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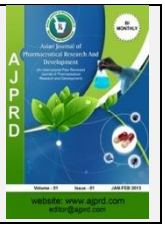

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Review Article

A Comprehensive Review on Solid Lipid Nanoparticles

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A B S T R A C T

This review provides a comprehensive analysis of solid lipid nanoparticles (SLNs) as promising drug delivery systems. SLNs have garnered significant attention due to their unique properties, including biocompatibility, controlled drug release, and improved stability. The abstract explores the key aspects of SLN formulation, emphasizing the influence of lipid composition, surfactants, and production methods on particle size, drug loading, and release kinetics. The impact of these parameters on the pharmacokinetics and therapeutic efficacy of SLN-incorporated drugs is discussed. Furthermore, the review delves into the various methods employed for characterizing SLNs, such as dynamic light scattering, transmission electron microscopy, and X-ray diffraction, highlighting their roles in ensuring product quality. The abstract also touches upon recent advancements in SLN research, including surface modification strategies and their implications for targeted drug delivery.In conclusion, this review consolidates current knowledge on SLNs, offering valuable insights into their formulation, characterization, and potential applications in pharmaceutical research. The synthesis of relevant literature provides a foundation for researchers and practitioners to navigate the evolving landscape of SLN-based drug delivery systems.

Key words: Solid lipid Nanoparticles (SLN), Ultrasonication, Stability, SEM, Administration

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INTRODUCTION:

Nanotechnology is a discipline that focuses on the deliberate manipulation of matter at the atomic or molecular scale, commonly known as the "nanoscale." This scientific field empowers researchers and engineers to conceive and fabricate materials, devices, and systems featuring distinctive properties and functionalities, all attributable to their diminutive size.Nanotechnology's ability to operate at such a small scale makes it extremely promising for advances in a range of technological, scientific, medical, and environmental fields. Scholars investigate and utilize the remarkable characteristics of nanomaterials through methods such as molecular manipulation, self-assembly, and nanolithography[1].This sector is still at the forefront of innovation and has the potential to have a big impact on many different businesses as well as daily life. In pharmacy, the primary focus is on the synthesis, characterization, and screening of nanoparticles. Nanoparticles are colloidal particles that have a size range of 10 to 1000 nm. These comprise macromolecular substances in which the medicine or biologically active ingredient is adsorbed, dissolved, encapsulated, or trapped. The word nano is derived from the Greek word "Nanos," which meaning dwarf or minuscule [2].

Many of the drawbacks of conventional drug delivery techniques include extreme adverse effects, fast degradation, low solubility, and nonspecific targeting. A promising answer to these problems is provided by nanoparticles because of their special chemical and physical characteristics.They can enhance the stability of the drug payload, prevent it from degrading, allow for prolonged release, and make it easier to distribute the medication to particular tissues or cells.Drug delivery uses a variety of nanoparticle forms, such as liposomes, dendrimers, solid lipid nanoparticles, metallic nanoparticles, and polymeric nanoparticles. Every variety has unique qualities and can be customized for certain uses. Because they can pass through a variety of biological barriers, including the blood-brain barrier, nanoparticles offer a number of benefits for drug

delivery, including the ability to deliver drugs to previously unreachable locations. With the enhanced permeability and retention (EPR) effect caused by the leaky vasculature found in tumors and inflammatory tissues nanoparticles can passively accumulate at the target site. Additionally, the surfaces of the nanoparticles can be functionalized with particular ligands or antibodies to actively target particular receptors or antigens, thereby increasing their efficacy and selectivity [3]. This tailored and accurate method minimizes harm to healthy tissues and lessens off-target effects, improving the efficacy of chemotherapy. The development and broad application of drug delivery systems based on nanoparticles, despite these encouraging benefits, still face obstacles. During their development and regulatory approval processes, concerns like possible toxicity, immune system clearance, and scale-up for mass production must be carefully considered. In conclusion, the use of nanoparticles in drug delivery systems is an innovative and revolutionary technology with enormous potential for the advancement of medicine. Nanoparticles have the potential to completely change how we treat a variety of diseases by giving patients safer, more precise, and more effective treatments as research and technology develop [4].

