time in SLN production. High pressure homogenizers push high pressure (100-2000 bar) liquid through narrow gaps (in the range of a few microns). The liquid accelerates to a very high speed (over 1000 km/h) over long distances. High shear stresses and cavitation forces destroy material down to the submicron range. A lipid content of 5-10% is generally used, but lipid content as high as 40% has also been investigated. In either case, the preparation step may involve applying the drug to the lipid mass by separating or dispersing the drug in the lipid solution.

2. Hot homogenization:

It is carried out at a temperature higher than the melting point of the lipid and is therefore considered homogenization of the emulsion. Pre-emulsion of the drug-loaded lipid solution and the aqueous emulsifier phase (at the same temperature) was obtained with a high shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of the pre-emulsion and it is desirable to obtain droplets of a few microns in size. In general, the higher the temperature, the smaller the size due to the decrease in the viscosity of the internal phase. However, temperature can also accelerate the degradation of the drug and carrier. The homogenization step can be repeated several times. It should be noted that high-pressure homogenization increases the temperature of the sample (approximately 10 °C at 500 bar). Generally, 3-5 homogenization cycles at 500-1500 bar are sufficient. High homogenization or multiple cycles often leads to an increase in size due to the combination of high kinetic energy of the product. The main product is a

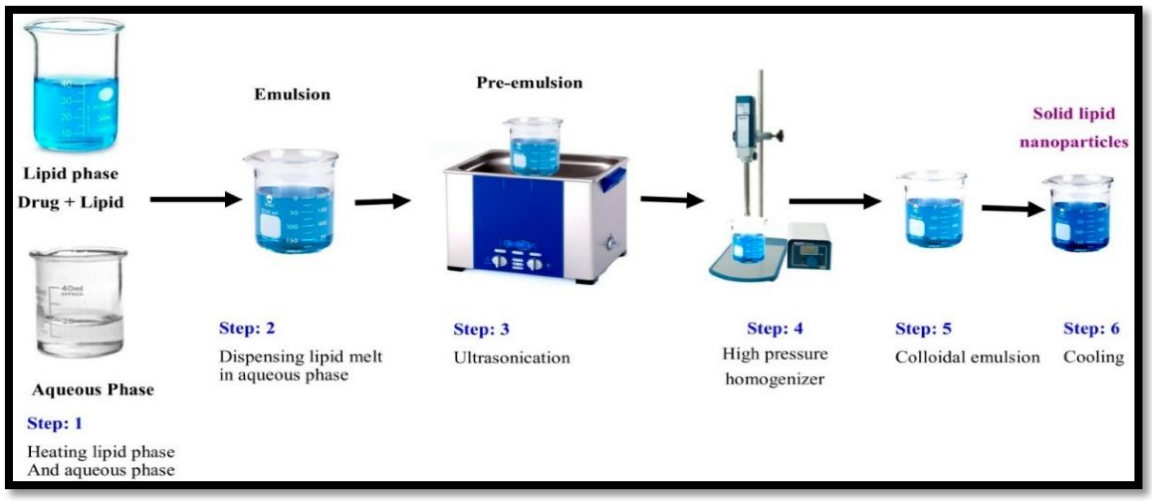

Fig.2 hot homogenization

nanoemulsion because lipids are liquid and form solids when cooled at room temperature. Due to its small size and the presence of emulsifiers, lipid crystallization will be very slow and the sample will remain in the supercooled molten state for several months

3. Cold homogenization :

The first preparation step is similar to the thermal homogenization process and involves dissolving or dispersing the drug in the lipid solution. But the next step is different. As a result, the lipid-containing drug is crushed into fine particles by ball milling/mortar milling. The resulting particle size is in the range of 50-100 microns. Freezing increases the risk of collision by increasing lipid fragility. SLN was dispersed in a cooled emulsifier solution. High-pressure homogenization of the dispersion is carried out at or below room temperature with temperature control taking into account the normal temperature rise during high-pressure processing. However, cold homogenized samples have smaller sizes and a larger difference than thermal homogenized samples. The cold homogenization method reduces but does not avoid thermal exposure of the sample due to the melting of the lipid/chemical mixture in the first step.

