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Solid Lipid Nanoparticles: A Brief Review from Solubility Enhancement to more Novel and Scientific Applications.

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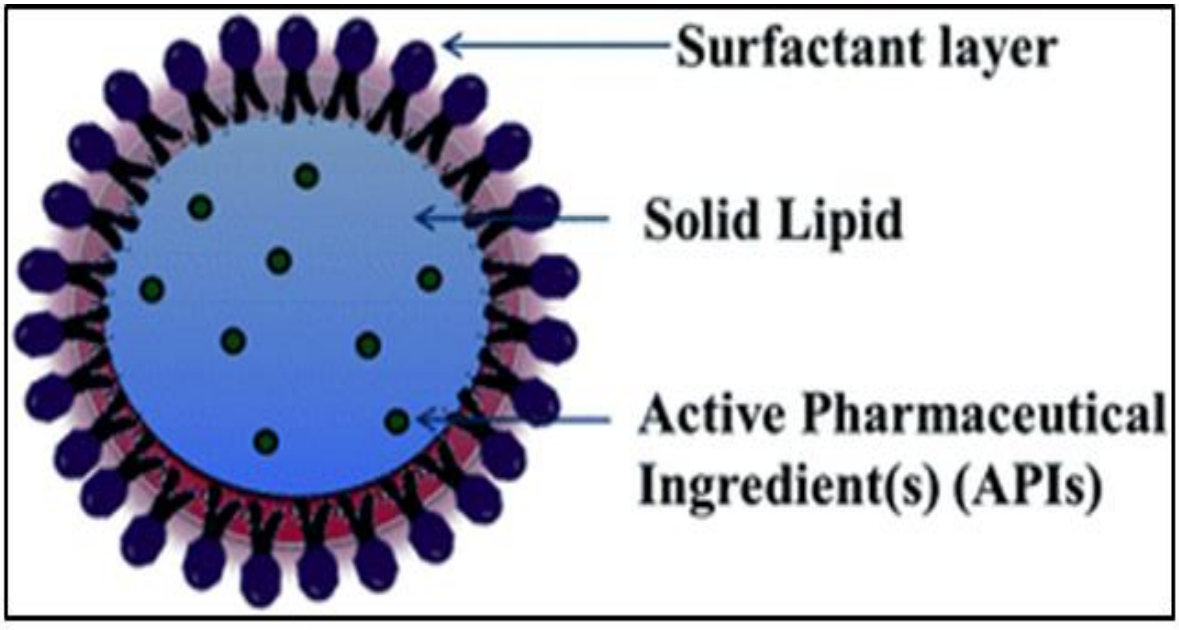
ABSTRACT
The last Decade have seen an increase in scientific and commercial interest in solid lipid nanoparticles (SLNs) as colloidal drug carriers. In comparison to other colloidal systems such polymeric nanoparticles, liposomes, and fat emulsions, they have emerged as a prospective substitute because it has been asserted that they combine their benefits while successfully overcoming their disadvantages. For its in vitro and in vivo applications, SLN formulations are thoroughly developed and characterised via a variety of routes, including parenteral, oral, pulmonary, ophthalmic, and cutaneous.The importance of excipient in formulation, stability, and the impacts of lipid nanoparticles in vitro and in vivo has been thoroughly covered in literature. Lipid nanoparticle biocompatibility is strongly influenced by the excipient type and composition. This review article covers the introduction, excipients used, models for incorporating drug into SLNs, methods of production,recent advances and patents in SLNs.

Keywords: Solid lipid nanoparticles,nanostructured lipid carriers, lipid drug conjugates, proteins and peptide delivery, patents on solid lipid nanoparticles, phase-inversion temperature.

I. INTRODUCTION:-

Colloidal drug carrier with diameter size range of 50nm to 1000nm are known as solid lipid nanoparticles (SLNs). For drug delivery applications, solid lipid nanoparticles are a highlybeneficialtechnique. They are non-toxic,biocompatible and easy to produce formulations. SLNs enables the entrapment of hydrophobic medicines with controlled release profile[1].

Solid lipid,surfactants,co-surfactants,or emulsifiers, as well as solvents and co-solvents, are often utilized in the formulation of SLNs.



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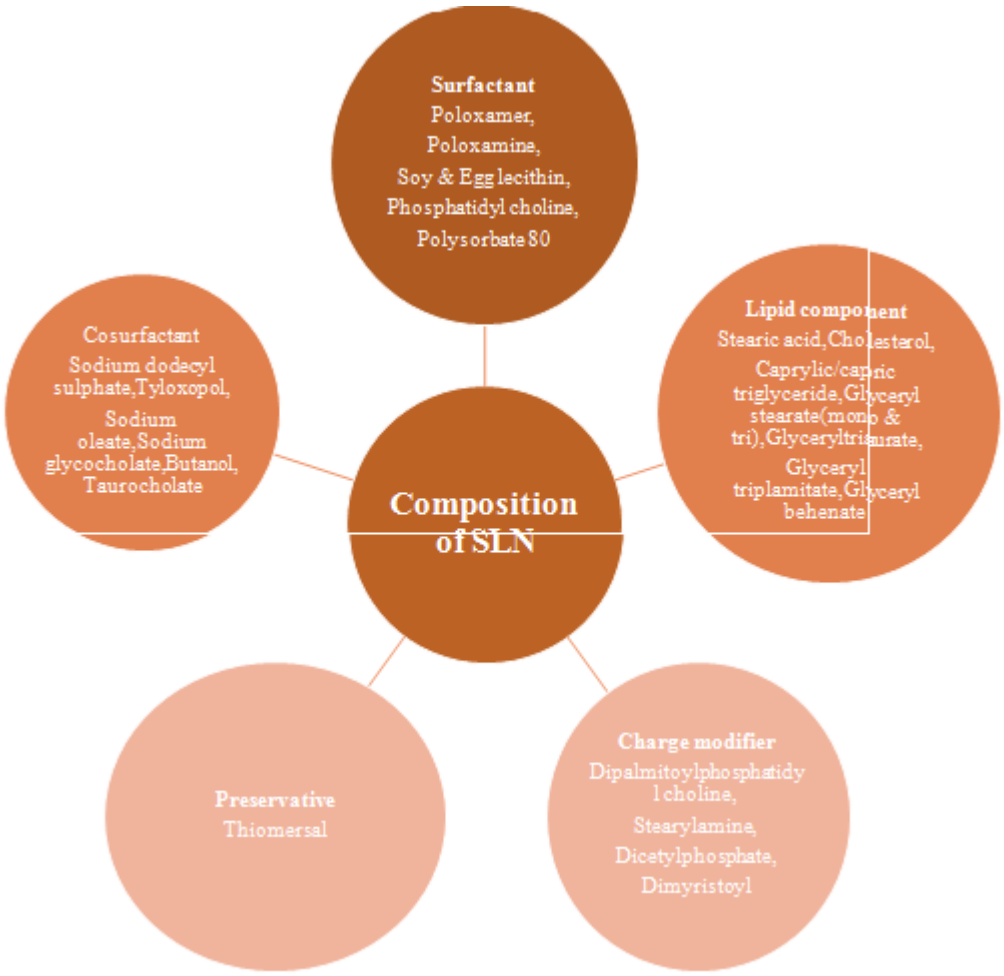

1) Solid lipid :-

Increasing the targeting specificity,transport effectiveness, and potency of pharmaceuticals has been accompalished by using lipids in the formulation of nanoparticles and nanocarriers. The different lipids used are triglycerides (tri-stearin), partial glycerides (Imwitor),fatty acids (stearic acid, palmitic acid), and steroids(cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (pluronic f68,f127) have been used to stabilize lipid dispersion.The selection of lipid is based on an assessment of their polymorphism,crystallinity, miscibility and physicochemical structure in order to ensure that the matrix maintains the solid state at room temperature[2].

Table 1: List of different types of lipids used for SLN preparation[3,4,5,6,7].

1	Triglycerides	Trimyristin
		Tristearin
		Trilaurin
		Tricaprin
		Tripalmitin
2	Acylglycerols	Glycerol monostearate
		Glycerol behenate
		Glycerol palmiostearate
3	Fatty acids	Stearic acid
		Palmitic acid

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		Decanoic acid
		Behenic acid
4	Waxes	Cetyl palmitate
5	Cyclic complexes	Cyclodextrin
6	Hard fat types	Witepsol W35
		Witepsol H35

2) Surfactants

Surfactants, or surface-active agents, are another crucial component of SLNs systems. Surfactants are amphiphilic substances with a lipophilic nonpolar and a hydrophilic polar moiety. The typical head and tail of surfactants are these two things taken together. Surfactants adhere to a system's surface or contact when utilised in low concentrations. They lower surface or interfacial free energy, which eventually results in a lower level of surface or interfacial tension between two phases[8].

The selection of the surfactant mainly depends on the chosen lipid, since they need to be physicochemically compatible.The type of the hydrophilic group and the HLB are both taken into consideration when choosing the surfactants that are generally employed in the manufacturing of SLN and NLC. Nonionic emulsifiers, such as Tweens, Spans, Mirjs tyloxapol, poloxamers, sugar esters, and esters of stearic, palmitic, oleic, and lauric acids, typically do not exhibit an ionic charge (e.g., monoglycerides of long-chain fatty acids).[9]

The required HLB (rHLB) of a final dispersion is predominantly dependent on the HLB of the lipid and on the HLB of the surfactant (and cosurfactant, if applied), and is determined applying the following equation :-

$$rHLB=[\%_{Lipid}xHLB_{Lipid}]=[\%_{Surfactant}xHLB_{Surfactant}]+[\%_{Cosurfactant}Xhlb_{Cosurfactant}]$$

The rHLB is crucial because the SLN and NLC dispersions are more stable when an optimised surfactant is used alone or in conjunction with other surfactants.Electrostatic interactions predominate when lipids and surfactants interact. These are injected into the lipid matrix or physically adsorbed onto the surface. Depending on the volume and chemical makeup of the hydrophilic moieties of the surfactant, the hydrophilic groups increase the repulsive forces[10].

To increase the surface electrical charge and prevent particle aggregationand/or sedimentation, anionic or cationic surfactants may be important.The molecules of the cationic surfactants, such as stearylamine, quaternary ammonium salts, N,N-di-(β-stearoylethyl)-N, N-dimethyl-ammonium chloride have a positive charge. The negative moiety in anionic surfactants (such as sodium cholate and sodium taurocholate) improves the absorption of particles in the gastrointestinal tract. The manufacture of SLN and NLC can also use phospholipids produced from soy or egg phosphatidyl choline, which have a varied fatty chain structure[11].

