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SOLID LIPID NANOPARTICLES- A NOVEL DRUG TARGETING CARRIERS

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ABSTRACT

Solid lipid nanoparticles represent a promising and novel approach in the field of nanotechnology. Among various colloidal drug carriers, solid lipid nanoparticles have been emerged as succeeding generation drug delivery carrier for incorporating lipophilic drugs. In present scenario, more consideration has been focused on solid lipid nanoparticles as they have umpteen advantages over traditional colloidal carriers. SLNs can be prepared by using various techniques, and these usually consist of Active-constituent along with lipids, surfactants, and /or co-surfactants. The prime aim of reviewing this article is to study the solid lipid nanoparticles' advantages, disadvantages, manufacturing, characterization and applications. If properly investigated, it may open new perspective in a therapy of complex diseases.

KEYWORDS: Solid lipid nanoparticles (SLNs), Manufacturing, Percentage entrapment efficacy, Characterization, Applications.

INTRODUCTION

During the period of last thirty years, the nanotechnology has been introduced as the novel multidisciplinary field of the science which initiated the impetus of research on the development of nanostructures. The significant area of research is the development of nanomaterials with potential applications in biomedical and pharmaceutical fields, specifically in the drug delivery.[1] Nanotechnology is defined as the science of matter and material which treats the particle size in nanometer.[2] There are several problems associated with typical drug delivery systems namely poor absorption, poor drug stability, rapid metabolism and elimination; to overcome these problems nano-sized technology for drug delivery had been developed.[3] In the early days of nineteenth century, Professor R. H. Müller from Germany and Professor M. Gascon from Italy introduced lipid nanoparticles as drug delivery systems.[4,5] In 1991, solid lipid nanoparticles (SLNs) were acquainted as a substitute carrier system to typical colloidal carriers.[6,7] The prepared SLNs are the droplets of lipids which are made up of oil and are solid at body temperature.[8] SLN amalgamate the merits of polymeric nanoparticles, emulsion and liposome as for example controlled drug release, cytotoxicity, avoiding drug leakage, low toxicity and higher bioavailability.[9] Solid lipid nanoparticles (SLN) not only combine the merits of colloidal drug carrier systems, but also avoid drawbacks associated with these systems.[10] SLN consist of pure solid lipids. The presence of appropriate lipid in SLN improved properties for drug loading, restrain of the drug release profile and enhance stability of drug during storage.[11] SLNs acquire a lipid matrix that can be stabilized by surfactants and it was solubilized lipophilic molecule.[12]

Advantages

1. Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production method.[6,13,14]
2. Improved bio-availability of poor water-soluble molecule.[2,6,13]
3. Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application.[13]
4. The possibility of controlled the drug release and the drug targeting.[13,15]
5. Protection of chemically labile agents from the degradation in the gut, and sensitive molecules from the outer environment.[2,6,13]
6. Enhance the bio-availability of entrapped the bio-active.[6,13]
7. The high concentration of a functional compound is achieved.[6,13]
8. The lyophilization is possible.[13]
9. Provide high stability to incorporate drugs.[2,16]
10. Ease in sterilization and scale-up.[2,16,14]
11. Broad spectrum of route of administration.[17]

Disadvantages

1. Poor drug loading capacity.[2,13]
2. Drug expulsion after polymeric transition during storage.[13]
3. Eccentric gelation propensity.[6,13]
4. Unforeseen motion of polymeric transition.[6,13,17]
5. Sophisticated equipment.[17]

Methods of solid lipid nanoparticles preparation
The basic production methods for SLNs are as follows.[18-29]

High pressure homogenization
There are two methods predominantly used to prepare SLNs by High pressure homogenization are as follows and shown in Figure 2.[18-22]

Advantages
Low capital cost
Established at lab scale

Disadvantages
Energy intensive process
Bimolecular damage
Polydisperse distribution

Ultrasonication/ high-speed homogenization
Advantages
Minimized shear stress.[23]

Disadvantages
Potential metal contamination.[23]
The growth of particle during storage leads to physical instability.[23]

Solvent emulsification- evaporation technique
The detailed procedure of solvent emulsification-evaporation technique is shown in figure 4.[22-24]

Advantages
Scalable
Mature technology
Continuous process

Disadvantages
Bi molecular damage
Extremely energy-consuming process.

