Comprehensive Review on Solid Lipid Nanoparticles

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Abstract: **Solid lipid nanoparticles (SLN) have attracted attention during recent years. Solid lipid nanopaticles were developed in early 1990s as an alternative to other traditional colloidal carriers like liposomes, polymeric nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. The present review focuses on the utility of SLN in terms of their advantages & disadvantages, production methodology and characterization. The network of the SLNs improves drug stability and releasing the drug in a controlled way, which additionally offer a few advantages over ordinary details, including great physical stability, spherical morphology, uniform size, positive zeta potentials, typical high cell penetration efficiency, core–shell pattern and excipients of GRAS status make the SLNs delivery system all the more promising. Recently, increasing attention has been focused on these SLN as colloidal drug carriers for incorporating hydrophilic or lipophilic drugs.**

Keywords: Solid lipid nanoparticles, High pressure homogenizer, Solid lipid, Surfactants, Drug incorporation.

1. INTRODUCTION:

Lipid nanoparticles as drug delivery systems were considered from the beginning of the 19th century by professor R. H. Müller from Germany and Professor M. Gascon from Italy. These nanoparticles are manufactured from solid or mixture of solid and liquid lipids and stabilized by emulsifiers. (1) LNPs were initially licenced as a medication delivery vehicle in 2018 for the siRNA medicine Onpattro. Some COVID-19 vaccines that utilise RNA vaccine technology coat the fragile mRNA strands with PEGylated lipid nanoparticles as their delivery vehicle (including both the Moderna and the Pfizer–BioNTech COVID-19 vaccines), making LNPs more well-known in late 2020 (2)

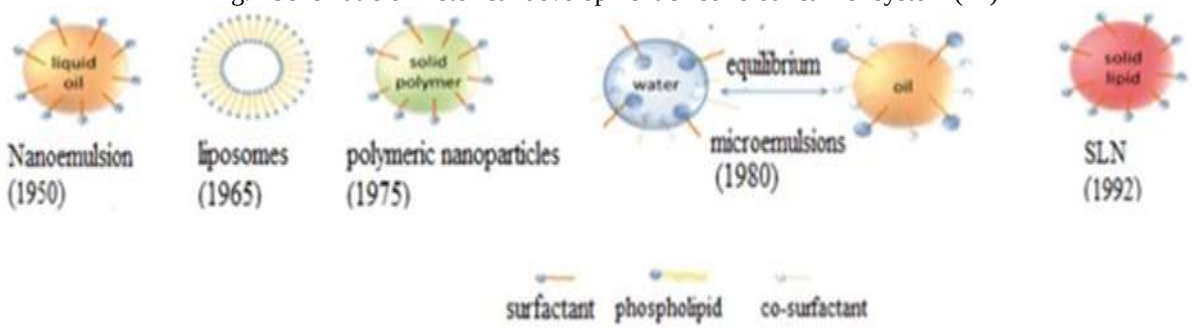
Targeted delivery of a drug molecule to specific organ sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, new frontiers have opened for improving drug delivery. Nanoparticles with their special characteristics small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems. (3) Some of the important Drug Delivery System developed using Nanotechnology principles are Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals. (4) SLNs introduced in 1991 represent an alternative and better carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. (5) These colloidal carriers have shown to improve the bioavailability of orally administered poorly soluble drugs, such as simvastatin, since the reduction of drug particles to the nanoscale increases dissolution velocity and saturation solubility, leading to improved in vivo drug performance. (6) The SLN structures remain solid at room temperature and also at human body temperature and are stabilized by suitable surfactant. These lipidic materials may contain purified triglycerides, complex glycerides mixtures, or waxes. (7)

The co– administration of lipids with drugs can also affect their absorption pathway although most orally administered compounds gain access to the systemic circulation via the portal vein, some highly lipophilic drugs are transported directly to the systemic circulation via intestinal lymphatic's, which improves oral bioavailability of Active Pharmaceutical Ingredient (API). (8) Since a decade, trials are being made to utilize solid lipid nanoparticles (SLN) as alternative drug delivery system to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles. SLN combines the advantages of different colloidal carriers and also avoids some of their disadvantages. SLN can be used to improve the bioavailability of drugs, e.g. cyclosporine A (9), and to obtain sustained release of lipophilic drugs like camptothecin. (10)

The point of this review is to explain the various techniques for solid lipid nanoparticles advantages,disadvantages, preparation, characterization.

2. PROGRESS OF LIPID NANOPARTICLES

Fig.1 Schematic of historical development of colloidal carrier system (11)



3. DEFINITION AND DESCRIPTION OF STRUCTURAL PROPERTIES OF SLNs

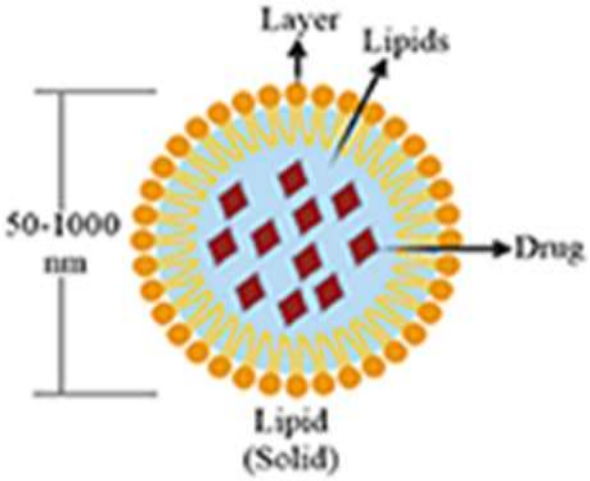


Fig.2 Structure of SLN (12)

