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SOLID LIPID NANOPARTICLES: MODERN FORMULATION TECHNIQUES IN THE FIELD OF DRUG DELIVERY

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ABSTRACT

The versatile applications of solid lipid nanoparticles (SLN) span across numerous domains including drug delivery, clinical medicine, research, and other scientific fields in nanotechnology. Early in 1990s, solid lipid nanoparticles were introduced as a replacement for traditional colloidal systems like liposomes, polymeric nanoparticles, and emulsions as they boast advantages like controlled drug release, targeted delivery, and enhanced stability. In recent times, SLNs have gained significant importance as drug delivery systems for incorporating hydrophilic and lipophilic substances. The nanoparticles, in the form of spheres with a nanometer range, are suspended in water or aqueous surfactant solutions, allowing for the presence of both lipophilic and hydrophilic drugs. The challenge of enhancing the solubility and bioaccessibility of poorly soluble drugs can be met by utilizing distinct biocompatible and biodegradable polymers, which can provide superior outcomes in terms of drug efficacy and safety while reducing the negative impacts of traditional drug delivery systems. Therapeutic proteins and antigens can be attached or integrated into SLN and the medication could continue to be given through injection sites or other methods like tablets, nasal sprays, and inhalers.

Keywords: Nanoparticles, Targeted Delivery, Lipid-based systems, Bioaccessibility.

1] INTRODUCTION

SOLID LIPID NANOPARTICLES (SLN)

In place of emulsions, liposomes, and polymeric micro- and nanoparticles, solid lipid nanoparticles (SLN) are presented in 1991 as an innovative carrier system. Solid lipid nanoparticles are generating significant interest as innovative colloidal vehicles for intravenous drug delivery, serving as proposed substitutes for existing particulate carrier systems[1]. SLN, which are sub-micron colloidal particles, comprise physiological lipids that have a size range of 50 to 1000 nm, and can be found suspended in water or aqueous surfactant solutions. The distinctive features of SLN, including small dimensions, expansive surface area, substantial drug capacity, and interface phase interaction, make them alluring for enhancing pharmaceutical efficacy.[2, 3, 4]

Lipid-based systems have garnered significant attention for various reasons, among which are,

1. The presence of lipids increases the effectiveness of oral medication and decreases plasma level inconsistencies.
2. Enhanced description of lipid-based formulations' components.
3. A more effective approach to addressing the significant issues related to technology transfer and manufacturing scale-up in pharmaceuticals.

Oil-like solid lipid nanoparticles serve as innovative colloidal vehicle options in place of polymers for parenteral nutrition, equivalent to oil-in-water emulsions, the emulsion's liquid lipid has been swapped for a solid lipid, as shown in Fig. 1.

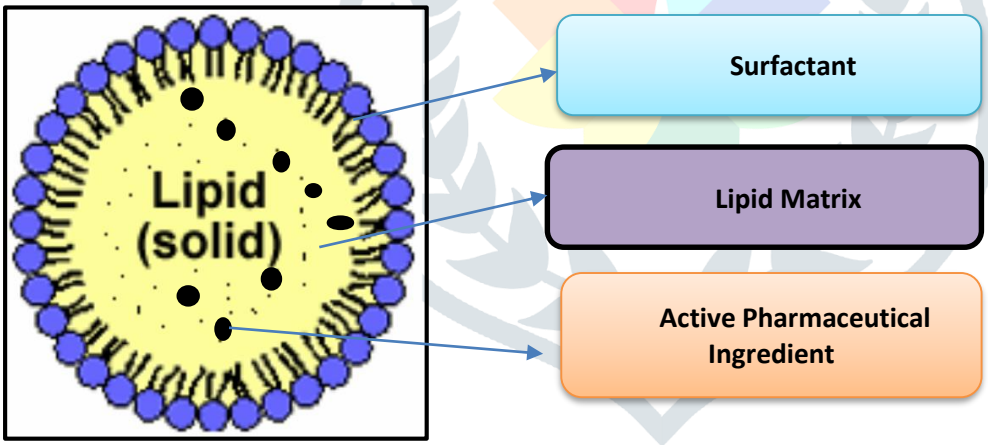


Fig. no.1: Structure of solid lipid nanoparticle (SLN)

The disadvantages of using a liquid lipid in the oil droplets were eliminated by converting it into a solid lipid, which subsequently formed solid lipid nanoparticles.

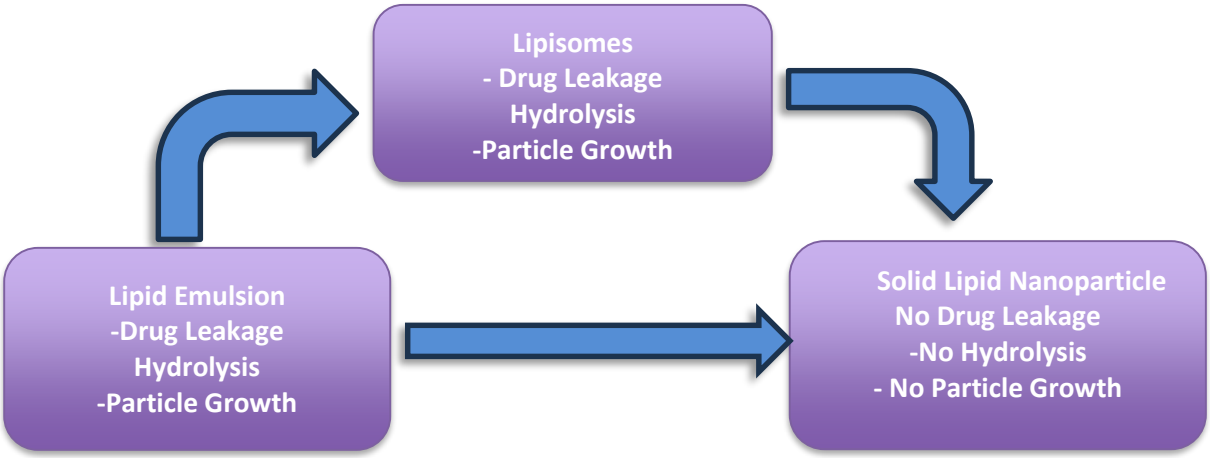
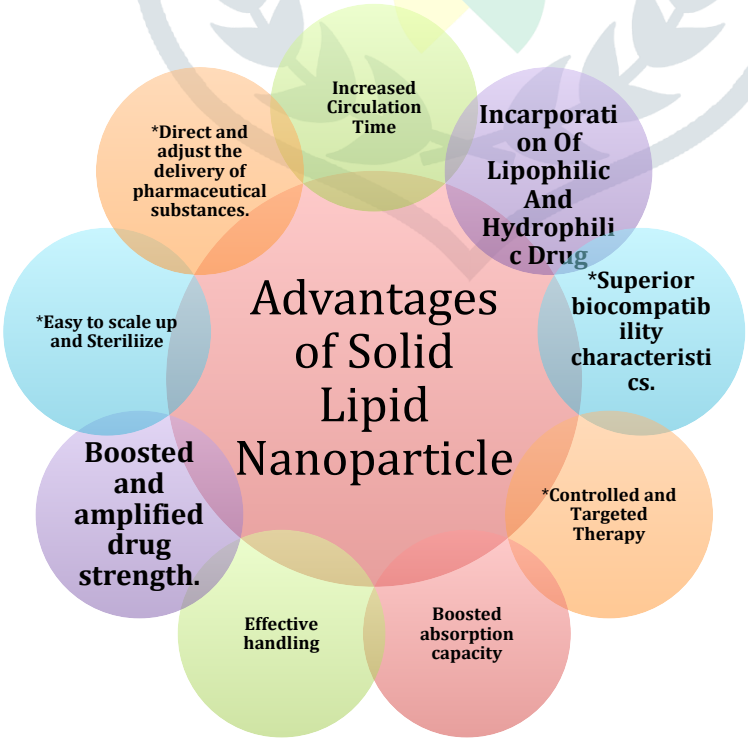


