Solid Lipid Nanoparticles - An Emerging for Ocular Drug Delivery System

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Abstract **- Drug delivery to the eye remains a complex process due to the nature and structure of the eye. Conventional dosage forms such as eye drops and ointments are inefficient in therapeutics because they possess low bioavailability and sometimes exhibit toxicity. So, there is a need to develop novel drug delivery carriers to increase ocular bioavailability and decreased local and systemic toxicity. Nanotechnology is one of the best approaches for ocular drug delivery. Many nano-structured systems have been employed for ocular drug delivery to get better results. One of the best nano structure developments is Solid Lipid Nanoparticles (SLNs). It is the best drug carrier system since 1991. SLNs are mainly used in ocular drug delivery because they increase corneal absorption and bioavailability of both hydrophilic and lipophilic drugs as they are prepared by physiological lipids. SLNs are mainly prepared by allowing autoclave sterilization, which is a major step for formulation of ocular preparations. This review gives the detailed note on various methods of preparation, characterization, sterilization and evaluation of SLNs. This also gives a note on nature of lipids and surfactants used in SLNs preparation.**

Index Terms **- Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers, Controlled Release, Lyophilization and Surfactants.**

1. INTRODUCTION

Drugs have several obstructions before reaching their target site to exert their pharmacological effect. The important thing is to cross the biological membrane by maintaining stability. These obstructions can be decreased by using Novel drug delivery carriers like Solid Lipid Nanoparticles (SLNs). SLNs are used because as it is made up of lipids and these particles can easily cross the biological membrane.

1.1 Ocular Drug Delivery:

Ocular drug delivery is a challenge for pharmaceutical scientists due to the nature and structure of the eye. For the successful ocular drug delivery system, the drug particles should be small in size i.e., less than 10 µm, should be non-irritant, adequately bioavailable, be compatible with ocular tissues and cause no blurred vision. The eye contains several barriers which limits the entry of drugs. The barriers are epithelial, aqueous-vitreous, blood-aqueous barrier and blood- retinal barrier. To treat some diseases like glaucoma or uveitis, the drugs have to penetrate into deeper posterior chamber. Most of the ophthalmic preparations are formulated as eye drops or as ointments. Eye drops count for more than 90% of ocular preparations. Eye drops are cost effective, patient compatible, simple in formulation. The major disadvantage of eye drops is that maximum amount of drug is washed away by tears or due to other mechanisms [1].

1.2 Barriers of the Eye:

1.2.1 Epithelial barrier

Epithelial route is the main route through which drugs reach the aqueous humour. The cornea is a multi-layered tissue consisting of the epithelium, endothelium and stroma. The epithelial layer consists of tight junctions that limit the entry of hydrophilic drugs and macromolecules into cornea (Fig. 1). This

barrier can be breached by sub-conjunctival infection. Beneath the epithelium, a hydrophilic layer called as stroma consisting of a large portion of the cornea where lies a single layer of flat epithelium like cells called as endothelium. It is a potential barrier to both hydrophilic and lipophilic drugs so it complicates the ocular barrier structure to a greater extent. Therefore, epithelium limits the entry of hydrophilic drugs while stroma and endothelium limits the entry of lipophilic drugs.

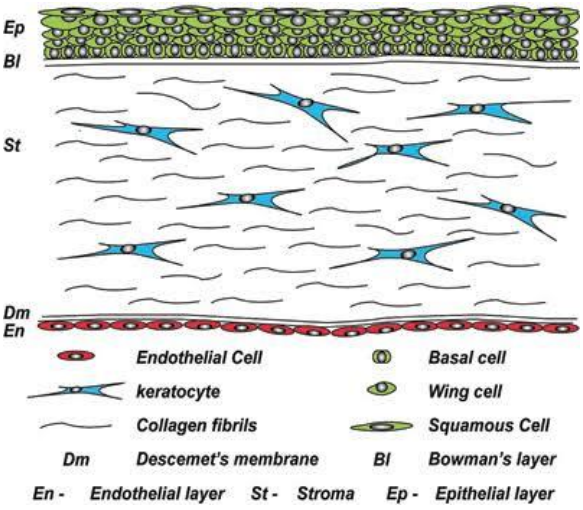

Fig. 1: Epithelial barriers

1.2.2 Blood-aqueous barrier

The blood-aqueous barrier is present in the anterior portion of the eye. It consists of endothelial cells of uvea. It limits the entry of hydrophilic drugs from the blood circulation into aqueous humour. This barrier may be disrupted sometimes due to inflammation and it leads to enhanced temporary drug permeation. Blood-aqueous barrier and blood-retinal barrier are together called as blood-ocular barrier. The epithelium of the iris and the ciliary bodies pump anionic drugs from the aqueous humour to the blood.

1.2.3 Blood-retinal barrier

This barrier is situated in the posterior chamber of the eye. This limits the entry of the drugs from blood to retina. It contains retinal pigment epithelium (RPE) and the tight walls of the retinal capillaries. The blood-retinal barrier (Fig. 2) along with blood-aqueous barrier protects the eye from entry of xenobiotic and harmful substances. This physiological defence mechanism limits drug delivery to the retina and vitreous humour. As well as systemic and topical administration, intravitreal injections, lipophilic pro-drugs and ocular implants been used in retinal drug delivery. Each method has its own advantages, disadvantages and limitations, so there is a need to develop novel drug carriers which are safe, convenient and efficient in crossing potential ocular barriers [2].