Solid Lipid Nanoparticles (SLNs)

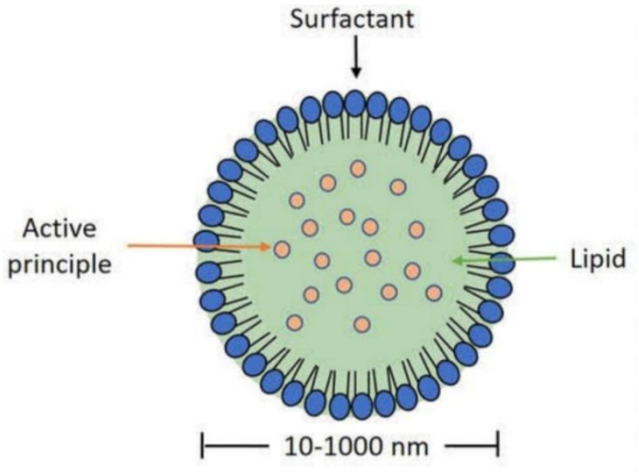


Figure: 1- Structure of Solid lipid nanoparticles

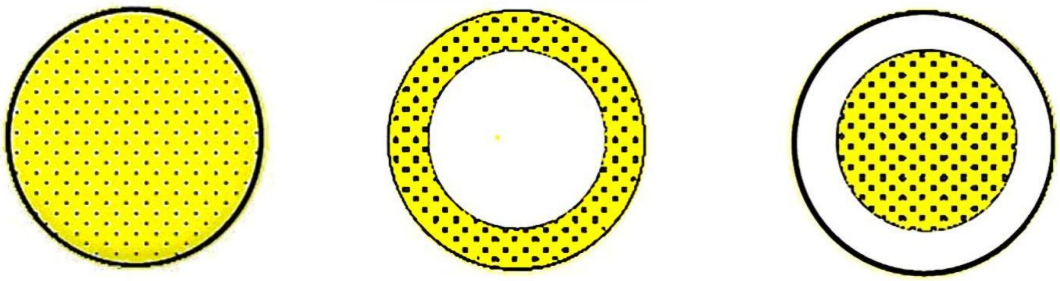
Colloidal systems made up of solid lipids and stabilized by a surfactant layer are known as solid lipid nanoparticles. The biomedical and pharmaceutical industries have shown a great deal of interest in solid lipid nanoparticles (SLNs), which are sophisticated drug delivery systems. When Gasco and Muller first presented them in 1991, they marked a significant development in the field of nanoparticle-based drug delivery technology [2,5].The primary goal of SLN development was to overcome the drawbacks of traditional liquid lipid-based delivery methods like liposomes and emulsions. Because the active ingredient in emulsions dissolves in the oily phase, there can be problems with drug leakage, instability, and possible degradation. Conversely, liposomes, which are made of phospholipids, frequently have early drug release and poor drug encapsulation efficiency [6].In contrast,solid lipid nanoparticles consist of solid lipids that combine to form a matrix that allows the active ingredient (such as drugs, therapeutic agents, or ingredients used in cosmetics) to be dissolved, entrapped, adsorbed, or attached. The encapsulated cargo is stabilized by this solid lipid matrix, which also inhibits leakage and degradation, improving drug delivery effectiveness and bioavailability [7].

The size range of the solid lipid nanoparticles is typically 50-1000 nm, with a spherical shape. The cellular uptake, drug release, and distribution are facilitated by their large surface area and small size, which increases the loaded compounds' therapeutic efficacy. Compared to conventional drug delivery methods, SLNs have a number of benefits, including better stability, reduced toxicity, controlled and sustained drug release, and improved targeting to particular tissues or cells.These characteristics make using SLNs to deliver different medications and therapeutic agents appealing. Since their discovery, solid lipid nanoparticles have been the subject of in-depth research and have been used in a variety of industries, such as drug delivery, gene therapy, cosmetics, and food [8]. In order to enhance SLNs' performance and expand their range of uses, research is still being conducted to better understand and optimize their formulations and properties. Drugs that are hydrophobic, hydrophilic, or amphiphilic can be incorporated and delivered in a stable and biocompatible environment thanks to the solid lipid matrix, which is frequently made of synthetic or natural lipids. Many different types of medications, such as nucleic acids, peptides, proteins, and small molecules, can be enclosed in SLNs [9].

Types of Solid Lipid Nanoparticles [10]

SLNs can be divided into 3 basic types on the basis of drug loading :-

1. ***Homogeneous matrix***
2. ***Drug-enriched shell***
3. ***Drug-enriched core***



A] Homogeneous matrix **B]Drug-enriched shell** **C] Drug-enriched core**

Figure: 2 Types of SLNs. A] Homogeneous matrix. B] Drug-enriched shell. C] Drug-enriched core.

Homogeneous matrix

Solid lipid nanoparticles(SLNs) with homogeneous matrices have uniform component distributions within these nanoscale drug delivery systems. Solid lipids, the medication or active ingredient, stabilizing surfactants, and a co-surfactant that is optional are important ingredients. Achieving homogeneity necessitates appropriate formulation and processing methods, such as high-pressure homogenization and ultrasonication essential for consistent drug encapsulation, controlled release, and stability. This ensures effective drug delivery and minimizes issues like crystallization or phase separation [11].