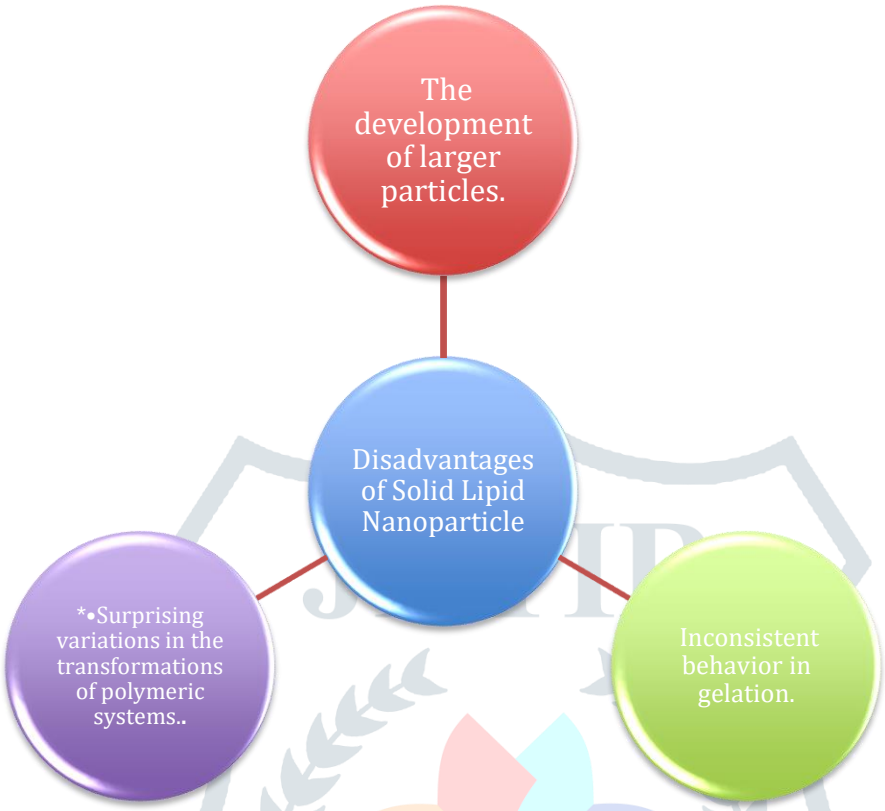
Fig. no.2: A diagrammatic representation on SLN over emulsions and liposomes.

SLNs, introduced in the early nineties, are recognized as the most efficient lipid-based colloidal delivery systems in the form of solid nanoparticles. One commonly used method to enhance the oral absorption of poorly water-soluble drugs is this approach. SLNs, measuring around 50-1000 nm in the submicron size range, consist of physiologically acceptable lipid elements that remain solid at room temperature. Figure 2 displays a comparison of the schematic diagrams of diverse particulate drug carriers, such as emulsions and liposomes, and their respective advantages with those of SLNs. SLNs integrate the advantages of polymeric nanoparticles, fat emulsions, and liposomes

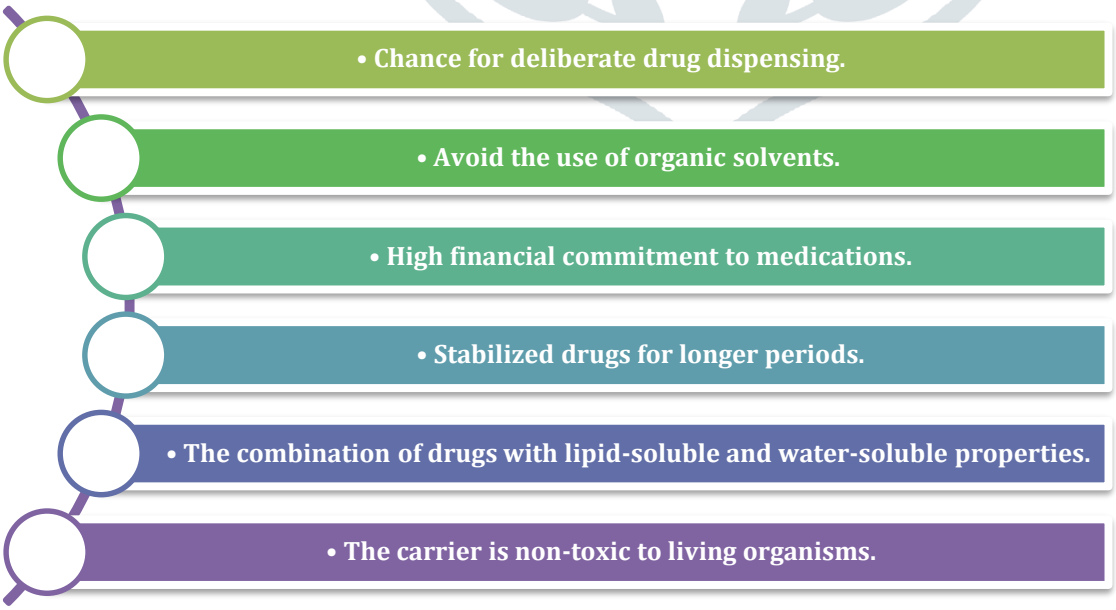
1.1] ADVANTAGE OF SLN [4, 5]



1.2] DISADVANTAGE OF SLN [4, 5]



2] AIMS OF SOLID LIPID NANOPARTICLE [5, 6]



3] DEVELOPMENT OF LIPID NANOPARTICLE [7]

The first experiments in producing lipid nanoparticles were conducted in academic labs in 1990. M. R. Gascoin in Italy, R. H. Muller, and J. S. Lucks in Kiel, North Germany, developed lipid nanoparticles independently at the same time. The particle matrix of these novel carriers is made of a solid lipid, making them different from nanoemulsions and fluid liposomes, which are called solid lipid nanoparticles (SLN). The term nanostructured lipid carriers (NLC) was adopted for the second generation of lipid nanoparticles in 1999. The matrix of these particles consists not just of lipids but also a combination of solid and liquid lipid oils. The superiority of NLC over SLN lies in its ability to accommodate a larger quantity of lipid-soluble substances. In contrast, SLN has a limited capacity for hydrophilic compounds.

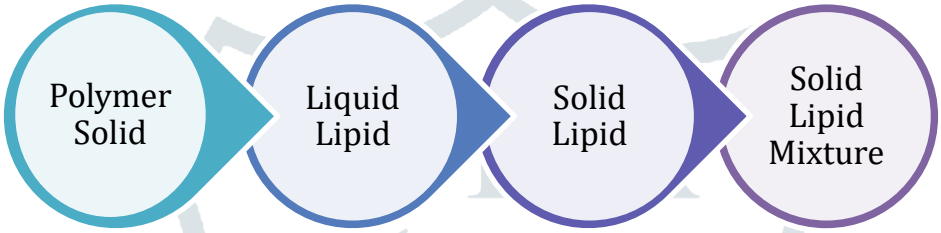


Fig no 3. Traditional Carriers and Lipid Nanoparticles

4] CHOICE OF DRUG CANDIDATES[8]

The Biopharmaceutical Classification System (BCS) functions as a valuable initial reference for identifying potential candidates for Solid Lipid Nanoparticles (SLNs). This classification separates chemical compounds into four classes. Compounds in class II possess high solubility and low permeability, while those in class IV have low solubility and low permeability. Therefore, compounds from classes II and IV are the prime choices for creating solid lipid nanoparticles.

