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A REVIEW ON SOLID LIPID NANOPARTICLES

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Abstract

Solid lipid nanoparticles are a new pharmaceutical delivery system or pharmaceutical formulation Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research, as well as in other varied sciences. Solid lipid nanoparticles (SLN) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. Drug delivery by inhalation is a noninvasive means of administration that has following advantages for local treatment for airway diseases: reaching the epithelium directly, circumventing first pass metabolism and avoiding systemic toxicity. Solid lipid nanoparticles (SLN) have emerged as a next-generation drug delivery system with potential applications in pharmaceutical field, cosmetics, research, clinical medicine and other allied sciences. Solid lipid nanoparticles (SLN) are introduced as the new generation of carriers for cosmetics, especially for UV blockers for the use on human skin and/or hair and production thereof is described. Lipid nanoparticles (LNPs) have attracted special interest during last few decades. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two major types of Lipid-based nanoparticles. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were developed as alternative to other colloidal carriers.

Keywords: Solid lipid nanoparticles (SLN), colloidal drug carriers, homogenization, TEM, PCS, Biodistribution, targeting.

Introduction

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological 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. Dispersed phase is solid fat, and surfactant is used as emulsifier. Lipid components of SLNs are solid at both body and ambient temperature and can be highly purified triglycerides, complex glyceride mixtures or even waxes. Surfactants are used in concentrations of about 0.5 to 5% to enhance stability. The proper selection of lipids and surfactants can affect physicochemical properties and quality of them such as particle size and drug loading. Compared to liposomes, they have drug stability and prolonged release and they are safer than polymeric carriers because of avoidance of organic solvents in their production.

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were developed as alternative to other colloidal carriers. They were designed to overcome lipid nanoemulsions and liposomes in stability and ability to control the release of an encapsulated substance, and at the same time to be better tolerated than polymeric nanoparticles. Since the patenting of SLN discovery, large amount of data became available on the behaviour of these systems in vitro. SLN/NLC have many prerequisites to be a well-tolerated carrier the currently available data seem to confirm it, but there are also some contradictory results. In this review, we collected the available data from various articles and compiled, so

that we can find the various methods of SLNs preparation used by researchers all over the world.

ADVANTAGES OF SLN:

- Control and/or target drug release
- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods (1)
- Improve stability of pharmaceuticals
- Improved bioavailability of poorly water soluble molecules (2)
- High and enhanced drug content (compared to other carriers)
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application
- Possibility of scaling up
- Feasibilities of carrying both lipophilic and hydrophilic drugs
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment
- Most lipids being biodegradable, SLNs have excellent biocompatibility
- SLNs have better stability compared to liposomes
- Water based technology (avoid organic solvents).
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- Easy to scale-up and sterilize
- High concentration of functional compound achieved
- More affordable (less expensive than polymeric/surfactant based carriers).
- Lyophilization possible
- Easier to validate and gain regulatory approval

DISADVANTAGES OF SLN

- Poor drug loading capacity,
- Drug expulsion after polymeric transition during storage
- Relatively high water content of the dispersions (70- 99.9%) (3).

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. The reasons for the increasing interest in lipid based system are many – fold and include.

- Lipids enhance oral bioavailability and reduce plasma profile variability.
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- Better characterization of lipoid excipients.
- An improved ability to address the key issues of technology transfer and manufacture scale-up.

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Figure 1. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.

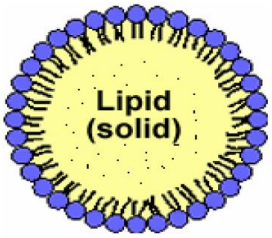

Fig. 1: Structure of solid lipid nanoparticle (SLN)

SLN PREPARATION:

SLNs are made up of solid lipid, 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). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently.