4. Solvent emulsification :

Nanoparticle dispersions are formed by precipitating lipophilic materials in oil-in-water emulsions. Lipophilic substances such as cholesterol acetate are dissolved in organic and emulsified in the aqueous phase. When the solvent evaporates, the lipids precipitate and form nanoparticles. In the study conducted by Sickmann and Westesen, lecithin/sodium glycocholate was used as an emulsifier and a particle size of 25-29 nm was obtained.

5. Supercritical fluid extraction :

This process uses the ability of SCF to dissolve in organic solvents, reducing the solubility (supersaturation) of solids in solution, leading to

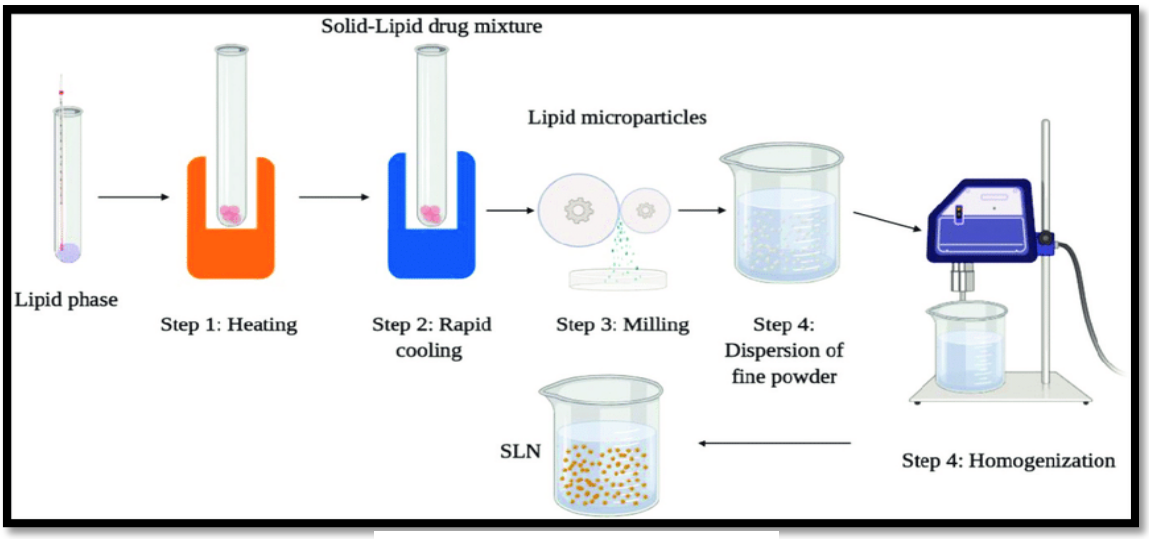

Fig.3 cold homogenization

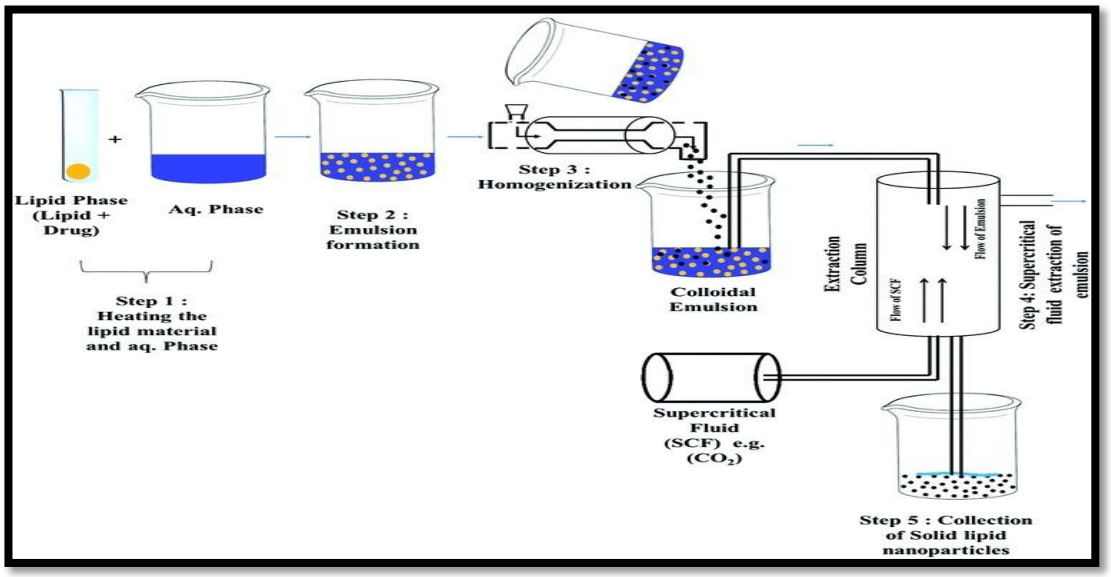

Fig.4 Supercritical fluid extraction

precipitation of solids. SCF acts as a reaction on the finished product. The dust collector is half filled with active chemicals. CO2 is then pumped to the required pressure and enters the container, preferably from the bottom, for better mixing with the solvent. After being stored for a period of time, the expanded solution is passed through the valve on the precipitator under isobaric conditions to clean and wash the precipitated particles. One of the disadvantages of this technology is that particle formation cannot be controlled. Advanced SAS technology, combining water/ethanol solution with atomization and anti-aging techniques to prepare lysozyme spherical nanoparticles.

6. Double emulsification :

To create warm water-in-oil-in-water (w/o/w) double microemulsions, a two-step process is employed. Initially, a w/o microemulsion is formed by combining an aqueous drug solution with a blend of melted lipid, surfactant, and co-surfactant at a temperature just above the lipid's melting point, resulting in a clear solution. Subsequently, this w/o microemulsion is introduced into a mixture of water, surfactant, and co-surfactant to produce a clear w/o/w system. Solid lipid nanoparticles (SLNs) can then be generated by dispersing the warm double microemulsions in cold water and washing them with a dispersion medium using an ultrafiltration system. Multiple emulsions are susceptible to inherent instabilities such as the coalescence of internal aqueous droplets within the oil phase, coalescence of oil droplets, and rupture of the layer on the surface of internal droplets. In the context of SLN production, stability is crucial for the few minutes between the preparation of clear double microemulsions and their cooling in a cold aqueous medium, a requirement that can be met.

