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Solid Lipid Nanoparticles (SLNs): A Comprehensive Review on Preparation, Characterization, and Drug Delivery Applications

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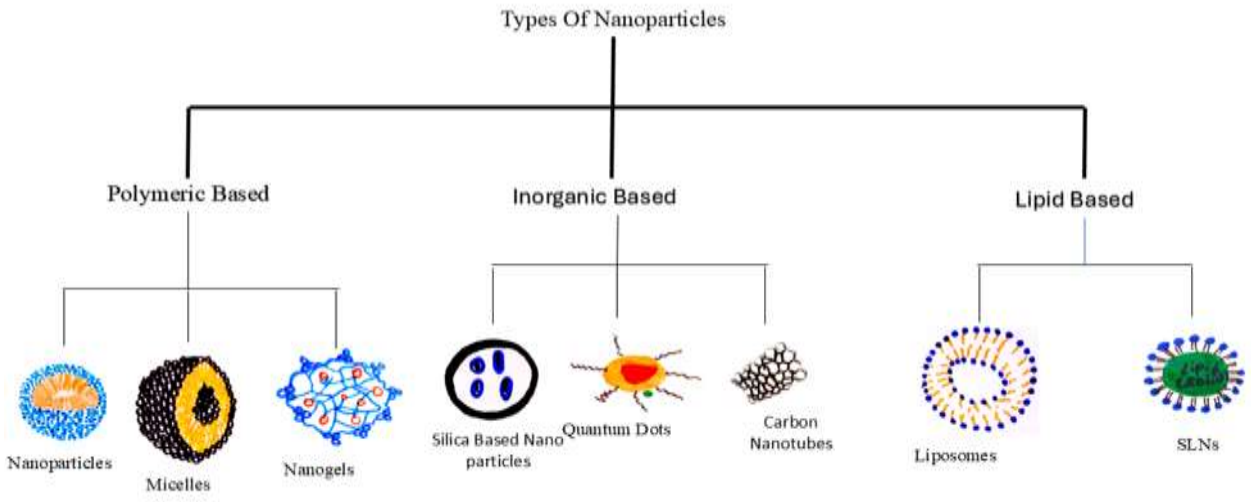
Abstract:
Solid Lipid Nano particles (SLNs)have become a viable drug delivery technology because of their special qualities, which include controlled drug release, biocompatibility, and biodegradability. There are numerous advantages to using these colloidal carriers in comparison to traditional delivery of drug techniques, including enhanced drug bioavailability, more precise distribution, and fewer adverse effects. Through the selection of suitable lipids and surfactants, SLNs (Solid Lipid Nano particles) can be customized to meet drug delivery requirements. Micro emulsion techniques, solvent emulsification evaporation, hot homogenization, and cold homogenization are some of the methods used to manufacture SLNs (Solid Lipid Nano particles). An extensive summary of SLNs (Solid Lipid Nano particles) is given in this review, covering their makeup, methods of preparation, characterization, and uses. Future directions for SLN technology research are also covered, emphasizing how these nanocarriers have the potential to completely transform administration of medication.

Keywords: Solid Lipid Nano particles, Drug delivery system, Nanocarrier technology, Targeted drug delivery, Biocompatibility.

1. Background

Nano particles are made of large molecules substances and that can carry drugs, adjuvants in vaccinations, dissolve, trap or capture the active drug and/or attach it to it. The dimensions of solid particles that are colloidal in nature and referred to as Nano particles that range from around 10 nm to 1000 nm. Nano particle-based drug delivery system provides a space to carry drugs which is larger in size such as hydrophobic and amphiphilic drug [1]. As mention in figure: 01

Figure: 01 Types of SLN's (solid lipid Nano particle)



Different types of Nano particles are as follows [2]:

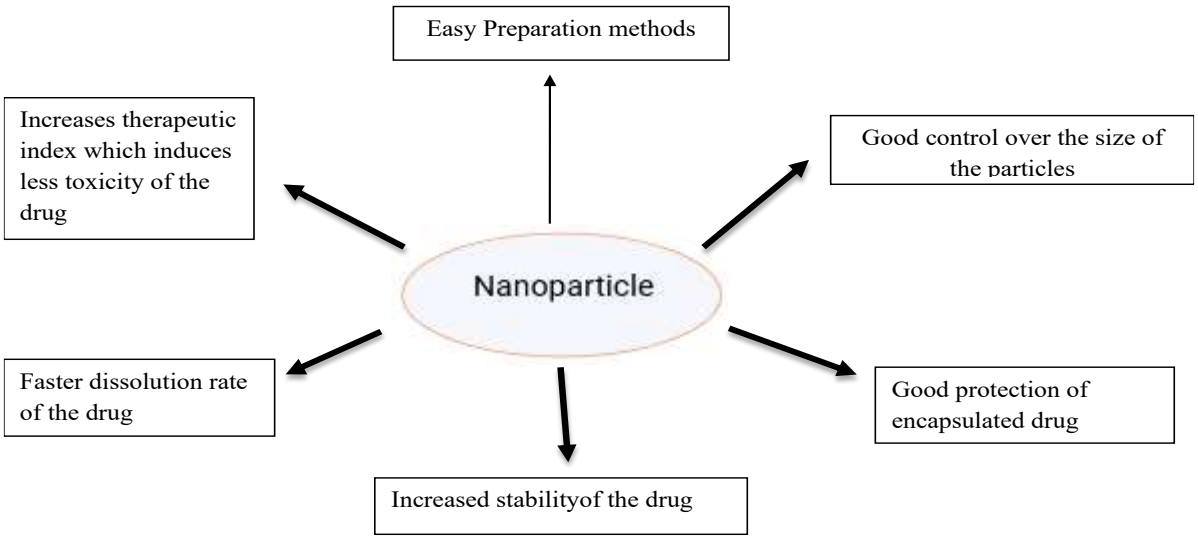
- Polymeric based NPs
- Inorganic based NPs
- Lipid based NPs.

The efficient drug release for the hydrophobic (water hating) drugs becomes a huge problem because of their nature in the Pharmaceutical Industry. For carrying out the formulation procedure of the hydrophobic drugs the chemicals that have to be added requires toxic chemical interference to it which causes drug impairment and side effects in the human kind [3].

1.1 Advantages of Nano particles [4,8]:

Nanoparticles provide benefits include improved medication solubility, precise distribution to designated living components in to the body, and regulated release behaviour of drug. They enhance treatment efficacy while reducing adverse effects and are versatile for use in various medical applications, including diagnostics and imaging. The advantages of Nano particles are huge in number because of their abundant cargos of good activity. The details were depicted in figure: 02

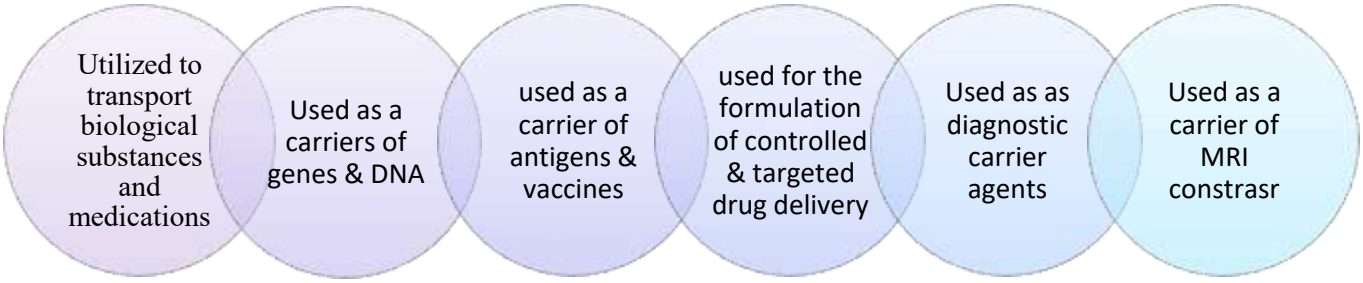
Figure: 02 Schematic diagram for Advantages of Nanoparticles



1.2 Therapeutic Application of Nanoparticles [4]:

Nanoparticles offer promising therapeutic applications due to their capacity to enhance pharmaceuticals dosage forms delivery, improve the drug's absorption, and facilitate therapy for target site. They are widely used in cancer treatment, antimicrobial therapies, and vaccine development, providing controlled release and reduced side effects. As mention in figure: 03

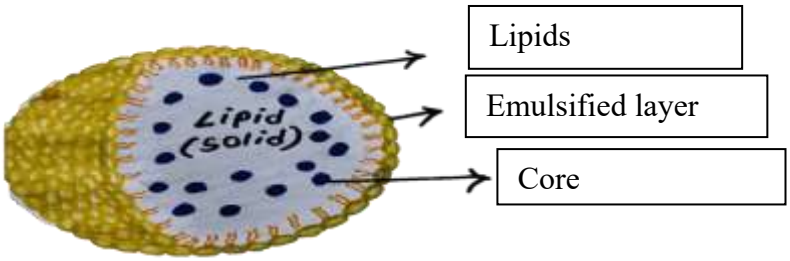
Figure: 03 Therapeutic Application of Nano particles