Table 2: commonly used surfactants for SLN preparation[12,13,14,15,16]

Ionic surfactants	**Sodium cholate, sodium glycocholate, sodium taurocholate, sodium deoxytauroglycocholate,etc.**
Amphoteric surfactants	Egg phosphatidylcholine(Lipoid E PC S),soy phosphatidylcholine(Lipoid S 100, Lipoid SPC),Hydrogenated egg phosphatidylcholine(Lipoid E PC-3),Hydrogenated soy phosphatidylcholine(Lipoid S PC-3, Phospholipon 80 H, Phospholipon 90 H),egg phospholipid(lipoid E 80, lipoid E 80 S),soy phospholipid(lipoid S 75)
Non-ionic surfactants	Poloxamer(188,182,407,908),Tyloxapor,Polysorbate(20,60,80),span (20 & 80), Brij 78,etc
Co-emulsifiers	Butanol, butyric acid , ethanol.

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3) **Agents for surface modification and ligands:** The methods employed for liposome functionlization are typically a major source of inspiration for techniques used to modify the surface of SLN. This is particularly true for the postinsertion approach, which several groups have adopted for usage with SLN, and the inclusion of unique functionalized lipids in the formulation. Another strategy involves employing N-hydroxy succinimide/1-ethyl-3-(3-dimethylaminopropyl)carbodimide(NHS/EDC) chemistry, which has been successfully applied to polymeric particles, to form a covalent bond between the coating agent and an excipient thought to be aessential component of SLN/NLC.The uptake of SLNs by the RES is decreased when the surfaces of the SLNs are modified with hydrophilic polymers. The mean retention time of the medications in the systemic circulation is increased by the long circulating or stealth carrier-based SLNs because they stay in the blood for an extended period of time.PEGderivatives, in particular, have been used frequently to obtain the steric stability of nanoparticles, hence lowering their uptake by RES cells[17].

By four hours, PEG-prepared nanoparticles could transfer 70–80% of the siRNA that had been administered to tumours. In comparison to non-stealth SLNs, SLNs made with dipalmitoylphosphatidylethanolamine-PEG2000 or stearic acid-PEG2000 shown a 30–40% reduction in absorption by murine macrophages. When compared to nonstealth SLNs, doxorubicin-loaded SLNs with stearic acid-PEG2000 showed less clearance and better biodistribution. In comparison to uncoated particles, which were uptaken by liver Kupffer cells at a rate of 66% in five minutes, lidocaine-loaded poly(lactic-co-glycolic acid) (80 kD)-PEG (20 kD) nanoparticles only attracted less than 30% of the cells after five hours. Doxorubicin-loaded poly(-benzylL-aspartate)-PEG co-polymer micelles displayed improved anticancer activity in comparison to free drug and demonstrated a prolonged drug release.PEG coatings that can shed in response to pH, enzyme concentration, redox potential, and other proteolytic enzymes have also been developed. These changes to PEG will increase the likelihood of therapeutic drug delivery that is site-specific while preserving the stealthy nature required for target site traversal[18].

Different hydrophilic or amphiphilic polymers were explored as PEG coating alternatives. As potential substitutes, polyvinyl pyrolidone and polyglycerols were suggested. Additionally, polyglycerol derivatives can act as a surfactant for the stabilisation of SLN/NLC.Nanoparticles coated with poly(N-vinyl-2-pyrrolidone) (PVP), poly(4-acryloylmorpholine), or poly(N,N-dimethylacrylamide) remained in the blood circulation of rats for a longer period of time even though their half-lives were shorter than those of PEG-coated nanoparticles. Repeated injections of PVP-coated nanoparticles at different time intervals, doses, or frequencies did not cause the ABC phenomenon, however PEG-coated nanoparticles did[19].

In particular for formulations meant for oral administration, surface modification by alginate coating aims at better mucoadhesive characteristics. A polysaccharide made up of β-d-mannuronic acid and α-l-gluronic acid, alginate normally has a negative surface charge (at neutral pH). Alginate was added to the outer aqueous phase of the double-emulsion-prepared SLN to ensure that adsorption would occur on the SLN/NLC surface. The authors found that alginate could contribute to both steric and electrostatic repulsion between individual particles, which would likely help to improve the stability of SLN/NLC.Alginate coating SLNs enhances their ZP and might potentially offer greater mucoadhesive qualities[20].

Chitosan is widely included in SLN/NLC formulations to improve mucoadhesive characteristics desired for oral formulations or interaction with sialic acid on eye surface for ocular formulations. For its biocompatibility, biodegradability, mucoadhesive characteristics, and ability to form stable complexes with nucleic acids, chitosan has attracted significant interest in pharmaceutical research.Recent studies have also shown that chitosan-coated SLN can effectively increase the in vivo absorption of encapsulated insulin by extending the period that insulin remains on the mucosa as a result of its improved mucoadhesive property[21].

Chitosan coating has been demonstrated to further increase the stability of SLN in simulated stomach conditions by producing a distinct and thick layer surrounding the SLN against its aggregation, as is clearly seen under TEM. For the creation of an oral drug delivery system for substances that are hydrophobic, chitosan-coated SLN exceeded alternative formulations[22].

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Hyaluronic acid (HA), also known as d-glucuronic acid and d-N-acetyl glucosamine, is a type of anionic polysaccharide that is frequently present in the extracellular matrix of different tissues and normally has a very high molecular weight. Its biological functions include regulating skin lesions' healing and tissue regeneration, specifically by encouraging cell migration and proliferation.

Cell-penetrating peptides are thought to be a viable approach for enhancing skin penetration or breaking through the blood-brain barrier. In order to isolate histidine-tagged peptides, histidine-tagged polyarginine of various chain lengths (i.e., arginine residues) were adsorbed on SLN surface utilizing the chelate complex formation method. This method boosted the transdermal distribution of two nonsteroidal anti-inflammatory medications in the case of SLNs. Peptides can also be attached to SLN surfaces by covalently joining them to the SA-PEG PEG chain, which can then be incorporated into the formulation of the SLN.

For the treatment of visceral leishmania, HP-CD-DDSLNs were discovered to be biocompatible and secure for oral delivery of hydrophobic and hydrophilic medicines that target the RES system[23].

Cyclodextrins (CDs) are cyclic oligosaccharides having a hydrophilic external surface and a hydrophobic interior cavity made up of a succession of naturally occurring macrocyclic d-glucose units. Due to their rigid toroidal structure and distinctive physicochemical properties, CDs can interact with numerous apolar medicinal molecules to form inclusion complexes in aqueous solutions. These interactions are known as host-guest or inclusion interactions.FDA-approved CDs have been widely used in the pharmaceutical industry using almost all routes of administration due to their excellent biocompatibility and extremely low toxicity. These benefits include improving bioavailability, increasing aqueous solubility and stability, and reducing the side effects of medications. By combining CD units with bifunctional agents to generate polymeric CDs, it is feasible to combine the characteristics of polymers and CDs, such as complex-forming CD features and three-dimensional networks of polymers with high molecular weight and high solubility.Positively charged poly-CDN+ was successfully deposited layer by layer over a negatively charged SLN core to create 1Layer and 2Layer SLN. These nanoparticles were made by sequentially depositing negatively charged poly-CDN+ and positively charged poly-CDS-. Particle size, size distribution, zeta potential, drug encapsulation, drug release patterns, and in vitro cell viability were used to monitor the coating process. It may be concluded that, hierarchical core-corona lipid nanoparticles may have benefits including controlled particle size, surface charge modification, greater physical and chemical stability, prolonged circulation time, and improved cellular interaction[24].

Incorporation of drug into Solid Lipid Nanoparticles:

Three alternative models of drug incorporation into SLNs have been proposed and published, depending on the preparation procedures. The lipids, active drug molecules, the surfactant, and the circumstances used during the production procedures, such as hot and cold homogenization, are all factors that affect the apparent structure obtained for SLNs. The homogeneous matrix model, also known as the solid solution model, the drug-enriched shell model, and the drug-enriched core model are three examples. These models are well discussed.

1. **Homogenous matrix model:**Solid solution model is synonym for the homogeneous matrix model. By using the cold homogenization approach and the hot homogenization method, extremely hydrophobic pharmaceuticals can be incorporated into SLNs without the addition of surfactants or drug-solubilizing agents, resulting in molecularly dispersed medications in a homogenous matrix or drugs present in amorphous clusters. The drug is molecularly distributed in the bulk lipid when the drug is homogenized cold. High-pressure homogenization combined with mechanical breaking produces nanoparticles with a homogeneous matrix structure. Similar results are obtained by chilling the oil droplet created by hot homogenization, which crystallizes with no evidence of a phase partition between the drug and lipid.The method relies on reducing droplet and particle size at extremely high pressures.In order to prepare SLNs and NLCs on a wide scale, it offers an efficient, dependable method.Stavudine-loaded SLNs and coenzyme Q10-loaded NLCs, for instance, were created using this technique at throughputs of 25 kg/h and 60 kg for batch sizes, respectively [25].

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2. **Drug-enriched shell model**:The lipid core in this model is encased in a drug-enriched outer shell. This suggested structure is produced by phase partition, which occurs when heated liquid droplets rapidly cool to form lipid nanoparticles. A lipid precipitation process can explain the structural morphology of the drug-enriched shell. Lipid precipitation happens during manufacture and as a result of the drug's redistribution during the chilling process. Each droplet after the heat homogenization process includes the medication and melting lipids. Rapid cooling of the lipid speeds up its precipitation in the centre while the concentration of the medication increases in the liquid outer lipid. A drug-enriched shell thus precipitates as a result of the cooling process when it is finished.Drug solubility in the water-surfactant mixture at elevated temperatures during manufacture plays a role in drug enrichment in the shell as well. Hot homogenization causes the medication to partially exit the lipid particle and dissolve in the aqueous phase. This is due to many medications' greater solubility in the outer phase (surfactant solution) at high temperatures[26].

(Figure 1,) enriches the medication inside the shell. A lipid precipitation mechanism that takes place during particle formation can account for this. Each droplet contains a mixture of the medicament and lipid following homogenization. After that, it is chilled. The TX solubility diagram is a two-dimensional graphical representation of the isobaric phase relationship in a binary system, with temperature and concentration coordinates. Depending on the solubility diagram, the lipid may precipitate before the drug to form a drug-free core or at least a core with reduced drug content. Lipid and drug precipitate concurrently in the particle's outer shell as a result of the particles reaching the eutectic composition and temperature[27].