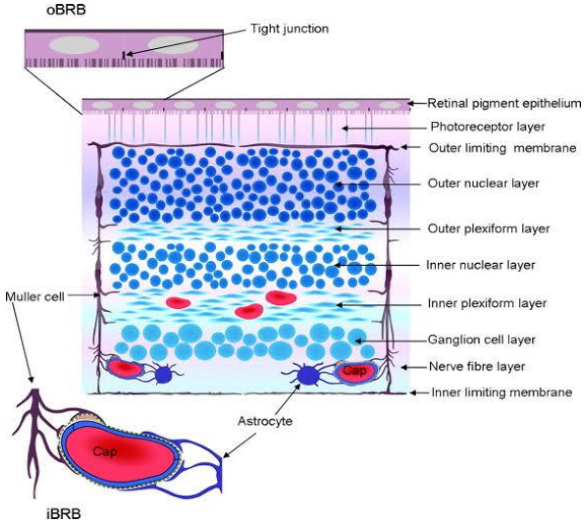

Fig. 2: Blood-retinal barrier

1.3 Solid Lipid Nanoparticles:

Solid Lipid Nanoparticles are the colloidal carriers with nanoscale in size range from 50-1000 nm. SLNs have been developed in the year since 1991. Its main advantage is to provide biocompatibility, storage stability and to prevent drug degradation. They are mainly made up of solid lipids to conquer the weaknesses. SLNs show distinctive features such as low toxicity, large surface area, prolonged drug release, superior cellular uptake as compared to traditional colloidal carriers as well as capability to improve solubility and bioavailability of drugs. The solid core of SLNs is hydrophobic with a monolayer coating of phospholipids and the drug is dispersed in the core (Fig. 3).

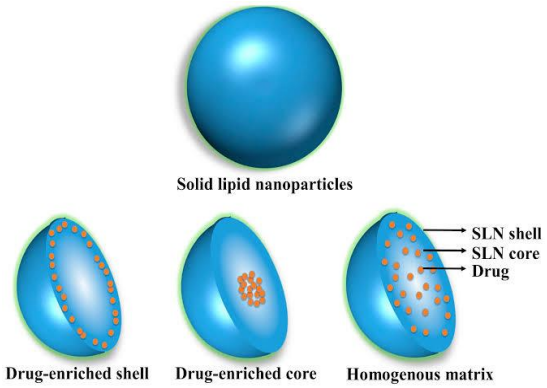

Fig. 3: Drug loaded Solid Lipid Nanoparticles

Advantages

- Provide high stability to incorporated drugs.
- Improve bioavailability of poorly water-soluble drugs.
- Ease of sterilization.
- Provide opportunities for targeted and controlled release of drugs.
- It is biocompatible and biodegradable.

Disadvantages

- There is a chance of drug expulsion.
- It has poor drug loading capacity.
- Difficulty of encapsulation.

1.4 Nanostructured Lipid Carriers:

Nanostructured Lipid Carriers (NLCs) are developed to overcome the difficulties of SLNs like expulsion and poor loading of drug. These NLCs which are non-ideal crystalline structures and they prevent drug expulsion by avoiding crystallization of lipids [4].

NLCs can be divided into three types like imperfect type, multiple type and amorphous type.

1. Imperfect type of NLCs is prepared by mixing solid lipids with small amount of oils.
2. In multiple type NLCs the amount of oily lipids are higher and yields high drug solubility.
3. Amorphous type NLCs contain some additional lipids to avoid crystallization of solid lipid upon cooling and prevent drug expulsion.

Advantages

- High capacity of drug loading.
- Leakage of the drug is low.
- Production of final dosage form is feasible [5].

2. MATERIALS AND METHODS

2.1 Formulation of Solid Lipid Nanoparticles:

Lipids and surfactants are the main components to prepare SLNs (shows in Table 1). By reducing the interfacial tension between the aqueous environment and the hydrophobic surface of the lipid core, surfactants help in stabilizing the SLNs structure [6].

Table 1: List of the ingredients used in formulation of SLNs

S. No	Name of the Ingredients	Examples
1	Lipids	Beeswax, Stearic acid, Cholesterol, Caprylic/Capric triglyceride, Cetyl palmitate, Glyceryl stearate (-mono, and -tri), Glyceryl trilaurate, Glyceryl trimyristate, Glyceryl behenate (Compritol), Glyceryl tripalmitate, Hardened fat (Witepsol E85, H5 and W35), Monostearate monocitrate, Solid paraffin and Behenic acid
2	Surfactants / Emulsifiers	Phosphatidyl choline, Soy and Egg lecithin, Poloxamer, Poloxamine and Polysorbate 80
3	Co-surfactants	Sodium dodecyl sulphate, Tyloxopol, Sodium oleate, Taurocholate sodium salt, Sodium glycocholate and Butanol
4	Preservative	Thiomersal
5	Cryoprotectant	Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol and Polyvinyl pyrrolidone
6	Charge modifiers	Dipalmitoyl phosphatidyl choline, Stearylamine, Dicetylphosphate and Dimyristoyl phophatidyl glycerol [7].

