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PAST AND PRESENT SCENARIO OF SOLID LIPID NANOPARTICLES:A LITERATURE REVIEW

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ABSTRACT:

Research and development of engineered multifunctional and versatile nanoparticles as pharmaceutical drug carriers have stimulated exponential growth in applications to medicine in the last decade. The potential success of the nanoparticles in the clinic relies on consideration of certain important parameters such as nanoparticle manufacturing strategies, their physical properties, partitioning behaviour of drug in solid as well as liquid lipids, drug loading efficiencies, drug release potential and, most importantly, minimum toxicity of the carrier system itself .Solid lipid nanoparticles bear the advantage of being the least toxic for in vivo applications and significant progress have been made in the area of theranostics using lipid-based nanoassemblies. SLN being a colloidal carrier system combines the advantages of emulsions, liposomes, and polymeric nanoparticles. SLNs are lipid based nanoparticles which exhibit higher drug loading capability and are both biocompatible and biodegradable thus very well suited to medicinal application in targeted drug delivery and in vivo imaging. This review paper provides an overview of SLN technology and describes different models of SLN, various formulation techniques, characterization and potential biomedical applications.

Keywords-Theranostics, solid lipid nanoparticles, nanoassemblies, characterization, polymeric Nanoparticles, liposomes

I. INTRODUCTION

Nanoparticles are colloidal particles ranging from 10 to 1000 nm (1.0 μm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and/or to which the active principle is adsorbed or attached [6].Solid lipid nanoparticles (SLN) are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiologic lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals [45].

Solid lipid nanoparticles introduced in 1991 represent an alternative carrier system to traditional colloidal carriers such as- emulsions, liposomes and polymeric nanoparticles [45]. Shortcomings often encountered with the colloidal schemes such as liposomes, nanocapsules, nanosponges and polymeric nanoparticles are the rapid degradation by the pH of the stomach or by the intestinal enzymes and the bile salts if taken orally, restricted physical and chemical steadiness throughout storage [8-10], need of large-scale output methods, a fast release of the drug from its carrier system, stability difficulties, the residues of the organic solvents used in the output

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method, the toxicity from the polymer [11,12] and many more. All of these points make these colloidal carriers not optimal as a pharmaceutical carrier system.

Among the nanoparticles being explored at present, lipid nanoparticles preside as a result of their high degree of biocompatibility and versatility [4]. Lipid drug delivery systems offer advantages as to controlled release, stability, targetability, drug load, biodegradability, and ability of certain carriers to hold both lipophilic and hydrophilic drugs [4, 5]. Certain unique properties of lipid nanoparticles such as high surface to mass ratio, ability to absorb and carry other compounds such as drugs, probes and proteins forms the basis for their application to medical purposes. In general, lipid based nanoparticles are divided into 2 types: Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs). The matrix of SLN is made of pure solid lipid which is solid at room temperature and at body temperature.

II. PROPERTIES OF SOLID LIPID NANOPARTICLES (SLNs)

SLN are composed of a core of solid lipid with bioactive material constituting a part of the lipid matrix (Fig. 1). Such particle is stabilized by the surfactant layer (or a mixture of surfactants).The term 'lipids' as used here includes triglycerides (e.g. tristearate), partial glycerides, fatty acids (e.g. stearic acid), steroids (e.g. cholesterol) and waxes (e.g. Cetyl palmitate). As for emulsifiers, all classes can be used to stabilize lipid dispersion. It has also been proved that the combination of various emulsifiers can bemore effective in preventing particle agglomeration. An obvious advantage of SLN is the fact that the lipid matrix is obtained from physiological lipids, which reduces the risk of acute and chronic poisoning[48].