Lower drug loading leads to formation of drug-enriched shell SLN which promote faster release.Incorporation of molecular sunscreens on SLNs showed synergistic effect on protective characteristics[28].

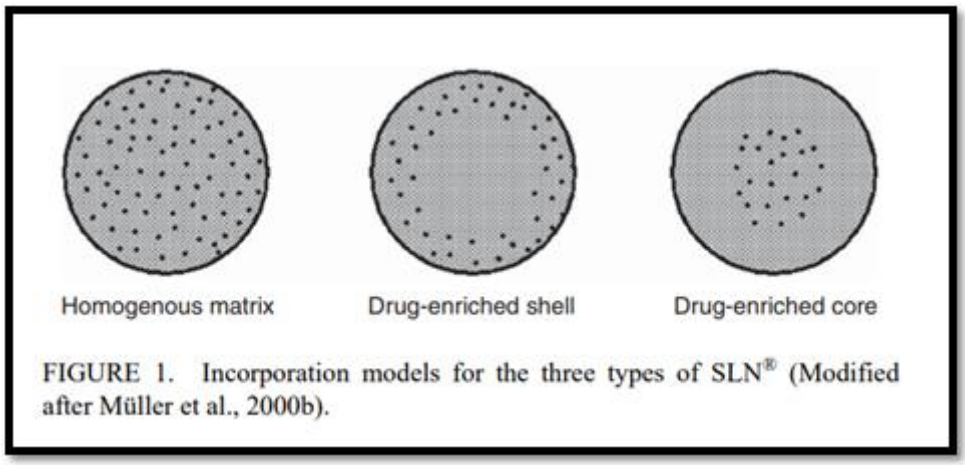

FIGURE 1. Incorporation models for the three types of SLN® (Modified after Müller et al., 2000b).

3. **Drug-enriched core model:**The lipid core in this model is encased in a drug-enriched outer shell. This suggested structure is produced by phase partition, which occurs when heated liquid droplets rapidly cool to form lipid nanoparticles. A lipid precipitation process can explain the structural morphology of the drug-enriched shell.In the drug-enriched shell model, the drug concentrates in the still-liquid outer shell of the SLN due to the fall in dispersion temperature, and a solid lipid core forms once the lipid recrystallization temperature is reached[29].The tetracaine and etomidate, faster release from lipid microparticulate was achieved through short diffusion path due to an enrichment of drug in the outer region of the SLN or drug deposition on the particle surface.Compared to drug-free particles, the presence of the drug in the lipid matrix appears to hasten the polymorphic switch to the stable modification. These findings were attributable to variations in drug deposition within the particle and high levels of interactions among lipid and drug molecules[30]**.**This paradigm is thought to be suitable for the inclusion of medications in

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SLNs with abrupt release profiles. For SLNs produced for dermatological uses, where enhanced penetration of the medications is required in addition to the occlusive actions of the SLNs, this faster release pattern of the drugs is specifically required[31].

PREPARATION TECHNIQUES OF SOLID LIPID NANOPARTICLES.

Different techniques are used to synthesize SLNs from solid lipids and surfactants utilising water as the solvent. Many different SLN preparation methods have been established with success. The choice of the method for SLN preparation depends on a number of variables, including the drug's physicochemical properties, stability, desired particle characteristics for the lipid nanoparticle dispersion, stability, and the availability of production equipment.

Typically, a dispersed system is needed as a precursor or template for the creation of nano- and microparticles; alternatively, particles are created using a specific piece of equipment.

Sr no.	Techniques	Precursors/template	Type of nanoparticles.
1	Hot homogenisation (high pressure homogenisation, high shear homogenisation, ultrasound homogenisation)	Emulsion	Solid lipid nanoparticles
2	Phase inversion temperature	Emulsion	Solid lipid nanoparticles
3	Melt dispersion	Emulsion	Solid lipid nanoparticles
4	Microemulsion dilution	microemulsion	Solid lipid nanoparticles
5	Microemulsion cooling	microemulsion	Solid lipid nanoparticles
6	Solvent displacement	Organic solvent solution	Solid lipid nanoparticles
7	coacervation	Micellar solution	Solid lipid nanoparticles
8	Solvent evaporation from emulsion	Organic solvent emulsion	Solid lipid nanoparticles
9	Solvent diffusion from emulsion	Organic solvent emulsion	Solid lipid nanoparticles
10	Particles from gas saturated solution/suspension	gas saturated solution/suspension	Solid lipid nanoparticles/ Solid lipid microparticles
11	Supercritical fluid emulsion	Supercritical fluid extraction of emulsion	Solid lipid nanoparticles
		Membrane contactor technique	Solid lipid nanoparticles
		Cryogenic micronisation	Solid lipid microparticles
		Spray-drying	Solid lipid microparticles
		electrospray	Solid lipid nanoparticles/ Solid lipid microparticles
		Spray-congealin	Solid lipid microparticles

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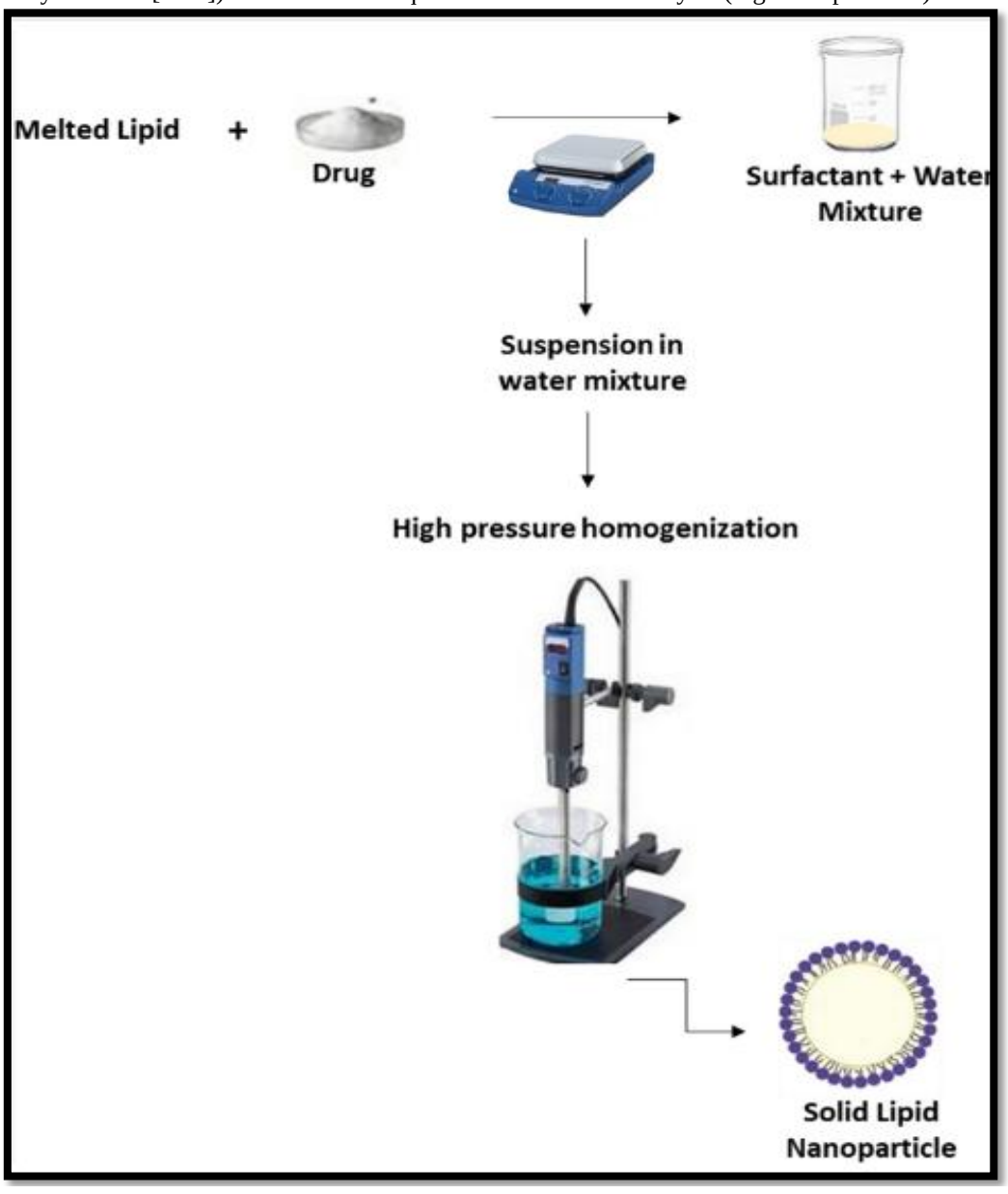
1. **Hot homogenization**

A. **High pressure homogenization:** High pressure homogenisation is the preferred method of manufacturing for the solid lipid nanoparticles (SLN).In the case of SLN, the medication is dissolved or distributed in a solid lipid melt, often at a temperature 5–10 °C or so above the lipid's melting point.It is advised to use dispersion-efficient, fast diffusing, electrostatically stabilizing, low molecular weight surfactants (such as sodium Dodecylsulfate [SDS]) in the subsequent homogenization process to achieve a high dispersity. They effectively stabilise the newly created tiny droplets and minimise subsequent coalescence occurrences by diffusing quickly into newly formed interfacial layers. Combining with a steric stabilizer is advised for maximum physical stability in gastrointestinal medium (e.g., Tween 80 or Poloxamer 188). Compared to electrostatic stabilization, steric stabilization is just slightly or barely hampered by the presence of electrolytes (high zeta potential).



