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A REVIEW ARTICLE ON SOLID LIPID NANOPARTICLES

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ABSTRACT

In recent years, there has been a lot of interest in solid lipid nanoparticles (SLNs), also known as lipid carriers, which have been the subject of a lot of research. Lipid nanoparticles have gained popularity due to the fact that they are generally considered to be non-toxic, biocompatible, and simple to manufacture formulations. Because they are biodegradable, nano-structured lipid carriers and SLNs are non-toxic to living organisms. Furthermore, they are extremely stable. Moreover, despite the fact that nano-structured lipid carriers and SLNs are based on lipids and surfactants, the effect of these two matrixes in the construction of excipients is also discussed, as is their pharmacological significance in novel drug delivery approaches, stability, and long-term preservation. The release mechanism of the drug as well as the various methods of preparation of solid lipid nanoparticles, as well as their advantages and disadvantages, are discussed in detail.

KEYWORDS: Solid lipid nanoparticles, Drug delivery, Controlled release, Drug release model, Homogenization.

Nanotechnology

Nanomaterial and nanotechnology are important components of emerging science and technology, and they have the potential to have a significant and long-lasting effect on the global economy. Having an impact on the newly developed tools for manipulating matter at the smallest scale are supporting revolutionary advances that will enable solutions to society's most pressing challenges and spur economic growth across a broad spectrum of economic segments, including agriculture, medicine, and energy.[2] [3]

Solid lipid nanoparticles (SLNs)

Solid lipid Nanoparticles (SLNs) are colloidal particles with sizes ranging between 10 and 1000 nm. They are made of synthetic or natural polymers and are particularly well suited for optimising drug delivery while also reducing toxicity.[7],[9] Over time, they have established themselves as a variable substitute for liposomes in the field of drug delivery. The ability of nanoparticles for drug delivery to penetrate through a variety of anatomical barriers, the sustained release of their contents, and their stability in the nanometer size range are all important factors in their successful implementation.[9] However, the scarcity of safe polymers with regulatory approval, as well as the high cost of such polymers, has prevented nanoparticles from being widely used in clinical medicine to date.[8] Lipids have been proposed as an alternate carrier to circumvent the constraints of polymeric nanoparticles, notably for lipophilic medicines.[19] These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators worldwide.[4] SLNs are colloidal carriers that were developed in the last decade as a replacement for traditional carriers (emulsions, liposomes and polymeric nanoparticles). They are a new class of submicron-sized lipid emulsions in which a solid lipid replaces the liquid lipid (oil). SLNs are appealing for their potential to improve the performance of medicines, neutraceuticals, and other materials due to their unique qualities such as tiny size, vast surface area, high drug loading, and phase interaction at interfaces.[4],[19] As a new colloidal drug carrier for intravenous applications, SLNs are gaining a lot of attention. SLNs are sub-micron colloidal carriers made up of physiological lipid that are dispersed in water or an aqueous surfactant solution. SLNs could usher in a new era of research and treatment.[4]

Advantages of SLNs

- Control and / or target drug release.
- Excellent biocompatibility
- Improve stability of pharmaceuticals
- High and enhanced drug content.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.

• Chemical protection of labile incorporated compounds.
• Much easier to manufacture than biopolymeric nanoparticles.
• No special solvent required.

Disadvantages of SLNs
• Particle growth
• Unpredictable gelation tendency.
• Unexpected dynamics of polymeric transitions.

Ingredients used for SLNs
As indicated in table 1.1, SLNs are made up of solid lipid, emulsifier, and water/solvent. Triglycerides, partial triglycerides, fatty acids, and waxes are some of the lipids that can be employed.[10],[11] To stabilise the lipid dispersion, various emulsifiers and their combinations were utilised. The use of multiple emulsifiers may help to prevent particle agglomeration.[12],[13]

Table 1.1 Various components of SLNs.

Lipids	Emulsifiers	Cryoprotectors
Triglycerides : Tristearin/ Glyceryl tristearate, Trilaurin, trimyristin, tripalmitin, hydrogenated- coglycerides	**Non-ionic** **Sorbitan ethylene/ propylene oxide copolymers:** Polysorbate 20, polysorbate 80, polysorbate 60 **Ethylene/ propylene oxide copolymers:** Poloxamer 188, poloxamer 182, poloxamer 407	Glucose Mannose Trehalose Sorbitol Polyvinylpyrrolidone Sucrose Maltose Mannitol
Partial glycerides: Glyceryl monostearate (Imwitor®900), Glyceryl distearate, Glyceryl behenate, Glyceryl palmitostearate	**Anionic** **Bile salts:** Sodium cholate, sodium lauryl sulphate, sodium taurocholate, sodium taurodeoxycholate	
Fatty acids: Stearic acid, palmitic acid, behenic acid, myristic acid	**Cationic** Cetrimonium bromide, chlorhexidine salts	
Waxes: Cetyl palmitate	**Amphoteric** **Phospholipids:** Egg lecithin (Lipoid®S75, Lipoid® E 80), Soya lecithin (Lipoid®E80)	