Sr. No.	Property	SLN	Polymer Nanoparticles	Liposomes	Lipid Emulsions
1	Systemic toxicity	Low	> or = to SLN	Low	Low
2	Cytotoxicity	Low	> = to SLN	Low	Low
3	Residues from organic solvents	No	Yes	May or may not	No

4	Large scale production	Yes	No	Yes	Yes
5	Sterilization by autoclaving	Yes	No	No	Yes
6	Sustained release	Yes	Yes	< or = to SLN	No
7	Avoidance of RES	Depend on size and coating	No	Yes	Yes

Regarding their comparative characteristics in the solid state, Table no.1 presents the properties of solid lipid nanoparticles, polymeric nanoparticles, liposomes, and lipid Emulsions [8]

5] TYPES OF SLN [7]

5.1] SLN Type I :-

The SLN Type I represents a uniform and simultaneous solidification (or crystallization) of lipid and active ingredients in a homogeneous matrix model.

5.2] SLN Type II :-

The drug-enriched shell in SLN Type II is formed through the hot high-pressure homogenization method when the drug concentration in the liquefied lipid is minimal. As the hot oil-in-water nano-emulsion cools, the lipid component undergoes solidification first, resulting in a progressive rise in the concentration of active substances within the remaining liquid lipid. A lipid core becomes active; once the active substance reaches its maximum solubility in the surrounding melt, a shell external to it solidifies, comprising both the active and lipid. The outer part of the particles undergoes enrichment, resulting in a burst release. The outer shell's content of active ingredients can be manipulated through controlled changes in the production process. Coenzyme Q10 is commonly integrated into an active shell model.

5.3] SLN Type III :-

The SLN Type III or drug-laden core model can be implemented when the active substance's lipid solution concentration is substantial and close to its saturation limit. In the majority of cases, the reduction of temperature in hot oil leads to a lower solubility of the active component; when the saturation solubility is exceeded; active molecules precipitate leading to the formation of a drug-enriched core. Mehnert's review brings attention to the problem of

inadequate drug payload for multiple drugs, low drug ejection during storage and high water content in SLN dispersions, which can result in the active ingredient precipitating.

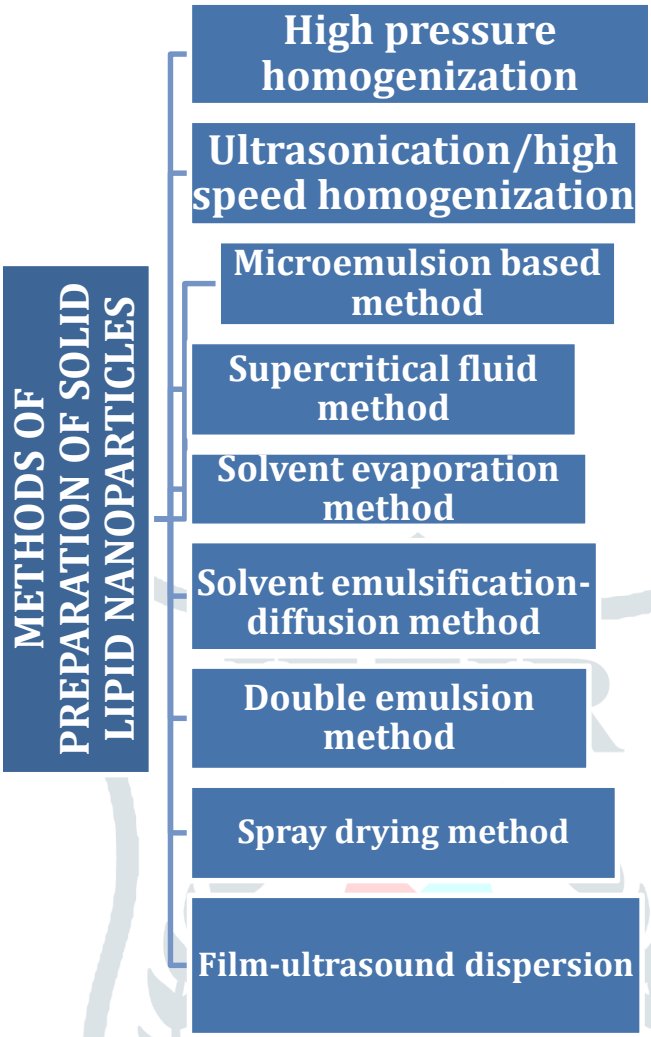
Table : Shows list of excipients used in SLN preparation Lipids[9]	Surfactants
Triglycerides Tricaprin Trilaurin Trimyristin (Dynasan 114) Tripalmitin (Dynasan 116) Tristearin (Dynasan 118) Hydrogenated coco-glycerides (SoftisanÒ 142) Hard fat types WitepsolÒ W 35 WitepsolÒ H 35 WitepsolÒ H 45 WitepsolÒ E 85 Acyl glycerols Glycerylmonostearate (ImwitorÒ900) Glyceryldistearate(Precirol) Glycerylmonooleate(Peceol) Glycerylbehenate (CompritolÒ 888 ATO) Glycerylpalmitostearate (PrecirolÒ ATO 5) Waxes Cetyl palmitate Fatty Acids Stearic acid Palmitic acid Decanoic acid Behenic acid Acidan N12 Cyclic complexes Cyclodextrin para-acyl-calix-arenes	Phospholipids Soy lecithin (LipoidÒ S 75, LipoidÒ S 100) Egg lecithin (Lipoid E 80) Phosphatidylcholine (Epikuron170, Epikuron 200) Ethylene oxide/propylene oxide copolymers Poloxamer 188 Poloxamer 182 Poloxamer 407 Poloxamine 908 Sorbitan ethylene oxide/propylene oxide copolymers Polysorbate 20 Polysorbate 60 Polysorbate 80 Alkylaryl polyether alcohol polymers Tyloxapol Bile salts Sodium cholate Sodium glycocholate Sodium taurocholate Sodium taurodeoxycholate Alcohols Ethanol ButanoL Butyric acid Dioctyl sodium sulfosuccinate Monooctylphosphoric acid sodium

Table no. 2: Shows list of excipients used in SLN preparation [9]

6] PREPARATION OF SOLID LIPID NANOPARTICLE [10, 11, 12]

The process of creating Small Lipid Nanoparticles involves the utilization of lipid, emulsifier, and water/solvent, and the methods employed in this preparation are detailed below.

METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES



1] HIGH PRESSURE HOMOGENIZATION (HPH)

The production of SLNs relies on a dependable and effective technique. High pressure homogenizers apply a pressure of 100-200 bars to force a liquid through a minuscule gap (approximately a few microns). In a very short span, the fluid experiences a significant increase in velocity, reaching over 1000 Km/h. Shear stress and cavitation forces, which are quite strong, break down particles into submicron ranges. Research has been conducted on lipid contents, with a focus on those up to 40% in addition to the standard 5-10%. HPH employs two major strategies: hot homogenization and cold homogenization, both focusing on integrating the drug into a lipid mass that has been melted.

A. HOT HOMOGENIZATION:

Homogenization of an emulsion is achieved through the application of heat, which is carried out above the melting point of the lipids. Through the application of intensive mixing using a high-shear device, a unified mixture of the medicinal substance-infused lipid solution and the aqueous emulsifier phase (both at the same temperature) is generated. The high shear homogenization process for the pre-emulsion is typically performed at temperatures exceeding the lipid's melting point. Generally, increased temperatures lead to smaller particle sizes because the inner phase's viscosity decreases. The degradation rate of the drug and its carrier is amplified by high temperatures. An enlargement of the particle size may occur when the homogenization pressure is intensified or the number of cycles is increased due to the particles' increased kinetic energy.