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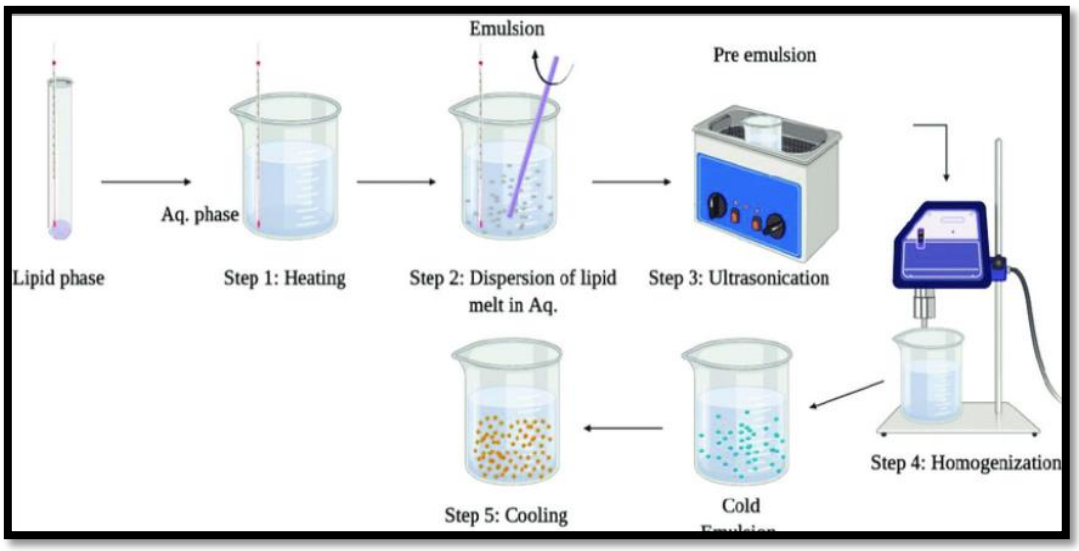
a) **Hot homogenization:**The active pharmaceutical components or medications are first dissolved in the lipid melt when using the heat homogenization procedure. A coarsepremulsion is created when the lipid melt is dispersed into the hot surfactant solution. The premulsion is then heated while being stirred to a temperature over the lipid's melting point.The heat homogenization process was examined in the latest study. The medication was mixed with the melted fat. Under constant stirring, the drug-loaded lipidic phase was dispersed in a hot aqueous surfactant solution to create a coarse o/w emulsion.Itwas then homogenized using a high pressure homogenizer at a temperature above the lipid's melting point to create an o/w nanoemulsion, which was cooled to room temperature for solidification and the production of solid lipid nanoparticles.

It is reported that the poorly soluble medicine efavirenz's solid lipid nanoparticles were successfully created and improved utilizing the high-pressure homogenization process and a systematic approach to design of experiments (DoE). In compared to the commercial formulation that was to be taken orally, the intranasal administration of the formulation demonstrated 150 times more brain targeting effectiveness and 70 times greater absorption potential (capsule) [32].Since hot homogenization can be carried out at temperatures beyond a lipid's melting point, it is the method of choice for creating solid lipid nanoparticles. Cavitations and turbulences during homogenization account for the reduction in particle size.With a particle size of 393.1 nm and a zeta potential of -15.1 mV, C4 formulation excelled all other preparations in terms of drug content (82.5%), entrapment efficiency (72.2%), and drug release (64%) following hot homogenization. The SEM results were also consistent with particle size and showed sphere-like shapes.The optimum approach was determined to be hot homogenization since the particle size was tiny and the entrapment effectiveness was high, possibly as a result of the surfactant's improved interaction with the lipid particles. This method was discovered to be straightforward, affordable, simple, and suited for producing SLNs. Comparing this process to other preparations, it can be scaled up. Additionally, it is possible that the produced nanoparticles will improve oral bioavailability. So using this hot homogenization procedure to create SLNs is successful[33].



b) **Cold homogenization:** The medications are first dissolved in the lipid by cold homogenization at a temperature above the lipid's melting point. After that, dry ice or liquid nitrogen are used to quickly cool the resulting combination. Rapid chilling is used to ensure that the medications are distributed evenly throughout the lipid. A mortar mill or ball mill is used to grind the solidified mixture into particles that are 50 to 100 microns in size. After that, a stabilizer or surfactant solution is used to suspend the resulting lipid

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microparticles in order to create a suspension. To create SLNs, this suspension is subsequently put through a high-pressure homogenization at room temperature or below.This quick cooling rate enables uniform medication dispersions within the lipid matrix. In a ball mill or mortar, the lipid-drug combinations are then crushed to a PS of 50–100 nm. Lipid microparticles are suspended in cold, surfactant-containing aqueous solutions, which are then homogenised at a low temperature (for example, 0–4 °C) during 5–10 cycles at 500 Bar [34].

2. **Precipitation from homogenous system:**Precipitation of SLNs from homogeneous liquids or colloidal systems is another method for creating SLNs. This procedure can be carried out using standard laboratory equipment because it doesn't require a lot of energy input. This method can produce small particles, but it is typically challenging to prevent supersaturation events, which results in larger SLNs.SLNs were created using the nanoprecipitation method and contained the lipids stearic acid, poloxamer 188, and lecithin (surfactant). Particle size measurement, polydispersity index, surface morphology analysis (Scanning and Transmission electron microscopy), cytotoxicity tests, and live-dead staining with acridine orange and ethidium bromide were used to evaluate the physicochemical characteristics.it can be of two types: precipitation from warm microemulsion and precipitation from water-miscible organic solvents. The former includes fatty acid as matrix building block.Using a mechanical stirrer, hot aqueous phase including water, emulsifier, and cosurfactant is thoroughly mixed with the drug and molten lipid matrix mixture. As a result, an optically transparent and homogenous colloidal system is created, which is subsequently diluted with cold water to precipitate SLNs.When the dispersion is substantially diluted, the concentration of lipids decreases and small particles of the dispersion are ultimately produced. Furthermore, higher surfactant concentrations are used while creating the initial microemulsion [37]. After their precipitation, ultrafiltration, dialysis, and centrifugation are used to separate the concentrated nanoparticles from the diluted solution and successfully remove the cosurfactant. They are put through freeze drying to stop the particles' development in aqueous phases while they are being stored. Whereas in precipitation from water miscible organic solvents the aqueous solution containing emulsifier is placed on an agitator or stirrer, and the solution containing the drug, stabilizers, and/or lipid matrix material is then injected into the mixture. This is often done at room temperature or at elevated temperatures for the aqueous or organic phase, or both, of the microemulsions. Because they promote solubility, using hot organic solutions has proven to be beneficial. Ultrasonication with or without heat or their vortexing is typically used to improve the dispersion of the lipid components. Removing any remaining organic solvents is crucial since their presence can have toxicological effects and cause dispersion instability.In the current investigation, researchers looked into the viability of adding paclitaxel to solid lipid nanospheres (SLNs), which are colloidal therapeutic systems made from heated oil-water microemulsions and suggested for a variety of delivery methods . SLNs would have the benefit of being made of biocompatible materials, like lipids, as a means of paclitaxel delivery. They must also prevent drug precipitation, which is one of the issues that arises when the commercial dosage form is diluted prior to infusion delivery; in fact, the infusion devices incorporate a filter to remove any precipitated paclitaxel. A warm o/w microemulsion that exclusively contained natural compounds like phosphatidylcholine and no synthetic surfactants was used to create paclitaxel-loaded SLNs.The formulation of the SLNs contained additional biocompatible and biodegradable ingredients. Additionally, diafiltration washings can significantly reduce the quantity of cosurfactants present in the SLNs dispersions, resulting in a pure final product[38].

3. **Microwave assisted microemulsion technique**: For the synthesis of SLNs, the microwave-assisted microemulsion process makes use of microwave heating. At a temperature greater than the solid lipid's melting point, all the ingredients—including the medication and the aqueous surfactant/cosurfactant system—are added to the controlled microwave heating system. The formulation is continuously heated and stirred using a microwave oven to create a hot microemulsion. The microwave-based

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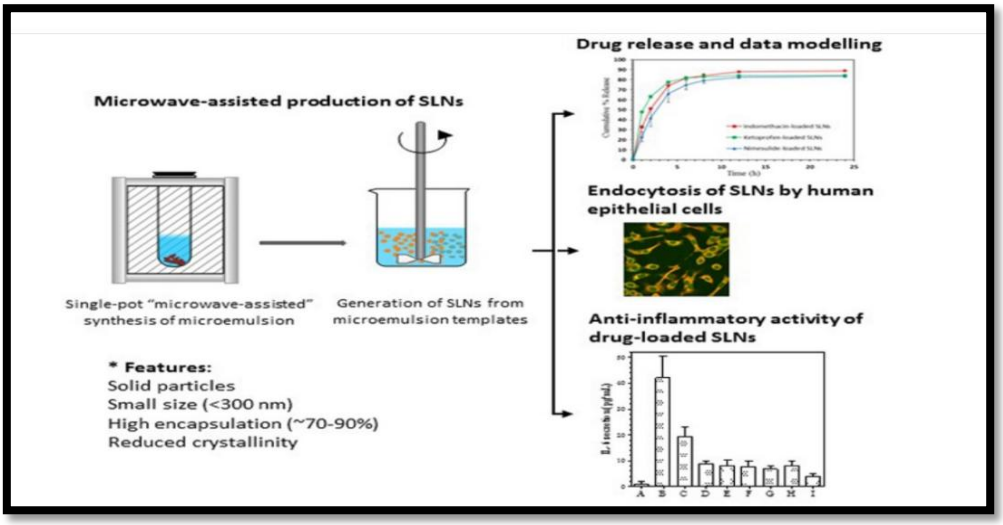
microemulsion process is referred to as "single pot" microemulsion production since all the materials are heated in a single step and one vessel, unlike other conventional microemulsion production procedures[39]. The resulting heated microemulsion is subsequently dispersed in cold water (at 24C) to produce SLNs.This study's major objective was to determine whether the microwave-assisted microemulsion technology could be used to encapsulate specific ionic drug substances, like econazole and miconazole nitrate. Small (250–300 nm), low polydispersity (0.20), high encapsulation efficiency (72–87%), and high loading capacity (3.6-4.3%) were all characteristics of the SLNs created using microwaves. Studies using differential scanning calorimetry (DSC) and X-ray diffraction (XRD) suggested that stearic acid in SLNs had a lower crystallinity.The preparation of SLNs loaded with ionic drugs was done using the microwave-assisted microemulsion technique. Miconazole nitrate and econazole nitrate, the chosen model lipophilic drugs, were successfully encapsulated inside the SLNs. The drug-loaded SLNs had positive zeta potential, narrow polydispersity, and tiny particle sizes. The microwave-assisted method was effective for producing SLNs with high levels of ionic drug encapsulation. Stearic acid's crystallinity in SLNs appears to have diminished, according to parallel DSC and XRD investigations. For both medications, the drug release profile indicated an initial burst release followed by a steady, sustained release for up to 24 hours.According to the study, SLNs were created using a microwave-assisted method that had better physicochemical properties than traditional SLNs. The use of SLNs created by microwaves is fairly novel and is still substantially studied. In this investigation, researchers aim to manufacture SLNs using the previously described microwave-assisted microemulsion technology as an alternate NSAID delivery strategy. Based on their physicochemical characteristics, the drugs indomethacin, ketoprofen, and nimesulide as our model medications were chosen. Themodel medications have been used to treat gout, synovitis, osteoarthritis, rheumatoid arthritis, and other inflammatory diseases.By using the microwave-assisted microemulsion technique, solid lipid nanoparticles with non-steroidal anti-inflammatory drug-encapsulated were successfully created. The drug-loaded SLNs had a loading capacity of 3.6-4.6% w/w, a zeta potential of -20 mV, and entrapment efficiency of 70-90%. They were nanoscale (250–300 nm). The "onepot" aspect of the microwave approach, which enables the simultaneous encapsulation of the drug and the production of the SLNs, may contribute in part to the high entrapment efficiency and loading capacity. Since the drug does not need to pass through the shell in order to be absorbed and since there is a larger effective surface area available (during SLN creation) for any adsorption, this could boost encapsulation efficiency and potentially change the process of encapsulation into the SLNs[40].