Mechanism of drug release from SLNs
The general standards of drug release from lipid nanoparticles are as per the following :
1) Because of the small size of the nanoparticles in the nanometer range, the surface area of the nanoparticles has a higher surface area, resulting in a higher medication discharge.
2) When the particles are homogeneously disseminated in the lipid framework, slow and controlled release can be achieved.
3) The lipid carrier's crystallisation behaviour and the medicine's high mobility result in rapid medication discharge.
4) In the drug-enriched shell model, fast initial drug release occurs in the first 5 minutes due to the outer layer of the particle's increased surface area of drug deposition on the particle surface.
5) As particle size increases, burst release decreases, and prolonged release is possible when the particles are sufficiently large, such as lipid macromolecules.
6) The type of surfactant and its concentration, which interact with the outer shell and impact its structure, should be addressed. A low surfactant concentration leads to a limited burst and prolongs drug release.
7) Drug release rate is directly influenced by a number of factors, including formulation composition (such as the presence of a surfactant, structural properties of the lipid and the drug), manufacturing method and conditions (such as production time, equipment, sterilisation, and lyophilisation), and drug release rate is directly influenced by the particle size.[14],[20]

Drug incorporation models in solid lipid nanoparticles
Table 1.2 Drug Release Models.

Homogenous matrix model	Drug enriched shell model	Drug enriched core model
Formation of this model in cold homogenization technique	Formation of this model in hot homogenization method	Dispersion cooling leads to supersaturation of the drug which is dissolved in the lipid.
use no drug solubilizing surfactants.	Formation of lipid core at recrystallization temperature of lipid.	Precipitation of drugs in the melted lipid.
Drug dispersed in a lipid matrix	Cooling of the obtained dispersion leads to the repartitioning of the drug to the lipid phase.	Finally, further cooling leads to the recrystallization of the lipid
There is a strong interaction between lipids and drugs.	The concentration of drug in the surrounding membrane	Formation of drug enriched core model.

Different Methods of Preparation of Solid Lipid Nanoparticles (SLNs)
General Ingredients
Table 1.3. General Ingredients of SLNs.

Name of the ingredients	Concentration
Lipid	3.33% w/v
Phospholipids	0.6-1.5%
Glycerol	2-4%
Poloxamer 188	1.2-5% w/w
Soy phosphatidyl choline	95%
Compritol	10%
Cetyl palmitate	10%w/w
Tego care 450 (surfactant)	1.2% w/w
PEG 2000	0.25%
PEG 4500	0.5%
Tween 80	50%
Ethyl oleate	30%
Na alginate	70%
Ethanol/butanol	2%
Tristearin glyceride	95%
PEG 400	5%
Isopropyl myristate	3.60%
Pluronic F 68	40%

SLNs Preparation
SLNs are made up of solid lipids, emulsifier and water/solvent. The lipids used may be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), and steroids (cholesterol) and waxes (cetyl palmitate).[6],[11] Various emulsifiers and their combination (Pluronic F68, F127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently.[12],[14] A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decrease the danger of acute and chronic toxicity.[15],[18] The choice of the emulsifier depends on the administration route with a suitable number of emulsifiers suitable for parenteral administration. Different methods of SLNs preparation are shown in Table 1.4.

Table 1.4. Different methods of SLNs preparation.

Various methods used for preparation of SLN	
Method	**High Pressure Homogenization (HPH)**
Mechanism	Shear due to intense turbulent eddies
Advantages	very effective dispersion technique
Disadvantages	Extremely energy intensive process
	Hot HPH
Mechanism	Intensive cavitations because of large pressure drop through the valve.
Advantages	Scalable, commercially available

Disadvantages	Drug distribution into the water phase during homogenization, temperature induced drug-degradation.
	Ultrasonication technique
Mechanism	Shear between adjacent particles formation, growth and implosive collapse of bubbles due to cavitation forces
Advantages	Low energy input, theoretical stability and low particle size
Disadvantages	During sonication, metallic contamination of the product may occur
	Super Critical Fluid method
Mechanism	Parallel processes of supercritical fluid extraction(diffusion) of organic solvents from emulsion and lipid dissolution; expansion of organic phase; leads to lipid crystallization
Advantages	Particles are obtained as a dry powder, carbon dioxide is the god choice as a solvent
Disadvantages	Very expensive method.
	Solvent emulsification diffusion method
Mechanism	Emulsification(or diffusion) of globules followed by evaporation leads to precipitation as particles.
Advantages	Avoidance of heat during the production procedure
Disadvantages	Instability of emulsion, insolubility of lipids in organic solvents
	Phase inversion technique
Mechanism	Spontaneous inversion of o\w to w/o transitional emulsion with increase in temperature
Advantages	Less energy intensive, solvent free good for heat labile molecules
Disadvantages	Instability of emulsion, incorporation of additional molecules influence inversion phenomenon.