2.2 Methods of Preparation of Solid Lipid Nanoparticles:

There are different methods involved in preparation of SLNs. They are hot homogenization, Cold homogenization, Ultrasonication / High-speed homogenization, Solvent evaporation, Microemulsion method, Double emulsion method, Supercritical fluid method and Precipitation method [8].

2.2.1 Hot Homogenization

Hot homogenization technique is carried out at temperatures above the melting point of the lipid and therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug-loaded lipid melts and the aqueous emulsifier phase is obtained by high-shear mixing device. In general, higher temperatures results in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particle (Fig. 4) [3].

Fig. 4: Hot Homogenization

2.2.2 Cold Homogenization

The cold homogenization technique overcomes the problems like, temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, complexity of the crystallization step of the nanoemulsions leading to several modifications or super cooled melts (Fig. 5). In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid micro particles and these lipid micro particles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenised at or below room temperature, the gravitation force is strong enough to break the lipid micro particles directly in to solid lipid nanoparticles.

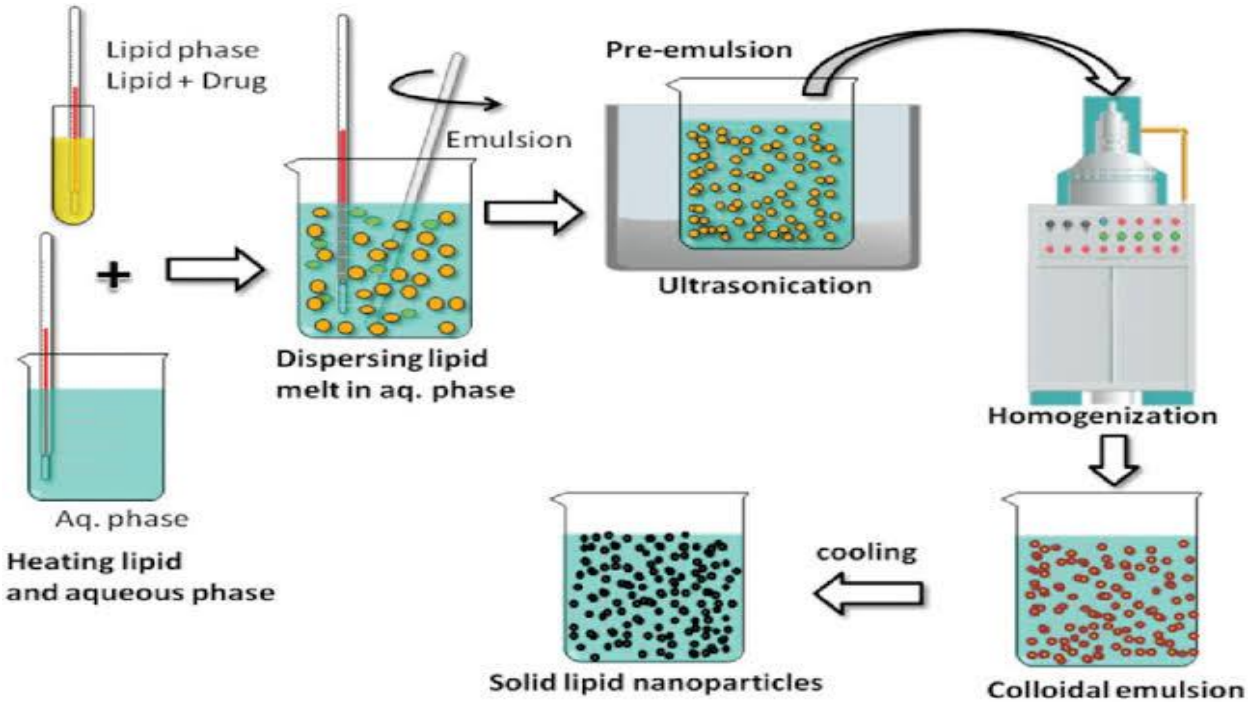

Fig. 5: Cold Homogenization

2.2.3 Ultrasonication / High-speed homogenization

Solid Lipid Nanoparticles also prepared by Ultrasonication or high-speed homogenization techniques. To reduce the particle size in to smaller, combination of both Ultrasonication and high-speed homogenization is required (Fig. 6).