Solid lipid nanoparticles (SLNs, LNPs), sometimes known as lipid nanoparticles (LNPs), are lipid-based nanoparticles. They're a revolutionary pharmaceutical drug delivery technology (and a component of nanoparticle drug delivery) as well as a novel pharmaceutical formulation**.** (13) Since 1990, SLNs have been promoted as a viable alternative to liposomes, emulsions, and polymeric nanoparticles as a carrier system. They have a spherical morphology with an average size of 40 to 1000 nm, which may be investigated using TEM and SEM (Transmission electron microscopy and scanning electron microscopy, respectively). A solid lipid nanoparticle is usually spherical, with a diameter ranging from 10 to 1000 nanometers. A solid lipid core matrix in solid lipid nanoparticles can solubilize lipophilic compounds. Surfactants help to keep the lipid core stable (emulsifiers). The type of emulsifier employed is determined by the mode of delivery, with parenteral treatments having additional restrictions. Triglycerides (e.g. tristearin), diglycerides (e.g. glycerol bahenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes are all examples of lipids (e.g. cetyl palmitate). (14)

To stabilise the lipid dispersion, all types of emulsifiers (in terms of charge and molecular weight) were utilised. The use of a combination of emulsifiers has been discovered to be more effective in preventing particle agglomeration. (15)

4. ADVANTAGES OF SLN

- Control or target drug release.
- The nanoparticles and SLNs particularly those in range between 120-200nm are not taken up by the cells of the RES (Reticulo Endothelial System) and thus bypass liver and spleen filtration.
- It can be freeze dried to form powdered formulation. (16)
- Excellent biocompatibility.
- Improve stability of pharmaceuticals.
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds. (17)
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable. Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures. (18)
- High encapsulation efficiency. (19)
- High ocular permeation. (20)
- Sustained and controlled release. (21)
- Good stability and biocompatibility. (22)
- Improve oral bioavailability (23)
- Reducing hepatic first pass metabolism (24)
- Scale up feasibility
- Long physical stability
- Lower cytotoxicity (25)
- Improve drug bioavailability (26)
- Good potential as vaccine adjuvants. (27)
- Aqueous dispersions of solid lipid nanoparticles (SLN) are usually physically stable for more than 3 years. (28)

5. DISADVANTAGE

- Particle growth.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions (29)
- Initial burst release from SLNs (19)
- Low drug loading capacity (30)
- Lipid dispersions contain high amounts of water (31)
- Drug expulsion during storage
- Limited loading capacity for hydrophilic drugs (32)
- Gelation of lipid dispersions (33)
- Polymorphic transition (34)
- Lack of wide clinical studies (35)
- Accumulation of lipid in liver and spleen may cause pathological alteration especially with Compritol-containing SLNs. (36)

6. COMPOSITION OF SLN

SLN mainly consists two parts matrix lipid and surface stabilizer. Other components include surfactant, preservatives, cryoprotectant, and charge modifiers. The matrix material constitutes of lipids, such as monoacid triglycerides (tristearin, tripalmitin, and trilaurin), fatty acids (stearic acid), steroids (cholesterol), waxes (cetylpalmitate), partial glycerides, fats, and waxes. The preferred surface stabilizers used include phospholipids, bile salts, soyabean lecithin, egg lecithin, phosphatidylcholine, poloxamers, and polysorbates. (37)