2. Solid Lipid Nanoparticles Overview:

A central solid with a drug possesses high point of melting was encircled by a liquid core made up of surfactants and the drug that belongs to the BCS Classification makes up solid lipid Nano particles, which are a colloidal system. [5] This colloidal system consists of Spherical solid lipid particles which consist of a collection of single covering of protein-attached lipids with a solid water-repellent core. [6]. Solid lipid Nano particles are the advanced drug carrier which are now used in the field of cosmetics, Nutraceuticals and at last pharmaceuticals. SLNs are reported to have more advantages compared to the older conventional method. These SLNs can be formed based on the two types one is which is based on solvent and the other one is non-solvent techniques. In the solvent based the solvent are subjected to evaporation process, whereas solid lipids are liquefied above melting in non-solvent procedures, which are subsequently cooled to produce solid lipid nanoparticles (SLNs).[7]. The most researched novel medication delivery technology is SLNs. [8]. According to a number of studies, when insoluble lipids are used in place of anhydrous lipids for making SLNs (Solid Lipid Nano particles), the Nano particles decompose more slowly, which causes the encapsulated medications to continue to release. Other major excipients of SLNs are aqueous surfactants. They stabilize the dispersion of SLNs and serve as an emulsifier to create o/w emulsion. The route of implementation of the SLNs is the primary determinant of the ingredient selection. The medication is usually dissolved or diffused in a solid lipid to create SLNs [9]. The allocation of active components through the cutaneous, peroral, parenteral, ophthalmic, through the lungs, and the rectal is one of the many health-related research applications for SLNs Better absorption, targeting, and increased therapeutic outcome, there have been reports of cytotoxicity against cancer cells resistant to many drugs after SLN was administered parenterally. [10,11]. A rough diagram of Solid lipid nano particle was depicted in figure: 04

Figure:04 Solid Lipid Nano particles: Advancing drug delivery systems



2.1 Advantages of Solid Lipid Nano particles [17,18,19]:

- The Potentiality of severe and extended toxicity is decreased by the application of biodegradable lipids.
- Solid lipid Nano particles help in increasing bioavailability of the active ingredients that are not very soluble in water.
- Improving the stability of medications that are chemically unstable by shielding them from the outside environment.
- Compared to alternative drug carriers like liposomes, SLNs have been considered to be superior stability.
- The active ingredients get high entrapment effectiveness.
- They have high potential for lyophilisation.

2.2 Disadvantages of Solid Lipid Nano particles:

- Its ability to load drugs is inadequate compared to NLC (Nanostructured Lipid Carrier).
- The dispersions contain a noticeable amount of water in the range between 70–99.9%. The sudden or unexpected incline to solidify.
- Polymeric changes and their unpredictable dynamics.
- Following a polymeric transition, drug ejection during storage.
- Particle growth is a possibility.

3. Composition of Solid Lipid Nano particles:

3.1 Role of Lipids in SLN's (Solid Lipid Nano particles)

Lipids form the core of SLNs providing a solid drug-encapsulation matrix, the drugs-controlled release. The choice of lipid is crucial for the chemical and physical properties of the SLNs and their stability and release of drug characteristics also. The lipids are divided in the subtypes such as triglycerides, monoglycerides, triglycerides, triglycerides mixture, hard fats, waxes and other lipids.

As the primary matrix for drug encapsulation and delivery, lipids are essential ingredients in the creation of SLNs. The structure, stability, and functionality of Solid Lipid Nano particles are significantly influenced by their characteristics, which are essential for the development of effective drug delivery systems.

3.1.1 Selection of Lipids:

Water, lipids, co-emulsifiers, and emulsifiers are often utilised components in the creation of SLNs as matrix materials. Charge modifiers, which are covert compounds that enhance the targeting ability and extended retention time, are also employed to satisfy the stability and requirements for targeting.

They should be able to produce particles that are small (in the range of nanometre size) and have a low concentration of micro particles (>5 μm).

- They should be able to load medications that are both lipophilic and potentially hydrophilic.
- They should be ready for autoclaving sterilization.
- They can be spray-dried or lyophilised. They can be stable in aqueous dispersions when stored for an extended period of time.
- They must be toxicologically free and must leave no residues in the work environment.

SLNs are produced using a variety of lipids, including Cetylpalmitate, tristearin, tripalmitin, and Trilaurin. When it comes to successful medication inclusion, SLNs (Solid Lipid Nano particles) made with lipids with less Glyceryl monostearate and glyceryl behenate are examples of organised crystal lattices are preferable to those made with lipids with highly ordered crystal packing, like solid paraffin, beeswax, cetylpalmitate, and tripalmitate. Although, there are significant differences in their long-term stabilities. Tribehenin and tripalmitate had the best physical stability among glycerides; this is because 15% of the monoglycerides in tribehenin have surfactant characteristics. However, glyceryl monostearate is incredibly unstable, and within a few days of production, there is a noticeable increase in particle size [27, 28]. The role of lipids material in SLN's delivery system were depicted in table: 01

Table: 01 Role of Lipids and surfactants in different SLNs formulation

S.No	Lipids	Surfactants	Pharmaceutical Ingredients	Therapeutic effect	References
01.	Argan oil, Precirol ATO5	Tween 80	Argan Oil	Dermal hydration is enhanced	[41]
02.	Labrasol, Tristearin	Tween 80, Phospholipid (90NG)	Adapalene	Improve epidermal delivery of drug	
03.	Precirol ATO5	Poloxamer F-127, Poloxamer F-68,	Amphotericin B	Topical antifungals have increased antifungal activity.	
04.	Compritol 888 ATO	Tween 80	Chloroquine	Enhanced impact on therapyand prevention of side effects from oral medications	
05.	Oleic acid, Stearic acid	Span 80 and Tween 80	Minoxidil	Improve drug delivery to skin	
06.	Glyceryl mono stearate	Span 80, Tween 80	Naproxen	Reduced systemic absorption and an increase in drug local concentration	

07.	Tristearin, Miglyol 812 N	Poloxamer 188	Progesterone	Elevated permeation of SC drugs	
08.	Stearic acid	Poloxamer 407, Soy Lecithin	Resveratrol	Improved treatments for hyperpigmentation and anti-aging	
09.	Cetyl palmitate	Tego care 450	Tretinoin	Reduced irritative action of drugs on the skin.	

3.2. Role of Emulsifiers and Co- Emulsifiers

Since emulsifiers are vital component in maintaining the stability of the lipid-water interface and averting Nano particle aggregation, they are integral parts of SLNs. The SLN-making emulsifiers and co-emulsifiers are Lecithin, Polysorbate 20, 60 and 80, Tyloxapol, Poloxamer 188 and 407, Tauro deoxycholic acid sodium, sodium chloride, sodium oleate, sodium dodecyl sulphate, sodium glycocholate, butanol and butyric acid, Cetyl pyridinium chloride, polyvinyl alcohol, and Cremophor EL.

3.2.1 Selection of Emulsifiers:

In the target to providing adequate stability to the SLNs by coating their surface, the emulsifier ought to be safe, work well in conjunction with additional adjuvants, and able to exert the necessary dimensions with the least quantity of input. The emulsifier's in vivo fate is another factor to take into account when choosing one. For example, the poloxamer series of emulsifier gives SLNslong-circulating properties by inhibiting the reticuloendothelial system (RES) uptake, allowing for passing the buck, whereas polysorbate 80-coated SLNs improved medication delivery to the brain targeting [29,30]. The amount of emulsifier that are being used should be optimum. If it is more which will give rise to problems such as burst of the Nano particle and also if we are adding more which will lead to decrease in the entrapment efficacy and if we are adding less which will lead to the particle aggregation problem [31].

3.2.2 Selection of Co- emulsifiers:

Phospholipids utilized to make SLNs do not produce high-dynamic micelles or dissolve well in the continuous phase. Throughout the homogenization process, the extra phospholipid molecules form tiny, primarily unilamellar vesicles, Vesicle-attached phospholipid molecules have limited mobility. Thus, upon the recrystallization of solid lipids, they can't cover the freshly created surfaces right away. The sudden absence on the surface of an emulsifier phospholipid molecules, which results in reduced mobility, causes the particles to aggregate and enlarge, increasing the size of SLNs Co-emulsifiers like glycocholate (ionic) and tyloxapol (Non-ionic polymer) are used to prevent this. Micelles are able to form from these kinds of water-soluble emulsions. More quickly than Polymer molecules can permeate vesicles and reach the particle surface. Furthermore, micelles are incredibly dynamic forms of colloids and serve as a reservoir [32]. The importance of other excipients was depicted in Table: 02

