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SOLID LIPID NANO PARTICLES

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ABSTRACT

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. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers. This review presents a broad treatment of solid lipid nanoparticles discussing their advantages, limitations and their possible remedies. The different types of nanocarriers which were based on solid lipid like solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates are discussed with their structural differences. Different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are described. Appropriate analytical techniques for characterization of solid lipid nanoparticles like photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry are highlighted. Aspects of solid lipid nanoparticles route of administration and their biodistribution are also incorporated. If appropriately investigated, solid lipid nanoparticles may open new vistas in therapy of complex diseases.

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

2. INTRODUCTION

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system totradition 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.[1] In order to overcome the disadvantages associated with the liquid state of the oil droplets, the lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. [Figure 1].

The reasons for the increasing interest in lipid based system are many – fold and include.

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipoid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale up.[1]

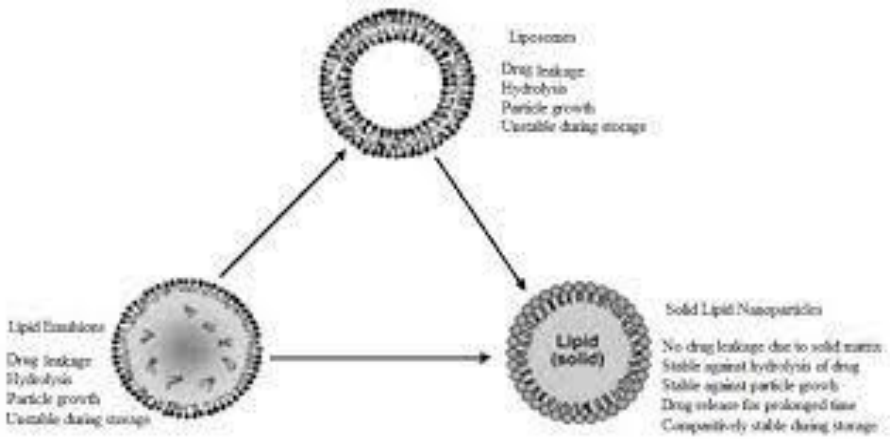

Figure. 1: Shows a diagrammatic representation on SLN over emulsions and liposome.

3. Characterstics of Solid Lipid Nanoparticles

A solid lipid nanoparticle is typically spherical with an average diameter between 10 and 1000 nanometers. Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). The emulsifier used depends on administration routes and is more limited for parenteral administrations. The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), diglycerides (e.g. glycerol bahenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently.

An SLN is generally spherical in shape and consists of a solid lipid core stabilized by a surfactant. The core lipids can be fatty acids, acylglycerols, waxes, and mixtures of these surfactants. Biological membrane lipids such as phospholipids, sphingomyelins, bile salts (sodium taurocholate), and sterols (cholesterol) are utilized as stabilizers. Biological lipids having minimum carrier cytotoxicity and the solid state of the lipid permit better controlled drug release due to increased mass transfer resistance. Shah et al in their book Lipid Nanoparticles: Production, Characterization and Stability discuss these in detail.

LNPs used in mRNA vaccines for SARS-CoV-2 (the virus that causes COVID-19) are made of four types of lipids: an ionizable cationic lipid (whose positive charge binds to negatively charged mRNA), a PEGylated lipid (for stability), a phospholipid (for structure), and cholesterol (for structure).[2] Because of rapid clearance by the immune system of the positively charged lipid, neutral ionizable amino lipids were developed. A novel squaramide lipid (that is, partially aromatic four-membered rings, which can participate in pi–pi interactions) has been a favored part of the delivery system used, for example, by Moderna.[3]

4. Commonly Used Preparation Techniques of SLNs

High Pressure Homonization

High-pressure homogenization ((U)HPH) is one of the emerging technologies being studied and developed for various applications in the food industry. (U)HPH was suggested as an effective tool for achieving microbial safety and extending the product shelf life of liquid foods in a continuous process while minimizing some negative attributes of thermal processing. The valve geometry, pressure level, inlet temperature, and the number of homogenization cycles are all factors affecting the level of microbial inactivation and the extent of the techno-functionalities of food biopolymers and matrices. Turbulence, high shear, cavitation, and temperature increase induced by (U)HPH treatments enhance emulsion stability, stabilize proteins in solutions, reduce particle size distributions, and increase the accessibility of health-promoting compounds. This review is a comprehensive and updated overview of the engineering aspects of the (U)HPH process, specifically focusing on (U)HPH modification of food components such as polysaccharides, proteins, and bioactive compounds. A detailed description of the potential applications in food products beyond microbialinactivation is also included.[4]