METHODS OF SLN PREPARATION:

The SLNS can be prepared using various methods and the most widely used methods are discussed here as follows

- High Shear Homogenization
- Hot Homogenization
- Cold Homogenization
- Ultrasonication or High Speed Homogenization
- SLN prepared by solvent emulsification/evaporation
- Micro emulsion based SLN preparations
- SLN preparation by using supercritical fluid

- Spray Drying Method
- Double Emulsion Method

Each method has its very own advantage and disadvantage. The method depends upon various factors like the nature of the product and also the nature of the materials and equipment's to be used. Some commonly used ingredients are given in table 1.

TABLE-1. LIST OF COMMONLY USED INGREDIENTS.

NAME OF THE INGREDIENTS	CONCENTRATIONS
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 85	0.5%
ETHYL OLEATE	30%
SODIUM ALGINATE	70%
ETHANOL/BUTANOL	2%
TRISTEARIN GLYCERIDE	95%
PEG 400	5%
ISOPROPYL MYRISTATE	3.60%
PLURONIC F 68	40%
TWEEN 80	50%

FIGURE-1. TYPES OF ENCAPSULATION.

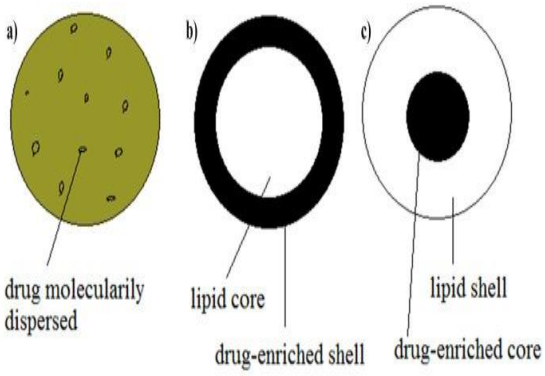

TABLE-2. LIST OF DRUGS AND POLYMERS USED FOR THE PREPARATION OF SLNS USING DIFFERENT METHODS:

Drug	Polymer	Method of preparation	Reference
Olanzapine	Hydrogenated soyaphosphatidylcholine	Modified high pressure homogenization (4)	Vivek et al. (2007)
Rizatriptan	Tristearin,Phospholipon80	Modified solvent injection method (5)	Nair et al. (2011)
Alendronate NP	PLGA,Ethyl acetate, PF68	Double emulsion solvent diffusion (6)	Cohen Sela et al. (2009)
Clozapine **Tetracaine,** **Etomidate,** **Prednisolone**	Dynasan114,116, Tristearin,Dynasan112, Campritol 888ATO, Lipoid S75	Hot homogenization (7)	Venkateswarlu et al. (2004) Zur Muhlen et al. (1998) Schwarz et al. (1994)
Vitamin A **Retinol** **Gatifloxacin** **Insulin**	Compritol 888ATO, Miglyol 812, Dynasan 116 Chitosan-Na aliginate PEG'Glycolated chitosan	Hot homogenization (8-12) Coacervation Ionic gelation	Muller et al. (1999) Jenning et al. (2000) Motwani et al. (2008) Zhang et al. (2008)
Paclitaxel **Insulin**	Tripalmitin, phosphatidylcholine Hydrophobized cholesterol bearing pullulan	Microemulsion Ultra sonication (12,13)	Cavalli et al. (2000) Akiyoshi et al. (1998)
Mitoxantrone (14)	Glyceryl behenate Campritol 888ATO, lecithin		Lu et al. (2006)
Vinpocetine	Glyceryl monostearate,DCM, soyalecithin	Ultrasonic solvent emulsification (15)	Luo et al. (2006)
Insulin	Cetyl palmitate	Solvent emulsification evaporation (16)	Sarmento et al. (2007)
5-Fluorouracil	Dynasan 114,118, triglyceride, soyalecithin	Double emulsion Solvent evaporation (17)	Yassin et al. (2010)
Methotrexate	Cetyl alcohol, Campritol 888 ATO, Tween 80	Microemulsion congealing (18)	Misra et al. (2002)
Gatifloxacin	Sodium alginate, Chitosan	Modified coacervation (19)	Motwani et al. (2008)

SLNs can be used to incorporate wide range of drugs, there are different methods of drug incorporation in

solid lipid nanoparticle synthesis which are discussed in Table-3.