B. COLD HOMOGENIZATION

Cold homogenization has been created to address the issues encountered with hot homogenization, including: The degradation of drugs due to temperature changes, the drugs entering the aqueous phase during homogenization, and the intricate crystallization process of nanoemulsions resulting in various modifications and/or supercooled melts.. This technique involves cooling the drug-infused lipid melt, grinding the solidified lipid into microparticles, and dispersing these microparticles in a cold surfactant solution to create a pre-suspension. The pre-suspension is then homogenized at or below room temperature, causing the lipid microparticles to be broken down directly into solid lipid nanoparticles due to the significant gravitational force.

Advantages

- Small financial outlay for startup.
- Achieved lab-scale proof of concept.

Disadvantages

- Process consuming large amounts of energy.
- In a laboratory setting, the Biomolecule sustained observable harm..
- Distributions with multiple dispersions.
- Multiple dispersion distributions.

2. ULTRASONICATION/HIGH SPEED HOMOGENIZATION

The production of solid lipid nanodispersions was the initial application of the ultrasonication technique, which operates through cavitation. The drug was introduced in the first instance to a solid lipid that had been melted. The second phase of the process included the addition of the heated aqueous phase, previously heated to the same temperature, to the melted lipid. This was carried out by employing probe sonication or high-speed stirring for emulsification, or by adding the aqueous phase to the lipid phase drop by drop and stirring magnetically. A probe sonicator with a water bath (at 0ºC) was employed for the ultrasonic treatment of the acquired pre-emulsion. To ensure the process didn't cause recrystallization, the temperature was maintained at least 5ºC above the lipid melting point. A 0.45µm membrane was used to filter the generated o/w nanoemulsion, eliminating impurities that had been introduced during ultrasonication. Subsequently, the SLN was kept at 4ºC. In order to improve the stability of the formulation, it was transformed into freeze-dried powder through lyophilization, and mannitol 5% was included as a cryoprotectant in SLNs on occasion.

Advantages

- A decrease in shear stress has occurred.

Disadvantages

- A decline in the force of shear stress has taken place.
- Instability arising from particle growth in physical form during storage

3. SOLVENT EVAPORATION

SLNs can be prepared via the solvent evaporation method, which entails dissolving a lipophilic material in a water-immiscible organic solvent (e.g. cyclohexane) and emulsifying it in an aqueous phase through solvent evaporation.

Through the process of solvent evaporation, the lipid particles settle out of the aqueous medium and coalesce to create nanoparticle dispersion with an average particle size of 25 nm. By employing high-pressure homogenization, the answer was transformed into an emulsion within a watery phase. The organic solvent was eliminated from the emulsion through evaporation under a reduced pressure of around 40-60 mbar.

Advantages

- Adaptable to growth.
- Able to modify to growing circumstances.
- Consistent and unbroken progression.
- Successfully tested in the market.

Disadvantages

- An extremely energy-hungry process.
- Distributions with multiple dispersions.
- Injury to biomolecules.

4. SOLVENT EMULSIFICATION-DIFFUSION METHOD

By employing this method, particles with an average diameter of 30-100 nm can be generated, with the key advantage being the reduction of heat during manufacturing.

5. SUPERCRITICAL FLUID METHOD

SLNs have been produced through a new technique that involves the application of fluids in their supercritical condition, which surpasses their critical pressure and temperature. Above the critical temperature, it is impossible to liquefy a gas by raising the pressure; instead, the gas transforms into a supercritical fluid exhibiting exceptional thermo-physical properties. Beyond the critical temperature, a gas cannot be liquefied through an increase in pressure; instead, it converts into a supercritical fluid, displaying remarkable thermal-physical characteristics. A gas, which shows negligible dissolving power for a substance under ordinary circumstances, can completely dissolve the substance when subjected to increased pressures within the supercritical zone. As a result, the solution's ability to dissolve is influenced by precise management of temperature and pressure adjustments. Among the gases tested for SCF technique, including CO2, ammonia, methane, and CH2FCF3, CO2 stood out as the optimal selection because of its safety and accessibility at crucial points, along with the absence of oxidation in pharmaceutical substances, non-detectable residue post-use, affordability, non-combustibility, eco-friendliness, and simple disposal or recycling, make this an ideal choice. Organic solvents such as DMSO and DMFA are commonly employed in the Supercritical Fluid (SCF) phase due to their complete solubility in SCF-CO2. Nanoparticle production in the technology is accomplished through methods such as SFEE, GAS/SAS, ASES, SEDS, and RESS. The main instruments used for SLN preparation are SAS and PGSS.

Advantages

- The application of solvents should be avoided.
- In contrast to particles being obtained as suspensions, they are available as a dry powder.
- Pressure and temperature levels that are not extreme.
- Carbon dioxide solution is the preferred choice for this procedure in terms of solvents.

6. MICROEMULSION BASED METHOD

The approach relies on the reduction of micro-emulsions' concentration. Since micro-emulsions are biphasic structures consisting of an inner and outer phase (for instance, water-in-oil micro-emulsions). At a temperature of 65-70°C, an optically clear solution is prepared by blending a low melting fatty acid (such as stearic acid), an emulsifier (like polysorbate 20), co-emulsifiers (for instance, butanol), and water. The micro-emulsion, which has been heated to a high temperature, is dispersed into cold water while being stirred. SLN dispersions can be employed as a fluid in the granulation process to generate a solid product, but if the particle concentration is low, a considerable volume of water must be taken out. Large temperature disparities expedite lipid crystallization and discourage aggregation. Nevertheless, the lipid quantities in formulations prepared in this manner are noticeably diminished due to the dilution phase.

Advantages

- Small amount of energy needed for mechanical processes.
- The consistency of theory.

Disadvantages

- Extremely sensitive to change.
- Formulation development requiring considerable effort and time
- A small amount of nanoparticles is present.

7. SPRAY DRYING METHOD

The process of creating a powder from a liquid or slurry through the use of high-temperature gas spray is referred to as spray drying. This technique is commonly employed for thermally-sensitive substances like foods and pharmaceuticals. In the operation of spray dryers, atomizers or spray nozzles are employed to distribute liquids or slurries into a regulated spray form, primarily in the form of rotary disk and single-fluid high pressure swirl nozzles. Lyophilization can be bypassed as an option for converting an aqueous SLN dispersion into a drug product using an alternative technique. Compared to lyophilization, this approach is more economical and suggests incorporating a lipid with a melting point of >7F0°C. This technique results in particle aggregation due to intense heat shear and partial melting of the particles. According to the findings of Freitas and Muller (1998) , the best results were obtained when the SLN concentration was 1%, specifically in a water solution with trehalose or in ethanol-water mixtures (10/90 v/v) with a specific volume proportion.

8. DOUBLE EMULSION METHOD

The double emulsion technique involved dissolving the hydrophilic drug in water and subsequently emulsifying it in melted lipid. The addition of a stabilizer, such as gelatin or poloxamer-407, ensured the stability of the primary emulsion, which was subsequently dispersed in an aqueous phase with the aid of a hydrophilic emulsifier like PVA. The double emulsion was extracted from the mixture by filtration after being stirred. The double emulsion technique streamlines the process of creating nanoparticles loaded with peptides by eliminating the need to melt lipids, allowing for their surface modification through steric stabilization using a lipid/-PEG derivative. Steric stabilization has led to a substantial increase in the resistance of colloidal systems against the gastrointestinal fluids, making it an essential technique for encapsulating hydrophilic drugs, particularly peptides.

9. PRECIPITATION METHOD

An organic solvent, such as chloroform, is used to dissolve the glycerides, which are subsequently emulsified within an aqueous phase. The nanoparticle formation occurs upon evaporation of the organic solvent and the subsequent precipitation of the lipid.

10. FILM-ULTRASOUND DISPERSION

Organic solutions containing the lipid and drug undergo decompression, rotation, and evaporation, resulting in the formation of a lipid film. This film is subsequently exposed to an aqueous solution containing emulsions. After applying the ultrasound probe to diffuse the solution, a small and uniformly sized Suspected Lymph Node is generated.