Drug-enriched shell

Drug-enriched shell solid lipid nanoparticles are a type of nanoscale drug delivery system in which the drug or active component is primarily concentrated in the SLNs' surface layer or outer shell.The medication can be released gradually from the outer layer while the inner core contains additional lipid or other components which enables precise control over drug release kinetics. This method is helpful for applications needing targeted or sustained drug release and can improve the therapeutic efficacy of the encapsulated drug [12].

Drug-enriched core

Drugs or active ingredients are concentrated in the inner core or central region of drug-enriched core solid lipid nanoparticles (SLNs). Because the drug must diffuse through the lipid matrix in order to be released, this design enables a gradual, controlled release of the drug. The drug can be stabilized and shielded from deterioration by the lipid core. This method works well in situations where it's important to protect sensitive drugs or have a longer-lasting drug release [13].

Advantages Of SLNs In Drug Delivery System [10,14]

- **Enhanced Drug Stability:**Compared to conventional formulations, the solid lipid matrix improves stability and shelf life by shielding medications from degradation.
- **Enhanced Bioavailability:** By improving drug absorption via oral, topical, and parenteral administration, SLNs can raise bioavailability and improve therapeutic efficacy [14].
- **Controlled Release:** SLNs enable controlled and sustained drug release, allowing for reduced dosing frequencies and maintaining therapeutic levels over an extended period.
- **Biocompatibility and Safety:**The risk of side effects is reduced because solid lipids used in SLNs are typically non-toxic and biocompatible.
- **Targeted Drug Delivery:**By adding ligands, antibodies or peptides to the surface of SLNs, one can actively target particular cells or tissues, lessen side effects, and enhance treatment results.
- **Ease of Manufacturing:**Since they can be prepared in a variety of ways, SLNs are reasonably simple to produce in large quantities [15].

Disadvantages [16]

- **Limited drug loading capacity:**The solid matrix and small particle size of SLNs may limit their ability to transport certain drugs.
- **Drug stability issues:** When included in SLNs, certain medications may experience deterioration or chemical instability that reduces their effectiveness and shortens their shelf life.
- **Risk of agglomeration:** Agglomeration of SLNs can lead to variations in particle size and possible problems with drug delivery consistency.
- **Clearance by the reticuloendothelial system:**The body's immune system may identify and eliminate SLNs, shortening their time in circulation and decreasing their potency [17].

KEY CONSIDERATIONS IN DESIGNING SLNs

Essential ingredients like lipids (matrix materials), emulsifiers, co-emulsifiers and water may be added to the formulation of Solid Lipid Nanoparticles (SLNs) in order to improve stability and accomplish targeted drug delivery. Various excipients used in SLNs formulation are listed in Table 01 [18].

Table 01: excipients used in SLNs formulation

Lipids	Emulsifiers	co-emulsifiers
Glyceryl tristearate	Polaxamer 188	Sodium oleate
Glycerylmonostearate	Tween 80	Butanol
Glyceryltripalmitate	Span 20	Sodium glycocholate
Compritol	Soya lecithin	Sodium dodecyl sulphate
Cetyl palmitate	Egg lecithin	Tyloxopol
Beeswax		Cholesterol hemisuccinate
Synchrowax HRSC		
Stearic acid		
Glyceryl trilaurate		
Glyceryl monooleate		
Witepsol HS		
Softisan 142		
Cyclodextrin		

Selection of lipid

The selection of lipid materials for the development of oral pharmaceutical dosage forms has been the subject of recent reviews. It is essential that lipid matrices have particular characteristics when creating solid lipid nanoparticles (SLNs) for intravenous (i.v) delivery [19].

Biocompatibility and Biodegradability: Lipid materials must demonstrate biocompatibility to ensure the absence of adverse effects upon iv.administration. Additionally, biodegradability is crucial for the eventual breakdown of lipid nanoparticles within the body.

Stability: Ensuring stability is paramount to prevent degradation during storage and administration, safeguarding the Integrity of drug-loaded nanoparticles and maintaining a consistent drug release profile [20].

Sufficient Loading Capacity: The lipid matrix should possess the capacity to encapsulate an adequate amount of the drug, guaranteeing the achievement of therapeutic concentrations.

Controlled Release: The lipid material needs to facilitate controlled and sustained release of the encapsulated drug, a key factor in achieving prolonged therapeutic effects and minimizing side effects.

Sterilizability: Lipid materials intended for iv. administration should be amenable to sterilization methods, such as filtration or heat sterilization, to ensure product safety [21].

Particle Size Control: Precise control over particle size is essential for SLNs to behave optimally in the bloodstream. Smaller particle sizes are generally preferred to minimize interactions with the vascular system and enhance drug delivery to target tissues.