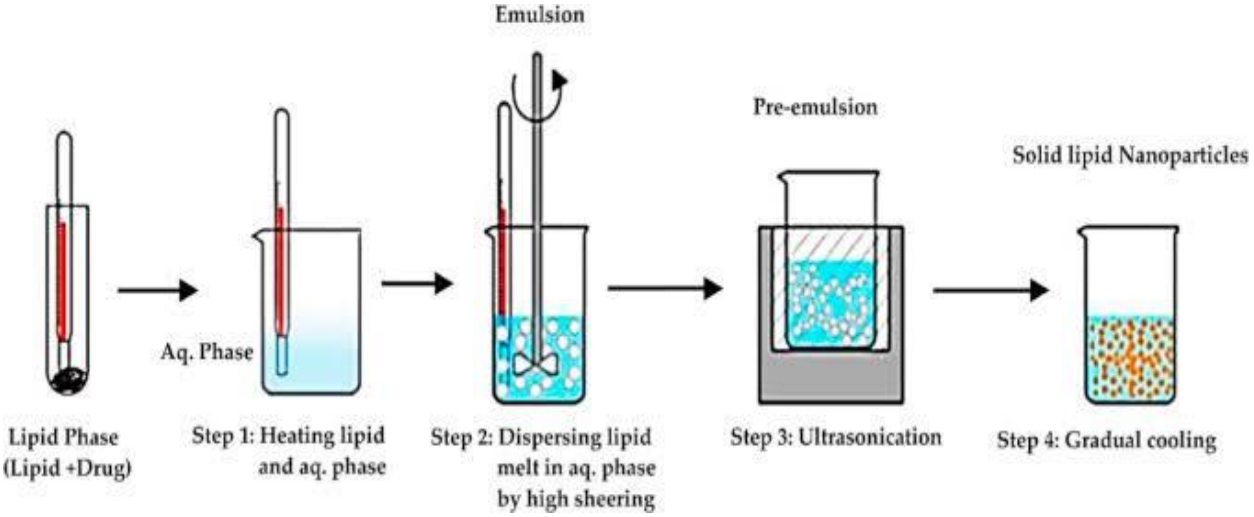

Fig. 6: Ultrasonication / High-speed homogenization

2.2.4 Solvent evaporation

SLNs can also be prepared by solvent evaporation method (Fig. 7). The lipophilic material is dissolved in an evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. The solution was emulsified in an aqueous phase by high-pressure homogenization. The organic solvent will be removed from the emulsion by evaporation under reduced pressure (40-60 mbar).

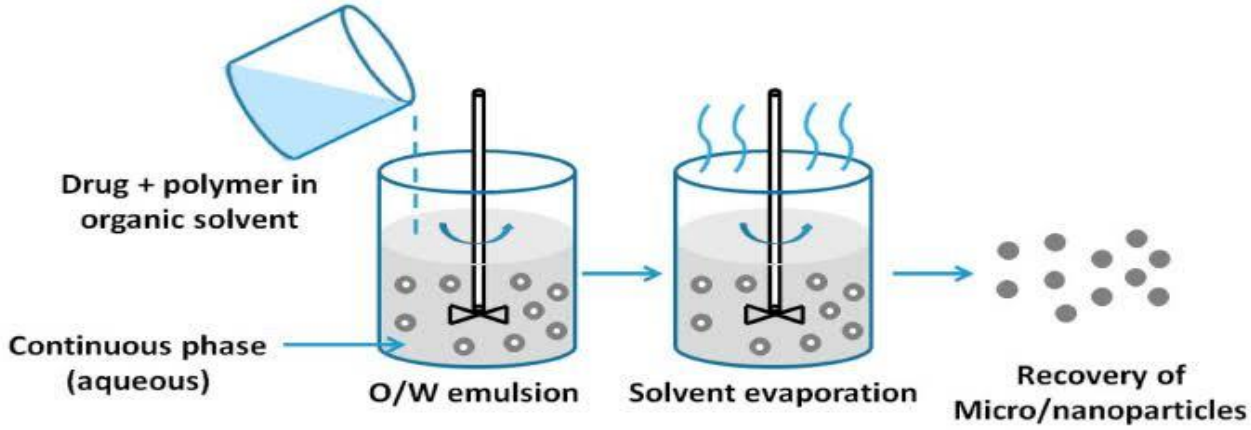

Fig. 7: Solvent evaporation

2.2.5 Microemulsion method

This method is based on the dilution of microemulsions. As microemulsions are, two-phase systems composed of an inner and outer phase (e.g., o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which is typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLNs dispersion can be used as granulation fluid for transferring into solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step, achievable lipid contents are considerably lower (Fig. 8) [9].