Table: 02Excipients commonly used in SLN Formulations

S.No	Drug name	Excipients	Purpose	References
01.	Adapalene	Tristearin, Triton X-100, and hydrogenated soy phosphatidylcholine Cetyl palmitate, tristearin, stearic acid, Span 20, Tween 80, Pluronic F68, and Brij 78 Sodium dodecyl sulfate, glyceryl monostearate, Glyceryl monooleate, Precirol ATO 5, Compritol® 888 ATO, Pemulen TR-1, Carbopol 980 NF, and Carbopol Ultrez 10 NF	For adapalene's efficient topical administration in acne Improvement of topical adapalene embedded gel's effectiveness and skin tolerability	[42]
02.	Benzoyl peroxide	Carbopol 934 NF, Tween 80, and Precirol ATO 5	Benzoyl peroxide SLN can lessen the negative effects of medications used to treat acne.	[43]
03.	Isotretinoin	Tocopherol, butylated hydroxy toluene, phosphatidylcholine, and Compritol® 888 ATO	Creation of an isotretinoin optimised SLN to lessen skin irritation and improve the medication's medicinal effects	[44]
04.	Retinoic Acid	Brij 58, cholesterol, stearyl amine, methyl paraben, butylated hydroxytoluene (BHT), Hydroxyethyl cellulose, vitamin A, and Compritol® 888 ATO	Assessment of topical acne therapy using retinoic acid-loaded SLN	[45]
05.	Tretinoin	Myristyl myristate, Chitosan Compritol 888 ATO, Precirol	Acne treatment with and without chitosan using tretinoin SLN preparation and evaluation.	[46]

3.3 Role of other excipients in SLN's formulation

Other than the lipids, emulsifiers and co-emulsifier the other excipients that which are employed in the creation of solid lipid Nanoparticles are Cryoprotectants, Charge modifiers and agents that are used for increasing the circulation time. The examples of different excipients are listed below:

3.3.1 Cryoprotectants

Cryoprotectants are substances that protect biological materials, such as cells, tissues, or organs, from damage during freezing and thawing. They help to prevent the formation of ice crystals, which can disrupt

cell membranes and cause cell death. The cryoprotectants are used in formulation of SLNs because cryoprotectants are often used in SLNs are formulated to increase their stability during freezing and thawing. This is particularly important for SLNs that need to be stored or transported under frozen conditions. Cryoprotectants are used in SLNs and how they work is by preventing ice crystal formation by reduce the freezing point of the SLN suspension thus by preventing the Freezing causes ice crystals. Ice crystals can damage the SLNs, leading to changes in their size, shape, and drug release properties. It also helps to dehydrate SLNs by creating dehydration of the SLNs, reducing the amount of water available to form ice crystals. This can further protect the SLNs (Solid Lipid Nano particles) from damage during freezing and thawing and also it protects encapsulated drugs within the SLNs from degradation during freezing and thawing [33].

3.3.2 Charge modifiers:

Charge modifiers are substances that can change a particle or molecule's surface charge. They are often used to modify the properties of materials, especially in fields like pharmaceuticals, cosmetics, and materials science. Charge modifiers work by creating ionic interactions which interact with the surface of particles through electrostatic forces, either by neutralizing or altering their charge. Also, they create chemical modification by chemically modifying the surface of particles and by introducing new functional groups that carry a charge. Surface charge is a key factor that affects what happens to the drug-carrying nanoparticles inside living cells. In increasing oral absorption of the SLNs (Solid Lipid Nano particles) preparation charge modification was done by converting or inducing a negatively charged, positively charged, and net neutral surface charge. And after the study was observed it was seen by inducing charge modifiers the oral absorption has increased but among the all three the net neutral charge shows more positive results. For observing the effect of the modifiers, the fluorescence bio imaging strategy was used to detect which shows the maximum efficacy and positive results [34].

3.3.3 Agents for increasing circulation time:

Agents that increase circulation time are often used techniques for drug administration that make it possible for drugs to stay in the body longer in the bloodstream, thereby enhancing its therapeutic effect. Factors that are affecting circulation time are molecular Weight the larger molecules tend to have longer circulation times due to slower clearance from the body. Hydrophobicity is another factor because hydrophilic molecules are generally cleared from the body more rapidly than lipophilic ones. Next is the renal excretion the drugs that are readily excreted by the kidneys generally have shorter circulation times. And at last, the hepatic clearance the drugs that are metabolized by the liver will also have shorter circulation times.

PEGylated preparation of the SLNs (Solid Lipid Nano particles) shown more positive results than the normal formulation of the SLNs (Solid Lipid Nano particles) When compared to SLN, the pharmacokinetic investigations demonstrated that SLNs had a 1.99-fold higher relative bioavailability, longer blood circulation durations, and better absorption efficiency. PEGylated solid lipid Nano particles were beneficial for increasing oral administration's bioavailability.[35].

PEGylated SLN has greater promise as a nanocarrier for putting medicine in the mouth. Not harmful, doesn't cause immune reactions or antibodies, and dissolves very easily in water. Poly (ethylene glycol) (PEG) is FDA-approved and has been thought to cause very little interference with the drug release Phenomena [36]. PEG can sterically stabilise particles and prevent plasma protein binding, which decreases reticuloendothelial system elimination and extends the drug's half-life in circulation. It can also decrease immunogenicity and improve permeability and retention in tumour tissue [37, 38, 39].

3.4 Selection of drug:

When choosing a drug, its stability is taken into account. Whether the drug nature is hydrophilic or lipophilic. Based on that the how the drug works is selected. If the dose of the drug is very less than it can be carried out for the formulation of the SLNs because the Nano particles follow a brick like structure arrangement which make it permissible for only small amount of drug to enter in the structure. In the selection of the drug higher melting point drug cannot be used. High Log is not good for formulating SLNs stability of the medication is a significant concern. The Pharmacokinetic and Pharmacodynamic studies also play very important role category of the drug is also seen where the drug lies whether it is for the therapy for arthritis, cancer, and other illnesses. The drug's distribution, metabolism, excretion, and absorption depend on the drug whether it will be used for the sustained release or controlled release [40].

4. Fabrication methods for Preparation of SLN's [21,26]:

The fabrication methods for preparing solid lipid Nano particles solid-lipid nano particles include high-pressure homogenization, ultra-sonication, and solvent emulsification techniques. These methods enable the production of Nano particles with uniform size and stability, ensuring efficient drug encapsulation. Advanced techniques, such as micro emulsion-based and double emulsion methods, offer enhanced control over SLN characteristics for tailored drug delivery applications.

Table 03: Various Techniques for the Fabrication of Solid Lipid Nano particles SLNs [47, 48, 49, 50, 51]:

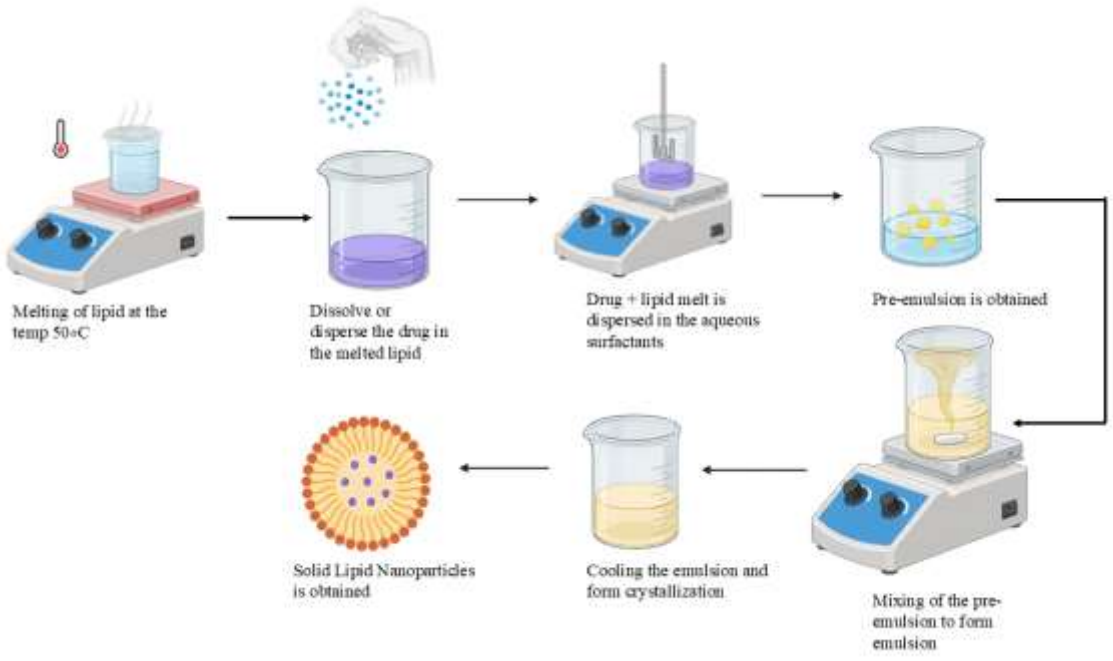
S.No	Category	Drugs	Methods
1.	Anti-Cancer	Cisplatin, Uorouracil, Epirubicin, and Doxorubicin	Double emulsion process
2.	Anti-Inflammatory drugs	Aspirin, Ketoprofen, Acetaminophen, Aceclofenac, and Diclofenac sodium, among others.	Double emulsion process
3.	Antibiotics drug	Ciprofloxacin, Clindamycin, Colistin, Doxycycline, Vancomycin, Erythromycin, Gentamicin, Norfloxacin, Cephalexin, Capreomycin, Cefazolin, and	Double emulsion process
4.	Proteins	Bovine serum albumin	Double emulsion method
5.	Nucleic acids	Hydrophilic nucleic acid	Double emulsion method
6.	Immunosuppressant	Cyclosporine	Emulsification diffusion method
7.	Anti- retroviral drug	Lopinavir	Hot self-nanoemulsification method
8	NSAID's	Diclofenac sodium	Emulsion/solvent evaporation method