Solvent emulsification- diffusion technique
The schematic procedure of this technique for SLNs preparation is illustrated in figure 4.[25]

Micro emulsion based method
The micro emulsion based method is illustrated in figure -5.[26,27]

Double emulsion technique
The steps involved in the double emulsion technique is shown in the figure 6.[27]

Spray drying method
It is another approach to the Lyophilization process that endorsed the utilization of lipid which has melting point more than 70^{o}C.[26-27]

Precipitation method
The method of precipitation of SLNs preparation is discussed in figure 7.[28]

Table 1.1: List of drugs and various aspects of solid lipid nanoparticles which have been researched.

S. No.	DRUG	Purpose/ Advantages	Methods used for making SLN	Lipid and emulsifiers used
1	Voriconazole[29]	Controlled the release and increased the precorneal residence time	Ultrasonication and Micro-emulsion technique	Stearic acid, tween-80
2	Ramipril[30]	Enhanced the oral bioavailability	Hot homogenization followed by Ultrasonication method	Glycerol Monostearate, Tween-80, Poloxamer-188, span-20
3	Etoricoxib[48]	Reduced the risk of systemic toxicity	Melt Emulsification and solidification at low temperature method	Stearic acid and tween-80
4	Raloxifene Hydrochloride[31]	Enhanced the bioavailability	SolventEmulsification/evaporation method	Compritol-888ATO, Pluronic F68
5	Miconazole[32]	Enhanced poor water solubility to enhance the anti-fungal activity	Hot Homogenization /Ultrasonication method	Precirol ATO5 and lecinol, Gelucire, Poloxamer and Cremophor RH40
6	Carbamazepine[33]	Improved antiepileptic property of lipophilic drugs	Solvent injection method	Tristearin, Phospholipon-R80H, Tween-80
7	ING4 gene[34]	Gene delivery to MCF-7 cells. (carrier systems for plasmid DNA delivery)	Hot Micro-emulsion method	Compritol HD5 -ATO (CHO5), Tween-80
8	Isoniazid[35]	Enhanced entrapment efficiency, prolonged drug release and better therapeutic effect	Ethanol injection method	Phospholipon R-80H, Tristearin, Tween-80.
9	Simvastatin[36]	Increased the oral Bioavailability	Hot melt emulsification method	Glyceryl behenate, Glyceryl –palmitostearate, Tween-80

10.	Zidovudine[37]	Improved the entrapment efficiency of the drug	W/O/W double-emulsion solvent-evaporation method	Stearic acid, tween-80

Table 1.2: List of drugs and various aspects of solid lipid nanoparticles which have been researched.

S. No.	DRUG	Purpose/ Advantages	Methods used for making SLN	Lipid and emulsifiers used
1.	Ezetimibe[38]	Enhanced dissolution and bioavailability	High pressure homogenization	Compritol88 ATO, Tween-80
2.	Darunavir[39]	Enhanced oral bioavailability	Hot Homogenization technique	Glyceryl caprylate, soya lecithin, Span-80, Poloxamer 188
3.	Loperamide[40]	Increased oral absorption	Modified solvent evaporation technique	Glyceryl trimyristate (dynasan114), sodium cholate
4.	Famotidine[41]	Boosting oral bioavailability	Solvent Emulsification Evaporation(SEE) technique	Stearic acid, Tween-80
5.	Levosulpiride[42]	Reduced the dose, side-effects and increased the bio-available fraction of drug	Solvent evaporation method followed by homogenization	Stearic acid, span-60, tween-80
6.	Ofloxacin[43]	Enhanced aqueous solubility and bioavailability	Hot Homogenization and Ultrasonication method	Palmitic acid, PAV.

Table 2.1: List of pharmaceutical, cosmeceutical and other applications of solid lipid nanoparticles through various routes.