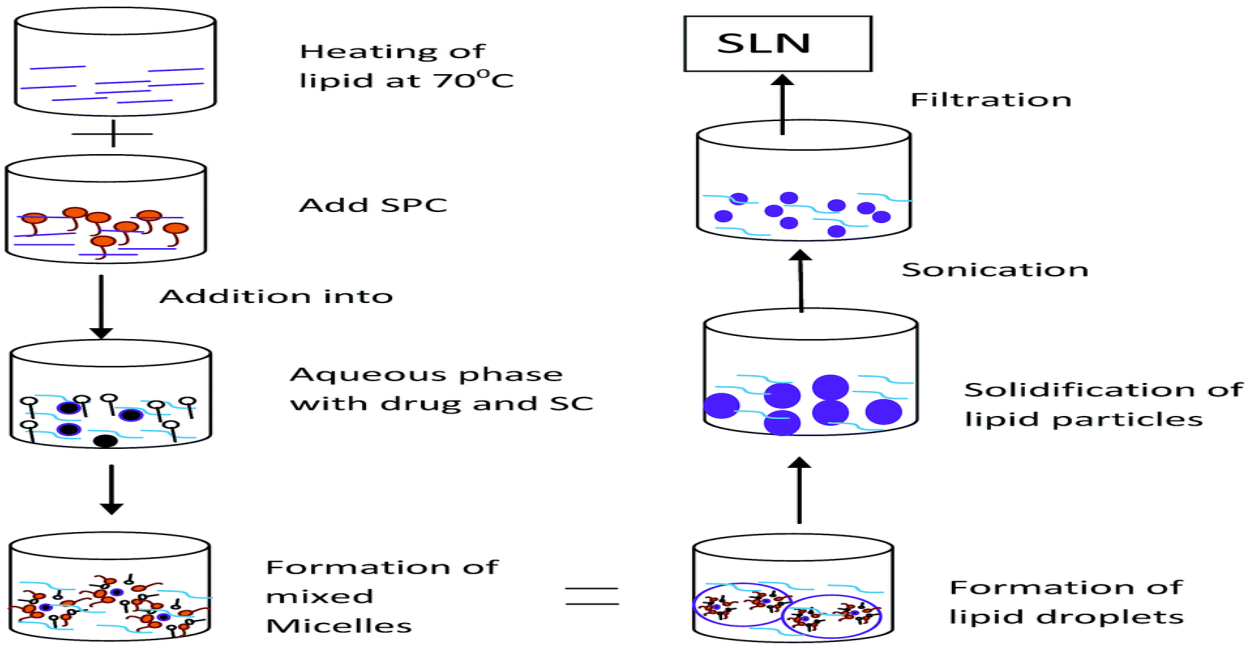

Fig. 8: Microemulsion method

2.2.6 Double emulsion method

In this method, the drug is encapsulated with a stabilizer to prevent the partitioning of drug into external water phase during solvent evaporation of w/o/w double emulsion (Fig. 9).

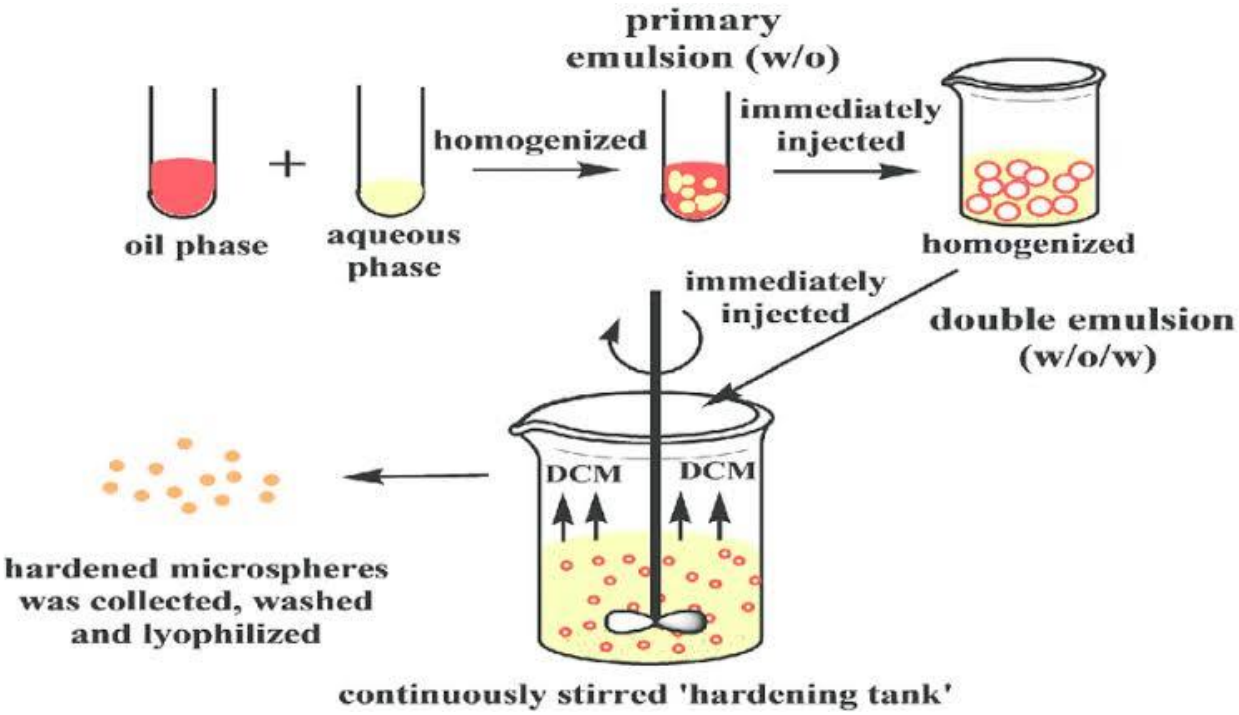

Fig. 9: Double emulsion method

2.2.7 Supercritical fluid method

This is the alternative method for preparing SLNs by particles from gas-saturated solutions. This method avoids the use of solvents and uses mild pressure and temperature conditions (Fig. 10).