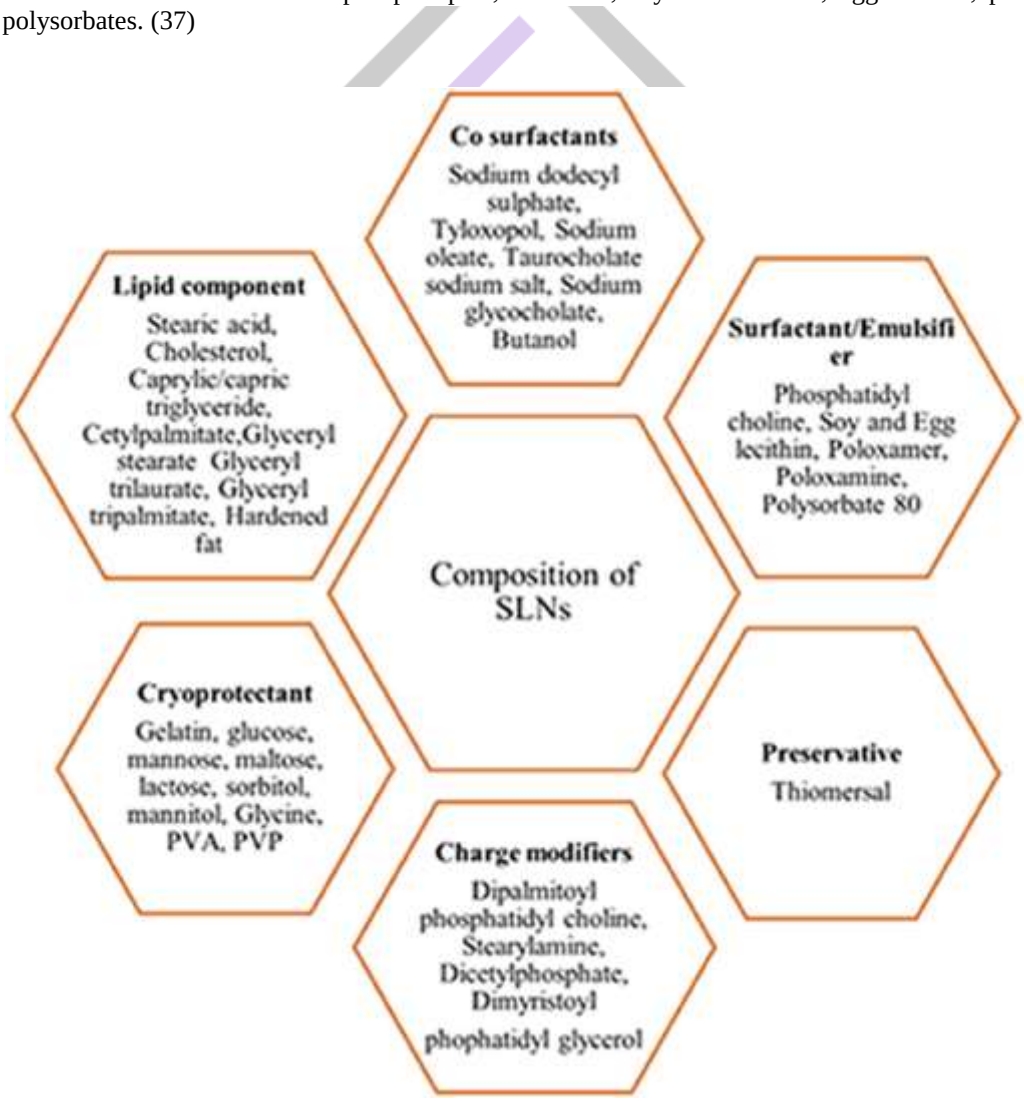


Fig. 3 Composition of SLN (37)

7. METHOD OF PREPARATION OF SOLID LIPID NANOPARTICLES

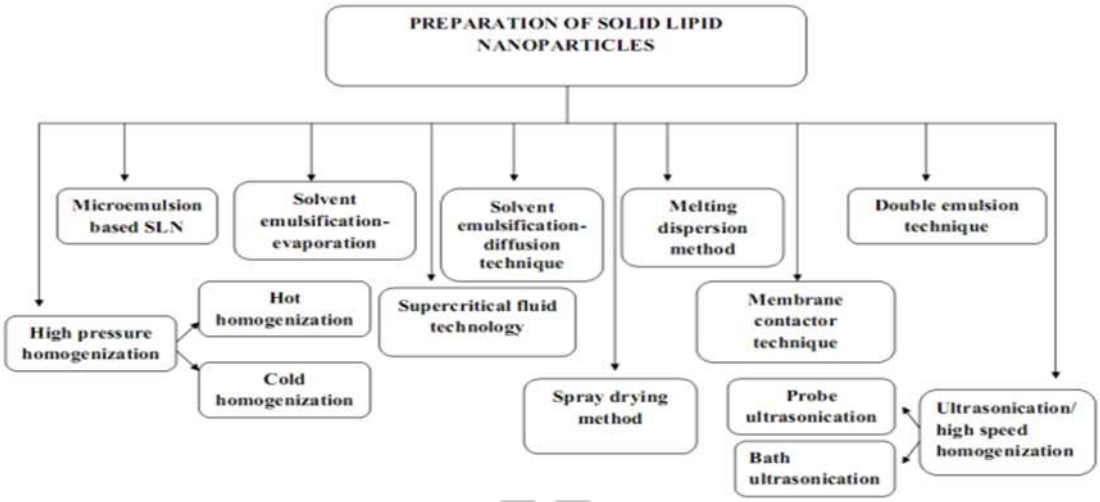


Fig-4 Method of preparations (38)

- High shear homogenization:

  a) Hot homogenization

  b) Cold homogenization

- High-Speed Stirring and Ultra-Sonication Methods
- Solvent emulsification/evaporation
- Micro emulsion based SLN preparations
- Spray drying method
- Double emulsion method

a) HIGH SHEAR HOMOGENIZATION

Any of various techniques used to make a mixture of two mutually insoluble liquids uniform throughout is known as homogenization or homogenisation**.** Initially, high shear homogenization techniques were employed to make solid lipid nanodispersions. (39) A high shear homogenization process was used to create SLN. In a nutshell, melted solid lipid, aqueous CTAB, and surfactant solution were pre-heated separately (10 °C above the lipid melting point) and combined and processed by Ultra Turrax (Ika, Staufen, Germany) for 10 minutes at 8000 rpm before being chilled on ice. 5 percent (w/w) solid lipid (IMW or COM), 0.5 percent (w/w) CTAB, and 0.25 percent (w/w) surfactant (Lutrol F68 or Miranol C-32 Ultra) comprised SLN. Higher stirring rates had little effect on particle size but did enhance the polydispersity index somewhat. (40)

HIGH PRESSURE HOMOGENISATION

A) HOT HOMOGENIZATION

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion and it is desirable to obtain droplets in the size range of a few micrometers. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also accelerate the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. It should always be kept in mind, that high pressure homogenization increases the temperature of the sample (approximately 10°C for 500 bar). In most cases, 3–5 homogenization cycles at 500–1500 bar are sufficient. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result high kinetic energy of the particles. The primary product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months. (41)

B) COLD HOMOGENISATION TECHNIQUE

In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the unmolten state of the lipid due to the increase in temperature during homogenization. Cold homogenization has been developed to over- come the following three problems of the hot homogenization technique:

1. Temperature-induced drug degradation
2. Drug distribution into the aqueous phase during homogenisation.

3. Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts.