9	Anti-metabolite drug	5-fluorouracil	Hot homogenization
10.	Anti-tumor,Anti-inflammatory, and Anti-fibrosis	Cryptotanshinone	Ultrasonic and high pressure homogenization

4.1 Hot Homogenization Technique [22]:

The thermal homogenization method begins by melting the lipid above its melting point, typically 5–10°C higher, to ensure it is in a liquid state. The medication is subsequently dissolved or disseminated in the liquefied lipid. Next, this lipid-core mixture is slowly added to a steaming mixture of water and surfactant, which is stirred vigorously to form a pre-emulsion. The pre-emulsion undergoes homogenization under high pressure. A process that reduces the particle size and creates a uniform dispersion of solid lipid Nano particles. After homogenization, the emulsion is permitted to reach ambient temperature, causing the lipid to solidify and stabilize the Nano particles, resulting in a stable SLN formulation. The schematic diagram of Hot Homogenization technique was discussed in Figure: 05

Figure:05 Hot Homogenization process for Solid lipid Nanoparticle Preparation



4.1.1 Advantages of the hot homogenization technique include:

- Efficient drug encapsulation: Enhances drug loading within the Nano particles.
- Uniform particle size: Achieves a consistent size distribution for better stability.
- Improved Bioavailability: Enhances the ability to dissolve and bioavailability of weakly water-soluble pharmaceuticals.
- Scalable process: This is appropriate for extensive synthesis of nanoparticles.

4.1.2 Disadvantages of the method:

- Heat sensitive material cannot be used for hot homogenization

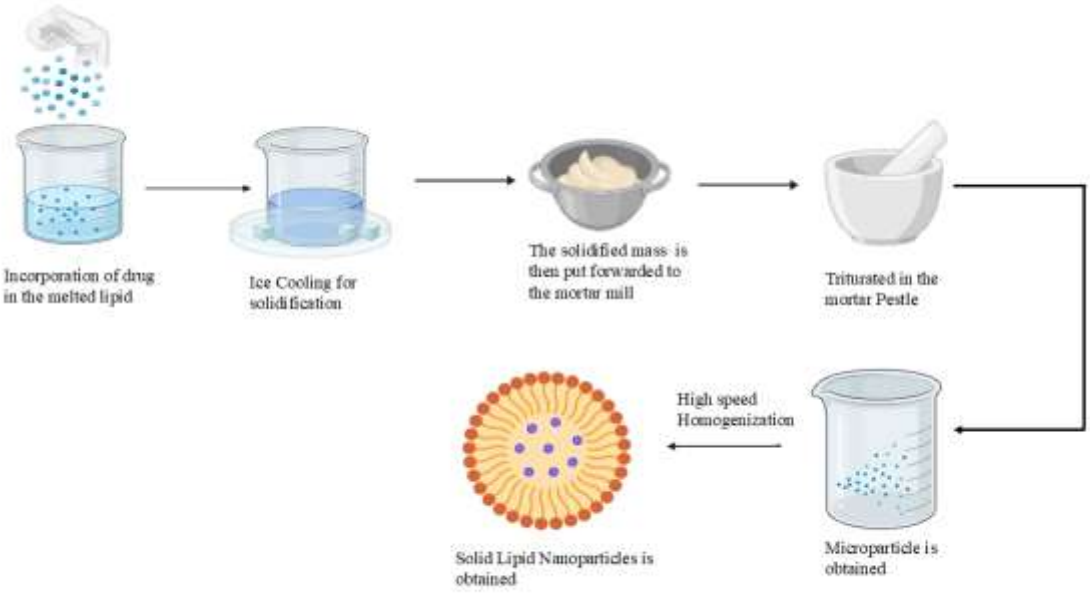
- Energy consumption is high in this technique which needs high energy input to maintain high temperature and pressure.
- If the technique is not properly controlled which will lead to denaturation or degradation of the material.
- The technique hot homogenization is a type of high-pressure homogenization, which is costly.
- Hot homogenization technique creates a lot of noise and vibration.

4.2 Cold Homogenization [22]**:**

Cold homogenization is another high-pressure homogenization (HPH) method used to create solid lipid Nano particles. This technique involves lowering the temperature while reducing the particle size in an emulsion or solution. The amalgamation is exposed to elevated pressure and shear forces at temperatures below the material's freezing point, resulting in the formation of Nano particles. First, the lipid and medicine are mixed together using the cold homogenization method. Then, the combination is cooled until it is under the lipid's melting point, which leads the lipid to solidify. The solid lipid-drug amalgamation is subsequently distributed in a solution of water comprising surfactants or stabilizers. The mixture gets emulsified using high-speed stirring or vortex mixing to create a coarse pre-emulsion.

The pre-emulsion undergoes homogenization under extreme pressure at ambient temperatures, which reduces the particle size and forms solid lipid nano particles. Finally, the combination is subsequently cooled to ambient temperature allowing the lipid to solidify and stabilize the Nano particles, resulting in a uniform size distribution and efficient drug encapsulation. This method is particularly beneficial for sensitive drugs that may degrade when exposed to higher temperatures. The detail procedure depicted in Figure: 06

Figure: 06 Cold Homogenization technique for Solid lipid Nano particlePreparation



4.2.1 Advantages of cold homogenization include:

- Heat-Sensitive drugs: Ideal for drugs that may degrade at higher temperatures.
- Efficient Particle size reduction: Achieves fine particle size with uniform distribution.

- Preservation of drug integrity: Maintains the stability of sensitive compounds.
- Scalable process: suitable for large-scale production of Nano particles.

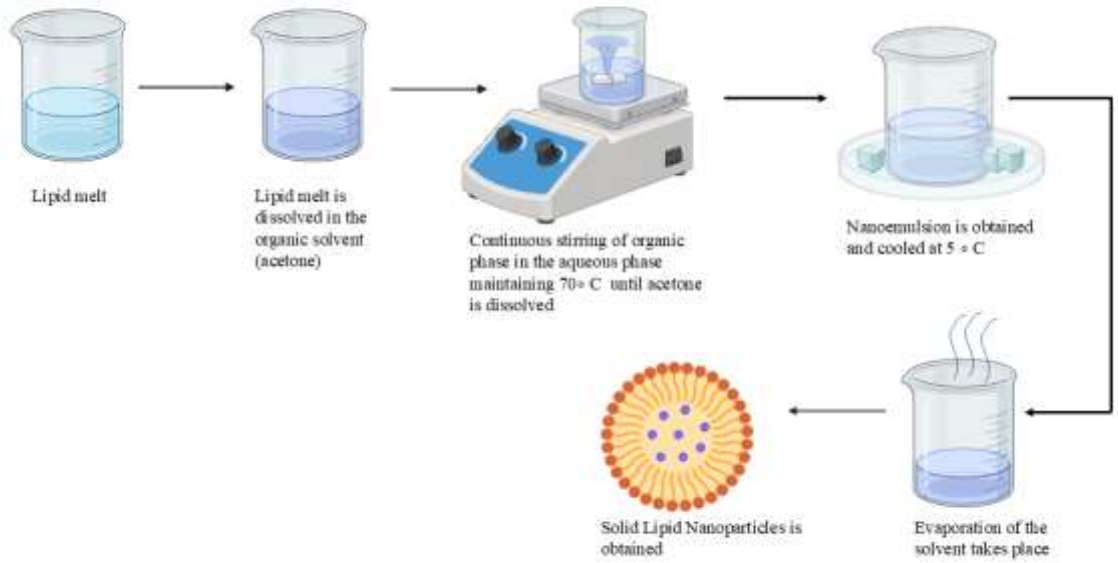
4.2.2 Disadvantages of cold homogenization include:

- This technique is not as efficient as hot homogenization method in reducing particle size.
- The equipment cost is more because the homogeniser that are used here are low temperature based.
- It might be difficult to keep the homogenization process at a low temperature, particularly in large-scale production.
- Despite being generally more energy-efficient than hot homogenization, cold homogenization nevertheless needs a large amount of energy to produce the required shear and pressure forces.

4.3 Solvent Emulsification-Evaporation Method:

This method, grounded on micro emulsion formation, is commonly used to create various types of Nano particles, including solid-lipid nano particles and polymeric Nano particles. This method begins by solubilizing the lipid in an appropriate solvent that is organic (such as chloroform or ethanol) to produce the phase known as organic. The medication is thereafter either digested or disseminated in the lipid solution. Next, the non-polar phase is slowly added to an aqueous phase containing surfactants or stabilizers, and the mixture is stirred vigorously to form a coarse emulsion. The solvent made up of organic is subsequently vaporized through gentle heating or reduced pressure, causing the lipid to solidify and form SLNs. Finally, the Nano particles are stabilized in the aqueous phase and cooled, completing the formulation. This method is widely used for encapsulating both hydrophobic and hydrophilic drugs in SLNs (Solid Lipid Nano particles). The entire procedure was illustrating in figure: 07

Figure: 07 Solvent Emulsification-Evaporation for SLN's Preparation



4.3.1 Advantages of the method:

- This method is considered to be versatile.

- The evaporation rate of the solvent and the emulsification process can be manipulated to regulate the size and distribution of nanoparticles.
- The process is appropriate for the large-scale manufacture of Nano particles since it can be scaled up for industrial use.