Surface Charge: SLNs with a neutral or slightly negative surface charge are preferred to minimize non-specific interactions with blood components, influencing their stability and biological compatibility.

Ease of Scale-Up and Manufacturing: Chosen lipid materials should facilitate scalable manufacturing processes, enabling the production of large quantities of SLNs with consistent quality.

Compatibility with Targeted Drug Delivery: If targeted drug delivery is a goal, lipid matrices should be compatible with surface modification techniques, such as ligand conjugation, to enhance the nanoparticles targeting capabilities.

Clinical Acceptance: Lipid materials with a history of safe use in pharmaceuticals are favored, streaming the regulatory approval process [22].

Loading capacity and intended use are important factors to take into account when selecting a drug carrier system. Complex glycerides, such as hard fats, melt at body temperature, making them inappropriate for applications requiring controlled release. Longer hydrocarbon chains make glycerides more lipophilic, which increases the solubility of lipophilic drugs in lipid melts containing longer fatty acid chains.The degree of crystallinity is one of the factors that must be taken into account when choosing lipids for the formulation of solid lipid nanoparticles (SLNs).

The drug's loading capacity depends on a number of variables in lipids, such as the drug's solubility and miscibility in the lipid melt, the lipid matrix's chemical and physical makeup, and the polymorphic state of the lipid materials. Drug expulsion can result from lipids like monoacid triglycerides that form highly crystalline particles with a perfect lattice. In contrast, more complex lipids form less perfect crystals with many imperfections. Examples of these include mixtures of mono, di, and triglycerides that contain fatty acids of different chain lengths. These flaws make space for drugs without having to worry about being kicked out [23].

Selection of emulsifier

For solid lipid nanoparticles (SLNs), the choice of emulsifier needs to meet a number of important requirements in order to guarantee peak performance. In addition to being non-toxic and compatible with other excipients, the emulsifier should be able to cover the surface of the SLNs and produce the desired particle size with a small amount of input. Furthermore, the fate of the emulsifier in vivo is taken into account. The poloxamer series, for example, has the capacity to give SLNs long-circulating characteristics, which hinder uptake by the reticuloendothelial system (RES) and enable passive targeting.However, polysorbate 80-coated SLNs exhibit enhanced medication delivery to the brain [24].The literature makes clear that the emulsifier type and quantity, preparation technique, and sterilization procedure such as autoclaving can all affect the stability and size of the particles. To sufficiently cover the surface of the nanoparticles, the right amounts of emulsifier are essential. An increase in particle size and particle aggregation may result from insufficient amounts. On the other hand, surfactant-related toxic effects, burst release seen in SLN release studies, and a decline in entrapment efficiency can all be avoided by avoiding excess emulsifier.Trotta and colleagues examined how emulsifiers affected the size of solid lipid nanoparticles (SLNs).Trotta et al. were able to create solid lipid nanoparticles (SLNs) by using glyceryl monostearate in conjunction with a variety of emulsifiers [25].

Selection ofco-emulsifier

Different from conventional emulsifiers, phospholipids added to the formulation of solid lipid nanoparticles (SLNs) display unique properties. They do not form highly dynamic micelles nor are they soluble in the continuous phase. Excess phospholipid molecules have a tendency to group together and form tiny, primarily unilamellar vesicles during the homogenization process. When these phospholipid molecules are attached to vesicles, their mobility is restricted. Thus, when solid lipids recrystallize, they are unable to quickly cover recently formed interfaces. Phospholipid molecules' low mobility increases the possibility of an abrupt emulsifier shortage on the particle surface, which can cause particle aggregation and a rise in the size of SLN particle. Co-emulsifiers like tyloxapol a nonionic polymer and an ionic glycocholate are used to solve this problem.These emulsifiers that dissolve in water have the capacity to form micelles. Interestingly, compared to vesicles, polymer molecules can diffuse to the particle surface more quickly.Micelles are extremely dynamic colloidal structures that serve as storage units. However, because of the potential for toxicity, it is advised against using surfactants that distribute quickly, such as sodium lauryl sulphate. Co-emulsifier selection must be done carefully in order to guarantee the stability and security of SLN formulations [26].

Solubility studies

Understanding the drug's affinity for the nanoparticle matrix and determining the ideal drug-to-lipid ratio are critical steps in determining the solubility of drugs in lipids or lipid combination. Solubility studies are a common part of studying solid lipids, and they are typically performed by heating the lipids to a temperature that is 10°C above their melting point. Small doses of the medication are added gradually throughout the procedure until lipid saturation is achieved. When there is an excess of solid medication that lasts longer than eight hours, saturation is recognized.This technique helps to design nanoparticle formulations with improved stability and drug-loading capacities by offering insightful information about how drugs and lipids interact [27].