The solubilization or dispersion of the drug in the bulk lipid melt is the first stage, which is the same as in the heat homogenization technique. The following phases, however, are distinct. The drug-containing melt cools quickly (e.g by means of dry ice or liquid nitrogen). The rapid cooling rate promotes a uniform medication distribution inside the lipid matrix. The solid lipid-containing medication is ground into microparticles. Particle sizes achieved by ball or mortar milling are typically in the 50–100 micron range. Low temperatures make lipids more fragile, allowing particle comminution to occur. In a cold emulsifier solution, solid lipid microparticles are dispersed. At or below room temperature, the pre-suspension is homogenised under high pressure. In general, cold homogenised samples have higher particle sizes and a wider size distribution than hot homogenised ones. The cold homogenization approach reduces the sample's heat exposure, but it does not eliminate it due to the first melting of the lipid/drug mixture. (42)

b) HIGH-SPEED STIRRING AND ULTRA-SONICATION METHODS

Dispersing procedures include high-speed stirring (high-shear homogenization) and ultrasonication. One of the simplest and most cost-effective techniques to make SLNs and NLCs is to use high-speed stirring . This process involves melting lipids at high temperatures (5–10 °C higher than the melting point of solid lipids), then dissolving or dispersing medicines uniformly in the molten lipids. The drug-lipid melt is then mixed with an aqueous phase containing surfactants (at the same temperature), and the mixture is homogeneously dispersed using a high-shear mixer. The shear of intense turbulent eddies produces a heated oil/water (o/w) emulsion. Cooling these dispersions produces SLNs and NLCs. Ultra sonication, which fractures droplets depending on the formation, development, and implosive collapse of bubbles, is frequently followed by high-speed stirring. The SLNs and NLCs produced when ultrasonication is performed without the high-shear mixing stage have a wide dispersion, likely because sonication energy is not distributed evenly throughout the batch. To generate SLNs and NLCs dispersions with narrow particle distributions, high-speed stirring and ultrasonication have been frequently combined. High-speed stirring (20,000 rpm for 1 min) and subsequent ultra-sonication (for 4 min) were used to make lycopene-loaded SLNs and NLCs with PSs of 200 nm and polydispersity indices (PDIs) of 0.22–0.32. Monostearin and medium-chain triglycerides were employed as lipids. Both, however, have the drawback of exposing pharmaceuticals to high temperatures over long periods of time. Furthermore, the size distributions of SLNs and NLCs produced by high-speed churning are broad, with micro-sized particles. Ultra-sonication has the problem of contaminating products with metals from the sonicator probes. Bath sonication can help to avoid this problem, but it must be used in conjunction with other treatments to lower PS and PDI values. Furthermore, considerable surfactant is required when using high-speed stirring and/or ultrasonication procedures, whereas total lipid concentrations are low. (43)

c) SOLVENT EMULSIFICATION/EVAPORATION

The lipophilic substance and the hydrophobic medication are dissolved in water-insoluble organic solvents such cyclohexane, toluene, and chloroform in this procedure. The combination is now emulsified in an aqueous medium using high-speed homogenization. The coarse emulsion is allowed to run through right away. To evaporate, the temperature is kept at ambient temperature and the pressure is reduced. Thermal stress is avoided with this method. It is possible to incorporate extremely thermolabile materials. (44)

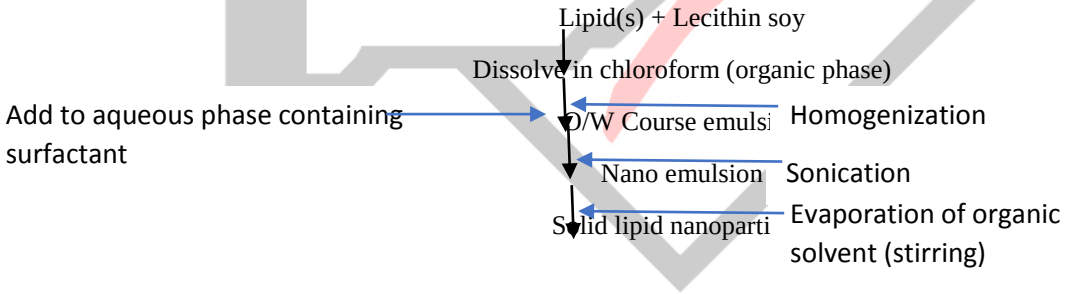


Fig. 5 Flow chart representing the preparation of SLN by Solvent emulsification/evaporation method

