ejpmr, 2024, 11(6), 391-401

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SOLID LIPID NANOPARTICLES AS ATTRACTIVE DRUG CARRIER: COMPOSITION, PREPARATION AND APPLICATION

Arathi T. P.*, Shripathy D. and A. R. Shabaraya

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Post Farangipette, Manglore-574143, Karnataka, India.

***Corresponding Author: Arathi T. P.**

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Post Farangipette, Manglore-574143, Karnataka, India.

Article Received on 19/04/2024 **Article Revised on 09/05/2024** **Article Accepted on 30/05/2024**

ABSTRACT

Solid lipid nanoparticle (SLN) introduced in 1991, have emerged as an alternative to traditional colloidal carriers like liposomes, polymeric nanoparticles, microparticles, and emulsions. SLNs show various distinctive features such as low toxicity, large surface area, prolonged drug release, targeted drug delivery, superior cellular uptake as compared to traditional colloidal carriers as well as capability to improve solubility and bioavailability of drugs. This paper gives an overview about the potential advantages and also the disadvantages of solid lipid nanoparticles, the excipients, classification of SLN, all the different methods involved in their production and biomedical application.

KEYWORDS: solid lipid nanoparticle, colloidal carriers, targeted drug delivery.

INTRODUCTION

In recent years, it has become more evident that the development of new drug in a suitable drug carrier system was sufficient to ensure progress in drug therapy. A promising strategy to overcome problems such as poor absorption, rapid metabolism, poor bioavailability, poor water solubility and high fluctuation of plasma levels, involves the development of drug carrier system. The in vivo fate of the drug is not only determined by the properties of the drug, but also by the carrier system, which should permit a controlled and targeted release of the active drug according to the specific needs of the therapy. The size of the carrier depends on the desired route of administration and ranges from few nanometres (colloidal carriers), to the micrometre range (microparticles) and to several millimetres (implants).[1]

The fate of a drug not only depend upon the properties of drug but by the carrier system. The carrier is one of the most important entities for the successful transportation of the drug.[2] Nowadays colloidal particles can be used for drug delivery such as oil-in water liposome, micelles, emulsions, nanoparticles and micro particles.[3]

The development of nanoparticle has expanded into a wide range of clinical application in nowadays. Nanoparticle can be used as carrier to deliver drugs to specific cells or tissues in the body. And it can also be designed to release the drug in a controlled manner, allowing sustained delivery of the drug over time. Nanoparticle has several advantages over conventional delivery system due to their small particle size, large surface area, and ability to change surface properties. Nanoparticle can be used to target drug delivery, maintain drug action, boost bioavailability, solubilize drugs for intravascular transport, improve drug stability against enzymatic degradation.[4]

The successful delivery medication by nanoparticles relies on their capacity to overcome barriers, release medicines constantly, and maintain stability. Nevertheless, the restricted availability and high cost of FDA-approved polymers have hindered their clinical use. To address these constraints, scientists and researchers have proposed lipids as alternate carriers. Solid lipid nanoparticles (SLNs) have gained global attention for their benefits. SLN introduced in 1991, have emerged as an alternative to liposomes, polymeric nanoparticles, microparticles, and emulsions as colloidal drug delivery techniques. SLNs are spherical in shape, with typical sizes ranging from 50-1000nm. SLN consists of natural and synthetic lipids. SLNs are the ideal carrier for lipophilic medicines because to their high yield, efficiency, and increased bioavailability. SLN exhibit sustained release effect due to immobility of drug within lipid as compared to emulsion formulation. This delivery system has been extensively used as carriers for proteins, protein drugs, vaccines, lipophilic and hydrophilic drugs.[5]

SLN made up of lipid particles having diameters of a few nanometres. Hydrophilic and lipophilic drugs can be

incorporated in to SLNs to provide controlled and targeted drug distribution. SLNs consist of water, an emulsifier and/or co-emulsifier, and solid lipids. A typical solid lipid melts at temperatures above body temperature (37°C) when used in these delivery systems. Lipid studies have included those on steroids (e.g. cholesterol), fatty acids (e.g. stearic acid), acylglycerols, triglycerides (e.g.: tristearin), waxes (e.g. cetyl palmitate), and their mixtures. To stabilize the lipid dispersion, several emulsifiers have been used, either alone or in combination. Non-ionic emulsifiers include lecithin, bile salts (such as sodium taurocholate), and ethylene oxide/propylene oxide. Other emulsifiers have been investigated, including copolymers, fatty acid ethoxylates, sorbitan esters, and their mixtures. Polyethylene glycol can be incorporated to SLN provide steric stabilization and inhibit immune clearance. Deionized water is used as the dispersion medium.[6]

In contrast to other colloidal carriers, SLNs contain solid lipid rather than liquid lipid. The use of solid lipid rather than liquid lipid is advantageous since it has been found to enhance control over the release kinetics of encapsulated chemicals and the stability of included chemically sensitive lipophilic ingredients. These potentially positive effects are due to a variety of physicochemical properties linked with the physical state of the lipid phase. Firstly, the mobility of reactive chemicals in a solid matrix is lower than in a liquid matrix, potentially slowing down chemical degradation events. Secondly, microphase separations of the active components and carrier lipid inside individual liquid particles may be regulated, thereby preventing the buildup of active chemicals at the surface of lipid particle where chemical degradation reaction occurs. Thirdly, the absorption of poorly absorbed drug has been shown to be increased after incorporation into solid lipid nanoparticles. And it is found that the use of a solid matrix instead of a liquid matrix leads to slow down lipid digestion thereby allowing for a more sustained release of the encapsulated drug. Other major excipients of SLNs are surfactants of aqueous type. It mainly act as emulsifier to form o/w type emulsion and stabilizer for SLNs dispersion and their choice depends on mainly the route of administration.[7]