Microemulsion Based SLNs

Microemulsions (ME) containing lipids are used as starting systems to obtain solid lipid nanoparticles (SLN) in alternative processes to those based on high pressure homogenization technique. SLN characteristics can be influenced by the microemulsion composition and the specific conditions adopted in the quenching process related to the transformation of WME into nanoparticles. To establish optimized conditions for the production of SLN starting from WME, in a first step of this work we have defined the microstructure of warm microemulsions highlighted in the lecithin (LCT)/water (W)/tripalmitin (TP)/1-butanol (B)/taurocholate sodium salt (ST) phase behavior at 70°C. Moreover, we have further studied the LCT/W/TP/B system by evaluating the effect on the microemulsion area due to the LCT/B weight ratio, the replacement of 1-butanol with different alcohols (ROH), and the addition of taurocholate sodium salt (ST) at different LCT/ST weight ratios. The microstructure of

the isotropic phase region obtained in the presence of ST has been characterized by both (1)H NMR PGSE measurements and electrical conductivity. The characteristics of final nanoparticles are discussed taking into account both the microstructure of the parent WME and the conditions of the quenching process leading to SLN. The present results highlight the relevance of the microstructural characteristic of WME to assure the obtainment of SLN with average diameter in the order of 100-2000 nm and narrow size distribution.[5][figure :2]

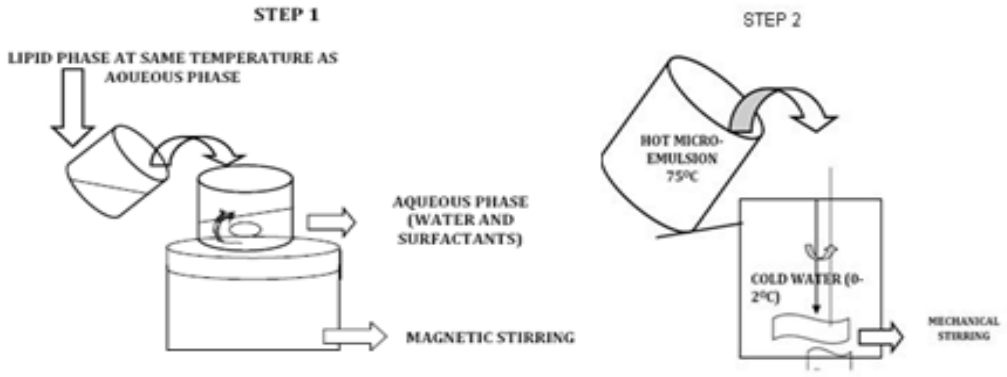

Figure: 2: Microemulsion method.

Solvent Emulsification

Nowadays, there has been an increased demand of nanoparticulate-based drug delivery as nanoparticles (NPs) generally give more advantages over the conventional drug carriers for targeting in various parameters like more drug encapsulation, more stability and site specificity, sustained release profile and the ability to deliver both lyophilic and lyophobic types of drug particles using different modes of administration. Nanocarriers have been expansively studied as particulate drug delivery in the field of pharmaceuticals, due to their controlled and sustained release properties, small size and biocompatibility with body tissues. Manufacturing technique used to prepare nanoparticles plays a vital role in achieving their desired properties for a particular application. Several methods to formulate nanoparticles have been developed during the last many decades, and these are classified based on whether the particle formation undergoes a polymerization reaction or a nanoparticle forms directly from a preformedpolymer or ionic gelation method. The choice of method for the preparation of nanoparticle is highly dependent on the physicochemical properties of both the polymer and the drug compound. Polymeric nanoparticles are generally manufactured by polymerization of monomers using anionic polymer or by preparing homogeneous dispersion of the dissolved polymers which gives nanoparticles using various methods such as solvent evaporation, emulsification solvent diffusion, salting out, emulsification diffusion and supercritical fluid (SCF) technology. This chapter emphasizes on how emulsification followed by solvent evaporation and solvent diffusion permits an emulsion of a polymer solution to customize as nanoparticles. The chapter also provides concise information on recent trends of research in specified domain.[6]

Melting Dispersion Method

Approximately 40% of new chemical entities (NCEs), including anticancer drugs, havebeen reported as poorly water-soluble compounds. Anticancer drugs are classified into biologicdrugs (monoclonal antibodies) and small molecule drugs (nonbiologic anticancer drugs) based oneffectiveness and safety profile. Biologic drugs are administered by intravenous (IV) injection dueto their large molecular weight, while small molecule drugs are preferentially administered bygastrointestinal route. Even though IV injection is the fastest route of administration and ensurescomplete bioavailability, this route of administration causes patient inconvenience to visit a hospitalfor anticancer treatments. In addition, IV administration can cause several side effects such assevere hypersensitivity, myelosuppression, neutropenia, and neurotoxicity. Oral administration isthe preferred route for drug delivery due to several advantages such as low cost, pain avoidance,and safety. The main problem of NCEs is a limited aqueous solubility, resulting in poor absorptionand low bioavailability. Therefore, improving oral bioavailability of poorly water-soluble drugs isa great challenge in the development of pharmaceutical dosage forms. Several methods such assolid dispersion, complexation, lipid-based systems, micronization, nanonization, and co-crystalswere developed to improve the solubility of hydrophobic drugs. Recently, solid dispersion is one ofthe most widely used and successful techniques in formulation development. This review mainlydiscusses classification, methods for preparation of solid dispersions, and use of solid dispersion forimproving solubility of poorly soluble anticancer drugs.[7]