d) MICRO EMULSION BASED SLN PREPARATIONS

Gasco and colleagues created SLN preparations with the goal of lowering the concentration of micro emulsions. (45) External and internal media make up these biphasic microemulsions. A low melting fatty acid (such as stearic acid), an emulsifier (such as polysorbate 20, polysorbate 60, and soy phosphatidylcholine), coemulsifiers (such as butanol and sodium mono cetyl phosphate), and water make up the combination. The heated microemulsion is diffused in cold water (2°C–3°C). The dilution process can be rectified using a mixture of microemulsions. There is no extra energy used in this process to achieve the submicron size. Microemulsion was prepared by mixing the component in proper ratio. The corresponding pseudoternary phase diagram monitored Microemulsion formation field of different lecithin/alcohol. Solid lipid nanoparticles (SLN) were prepared by dispersing warm microemulsion in cold water under magnetic stirring. Then appropriate microemulsions that can contain more water phase and suitable oil phase were selected to prepare SLN. (46)

e) SPRAY DRYING METHOD

Spray-drying of aqueous dispersions of solid lipid nanoparticles resulted in dry, reconstitutable powders that may be kept for a long time. The particle size distribution and toxicity of the resultant granulates were still suitable for i.v. administration after

redispersion. Only physiologically acceptable excipients were added to the SLN dispersions before spraying, such as carbohydrates and alcohols (ethanol and methanol). The spraying settings, the chemical nature of the lipid phase, the kind of carbohydrate and the spraying, and the redispersion medium all had an impact on particle size. The following steps were used to achieve an equal size distribution before and after the spraying process: lowering the temperature by spraying alcoholic dispersions, lowering the lipid content while raising the sugar concentration, and redispersion in a poloxamer 188 solution. (47)

f) DOUBLE EMULSION METHOD

Based on solvent emulsification–evaporation, this approach is used to make hydrophilic loaded SLNs. The medication is first dissolved in aqueous-based solutions, followed by a liquid melt. The primary emulsion is stabilised with the help of a stabiliser. (48) The hydrophilic emulsifier disperses this primary emulsifier in the aqueous phase. The double emulsion is now mixed and sifted to separate it. The principal w/o emulsion emulsification technique requires poly (lactic-co-glycolic acid) (PLGA). It has been discovered that increasing the concentration of PLGA improves loading capacity, emulsion stability, and encapsulation efficiency. The size of SLN particles is unaffected by PLGA, and the zeta potential decreases significantly as the concentration of PLGA rises. (49)

8. SECONDARY PRODUCTION STEPS

a) STERILIZATION

Autoclaving (steam sterilisation), gamma-irradiation, and filtration are the procedures used to sterilise SLNs and NLCs. The steam sterilisation approach is used to sterilise nanoparticles containing thermostable medicines**.** (50)(51) For thermosensitive pharmaceuticals, gamma irradiation is the most extensively utilised alternative sterilising method. Irradiation, on the other hand, may cause lipid chemical breakdown. For particles larger than the filter pores, the filtration-sterilization method can be used. (52)

b) LYOPHILIZATION

Lyophilization of synthesised SLNs and NLCs is critical for long-term preservation since it helps to retain their chemical and physical stability. It is especially important for products containing hydrolyzable medicines or for products that are appropriate for peroral delivery. During a three month period, lyophilized SLNs stored at 4°C exhibited the greatest stability, showing no change in the particle size and a minimal reduction (53)

c) SPRAY DRYING

Spray drying is a less expensive alternative to lyophilization for maintaining SLN chemical and physical stability**.** (54)

9. CHARACTERIZATION OF SLN

The SLN are mainly characterized for particle size, morphology, polydispersity index (PI), zeta potential, percentage drug entrapment efficiency, drug crystallinity, and stability.

a) PARTICLE SIZE, POLYDISPERSITY INDEX, AND ZETA POTENTIAL

The average particle size, PDI, and zeta potential of the SLN can be measured using Zetasizer Nanoseries Nano-ZS, Malvern Instruments. DLS AND Laser Doppler Electrophoresis also used for the determination of particle size and zeta potential.

b) ENTRAPMENT EFFICIENCY

EE determine the amount of free drug spectrophotometrically at particular wavelength in the supernatant after centrifugation of the known amount of nanoparticulate dispersion at 10000 RPM using refrigerated centrifuge for 15 minutes.

$$EE\% = \frac{\text{Practical yield}}{\text{Theoretical yield}} * 100$$

c) SURFACE MORPHOLOGY

Surface morphology of the optimized SLN can be investigated using Scanning electron microscopy and transmission electron microscope. (55)

d) DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC is widely used to measure reaction kinetics, glass transition temp., specific heat capacity, compatibility, the stability of samples, the effect of aging, and the impact of additives on crystallization and characterization of the drug substance.

e) X-RAY DIFFRACTION (XRD)

X-ray diffraction (XRD) is one of the most extensively used techniques for the characterization of NPs. Typically; XRD provides information regarding the crystalline structure, nature of the phase, lattice parameters and crystalline grain size.

f) IN VITRO RELEASE

The effect of pH on the release array of the drug from SLN was evaluated by performing dissolution studies separately as per specified in a monogram.

g) ACCELERATED STABILITY STUDIES

The freeze-dried SLNs were stored in capped glass vials at 40 ± 2 °C/75 ± 5% RH for a period of 90 days. Samples were withdrawn at the end of 0, 30, 60 and 90 days to evaluate the PS, EE, zeta potential and drug release as described before. (56)

REFERENCES

1. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. Eur J Pharm Biopharm. 2000 Jul;50(1):161-77. doi : 10.1016/s0939-6411(00)00087-4. PMID: 10840199.
2. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6(12):1078-1094. doi: 10.1038/s41578-021-00358-0. Epub 2021 Aug 10. PMID: 34394960; PMCID: PMC8353930.