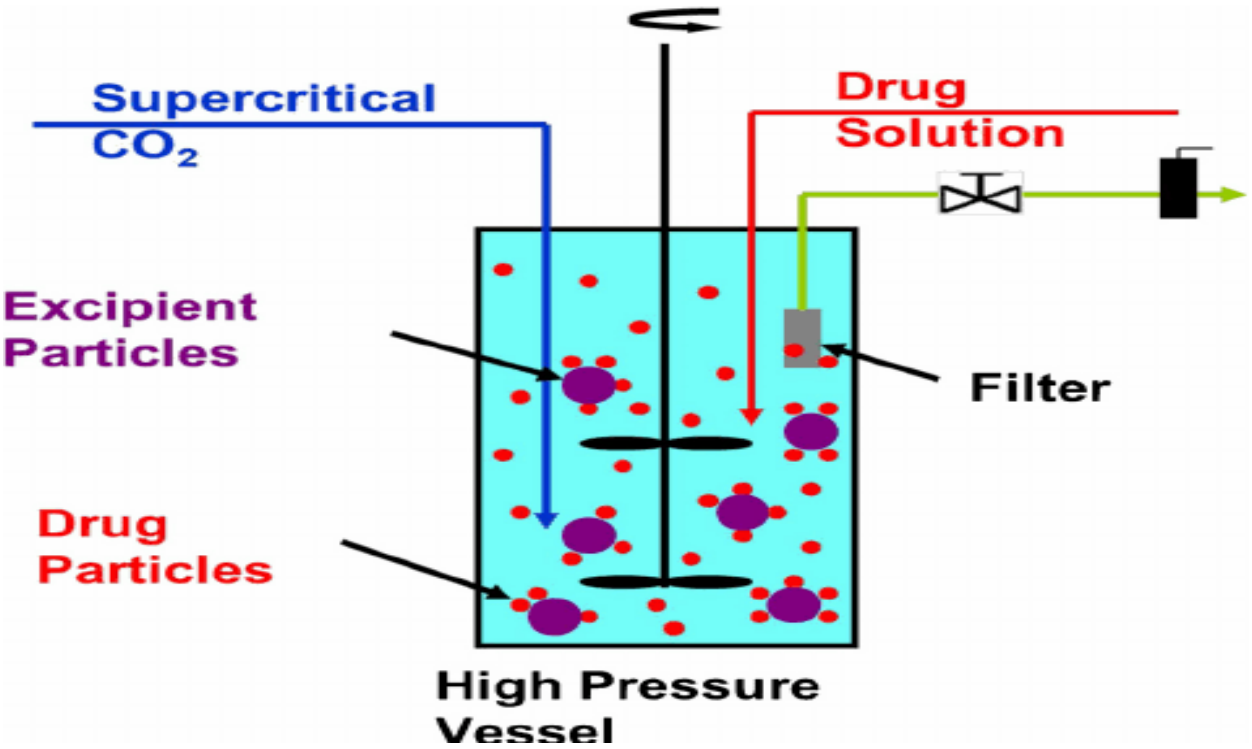

Fig. 10: Supercritical fluid method

2.2.8 Precipitation method

The glycerides are dissolved in an organic solvent and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent, the lipid will be precipitated forming nanoparticles (Fig. 11).

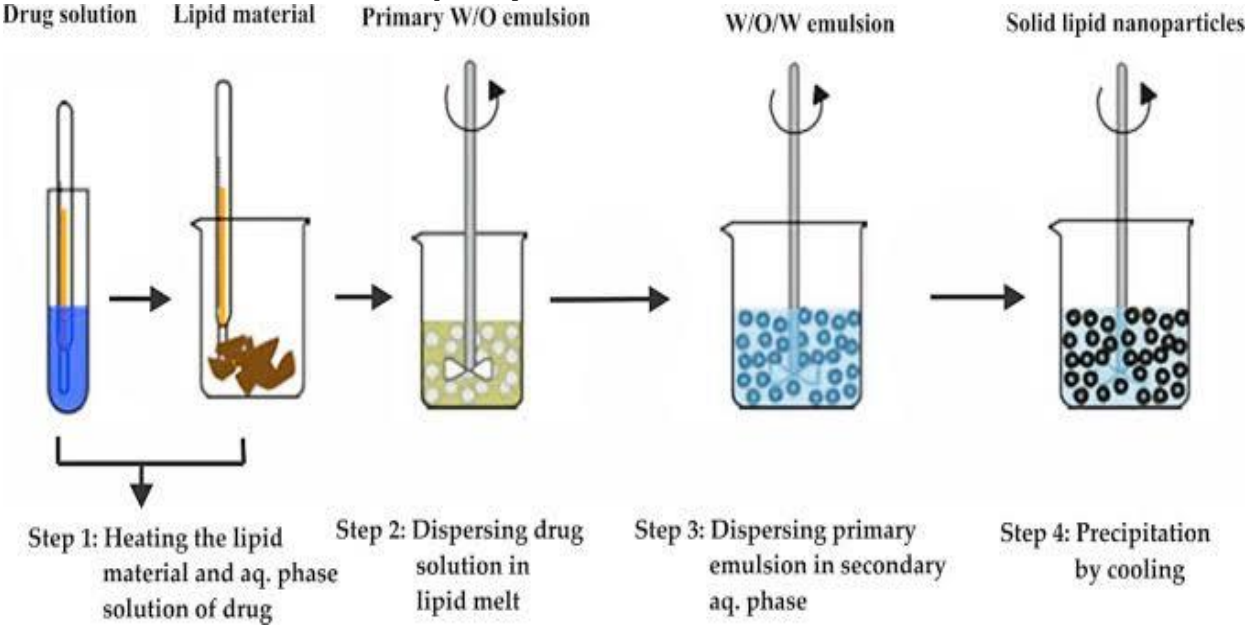

Fig. 11: Supercritical fluid method

2.3 Drying Techniques of Solid Lipid Nanoparticles:

There are different techniques for drying of SLNs. They are,

2.3.1 Spray Drying

Subsequently spray drying of prepared SLNs converted into a redispersable powder is obtained. By

the addition of the carbohydrates and lower amount of lipid during spray drying, the colloidal particles are shielded and by the addition of ethanol-water mixtures lipid is reduced. It was suggested that for the optimum result, SLNs concentrations of 1% in solution of 30% trehalose in water or 20% trehalose in ethanol-water mixtures (10 / 90 v/v) could be used.

