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Review Article

SOLID LIPID NANOPARTICLES: REVIEW ON RECENT DEVELOPMENT

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ABSTRACT

Objective: Solid lipid nanoparticles (SLN) are rapidly developing field in nanotechnology which has several potential advantages in drug delivery, research as well as in clinical practice. They have unique properties that give them edge over other Nano-carrier systems.
Method: Various research papers were reviewed and thoroughly studied from various research sites viz., PubMed, Science direct, MJPMS, etc. An attempt has been made to clarify and support why SLNs are more revolutionary method in comparison to other drug delivery systems especially in case of drugs with low bioavailability even at higher dose.
Result: SLN can incorporate hydrophilic as well as hydrophobic drugs which makes it a choice of Nano-carrier over others. These nanoparticles have site-specific delivery so that it reduces the dose of a drug and causes minimum side effects. They can be incorporated in primary, secondary as well as in tertiary targeting.
Conclusion: This paper reviews the advantages, disadvantages, and effects on SLN stability after PEG coating, cosmetic application of SLN & different methods of preparation which are very useful for large scale production. Additionally, it mainly focuses on the recent work that has been performed by the different researchers on SLN which include method they adopted for preparing SLN, route used for delivery of SLN, indications against which they prepare the SLN.

Key words: Solid lipid nanoparticles (SLN), preparation of SLN, targeting, Nano-carrier system, homogenization, bio-distribution.

INTRODUCTION

Solid Lipid Nanoparticles are the substituted carrier system of traditional colloidal carriers such as liposomes, emulsions, polymeric nanoparticles and polymeric micro particles[1][2][3][4]. These are the novel generation of submicron-sized lipid emulsions where the solid lipids come in place of liquid lipid. Solid lipid nanoparticles range in between 10-1000nm[5][6][7][8]. Due to the size-dependent characteristics of SLN, utilize to improve the absorption and bioavailability of drugs, particularly the Biopharmaceutics Classification System (BCS) class IIdrugs[9]. On the other side the probability of controlled drug release from nanoemulsion is restricted due to small size and liquid state of the carries so the use of solid lipids instead of liquid oils is a very fascinating idea to achieve a controlled drug release and also the motility of drug decreases as compare to liquid oil[10][11]. Nearly at 25-35˚C SLN are turns into solid- state hence the mobility of entrapped drug is reduced so the SLN act as controlled release dosage form as well[10][12]. SLN administered by oral, topical and parenteral routes, as these are not only for pharmaceuticals but for cosmetic products as well[7][9][13].

Main reasons for SLN preparation

- Drugs having poor solubility after oral administration/aqueous drug solution exception intravascular injection
- Inadequate drug concentration due to poor absorption as well as rapid metabolism & excretion of drugs
- Major fluctuation is seen in the plasma level due to unpredictable bioavailability after peroral administration[14].

For the avoidance of these problems development of a drug carrier system is necessary[15][16].

Effect of PEG coating on physical properties of SLN and bioavailability of drugs

PEG coating provides good physical stability and disperse ability of colloids, improving the presence of colloids in blood circulation for systemic use, increasing the stability of colloids in body fluids such as GI fluids, increasing the biocompatibility[17] and decreasing thrombogenicity of drug carriers, providing reservoir function to colloidal particles carrying hydrophobic drugs due to hydrophilic coating around the particles and also modulation of interaction of colloids with mucosa for specific delivery requirements and drug targeting[7][15].

Cosmetic applications of SLN

The protection of labile compounds against chemical degradation has been shown, **e.g. for retinol and tocopherol**[18][19][20]**.** Depending on the produced SLN-type, the controlled release of the active ingredients is possible[21][13]. SLN with a **drug-enriched shell show burst release** characteristics whereas SLN with a **drug-enriched core leads to sustained release**[6].SLN act as **occlusive**, i.e. they can be used in order to increase the water content of the skin[22][19]. SLN shows a **UV-blocking potential**, i.e. they act as physical sunscreens on their own and can be combined with molecular sunscreens in order to achieve improved photo protection[20].