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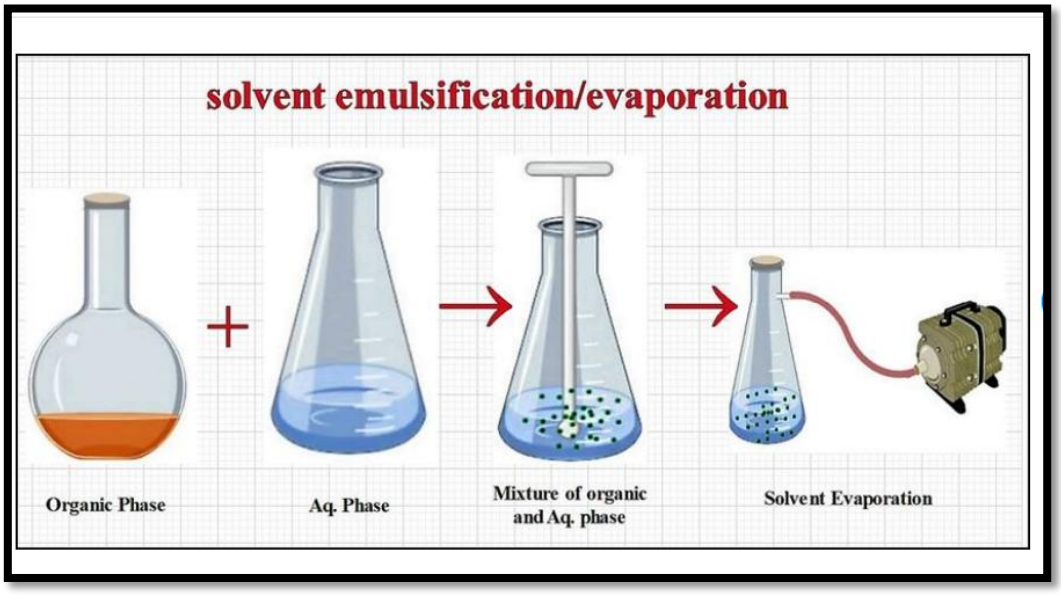
4. **Solvent emulsification-evaporation method:** This method is based on dissolving solid lipid in an organic solvent that is water immiscible, such as cyclohexane, chloroform, ethyl acetate, or methylene chloride, and then dissolving or dispersing the active component in the solution. The resulting organic phase containing medication is then vigorously mechanically stirred into an aqueous surfactant solution. Mechanical stirring or lowered pressure are utilised to remove organic phases. The precipitation of the lipid phase in the aqueous surfactant solution is the source of the lipid nanoparticles dispersion. The removal of the organic solvents occurs more quickly in order to stop the particles from aggregating. The method involves creating a w/o/w emulsion and dissolving the drug in the internal water phase to include hydrophilic medicines.SLN were created in the investigation using just one emulsification-solvent evaporation technique. The kind and quantity of lipid, the amount of surfactant, the amount of cosurfactant, and the volume of organic phase were among the formulation factors for which the preparation of SLN was optimized. Similar to this, the size and surface potential of SLN were determined and optimized in relation to factors associated to the homogezation, sonication, and stirring processes[41].

Ramipril-loaded solid lipid nanoparticles were synthesized using the solvent emulsification and evaporation methods, with phosphatidylcholine and stearic acid functioning as the lipid and surfactant, respectively. Particle size analysis, percent entrapment efficiency, Zeta Potential, SEM, X-ray diffraction research, FTIR, NMR spectroscopy, in vitro release study, and stability study were all performed on the produced formulations.The results were observed to be within the acceptable ranges. The FT-IR analysis of the formulations indicated that there was no interaction between Ramipril and other excipients. The developed formulations' sizes, according to particle size analyses, lay between 200 and 350 nm. The range of the percent entrapment efficiency was found to be between 70.61 and 91.60%. The R5 batch of nanoparticles' entrapment outcome and particle size were determined.The designed formulation recorded a cumulative drug release of 70.50% over the course of 7 hours. The planned batch displayed good formulation stability with a mean zeta potential of -29.4 mV.The proposed formulation was discovered to be stable, and it offers a potential method for the controlled and sustained release of ramipril[42].



5. **Double-Emulsion based method:**The production of warm w/o/w double microemulsions requires two processes. When aqueous drug solution is introduced to a mixture of cosurfactant, melted lipid, surfactant, and cosurfactant at a temperature just a little bit over the melted lipid's melting point, w/o microemulsion is initially produced.

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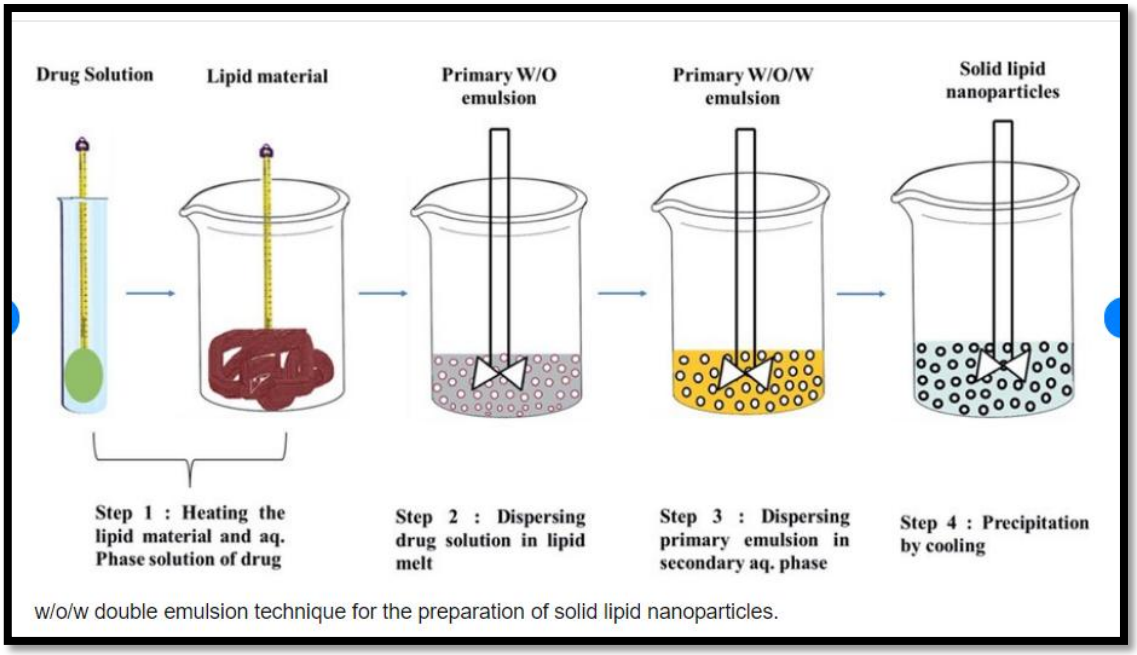
As a result, a transparent system is created. The second stage now involves adding the water, surfactant, and cosurfactant combination to the w/o microemulsion created in the first step. Consequently, a distinct w/o/w system develops. The warm double microemulsion is now cooledto produce SLNs, which are subsequently washed with dispersion media using an ultrafiltration system[43,44].The study's objective was to produce SLN-ferrous sulphate from stearic acid and monolaurin-rich fat. Different quantities of ferrous sulphate (5%, 10%, and 15% w/w lipid) and monolaurin-rich fat (20%, 30%, and 40% w/w lipid) were used to synthesize SLN-Ferrous Sulfate. The results demonstrate that the optimum characteristics, including high entrapment efficiency and loading capacity of 0.06%, were achieved by using monolaurin-rich fat at a ratio of 40% w/w lipid and 15% w/w ferrous sulphate. The polydispersity index (PI) of SLN was 1.03 and its Z-average value was 292.4 nm. The shape of the SLN-ferrous sulphate was spherical, and the nanosphere system formed by the Fe trapped in the SLN was uniformly distributed throughout the lipid matrix.SLN-ferrous sulphate was successfully encapsulated with excellent entrapment efficiency and favourable physicochemical features using a double emulsion technique based on stearic acid and fat rich in monolaurin[45].



w/o/w double emulsion technique for the preparation of solid lipid nanoparticles.