Route	S. No.	Drug Incorporated	Purpose	Use
Oral route	1	Curcumin[58]	Enhanced instability and poor solubility of curcumin/(enhanced anticancer efficiency of curcumin in breast cancer)	Breast cancer
	2	Paclitaxel[59]	Enhanced instability and solubility of paclitaxel	OVCAR-3 human ovarian cancer cell line and MCF-7 breast cancer cell line
Topical route	1	Zaltoprofen (ZLT) [60]	For prolonged effect (Sustained and Controlled release) and its ability to decrease side effects caused due to oral administration	NSAID drug
	2	Mometasone furoate (MF)[61]	Increasing skin deposition as well as provide sustained release.	Chronic inflammation and Psoriasis
	3	Isotretinoin[62]	Improve the skin uptake and reduce systemic absorption of isotretinion	Severe acne and other dermatological diseases
Intravenous route	1	Quercetin (natural flavonoids)[63]	Improved its permeation across the BBB into the CNS and eventually, to improve its therapeutic efficacy in Alzheimer's disease.	Alzheimer's disease. *Targeted organ- Brain
	2	Aclacinomycin A[64]	Improved pharmacokinetic behavior of ACM was greatly by lyophilized injection of SLN with sustained drug release and high bioavailability.	Liver, stomach, lung and ovarian carcinoma; Malignant lymphoma and acute leukemia (tumor)

Table 2.2: List of pharmaceutical, cosmeceutical and other applications of solid lipid nanoparticles through various routes.

Cosmetics (Dermal application)	1	Curcuminoids[65] (Rhizomes of Turmeric)	Promote stability of the active compounds by protecting them from photo degradation, hence	Anti-aging agent (Facial cream)

			prolonging their release from the system	
	2	CoQ10 (Coenzyme) [66]	Increased penetration of CoQ10 into the skin	Anti-wrinkle creams (Ex.-Xcelent Uplift Q10)
	3	Heptapeptide (acetyl-DEETGEF- OH)[67]	Improving peptide delivery into skin	Cosmetic Anti-aging application
Ocular delivery	1	Indomethacin[68]	Improved ocular bioavailability	Ocular inflammation (non-steroidal anti-inflammatory drug)
	2	Natamycin[69]	Sustained drug release and increase corneal penetration	Corneal keratitis
Pulmonary route	1	Budesonide (BUD)[70]	Improved its solubility and absorption	Asthma
	2	Insulin (Ins) [71] *(Exubera (2006) & Afrezza (2014)- first two rapid acting inhaled insulin approved in EU but unfortunately taken out of production due to poor sales volume)	Prolonged drug release, improved stability and effective inhalation	Diabetes (hyperglycemia)
Subcutaneous injection	1	Mitoxantrone[72]	Minimize the toxicity and enhance the bioavailability	Breast cancer and lymph node metastases
Lymphatic transport	1	Atorvastatin[73]	By pass hepatic first pass metabolism and enhanced bioavailability	Anti-hyperlipidemic drug

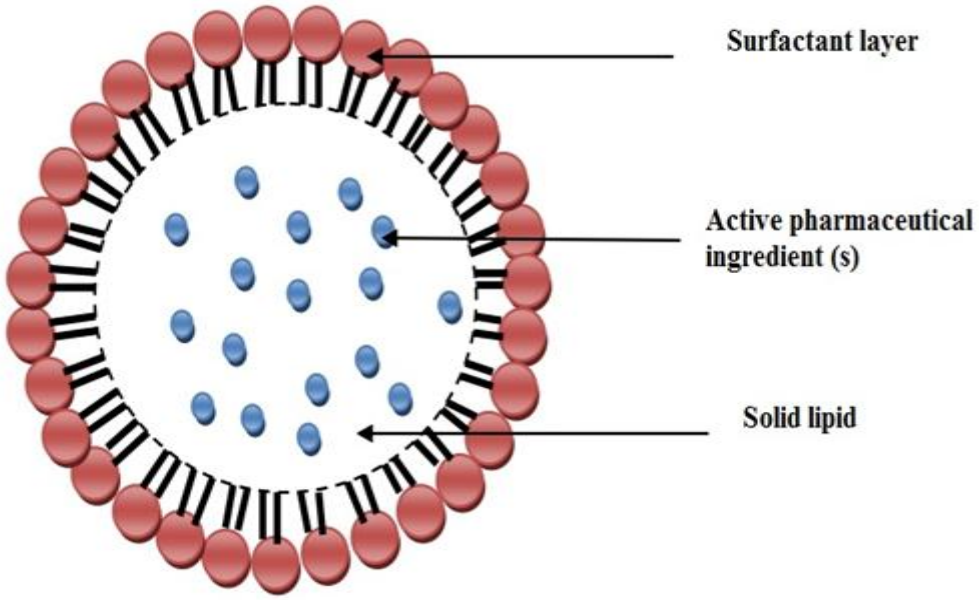

Figure 1: Structure of solid lipid nanoparticles.