STERILIZATION

Autoclaving, an effective sterilization method, is necessary for nanoparticles used in parenteral administration and heat-resistant drug formulations. The impact of sterilization on particle dimensions has been explored, resulting in a discernible enlargement.

7] INFLUENCE OF EXCIPIENTSON PARTICLE SIZE [13, 14]

Particle size

Significant changes in size bring about substantial impacts on the physical integrity, biological behavior, and delivery speed of SLNs' lipid particles and encapsulated drug. Therefore, the size of SLNs needs to be maintained within a practical range. To adhere to the colloidal particle definition, well-structured systems such as liposomes, nanospheres, and nanoparticles must exhibit a narrow particle size distribution, which is less than 1 micron in size and situated within the submicron range.

1. Influence of the ingredients on product quality

The size of lipid nanoparticles is influenced by several factors, including the formulation's composition (surfactant blend, lipid characteristics, and drug properties), as well as the production techniques and conditions. In contrast to the large particle size obtained at lower temperatures in the large-particle process, hot homogenization yields smaller particles, typically under 500 nm in size, and a more consistent particle size distribution. The mean particle size and PI values have been observed to decrease as homogenization pressure increases, reaching a maximum of 1500 bars, and with an increase in cycles number (3-7 cycles).

2. Influence of the lipids

Through the application of hot homogenization, research has revealed that the typical particle size of SLN dispersions grows larger as the melting lipids are increased. The specific factors influencing nanoparticle production will vary for distinct lipids. The lipid crystallization velocity and hydrophilicity are demonstrated through various examples, affecting self-emulsifying characteristics and the lipid crystal shape (consequently influencing surface area). In the majority of instances, raising the lipid content beyond 5-10% led to an expansion in particle size and the emergence of larger particles, including micro-particles, with wider distribution.

3. Influence of the emulsifiers

The level of surfactant/surfactant blend significantly influences the dimension of lipid nanoparticles. Generally, particles exhibited smaller sizes when a greater proportion of surfactant to lipid was employed. The reduction in

surfactant concentration brought about an expansion of particle size while in storage. Surfactants lower the surface tension between the particles, enabling them to spread out and increase their contact with the surrounding medium.

8] DRUG INCORPORATION MODELS OF SLN [12,13, 15]

Loading capacity of a drug in lipids is subject to numerous influencing factors:

1. The drug's ability to dissolve in melted lipids.
2. The ability of a drug melt to blend with a lipid melt.
3. The lipid's chemical and physical makeup in its solid state.
4. Lipid matter in various shapes and forms.

Drug incorporation models are as follow

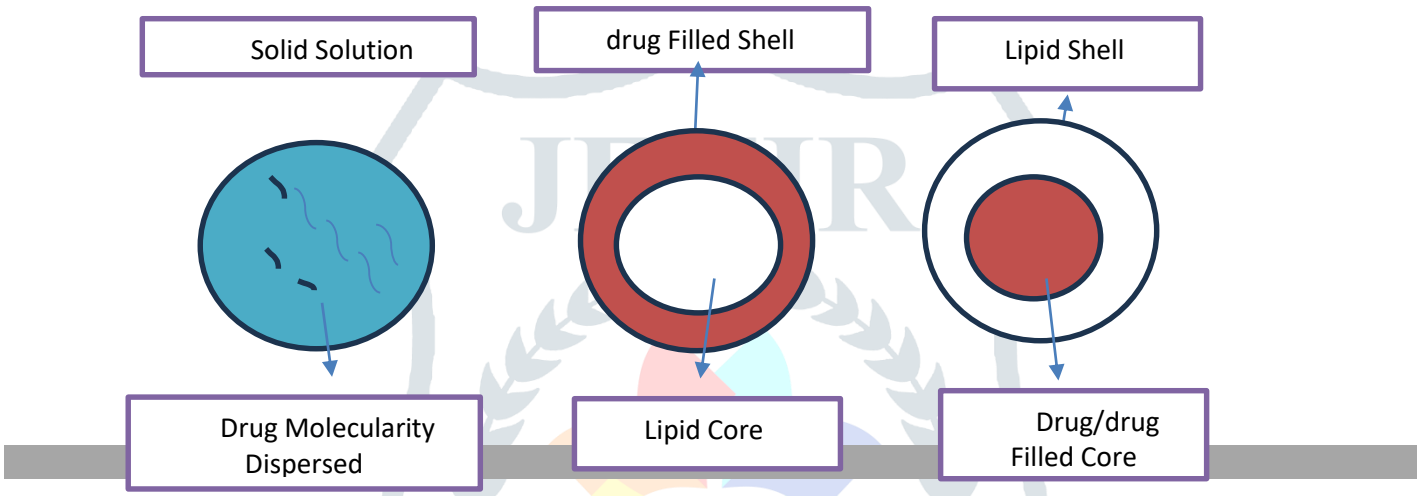


Fig. no.9: Drug incorporation models

Solid solution model:

- When preparing SLN by cold homogenization, the process distributes the drug molecularly in a lipid matrix.
- Drug-enriched shell model.
- A solid lipid core forms upon recrystallization temperature of the lipid is reached.
- Drug-enriched core model.
- Cooling the nanoemulsion causes the dissolved drug to supersaturate in the lipid melt, leading to the recrystallization of the lipid.

9] Fate of SLN after Oral Administration

The oral route remains both challenging and the most appealing method for drug administration due to its undeniable commercial potential. Using lipid nanoparticles to incorporate drugs can improve bioavailability, make it less variable, and extend plasma levels. These systems offer the highest flexibility in altering the drug release profile within the GIT and protect against the chemical degradation of unstable drug molecules. (Peptide drugs).

Drug incorporation and loading capacity [15]

The lipid type (triglycerides, fatty acids, steroids, waxes, etc.), emulsifier (anionic, cationic, non-ionic), and preparation method influence the particle size, loading capacity, and size distribution of SLNs.

Factors determining the loading capacity of the drug in the lipid are

1. How the lipid dissolves when melted.

- When subjected to heat, the lipid transitions into a liquid state, enabling it to dissolve other substances more effectively. The degree to which this occurs depends on the lipid's properties and temperature.

2. How the drug and lipid melt mix together.

- Upon melting, both the drug and the lipid become fluids, which allows them to combine into a uniform mixture. The ease of this process varies based on the compatibility of the drug's and lipid's molecular structures.

3. How the solid lipid matrix's chemical and physical structure appears.

- The solid lipid matrix, once formed, exhibits a specific chemical and physical architecture. This structure is crucial in determining its stability, release mechanism, and interaction with the drug.

4. How the lipid material exists in different polymorphic states.

Lipid materials can crystallize into different polymorphic forms, each with its unique arrangement of molecules. These variations can significantly influence the material's melting point, stability, and how it interacts with other substances.

The lipid melt must have a sufficiently high solubility for the drug to achieve a sufficient loading capacity. The solubility in the lipid melt should be higher than required to ensure adequate dissolution. However, solubility decreases when cooling the melt, making it even lower in the solid lipid. To boost solubility, solubilizers can be added effectively. The inclusion of mono and diglycerides in the lipid matrix material significantly enhances drug solubilization. The chemical nature of the lipid is crucial because highly crystalline lipids with a perfect lattice structure effectively expel drugs

.

Estimation of incorporated drug

Entrapment efficiency [16, 17]

The prime importance of optimizing the drug loading in SLN lies in its significant impact on the drug release characteristics. I confidently assert that the precise determination of the drug encapsulation amount per unit weight of nanoparticles, following the separation of the entrapped drug from the SLN formulation, is a crucial aspect of this process. With the use of techniques such as ultracentrifugation, centrifugation filtration, and gel permeation chromatography, this separation can be confidently executed.