Evaluation Parameter of Solid Lipid Nanoparticles
Particle Size, PDI, and Zeta Potential
DLS (Delsa Nano C, Beckman Coulter) was used to determine particle size, and the zeta potential was calculated using electrophoretic mobility under an electric field. For the particle size and polydispersity index (PDI) analysis, samples were diluted with distilled water prior to measurement, and measurements were taken at a fixed angle of 165° at 25°C for each sample. Prior to analysis, samples were diluted in a 1:40 ratio with filtered water (v/v) in order to determine the zeta potential of the solution. The average particle size, particle distribution index (PDI), and zeta potential were then determined in triplicate.[5]

Entrapment Efficiency
The centrifugation method was used to determine the entrapment efficiency of the SLN dispersion in this study. It was necessary to centrifuge an SLN dispersion (containing an equivalent to 5 mg of drug) at 20000 rpm for one hour in order to collect the supernatant liquid, which was stored at -20°C. After a suitable dilution with a fresh phosphate buffer saline pH 7.4 solution, the collected liquid was filtered to determine the concentration of free drug present.[1] The absorbance at 207 nm was measured with a UV spectrophotometer to determine the entrapment efficiency, which was calculated using the following formula:

$$\%\,EE = \frac{\text{Total drug content} - \text{Free drug}}{\text{Total drug content}} \times 100.$$

Surface Morphology
The scanning electron microscope was used to examine the surface morphology of the best formulation. The results were promising (SEM). The formulation was poured into a circular aluminium plate and dried in a vacuum oven to form a dry film, which was then examined under a scanning electron microscope to determine its composition (FEI, Quantum 200E Instrument).

***In Vitro* Release Studies**
Dialysis bag method with dialysis membrane with molecular weight of 12,000–14,000 daltons was used to conduct the in vitro release studies using pH 6.8 phosphate buffer containing 0.5 percent (v/v) polysorbate 80 using dialysis membrane with molecular weight of 12,000–14,000 daltons. To prepare the SLN dispersion, an amount equal to 0.4 mg of drug was placed in a dialysis membrane bag that was tied at both ends and placed in an open beaker that contained 100 mL of diffusion medium. The temperature and speed were maintained at 372°C and 100 rpm, respectively, with the aid of a magnetic stirrer. In order to maintain the sink condition, samples were drawn at predetermined intervals and the same volume of buffer was replaced with fresh buffer. The samples were analysed spectrophotometrically at 285 nm using ultraviolet light. The amount of drug released was then multiplied by the cumulative percentage release to arrive at the final result. The release kinetics were determined using kinetic

equations such as zero order (cumulative percent release versus time), first order (log percent drug remaining versus time), Higuchi's model (cumulative percent drug release versus square root of time), and Korsmeyer-Peppas model (cumulative percent drug release versus square root of time) (log drug release versus log time).[16],[17] From the linear curve obtained through regression analysis of the plots, we were able to calculate the values for r^2 and k. The n value was calculated in the case of the Korsmeyer-Peppas model.

Fourier Transform Infrared Studies

The interaction between the lipids and drug was identified from the fourier transform-infrared (FT-IR) studies.

Differential Scanning Calorimetry

Differencential scanning calorimetry (DSC) is a thermal analysis technique that is widely used to monitor both endothermic and exothermic processes (such as melting, solid-solid phase transitions, and chemical degradation) in the laboratory (crystallization and oxidative decomposition). The presence of possible drug-excipient or excipient-excipient interactions in a formulation could be extremely useful in preformulation studies, as it would indicate the presence of such interactions. In order to obtain the thermograms of the samples, the researchers used a differential scanning calorimeter (TA Instruments Q 2000). A dry nitrogen atmosphere was used to scan the samples, which were weighed directly into a DSC aluminium pan that had been pierced. The temperature range was 25–300°C. The heating rate was 10°C/min, and the thermograms obtained were analysed to determine whether there was any interaction between the drug and the excipient.

CONCLUSION

Because SLNs have the potential to incorporate hydrophilic and lipophilic drugs, in addition to proteins and nucleic acids, they open up new avenues for drug and gene delivery research and development. SLNs are capable of delivering drugs to the target site that are incompatible with the body's physicochemical makeup, have a lower pharmacokinetic profile, or are thermolabile. The ability of SLNs to release drugs over an extended period of time ensures that the drug is delivered effectively to the target tissue. SLN are extremely complex systems that have distinct advantages and disadvantages when compared to other colloidal transporters. Further research is needed to better understand the structure and dynamics of SLN at the molecular level, both in vitro and in vivo studies, among other things. Although SLNs have the potential to be a futuristic delivery system, extensive research is required to improve the quality, efficacy, and safety profile of drugs, genes, and nucleic acids delivered through them.

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