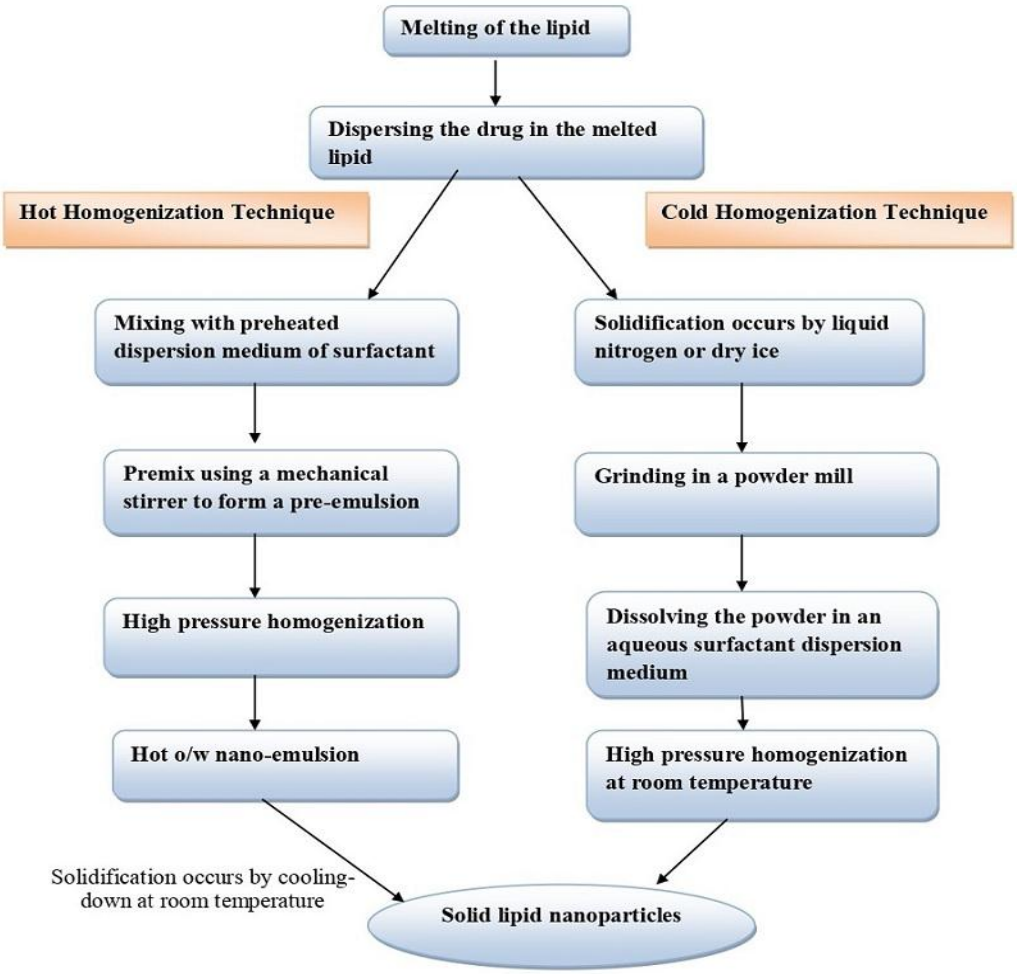

Figure 2: High pressure homogenization techniques (hot homogenization and cold homogenization)