4.3.2 Disadvantages

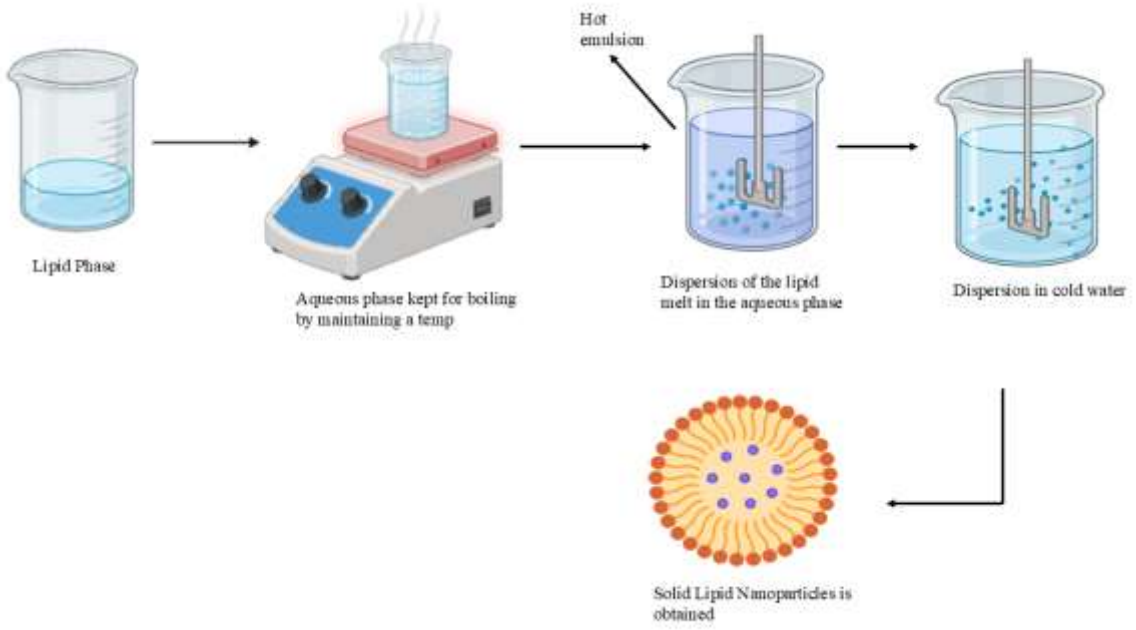
- Complete solvent removal becomes a problem in this case.
- Aggregate formation can happen while the solvent evaporates, producing a diverse population of Nano particles.
- Environmental issues may arise from use of organic solvents.
- Though it may be difficult to create extremely tight size distributions, solvent emulsion evaporation can offer some control over particle size

4.4 Micro-emulsion Technique:

Micro-emulsion-based methods are widely used for preparing solid lipid Nano particles. This technique involves forming a stable dispersion of oil, water, and surfactants, to which a solid lipid is then added. The micro-emulsion-based method for preparing SLNs commence by liquefying the solid lipid beyond its melting point and dissolving it in an appropriate oil phase, such as triglycerides or other lipophilic solvents. A water-based phase is then formulated by soaking surfactants (e.g., Tween 80) and co-surfactants (like ethanol) in water.

The oil phase is gradually incorporated into the water phase with moderate stirring to create an enduring micro-emulsion. Once the micro-emulsion is formed, the mixture is cooled, allowing the lipid to solidify and leading in development of SLNs. If necessary, excess solvent is removed through evaporation or dialysis, ensuring a pure Nano particle dispersion. This technique is effective for producing SLNs with controlled size, high stability, and efficient drug encapsulation. The in-detail procedure was demonstrated in figure: 08

Figure:08 Micro-emulsion Technique for Solid lipid Nano particle Preparation



5. Solid Lipid Nano particles' Characterization [8]:

Characterization is a crucial process in the pharmaceutical industry, ensuring that substances like SLNs meet quality standards such as particle size, drug loading, and stability. It also helps in understanding the relationship between formulation parameters and resulting SLN properties. Characterization also aids in optimizing by offering information about drug release, drug delivery kinetics, bio distribution, and targeting efficiency. It is often required for regulatory approval of SLN-based drug products. Characterization also allows for comparison and benchmarking against established standards, identifying potential issues and guiding formulation optimization. It also provides insights into drug-lipid interactions. Proper characterization of the Solid Lipid Nano particles is very much needed to check its proper quality. This characterization of the Solid Nano particles is very much necessary but it becomes a problem which is because of size of particle and nature of colloidal system.

The different characterization techniques are listed below:

- Zeta potential and Particle size
- Electron microscopy
- Atomic force microscopy (AFM)
- Determination of incorporated drug
- In vitro release studies
- Release order kinetics/ mechanisms

5.1 Zeta potential and Particle size:

Zeta potential is a crucial metric for evaluating the durability of solid lipid nanoparticles (SLNs). It denotes the potential for electrostatic charges at the outermost layer of the particle and serves as a measure of the repellent forces among particles. A significant overall value of zeta voltage (often exceeding ±30 mV) indicates robust electrical attraction among particles, hence inhibiting aggregation and preserving the stability of colloidal particles. In contrast, low zeta possible values may cause accumulation of particles, resulting in instability of the SLN formulation.

The size of SLNs is another critical factor that influences their drug delivery performance, including release rate, bioavailability, and stability. Smaller particles, typically ranging from 50 to 200 nm, offer a larger surface area, which significantly improves drug absorption and solubility. The particle size is commonly measured using advanced techniques like dynamic light scattering (DLS) or nanoparticle tracking analysis (NTA). Consistent particle size is essential for uniform drug distribution and predictable therapeutic outcomes. Large particles can cause undesirable effects, such as rapid clearance from the body or reduced cellular uptake.

Both zeta potential and size of nano particle are essential for guaranteeing the efficacy, stability, and regulated release of pharmaceutical nano particle from SLNs and also the few studies were reported the fluidity of the oil and aqueous phase, drug to lipid ratio, lipid matrix, surfactant mix, and production factors all affect the SLNs (Solid Lipid Nano particles) particle size.

5.2 Electron microscopy:

The technique known as electron microscopy (EM) employs an electron beam rather than light to create highly magnified images of objects. This allows for much higher resolution than traditional light microscopy, making it invaluable for studying structures at the nanoscale. Nano particles can be directly examined with scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

However, SEM performs morphological examinations more effectively than TEM, which has a limited detection criterion's size limit.

5.2.1 Specific Applications of Electron Microscopy in SLN Characterization:

- Particle Size and Distribution
  - Transmission Electron Microscopy (TEM): This technique accurately measures the size and distribution of individual SLNs by producing high-resolution pictures of them.
  - Scanning Electron Microscopy (SEM): SEM can be used for visualizing Surface characteristics of SLNs and assess their aggregation or agglomeration.
- Internal Structure
  - TEM: TEM can reveal the internal structure of SLNs, including the distribution of the encapsulated drug and the presence of any voids or defects.
  - Cryo-TEM: For studying the hydrated state of SLNs, cryo-TEM can be used to visualize their structure without the need for dehydration.
- Drug Localization
  - TEM can be used to localize the drug within the SLNs, helping to understand the drug-lipid interactions and the release mechanism.
- Interaction with Cells
  - EM can be used to visualize the relationship of solid lipid nanoparticles with cells, providing insights into their uptake, distribution, and cellular response.
- Comparison with Other Techniques
  - EM can be used in conjunction with other methods, like atomic force microscopy (AFM) or dynamic light scattering (DLS) to obtain a more comprehensive understanding of SLN properties.

5.2.2 Advantages of Electron microscopy for SLN Characterization:

- High resolution: EM provides high-resolution images, allowing for detailed visualization of SLN morphology and internal structure.
- Versatility: Both TEM and SEM can be used to study different aspects of SLNs (Solid Lipid Nano particles)
- Direct visualization: EM allows for direct observation of SLNs, providing valuable insights into their physical properties.

5.2.3 Challenges and Considerations:

- Sample Preparation: Proper sample preparation is crucial for obtaining high-quality EM images. This involves techniques like fixation, dehydration, and embedding.
- Imaging Conditions: Optimizing imaging conditions, such as electron beam intensity and focus, is essential for obtaining meaningful results.
- Interpretation: Interpreting EM images requires expertise and knowledge of the specific techniques used.

5.3 Atomic force microscopy (AFM):

According to the forces exerted between the probe's needle and the outermost layer, a topological map is created by dispersing a probed tip exhibiting atomic-scale sensitivity throughout a sample. Depending on the particular force employed, probe may have been either moved across the sample (contact mode) or suspended slightly above it (non-invasive mode). This allows for differentiation between the various sub-

techniques. AFM is a powerful tool that provides ultrahigh resolution and maps samples based on attributes like colloidal attraction and deformation resistance, beyond just size.

Atomic force microscopy is an additional sophisticated microscopic method for characterisation of Nano particles (AFM). The particles' original, unaltered shape and surface characteristics may now be seen thanks to this new tool. This method enables a spatial resolution of up to 0.01 nm due to the force that exists among the exterior surface and the pointed tip. The preparation of the samples is simple and does not require that they be conductive. It thereby makes it possible to examine samples that contain water and/or solvent.