DIFFERENT METHODS FOR THE PREPARATION OF SOLID-LIPID NANO-PARTICALS

SLNs are prepared from lipid, solvent or water and emulsifier by using different methods which are discussed below.

1. High shear homogenization
    a) Hot homogenization
    b) Cold homogenization
2. Solvent emulsification/evaporation
3. Micro emulsion-based SLN preparation
4. The Supercritical fluid used for the SLN preparation
5. Double emulsion method
6. Spray drying method

High shear homogenization

It is a robust technique for the preparation of SLN. By the use of this technique, we can produce different sizes of SLN. This technique was used for the production of solid lipid nanodispersion[8]. Melt dispersion type/form of SLN produced by high-speed homogenization[3]. High-pressure homogenization

process increased the temperature of the sample as well[17][23]. It propels the liquid with a high pressure 100-2000 bar through a narrow gap which is micron in size range[24][5]. The fluid drives faster with a high velocity (more than 100 km/h) from a very short distance results break the particles in the submicron size range[25]. 5-10% lipid content is used but nearly 40% has been investigated as well[13][12].

HPH is a very prominent method for the preparation of SLN

Its prominence is due to the many advantages

- Avoidance of organic solvents
- Short production time and easy scale-up
- Generate particles of very low polydispersity index

The beauty of this method is the submicron particle size produced by turbulence

Hot homogenization

In this technique of SLN preparation firstly drug is introduced in lipid which is in the melted form[11][26]. Later on it formed a drug-lipid complex[27][28]. Then this drug-lipid complex is introduced into the hot aqueous solution of surfactant this results in the formation of pre-emulsion takes place and this pre-emulsion is then homogenized after solidification[15][27][28].

This hot homogenization process is carried out the temperature above the melting point of lipid[11]. The quality of formed pre-emulsion affects the quality of formed SLN to a very huge extent so that it is very important to acquire the droplets in the micrometer/submicron size range[16][29].

As the name suggests it is hot homogenization process temperature is increased and viscosity of the inner phase decreased which leads to decrease particle size. Hot homogenization process decreased the degradation speed of the drug as well as a carrier[30].

Production condition: 500 bar & 2 OR 3 homogenization cycle[5].

There are some limitations of hot homogenization technique:

- Drug degradation occurs due to increased temperature[30]
- Distribution of drug into the aqueous phase takes place during homogenization[24]
- During the crystallization process complexity of the nanoemulsion causes many modifications[11][5]

HOT HOMOGENIZATION METHOD

An active compound containing lipid melt

↓

Dispersed into hot surfactant solution of the same temp.by high speed

↓

Pre-emulsion

↓

Passed through high- pressure homogenization

↓

Hot O/W nanoemulsion

↓

After solidification at room temperature

↓

SLN

Cold homogenization

Melted lipid-containing drug cooled firstly, then this solid lipid crushed to lipid micro-particles of size range approximately 50-100 micrometre[5][2]. Then this formed micro-particles dispersed into a cold surfactant solution that is known as pre-emulsion[24][15]. Formed pre-emulsion homogenized at or below room temperature. Care to take that this homogenized force should be in that range which breaks the nanoparticles into SLN. The homogenization process itself increases the temperature of the sample about 10-20˚C per homogenization cycle[7][31].

Advantage

These processes avoids or minimize the loss of hydrophilic drugs to the water phase.

COLD HOMOGENIZATION METHOD

An active compound containing lipid melt is cooled

↓

After Solidification lipid mass ground

↓

Micro-particles

↓

Dispersed in cold surfactant solution by stirring

↓

Macro-suspension

↓

High - pressure homogenization

↓

Micro-particles

↓

SLN

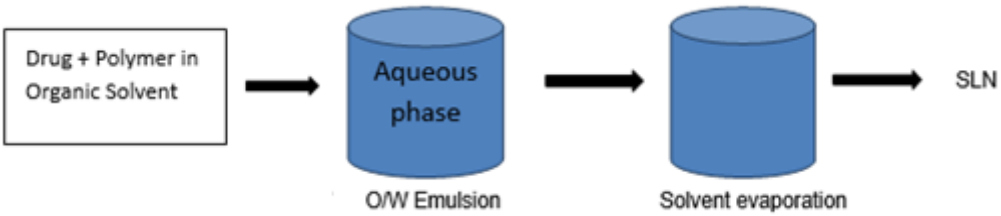
Solvent emulsification/evaporation

In this method lipophilic material dissolved in the water-immiscible organic solvent, that is emulsified in an aqueous phase[5].