The benefit of SLN is that the lipid matrix is composed of physiological lipids, which reduces the risk of acute and chronic toxicity, the avoidance of organic solvents throughout the production process, as well as a broad possible use range (dermal, oral, and intravenous). Furthermore, better bioavailability, protection of sensitive drug molecules from the environment (water, light), regulated and/or targeted drug release, improved pharmaceutical stability, high drug pay load the capacity to transport both lipophilic and hydrophilic medications, and the fact that most lipids are biodegradable. SLNs are more stable and easier to scale up to manufacturing than liposomes. SLN formulations stable for three years can be developed.[8]

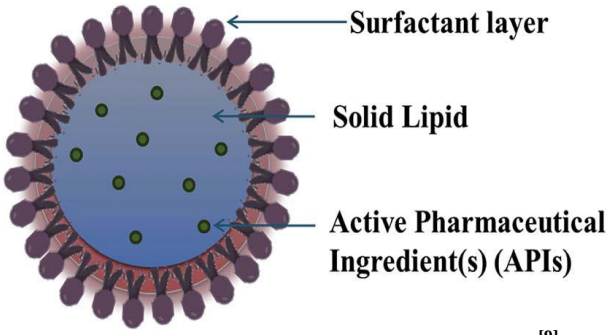

Fig 1: Structure of solid lipid nanoparticle.[9]

Advantages of SLNs[10]

- The cells of reticuloendothelial system (RES) are unable to take up SLNs because of their nanosize range, thus enabling them to bypass spleen and liver filtration.
- Provide high stability to incorporated drugs.
- Feasibility of incorporating both hydrophilic and lipophilic drugs.
- Improve bioavailability of poorly water soluble molecules.
- Ease in sterilization and scale up.
- Immobilizing drug molecules within solid lipids provides protection from photochemical, oxidative, and chemical degradation of sensitive drugs, with reduced chances of drug leakage.

Disadvantages of SLNs[11]

- SLNs are compactly packed lipid matrix networks (ideal crystalline structure) having low space for drug encapsulation, leading to poor drug loading capacity.
- Various factors affect the loading or encapsulation of drugs in SLNs, such as interaction of drug and lipid melt, nature or state of lipid matrix, drug miscibility with lipid matrix, and the drug being dispersed or dissolved in the lipid matrix.
- Chances of drug expulsion following polymeric transition during storage.
- The dispersions have a high (70–90%) water content.

Table 1: Ingredients used for SLN formulation.[12]

SLN composition	Class	Example
Lipid	Fatty acids	Myristic acid Stearic acid Palmitic acid Arachidic acid
	Glycerol esters	Glyceryl trimyristate Glyceryl tristearate Glyceryl tripalmitate Glyceryl trioleate Soybean oil
	Waxes	cetyl palmitate Beeswax Carnauba wax
Emulsifiers	Phospholipids	Egg lecithin Soya lecithin Hydrogenated soya lecithin Cholesterol Cholesterol oleate
	Steroids	Poloxamer 188 Poloxamer 407
	Non-ionic surfactant	Polysorbate 20 Polysorbate 80 Polyoxyethylene-20-cetyl ether Polyoxyethylene-20-oleyl ether Polyvinyl alcohol
Co-surfactants	Anionic surfactants Alcohols Bile salt	Sodium lauryl sulfate Butanol Cholate

CLASSIFICATION OF SLNs

SLN can be classified into three types based on their structure and location of drug in lipid matrix.

1. Homogeneous matrix-based SLN (solid solution model),
2. Drug enriched shell-based SLN.
3. Drug enriched core-based SLN.[13]

1. HOMOGENEOUS MATRIX BASED SLN

SLNs are made up of drug molecules that are either molecularly dispersed in the lipid matrix or scattered as amorphous clusters. When a highly lipophilic medication needs to be encapsulated in SLNs, cold high-pressure homogenization or hot homogenization is used.

2. DRUG ENRICHED SHELL-BASED SLNS

It is generated during the cooling phase of phase separation, when the drug concentration in the melting lipid matrix is extremely low. Here, the lipid precipitates first, creating a drug-free lipid core. When the drug reaches saturation solubility in the residual melting lipids, an outer shell of drug and lipid hardens around the drug-free lipid core. Because of this structural arrangement of SLNs, the drug primarily concentrates on the surface of SLNs, and burst and quick release of drug is usually observed.[14]

3. DRUG ENRICHED CORE-BASED SLNS

SLN are formed when drugs precipitate before lipid recrystallization. When the drug is dissolved in melted lipid nearing saturation solubility, it concentrates on the core of the SLNs. As a result, the drug precipitates prior to lipid recrystallization, creating a drug-free lipid shell around the drug core.[15]

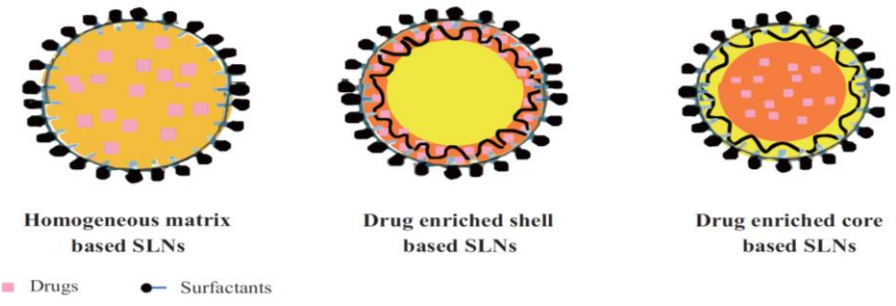

Fig 2: Schematic representation of different types of SLNs based on drug location.[15]

METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLE

1. High pressure homogenization
a) Hot homogenization
b) Cold homogenization
2. Ultrasonication /high speed homogenization
a) Probe ultrasonication
b) Bath ultrasonication
3. Solvent evaporation Method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Double emulsion method
8. Precipitation technique
9. Film-ultrasound dispersion
10. Solvent Injection Technique
11. Using Membrane Contractor

1. High pressure homogenisation (HPH)

High pressure homogenization (HPH) is a reliable and effective technique for the preparation of SLN. HPH pushes liquid with high pressure about 100-2000bar through a narrow gap. The fluid moves to a very short distance at high velocity. There are two methods of homogenization, hot and cold homogenisation methods. In both methods it involves incorporation of drug into bulk of lipid by dissolving or dispersing drug in lipid melt.