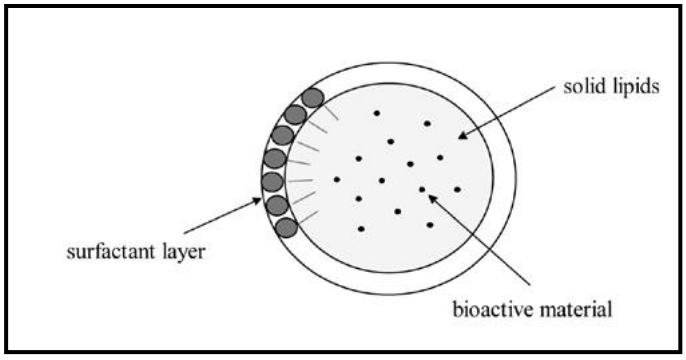

Fig. 1: Structure of SLN stabilized by surfactants

As previously mentioned SLN combine the advantages and are free of faults typical for other colloidal carriers such as liposomes, polymeric nanoparticles and emulsions. The key advantages of SLN are:

- Controlled release and orientation of active substance
- The capability to include lipo- and hydrophilic substances
- No bio toxicity
- No necessity to use organic solvents
- No problems related to large-scale production and sterilizing
- High loading of drug

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III. TYPES OF SOLID LIPID NANOPARTICLES (SLNs)

Different models have been described in the literature for how active molecules can be incorporated into SLN. The type of SLN depends on the chemical nature of the active ingredient and lipid, and the solubility of actives in the melted lipid, nature and concentration of surfactants, types of production and the production temperature [46]. Factors affecting loading capacity of a drug in lipid are [46]:

- Solubility of drug in lipid melt,
- Miscibility of drug melt and lipid melt,
- Chemical and physical structure of solid matrix lipid,
- Polymorphic state of lipid material

Three different types can be described as:

1. SLN Type I or Homogeneous matrix model or Solid solution model
2. SLN Type II or drug- enriched shell model
3. SLN Type III or drug enriched core model

SLN Type I:

The SLN Type I corresponds to a homogeneous matrix model where the lipid and active ingredient are solidified (or crystallized) simultaneously and uniformly.In this model, the drug is molecularly dispersed in the lipid matrix when the particles are produced by the cold homogenization technique and using no surfactant or no drug solubilizing surfactant.

SLN Type II:

The SLN Type II or drug- enriched shell model is achieved when SLN are produced via the hot HPH technique and the active ingredient concentration in the melted lipid is low. The enriched shell model is characterized by drug selectively locating at the interface, either by fast solidification of the matrix lipid or by successful competition of the drug for the interface. Drug dispersed by such a model might exhibit a successful burst effect during drug. According to the drug-enriched shell model of drug incorporation, a solid lipid core forms when the recrystallization temperature of the lipid is reached [47].A typical example of an active-enriched shell model is the incorporation of coenzyme Q10.

SLN Type III:

The SLN Type III or drug-enriched core model can take place when the active ingredient concentration in the lipid melt is high and at or relatively close to its saturation solubility [46]. This model is characterized by drug selectivity located at the core of the solid lipid nanoparticles, perhaps due to more rapid solidification of the drug relative to the matrix material. According to the drug-enriched core model of drug incorporation, cooling the nanoemulsion leads to a super saturation of the drugwhich is dissolved in the lipid melt at or close to its saturation solubility and the drug precipitates prior to lipid recrystallization [47].

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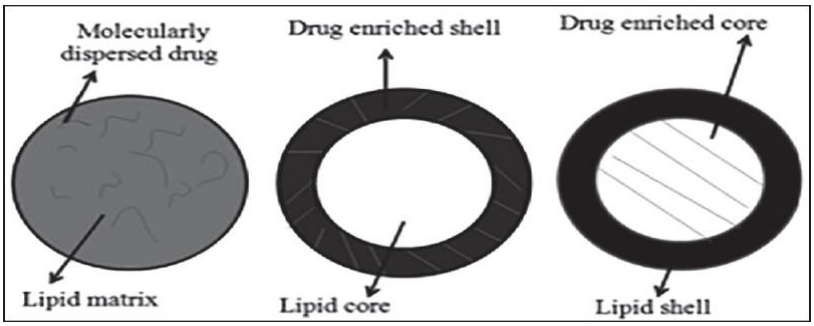

Fig. 2: Drug incorporation model of SLN

IV. PRODUCTION TECHNIQUES OF SLN

There are various formulation approaches that exist for the production of nanolipid carriers. These approaches have been adopted from polymeric nanoparticle production procedure. The various methods applied in the preparation of SLN are high pressure homogenization [21, 22], microemulsion [23, 24], phase inversion [25, 26], emulsification sonification [27], solvent emulsification-evaporation [28], solvent diffusion, solvent injection/ solvent displacement method [29], membrane contractor etc. [30]. SLN may be produced by various traditional techniques, the preferred production method being high pressure homogenization through which large scale production is possible.

