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Review Article

Solid Lipid Nanoparticles System: An Overview

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ABSTRACT

Development of novel drug delivery has been a growing interest among the researchers. The novel drug delivery usually aims for maximal drug bioavailability, tissue targeting, controlled release kinetics, minimal immune response, ease of administration, and the effective delivery of traditionally difficult drugs such as lipophiles, amphiphiles and biomolecules. Colloidal drug carriers are one of the most acceptable approach to attain the goals of the novel drug delivery system. Colloidal drug carriers include vesicular drug carriers and microparticulate drug carriers, which successfully prolong the existence of the drug in systemic circulation and lower the toxicity. A number of colloidal drug carriers such as liposomes, niosomes, pharmacosomes, virosomes, immunoliposomes, microparticles, nanoparticles, albumin microspheres have been developed, however, these carriers still have some drawbacks. To combat these drawbacks, Solid Lipid Nanoparticles (SLN) were introduced as a new class of colloidal drug carries. This paper presents an overview about the definition, advantages, selection of ingredients and formulation techniques of the SLN.

Keywords: Solid lipid nanoparticles; colloidal carrier; hot homogenization.

1. Introduction

The market shift towards advanced drug delivery formulations reflects the society desire to improve therapeutic efficacy and the economic pressure confronting the pharmaceutical industry. Medical professionals continually seek better therapies and faster diagnostic capabilities, while the patients desire effective, inexpensive treatments that minimize harmful side effects (Triplett, 2004). A drug's therapeutic efficacy depends on four major pathways of drug transport and modification within the body: absorption into the plasma from the administration site; distribution between the plasma and tissues, metabolism within the tissues; and elimination from the body. Since the delivery systems affect each pathway so greatly, the delivery system plays a very crucial role in drug design components in pharmaceutical sciences (Triplett, 2004).

Advanced drug delivery research and development activity has helped to minimize the side effect and improve the efficacy. Commonly accepted aims of advanced drug delivery systems include maximal drug bioavailability, targeting, controlled release kinetics, minimal immune response, ease of administration, and the ability to deliver drugs such as lipophiles, amphiphiles, and biomolecules.

Despite the intense research in the past several decades, targeted and controlled delivery of lipophilic drug remain elusive to pharmaceutical scientists (Muller et al., 2000: 161-177). Nanoparticles made from solid lipid are attracting attention as novel colloidal drug carrier for intravenous application. SLN as colloidal drug carrier combines the advantage of polymeric nanoparticles, emulsions and liposomes also avoid some of their disadvantages.

2. Solid Lipid Nanoparticles (SLN) Overview

SLN typically are spherical with average diameter less than 1000 nm, preferably between 50 to 500 nanometers. SLN possess a solid lipid core matrix where the lipophillic molecules can be solubilized. The lipid core is stabilized by surfactants (emulsifiers). To achieve and maintain a solid lipid particle upon administration, the lipid nanoparticle's melting point must exceed body temperature (37°C). Table I Lists various type of lipids and surfactants reported in solid lipid nanoparticle formulations. High melting point lipids investigated include triacylglycerols (triglycerides), acylglycerols, fatty acids, steroids, waxes, and their combinations. Surfactants studied include biological membrane lipids such as lecithin, bile salts like sodium taurocholate, biocompatible nonionic like ethylene oxide/propylene oxide copolymers, sorbitan esters, fatty acid ethoxylates, and their combinations (Mehnert and Mader, 2001: 165-196). Table II enlists various drugs encapsulated in SLN. Drugs categories such as anticancer, anti-

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Table 1: Lipids and surfactants used in solid lipid nanoparticles production