A. Hot homogenisation

It is carried out at temperature above the melting point of lipid. It involves first dispersing the drug loaded lipid in a hot aqueous surfactant mixture. Pre-mix using a stirrer to form a coarse pre-emulsion. Pre-emulsion is homogenised at high temperature above the lipids melting point. Finally, the formed o/w nano emulsion is cooled down to room temperature to solidify SLNs.

Higher temperature results in lower particle sizes but it also causes increase in the degradation rate of the drug and the carrier. Increasing the homogenization pressure results in an increase of the particle size due to particle coalescence which occurs due to the high kinetic energy of the particles.[16]

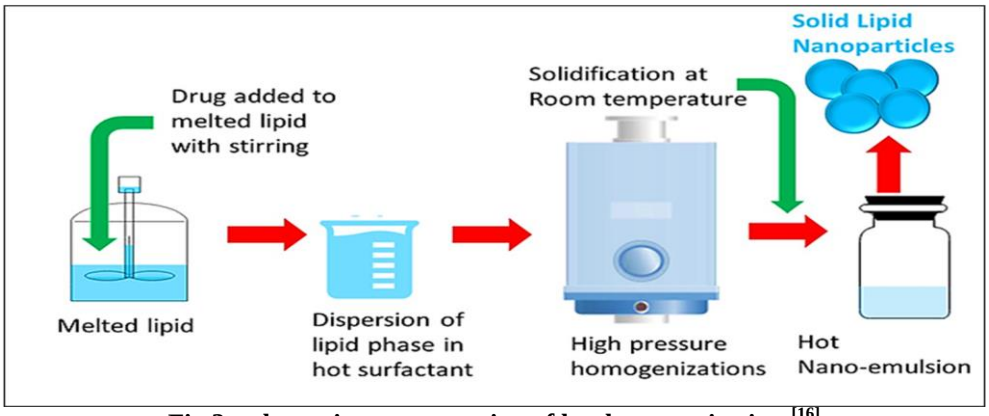

Fig 3: schematic representation of hot homogenisation.[16]

B. Cold homogenisation

In this method, dispersing drug in the melt of lipid. The drug containing melt is rapidly cooled by means of liquid nitrogen. Rapid cooling helps the homogenous distribution of drug in the lipid matrix. The solidified product is milled to microparticle. Dispersing the powder in a aqueous surfactant dispersion medium to form pre-suspension. Then it undergoes high pressure homogenisation at room temperature to form solid lipid nanoparticle.[16]

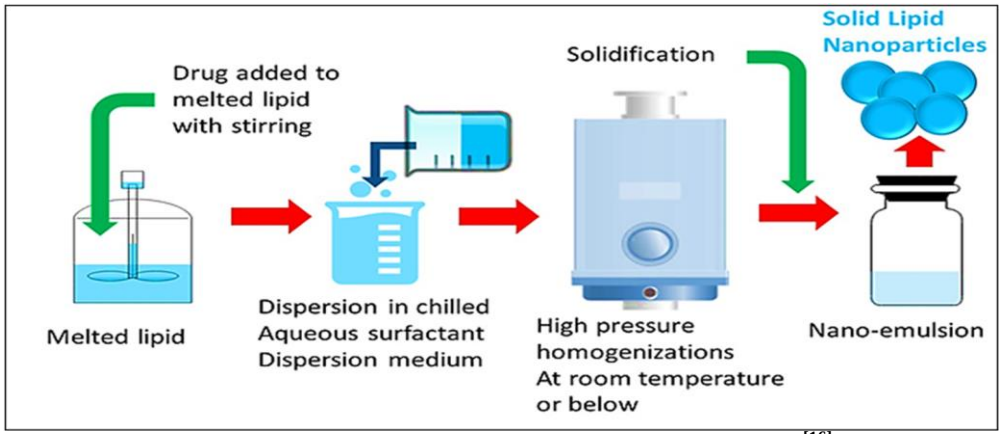

Fig 3: schematic representation of cold homogenisation.[16]

2. Ultrasonication /high speed homogenization

This technique is wide spread and easy to handle. To obtain smaller particle size both methods can be used. It does not involve organic solvents. Melted lipid dispersed in aqueous surfactant solution under high shear homogenization or ultrasonication and the formed emulsion is cooled down to room temperature. Homogenizer such as a rotor-stator homogenizer is used for high shear homogenization and for ultrasonication probe sonicator can be used.[17]

This technique reduces shear stress but has some disadvantages like low dispersion quality, potential metal contamination, physical instability like particle growth upon storage.[18]