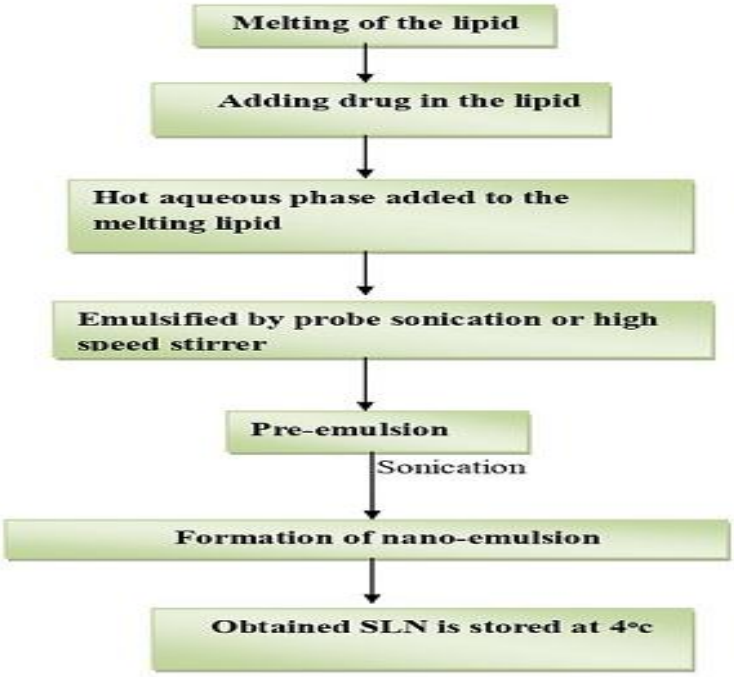

Figure 3: Ultrasonication method.

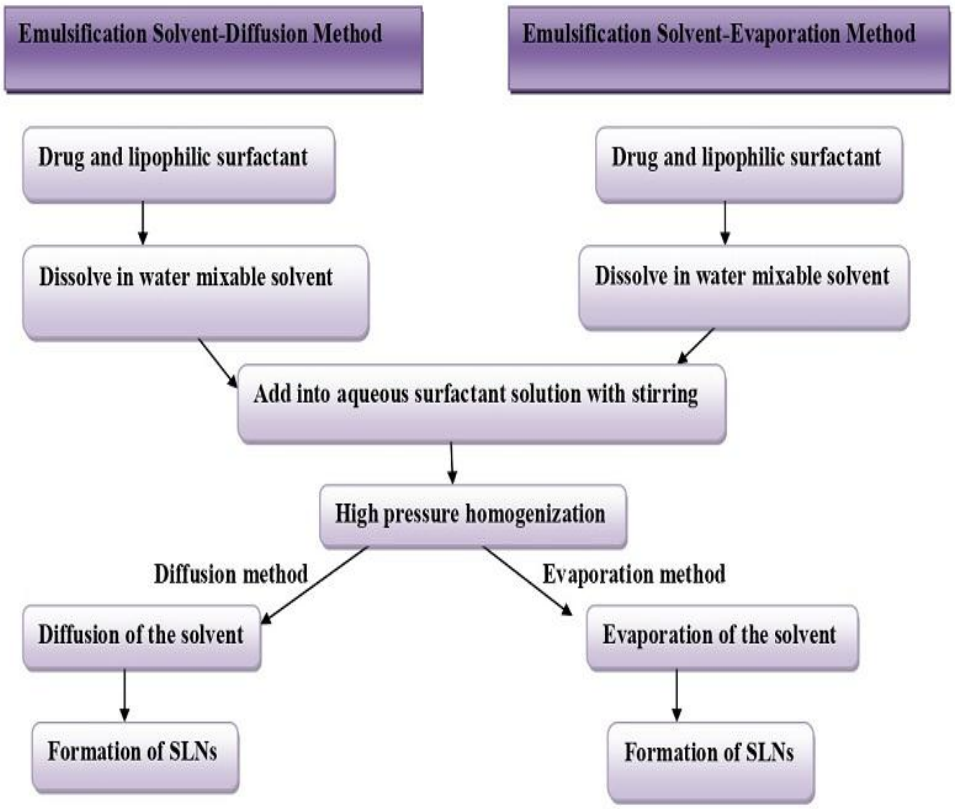

Figure 4: Preparation procedure of SLNs: emulsification solvent-diffusion method and emulsification solvent-evaporation method.