Lipids	Surfactants
Triacylglycerols	**Phospholipids**
Tricaprin	Soy lecithin
Trilaurin	Egg lecithin
Trimyristin	Phosphatidylcoline
Tripalmitin	**Ethylene oxide/propylene oxide copolymers**
Tristearin	Poloxamer 188
Acylglycerols	Poloxamer 182
Glycerol monostearate	Poloxamer 407
Glycerol behenate	Poloxamine 908
Glycerol palmitostearate	**Sorbitan ethylene oxide/propylene oxide**
Fatty acids	**Copolymers**
Stearic acid	Polysorbate 20
Palmitic acid	Polysorbate 60
Decanoic acid	Polysorbate 80
Behenic acid	**Alkylaryl polyether alcohol polymers**
Waxes	Tyloxapol
Cetyl palmitate	**Bile salts**
Cyclic complexes	Sodium cholate
Cyclodextrin [Dubes 2003]	Sodium glycocholate
Para-acyl-calix-arenes	Sodium taurocholate
[Shahgaldian 2003]	Sodium taurodeoxycholate
	Alcohols
	Ethanol
	Butanol

fungal, antiviral and many more agents are encapsulated in the SLN for controlled release and targeted type of drug delivery systems.

3. History of SLN Development

Decades ago submicron-sized vegetable oil-in-water (o/w) emulsions were introduced as carrier systems for poorly water soluble drugs. These o/w emulsions are claimed to be biodegradable, biocompatible and easy to manufacture. However, only a few drug containing emulsions have reached the market because of several formulation problems. Traditionally o/w emulsion were considered to be unsuitable for sustained release because of the low viscosity of the dispersed liquid phase, combined with high specific surface area of colloidal dispersion that causes rapid drug diffusion out of the droplets (Magenheim et al., 1993: 115-123). So, colloidal carriers such as liposomes were developed to get the sustained release effect of the drug. Here the drug is enclosed in the phospholipid in aqueous solution. The phospholipids are sensitive to the temperature and pH change and therefore were not easy to manufacture and administer. Later on liposomes were replaced by the niosomes because non-ionic surfactants were employed instead of phospholipid. Nanoparticles were introduced with the aim to overcome the deficiencies in the colloidal carriers. The polymers used as the building blocks of nanoparticulate composites, belong to natural or synthetic origins. The polymers of natural origin however, suffer from some disadvantages including (a) batch-to-batch variation, (b) conditional biodegradability and (c) antigenicity. Parenteral administration of polymeric nanoparticles has hurdles mainly due to antigenicity (Vyas and Khar, 2002: 331-386). SLN were introduced in the early 1990's by replacing the liquid lipid (oil) of emulsions for the parenteral nutrition by a solid lipid. Formulation ingredients typically include a lipid carrier, a drug (generally lipophillic for satisfactory encapsulation efficiency), water as the dispersion phase, and a surfactant and/or a co-surfactant (Ugazio et al., 2002: 341-344; Bargoni et al., 2001: 497-502; Cavalli et al., 2002: 241-245; Cavalli et al., 2003: 1085-1094; Koziara et al., 2004: 259-269; Koziara et al., 2005: 1821-1828; Oyewumi et al., 2004: 613-626; Wong et al., 2004: 1993-2008; Wong et al., 2006: 1574-1585). These ingredients, after undergoing various formulation techniques, can entrap/adsorb the drug into/onto the particle surface (Muller et al., 2000: 161-177).

4. Advantages of Solid Lipid Nanoparticle (SLN)

SLN has proved to be a preferred carrier system than conventional o/w emulsions, when a prolonged release or a protection of drug against chemical degradation is the objective (ZurMuhlen et al., 1998: 149-155). SLN possesses some advantages like small size, narrow size distribution which provides biological opportunities for site specific drug delivery, controlled release over a long period, possible sterilization by autoclaving or gamma irradiation. SLN can be lyophilized as well as spray dried, low toxicity issues, and avoidance of organic solvents (ZurMuhlen et al., 1998: 149-155). Also SLN increases bioavailability, reduces side effects, smaller dosage form, dosage form stability, and increased active agent surface area giving rise to faster dissolution