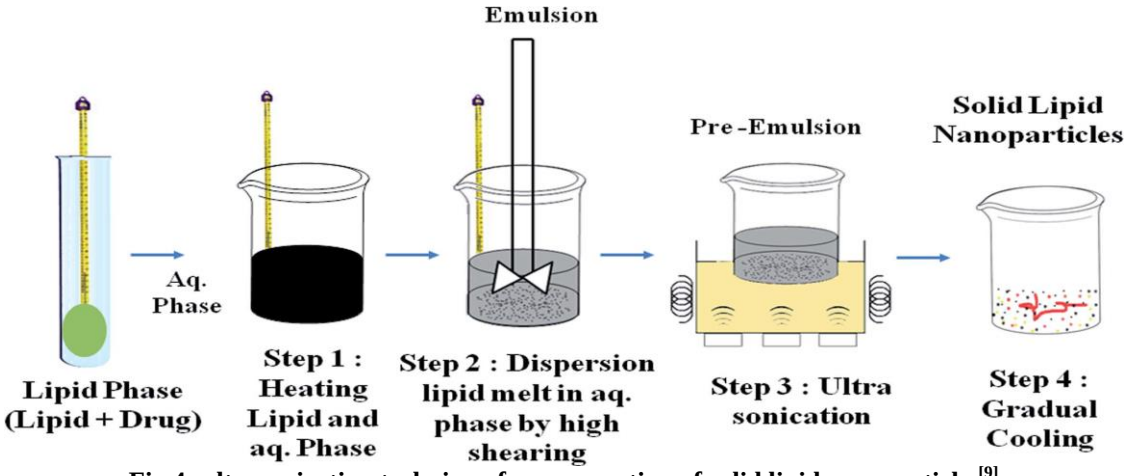

Fig 4: ultrasonication technique for preparation of solid lipid nanoparticle.[9]

3. Solvent evaporation Method

The lipophilic substance is dissolved in a water-immiscible organic solvent (such as cyclohexane) and emulsified in an aqueous phase. Upon solvent evaporation, nanoparticle dispersion is created by lipid precipitation in the aqueous media, resulting in nanoparticles with a mean size of 25 nm. The solution was emulsified in an aqueous phase using high-pressure homogenization. The organic solvent was removed from the emulsion through evaporation at decreased pressure (40-60 mbar).[19]

4. Solvent emulsification-diffusion method

In this method lipid dissolved in a water-immiscible organic solvents like chloroform or cyclohexane is emulsified in a aqueous phase containing surfactant solution by mechanical stirring to form oil-in-water emulsion and kept in ambient condition to allow the evaporation of solvent.[9,20]

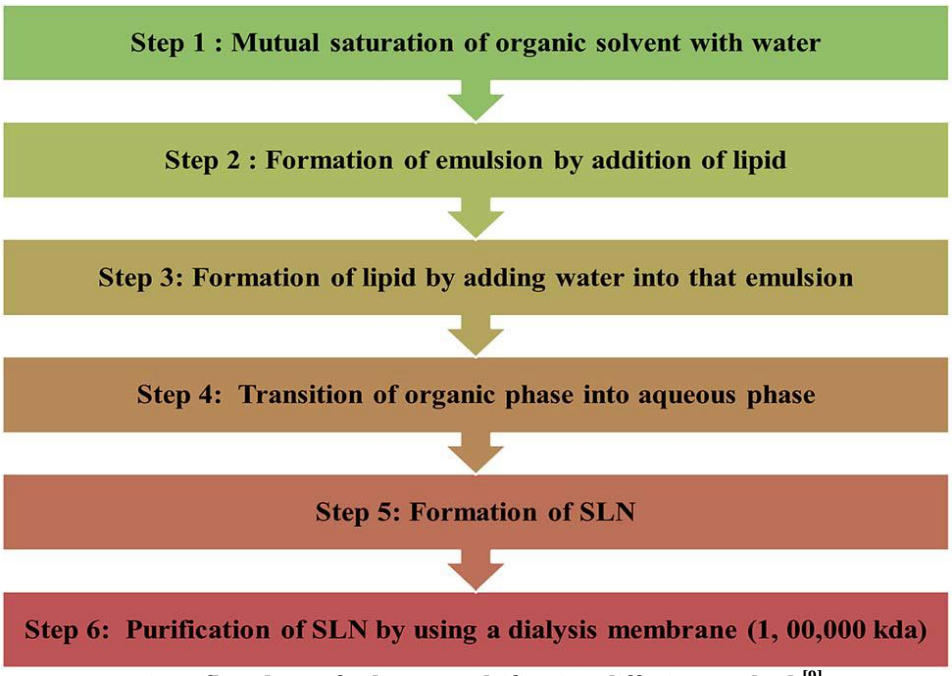

Fig 5: flowchart of solvent emulsification diffusion method.[9]

5. Supercritical fluid method

It is a novel technique for the preparation of SLN. This technique uses a super critical fluid like carbon dioxide for solvent extraction from o/w emulsions.[21]

6. Microemulsion based method

In this method a low melting fatty acid, an emulsifier, co-emulsifiers and water are stirred at 65-75℃ to obtain hot microemulsion. Then it is dispersed in cold water (2-3°C) under stirring. The volume ratios of the hot microemulsion to cold water are in the range of1:25 to 1:50.[22]