Centrifugation filtration [18]

Advanced filters like ultra-free-mc and ultra-sort 10 are effectively used with traditional centrifugation methods. The degree of encapsulation can be assessed indirectly by determining the amount of drug

remaining in the supernatant after centrifugation filtration/ultra-centrifugation of SLN suspension alternatively by dissolution of the sediment in an appropriate solvent and subsequent analysis.

10] PRINCIPLES OF DRUG RELEASE [17, 18]

The general drug principles of drug release from lipid nanoparticles are as follows:

• The partition coefficient of a drug inversely influences the drug release rate.

• Due to the increased surface area associated with smaller particle sizes in the nanometer range, drug release is accelerated.

• A consistent drug distribution within the SLNs' lipid shell contributes to a protracted drug release, with the SLN composition and encapsulation technique playing a significant role.

• Due to its high mobility and lipid crystallinity, the drug undergoes quick release. The level of crystallization and drug mobility are negatively linked.

The significant surface area, tiny molecular dimension, low viscosity of the surrounding medium, and short diffusion path length δ expedite the process of drug delivery.

Storage stability of SLN [19, 20]

SLNs' physical properties during storage can be assessed by monitoring changes in zeta potential, particle size, drug content, appearance, and viscosity over time. The external factors of temperature and light seem to significantly influence long-term stability. For a dispersion to stay physically stable, its zeta potential needs to be higher than -60mV on average. The preferred temperature for storage is 40°C. The drug-loaded SLNs did not undergo aggregation or drug loss during long-term storage at 20°C. On the other hand, a noticeable growth in particle size was observed at 50°C.

11] In Vitro and Ex Vivo Methods for the Assessment of Drug Release from SLN[21, 22]

SLNs have been theorized to be capable of encapsulating a multitude of drugs, including those with substantial hydrophilic properties.

Various methods used to study the in vitro release of the drug are:

• Side-by-side positioning of cells with artificial or biological membrane partitions.

• Technique for diffusing substances through a dialysis bag.

• Procedure for implementing a dialysis bag in a back-to-front way.

• Agitation ensuing ultracentrifugation or centrifugal ultrafiltration.

In vitro drug release

Dialysis tubing

Dialysis tubing can be employed to facilitate in vitro drug release. The solid lipid nanoparticle suspension is put into dialysis tubing that has been rinsed and sealed hermetically. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged, and analyzed for the drug content using a suitable analytical method.

Reverse dialysis

A large quantity of tiny dialysis bags filled with 1 mL of solubilizing fluid are incorporated into the SLN mixture. The SLN particles are subsequently drawn into the medium.

Ex vivo model for determining permeability across the gut [23]

Enalaprilat SLNs were shown to traverse the rat jejunum, specifically the 30 cm segment distal to the pyloric sphincter, by Ahlin and colleagues. In their permeability studies, Qing Zhi Lu et al. took 10 cm long samples from the duodenum, jejunum, ileum, and colon. Upon removal, these samples were cannulated and ligated.

12] CHARACTERIZATION OF SLN [24,25,26,27]

1. Measurement of particle size and zeta potential

The techniques of photon correlation spectroscopy (PCS) and laser diffraction (LD) hold the greatest power for standard particle size measurements. Particle movement is the source of the intensity fluctuations detected in PCS (dynamic light scattering) measurements. This technique applies to particles with sizes ranging from a few nanometers to around 3 microns. PCS is effective for nanoparticle characterization, but it cannot identify micro-particles. In contrast to PCS and LD techniques, Electron Microscopy delivers precise information regarding particle shape. The stability of refined SLN dispersions is usually maintained for over a year.

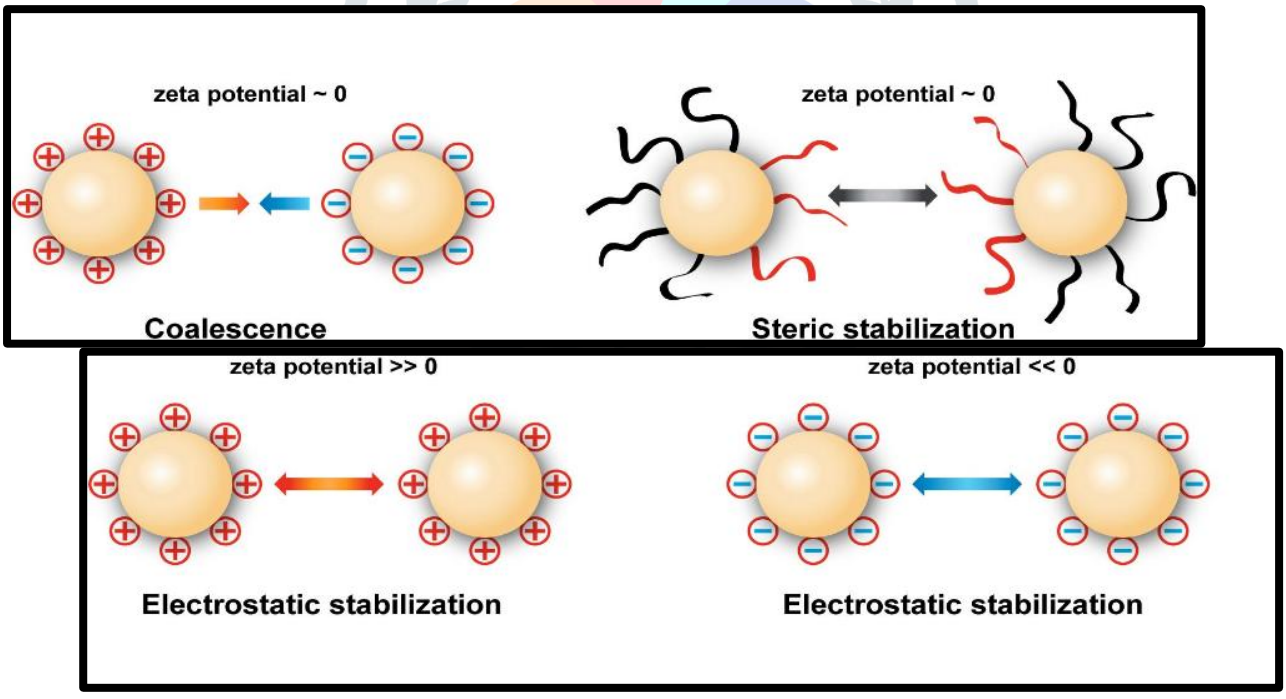


Fig. no. 10 Measurement of particle size and zeta potential

1.2 Photon Correlation Spectroscopy (PCS)

This technique, which relies on the dynamic scattering of laser light resulting from Brownian motion in liquids, is an established one for measuring particles with sizes between 3 nm and 3 mm. A PCS device comprises a laser, a temperature-regulated sample cell, and a photomultiplier serving as its detector to

identify scattered light. The size of the PCS diameter is influenced by the intensity of the light scattering caused by the particles.

[1.2] Electron Microscopy

The shapes and morphologies of lipid nanoparticles can be assessed using techniques like Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) in Electron Microscopy. SEM allows for the identification of particle sizes and distributions, utilizing transmitted electrons from the sample's surface.

1.3 Atomic Force Microscopy (AFM)

This technique, which is an advanced microscopic method, is used to accurately image the original, unaltered shape and surface properties of particles. AFM provides a spatial resolution of up to 0.01 nm for imaging by measuring the force between the sample surface and the probe tip.