2.3.2 Lyophilization

Lyophilization increases both the physical and chemical stability of SLNs over long storage. It prevents degradation responses and preserves the initial particle size. The SLNs formulation should be unaffected by temperature variations during shipping. Lyophilization involves surfactant protective effect. The lipid content of SLNs dispersion should not exceed 5% for avoiding the increase in particle size [10].

3. CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

Characterization of SLNs is necessary for its quality control determination. This characterization is a serious challenge due to colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters evaluated for the SLNs are particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification, coexistence of additional colloidal structures, time scale of distribution processes, drug content and surface morphology [11].

3.1 Particle size and Zeta potential:

The physical stability of SLNs depends on the particle size. Photon Correlation Spectroscopy (PCS) and Laser Diffraction (LD) are the most powerful techniques for the determination of the particle size. The fluctuation of intensity of the scattered light is measured by PCS. The particle size determination of PCS detects size range of 3 nm to 3μm and by laser diffraction in size range of 100 nm to 180μm. Smaller particles cause more intense scattering at high angles compared to the larger ones.

Zeta potential measurement can be carried out using zeta potential analyzer or zeta meter. Before measurement, SLNs dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement. Zeta potential measurements allow the predictions about the storage stability of colloidal dispersions [12].

3.2 Electron microscopy:

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) provide way to directly observe nanoparticles. SEM is better for morphological examination. TEM have small size limit of detection.

3.3 Atomic Force Microscopy (AFM):

In this Atomic Force Microscopy (AFM), a probe tip with the atomic scale sharpness is rastered across the sample to produce a topological map based on the forces at play between the tip and the surface. The probe tip can be dragged across the sample. That ultra-high resolution is obtained with this approach, which along with the ability to map a sample according to properties in addition to size [13].

3.4 Acoustic method:

This method measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge [14].

4. APPLICATIONS OF SOLID LIPID NANOPARTICLES

Solid Lipid Nanoparticles enhance the bioavailability of entrapped drugs by modification of the dissolution rate and can be used to improve the tissue distribution and targeting of drugs (Fig. 12) [15].

Fig. 12: Applications of Solid Lipid Nanoparticles

4.1 Solid Lipid Nanoparticles as potential new adjuvant for vaccines:

Adjuvants are used in vaccination to improve the immune response. New developments in the adjuvant area are the emulsion system and SLNs. These are oil-in-water emulsions that degrade rapidly in the body. Being in the solid state, the lipid components of SLNs will be degraded more slowly providing a lasting exposure to the immune system.

4.2 Solid Lipid Nanoparticles in cancer chemotherapy:

Several chemotherapeutic agents have been encapsulated in SLNs and their in-vitro and *in-vivo* efficacy has been evaluated. This leads to increase in efficacy of chemotherapeutic drugs and decrease the side effects.

4.3 Solid Lipid Nanoparticles for delivering peptides and proteins:

Solid Lipid Nanoparticles are the alternative carriers for the therapeutic peptides, proteins and antigens. Proteins and antigens intended for therapeutic purposes might be incorporated or adsorbed on to SLNs and further administered by parenteral routes such as oral, nasal and pulmonary. SLNs confer improved protein stability and prevented avoids proteolytic degradation.

4.4 Solid Lipid Nanoparticles for targeted brain drug delivery:

The extremely small particle size of SLNs, which is less than 50 nm, might be beneficial with respect to drug targeting. Small carrier size generally reduces the uptake by the reticuloendothelial system. SLNs can improve the ability of the drug to penetrate through the blood- brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders.

4.5 Solid Lipid Nanoparticles for parasitic diseases:
Parasitic diseases are one of the major problems around the globe. Anti-parasitic chemotherapy is the choice of treatment for the parasitic diseases. SLNs and NLCs due to their particulate nature and inherent structure exhibit good potential in the treatment of parasitic infections. These matrices in order to extend versatility with respect to encapsulation ability and target ability may be an effective and economical approach for the delivery of anti-parasitic drugs.

4.6 Solid Lipid Nanoparticles as gene carrier:
Several studies have carried out on SLNs bearing genetic materials such as plasmid deoxyribonucleic acid (p-DNA), DNA and other nucleic acids. SLNs based vectors could act as a beneficial system of gene delivery for management of corneal diseases and inflammation [16].

4.7 Solid Lipid Nanoparticles for topical use:
Solid Lipid Nanoparticles can be used topically to deliver various drugs like vitamin A, isotretinoin and flurbiprofen. The flurbiprofen-loaded SLNs gel might be applied directly to the site of action, to induce higher tissues concentrations of the drug in controlled manner.