Ultrasonication / High Speed Homogenization

The disintegration efficiencies of microalgal Parachlorellakessleri cells by ultrasonication (US) and high pressure homogenization (HPH) treatments were

investigated. The applied procedures included individual US, individual HPH, or combined US followed by HPH treatments. The test concentrations of cell suspensions were 1% and 10% dry matter. The microstructures of cell suspensions were analyzed using scanning electron microscopy, light microscopy and light scattering techniques. Extraction was characterized by the ionic, Zi, carbohydrate, Zc, protein, Zp, and pigment (dyes), Zd, extraction indexes. Application of US treatment (1% dry matter, 400 W, 30 min) gave $Zi \approx 0.10$, $Zc \approx 0.45$, $Zp \approx 0.16$, and application of HPH treatment (1% dry matter, 400 bar, 4 passes) gave $Zi \approx 0.10$, $Zc \approx 0.20$, and $Zp \approx 0.11$. In both cases, the efficiency of extraction can be arranged as follows: $Zi < Zp < Zc$. Application of a preliminary US treatment with 10% dry matter and a final HPH treatment with 1% dry matter allows increasing the extraction efficiency and decreasing the energy consumptions. For example, US (1% dry matter, 400 W, 30 min) + HPH (1% dry matter, 1200 bar, 4 passes) treatment (≈105.6 kJ/g dry matter) gave $Zi \approx 0.49$, $Zc \approx 0.69$, and $Zp \approx 0.32$, whereas US (10% dry matter, 400 W, 30 min) + HPH (1% dry matter, 1200 bar, 4 passes) treatment (≈53.8 kJ/g dry matter) gave $Zi \approx 0.76$, $Zc \approx 0.83$, $Zp \approx 0.74$.[8]

5. Route of Administration of Nano Drug Particles

Oral Route

The oral route, being a natural route of entry of substances to the organism, enjoys the greatest acceptability, as well as some technological advantages, since oral pharmaceuticals mostly comprise non-sterile solids dosage forms. For a successful therapy by the oral route, though, a drug must generally fall within certain ranges of lipophilicity, molecular weight, and hydrogen bonding ability, as well as aqueous solubility and permeability, which altogether contribute to its druglikeness.[9]

Curcumin, for example, represents a real challenge for its formulation as oral product, due to its very low aqueous solubility, poor absorption, rapid metabolism and pH-dependent degradation rate.[10] Oral BA of curcumin has been reported to be as low as 1%. On the other hand, successful outcomes of curcumin in both preclinical and clinical trial of different diseases make it a very promising drug, that seems to be able to modulate several cell signaling pathways and, thus, holds a great therapeutic potential against a wide range of human diseases (e.g., cancer, infections, inflammatory, metabolic and neurodegenerative diseases, among others)[11] Furthermore, there is enough evidence to support the hypothesis of dose-dependent pharmacological activity of curcumin, with the anticancer properties corresponding to the highest doses.[12]

Regardless the somehow inconsistent reports on curcumin oral BA (possible due to variations in experimental conditions), there is agreement on the positive increment in the oral BA of curcumin formulated within nanosystems, with respect to the free drug in solution.[13] Predictably, the publications reviewed here confirmed that trend, since curcumin oral BA achieved with SLN/NLC was from 2 to more than 10-fold higher than that of the free drug solution.[14] The examination of the PK profiles seems to indicate that the BA improvement of curcumin is related to the combined effect of a higher absorption and a minor elimination of the encapsulated drug, similarly to what was described for LPV-SLN.

Among the reviewed articles, the aforementioned trend is confirmed by many other examples. Administration as SLN/NLC greatly increases the oral BA of drugs with very low aqueous solubility such as aripiprazole,[15] zaleplon, miconazole, raloxifene, efavirenz, doxorubicin, asenapine, linagliptin, and niclosamide, among several others.