6. **Emulsification – diffusion technique:** This approach involves first saturating an organic solvent that is somewhat miscible with water, such as benzyl alcohol, isobutyric acid, or tetrahydrofuran, at room temperature or with the use of a controlled heating system[46]. The somewhat water-miscible solvent is then used to dissolve the solid lipid substance. Mechanical stirring is used to emulsify the solid lipid solution in a partially water-miscible organic solvent in an aqueous solution including surfactant to create an o/w emulsion system. At a regulated temperature, extra water is added to the resulting o/w emulsion, which causes the solvent to diffuse into the exterior phase and precipitate SLNs. The use of ultrafiltration and distillation to get rid of the organic solvent[47].Using isovaleric acid (IVA) as the organic phase, glyceryl mono-stearate (GMS) as the lipid, soy lecithin, and sodium taurodeoxycholate (TDC) as emulsifiers, insulin-loaded solid lipid nanoparticles (SLN) were created. Insulin and lipids were both dissolved using IVA, a low-toxicity, somewhat water-miscible solvent. By merely diluting the O/W emulsion in water, SLN with a spherical shape were produced. In addition, insulin did not experience any chemical modification within the nanoparticles and the majority of it remained stable after the SLN was incubated with trypsin solution, according to analysis of its content after processing, which revealed an interesting

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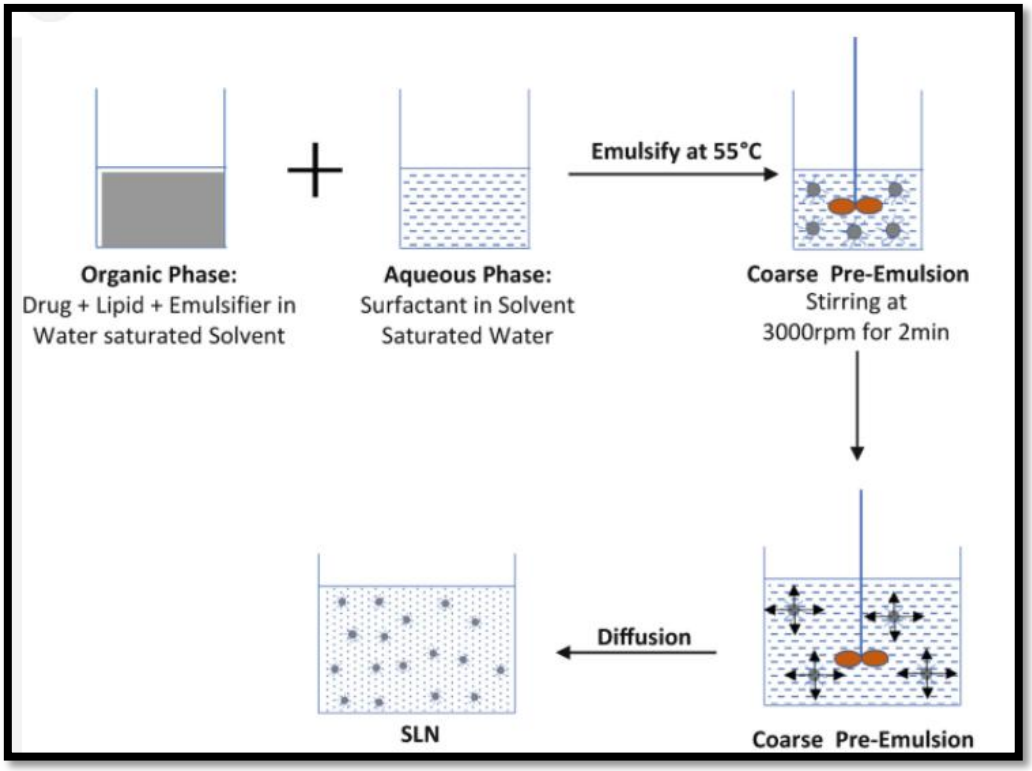
encapsulation efficiency with respect to therapeutic doses[48,49].



7. **Solvent displacement/injection method:** This technique relies on the lipid precipitating out of its solution. The lipid is initially dissolved by this approach in a water-miscible organic solvent such as isopropanol, acetone, or alcohol, or in a mixed solvent solution including both water and a water-miscible organic solvent. The stirring aqueous phase with or without surfactant is then injected with the lipid solution. The resulting lipid dispersion is filtered via filter paper to get rid of the extra lipid. The aqueous phase is typically combined with an emulsifier to create stable SLNs, which aids in the formation of lipid droplets at the injection site by lowering the surface tension between the aqueous phase and organic solvent[50,51].

The EVG loaded SLNs were prepared using the solvent injection approach, which relies on the quick diffusion of solvent through the solvent-lipid interface with the aqueous phase. Process variables such stirring speed, stirring time, sonication time, and the impact of variation in lipid content on particle size, PDI, and EE were all taken into consideration when designing EVG-SLNs. In the investigation, it was discovered that the mean particle sizes of EVG-SLN1, EVG-SLN2, EVG-SLN3, and EVG-SLN4 were 151.0, 174.8, 182.3, and 199.1 nm, respectively, with unimodal distribution[52].

8. **High shear homoginization/ultrasound method:**The manufacturing of SLNs uses a dispersing technique called high shear homogenization/ultrasonication. This approach allows for the formulation of SLNs by distributing molten lipid in the aqueous phase, followed by the stabilisation of the lipid with surfactants. According to Speiser (1986), lipid nanopellets for oral medication delivery were created by first homogenising at a high shear and then ultrasonically. The resulting lipid nanopellets had an average particle diameter of 80800 and were thus determined to be suitable for oral medication delivery [53]. In essence, this process involves heating a solid lipid to a temperature that is 510C or more above its melting point. The lipid melt is then thoroughly mixed with an aqueous surfactant solution at the same temperature to create an emulsion.Hot HSHM and BBD have successfully created the MCN-loaded SLN dispersion, which has been in vitro studied and optimised. The optimised formulation was discovered to be unstable under accelerated

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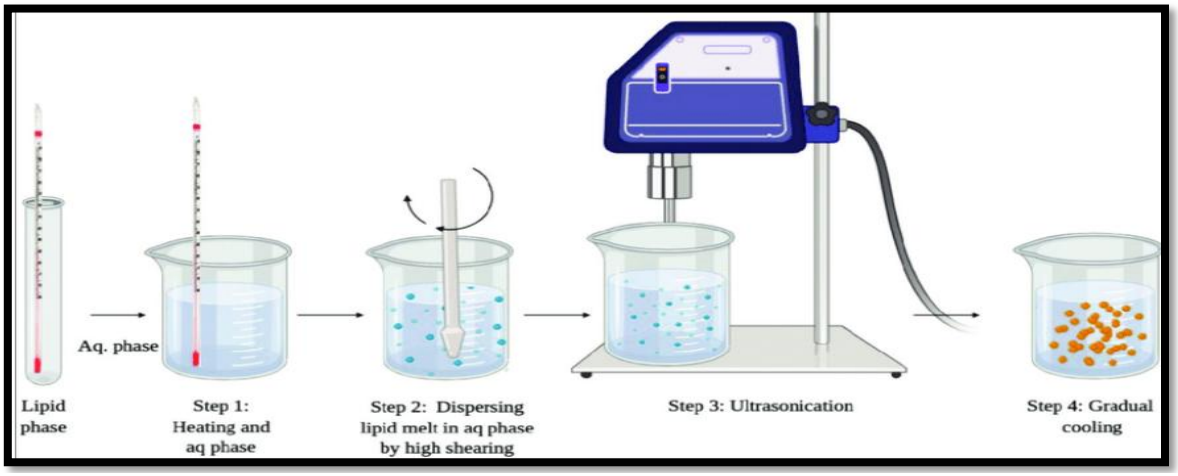
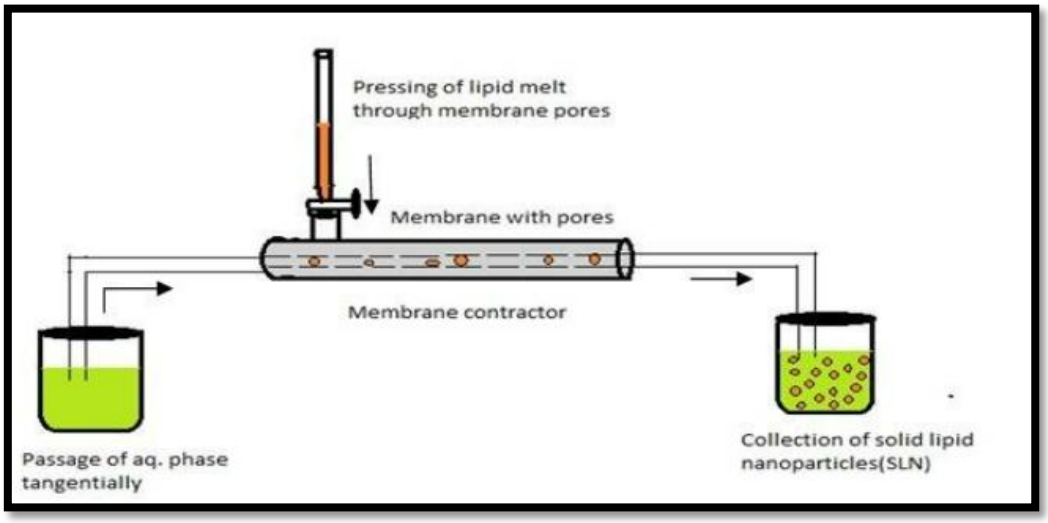
conditions, but it was discovered to be stable under refrigeration conditions for six months. As a result, MCN-loaded SLN dispersion can be stored without risk at 5°C 3°C [54].



9. **Membrane contractor method:** This approach uses a Kerasep ceramic membrane with 0.1, 0.2, or 0.45 pore sizes. The lipid phase and the water phase, which circulates tangentially to the membrane surface, are separated by the membrane. The lipid phase is heated past its melting point in a pressurized vessel, then transferred to the module via a tube and forced through the membrane pores. Small droplets are produced as a result, and tangential water flow separates them from the membrane pores. After cooling the resulting water dispersion, SLNs are produced.The current study examines a novel method for producing SLN that makes use of a membrane contactor. Small droplets are created when the lipid phase is forced through the membrane pores at a temperature higher than the lipid's melting point. The droplets that develop at the pore outputs are swept away by the aqueous phase as it circulates inside the membrane module. The preparation is subsequently cooled to room temperature to create SLN. On the SLN size and on the lipid phase flux, the effects of process factors (aqueous phase and lipid phase temperatures, aqueous phase crossflow velocity and lipid phase pressure, and membrane pore size) are examined.It is demonstrated that the membrane contactor enables the fabrication of SLN with a mean SLN size between 70 and 215 nm and a lipid phase flux between 0.15 and 0.35 m^3 /hm^2. The simplicity of usage, ability to scale up, and control of SLN size by process parameter selection are the benefits of this innovative method[55,56].