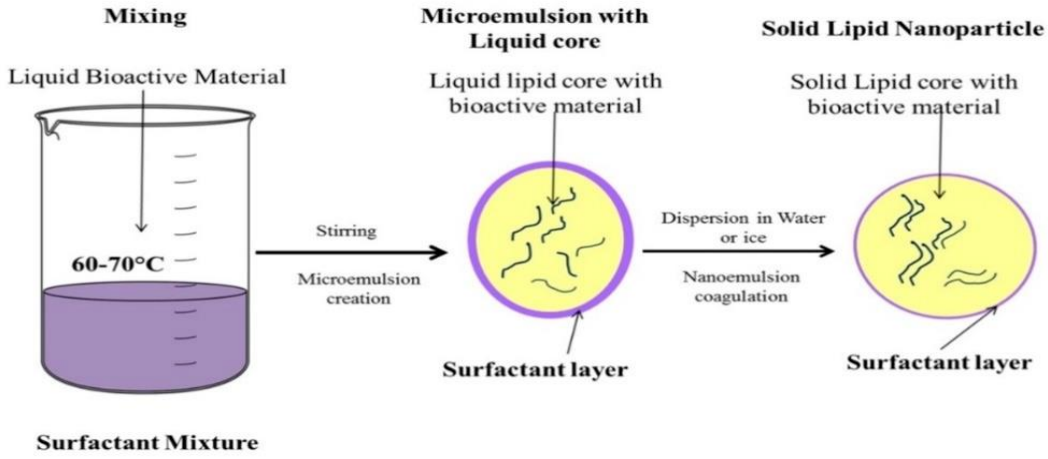

Fig 6: microemulsion method.[22]

7. Double emulsion method

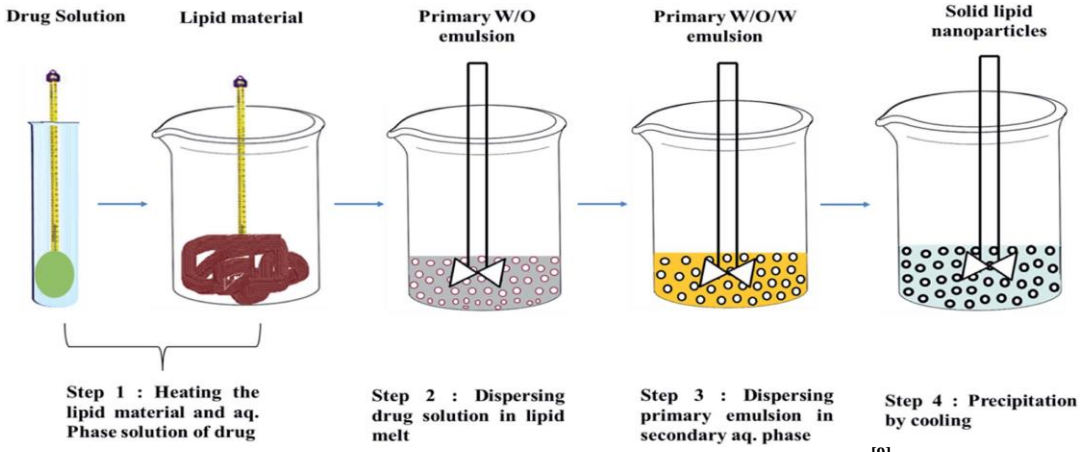

Fig 7: schematic representation of double emulsion method.[9]

The double emulsion approach is commonly employed for the production of hydrophilic drugs. firstly, w/o microemulsion is created by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant, and co-surfactant at a temperature slightly higher than the melting point of the lipid. In the second step, the generated w/o microemulsion is combined with a mixture of water, surfactant, and co-surfactant to produce a transparent w/o/w system.[22]

8. Precipitation technique

The lipid dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.[7]

9. Film-ultrasound dispersion.

The lipid and drug were immersed in suitable organic solutions; following decompression, rotation, and evaporation, a lipid film developed; and the aqueous solution containing the emulsions was added. Finally, using ultrasound with the probe to diffuser, the SLN with small and uniform particle size is generated.[23]

10. Solvent injection method

In this method the lipids are dissolved in a water-miscible solvent and the dissolved lipids are injected through an injection needle into a stirring aqueous solution with or without surfactant. The resulted dispersion is filtered through a filter paper in order to remove any excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent

diffusion was complete by reducing the surface tension between water and solvent.[23]

11. Membrane contractor method

The lipid phase was forced through the membrane pores at temperatures higher than the lipid's melting point, causing tiny droplets to form. The aqueous phase flowed inside the membrane module, sweeping away droplets that formed at the pore exits. SLN were generated after cooling the preparation to room temperature.[7,24]

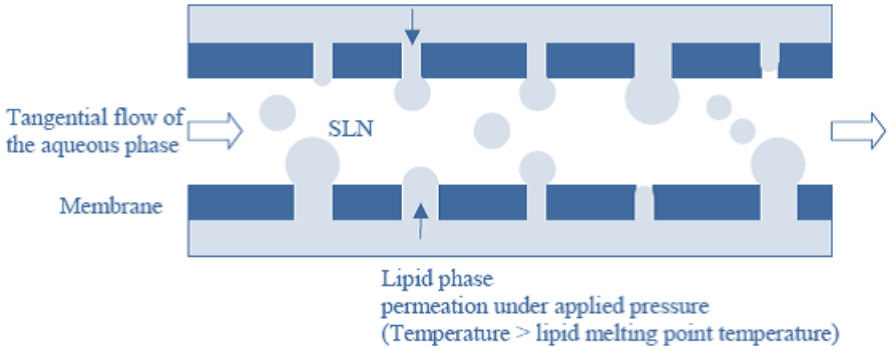

Fig 8: schematic representation of membrane contractor method.[7]

Table 2: SLN formulations reported by different researchers.