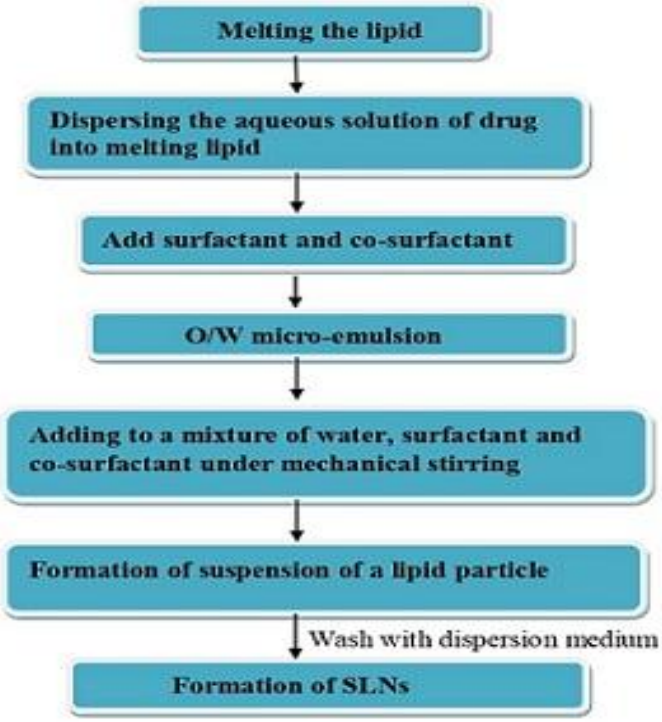

Figure 5: Preparation procedure of SLNs by micro emulsion based method.

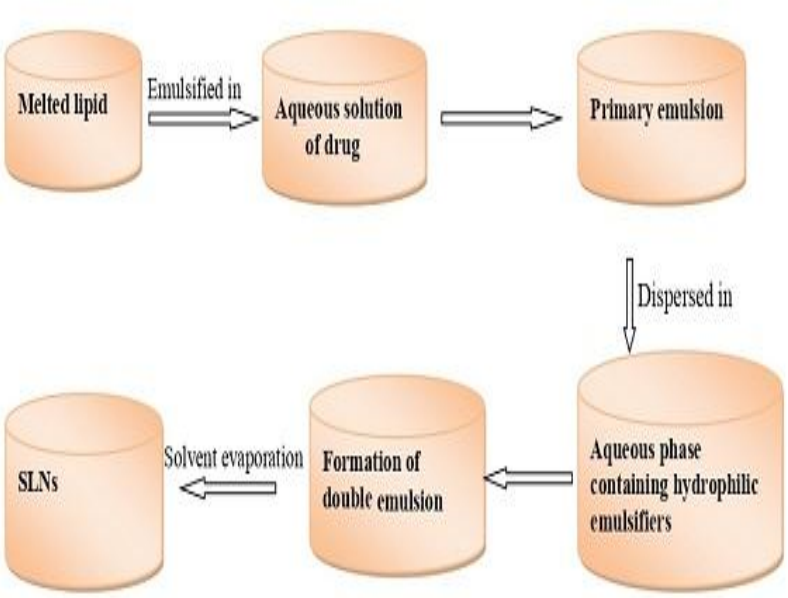

Figure 6: Double emulsion method of SLNs preparation.

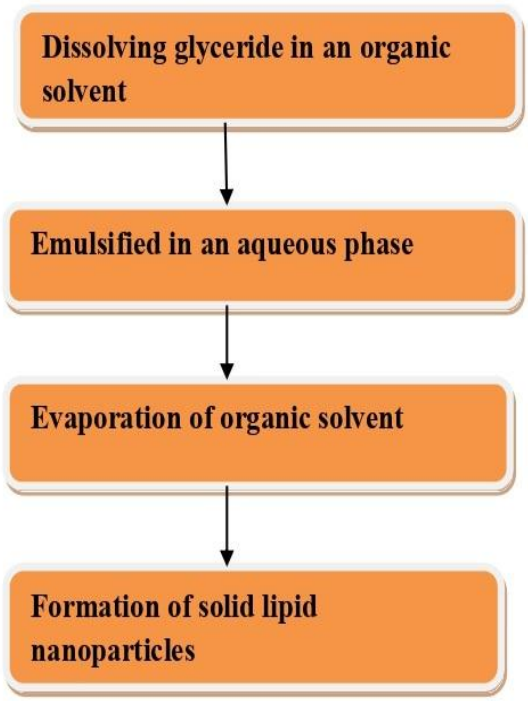

Figure 1: Schematic procedure of precipitation method of SLNs.