4.1 HPH (High Pressure Homogenization)

HPH has been used as a reliable and powerful technique for the large-scale production of SLNs. The lipid is pushed with high pressure (100 – 2000 bars) through a very high shear stress, resulting in disruption of particles down to the submicrometer or nanometer range. Normally the lipid contents are in the range of 5 – 10%. In contrast to other preparation technique, high pressure homogenization does not show scaling up problem. Homogenization may be performed either at elevated temperature (hot homogenization) or below room temperature (cold homogenisation) [32].

4.2 Hot Homogenization Technique

In this technique the drug along with melted lipid is dispersed under constant stirring by a high shear device in the aqueous surfactant solution of same temperature. The pre-emulsion obtained is homogenised by using a piston gap homogeniser and the obtained nanoemulsion is cooled down to room temperature where the lipid recrystallises and leads to formation of nanoparticles [33].

4.3 Cold Homogenization Technique

Cold homogenisation has been developed to overcome the problems of the hot homogenisation technique such as, temperature mediated accelerated degradation of the drug payload, partitioning and hence loss of drug into the aqueous phase during homogenisation. The first step of both the cold and hot homogenisation methods is the same. In the subsequent step, the melt containing drug is cooled rapidly using ice or liquid nitrogen for distribution of drug in the lipid matrix. Cold homogenisation minimises the thermal exposure of the sample [34]. Fig. 3 shows the formation of solid lipid nanoparticles using homogenization technique.

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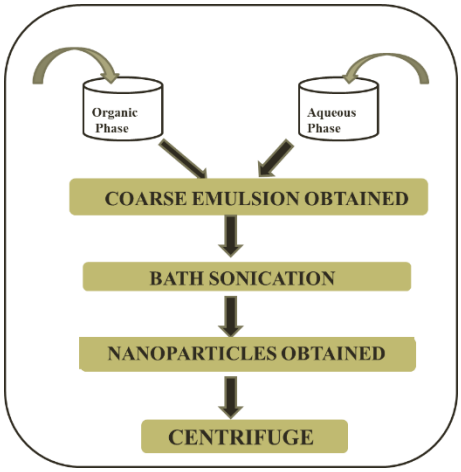

Fig.3: Formation of solid lipid nanoparticles

4.4 Microemulsion Technique

In this technique, the lipids are melted and drug is incorporated in molten lipid. A mixture of water, co-surfactant(s) and the surfactant is heated to the same temperature as the lipids and added under mild stirring to the lipid melt. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratios for microemulsion formation. This microemulsion is then dispersed in a cold aqueous medium under mild mechanical mixing of hot microemulsion with water in a ratio in the range 1:25 – 1:50. This dispersion in cold aqueous medium leads to rapid recrystallisation of the oil droplets [35]. Surfactants and co-surfactants include lecithin; biliar salts along with alcohols such as butanol. The microemulsion is prepared in a large, temperature-controlled tank and then pumped from this tank into a cold water tank for the precipitation step [36].

V. CHARACTERIZATION OF SLNs

Intensive characterisation of the structure and mixing behaviour of NLCs is essential for studying their behavior.

5.1 Particle size and zeta potential

Photon Correlation Spectroscopy (PCS) is an established technique used for measurement of size and distribution Polydispersity Index (PI) of SLN [13].

5.2 Entrapment efficiency (%) and Drug Loading

Drug entrapment efficiency (EE) and drug loading (L) of nanoparticles can be calculated after separation ofthe free drug from aqueous NLC dispersion, using centrifugation or ultrafiltration (Hu et al., 2006).

5.3 Polydispersity Index (PDI)

Due to poly disperse nature of Nanostructured lipid carriers, measurement of poly dispersity index (PI) is important to know the size distribution of the nanoparticles. The lower the PI value, the more mono dispersed the nanoparticle dispersion is.

5.4 Shape and Morphology

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are very useful techniques to determine the shape and morphology of SLNs. These techniques can also determine the particle size and size distribution. SEM utilizes electron transmission from the sample surface, whereas TEM utilizes electron

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transmission through the sample.Although normal SEM is not very sensitive to the nanometer size range, field emission SEM (FESEM) can detect nanometer size range [41]. Spherical shape of the Solid lipid nanoparticles is reported.