5.3.1 Applications of AFM for SLN Characterization:

- Particle Size and Distribution: AFM measures SLN size and distribution accurately, even in heterogeneous samples.
- Surface Topography: Reveals SLN shape, roughness, and surface features.
- Mechanical Properties: Assesses elasticity and stiffness for biological context insights.
- Drug Release: Monitors changes in size and surface morphology to study drug release.
- Cell Interaction: Examines SLN uptake and cellular response.

5.3.2 Advantages

- High Resolution: AFM can provide images at the nanometre scale, allowing for detailed characterization of SLN morphology.
- Non-Destructive: Since AFM is a non-destructive method, the sample is not harmed during analysis.
- Versatility: Numerous characteristics, including as size, form, mechanical characteristics, and surface interactions, can be studied using AFM.
- Real-Time Imaging: AFM can be used to monitor changes in SLNs over time, providing valuable information about their stability and drug release.

5.3.3 Limitations:

- Sample Preparation: Sample preparation for AFM can be challenging, especially for soft or delicate samples.
- Imaging Time: AFM can be time-consuming for large or complex samples.

5.4 Determination of incorporated drug:

To determine integrated drug content, techniques such as ultracentrifugation, centrifugation filtration, and gel permeation chromatography are employed to separate the free drug and solid lipid from the aqueous medium. A solvent can be used to remove the contents, producing SLNs as the final product.

Drug selective localization at the interface is a feature of the enriched shell model. This can be caused by the drug successfully competing for the interface or by the matrix lipid solidifying quickly. Such a model may distribute drugs that show a successful burst effect during medication a release. Similar to solid solution, medication is uniformly distributed throughout homogeneous matrix model.

Maybe as a result of the drug solidifying more quickly than the matrix material, the enhanced core model exhibits drug selectivity at centre of SLN's. To produce membrane-controlled release, the enriched core model might be helpful. Further study is still needed to validate these ideas, even though the location of medicines within aggregates is largely determined by their chemical stability and release kinetics [35].

5.5 *In-vitro* drug release:

A multi-compartment rotating cell system with a donor compartment and a receiver compartment was

used to conduct an experiment using the drug paclitaxel to confirm in-vitro drug release study. To conduct the experiment, a dialysis membrane cut-off of 12,000 was utilised.30% ethanol was added to the receptor compartment, 0.4 cc of SLN dispersion was placed in the donor's cell. The receptor solution was pipetted out of the receiver compartment solution at predetermined intervals and concurrently replaced with 30% ethanol. The HPLC technique was employed to analyze the receptor's solution. In order to ascertain the drug concentration. [46].

The assessment of *In vitro* drug release can be checked by few methods such as [52]:

- Dialysis tubing
- Franz diffusion cell
- Reverse dialysis

5.5.1 Dialysis tubing:

Dialysis tubing can be used to accomplish the first technique for in vitro medication release. The SLN dispersions are placed inside a previously cleaned and hermetically sealed dialysis tubing. After dialysing the dialysis sac at ambient temperature in conjunction with an appropriate dissolving medium, specimens are removed from medium at predetermined intervals and centrifuged, and subjected to an appropriate procedure (High performance Liquid chromatography and U.V. spectroscopy, etc.) to determine the drug concentration. It's crucial to keep your sink in good shape.

5.5.2 Reverse dialysis:

SLN dispersion is used in this procedure to hold several tiny dialysis units, each holding one millilitre of dissolving liquid. Once in the dissolving medium, the SLNs are removed. This approach allows for direct dilution of SLNs yet, it is not possible to quantify the quick release.

5.5.3 Franz diffusion cell:

The donor compartment of the Franz diffusion cell, covered using a transparent film, is where SLN dispersions are stored. Following the dialysis of the mixture with an appropriate solvent at ambient temperature, Samples are extracted from the medium at the proper times, and the content of drug is ascertained using the proper method (HPLC, UV spectroscopy, etc.). The condition of the washbasin must be maintained.

5.6 Mechanism of drug release:

The drug release mechanism from SLNs is a rigid process influenced by various factors, like the properties of the lipid rigid, the encapsulated core material, and the surrounding environment. Drug incorporation and release studies play a vital role in formulating and assessing novel medication delivery methods. In solid lipid Nano particles (SLN), drugs are released through surface erosion, breakdown, and diffusion within the lipid matrix. The drug's discharge from solid lipid nanoparticles is contingent upon its positioning within the particle. Localizing the drug in core of the solid lipid matrix can result in sustained drug release. However, when drug is located on the particle surface, it may lead to burst release followed by more gradual release because of its localization in the lipid matrix.

5.6.1 Drug release kinetics:

The principal process via which medicines are released from SLNs is diffusion. Drug molecules are transferred from higher concentration areas within the SLNs to lower concentration areas, like the surrounding environment. Drug release from solid lipid Nano particles is primarily influenced by: Diffusion, the drug diffuses through the lipid matrix. Erosion: the lipid matrix degrades, releasing the drug.

Swelling and Burst release: SLNs swell, releasing the drug in a burst and matrix degradation: The lipid matrix itself degrades, releasing the drug.

The primary diffusion processes of Solid Lipid Nanoparticles are as follows:

5.6.1.1 Passive Diffusion:

Drug molecules diffuse spontaneously through the lipid matrix of SLNs (Solid Lipid Nano particles) in this most prevalent method. Lipophilicity, permeability of lipid matrix, and molecular weight of drug are some of the parameters that affect rate of passive diffusion.

Porous Matrix diffusion:

Drug diffusion through the holes in certain SLNs (Solid Lipid Nano particles)' structure is possible. The rate of drug release may be hampered by the size and distribution of these pores.

Matrix Degradation:

Diffusion of drugs can be aided by the formation of pores or channels created by the lipid matrix's eventual degradation.

5.6.1.2 Erosion in SLNs (Solid-lipid Nano particles):

Erosion, as it relates to SLNs, is the term used to describe the slow disintegration or deterioration of the lipid matrix that forms the structure of the nano particle. The medication that is encapsulated may release as a result of this breakdown.

- Hydrolysis: The lipid constituents of surface-level nanomedicines have the ability to hydrolyse and fragment into smaller molecules. The encapsulated medication may be released through pores or channels created by this mechanism in lipid matrix.
- Oxidation: Degradation of the SLN structure and drug release can also result from oxidation of the lipid components.
- Enzymatic Degradation: Enzymes found in the environment or the body may occasionally decompose the lipid matrix, facilitating the more efficient release of the medication.

5.6.1.3 Degradation of SLNs (Solid Lipid Nano particles):

When discussing drug release from solid lipid Nano particles SLNs, degradation pertains to the dissolution or breakdown of the fatty rigid that contains the core. The medication may discharge into the surrounding environment as a result of this degradation, which can happen through a variety of processes.

- Hydrolysis: The encapsulated medicine can be released through hydrolysis, which is the breakdown of the lipid components of SLNs into smaller molecules. Temperature, pH, and the presence of enzymes are some of the variables that affect this procedure.
- Oxidation: Oxidation of the lipid components can arise from exposure to oxygen, which can lead to medication release and degradation.
- Enzyme Degradation: The lipid matrix can be broken down by enzymes found in the body or environment, which allows for the release of drugs.
- Mechanical stress: The handling, storage, or administration of SLNs may expose them to mechanical stress. Under this kind of stress, the medication may be liberated from the matrix of lipids through degradation.

The following guidelines control the medication that is entrapped and released from the SLNs:

- There is a negative correlation between the drug's partition coefficient and its release.
- Higher surface area, which is encouraged by smaller particle size, results in increased drug release.
- The medicine releases gradually due to its homogeneous distribution in lipid rigid.

- Core substance release from SLNs occurs quickly due to lipid crystallinity and strong drug mobility [53].

Particle size and/or surface area affect how much medication is released in a burst from SLNs Less than a minute was required for 100% drug release from SLNs containing Tetracaine and Etomidate to exhibit burst release. The wide surface area and higher drug content in outer layer of the Nano particles were cited as the reasons for this release pattern. There was a burst release of the medication when it was discovered to have accumulated in outer shell of Nano particles with a comparatively short diffusion distance. On the other hand, lipid-soluble prednisolone-loaded SLNs showed a longer drug release profile. The medication is molecularly dispersed into a lipid matrix in a "solid dispersion model," which could explain this. According to this study's findings, SLNs combined with lipophilic medications exhibit delayed release patterns [55]. Modulating the process parameters can therefore be used to provide the appropriate medication release. The factors which affect drug release from SLNs (Solid Lipid Nano particles) include temperature, drug content, lipid and drug structures, production duration, processing equipment, lyophilisation, and sterilization [54]. Temperature and the presence of a surfactant are the two primary variables that influence the drug's release from the SLNs.

Drug incorporation and release studies play a vital role in developing and evaluating new drug carrier systems. In solid lipid Nano particles (SLN), drugs are released through surface erosion, breakdown, and diffusion within the lipid matrix. Release of drug from SLN depends on its localization within the particle. Localizing drug in core of the solid lipid matrix can result in sustained drug release. However, when that drug is located on the particle surface, it may lead to burst release followed by one more gradual release because of its localization in the lipid matrix.