Later on the evaporation of the solvent at low pressure, a dispersion of nanoparticles is formed by the precipitation of lipid in the aqueous medium[24][32][33].

In this method of preparation of SLN particles mean diameter 25 nm[3].

Main advantage of this technique: Heat is not required[7].



SLN preparation by using supercritical fluid

It is a relatively latest technique for the production of SLN. By this method, SLN can be prepared by a rapid expansion of Supercritical carbon dioxide solution that is RESS method[2][15]. In this method solvent used is carbon dioxide 99.99% which was the good choice[15][34].

Advantages

- It is the solvent less process[35][33][8]
- Temperature and pressure conditions are mild
- Obtained particles are in dried form in place of suspension

SLN preparation by Double Emulsion Method: Preparation of SLN which is loaded by hydrophilic used for this method. It is the novel method based on solvent emulsification-evaporation[32]. Here the drug is encapsulated with a stabilizer for the prevention of partitioning of the drug to the external water phase during the solvent evaporation in the external water phase of W/O/W double emulsion[22][19][7].

Microemulsion based SLN preparation: Transparent emulsion is made by stirring a mixture of low melting point fatty acid that is stearic acid, an emulsifier, co-emulsifier and water at the temperature of 60-70˚C [3][7][15]. Then this hot microemulsion is dispersed in cold water with continuously stirring with a temperature of 2-3˚C[15][19][36][27]. The ratio of hot microemulsion and cold water should be 1:25 to 1:50[33][37]. This technique is based on the dilution of microemulsion[8]. The dilution process is based on the composition of microemulsion[38][35].

Advantages

- Low mechanical energy required[4].

Disadvantages

- High labour cost
- Concentration of nanoparticles are less
- Highly sensitive for change

SLN preparation by spray drying method

This method is based on the lyophilisation process[29]. In this method, aqueous solid lipid nanoparticles dispersion is transformed into a drug product[39]. Lipid used in this method for the preparation of SLN with a melting point >70˚C[29][40][41][35][42][43]. Better results were obtained with 1% SLN concentration in trehalose, water solution or in the ethanol-water mixture containing 20% trehalose[16][31].

Advantages

- Cheap method as compare to lyophilisation.

Disadvantages

- Partially melting of the particles.
- Aggregation of the particles due to high temperature.

FUSION OF ACTIVE COMPOUNDS INTO SLN

1. Homogeneous matrix model[18]
2. Drug- enriched shell model[6]
3. Drug-enriched core model[5]

ADVANTAGES OF SLN COMPARE TO LIPOSOMES & EMULSIONS

Incorporated active compounds are protected from the degradation of chemical compounds & more flexibility in modulating the release of compounds[20][29]. SLN can also be formed by the combination of emulsion as well as liposomes[24].

Other advantages are

SLN has the ability to improve the absorption and bioavailability of entrapped drug[44][9]. It offers long-term stability profile of incorporated drug[10][1][7].It can be encapsulated very high amount of drug[10][33][45]. It can be easy to scale up and sterilized as well[7][28][1]. Drugs either lipophilic or hydrophilic both are adequately entrapped[46][15][38][5]**.** SLN has the ability to avoid the use of toxic and organic solvents[13]. They are less expensive, non-irritating, non-toxic, biocompatible, highly versatile and could be readily lyophilized and sterilized for commercial purposes[47][36]**.** The production process of SLN in PEG 600 and oil for oral drug delivery can be directly filled into the soft gelatine capsule[27][34].