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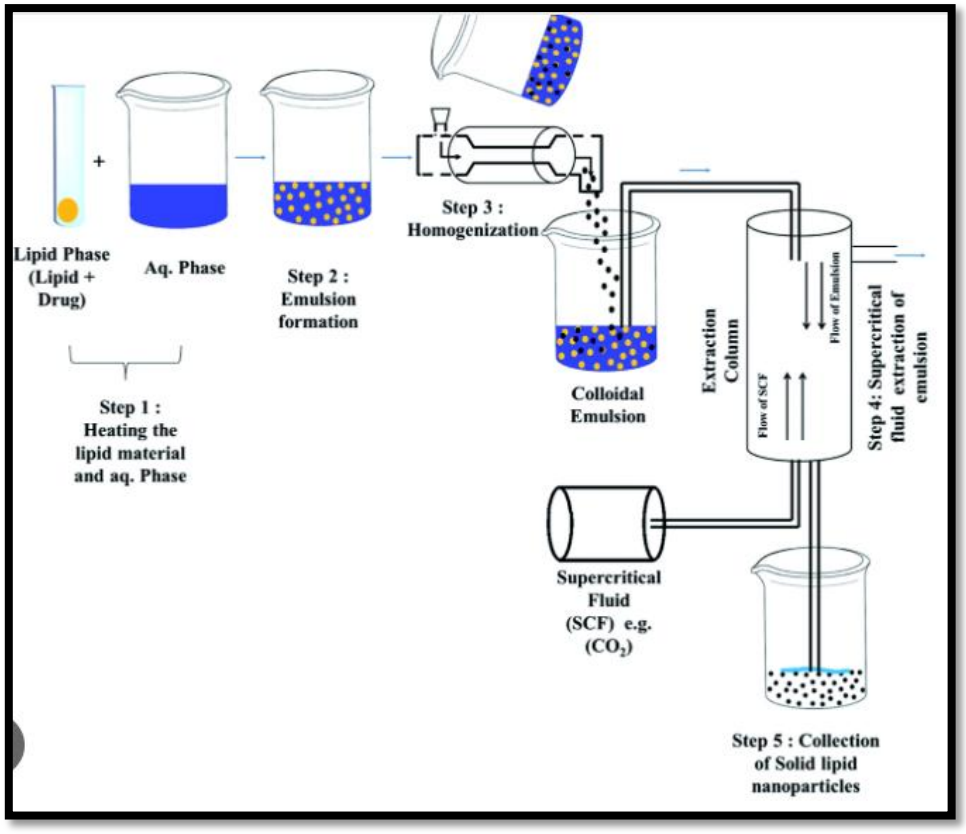
10. **Supercritical fluid technology:**This approach employs a supercritical fluid, such as carbon dioxide, which results in the precipitation of microparticles or medicines. The process begins with the medicines being dissolved in a solvent. The next step is to select a supercritical fluid that is completely or partially miscible with the solvent yet functions as an antisolvent to the pharmaceuticals that have been dissolved in the solvent[57,58]. When drug solutions are sprayed into a moving supercritical fluid, they precipitate as submicron-sized drug particles.The method for producing lipid nanoparticles with supercritical fluid is called "supercritical extraction of emulsions". in an organic solvent, the medication and lipid components are dissolved before the chosen surfactant is introduced. A cosurfactant may or may not be present in the aqueous solution into which this organic solution is disseminated. The o/w emulsion is then created by passing the mixture through a high-pressure homogenizer. Currently, the supercritical fluid, which is kept at a constant temperature and pressure, is delivered countercurrently into the extraction column from its top end at a constant flow rate. The continual extraction of solvent from the o/w emulsions yields the lipid nanoparticle dispersion[59].

The RESS technique was used in the experiment to produce submicron stearic acid. Through the use of scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectrophotometry, the unprocessed and treated stearic acid powders were evaluated (FT-IR). The degree of crystallinity was lowered without any chemical structural change, according to FT-IR analysis and XRD results of treated stearic acid. According to DSC research, the melting point was 2.7°C lower than that of bulk stearic acid. Additionally, RESS processing of stearic acid results in spherical particles in the 40–200 nm range that are nearly 600 times smaller than the unprocessed powder, as shown by SEM measurements[60].



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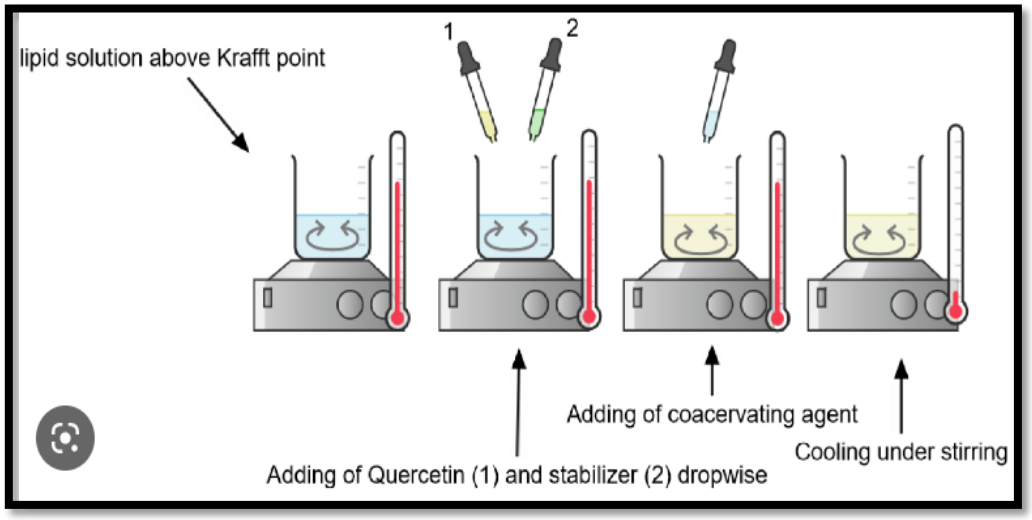
11. **Coacervation method:**The primary precursor for SLN preparation in this process is either fatty acid or soap micellar solution. The Krafft point, or the temperature at which soap dissolves in water, is above the temperature at which this micellar solution is produced. Either the drug is dissolved directly in the micellar solution or the micellization is increased by first dissolving the drug in a tiny volume of ethyl alcohol. Due to the improved solubilizing capabilities of micellar solution, the approach is appropriate for integrating hydrophobic medicines in SLNs with maximal drug loading efficiency.The sodium stearate, sodium arachidate, sodium behenate, sodium myristate, and sodium palmitate at 15% w/w concentration are the most common alternatives for the fatty acid salt[61].

Dextrans, hydroxypropylmethylcellulose, polyoxyethylene/polyoxypropylene copolymers, polyvynl acetate/polyvynl alcohol, and other nonionic polymeric surfactants are utilised as stabilising agents. Above the Krafft point of the sodium salt of fatty acids, the acidification typically takes place at a temperature between 40C and 50C. Temperatures must be raised for the sodium arachidate and behenate fatty acid salts. The resulting dispersion is rapidly cooled to a temperature of 15C.The formation of a homogeneous and stable nanoparticle suspension is always the result of choosing an appropriate coupling between the fatty acid alkaline salt and the appropriate coacervating solution.In the study, stearic acid was used as a core lipid, Arabic gum as a stabiliser, and a coacervation technique to create quercetin-loaded, negatively charged solid lipid nanoparticles. Dynamic light scattering (DLS), Zeta Potential, Surface infrared spectroscopy (FTIR-ATR), and Time of flight secondary ion mass spectrometry were used to qualitatively assess the samples (ToF-SIMS) [62]. By using UV-VIS spectrophotometry in vitro, the effectiveness of the encapsulation, drug release, and antioxidant action against ABTS•+ were assessed.The system displayed a controlled antioxidant effect in comparison to free Quercetin, illustrating that the encapsulated nutraceutical maintains its antioxidant activity to a significant extent (81% of that of free Quercetin). The release profile of QuercSLN accompanied an exponential plateau pathway within 26 h, showing a homogeneous distribution of the drug within the SLNs.Based on these findings, it was shown that coacervation-produced solid lipid nanoparticles are promising candidates for systems for the regulated delivery of quercetin and other lipophilic medications or nutraceuticals [63].



12. **Phase inversion temperature method:** first of all an oil phase is formed through by the mixture of solid lipids and nonionic surfactants. An aqueous phase is also constituted that contains a salt, usually NaCl. Both the oil and aqueous phases are separately heated at about 90C, above the PIT[64]. To formulate a w/o emulsion, the aqueous phase is added drop wise to the oil phase with continuous stirring at constant temperature. Then, the mixture is cooled to room temperature by continuous and controlled

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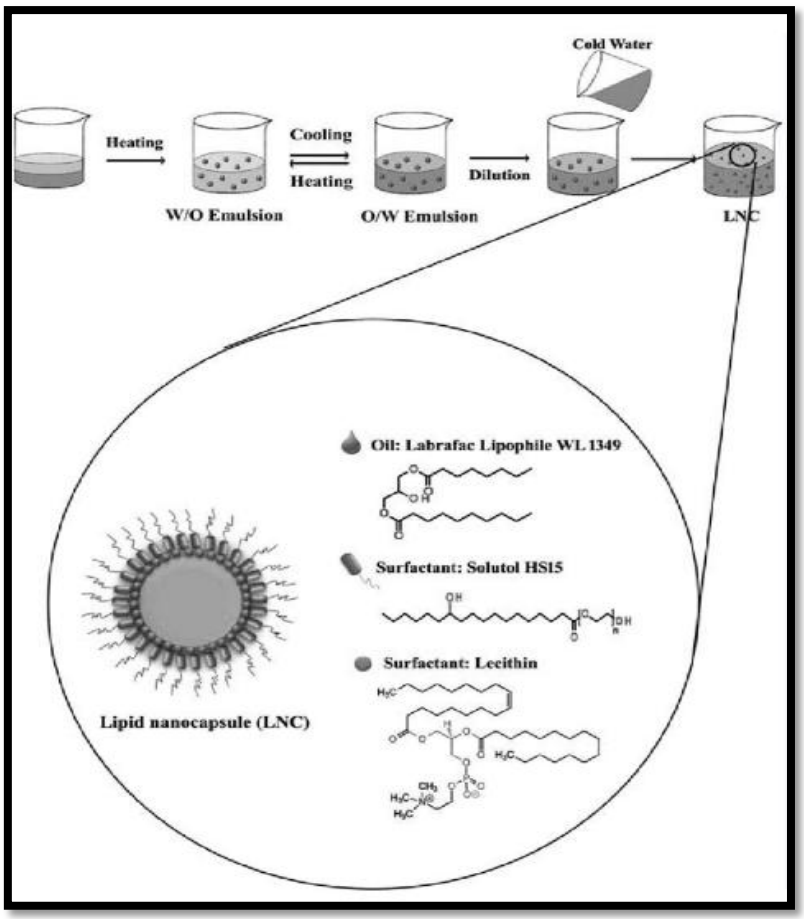
stirring. When temperature reaches PIT, the mixture gets transparent and when it reaches below PIT, an o/w nanoemulsion is formed. When it comes below the melting point of lipid, it starts turning in SLNs.First, an oil phase is created by combining nonionic surfactants with solid lipids. Additionally, a salt-containing aqueous phase is created, often NaCl. Separate heating is applied to the oil and aqueous phases at a temperature of about 90C, above the PIT. The aqueous phase is added dropwise to the oil phase while continuously swirling it at a steady temperature to create a w/o emulsion[65]. The mixture is then continuously and carefully stirred to cool to room temperature. The combination turns transparent when the temperature exceeds PIT, and an o/w nanoemulsion forms when the temperature falls below PIT. When it drops below lipid's melting point, it begins to transform into SLNs.The incorporation of rosemary oil (RMO) into solid lipid nanoparticles (SLNs) made from solid lipids with various chemical structures was accomplished utilising the phase-inversion temperature approach. Trilaurin (TLR) demonstrated the lowest particle size and good durability following a temperature cycling test among the solid lipids included in the formulations. SLNs made with a 1:3 RMO to TLR ratio were able to load QCT with an entrapment efficiency of more than 60% and a drug loading of less than 2% w/w. The polyoxyethylene-hydrogenated castor oil RH40 produced the smallest particles, and the particle size was concentration-dependent. Long-lasting biphasic release for more than 24 hours was visible in the QCT TLR drug-release profile. A cell viability percentage of >75% at 2% v/v showed that QCT TLR was a safe formulation[66].