The principal process via which medicines are released from solid lipid Nano particles SLNs is diffusion. Drug molecules are transferred from higher concentration areas within the SLNs to lower concentration areas, like the surrounding environment.

5.6.2 Influence of Temperature:

According to drug release studies, the greatest burst release happens when hot homogenisation is employed as the manufacturing method and at the highest production temperatures. Burst release decreases as the production temperature decreases and is insignificant when using cold homogenisation technique. Use of high temperatures promotes the drug's solubility in aqueous phase, so using lesser production temperatures might prevent burst release. SLN (Sold Lipid Nano particle) release profiles usually exhibit a biphasic trend. [54, 55].

5.6.3 Influence of Surfactants:

Amount of surfactant in SLN formulations influences burst release of drug. Higher surfactant concentrations lead to higher burst release, while lower concentrations reduce it. This phenomenon occurs during the hot homogenization process, where the drug redistributes between the phases of lipids and water. As the temperature decreases, the drug's solubility in water decreases, causing it to return to lipid phase. However, once lipid core crystallizes, the drug cannot fully incorporate, resulting in a supersaturated aqueous phase and higher burst release. Using less surfactant or no surfactant can help reduce burst release [54, 55].

6. Applications of SLNs in drug delivery:

6.1 Oral drug delivery:

SLNs extra vascular administration are possible by aqueous dispersion other than the conventional drugs.

SLNs can be administered into tablet by converting the Solid Lipid Nano particles first into the powder form and for drying (for e.g. Spray drying) is used and then it is mixed with the powder mixture of the tablet and carried out for the tablet process. Dried SLNs powdered is compressed encapsulate into tablets or incorporate into pellets. SLNs are used in the filling of the hard gelatine capsules [56]. The route after the oral administration of the drug is either carried out by the paracellular or the transcellular pathways. An essential function of SLNs is to facilitate the development of mixed micelles, which aid in the oral administration of medicinal drugs in a solubilized form to the gastrointestinal tract (GIT)by creating induction by secreting bile salts and phospholipids endogenously. Due to increased surface area facilitates the interaction of lipid molecules with epithelial membranes and creating a bio adhesion of the SLNs to the GI wall which creates a prolong residences time in GIT which outcome results in the improved oral absorption and bioavailability [57,58,59].

6.2 Targeted delivery:

For the treatment of cancer SLNs (Solid Lipid Nano particles) has seen to be beneficial for the treatment rather than the conventional drug delivery system. SLNs is most preferred drug carrier rather that other drug carrier because it bears the benefits of being biocompatible, non-toxic and many more properties. Recently many formulations are available which drug incorporated SLNs drug delivery system is. It is also known as Nano drug delivery systems. Also, it has been noticed that by altering the surface or by creating modification the SLNs (Solid Lipid Nano particles) becomes more prominent to active targeting and binding with the specific tissues or the cells and provide a good response in the treatment [60].

6.3 Transdermal delivery:

Among other routes of pharmaceutical administrationtransdermal route is regarded as one of the most beneficialroutes because it carries with it numerous advantages, including the elimination of first-pass metabolism, and also it has no link with the gastrointestinal fluid. However, there is only one problem which is the skin permeability which only allows selective particles to enter. SLNs (Solid Lipid Nano particles) is one of the novel transdermal drug delivery systems. Nano size of SLNs (Solid Lipid Nano particles) provides a good contact with stratum cornea which is the epidermis. Here the particles of the active core drug passes in systemic circulation through microcirculation. Because of the good contact of the SLNs (Solid Lipid Nano particles) with the stratum contact with the drug so the agents pass the layer and gets accumulated and show a good response of the action of the drug considered to the other drugs with bigger size and the binding is good for the lipophilic drugs [61, 62].SLNs (Solid Lipid Nano particles) can be used in the damaged or inflammation skin because due to its nontoxic or non-irritant lipid core [63].

Another more point is that SLNs (Solid Lipid Nano particles) forms an occlusive layer in the top of skin which prevents loss of water through the epidermis, simultaneously expanding epidermal poresfor which leads to increase in the hydration and therefore increased in the permeability [64].To promote transdermal absorption, the SLNs (Solid Lipid Nano particles) formulation can be reformed into foams and hydrogels to provide the required and increased skin contact duration [65,66]. It has been found that the cosmetic preparation of SLNs (Solid Lipid Nano particles) has UV reflecting properties [67]. SLNs (Solid Lipid Nano particles) has shown to be one of the most exciting new drug delivery systems usingtransdermal route. Whether the drug is either pharmaceutical or cosmeceutical or cosmetics, deliver of the drug through SLNs (Solid Lipid Nano particles) nano carrier is very useful.

6.4 Parenteral delivery:

Despite the medicine's limited bioavailability and narrow therapeutic index, the parenteral route of admini-

stration is the most used method of drug delivery. [68, 69]. The small size of the SLNs which make it an important component to be incorporate in the syringe for the administration of the drug. After introduction of SLNs in the syringe the dosing frequency of the parenteral changed a lot because the dosing is converted for the benefit of the patient compliance to sustained and controlled release for the drug so that it can work for a prolonged period of time in the body and provide pharmacodynamics results [70,71]. Peptide and protein which are the biotechnology drugs have been incorporated into the to prevent the extra vascular administration of drug because protein and peptide drugs can be degraded by enzymes. SLNs has solved a big problem towards repeatedly administration of the drug through vaccines now its prevented due to SLNs (Solid Lipid Nano particles) provide a sustained release of drug [72,73,74,75,76].

6.5 Role of Solid Lipid Nano particles as Vaccine adjuvants:

In the vaccine formulation, adjuvants are employed to boost the immune response following medication administration. The Common adjuvants include aluminium hydroxide particles, Freund's incomplete adjuvant (FIA), Freund's complete adjuvant (FCA), and emulsion systems such as SAF 1 and MF 59. However, these adjuvants might cause side effects or disintegrate quickly in the body. Because SLNs (Solid Lipid Nano particles) are solid, their lipid components will break down very slowly, giving the immune system a prolonged exposure time. Sterile stabilising surfactants that prevent enzyme complexes from anchoring can further slowdown the degradation of SLNs (Solid Lipid Nano particles). The biodegradation of SLN and its superior body tolerability are advantages over typical adjuvants. [50].

7. Recent Advances and Innovations:

Nanostructured lipid carriers (NLCs) and solid lipid Nano particles are the two main categories of solid lipid-based Nano particles (SLBNs). A number of techniques, such as solvent emulsification (also known as diffusion evaporation), high pressure homogenization, and micro emulsion technologies, could have been used to create SLBNs. SLBNs are effective carrier systems that are well-tolerated for parenteral, oral, inhalational, ophthalmic, and cutaneous uses [77]. Current developments in SLBN-based medication delivery are –

7.1Parenteral drug delivery and targeting:

Parenteral SLBN treatment has the potential to enhance both systemic exposure profile and targeting. To reduce side effects and maximize the effectiveness of parenteral administration, docetaxel-loaded NLCs were created [78]. When compared to drug solution, the AUC for plasma concentration-time curves of dexamethasone-loaded solid lipophiles. SLNs (Solid Lipid Nano particles) for distribution to specific lung areas was 17.8 times larger [79].

Actarit, an anti-rheumatic drug, was loaded into SLNs to improve therapeutic efficacy, decrease adverse effects, and enhance passive drug targeting. When administered intravenously to mice, the SLNs (Solid Lipid Nano particles) significantly reduced the renal distribution in comparison to drug solution, and they demonstrated an increased maximizing spleen efficiency from 6.31% to 16.29% [80]. In order to treat cancer, docetaxel-loaded stem-like Nano particles SLNs were created. For use in cancer treatment, docetaxel-loaded stem cell Nano particles SLNs (Solid Lipid Nano particles) demonstrated improved cellular absorption and tumour targeting efficacy [81].

7.2 Oral drug delivery:

Drugs contained in SLBNs can enhance the effects of lipids on absorption; when SLBNs are taken orally, they may attach to gut wall, causing the drug to be released near absorption site [82]. In addition, SLBNs may be broken down by the entanglement of surface lipase/co-lipase complex, breaking down the

triglycerides into monoglycerides that are surface-active, which form micelles, trapping drugs contained in degrading lipids. The Interactions between these micelles and bile salts in the digestive tract, resulting in the mixed micelles produced. Furthermore, when micelles interact with bile salts found in the GI system, mixed micelles can be formed. Due to the lipids' primary absorption into the lymphatic system through chylomicron production, the medication then (the Trojan horse effect) "goes with the lipid"[83]. Furthermore, it is well known that SLBNs and other Nano particulate systems may improve medication absorption in the oral cavity via means of intracellular uptake by the M-cells of Peyer's patches in the gut [84]. Therefore, based on the aforementioned principles, SLBNs have the potential to be a useful method for administering drugs orally.