The group of calcium channel blockers derived from dihydropyridine, for example, is characterized by its low oral BA due to its low water solubility and high rate of first-pass metabolism. Administered as lipid-based nanosystems, significant increases in the oral relative BA was observed for isradipine, nisolpine, felodipine, and cilnidipine. These are very promising results taking into consideration that, when administered as conventional formulations, the oral BA of these four drugs is in the range of 5-20%.[16]

Percutaneous Route

The skin is composed of two main histological layers, the epidermis at the surface, and the dermis below. In turn, the outermost layer of the epidermis is the stratum corneum or the hornylayer, which is the real barrier that prevents the entry of foreign (and potentially harmful) substances into the body. The stratum corneum is formed by cells named corneocytes or keratinized cells, surrounded by shallow valleys that comprise the intercellular regions filled with lipid multilamellae, rich in ceramides, fatty acids and cholesterol.

The ability of a drug to penetrate the skin depends on its physicochemical properties (mainly its size, molecular weight, pKa and partition coefficient) as well as the vehicle in which it is formulated. There are substances known as “permeation enhancers” which are capable of reversibly disorganizing the stratum corneum, facilitating the drug entry (e.g., fatty acids and alcohols with long carbon chains, surfactants, terpenes and fatty esters, Gupta et al., 2019). These excipients are commonly used in classic semi-solids preparations like emulsions, lotions and ointments, as well as of their more recent relatives’ lipid-based nanoformulations. Hence, it is logical that these formulations are, among other nanosystems, the first choice for percutaneous/transdermal applications.

The most studied nanoparticulate systems for percutaneous application are, by far, liposomes. And although it has been shown that the constituent lipids of

liposomes are capable of reaching the deeper layers of the skin (i.e., the dermis), it still remains unclear if they can act as carriers, penetrating through the skin, or if they only act as penetration enhancers, changing the skin physical properties in a way that facilitates the (free) drug penetration through it (Peralta et al., 2018).

6. Disposition in the Body and Penetration to the CNS

Studying the distribution of these drug delivery nanosystems within the body is one of the main research challenges in the field. Although the advances that so far have been achieved in terms of the development of SLN/NLC are relevant, only a few works are dedicated to a detailed study of the fate of this type of NPs once they enter the organism. This section is intended to describe the main mechanisms involved in the uptake, transport and distribution of NPs into the body, as well as how these structures face the natural barrier that protects the CNS.

7. Applications

SLNs in Cosmetics and Topical Drugs

SLNs in Cosmetics and Topical Drugs Particularly beneficial SLNs features in dermal applications include.[17]

- **Excellent tolerability:** SLNs are composed of physiological and biodegradable lipids that exhibit low toxicity and low cytotoxicity.
- **Excellent transdermal delivery:** the small size of SLNs ensures close contact with the stratum corneum, increasing the amount of drug penetrating through the skin.
- **Hydration Benefits:** SLNs provide occlusive properties that result in increased skin hydration.

SLNs and Cancer Drugs

SLNs are being currently used in numerous studies as drug delivery systems for cancer drugs.[18,19,20,21] Due to their small size and structure, SLNs create the ideal drug delivery system for allowing penetration into cancer tumors. There are a few notable examples of anticancer drugs in recent drug delivery research using SLNs.5-Fluorouracil (5-FLU), a commonly used antimetabolite anticancer treatment for lung carcinoma, was incorporated into an SLN complex to create a more efficient drug delivery system. Like many problems with anticancer drugs, 5- fluorouracil was limited in its use due to its high toxicity, short half-life, and low bioavailability.[19] SLN formulations allowed 5-FLU to be encapsulated within its matrix, protecting it from chemical degradation, increasing drug bioavailability and decreasing the dosing frequency.[19] Studies of 5-FLU were done on rats, comparing intravenous injections of 5-FLU-SLN suspensions and a placebo mixture of 5-FLU/ 5% (w/v) glucose solution control group.

SLNs and Parkinson's Treatment

To reduce the deficiency of dopamine (DA), agonist drugs such as Bromocriptine (BK) are given to Parkinson's patients. BK is said to exhibit a slow onset of action and prolonged half-life, which may contribute to the lower dyskinesia (involuntary movement) in patients.[22] Therefore, Esposito's et al prepared BK-SLNs that prolonged the uptake of BK and increased its half-life, effectively reducing dyskinesia in patients. BK-SLNs were prepared using a combination of two lipids (of tricarpin, monostearin, tristearin, tribehenin) in various concentrations. Poloxamer 188 was used as a surfactant. These BKSLNs were found to have long-term stability and prolonged drug release.[22] The SLNs were able to cross the blood brain barrier, showing great potential in brain targeting fo-r Parkinson's treatment.

CONCLUSION

In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept; the idea that drugs reaches the right site in the body, at the right time, at right concentration. It should not exert side effects, neither on its way to the therapeutic target, nor at the target site, nor during the clearance process. The SLNs have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is aptly achievedwith SLNs. They 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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