Disadvantages

Growth of lipid particle, the propensity to gelation, dynamics of polymorphic transitions and their inherent low incorporation rate due to the crystalline structure of the solid lipid[10][12][11].

Table 1: SLN prepared in recent years, the method adopted for preparation, route of administration employed and their purpose.

Sr. no	TITLE	METHOD USED FOR SLN PREPARATION	ROUTE OF ADMINISTR-ATION OF SLN	PURPOSE OF PREPARED SLN	Ref.
1.	Chitosan coated stabilized SLN (Compritol 888 ATO)	Solvent diffusion & Hot homogenization	Oral	Improved mucoadhesive property of SLN	[34]
2.	Curcumin loaded SLN	Microemusification	Oral	Enhance oral bioavailability of Curcumin for neurodegenerative & cancerous disorders in humans	[37]
3.	Galactose engineered SLN	Solvent injection	I.V	Targeted delivery of Doxorubicin	[36]
4.	Encapsulation of Hydroquinone into SLN	Hot melt homogenization	Topically treatment of Hyper-pigmentation	Enhanced stability & dermal delivery of Hydroquinone	[15]
5.	Sustained-release SLN of Carbendazim& Tebuconazole in agricultural application	Emulsification/solvent evaporation		Prevention & control of fungal disease	[44] [20]
6.	Preparation of ultrafine powders from polysaccharide-coated SLN	Combination of hot homogenization & spray drying technology	Ultrafine lipid particle powders	Five polysaccharides(Pectin, gum Arabic, Alginate, Carboxymethyl cellulose90,000 Da & Carrageenan)	[39]
7.	A novel sunscreen system based on Tocopherol acetate incorporated in SLN	High-pressure homogenizer	Gel, Cream	Prevent chemical degradation & increase the UV blocking capacity	[20]
8.	Resveratrol & grape extract	High shear homogenizer	I.V	Treatment of Alzheimer's disease	[28]