2] Determination of Incorporated Drug

The amount of drug in SLNs significantly affects their release properties, making it crucial to accurately measure the drug quantity. The amount of drug encapsulated per unit wt. of nanoparticles is determined after the separation of the free drug and solid lipids from the aqueous medium and this separation can be done by ultracentrifugation, centrifugation filtration or gel permeation chromatography. The drug can be analyzed using techniques such as spectrophotometry, spectrofluorometry, HPLC, or liquid scintillation counting.

2 In vitro drug release

3.1 Dialysis tubing

Dialysis tubing can be used to achieve in vitro drug release by placing the solid lipid nanoparticle dispersion inside, which can then be hermetically sealed. The dialysis sac is soaked in a suitable dissolution medium at room temperature for dialysis; The drug content is measured in samples taken from the dissolution medium at appropriate intervals, centrifuged, and analyzed using a suitable analytical method.

3.2 Reverse dialysis

Place small dialysis sacs with 1 mL of dissolution medium in SLN dispersion. The SLNs will move into the medium.

4) Rheology

The Brookfield Viscometer can be used for rheological measurements of formulations with an appropriate spindle number. The viscosity changes as the dispersed lipid content increases, becoming non-Newtonian..

5) Acoustic methods

Acoustic spectroscopy is an ensemble approach that measures the attenuation of sound waves to determine size by fitting relevant equations. The oscillating electric field generated by charged particles moving under acoustic energy can be detected to provide information on surface charge.

6) Nuclear magnetic resonance (NMR)

NMR is used to determine the size and qualitative nature of nanoparticles. Chemical shift selectivity and molecular mobility sensitivity together provide information on the physicochemical status of nanoparticle components.

7) X-ray diffraction (powder X-ray diffraction) and differential scanning calorimetry (DSC)

The scattering of radiation from crystal planes in a solid determines the presence or absence of crystallinity. A different method for implementation with non-bulk materials, DSC is used to identify and classify the crystallinity of nanoparticles by measuring their glass and melting point temperatures and the corresponding enthalpies.

13] Routes of Administration and Their Biodistribution [28, 29]

The behavior of SLN particles in living organisms primarily relies on the following factors:

ADMINISTRATION ROUTE

The SLN interacts with its biological environment through processes such as adsorption of biological material and desorption of SLN components, as well as enzymatic reactions. The administration can be given through different routes:

1) PARENTERAL ADMINISTRATION

Peptide and protein drugs are primarily administered parenterally due to enzymatic degradation in the GI tract, making oral administration impractical. Parenteral application of SLN (site-specific nanoparticles) enhances drug bioavailability and minimizes side effects. These systems effectively target drugs.

2) Oral administration

The controlled release behavior of SLNs allows the encapsulated drug to bypass gastric and intestinal degradation and be absorbed through the intestinal mucosa. The stability assessment of colloidal carriers in GI fluids is crucial for determining their suitability for oral administration.

3) Rectal administration

For swift medication effects, parenteral or rectal administration is the preferred method in certain situations. This approach is commonly used for pediatric patients due to its ease of application.

4) Nasal administration

The nasal route is the best option for administering drugs due to its quick absorption and immediate effect. It bypasses the stomach, preventing the degradation of labile drugs and ensuring efficient transport across epithelial cell layers.

5) Respiratory delivery

Nebulization of solid lipid particles carrying anti-tubercular, anti-asthmatic, and anti-cancer drugs improved drug bioavailability and reduced dosing frequency for effective management of pulmonary conditions.

6) Ocular administration

SLN's biocompatibility and mucoadhesive properties enhance their interaction with the ocular mucosa, prolonging the corneal residence time of the drug for effective ocular drug targeting.

7) Topical administration

SLNs are effective colloidal carrier systems for skin applications due to their additional benefits for the skin. These products are effective for damaged or inflamed skin due to their non-irritant and non-toxic lipid base.

14] APPLICATION OF SLN [30-37]

SLNs have various potential uses, some of which are detailed below:

- **SLN as potential new adjuvant for vaccines**

In vaccinations, adjuvants are employed to boost the body's immune reaction. Since newer, safer subunit vaccines have reduced efficacy, the need for effective adjuvants arises. The latest advancements in adjuvant technology revolve around emulsion systems. These are oil-water emulsions that break down swiftly in the body. In their solid form, lipid elements of SLNs undergo slower degradation, resulting in a prolonged interaction with the immune system.

- **Solid lipid nanoparticles in cancer chemotherapy**

In vitro and in vivo effectiveness of various chemotherapeutic agents encapsulated in SLNs during the last two decades has been examined. These studies have proven that their outcomes lead to increased potency of chemotherapeutic drugs and a decrease in their unwanted side effects. Encapsulation of chemotherapeutic agents with diverse physicochemical properties leads to improved drug stability, increased therapeutic efficacy, enhanced pharmacokinetics, and reduced in-vitro toxicity are the important features of SLN which make them a suitable carrier for delivering chemotherapeutic drugs. SLN delivery can help alleviate some of the issues that frequently arise when using anticancer compounds, such as normal tissue toxicity, poor targeting, and instability, as well as the high

occurrence of drug-resistant tumor cells. The efficient clearance of colloidal particles by macrophages in the RES poses a significant challenge for targeting tissues like bone marrow and solid tumors.

- **SLN as targeted carrier for anticancer drug to solid Tumor**

SLN have proven effective in serving as vehicles for administering drugs, specifically tamoxifen in the case of breast cancer treatment. Targeted delivery of methotrexate and camptothecin to tumors has been accomplished through the use of SLNs.

- **SLN in breast cancer and lymph node metastases**

Local injections of Mitoxantrone SLN formulations were developed to minimize toxicity, enhance safety, and boost the drug's bioavailability.

- **Solid lipid nanoparticles for delivering peptides and Proteins**

Therapeutic peptides, proteins, and antigens have found solid lipid particulate systems, including solid lipid nanoparticles (SLN), lipid microparticles (LM), and lipospheres, to be potential alternatives to conventional carriers. Their research in this sector demonstrates that, when optimally produced, these carriers can efficiently accommodate hydrophobic or hydrophilic proteins and function as a top-tier protein delivery vehicle. SLNs can be utilized to deliver therapeutic proteins and antigens for medical purposes through injection sites or alternative routes like the mouth, nose, and lungs. Protein stability is optimized, proteolytic degradation is minimized, and the continuous release of encapsulated molecules is achieved through the application of SLN formulation. Significant peptides including cyclosporine A, insulin, calcitonin, and somatostatin have been integrated into solid lipid particles and are presently being explored. Multiple potential therapeutic uses can be anticipated, including protein antigen vaccinations, treatment of infectious diseases, management of chronic conditions, and cancer therapy.

- **Solid lipid nanoparticles for targeted brain drug Delivery**

The minuscule particle dimension of solid lipid nanoparticles, measuring under 50 nm, could offer advantages in drug delivery due to their size. The small carrier scale typically results in decreased interaction with the reticuloendothelial system. The modification of solid lipid nanoparticles' surfaces could enable drug targeting. SLNs show promise as a drug-targeting system for central nervous system disorders due to their ability to help drugs cross the blood-brain barrier. To improve brain access to the drug 5-fluoro-2'-deoxyuridine (FUdR), researchers synthesized and incorporated 3', 5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR) into solid lipid nanoparticles (DOFUdR-SLN). The current research focuses on using surfactant-coated poly (alkylcyanoacrylate) nanoparticles designed for brain targeting in solid lipid matrices. The merits of solid lipid nanoparticles in comparison to polymeric nanoparticles are explained as follows:

1) Lower cytotoxicity.

2) Higher drug loading capacity

3) Best production scalability.

The development of brain-targeting formulations relies heavily on the specific physicochemical characteristics of solid lipid nanoparticles.