PREPARATION METHODS OF SLNs

A. High-pressure homogenization
   - Hot homogenization
   - Cold homogenization

B. Ultra-sonication /high speed homogenization
   - Probe ultra-sonication
   - Bath ultra-sonication

C. Solvent emulsification-evaporation method

D. Solvent emulsification-diffusion method

E. Microemulsion base method

F. Membrane contractor method

G. Double emulsion method

H. Supercritical fluid method

I. Solvent injection method

J. Spray drying method

A. High-pressure homogenization:

Solid lipid nanodispersions were first produced using the high-pressure homogenization approach, which is a commonly used and manageable technology. However, the existence of microparticles frequently degrades the dispersion's quality. A study on the high-speed homogenization technique for produced solid lipid nanoparticles (SLN) was carried out by Olbrich et al.The study examined the effects of several process variables on particle size and zeta potential, including emulsification time, stirring rate, and cooling conditions.The lipids used in the investigation were glycerol behenate, trimyristin, and tripalmitin, a combination of mono, di, and triglyceride. Moreover, a 0.5% w/w concentration of poloxamer 188 was employed as a steric stabilizer. For Witepsol W35 dispersions, 8 minutes of 20,000 rpm stirring was followed

by 10 minutes of cooling and then 5 minutes of room temperature stirring to obtain the best SLN quality [28].

- ***Hot homogenization:***

hot homogenization is processing at temperatures higher than the lipid's melting point. The drug-loaded lipid melt and the aqueous emulsifier phase are mixed at high shear and kept at the same temperature using a high-shear mixing apparatus such as a Silverson-type homogenizer to create a pre-emulsion.The quality of the pre-emulsion has a major impact on the outcome, and droplets with a size range of a few micrometers are excellent.Above the lipid melting point, the pre-emulsion undergoes high-pressure homogenization. Higher processing temperatures usually result in lower particle sizes because of the lipid phase's decreased viscosity, but they can also hasten the drug and carrier's breakdown.When the pre-emulsion is sent through the high-pressure homogenizer (HPH) multiple times, usually between three and five runs, the best results are obtained.The sample temperature rises (by around 10°C at 500 bar) during the high-pressure processing. Generally speaking, three to five homogenization cycles at pressures between 500 and 1500 bar are sufficient.It's crucial to remember that increasing the number of homogenization cycles may cause particle coalescence, a phenomena fueled by the particles' high kinetic energy, which might result in an increase in particle size [29].

- ***Cold homogenization:***

In the cold approach, the drug-lipid melt is ground in a mortar or ball mill after being cooled with liquid nitrogen or dry ice. After that, the powder is mixed with a cold aqueous-surfactant solution and homogenized at room temperature or below using a high-pressure homogenizer.The high-pressure homogenization technique is inexpensive and easy to use. The hot method's requirement for high temperatures during homogenization, however, limits the use of thermolabile medications.This problem is effectively resolved by cold homogenization, which is a proven and useful process for large-scale production that does not require organic solvents [30].

B. Ultrasonication/ high speed homogenization:

The procedure entails heating the drug-lipid mixture over the melting point of the lipid and then using a high-shear mixer to disperse it into an aqueous-surfactant solution that is kept at the same temperature.The resultant emulsion is then cooled to room temperature to produce the final nanoparticles, after which it is ultrasonically sonicated to reduce particle size. It's crucial to remember that the possibility of metal contamination during the ultrasonication procedure is a possible disadvantage [31].

C. Solvent emulsification-evaporation method:

Water-immiscible organic solvents,like dichloromethane, cyclohexane, toluene, and chloroform, are used in this technique to produce Solid Lipid Nanoparticles (SLNs) by the solvent emulsification-evaporation method.This procedure involves dissolving the medication and lipids in a selected solvent or mixture of solvents, and then emulsifying the resultant solution in an aqueous phase to produce nanodispersions.The organic solvent is then eliminated using a rotary evaporator or mechanical stirring. Solid Lipid Nanoparticles are created when lipids precipitate after the solvent evaporates [32].

D. Solvent emulsification-diffusion method:

In 2003, Trotta et al. pioneered the preparation of Solid Lipid Nanoparticles (SLNs) using the solvent emulsification-diffusion process, which is mainly used for the synthesis of polymeric nano-carriers. Typically, this method uses organic solvents including butyl lactate, methyl acetate, ethyl acetate, isopropyl acetate, and benzyl alcohol that show partial miscibility with water.The process starts with mutual saturation between the water and the organic solvent, which creates the first thermodynamic equilibrium for both phases.Then, after dissolving the medicines and lipids in the water-saturated solvent, the mixture is emulsified under stirring to create an oil-in-water (o/w) emulsion in the aqueous phase, which consists of solvent-saturated water with a stabilizer.After that, the emulsion is diluted with water (at a volume ratio between 1:5 and 1:10) to facilitate the solvent diffuse into the continuous phase. Solid Lipid Nanoparticles (SLNs) are produced spontaneously by lipid precipitation, and the solvent is extracted by vacuum distillation or lyophilization [33].