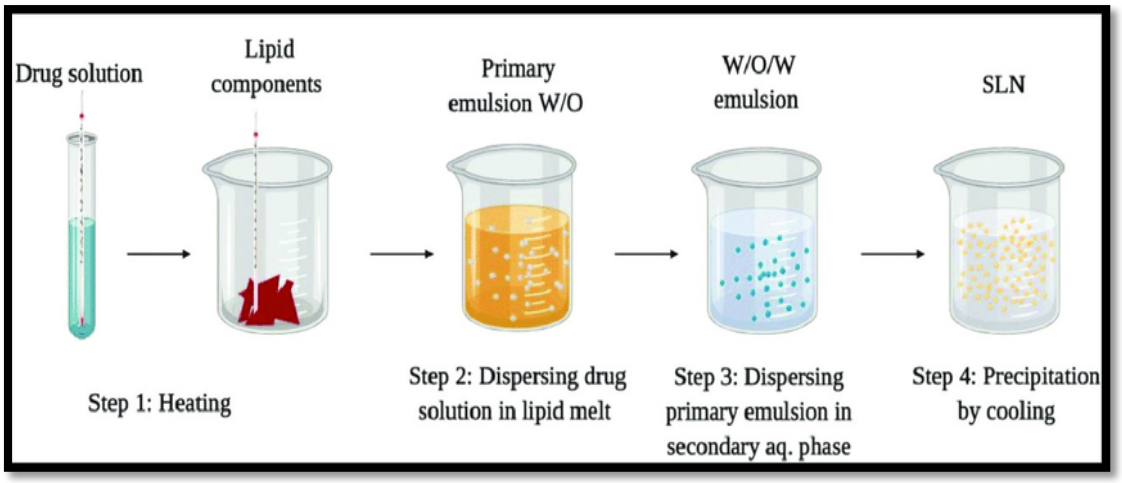

Fig.5 Double emulsification

CHARACTERIZATION OF SLNs :

Characterizing SLNs is crucial for maintaining the quality of the manufactured products. Investigators often face challenges due to the system's complexity, especially its small particle size. Several parameters need assessment due to their significant influence on stability and drug release kinetics.

SLNs can be characterized by following techniques :

SR NO.	EVALUATION PARAMETERS	CHARACTERIZATION METHOD
1.	Particle size	Particle size laser diffraction spectroscopy (LD), dynamic light scattering (DLS), size exclusion chromatography (SEC)
2.	Surface morphology	Scanning electron microscopy (SEM) Transmission electron microscopy (TEM). Atomic force microscopy (AFM)

3.	Surface load	Degree loaded Zeta potentiometer, Laser Doppler anemometer (LDA)
4	Determination of lipid polymorphisms and crystallinity	Differential scanning calorimetry (DSC) X-ray diffraction (XRD) Small angle X-ray scattering (SAXS) Thermal gravimetric analysis (TGA) Nuclear magnetic resonance spectroscopy (NMR) Infrared (IR) and Raman spectroscopy Electron spin resonance (ESR)
5.	Load capacity and entrapment efficiency	High-performance liquid chromatography (HPLC) UV spectrophotometry Fluorescence spectroscopy
6.	Release profile	In vitro release studies Fluorescence correlation spectroscopy (FCS)

1. Particle size and particle size distribution:

Particle size has a great impact on the properties and performance of SLN. Techniques such as dynamic light scattering (DLS), laser diffraction or nanoparticle detection (NTA) are used to measure particle size and distribution. Controlling particle size is important to optimize drug loading, stability, and biodistribution.

2. Surface charge (zeta potential):

Zeta potential indicates the surface charge of a nanoparticle and affects its stability and interaction with biological organisms. It is measured using techniques such as electrophoretic mobility or laser Doppler velocimetry. SLNs with high zeta potential generally exhibit better stability due to electrostatic repulsion that prevents aggregation.

Zeta potential measurements can provide information about the colloidal stability of the product and the shelf life of colloidal dispersions. \\