7.3 Ocular and Inhalational drug delivery:

The ocular drug delivery benefits of SLBNs include controlled drug release, improved penetration, longer retention, and bio tolerance. As an initial ocular medication for the treatment of post-cataract miosis, flurbiprofen-loaded NLCs have received approval [85]. Additionally, for tobramycin [86], cyclosporine A [87], and timolol [88], SLNs (Solid Lipid Nano particles) improved ocular retention time bioavailability. Inhalational medication delivery using SLBNs has been investigated for treatment of the pulmonary illnesses. Following inhalational dosing, the alveolar area was the site of deposition of celecoxib-loaded NLCs. of Bulb mice, exhibiting a prolonged residence duration [89]. The inhalation of SLNs (Solid Lipid Nano particles) loaded with anti-tubercular medicines resulted in the lungs of tuberculosis-infected guinea pigs at an undetectable bacilli level [90]. Insulin-loaded SLNs (Solid Lipid Nano particles) loaded with fluorescent labels distributed uniformly in lung alveoli, improved drug stability in vivo and in vitro, increased bioavailability, and sustained hypoglycaemic effects [91].

7.4 Dermal drug delivery:

SLBNs as an undetectable and an occlusive plastic film that improves penetration [92]. Additionally, their non-irritant and non-toxic lipid base makes them suitable for application on irritated or damaged skin. SLNs (Solid Lipid Nano particles) have improved skin penetration and pharmacological effects for glucocorticoids [93], cyproterone [94], and sphingosin-1-phosphate, while reducing adverse effects. NLCs were used to improve pharmacological effects and skin penetration for ketoprofen [95], celecoxib [96], coenzyme Q10 [97], cyproterone [98], and calcipotriol [99].

7.5 Role of SLN's in Gene Therapies:

A safe and efficient method of delivering different medications, peptides, DNA, and other biological macromolecules is using SLNs (Solid Lipid Nano particles) In contrast to other colloidal systems, SLNs (Solid Lipid Nano particles) are biodegradable, stable over time, and simple to scale up. It has been demonstrated that SLNs can transport medications to actively phagocytic liver cells. Their controlled release and colloidal size make them suitable for both intravenous and extra venous medication delivery. [100,101,102,103].

Successful gene therapy involves expressing gene that targets a specific organ or tissue for treatment. In the field of gene therapy, two main approaches exist: viral two methods of delivering genes: viral vector and non-viral. The first form involves a virus transferring genes into cells through its ability to penetrate them. Even though there are cases where viral gene transfer leads to extremely high gene expression levels, it can also cause carcinogenic and immunogenic effects, as well as inflammation, making transgenic expression transitory. When compared to viral vectors, non-viral vectors provide some benefits in terms of safety and production addressing some of their issues. It has been demonstrated that siRNAs and DNA

can be efficiently transported using a variety of non-viral delivery methods, including cationic polymers, liposomes, lipids, cell-penetrating peptides, and carbon nanotubes. [104-110].

The use of SLNs for gene delivery has gained popularity recently. Because the lipids with positive charges and DNA with negative charges join together electrostatically to form a complex known as a lipoplex, cationic SLNs (Solid Lipid Nano particles) are frequently used for gene transfer. DNA can be protected and delivered to target cells by lipoplexes. [111,112].

The study was reported on the siRNA-PEG/SLN, which has no obvious systemic toxicity and can pass through the blood-brain barrier to the tumour location [161]. Montana et al. examined the efficacy of cationically modified SLN as a nonviral gene delivery vector by using it to transport Paracentrotus lividus bep3 RNA [113].

8. Current challenges in SLN development

Challenges in SLN development include drug degradation during high-pressure processing [114], insufficient ability to load drugs [115], and drug loss as a result of polymorphism changes during storage [116]. Low entrapment efficiency [117] and high-water content in dispersions further limit their application [118]. Freeze-drying often leads to Nano particle aggregation [119], while autoclave sterilization can alter particle size [120]. Oral administration of SLNs (Solid Lipid Nano particles) faces challenges such as harsh gastrointestinal conditions and the mucus layer acting as a barrier [121]. Concerns regarding toxicity, excipient status, and required toxicity studies delay clinical adoption [122]. Despite these issues, SLNs (Solid Lipid Nano particles) show promise, as evidenced by sustained plasma levels of drugs like paclitaxel following intravenous administration.

9. Future Directions of Solid Lipid Nano particles (SLNs (Solid-lipid Nano particles))

These systems have been shown immense potential in drug delivery, but ongoing research is focused on overcoming current limitations and exploring new possibilities for their application. Some detailed future directions for SLN development are:

9.1Advanced Surface Modification

Targeted Delivery: Surface modification with ligands like antibodies, peptides, or aptamers can enable SLNs (Solid Lipid Nano particles) to specifically target diseased cells, such as cancerous tissues, minimizing off-target effects [123].

PEGylation: Polyethylene glycol (PEG) coatings can improve circulation time in the circulation via decreasing reticuloendothelial system (RES) identification and clearance.

PH-Responsive Coatings: Stimuli-responsive surface modifications can enable drug release in specific environments, such as acidic tumour microenvironments.

9.2Stimuli-Responsive SLNs (Solid-lipid Nano particles)

Smart Drug Delivery: Incorporating stimuli-responsive materials (e.g., temperature, pH, or enzymatic triggers) into SLNs (Solid Lipid Nano particles) can allow precise control over drug release, improving therapeutic outcomes [124].

Multimodal Systems: Dual-responsive or multi-responsive SLNs (Solid Lipid Nano particles) can be designed for enhanced control in complex physiological environments.

9.3Enhancing Drug Loading Capacity

Hybrid Lipid Systems: Combining solid lipids with liquid lipids or polymers to form nano based structured lipid carriers (NLCs) can improve drug loading efficiency [125].

Optimized Lipid Matrices: Research into novel lipid matrices that stabilize drugs and prevent expulsion during storage is critical.

9.4Innovations in Production Techniques

Scalable Manufacturing: Development of scalable and cost-effective production methods, such as continuous flow processes, is essential for large-scale SLN production.

Green Synthesis Approaches: Environmentally friendly methods that avoid harmful solvents or high energy inputs are being explored to make SLN production more sustainable [126].

9.5Exploration of New Therapeutic Applications

Gene and Nucleic acid delivery: SLNs (Solid Lipid Nano particles) can be engineered to deliver siRNA, mRNA, or plasmids for gene therapy applications, expanding their use in personalized medicine.

Vaccination platforms: SLNs (Solid Lipid Nano particles) are being investigated as carriers for antigens, enhancing immune responses in vaccine development [127].

Theragnostic: SLNs (Solid Lipid Nano particles) can be functionalized for so that diagnostic imaging and drug delivery can occur simultaneously, allowing for the monitoring of treatment effects in real-time.

9.6Overcoming Biological Barriers

Oral Bioavailability Enhancement: Strategies to improve SLN stability in harsh gastrointestinal environments and enhance mucus penetration are under development [128].

Crossing the Blood-Brain Barrier (BBB): Nano particles are being tailored for neurotherapeutic applications, enabling medications to traverse the blood-brain barrier and treat central nervous system (CNS) disorders.

9.7 Toxicity and Biocompatibility Studies

Comprehensive Safety Evaluations: It is essential to conduct biocompatibility and long-term toxicity studies to guarantee SLNs (Solid Lipid Nano particles) are safe for clinical use [129].

Alternative Excipients: The development of biocompatible and FDA-approved excipients can accelerate SLN adoption in pharmaceutical markets.

9.8 Personalized Medicine

SLNs (Solid Lipid Nano particles) can be tailored to individual patient needs by encapsulating specific drug combinations or customizing release profiles, contributing to precision medicine initiatives [130].

9.9 Combination Therapies

Co-Delivery of Drugs: SLNs (Solid Lipid Nano particles) can be designed to deliver multiple drugs with synergistic effects, such as chemotherapeutics and gene silencers for cancer treatment [131].

Integration with Nanotechnology: Combining SLNs (Solid Lipid Nano particles) with other nanocarriers, such as dendrimers or quantum dots, can create hybrid systems with enhanced functionalities.

9.10Regulatory and Clinical Advancements

Standardizing SLN formulations, production processes, and characterization techniques will facilitate regulatory approvals and clinical translations [132].

By addressing these areas, SLNs (Solid Lipid Nano particles) can become a more versatile and effective drug delivery platform, expanding their applications across various therapeutic domains.

10. Conclusion:

SLNs have emerged as a versatile and promising drug delivery system with the potential to address various challenges in modern medicine. Their biodegradability, regulated drug release, and biological compatibility are just a few of the unique qualities that make them appealing for many therapeutic uses.

SLNs offer several advantages over traditional medicine distribution methods, as like enhanced drug solubility, targeted delivery, and reduced side effects. The composition of nano particles can be tailored to specific drug delivery requirements by selecting appropriate lipids and surfactants. Various techniques, including homogenization, hot and cold emulsification associated with solvent evaporation, and micro emulsion methods, are employed to prepare SLNs (Solid Lipid Nano particles) While significant progress has been made in SLN research, there are still challenges to be addressed, such as scale-up manufacturing, long-term stability, and in vivo toxicity studies. Future research should focus on developing innovative SLN formulations, exploring novel drug delivery strategies, and conducting rigorous clinical trials to translate the potential of SLNs (Solid Lipid Nano particles) into real-world applications. By addressing these challenges and capitalizing on their unique advantages, SLNs (Solid Lipid Nano particles) have the ability to enhance patient outcomes while completely transforming the delivery of drugs.

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