3. Garud, A., Singh, D., & Garud, N. (2012). Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications. In International Current Pharmaceutical Journal (Vol. 2012, Issue 11). http://www.icpjonline.com/documents/Vol1Issue11/08.pdf
4. Maravajhala, V., Papishetty, S., Bandlapalli, S., Padmavathi, S., Viswavidyalayam, M., Tirupathi, A., & Pradesh, I. (2012). NANOTECHNOLOGY IN DEVELOPMENT OF DRUG DELIVERY SYSTEM. IJPSR, 3(1), 84–96. www.ijpsr.com
5. Ekambaram, P., Abdul, A., Sathali, H., & Priyanka, K. (2012). SOLID LIPID NANOPARTICLES: A REVIEW. Sci. Revs. Chem. Commun, 2(1), 80–102. www.sadgurupublications.com
6. Vitorino C, Carvalho FA, Almeida AJ, Sousa JJ, Pais AA. The size of solid lipid nanoparticles: an interpretation from experimental design. Colloids Surf B Biointerfaces. 2011 May 1;84(1):117-30. doi: 10.1016/j.colsurfb.2010.12.024. Epub 2010 Dec 24. PMID: 21242064.
7. Kumar, S., Dilbaghi, N., Saharan, R. et al. Nanotechnology as Emerging Tool for Enhancing Solubility of Poorly Water-Soluble Drugs. BioNanoSci. 2, 227–250 (2012). https://doi.org/10.1007/s12668-012-0060-7
8. Chenthamara, D., Subramaniam, S., Ramakrishnan, S. G., Krishnaswamy, S., Essa, M. M., Lin, F. H., & Qoronfleh, M. W. (2019). Therapeutic efficacy of nanoparticles and routes of administration. In Biomaterials Research (Vol. 23, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s40824-019-0166-x
9. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. Eur J Pharm Biopharm. 2000 Jul;50(1):161-77. doi: 10.1016/s0939-6411(00)00087-4. PMID: 10840199.
10. Yang, S., Zhu, J., Lu, Y. et al. Body Distribution of Camptothecin Solid Lipid Nanoparticles After Oral Administration. Pharm Res 16, 751–757 (1999). https://doi.org/10.1023/A:1018888927852
11. Naseri, Neda et al. "Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application." Advanced pharmaceutical bulletin vol. 5,3 (2015): 305-13. doi:10.15171/apb.2015.043
12. Dhiman N, Awasthi R, Sharma B, Kharkwal H, Kulkarni GT. Lipid Nanoparticles as Carriers for Bioactive Delivery. Front Chem. 2021 Apr 23;9:580118. doi: 10.3389/fchem.2021.580118. PMID: 33981670; PMCID: PMC8107723.
13. Bandawane, A., and R. Saudagar. "A Review on Novel Drug Delivery System: A Recent Trend". Journal of Drug Delivery and Therapeutics, Vol. 9, no. 3, May 2019, pp. 517-21, doi:10.22270/jddt.v9i3.2610.
14. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009 Jul;71(4):349-58. doi: 10.4103/0250-474X.57282. PMID: 20502539; PMCID: PMC2865805.
15. Kovačević, A. B., Müller, R. H., Savić, S. D., Vuleta, G. M., & Keck, C. M. (2014). Solid lipid nanoparticles (SLN) stabilized with polyhydroxy surfactants: Preparation, characterization and physical stability investigation. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 444, 15–25. https://doi.org/10.1016/j.colsurfa.2013.12.023
16. D. Thulasi Ram, Subhashis Debnath, M. Niranjan Babu, T. Chakradhar Nath, Thejeswi B. A Review on solid Lipid Nanoparticles. Research J. Pharm. and Tech. 5(11): Nov. 2012; Page 1359-1368.
17. Hanumanaik, M., Kumar, S., Kumar Patel, S., & Ramya Sree, K. (2013). SOLID LIPID NANOPARTICLES; A REVIEW Periodontal treatment View project Application of Nanotechnology in environment and medical View project SOLID LIPID NANOPARTICLES; A REVIEW. Article in International Journal of Pharmaceutical Sciences and Research, 4(3), 928–940. www.ijpsr.com
18. Ghasemiyeh, Parisa, and Soliman Mohammadi-Samani. "Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages." Research in pharmaceutical sciences vol. 13,4 (2018): 288-303. doi:10.4103/1735-5362.235156
19. Attama AA, Reichl S, Müller-Goymann CC. Diclofenac sodium delivery to the eye: in vitro evaluation of novel solid lipid nanoparticle formulation using human cornea construct. Int J Pharm. 2008 May 1;355(1-2):307-13. doi: 10.1016/j.ijpharm.2007.12.007. Epub 2007 Dec 17. PMID: 18242022.
20. Li X, Nie SF, Kong J, Li N, Ju CY, Pan WS. A controlled-release ocular delivery system for ibuprofen based on nanostructured lipid carriers. Int J Pharm. 2008 Nov 3;363(1-2):177-82. doi: 10.1016/j.ijpharm.2008.07.017. Epub 2008 Jul 26. PMID: 18706987.
21. Sánchez-López E, Espina M, Doktorovova S, Souto EB, García ML. Lipid nanoparticles (SLN, NLC): Overcoming the anatomical and physiological barriers of the eye - Part I - Barriers and determining factors in ocular delivery. Eur J Pharm Biopharm. 2017 Jan;110:70-75. doi: 10.1016/j.ejpb.2016.10.009. Epub 2016 Oct 24. PMID: 27789358.
22. Andrade LM, Rocha KA, De Sá FA, Marreto RN, Lima EM, Gratieri T, Taveira SF. Voriconazole-Loaded Nanostructured Lipid Carriers for Ocular Drug Delivery. Cornea. 2016 Jun;35(6):866-71. doi: 10.1097/ICO.0000000000000825. PMID: 27055213.
23. Müller RH, Runge S, Ravelli V, Mehnert W, Thünemann AF, Souto EB. Oral bioavailability of cyclosporine: solid lipid nanoparticles (SLN) versus drug nanocrystals. Int J Pharm. 2006 Jul 6;317(1):82-9. doi: 10.1016/j.ijpharm.2006.02.045. Epub 2006 Mar 31. PMID: 16580159.
24. Sangsen Y, Wiwattanawongsa K, Likhitwitayawuid K, Sritularak B, Wiwattanapatapee R. Modification of oral absorption of oxyresveratrol using lipid based nanoparticles. Colloids Surf B Biointerfaces. 2015 Jul 1;131:182-90. doi: 10.1016/j.colsurfb.2015.04.055. Epub 2015 May 4. PMID: 25988282.
25. Wissing SA, Kayser O, Müller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev. 2004 May 7;56(9):1257-72. doi: 10.1016/j.addr.2003.12.002. PMID: 15109768.
26. Hosseini M, Haji-Fatahaliha M, Jadidi-Niaragh F, Majidi J, Yousefi M. The use of nanoparticles as a promising therapeutic approach in cancer immunotherapy. Artif Cells Nanomed Biotechnol. 2016 Jun;44(4):1051-61. doi: 10.3109/21691401.2014.998830. Epub 2015 Jan 23. PMID: 25612903.
27. Joshi MD, Müller RH. Lipid nanoparticles for parenteral delivery of actives. Eur J Pharm Biopharm. 2009 Feb;71(2):161-72. doi: 10.1016/j.ejpb.2008.09.003. Epub 2008 Sep 13. PMID: 18824097.