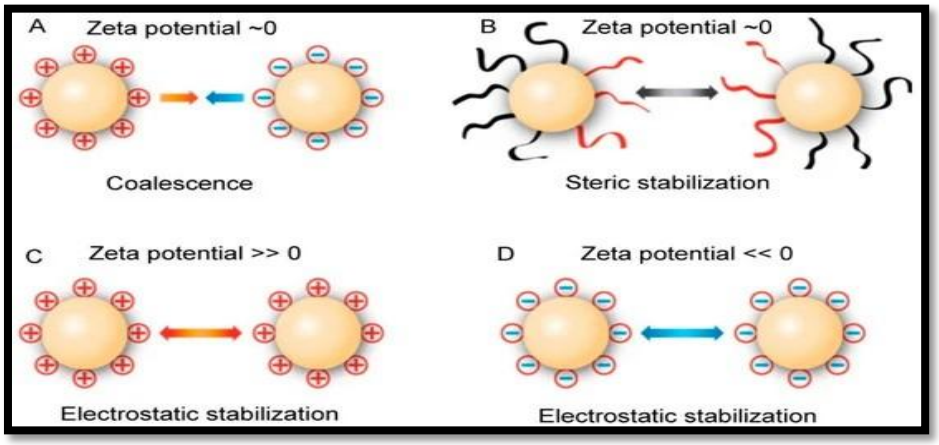

Fig.6 Zeta potential

As a general rule, high values of zeta potential (e.g. more than 30 mV) can stabilize colloidal dispersions through electrostatic repulsion under normal conditions. Electrostatic repulsion causes the particles to collide so they do not clump together. However, products with a zeta potential close to zero

can remain stable during storage. This stability can be achieved by coating with a hydrophilic polymer (e.g. PEG) to create a physical barrier that prevents aggregation. This type of stability is called steric stability. The suitability of the nanocarrier formulation for an application method depends mainly on the size, dimension and colloidal stability of the nanocarrier. Therefore, their control and effectiveness are very important for the success expected from drug nanocarrier formulations.

3. Morphology:

Electron microscopy techniques such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM) can provide detailed information about the morphology of SLNs. They help measure particle quality, surface properties, and lipid matrix integrity.

4. Determination of polymorphism and crystallinity :

Determining the polymorphism and crystallinity of lipid nanoparticles often involves techniques such as X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and Microscopy methods such as scanning electron microscopy (SEM) or transmission. . microscopy and electron microscopy (TEM). While XRD can identify different crystal forms, DSC can provide information about crystallinity by detecting phase transitions and melting points. FTIR can help identify functional groups and polymorphs. Microscopy techniques provide excellent visual and detailed information. Integrating these methods allows a comprehensive analysis of the polymorphism and crystallinity of these lipid nanoparticles.

5. Loading capacity and entrapment efficacy :

Loading capacity (DI.) and encapsulation efficiency (EF) play an important role in determining the quantity and performance of nanoparticles. API loading capacity (DL) represents the ratio of affected product to the total weight of the product, while entrainment efficiency (EE), also known as encapsulation efficiency, relates to the value of the active ingredient in the product compared to the total weight of the product.

The loading capacity (DL%) and the encapsulation efficiency (EE%) are determined using the following equations:

$$DL\,(\%) = \frac{amount\ \ ofAPI\,determined\ \ experimentally(mg)}{total\ \ weight\ \ ofSLN(mg)} \times 100$$

$$EE\,(\%) = \frac{amount\ \ ofAPI\,determined\ \ experimentally(mg)}{amount\ \ of\ \ theoreticalAPI\,in\ \ the\ \ formulation(mg)} \times 100$$

Fig.7 loading capacity and entrapment efficacy formula

Unfortunately, most research articles do not report loading capacity, and reported results range from 0.1% to 80%. Therefore, it is important to determine packaging efficiency.

1. **Chemical Release Kinetics:**
   Characterization of films released by SLNs to understand their release behavior. A variety of in vitro release studies, such as dialysis membrane diffusion, water bath, or Franz diffusion cells, are used to measure drug release kinetics over time.

2. **Stability :**
   Stability studies were conducted to evaluate the physical and chemical stability of SLN under various storage conditions. Parameters such as size, zeta potential, chemical content and physical appearance are monitored over time to assess stability and shelf life. Material, appearance and viscosity. This can be done by thin layer chromatography. The zeta potential generally needs to be kept above 60 mV for the burst to remain stable. > 50 °C - rapid particle growth is observed

3. **Tolerability and toxicity** are important for their safety. In vitro assays using cell lines or ex vivo studies in tissue models can evaluate cytotoxicity, hemocompatibility, and immunogenicity. In vivo studies in animal models provide further information on the systemic toxicity and biocompatibility of SLN.