E. Microemulsion based method:

Microemulsions are dispersions that are transparent, thermodynamically stable, and microheterogeneous. They are made up of water, a surfactant, a co-surfactant, and a lipophilic phase (lipid). The synthesis of Solid Lipid Nanoparticles (SLNs) was accomplished by the Gasco research group using this technique. This approach involves first melting a lipid (fatty acid/glyceride) and then dispersing the medication into the molten lipid. Simultaneously,the temperature of a solution containing water, surfactant, and co-surfactant is raised to a level that is at least as high as the lipid's melting point.A transparent microemulsion is produced by adding the aqueous surfactant solution to the lipid melt while gently stirring.Then, with gentle mechanical stirring, this microemulsion is dispersed in cold water (2°C–10°C), with volume ratios of the heated microemulsion to cold water ranging from 1:25 to 1:50. Solid Lipid Nanoparticles are created when oil droplets quickly recrystallize after being dispersed in a cold aqueous media (SLNs). Importantly, SLNs are generated through the precipitation process rather than the stirring itself.The resultant dispersion of lipid nanoparticles can be lyophilized after being washed with water using diafiltration.The surfactants and co-surfactants utilized in this technique include butanol, taurodeoxycholate sodium, lecithin, and bile salts [34].

F. Membrane contractor method:

In this method, a drug-lipid melt is driven through a hydrophobic porous membrane into an aqueous-surfactant solution circulating within the membrane module.When the aqueous phase cools to room temperature, the lipid droplets are successfully removed, which eventually leads to the creation of nanoparticles. This method's main advantages are its ease of use and its capacity for continuous output [35].

G. Double emulsion method:

There are two steps involved in the generation of warm w/o/w double microemulsions. First, a clear system is created by adding an aqueous solution containing the medication to a mixture of melted lipid, surfactant, and co-surfactant at a temperature slightly above the melting point of the lipid. This creates a w/o microemulsion. A transparent w/o/w system is produced in the second step by mixing the resulting w/o microemulsion with a solution of water, surfactant, and co-surfactant. The warm double microemulsions can be dispersed into cold environments to produce solid lipid nanoparticles (SLNs), which can then be cleansed using an ultrafiltration system with a dispersion medium.Instabilities such as the coalescence of internal aqueous droplets within the oil phase, the coalescence of oil droplets, and the rupture of the layer on the surface of the internal droplets are intrinsic to multiple emulsions. For the short time between creating the transparent double microemulsions and quenching them in a cold aqueous media, stability is vital in the SLNs production process. During this time frame, this stability can be attained [36].

H. Supercritical fluid method:

This is a relatively new technique that has the remarkable benefit of not requiring the use of solvents in the production of solid lipid nanoparticles (SLNs). There are several variations available within this powder and nanoparticle preparation platform technology.The Rapid Expansion of Supercritical Carbon Dioxide Solutions (RESS) technique is specifically capable of producing SLNs. Notably, the procedure works exceptionally well using carbon dioxide (99.99%) as a solvent [37].

I. *Solvent injection method*:

A water-miscible organic solvent, such as methanol, acetone, or isopropanol, or a combination of water-miscible solvents, is used to dissolve lipids and active components. The organic solution is then stirred while being injected via an injection needle into an emulsifier aqueous solution. Precipitation of nanoparticles and solvent migration are caused by this injection process. This technology has several noteworthy benefits, such as simple equipment, ease of handling, and quick output [38].

J. Spray drying method:

A more economical and non-lyophilization method uses lipids that have a melting point higher than 70°C.Use of solid lipid nanoparticles (SLN) at 1% concentration in a trehalose in water solution or a 20% trehalose in ethanol and water mixture produced the best results. Maintaining the colloidal particle size throughout the spray-drying process is facilitated by the addition of carbohydrates and a low lipid content. Ethanol-water combinations are favoured over pure water to reduce lipid melting because they produce smaller, more uniform crystals at lower inlet temperatures. Ethanol-water combinations are favoured over pure water to reduce lipid melting because they produce smaller, more uniform crystals at lower inlet temperatures [39].