28. Freitas C, Müller RH. Correlation between long-term stability of solid lipid nanoparticles (SLN) and crystallinity of the lipid phase. Eur J Pharm Biopharm. 1999 Mar;47(2):125-32. doi: 10.1016/s0939-6411(98)00074-5. PMID: 10234536.
29. Patil, P., Harak, K., & Saudagar, R. (2019). Solid Lipid Nanoparticles: A Review. Journal of Drug Delivery and Therapeutics, 9(3), 525–530. https://doi.org/10.22270/jddt.v9i3.2773
30. Chetoni P, Burgalassi S, Monti D, Tampucci S, Tullio V, Cuffini AM, Muntoni E, Spagnolo R, Zara GP, Cavalli R. Solid lipid nanoparticles as promising tool for intraocular tobramycin delivery: Pharmacokinetic studies on rabbits. Eur J Pharm Biopharm. 2016 Dec;109:214-223. doi: 10.1016/j.ejpb.2016.10.006. Epub 2016 Oct 24. PMID: 27789355.
31. Beloqui, A., Solinís, M. A., Delgado, A., Évora, C., Isla, A., & Rodríguez-Gascón, A. (2014). Fate of nanostructured lipid carriers (NLCs) following the oral route: Design, pharmacokinetics and biodistribution. Journal of Microencapsulation, 31(1), 1–8. https://doi.org/10.3109/02652048.2013.788090
32. Poonia N, Kharb R, Lather V, Pandita D. Nanostructured lipid carriers: versatile oral delivery vehicle. Future Sci OA. 2016 Jul 15;2(3):FSO135. doi: 10.4155/fsoa-2016-0030. PMID: 28031979; PMCID: PMC5137980.
33. Tran TH, Ramasamy T, Truong DH, Choi HG, Yong CS, Kim JO. Preparation and characterization of fenofibrate-loaded nanostructured lipid carriers for oral bioavailability enhancement. AAPS PharmSciTech. 2014 Dec;15(6):1509-15. doi: 10.1208/s12249-014-0175-y. Epub 2014 Jul 18. PMID: 25035071; PMCID: PMC4245431.
34. Pandita, D., Kumar, S., Poonia, N., & Lather, V. (2014). Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. Food Research International, 62, 1165–1174. https://doi.org/10.1016/j.foodres.2014.05.059
35. Wong HL, Bendayan R, Rauth AM, Li Y, Wu XY. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Adv Drug Deliv Rev. 2007 Jul 10;59(6):491-504. doi: 10.1016/j.addr.2007.04.008. Epub 2007 May 1. PMID: 17532091.
36. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages. Res Pharm Sci. 2018 Aug;13(4):288-303. doi: 10.4103/1735-5362.235156. PMID: 30065762; PMCID: PMC6040163.
37. Dhiman N, Awasthi R, Sharma B, Kharkwal H, Kulkarni GT. Lipid Nanoparticles as Carriers for Bioactive Delivery. Front Chem. 2021 Apr 23;9:580118. doi: 10.3389/fchem.2021.580118. PMID: 33981670; PMCID: PMC8107723.
38. Ram, D. & Debnath, Subhashis & Babu, M. & Nath, T. & Thejeswi, B.. (2012). A review on solid lipid nanoparticles. Research Journal of Pharmacy and Technology. 5. 1359-1368.
39. Britannica, The Editors of Encyclopaedia. "homogenization". Encyclopedia Britannica, 20 Apr. 2021, https://www.britannica.com/science/homogenization. Accessed 25 May 2022
40. Doktorovova S, Silva AM, Gaivão I, Souto EB, Teixeira JP, Martins-Lopes P. Comet assay reveals no genotoxicity risk of cationic solid lipid nanoparticles. J Appl Toxicol. 2014 Apr;34(4):395-403. doi: 10.1002/jat.2961. Epub 2013 Nov 15. PMID: 24243595.
41. Khatak, S., Goel, R. K., Yadav, N., Vir, U., & Sara, S. (2013). Solid lipid nanoparticles-A review. https://www.researchgate.net/publication/287716187
42. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001 Apr 25;47(2-3):165-96. doi: 10.1016/s0169-409x(01)00105-3. PMID: 11311991. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001 Apr 25;47(2-3):165-96. doi: 10.1016/s0169-409x(01)00105-3. PMID: 11311991.