Characterization Parameters

Particle size and zeta potential: - The most impressive methods are for calculating the particle size are PCS (Photon Correlation Spectroscopy) and LD (Laser Diffraction). The particle movement is caused by the inconstancy of the intensity from the scattered light measured with the help of PCS (also called dynamic light scattering). The LD method is evolved from the dependence of the diffraction angle on the particle size. As compared to larger particles, smaller particles can originate more intense scattering.[29,30]

Zeta potential measurement of SLNs gives an idea about the storage stability of a colloidal dispersion. The estimation of zeta potential can be carried out using a zeta potential analyzer or zeta sizer (Malvern zeta sizer).[31] Before an assessment, the dispersion of solid

lipid nanoparticles is diluted fifty times with the original dispersion medium for zeta potential measurement.[29-31]

Surface morphology: - Surface morphology of solid lipid nanoparticles has been determined by using SEM (Scanning Electron Microscopy)[32] One drop of the sample was fixed on a slide and left to remove moisture at room temperature. Then the slide hooked up to the specimen holder with the help of double-coated adhesive tape and gold-coated under vacuum using a sputter coater for ten minutes, and investigated at 20KV.[33]

Drug entrapment efficiency: - The entrapment efficiency is determined by Spectrophotometrically[34] Solid lipid nanoparticles dispersion was centrifuged at 15000rpm for 30 minutes in a refrigerated centrifuge to collect the supernatant liquid. Then the collected liquid was filtered to measure the free drug concentration after suitable dilution and absorbance were measured in an Ultra-violet Spectrophotometer at a particular wavelength. Drug entrapment efficiency was estimated by using the following formula.[35]

Percent entrapment efficiency = (Weight of drug incorporated / Weight of drug initially taken) × 100

Total drug content: - The prepared solid lipid nanoparticles are dissolved in a solvent. Hence a drug quantity is determined by using Ultra-violet Spectroscopy at a particular wavelength. Likewise, a drug containing solid lipid nanoparticles, a placebo formulation prepared is used as a blank and then the total drug content was then calculated.[36]

In-vitro drug release: - In vitro release studies of SLNs were performed with the help of a modified Franz diffusion cell. Dialysis membrane used for drug release studies having pore size 2.4nm, molecular weight cutoff 3500 Dalton, was used. Before mounting in a Franz diffusion cell, the membrane was soaked in double-distilled water for twelve hours. SLN dispersion was placed in the donor compartment and the receiver compartment was filled with dialysis medium. At fixed time intervals, 100 micro liters of the sample were withdrawn from the recipient compartment through a side tube. A fresh medium was placed to maintain a constant volume. Then the samples were examined by using the UV Spectroscopic method to determine the release profile of the drug.[37]

Applications

Solid lipid nanoparticles used for intra-vaginal delivery of progesterone in cases of risk of abortion or to increase fertility.[38]

Solid lipid nanoparticles used to target the brain for various diseases. Solid lipid nanoparticles enhance the capability of the drug to penetrate the Blood-Brain Barrier and avoidance of the reticuloendothelial system (RES)[40]

Solid lipid nanoparticles shows an ultra-violet blocking potential, that's why they act as physical sunscreens on their own and can be combined with molecular sunscreens to achieve improved photo protection.[41]

Solid lipid nanoparticles used to enhance the bioavailability, therapeutic effect and controlled the release of antibacterial drugs.[42]

Solid lipid nanoparticles used as a transporter system for tumor-targeting drug delivery.[6]

In ophthalmic dosage forms the major drawback is the fast eviction of drug from the eye leading to low drug concentration at the desired site. That's why solid lipid nanoparticles have been used as a carrier for the controlled release of drug to get higher drug level at the desired site.[2]

Solid lipid nanoparticles used for the treatment of cancer and metastases. Mitoxantrone solid lipid nanoparticles injections minimize the toxicity and better the safety and bioavailability of the drug.[7]

Solid lipid nanoparticles are used to treat malaria infection. Traditional malaria chemotherapy's main drawbacks are the development of multiple drug resistance and the nonspecific targeting to intracellular parasites, resulting in high dose requirements and subsequent intolerable toxicity. Solid lipid nanoparticles diminishing the side effects of drug therapy, such as poor bioavailability, and the selectivity of drugs.[6]

CONCLUSION

In the forthcoming prospect; a solid lipid nanoparticles, emphasizes upcoming and undoubtedly a novel approach in the field of nanotechnology. SLNs combine the merits of colloidal drug carrier systems and also avoid drawbacks associated with these systems. This review article has focused on the study of the solid lipid nanoparticles advantages, disadvantages, a method of manufacturing, characterization and applications. Advantages include improved bioavailability, a site-specific delivery of drugs, a broad spectrum of the route of administration and controlled release of the drug. Due to their various applications, SLNs are a promising

approach to enhance the properties of traditional drug delivery systems.

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