CHARACTERIZATION OF SLNs [40-45]

For efficient quality control, solid lipid nanoparticles (SLNs) must be accurately and completely characterized. Nevertheless, because of the delivery system's complexity and dynamic nature as well as the particles' colloidal size, characterizing SLNs is a difficult task.Particle size, degree of crystallinity, lipid modification (polymorphism), presence of additional colloidal structures (like micelles, liposomes, supercooled melts, and drug nanoparticles), timescale of distribution processes, drug content, in vitro drug release, and surface morphology are important parameters that need to be evaluated for SLNs [40]

Particle size:

Solid lipid nanoparticles can be evaluated for size, shape, and surface properties using a variety of techniques, such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and photon-correlation spectrometry (PCS). Electron cannon are used in scanning electron microscopy (SEM) to produce a regulated electron beam. After that, the beam is guided through the microscope vertically until it comes into contact with the samples. When the samples collide, they release X-rays and electrons. The X-rays and dispersed electrons are then collected by detectors, allowing for the production of a three-dimensional image of the sample.Nanoparticles (NPs) can be better understood by using SEM, which provides information on their size, shape, aggregation, and dispersion. In TEM, the analyte, which is usually made up of extremely small particles, is crossed by a high-energy electron beam.These electrons' interactions with the analyte's atoms allow for the identification of specific features like grain boundaries and dislocations, as well as aspects like crystal structure [41].

Measurement of crystallinity:

To describe the quality of solid lipid nanoparticles (SLNs), attention must be paid to lipid crystallinity evaluation in addition to particle size analysis. The process of X-ray diffraction analysis (XRD) involves subjecting a material to incident X-ray radiation and then determining the scattering angles and intensities of the resulting X-rays. It is a widely used technique to analyse the phase and crystallinity of nanoparticles (NPs). However, when samples have highly amorphous properties with varying interatomic distances or when the NPs are on a scale smaller than several hundreds of atoms, the accuracy and resolution of XRD may be affected [42]

Zeta potential analysis:

Zeta potential values are often used to estimate the surface charge magnitude in aqueous dispersions through the use of electroacoustic or electrophoretic mobility measurements.Zeta potential can be estimated using methods like dynamic light scattering (DLS) and laser diffraction (LD), which can be used as markers of the long-term physical stability of nanoparticles. It has been reported that absolute values greater than 30 mV are required in order to guarantee stability mainly through electrostatic interactions. Nevertheless, an absolute value of 20 mV is considered adequate for nanoparticle stabilization when surfactants are used to provide steric stabilization [43].

Entrapment efficiency:

Quantifying the amount of drug present in solid lipid nanoparticles (SLNs) is important since it affects the release properties. The percentage of the total amount of medicine

added to the particle that is incorporated into it is known as entrapment efficiency.Separating the free drug and solid lipids from the aqueous medium allows one to calculate the amount of drug encapsulated per unit weight of nanoparticles. For this separation procedure, methods like gel permeation chromatography, centrifugation, and filtration can be used [44].

$$\text{Entrapment efficiency (EE)} = \frac{\text{Amount of drug in nanoparticles}}{\text{Initial amount of drug}} \times 100$$

In-vitro drug release from SLNs

Dialysis tubing is used to accomplish in vitro medication release. The solid lipid nanoparticle dispersion is inserted into dialysis tubing that has been previously cleaned and sealed hermetically.The dialysis sac is then dialyzed at room temperature against an appropriate dissolving media. Samples are taken out of the dissolution medium at predetermined intervals, centrifuged, and then their drug content is determined using the proper analytical technique [45].

ROUTE OF ADMINISTRATION

Solid lipid nanoparticles show great promise as drug delivery vehicles for a range of delivery routes, such as oral, parenteral, topical, intranasal, ophthalmic, and pulmonary [46].

Oral administration:

Solid Lipid Nanoparticles (SLNs) are a promising drug delivery method that can be administered orally because of their many benefits, including patient compliance, simplicity, and cost effectiveness. Drugs that are formulated in lipid nanoparticles for oral administration have many benefits, such as improved GI tract drug solubilization, protection for drugs that are labile, potential controlled release characteristics, longer residence times, and the possibility of selective drug delivery.Additionally, nanoparticles absorb via lymphatic flow, which increases their bioavailability and prolongs their half-life.This is especially advantageous for medications that are metabolized by the liver in the first pass.Lipid nanoparticles work well in situations where the medicine has hazardous byproducts. The potential of Solid Lipid Nanoparticles (SLNs) for the oral delivery of different medications and natural items to treat a range of diseases has recently been explored by researchers. Treatments for ailments like cancer, illnesses of the central nervous system, heart disease, infections, diabetes, and osteoporosis are among them [47].