Drug	Composition	Method of preparation	Researcher
Amphotericin B	Stearic acid, Pluronic F-68, Pluronic F-127, Tween 80	Solvent diffusion method	Butani D, Yewale C, et al[25]
Camptothecin	Soybean lecithin, stearic acid Pluronic F-68, Tween80,PEG 400,	Hot HPH	Yang S, Zhu J, et al[26]
Carvedilol	Stearic acid Pluronic® F-68 Sodiumtaurocholate	Microemulsion	Sanjula B, et al[27]
Curcuminoids	Tween 80, Lecithin, and beeswax	Hot melt emulsion method by homogenization	Zamarioli CM, et al[28]
Doxorubicin Hydrochloride	Glycerylcaprate Polyethylene glycol 660 Hydroxy-stearate	Ultrasonic homogenization	R K subedi et al[29]
Hydrocortisone	Precirol ATO 5, Compritol 888 ATO, Tween 80	Hot high Pressure homogenization	Jensen LB et al[30]
5-Fluorouracil	Stearic acid, Lecithin, and Poloxamer 188	Double emulsion method by homogenization	Khallaf RA, et al[31]
Vitamin A	Compritol ATO 888 and Miglyol 812 (caprylic/ capric triglycerides)	High-pressure homogenization method	Jenning V et al[32]
Hydroquinone	Poloxamer 407, Precirol ATO5, and Span 20	Hot melt homogenization method	Ghanbarzadeh S et al[33]
Lopinavir	Compritol ATO 888, Poloxamer 407	High-pressure homogenization	Alex MA, et al[34]
Glucocorticoids	Precirol ATO 5, Oleic oil, and Tween 80	Melt emulsification combined with ultrasonication technique	Schlupp P,et al (35)

Ibuprofen	Stearic acid Pluronic F127	High pressure homogenization	S. G. Potta, et al[36]
Idarubicin	Stearic acid Epikuron 200	Microemulsion	G. P. Zara, et al[37]
Cyclosporine A	Imwitor 900 Tagat S, sodium cholate	Hot homogenization	Müller RH, et al[38]
Methotrexate	Stearic acid,Soya lecithin, sodium taurodeoxycholate	micro emulsification solidification method.	Ruckmani K, et al[39]
Praziquantel	Hydrogenated castor oil, Poly vinyl alcohol	Hot homogenization	S Xie, et al[40]
Quercetin	Glyceryl monostearate soy lecithin Tween-80, PEG 400	Emulsification-solidification	Li H et al[41]
Rifampicin	Stearic acid PVA	Emulsion-solvent diffusion	Pandey R et al[42]
Tobramycin	Stearic acid Epikuron 200	Microemulsion	Cavalli R et al[43]
Nitrendipine	Triglyceride and phosphatidylcholine Pluronic F68	Hot homogenization Ultrasonication method	Manjunath K et al[44]

APPLICATION OF SOLID LIPID NANOPARTICLE

1. Controlled release of drug

SLNs can control drug release by changing the loading method or surface features. A recent study used SLN loaded with TNF-α siRNA to treat rheumatoid arthritis by extended release. SLNs biocompatible lecithin and cholesterol were used in a solvent displacement approach to encapsulate siRNA complexed with 1,2-dioleoyl-3-trimethylammonium-propane. An in vitro study of siRNA release from SLNs found no burst release and just 5% release after 30 days. The addition of cholesterol and siRNA complex in the formulation resulted in extended release without bursts.[45]

2. SLN for anticancer drug delivery

Research suggests that SLNs containing anti-neoplastic drugs can effectively cure breast cancer due to their prolonged release of tamoxifen.[46]

3. SLN as a gene carrier

Several experiments have been carried out on genetic materials such as plasmid deoxyribonucleic acid (p-DNA), DNA, and other nucleic acids loaded into SLN. Vicente-Pascual et al. reported that SLN-based vectors could operate as a useful gene delivery strategy for managing ocular disorders and inflammation.[47]

4. SLNs for Targeted Brain Drug Delivery

SLN is a candidate for drug administration into the central nervous system (CNS) because of its natural ability to pass the blood-brain barrier (BBB) due to their lipidic nature. Studying the pharmacokinetics of two anticancer agents, namely camptothecin and doxorubicin, drug accumulation into the brain was observed after both oral and i.v. administration when loaded into SLN.[48]

5. SLN in a Alzheimer's disease

Resveratrol loaded in SLN decreased the clustering of β-amyloid protein, which is linked to Alzheimer's disease. The drug's formulation into SLN avoided first-pass liver metabolism. The resveratrol SLNs were coupled with antibody-like OX26 mAb for effective delivery of the encapsulated drug into the brain.

6. SLN for antitubercular therapy

Anti-tubercular medications, such as pyrazinamide, rifampicin, and isoniazid, were developed as SLNs and used to restrict the high frequency of dose. It was also noted that the nebulization of the formulation in an animal model by adding these medications as SLNs increased their bioavailability and improved the therapeutic efficacy of the medication.[49]

7. SLN for antimicrobial activity

SLNs, or solid lipid nanoparticles, are highly effective formulations for delivering antifungal drugs to the skin. A topical gel containing fluconazole (FLZ)-loaded SLNs has been shown to be more effective in treating Pityriasis Versicolor than the marketed product CandistanVR. The developed FLZ-SLNs gel had better skin penetration due to increased contact between the gel and the skin.[50]

8. SLN for topical use

SLN loaded non-steroidal anti-inflammatory drug, had developed for the effective management of rheumatoid arthritis. In order to avoid the irritation of the gastrointestinal tract and minimizing the systemic toxicity during the oral administration can be performed by formulating to topical formulation could be useful in the treatment of inflammatory diseases.[51]

CONCLUSION

Solid lipid nanoparticles offer promising prospectus in various fields due to their unique properties and versatile

applications. SLN exhibit excellent biocompatibility, stability and controlled release characteristics. Clear advantages of SLN include its composition physiological compounds, the rapid and effective production process including the possibility of largescale production, the avoidance organic solvents and the possibility to produce high concentrated lipid suspensions. However challenges such as low drug-loading capacities, the presence of alternative colloidal structure, the complexity of the physical state of the lipid which cause stability problems during storage or administration like gelation, particle size, increase, drug expulsion still exist, necessitating further research and development effort.