4.8 Solid Lipid Nanoparticles for cosmetics:
Solid Lipid Nanoparticles are novel nanocarriers that can replace the conventional delivery such as creams, gels and ointments usage in cosmetics. The comparison of lipid nano-based systems and traditional cosmetic products because of occlusiveness. SLNs based products showed great activity of UV- blocking and photo protection [17].

4.9 Solid Lipid Nanoparticles in bio imaging:
The detection and removal of lipopolysaccharide (LPS) from pharmaceutical preparations and food is vital for safe administration and prevent septic shock. An abiotic system prepared using SLNs aim at reversible capture, detection, and removal of LPS in aqueous solutions. Moreover, the regenerated particles also act as colorimetric labels in the blot bioassays for basic and prompt evaluation of the LPS elimination.

5. CONCLUSION

Solid Lipid Nanoparticles have the properties of both the liposomes and polymer-based carriers, where encapsulation of both lipid soluble and water-soluble drugs could be possible. SLNs production is inexpensive, they pose high stability during their shelf life, and wide range of lipids is available for tuning the release kinetics. SLNs have emerged as efficient drug delivery systems and the future of lipid based drug delivery is largely dependent on SLNs due to their various significant properties. Scientists have already filed many patents related to SLNs and we can anticipate more patented SLNs-based delivery systems in the near future.

REFERENCE

[1] Ali S, John S and Raida AK, Solid lipid nanoparticles for ocular drug delivery, *Drug Delivery*, 17, 467-489, 2010.
[2] Hironaka K, Inokuchi Y, Tozuka Y, Shimazawa M and Hara, Design and evaluation of a liposomal delivery system targeting the posterior segment of the eye, *J Contr Rel*, 136, 247-53, 2009.
[3] Vijay M, Kuldeep KB, Asit V, Nishika Y, Sourav T, Kalvatala S and Jessica MR, Solid lipid nanoparticles: Emerging Colloidal Nano Drug Delivery Systems, *Pharmaceutics*, 10, 191, 2018.
[4] Ramteke, Joshi K.H and Dhole S.A, Solid lipid nanoparticles: A Review, *IOSR J. Pharm*, 2, 34-44, 2012.
[5] Ekambaram, Sathali P and Priyanka A, Solid lipid nanoparticles: A review, *Sci. Rev. Chem. Commun*, 2, 80-102, 2012.
[6] Kamble V. A, Jagdale D.M and Kadam, Solid lipid nanoparticles as a drug delivery system, *Int. J. Pharm. Biol. Sci*, 1, 1-9, 2010.
[7] Ebrahimi, Javadzadeh, Hamidi and Jalali, Repaglinide-loaded solid lipid nanoparticles: Effect of using different surfactants/ stabilizers on physicochemical properties of nanoparticles, *DARU J. Pharm. Biol. Sci.* 23-46, 2015.
[8] Akanksha Garud, Deepti Singh and Navneet Garud, Solid lipid nanoparticles (SLN): Method, Characterization and Applications, *International Current Pharmaceutical Journal*, 1(11), 384-393, 2012.

[9] Cavalli R, Gasco M.R, Chetoni P, Burqalasi S and Saettone M.F, Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin, *Int. J Pharm,* 238(1-2), 241-245, 2002.
[10] Chowdary K.P.R and Rao AS, Nanoparticles as drug carriers, *Indian Drugs,* 34(10), 549-556, 1997.
[11] Muller RH, Mehnert W, Lucks JS, Schwarz C, Zur Muhlen A and Weyhers H, Solid lipid nanoparticles (SLN): An alternative colloidal carrier system for controlled drug delivery, *Eur J Pharm Biopharm*, 41, 62-69, 1995.
[12] Zur Muhlen A and Mehnert, Drug release and release mechanisms of prednisolone loaded solid lipid nanoparticles, *Pharmazie,* 53, 552-555, 1998.
[13] Venkateswarlu V and Manjunath, Preparation, characterization and in vitro release kinetics of clozapine solid lipid nanoparticles, *J Control Releas*, 95(3), 627-638, 2004.
[14] Sultana Y, Jain R, Aqil M and Ali A, Review of ocular drug delivery, *Curr Drug Deliv*, 3, 207-217, 2006.
[15] Videira M.A, Botelho M F and Santhos, Lymphatic uptake of pulmonary delivered solid lipid nanoparticles, *J Drug Target*, 10(8), 607-613, 2002.
[16] Monica Vicente-Pascual, Andrea Albano, Marıa A. Solinıs, Loredana Serpe, Alicia Rodriguez-Gascon, Federica Foglietta, Elisabetta Muntoni, Josune Torrecilla, Ana del Pozo-Rodriguez and Luigi Battaglia, Gene delivery in the cornea: in vitro & ex vivo evaluation of solid lipid nanoparticle-based vectors, *Nanomedicine*, 13(15), 1847-1854, 2018.
[17] Jobin Jose and Gladyston Netto, Role of solid lipid nanoparticles as photoprotective agents in cosmetics, *J Cosmet Dermatol,* 18(1), 315-321, 2019.