ROUTES OF ADMINISTRATION :

Solid Lipid Nanoparticles (SLNs) are a type of nanocarrier used for drug delivery. They offer several advantages, including improved drug stability, controlled release, and the ability to target specific sites in the body. SLNs can be administered via various routes, each with its own benefits and challenges. Here are the primary routes of administration for SLNs in detail:

1. Oral Administration

- **Advantages:**
  a. Convenient and non-invasive.
  b. High patient compliance.
- **Challenges:**
  a. SLNs must withstand the acidic environment of the stomach and enzymatic degradation in the gastrointestinal tract.
  b. Potential issues with absorption and bioavailability.
- **Applications:**
  a. Used for drugs that target systemic circulation or gastrointestinal conditions.
  b. Example: Improving the bioavailability of poorly soluble drugs.

2. Parenteral Administration (Injectable)

- **Advantages:**
  a. Bypasses the gastrointestinal tract and avoids first-pass metabolism.
  b. The dosage and release of the drug can be precisely controlled.
- **Challenges:**
  a. Requires sterile preparation and can be invasive.
  b. Potential for adverse reactions at the injection site.
- **Applications:**
  a. Used for drugs requiring rapid onset of action or targeted delivery.
  b. Example: Delivering anticancer drugs directly to tumors.

3. Topical Administration

- **Advantages:**
  a. Non-invasive and easy to apply.
  b. Local delivery reduces systemic side effects.
- **Challenges:**
  a. Limited to drugs that can penetrate the skin barrier.
  b. Potential for skin irritation.
- **Applications:**
  a. Used for dermatological treatments and transdermal delivery.
  b. Example: Anti-inflammatory drugs for skin conditions.

4. Ocular Administration

- **Advantages :**
  a. Targeted delivery to the eye, reducing systemic exposure.
  b. Can provide sustained release for chronic conditions.
- **Challenges:**
  a. Requires formulation to ensure compatibility with ocular tissues.
  b. Potential for irritation or discomfort.
- **Applications:**
  a. Used for treating eye diseases such as glaucoma or retinal disorders.
  b. Example: Delivering anti-glaucoma medications.

5. Pulmonary Administration

- Advantages:
  a. Direct delivery to the lungs for respiratory conditions.
  b. Rapid absorption due to the large surface area of the alveoli.
- **Challenges:**
  a. Formulating SLNs for inhalation can be complex.
  b. Potential for irritation or allergic reactions.
- **Applications:**
  a. Used for treating respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD).
  b. Example: Delivering bronchodilators or corticosteroids.

6. Intranasal Administration

- **Avantages:**
  a. Non-invasive and convenient.
  b. Potential for bypassing the blood-brain barrier for central nervous system (CNS) targeting.
- **Challenges:**
  a. Limited by the small volume that can be administered intranasally.
  b. Potential for nasal irritation.
- **Applications:**
  a. Used for CNS drugs or vaccines.
  b. Example: Delivering peptides or hormones like insulin.

7. Rectal Administration

- **Advantages:**
  a. Useful for patients who cannot take drugs orally.
  b. Can bypass first-pass metabolism.
- **Challenges:**
  a. Limited patient acceptance.
  b. Potential for variable absorption.
- **Applications:**
  a. Used for localized treatment of rectal conditions or systemic delivery.
  b. Example: Anti-inflammatory drugs for rectal diseases.

Each route of administration has unique characteristics that must be considered when designing SLNs for drug delivery. The choice of route depends on the therapeutic goals, the properties of the drug, and patient factor.

CONCLUSION :

Solid Lipid Nanoparticles (SLNs) offer promising benefits in drug delivery, including biocompatibility, large-scale production feasibility, and avoidance of organic solvents. However, stability remains a critical challenge, influenced by factors like lipid transformations and high water content. Ensuring stability through multidisciplinary approaches and precise characterization is essential for their effective application. Addressing these challenges will be pivotal for optimizing SLNs for controlled release and long-term therapeutic use.

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