VI. APPLICATIONS OF SLNs

Solid lipid carriers as nano carriers can find applications in various fields. The various applications can be broadly categorized into therapeutic applications which mainly focuses on the various routes of administration in drug delivery [20].

6.1 Therapeutic Applications

6.1.1 SLNs for topical drug delivery

The biggest achievement by SLN technology is in the field of topical application. The continuous progress in the field of nanotechnology has allowed the scientists to develop the drug carriers to improve the penetration of skin and also in targeting to specific layers. SLN ensure increased penetration of drug into the epidermis by close contact with the stratum corneum. SLNs have the potential to induce epidermal targeting which is derived by the studies on topical glucocorticoids. The highest permeation rate, sustained effects, and the anti-inflammatory effects were observed with solid lipid nanoparticles. SLNs have been used for various drug such as anticancer, vitamin-A, isotretinoin, flurbiprofen, ranitidine[47].

3.1.2 SLNs for Brain Targeting

In this field of application, one of the first inventions relates to the treatment of Alzheimer's disease and other age-related disorders using a curcuminoid-loaded composition [37]. A recent SLN formulation consisting of glyceryl disterate and glyceryl behenate as solid lipid and glyceryl triacetate as liquid lipid at room temperature has been recently patented for the delivery of antioxidants (coenzyme Q10), for thetreatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [37]. The SLN are gaining interest as carriers across the Blood-Brain Barrier (BBB).

6.1.3 SLNs for Oral Delivery

Oral administration of SLNs is possible as aqueous dispersion or in traditional dosage form i.e. tablets, pellets, capsules or powders in sachets. SLNs have been proved as one of the beneficial systems for peroral administration of poorly water soluble drugs having low bioavailability. Another important feature is the high dispersity of SLNs due to which they exhibit a high specific surface area for enzymatic attack by intestinal lipases. Other advantages include increased drug loading; improved drug inclusion; patient compliance; high particle concentration and cream like consistency of the carrier [20].The mechanisms involved in the absorption of the SLN from the intestine include direct uptake through the GI tract, increase in permeability by surfactants and decreased degradation and clearance. Besides this, the SLNs can also adhere on to the gut wall prolonging the residence time, and consequently the absorption [20]. Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance[47].

6.1.4 NLCs for Ocular Drug Delivery

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Recent reports indicated that SLN could increase the ocular bioavailability of lipophilic drug, ibuprofen. Our previous research showed that SLN could improve the penetration of bioactive compounds into ocular tissues with a good ocular tolerance.

6.1.5 Diagnostics and Imaging

An interesting invention for applications of SLN in imaging, provides the formulation of novel lipid nanoparticles with metal or nonmetal core for multimodality imaging. An application regarding the use of synthetic nanoparticles for the delivery of imaging agents used in MRI, computerized tomography scanning, gamma scintigraphy or optical imaging techniques for diagnostic applications [44].

VII. LIMITATIONS OF SLNs

Despite the great potential of SLNs in targeted delivery, they face certain limitations such as cytotoxic effects related to the nature of matrix and concentration, irritative and sensitizing action of some surfactants and lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair [20]. Other drawbacks of SLNs include low active substance load capacity of the carrier, problematic stability in storage combined with the possibility of occurrence of processes such as gelation, particle size increase or discharging active substance[47].

VIII. CONCLUSION

The SLN are exciting carrier systems for encapsulating bioactive substances with considerable potential for application. The current review focuses on various applications of solid lipid nanoparticles in different bio medical and diagnostic areas. Solid lipid nanoparticles (SLNs) provide a potential perspective for improving the bioavailability of highly lipophilic drugs with poor aqueous solubility so that they can be exploited for theranostics applications. The obvious advantages of SLN are firstly: composition (physiological compounds), rapid and effective obtaining, including large-scale production capability, no necessity to use solvents and the ability to obtain highly concentrated lipid suspensions.The use of SLN for simultaneous *in vivo* imaging and drug delivery is an interesting approach for safe theranostics applications considering their biocompatibility and biodegradability**.**

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