- **Solid lipid nanoparticles for parasitic diseases**

Malaria, leishmaniasis, and trypanosomiasis are among the most pressing parasitic diseases confronting the global community. For these parasitic infections, antiparasitic medication is the sole treatment option due to the lack of a significant immune response, making vaccination an ineffective solution. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) signify the next level of colloidal delivery systems, surpassing liposomes in effectiveness primarily because of their better stability profile, ease of scalability and commercialization and relative cost efficacy. The particle characteristics and inherent structure of SLN and NLC make them effective candidates for treating parasitic infections. Our investigation, as well as other recent findings, have confirmed their usefulness to a certain degree. However, the need of hour is to undertake extensive investigations on SLN and NLC matrices in order to extend their versatility with respect to encapsulation ability and target ability and to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.

- **Solid lipid nanoparticles for ultrasonic drug and Gene delivery**

The application of micelles and nanoparticles in drug delivery research has expanded considerably in the area of ultrasonic drugs and gene therapy in recent times. The application of these nano vehicles in medicine is noteworthy due to their ability to target diseased tissues with high doses of cytotoxic drugs, minimizing the impact on healthy cells. In diagnostic medicine, ultrasound is increasingly being utilized for drug delivery in conjunction with nanoparticles. The non-invasive and tissue-targeted qualities of acoustic waves have earned them recognition for facilitating the discharge of drugs from nanocarriers and enhancing cell membrane penetrability. The non-invasive and tissue-targeted qualities of acoustic waves have earned them recognition for facilitating the discharge of drugs from nanocarriers and enhancing cell membrane penetrability. The collapse of cavitation bubbles during ultrasound treatment is believed to result in drug release from micelles through shear stress and shock waves. The rupture of cavitation bubbles during ultrasound therapy is thought to lead to drug expulsion from micelles as a result of shear stress and shock waves. The potential of ultrasonic drug and gene delivery via nanocarriers is immense due to the broad range of medicines and genetic material that can be transported to specific tissues using relatively non-intrusive methods.

- **SLN applications for improved delivery of antiretroviral drugs to the brain**

The human immunodeficiency virus (HIV) enters the central nervous system during the early course of primary disease. In the brain, the virus begins to replicate independently, leading to neurological complications, latent infection, and drug resistance. The HIV viral load in the brain is not effectively suppressed by current antiretroviral medications (ARVs). The inadequate transport of certain ARVs, including protease inhibitors, across the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSBF) contributes to this issue. Nanocarriers such as polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLN), and micelles have been the subject of numerous research studies. Through the use of nanocarriers for transporting ARVs, a substantial enhancement of the drugs' ability to reach the brain is anticipated. The delivery of ARVs can be made more precise and productive by incorporating nanocarriers, brain-targeting peptides, or inhibitors of ABC transporters. The focus of ARV research should shift towards developing a safe, efficient, and cost-effective means of delivering these drugs to the brain in the future.

- **SLN applied to the treatment of malaria**

Malaria, an infectious disease, continues to pose a major health concern despite the era of advanced technology and innovation. Conventional malaria therapy faces significant limitations, including the development of drug resistance and the inability to specifically target intracellular parasites, resulting in high doses and intolerable toxicity. Nanoscale delivery systems have gained significant focus for reducing the drawbacks of pharmaceutical treatments, including low drug availability and specificity. Animal studies have demonstrated the effectiveness of several nanosized delivery systems in combating malaria. This review delves into several techniques for transporting antimalarials through nanocarriers and how they are directed to plasmodium spp-infected cells. Considering the unique characteristics of malaria parasites, emphasis is given to nanocarriers such as liposomes, solid lipid nanoparticles, nanoemulsions, nanocapsules, and nanospheres, which are based on lipids and polymers.

- **Targeted delivery of solid lipid nanoparticles for the treatment of lung diseases**

Pharmaceutical research is dedicated to finding effective methods for delivering drugs to specific organs or sites. The invention of colloidal delivery systems such as liposomes, micelles, and nanoparticles marked a significant advancement in the field of drug delivery. Compared to other delivery systems, nanoparticles boast distinct advantages thanks to their small particle size, large surface area, and adjustable surface properties. Delivering nanoparticles specifically to the lungs is a growing field of research

- **Solid lipid nanoparticles in tuberculosis disease.**

Compared to liposomes, SLNs provide greater stability and more effective encapsulation, and their production process uses fewer organic solvents than polymeric nanoparticles.

Anti-Tubercular Drugs (ATD) have been enclosed in SLN, which demonstrated effectiveness in tuberculosis experiments. The administration of anti-tubercular medications like rifampicin, isoniazid, and pyrazinamide in SLN systems resulted in less frequent dosing and enhanced patient adherence SLN incorporated ATD for the assessment of their suitability in tuberculosis therapy through the oral administration route. The study's outcome suggested that SLN may offer a more efficient approach to delivering ATD, reducing the frequency of doses and improving patient compliance for better tuberculosis management.

- **Transfection agent**

The process of creating cationic stable nanoparticles for gene transfer involves utilizing the same cationic lipid as used in liposomal transfection agents. A comparison of their structural and functional characteristics was carried out according to PCS and AFM measurements, the SLNs had a smaller diameter than liposomes. The difference in DNA binding was minimal. The arrangement of a cationic lipid composition influences the in vitro transfection effectiveness more than its colloidal structure. The utilization of cationic SLNs expands the capabilities of non-viral transfection agents, offering favorable and distinctive technological attributes.

Transfection efficiency was amplified by a factor of 100 when cationic SLNs were employed alongside the TAT2 nuclear localization signal.

- **SLN in cosmetic and dermatological preparation**

Products incorporating SLN technology in topical formulations represent a substantial opportunity with a swift market entry, applicable to both pharmaceuticals and cosmetics. Liposomes are surpassed by SLN as the upcoming delivery system. The advantage of topical treatment for skin diseases lies in its reduced risk of systemic side effects, but the stratum corneum poses a barrier to the penetration of xenobiotics into living skin. Particulate systems could serve as effective means to boost dermal penetration. The significant concentration of epidermal lipids within the skin's penetration barrier makes lipid vehicles that adhere to the skin surface and enable lipid exchange between the outermost layers of the stratum corneum and the carrier an attractive option Liposomes are not the only nanoparticles that have been extensively investigated; solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have also been a focus. The lipid nano dispersion applied to the skin surface dries, leaving behind a cohesive layer of lipid particles. By relaxing corneocyte conglomeration and expanding inter-corneocyte fissures, the stratum corneum's hydration may be amplified, thereby improving drug penetration into deeper skin tissues. The relationship between particle size and occlusive effects is quite pronounced. The occlusivity of nanoparticles is 15 times greater than that of micro-particles, and particles smaller than 400 nm in a lipid dispersion with a high degree of crystallinity have been the most effective.

- **Solid lipid nanoparticles for lymphatic targeting**

The lymphatic uptake of solid lipid nanoparticles (SLN) was investigated after intraduodenal administration to rats, which were previously developed and evaluated.

- **SLN for potential agriculture applications**

The essential oil derived from Artemesiaarborensis L in SLN formulations effectively decreases evaporation rates more than emulsions, making them a viable option as pesticide carriers in agriculture.

CONCLUSION

SLN, with its successful enclosure of active ingredients, presents an engaging colloidal drug delivery system. SLN provides an affordable and patient-convenient device for delivering medications through multiple routes to enhance therapeutic benefits while minimizing harm to non-target cells. The potential uses of SLN in formulations have been extensively studied for over 20 years, providing promising solutions for drugs with limited aqueous solubility, brief half-lives, and fragile chemical structures. For drugs that exhibit poor aqueous solubility, short half-lives, and low chemical stability, parenteral formulations offer additional avenues for effective administration. The targeted application of SLN as a drug delivery system is expected to increase, allowing for the selective transport of drugs to certain organs and decreasing systemic harm. Therefore, they present alternatives for APIs that failed clinical assessments due to inaccurate tissue targeting.

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