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Recent advances in solid lipid nanoparticles

Proteins may be exposed to undesirable circumstances during incorporation techniques, such as organic solvents, high temperatures, mechanical stress, etc. By adsorbing the proteins onto prefabricated SLNs, all of this can be avoided. Therapeutic proteins and antigens have been employed extensively in adsorption onto polymeric nanoparticles [67]**.** With the intention of examining the interaction of blood components with intravenously injected SLN and expediting circulation time, plasma proteins were adsorbed onto SLN[68]**.**Results from the oral delivery of proteins containing SLN have been encouraging. In caco-2 cells, the absorption of calcitonin-loaded PEG- and chitosan-coated lipid nanoparticles was shown. Texas Red®-dextran permeability and the Transepithelial Electric Resistance (TEER) were used to evaluate how well SLNs were able to reversibly improve the transport of hydrophilic macromolecules through the monolayers. PEG-coated SLNs had no effect on Caco-2 monolayer permeability, but chitosan-coated SLNs resulted in a dose-dependent decrease in TEER and improved dextran transport. In contrast to the control calcitonin solution, oral administration of chitosan-coated nanoparticles containing calcitonin in rats resulted in a significant and prolonged hypocalcaemic effect. PEG-coated particles did not exhibit this effect, which was attributed to chitosan's ability to open tight junctions.The serum calcium levels were significantly and quickly reduced in response to CS-coated nanoparticles. These low calcemia levels were also kept constant for at least 24 hours [69]. By synthesising and encapsulating highly luminescent semiconductor CdSe/ZnS core-shell Quantum Dots (QDs) in SLNs, fluorescent nanocomposite particles were produced. Encasing QDs in colloidal carriers may help to address some of their problems, including their poor hydrophilicity, biocompatibility, and fluorescence stability. The TEM image showed that the QDs were homogenous, virtually monodisperse, and had an average diameter of about 4 nm. According to PCS, the average particle size of the unloaded and QDs-loaded SLNs was 70.6 nm and 92.3 nm, with PDIs of 0.141 and 0.235, respectively. The results showed that a homogeneous size distribution of particles was created by the preparation method [70].In vaccination preparations, adjuvants like aluminium hydroxide are used to boost the immunological response. In comparison to fluid and adjuvanted vaccines with aluminium hydroxide, polymer vaccines are more resistant to heat inactivation. Since SLNs have lipid components in their solid state and hence disintegrate more slowly, the immune system is exposed for a longer period of time. Sterically stabilising surfactants can delay down degradation even more. SLNs have advantages over conventional adjuvants in that they biodegrade quickly and are well tolerated by the body.

Patent scenario of SLNs :

I. Speiser first discussed the creation of lipid micropellets through spray congealing at the start of the 1980s. P. Speiser created and patented lipid nanopellets for oral ingestion after these first generation lipid pellets. However, this system did not undergo further development, and now, patent protection is nonexistent in many nations. The second generation, known as "solid lipid nanoparticles," was created at the start of the 1990s (SLN)[71].

II. R. H. Muller was successful in getting a patent on the high-pressure homogenization method of SLN preparation. The current owner of the global patent rights to this technology is Skye Pharma/London[72].

III. In parallel, a technology to prepare SLN utilising a microemulsion process was developed and patented by Gasco et al[73]. A lipid component or a combination of lipid components that may contain a pharmacologically active chemical is heated to the melting point in order to create the aforementioned microspheres; Separately, an aqueous solution including one or more surfactants and perhaps one or more co-surfactants is made, and the finished product is heated to a temperature that is at least as high as the melting point of the individual or combination of lipid components. This solution is combined with the aforementioned lipid component or lipid mixture while gently swirling to create a microemulsion, which is then poured into water heated to 2 to 10^0C to produce well-dispersed lipid microspheres.The dispersion is diluted with appropriate diluents and surface-active agents that encourage redispersion before being lyophilized. The produced microspheres have average diameters and polydispersions that are, respectively, ideally between 100 and 400 nm and 0.1 and 0.7. The invention promises

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improved particle dimension control, reduced energy usage, and significantly simplified operation. Vectorpharma/Italy has been granted a licence for the large-scale production of SLNs based on this technology [74].

IV. As a competitor product to SandimmunNeoral, Pharmatec (Milan/Italy) created a cyclosporine SLN formulation for oral treatment. The cyclosporine-loaded solid, particulate lipid-based excipients described in the invention demonstrated superior cyclosporine biopharmaceutical qualities in vivo and are asserted to be of higher quality in terms of particle fineness, homogeneity, drug inclusion, and physical stability. According to the findings of the patent's animal study, the cyclosporine SLN combines the benefits of the old and new Sandimmun microemulsions, avoiding large plasma peaks and having low variability in plasma profiles. The creation of cyclosporine formulations that permit its delivery to the dermis for use as an efficient topical treatment is also said to be a benefit of the discovery [75].

V. Small interfering RNA (si RNA) and nucleic acids, specifically polynucleotides and oligonucleotides, are used in the synthesis and application of SLN that was reported by Gasco. The following procedures are followed when preparing SLNs: A microemulsion is created by melting one or more lipids, adding a surfactant, an aqueous nucleic acid solution, and a co-surfactant, all at the same temperature. Following a dispersion ratio of 1:1 to 1:10 (microemulsion: cold water), the heated microemulsion is then diluted in water between 2 and 8^0C and cleaned by diafiltration. An amino acid, preferably a basic amino acid, may be present in the water used for the washing stage.The effectiveness of the delivery method represented by nanoparticles that carry synthetic or natural polynucleotides is claimed to enable its use for transfection in the present invention. According to claims, the particles have a specific ability to treat disorders of the posterior portion of the eye, including diabetic retinopathy, macular degeneration, and angiogenesis [76].

VI. One of the inventions describes the creation of lipid oil-in-water emulsions using ethyl stearate as a gene transfection agent and SLN made of triglyceride and non-triglyceride oils. According to the inventors, ethyl stearate-based SLNs or, more broadly, ethyl esters of fatty acids with C10–18 straight chains, have never been employed as gene carriers. Furthermore, prior to this discovery, no lipophilic or amphiphilic medication was carried by ethyl stearate SLNs. The process for making SLNs loaded with a medicine involves creating an aqueous phase with one or more emulsifiers, 0.1–10% drug that is lipophilic or amphiphilic, and 2-30% ethyl stearate. The aqueous and oil solutions are combined to create the drug-loaded SLNs.

VII. The Shekunov et al. invention describes a device and a process for creating solid composite lipid drug nanoparticles for controlled drug delivery. These methods and devices are said to have several advantages over traditional processing methods, including the ability to consistently create solid composite lipid drug particles with an average diameter below 100 nm, high drug loading, and low temperature processing. A lipid and a medicine are dissolved in an appropriate organic solvent to produce a solution, which is then emulsified in a liquid according to the invention's "Particles from Supercritical Fluid Extraction of Emulsions" method.The emulsion is in contact with a supercritical fluid, which removes the organic solvent from the micelles and causes them to precipitate as solid composite lipid drug nanoparticles that are suspended or disseminated in the liquid and are free of organic solvent.

VIII. An further invention described formulations for the controlled release of perfumes and smells in the form of SLNs dispersion, where the nanoparticles are based on lipids and stabilised using a monolayer emulsifier, one or more membrane layers, or other adjuncts. The nanoparticles, the monolayer of emulsifier, or the membrane layer all include scents and/or odours.

II. CONCLUSION

For the delivery of lipophilic but also hydrophilic pharmaceuticals, the three different types of lipid nanoparticles—SLN®, NLC®, and LDC®—represent a promising toolbox, particularly for hydrophilic drugs demonstrating a

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lower stability in the gut and a limited bioavailability. Lipid nanoparticles take advantage of lipids' abilities to increase absorption. These abilities are now frequently exploited in oral dosage forms and new, enhanced delivery systems. Lipid nanoparticles meet important aspects for launching a new formulation on the market. Low-cost manufacture, clinical and massive production facilities, and approved status of excipients are some examples of such requirements. They are not only a lower technology than liposomes, but they are also physically more stable.

The review has emphasized on the different aspects of lipid nanoparticles and how they can be utilised to encapsulate different medications as well as biopharmaceutical and biotechnological products like proteins, peptides, and vaccines.

In the context of cancer therapies, lipid nanoparticles have also demonstrated potential as a delivery mechanism. The same is applicable to gene delivery and a number of diseases, such as osteoarthritis. The production techniques that are commercially viable further strengthen the applicability. Solid lipid nanoparticles have evolved over time into more advanced delivery systems such lipid drug conjugates and nanostructured lipid carriers, which are expected to soon play important roles in lipid nanoparticles' therapeutic and diagnostic applications.These lipid-based nanoparticles may soon take the place of several difficult carriers due to their biocompatibility, industrial viability, and scalability. They also have a lot of promise for use in the fields of cosmetics and diagnostics. Drug targeting using the several generations of SLNs has showed potential at all levels, including organ, tissue, and cell targeting.

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