TABLE-3. THREE MODELS OF DRUG INCORPORATION INTO SLNS:

Solid solution model	Core-shell model (drug-enriched shell)	Core-shell model (drug-enriched core)
Formation of this model in cold homogenization technique	Formation of this model in hot homogenization technique	Dispersion cooling leads to a supersaturation of the drug In which is dissolved in lipid.
Using no drug-solubilizing surfactant	Formation of lipid core at recrystallization temperature of lipid	Precipitation of drug in melted lipid
Drug dispersed in lipid matrix	Cooling of the obtained dispersion leads to re-partitioning of the drug to the lipid phase	Finally, further cooling lead to recrystallization of the lipid
There is a strong interaction between lipid and drug	Concentration of drug in surrounding membrane	Formation of drug-enriched core

APPLICATION OF SLN:

1. Oral drug delivery applications:

Oral drug administration is common and preferred route due to good patient compliance, non-invasiveness and therapeutic success, but poorly water-solubility of drugs is limiting step for the absorption of them. Thus an approach is needed to improve the bioavailability of drugs. Lipid-based delivery systems in the recent decades have shown many advances for this purpose. These systems include a wide range of formulations such as self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), nanoemulsions, SLNs and NLCs. Since in these systems, drug is dissolved in the lipid thus makes the potential for improving the bioavailability of poorly soluble drugs in water, especially lipophilic drugs.

2. Pulmonary drug delivery applications:

LNPs easily incorporated into carriers which inhaled to the lungs, therefore able to provide a deep lung deposition, good adhesion and elongated retention in the lung. Also due to improved and prolonged therapeutic effects, SLNs and NLCs have a longer dosing interval and better compliance for patients. They are typically particulate systems for various drug delivery applications. Advantages of drug release of fat in the lungs including: control of the release profile, prolonged release, faster in vivo degradation and better tolerability compared to particles made from some polymeric materials such as PLA or PLGA. Pulmonary delivery of SLNs is not widely accepted because of toxicity issues but when the physiologic lipids are used, is estimated to be safer than polymer-based systems.

3. Gene transfer applications:

LNPs penetrate to biological membranes effectively through receptor-mediated pathway because lipids are the most important components of cell membranes. Thus enhance the uptake of genetic compounds. The delivery of some bioactive to particular sites in the body and their release behavior is directly dependent to particle size. The achievement of gene therapy (with DNA and RNA transfer) depends on the new bioactive delivery techniques. While 1980; more than 400 clinical studies in gene therapy have been reported. Delivery vectors are used in gene transfer due to restricted ability of naked DNA transfer to cells owing to propensity to enzymatic degradation.

4. Cosmetic application:

LNPs such as SLNs and NLCs are one of the excellent vehicles for cosmetic and dermatological application. They have some characteristics which make them talented carriers for cosmetic applications for instance protection of sensitive compounds against chemical degradation and enhancement the water content of the skin. The use of LNPs as carriers for sunscreens, anti-acne and anti-ageing actives has been investigated. In fact, due to the high control behaviors of LNPs on skin penetration of active substances, they have UV-blocking and skin hydration behavior. In cosmetic products, reduction of the desire to scratch and skin damage is important. Since these formulations bear a resemblance to skin structure, there is no disruption and toxic effect when used topically.

5. Food application:

LNPs are of particular interest to food manufacturers as novel delivery systems for encapsulation of bioactive compounds. LNPs are excellent potential carriers for sensitive compounds in food industry because they improve the industrial and the nutritional quality of a lipid containing food. Quality of them is affected by the lipid oxidation at storage and processing steps. Therefore must use antioxidants to prevent this process. Examples of active substances enclosed in LNPs for food industry are Beta-carotene, Lutein and Lycopene.

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