	loaded SLN	& Ultra sonication			
9.	Apoliprotein E-derived peptide (SLN-mApoE)	Oil/water warm microemulsion technique	IV &Intraperitoneal administration	Improving brain delivery of therapeutics	[48]
10.	Nose to brain delivery of BACE1 siRNA loaded in SLN	Solvent emulsification/evaporative method based on W/O/W double emulsion technique	Intranasal route	Alzheimer therapy	[31][48]
11.	Doxorubicin loaded SLN	Microemulsion method	Topically	Influence of Iontophoresis on the penetration of Doxorubicin delivery in SLN	[27][41] [36]30]
12.	Nebulizer compatible SLN	Reverse micelle double emulsion method	Pulmonary route	Enhance BA of Insulin	[18]
13.	Retinoic acid &Lauric acid loaded SLN	Hot melt homogenization	Topically	Treatment of Acne Vulgaris	[46]
14.	Mucoadhesive Chitosan-coated SLN loaded with Rifampicin	Hot ultra-sonication method	Pulmonary delivery	Better management of Tuberculosis	[31]
15.	Astraxanthin encapsulated within SLN	High-pressure homogenizer	Oral tablet, I.V injection & Percutaneous absorption	Antioxidant activity in food & cosmetic products	[7]
16.	Camptothecin loaded SLN coated with polaxane 188	High-pressure homogenizer	Paroral route	Scrutinize the specific changes in body	[15]
17.	Ubidecarenone loaded SLN	High pressure homogenizer		Impact of drug incorporation on melt-homogenized Tripalmitin nanoparticles is investigated with Ubiledecarenone as a model drug	[11]
18.	Bromocriptine loaded SLN	Homogenization or Ultra sonication	Intraperitoneally	Development of new drug delivery system for Bromocriptine	[44]
19.	Thymopentin loaded SLN	Co-spray drying	Pulmonary route	Prepare the hybrid micro particles & evaluate their feasibility for Pulmonary route	[50]
20.	Camptothecin loaded SLN	High pressure homogenizer[29][29][29][29]	Sustained release delivery	ANOVA method used to evaluate the preparation of Camptothecin- SLN & perform production optimization	[15]
21.	Mannan-modified SLN	Solvent displacement technique[43][43][43][43]	Intra-tracheal instilled into Rat lungs	Mannan based PE grafted ligand used for the surface modification of DNA-loaded cationic SLN to prepare Man-SLN-DNA	[47]
22.	Rifampicin loaded SLN	Modified lipid film hydration method	Pulmonary route	Enhanced Rifampicin delivery to Alveolar macrophages by SLN	[51][23]
23.	Anti-micro RNA Oligonucleotide loaded SLN	Solvent diffusion method	Intra-cellular	Suppression of MicroRNA-21 functions in human lung cancer cells	[35][13]
24.	Doxorubicin loaded SLN	Solvent diffusion method	I.V	Investigate the targeting potential of Phenylalanine-coupled SLN loaded with ionicallycomplexed Doxorubicin HCL	[27][41][36]
25.	Triptolide loaded SLN	Microemulsion	Topically	Find new ways for administration of Triptoline& remove its disadvantages	[13]
26.	N3-O-Toluyl-Fluorouracil loaded cationic SLN	Film dispersion Ultra sonication method	Orally	Enhance oral absorption of TFu	[4]
27.	Vorinostat-loaded SLN	Hot homogenization	Oral & I.V	Enhance PK & efficacy of Vorinostat against multidrug-resistant Cancer cell	[52]
28.	Diclofenac-Sodium loaded SLN	Emulsion/Solvent evaporation method	Oral	Enhance the incorporation of a water-soluble drug Diclofenac into SLN	[16]
29.	Paclitaxel loaded SLN	Film ultra-sonication method	I.V	To develop tumor targeted drug delivery system based on SLN conjugated with PEG	[53]
30.	Tricaprin loaded SLN	Melt homogenized method	Injection of retrovirus into malignant lung lesions	Enhanced non-vector p53 mediated Gene transfer to lung cancer cells	[36][44]
31.	Tobramycin loaded SLN	O/W microemulsion	Intra-ocular	Determine Tobramycin incorporated in mucoadhesive SLN reaches the inner part of the eye favouring drug activity	[3]
32.	SLN in Lymph & plasma	Warm O/W emulsion	Inta-duodenal	Evaluate uptake & transport of SLN which have been used as alternative drug carriers	[27][26][40]
33.	Metoclopramide loaded SLN	High shear homogenization	Rectal suppository	Formulate & characterize Metoclopramide SLN & incorporated into suppository for the treatment of Nausea & Vomiting	[10]

34.	PEG-stearate coated SLN as Levothyroxine carriers	Microemulsion technique	Oral administration	Evaluation of the release kinetic of prepared colloidal carriers	[38]
35.	Cyclosporine loaded SLN	High pressure homogenization	Orally	Improved oral formulation	[5][7]
36.	Vitamin- A loaded SLN	High pressure homogenization	Topically	Evaluate the use of SLN in dermatology & cosmetics	[18]
37.	Valsartan loaded SLN	Solvent injection method	Orally	Development & characterization of Valsartan loaded SLN to enhance the solubility, bypass the F.P.M & enhance lymphatic absorption leading to Bioavailability	[54][55]
38.	Cisplatin magnetic loaded SLN	Film scattering Ultra sonication technique	External magnetic field (I.V)	Improve the formulation of targeting chemotherapy	[33]

CONCLUSION

The various SLN preparation showed a magnificent contribution in the field of drug and development. We studied research articles &observed the different methodology of SLN preparation. It has been shown that High Shear Homogenization was widely used in the preparation of Solid Lipid Nanoparticles. Hence Controlled Drug Delivery is aptly achieved with SLN. The objectives of SLN preparation is not achieved till date due to failure in commercialization in the market. There are many co-factor which caused the failure of commercialization like manufacturing cost, lengthy procedure, and sophisticated machinery. Hence there is a need for the precise drug development with low cost and easily available.

Apart from these, SLNs are relatively young drug delivery systems, having received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of SLNs in the future.

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