43. Duong VA, Nguyen TT, Maeng HJ. Preparation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Drug Delivery and the Effects of Preparation Parameters of Solvent Injection Method. Molecules. 2020 Oct 18;25(20):4781. doi: 10.3390/molecules25204781. PMID: 33081021; PMCID: PMC7587569.
44. Liu, D., Jiang, S., Shen, H., Qin, S., Liu, J., Zhang, Q., Li, R., & Xu, Q. (2011). Diclofenac sodium-loaded solid lipid nanoparticles prepared by emulsion/solvent evaporation method. Journal of Nanoparticle Research, 13(6), 2375–2386. https://doi.org/10.1007/s11051-010-9998-y
45. Garud, A., Singh, D., & Garud, N. (2012). Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications. In International Current Pharmaceutical Journal (Vol. 2012, Issue 11). http://www.icpjonline.com/documents/Vol1Issue11/08.pdf
46. Mao SR, Wang YZ, Ji HY, Bi DZ. [Preparation of solid lipid nanoparticles by microemulsion technique]. Yao Xue Xue Bao. 2003 Aug;38(8):624-6. Chinese. PMID: 14628457.
47. Freitas C, Müllerä RH. Spray-drying of solid lipid nanoparticles (SLN TM). Eur J Pharm Biopharm. 1998 Sep;46(2):145-51. doi: 10.1016/s0939-6411(97)00172-0. PMID: 9795036.
48. Becker Peres L, Becker Peres L, de Araújo PHH, Sayer C. Solid lipid nanoparticles for encapsulation of hydrophilic drugs by an organic solvent free double emulsion technique. Colloids Surf B Biointerfaces. 2016 Apr 1;140:317-323. doi: 10.1016/j.colsurfb.2015.12.033. Epub 2015 Dec 29. PMID: 26764112.
49. Panigrahi, D., Sahu, P.K., Swain, S. et al. Quality by design prospects of pharmaceuticals application of double emulsion method for PLGA loaded nanoparticles. SN Appl. Sci. 3, 638 (2021). https://doi.org/10.1007/s42452-021-04609-1
50. Huang, Zr., Hua, Sc., Yang, Yl. et al. Development and evaluation of lipid nanoparticles for camptothecin delivery: a comparison of solid lipid nanoparticles, nanostructured lipid carriers, and lipid emulsion. Acta Pharmacol Sin 29, 1094–1102 (2008). https://doi.org/10.1111/j.1745-7254.2008.00829.x
51. Khatak, S., Goel, R. K., Yadav, N., Vir, U., & Sara, S. (2013). Solid lipid nanoparticles-A review. https://www.researchgate.net/publication/287716187
52. Manjunath K, Reddy JS, Venkateswarlu V. Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol. 2005 Mar;27(2):127-44. doi: 10.1358/mf.2005.27.2.876286. PMID: 15834465.

53. Howard MD, Lu X, Jay M, Dziubla TD. Optimization of the lyophilization process for long-term stability of solid-lipid nanoparticles. Drug Dev Ind Pharm. 2012 Oct;38(10):1270-9. doi: 10.3109/03639045.2011.645835. Epub 2012 Jan 12. PMID: 22235767.
54. Jose J, Netto G. Role of solid lipid nanoparticles as photoprotective agents in cosmetics. J Cosmet Dermatol. 2019 Feb;18(1):315-321. doi: 10.1111/jocd.12504. Epub 2018 Feb 13. PMID: 29441672.
55. Gupta, S., Kesarla, R., Chotai, N., Misra, A., & Omri, A. (2017). Systematic approach for the formulation and optimization of solid lipid nanoparticles of efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. BioMed Research International, 2017. https://doi.org/10.1155/2017/5984014
56. Bhalekar,M, Upadhaya, P. & Madgulkar, A. Formulation and characterizationof solid lipid nanoparticles for an anti-retroviral drug darunavir. Appl Nanosci 7, 47-57 (2017). https://doi.org/10.1007/s13204-017-0547-1