Parenteral administration:

For the delivery of bioactive pharmacological agents with limited bioavailability and narrow therapeutic index values, parenteral administration is the most effective form of administration. This is especially true for medications prescribed for patients who are unconscious.Subsequently, sophisticated systems that provide sustained or regulated release of parenteral drugs as well as drug targeting have been developed as a result of major technological developments in parenteral drug delivery. Oral administration of proteins and peptide medicines necessitates frequent compensation due to their high susceptibility to enzymatic breakdown. Notably, parenterally administered Solid Lipid Nanoparticles (SLNs) with regulated drug release mechanisms have become viable therapeutic approaches.These formulations address issues with patient adherence and the requirement for frequent administration in addition to providing controlled medication release. quick clearance by the reticuloendothelial system is the main drawback to their intravenous delivery.This difficulty can be lessened by altering the surface with substances like Pluronic F68 or polyethylene glycol [48].

Topical administration:

The topical use of Solid Lipid Nanoparticles (SLNs) is a novel drug delivery method that has many benefits for dermatological uses.SLNs, which are lipid-based colloidal carriers, offer a special platform for the regulated delivery of medications through the skin. Their large surface area and tiny particle size allow for better medication absorption and bioavailability.Furthermore, lipophilic medications are better soluble in lipid-rich SLNs, which aids in their efficient distribution to the desired skin layers.In addition, SLNs' biocompatibility and stability make them appropriate for topical applications.Moreover, SLNs can be modified for prolonged release, which reduces application frequency and improves therapeutic results.SLNs can be used for a wider range of dermatological problems since they have the ability to contain both hydrophobic and hydrophilic medicines. All things considered, topical SLN delivery shows potential for improving the effectiveness and patient adherence to dermatological therapies [49].

Intranasal delivery:

A viable and non-invasive option for medicine delivery is intranasal administration. By avoiding the breakdown of delicate medications like peptides and proteins in the digestive system, this method provides quick absorption and onset of drug action.It also tackles issues with insufficient transport through epithelial cells. Intranasal delivery of medication is a feasible and non-invasive approach. Solid lipid nanoparticles (SLNs) administered intranasally are a novel and exciting development in the realm of medication delivery. Solid lipid nanoparticles provide a stable and controlled substrate for the encapsulation of different medicinal medicines because they are made of biocompatible lipids.When SLNs are delivered intranasally, they can quickly and directly penetrate the systemic circulation by using the extensive surface area of the nasal mucosa and its rich vascular network.For medications that have a low bioavailability or are vulnerable to enzymatic breakdown in the gastrointestinal system, this delivery method is very beneficial. Furthermore, compared to conventional administration techniques, the nasal route is a non-invasive, patient-friendly option that may improve patient compliance. Solid lipid nanoparticles have special physicochemical characteristics that promote drug solubility and sustained release while also increasing therapeutic efficacy. These characteristics include their tiny particle size and high surface area.Overall, the intra-nasal administration of solid lipid nanoparticles has a lot of potential for improving drug delivery, permitting increased

bioavailability, and providing focused therapy for a range of medical disorders [50].

Ocular administration:

The ocular administration of solid lipid nanoparticles has emerged as a promising strategy to address challenges associated with conventional ocular drug delivery.Rapid drug clearance after administration is a major challenge for ocular formulations.This problem is addressed by SLNs because of their lipid matrix and small particle size, which promote enhanced corneal penetration and extended drug release.This novel strategy increases bioavailability, reduces the requirement for repeated doses, and offers a possible means of improving patient adherence.Moreover, the chance of ocular discomfort is reduced by SLNs' biocompatibility. Enhancing the accuracy and effectiveness of ocular medicine delivery is possible with the use of solid lipid nanoparticles administered intraocularly[51].

APPLICATIONS

- **Cancer Therapy:**SLNs have demonstrated promise in the delivery of anticancer medications, enhancing their therapeutic index through more precise tumour targeting and decreased systemic toxicity.
- **Neurological Disorders:**The blood-brain barrier can be crossed by SLNs, allowing for the targeted delivery of medications to the brain to treat neurological conditions.
- **Infectious Diseases:** SLNs have been explored for the delivery of antimicrobial agents to combat infectious diseases caused by bacteria, viruses, and fungi [52].
- **Skin Disorders:**SLNs provide regulated medication release and improve drug penetration into the skin layers in topical formulations used to treat skin conditions.
- **Gene Delivery:** SLNs can deliver nucleic acids, such as siRNA and mRNA, for gene therapy applications [53].

CONCLUSION

Solid lipid nanoparticles (SLNs) have garnered considerable attention from researchers due to their exceptional properties and advantages over conventional dosage forms. The unique attributes of SLNs, such as improved stability, enhanced bioavailability, and the ability to encapsulate both hydrophilic and hydrophobic drugs, make them a focal point in pharmaceutical research. This heightened interest underscores the potential of SLNs to overcome limitations associated with traditional drug delivery systems, paving the way for innovative and improved therapeutic approaches.

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