REFERENCES

1. You J, Wan F, De Cui F, Sun Y, Du YZ, Qiang Hu F. Preparation and characteristic of vinorelbine bitartrate-loaded solid lipid nanoparticles. International journal of pharmaceutics, 2007; 343(1-2): 270-6.
2. Pople PV, Singh KK. Development and evaluation of topical formulation containing solid lipid nanoparticles of vitamin A. American association of pharmaceutical scientist, 2006; 7(4): E63-9.
3. Chien YW. Transdermal drug delivery and delivery systems. Novel Drug Delivery Systems, 2nd edition, Chapter 7, New York, Marcel Dekker, 1992; 301-380.
4. Yusuf A, Almotairy ARZ, Henidi H, Alshehri OY, Aldughim MS. Nanoparticle as drug delivery system: A review of the implication of nanaoparticles, physicochemical properties on responses in biological system. Polymers. 2023; 15(7): 1596.
5. Shah KA, Date AA, Joshi MD, Patravale VB. Solid lipid nanoparticles (SLN) of tretinoin: potential in topical delivery. International journal of pharmaceutics, 2007; 345(1-2): 163-71.
6. Singh A, Singh MS, Sethi VA. To formulate and evaluate solid lipid nanoparticles of an itraconazole. European chemical bulletin, 2023; 12(5): 3960-67.
7. Yadav N, Khatak S, Sara US. Solid lipid nanoparticles-a review. International journal of applied pharmaceutics, 2013; 5(2): 8-18.
8. Nair et al.: Formulation and evaluation of chitosan solid lipid nanoparticles of carbamazepine. Lipids in Health and Disease, 2012; 11: 72.
9. Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, Kumar NS, Vekariya RL. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. RSC advances, 2020; 10(45): 26777-6791.
10. Lingayat VJ, Zarekar NS, Shendge RS. Solid lipid nanoparticles: a review. Nanosci. Nanotechnol. Res, 2017; 4(2): 67-72.
11. Hanumanaik M, Patel SK, Sree KR. Solid lipid nanoparticles: a review. Int J Pharm Sci Res, 2013; 6: 928-40.
12. Geszke-Moritz M, Moritz M. Solid lipid nanoparticles as attractive drug vehicles: Composition, properties and therapeutic strategies. Materials Science and Engineering: C., 2016; 68: 982-94.
13. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev, 2002; 54(Suppl. 1): S131-55.
14. Ganesan P, Narayanasamy D. Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustain Chem Pharm, 2017; 6: 37-56.
15. Liu M, Sharma M, Wen J. Solid lipid nanoparticle for topical drug delivery: Mechanism, dosage form, perspectives, and translational status. Bentham science publishers, 2020; 26: 3203-17.
16. Ghesemiyeh P, Samani SM. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery system: applications, advantages and disadvantages. Research in pharmaceutical sciences, 2018; 13(3): 288-303.
17. Triplett MD, Rathman JF. Optimization of β-carotene loaded solid lipid nanoparticles preparation using a high shear homogenization technique. Journal of nanoparticle research, 2009; 11: 601-14.
18. Uner M. Preparation, characterization and physico-chemical properties of Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC): Their benefits as colloidal drug carrier systems. Pharmazie, 2006; (61): 375-86.
19. Patel D, Kesharwani R, Nair SK. Solid Lipid Nanoparticle (Sln): A Modern Approach for Drug Delivery. Asian Journal of Pharmaceutical Research and Development, 2015 Sep 1: 1-7.
20. Zhang X, Lü S, Han J, Sun S, Wang L, Li Y. Preparation, characterization and in vivo distribution of solid lipid nanoparticles loaded with syringopicroside. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 2011; 66(6): 404-7.
21. Chattopadhyay P, Shekunov BY, Yim D, Cipolla D, Boyd B, Farr S. Production of solid lipid nanoparticle suspensions using supercritical fluid extraction of emulsions (SFEE) for pulmonary delivery using the AERx system. Advanced drug delivery reviews, 2007 Jul 10; 59(6): 444-53.
22. Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, Rosenholm JM. Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics, 2018 Oct 18; 10(4): 191.
23. Parhi R, Suresh P. Preparation and characterisation of solid lipid nanoparticles- A Review. Current Drug Discovery Technologies, 2012; 9: 2-16.
24. Charcosset C, Bernard S, Fiaty K, Bechelany M, Cornu D. Membrane techniques for the preparation of nanomaterials: nanotubes, nanowires and nanoparticles: a review. Dyn. Biochem. Process

Biotechnol. Mol. Biology. Glob. Sci. Books, 2007; 1: 15-23.
25. Butani D, Yewale C, Mishra A. Topical amphothericin B loaded solid lipid nanoparticles: Design and development. Colloida surfs B Biointerfaces, 2016; 139: 17-24.
26. Yang S, Zhu J, Lu Y, Liang B, Yang C. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharmaceutical research, 1999 May; 16: 751-7.
27. Sanjula B, Shah FM, Javed A, Alka A. Effect of poloxamer 188 on lymphatic uptake of carvedilol-loaded solid lipid nanoparticles for bioavailability enhancement. Journal of drug targeting, 2009 Apr 1; 17(3): 249-56.
28. Zamarioli CM, Martins RM, Carvalho EC, Freitas LAP. Nanoparticlescontaining curcuminoids (Curcuma longa): development of topical delivery formulation. Rev Bras Farmacogn, 2015; 25(1): 53-6
29. Subedi RK, Kang KW, Choi HK. Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin. European journal of pharmaceutical sciences, 2009 Jun 28; 37(3-4): 508-13.
30. Jensen LB, Magnussson E, Gunnarsson L, Vermehren C, Nielsen HM, Petersson K. Corticosteroid solubility and lipid polarity control release from solid lipid nanoparticles. International journal of pharmaceutics, 2010 May 5; 390(1): 53-60.
31. Khallaf RA, Salem HF, Abdelbary A. 5-Fluorouracil shell-enriched solid lipid nanoparticles (SLN) for effective skin carcinoma treatment. Drug Deliv, 2016; 23(9): 3452-60.
32. Jenning V, Gysler A, Schäfer-Korting M, Gohla SH. Vitamin loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Eur J Pharm Biopharm, 2000; 49(3): 211-8.
33. Ghanbarzadeh S, Hariri R, Kouhsoltani M, Shokri J, Javadzadeh Y, Hamishehkar H. Enhanced stability and dermal delivery of hydroquinone using solid lipid nanoparticles. Colloids Surf B Biointerfaces, 2015; 136: 1004-10.
34. Alex MA, Chacko AJ, Jose S, Souto EB. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. European journal of pharmaceutical sciences, 2011 Jan 18; 42(1-2): 11-8.
35. Schlupp P, Blaschke T, Kramer KD, Höltje HD, Mehnert W, Schäfer-Korting M. Drug release and skin penetration from solid lipid nanoparticles and a base cream: a systematic approach from a comparison of three glucocorticoids. Skin pharmacology and physiology, 2011 Feb 24; 24(4): 199-209.
36. Potta SG, Minemi S, Nukala RK, Peinado C, Lamprou DA, Urquhart A, Douroumis D. Preparation and characterization of ibuprofen solid lipid nanoparticles with enhanced solubility. Journal of microencapsulation, 2011 Feb 1; 28(1): 74-81.
37. Zara GP, Bargoni A, Cavalli R, Fundarò A, Vighetto D, Gasco MR. Pharmacokinetics and tissue distribution of idarubicin-loaded solid lipid nanoparticles after duodenal administration to rats. Journal of pharmaceutical sciences, 2002 May 1; 91(5): 1324-33.
38. Müller RH, Runge SA, Ravelli V, Thünemann AF, Mehnert W, Souto EB. Cyclosporine-loaded solid lipid nanoparticles (SLN®): Drug–lipid physicochemical interactions and characterization of drug incorporation. European journal of pharmaceutics and biopharmaceutics, 2008 Mar 1; 68(3): 535-44.
39. Ruckmani K, Sivakumar M, Ganeshkumar PA. Methotrexate loaded solid lipid nanoparticles (SLN) for effective treatment of carcinoma. Journal of nanoscience and nanotechnology, 2006 Sep 1; 6(9-10): 2991-5.
40. Xie S, Pan B, Wang M, Zhu L, Wang F, Dong Z, Wang X, Zhou W. Formulation, characterization and pharmacokinetics of praziquantel-loaded hydrogenated castor oil solid lipid nanoparticles. Nanomedicine, 2010 Jul; 5(5): 693-701.
41. Li H, Zhao X, Ma Y, Zhai G, Li L, Lou H. Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. Journal of Controlled Release, 2009 Feb 10; 133(3): 238-44.
42. Pandey R, Sharma S, Khuller GK. Oral solid lipid nanoparticle-based antitubercular chemotherapy. Tuberculosis, 2005 Sep 1; 85(5-6): 415-20.
43. Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MF. Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. International journal of pharmaceutics, 2002 May 15; 238(1-2): 241-5.
44. Manjunath K, Venkateswarlu V, Hussain A. Preparation and characterization of nitrendipine solid lipid nanoparticles. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 2011 Mar 10; 66(3): 178-86.
45. Aldayel AM, O'Mary HL, Valdes SA, Li X, Thakkar SG, Mustafa BE, Cui Z. Lipid nanoparticles with minimum burst release of TNF-α siRNA show strong activity against rheumatoid arthritis unresponsive to methotrexate. Journal of Controlled Release, 2018 Aug 10; 283: 280-9.
46. Lakkadwala S, Nguyen S, Lawrence J, Nauli SM, Nesamony J. Physico-chemical characterisation, cytotoxic activity, and biocompatibility studies of tamoxifen-loaded solid lipid nanoparticles prepared via a temperature-modulated solidification method. Journal of microencapsulation, 2014 Sep 1; 31(6): 590-9.
47. Vicente-Pascual M.; Albano A.; Solinís M.A, Serpe L, Rodríguez-Gascón A, Foglietta F, Battaglia L. Gene delivery in the cornea: In vitro and ex vivo evaluation of solid lipid nanoparticle-based vectors. Nanomedicine, 2018 May 24; 13(15): 1847-54.
48. Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid lipid nanoparticles for targeted brain drug

delivery. Advanced drug delivery reviews, 2007 Jul 10; 59(6): 454-77.
49. Mohammed HA, Khan RA, Singh V, Yusuf M, Akhtar N, Sulaiman GM, Albukhaty S, Abdellatif AA, Khan M, Mohammed SA, Al-Subaiyel AM. Solid lipid nanoparticles for targeted natural and synthetic drugs delivery in high-incidence cancers, and other diseases: Roles of preparation methods, lipid composition, transitional stability, and release profiles in nanocarriers' development. Nanotechnology Reviews, 2023; 12(1): 1-31.
50. El-Housiny S, Shams Eldeen MA, El-Attar YA, Salem HA, Attia D, Bendas ER, El-Nabarawi MA. Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasis versicolor: formulation and clinical study. Drug Delivery, 2018 Jan 1; 25(1): 78-90.
51. Akbari J, Saeedi M, Morteza-Semnani K, Rostamkalaei SS, Asadi M, Asare-Addo K, Nokhodchi A. The design of naproxen solid lipid nanoparticles to target skin layers. Colloids and Surfaces B: Biointerfaces, 2016; 145: 626-33.