Table 2: Example of various drugs encapsulated in SLN

Drugs	Lipid	Surfactant	Particle size	References
Paclitaxel	Emulsifying wax	polyoxyl 20stearly stearate	100	(Koziara et al., 2004: 259-269)
Comtothecin	Stearic acid	Pluronic ® F68	196.8	(Yang et al., 1999: 751-757)
Idarubicin	Stearic acid	Epikuron 200	80	(Zara et al., 2002: 1324-1333)
Etoposide	Tripalmitin	Soy Phosphatidyl Choline	391	(Reddy and Murthy, 2005)
Tobramycin	Stearic acid	Epikuron 200	85	(Bargoni et al., 2001: 497-502)
Lovastatin	Dynasan 114, Dynasan 116	Epikuron 200, Poloxamer 188	60-119	(Suresh et al., 2007: Article 24)
Miconazol Nitrate	Compritol 888 ATO, Precirol ATO 5, Emulcire 61,Glyceryl Mono-Stearate	Tween 80	244-766	(Bhalekar et al., 2009: 289-296)
Podophyllotoxin	Tripalmitin	Poloxamer 188, Soyabean lecithin	73.4	(Chen et al., 2006: 296-306)
Mifepristone	Glycerol Monostearate	Tween 80	106	(Hou et al., 2003: 1781-1785)
Diazepam	Compritol®ATO888, or Imwitor® 900K	Tween 80, or Poloxamer 188	Less than 500 nm	(Abdelbary and Fanmy, 2009: 211-219)
Cisplatin	Stearic acid	Soy lecithin and Sodium glycolate	250-500 nm	(Doijad et al., 2008: 203-207)
Vitamin A	Compritol 888 ATO	Sodium Lauryl Sulfate, Sorbitan monooleate	350 nm	(Popli and Singh, 2006: Article 91)

of active agent in an aqueous environment such as human body. Faster dissolution generally equate with greater bioavailability, smaller drug doses, less toxicity, and reduction in fed/fasted variability.

Its large-scale production is possible by the simple process of high pressure homogenization. While compared to liposomes, SLN possesses the advantage of offering better protection to drug against hydrolytic chemical degradation, as there is no or little access of water to the inner core of lipid particles. Depending on the nature of the drug, a higher pay load might be achieved (Vyas and Khar, 2002: 331-386). Incorporation of drug in SLN can reduce the overall toxicity and side effect of the drug, eg Thrombophlebitis that is associated with iv injection of diazepam or etomidate. Surface modification can easily be accomplished with SLN and hence can be used for site-specific drug delivery system (ZurMuhlen et al., 1998: 149-155). Apart from that, lower cytotoxicity, due to the absence of organic solvents in the production process and a relatively low cost for the excipients are other advantages (Vyas and Khar, 2002: 331-386).

5. Various Formulation Techniques

In the 1980's Speiser and coworker were the first to report making solid lipid particles for drug delivery applications (Eldem et al., 1991: 47-54). Subsequently, numerous research groups started research efforts to improve solid lipid nanoparticle synthesis. Most researchers have approached solid lipid nanoparticle synthesis as some variation of a two step process: (i) the creation of a oil-in-water 'nano' emulsion which was the precursor for the next step and (ii) subsequent solidification of the dispersed lipid phase.

Production techniques of SLN vary from large scale to lab scale techniques. Various techniques which are currently in use, with their advantages and disadvantages are presented in Table III.

5.1. Microemulsion Precursors Technique

Microemulsions can be defined as low viscous, isotropic, thermodynamically stable dispersion. Microemulsions can be formed by spontaneous homogenization of water, oil and an amphiphile in appropriate proportions (Moulik and Paul, 1998: 99-195). The use of co-surfactant is avoided/not essential to the formation of microemulsion, as the commonly used co-surfactant such as medium chain alcohols (1-butanol, 2-butanol) can cause toxicity, irritation and is not approved for in-vivo administration (Flanagan and Singh, 2006: 221-237). Gasco et al have patented the use of a microemulsion precursor for preparing SLN. In this approach, a clear or translucent microemulsion is formed by mixing a molten lipid, surfactant, and water, which is then

Table 3: Advantages and drawbacks of existing SLN formulation techniques (Muller et al., 2000: 161-177; Vyas and Khar, 2002: 331-386; Triplett, 2004)

S. No	Techniques	Advantages	Drawbacks
1	Microemulsion Precursors Technique	Low mechanical energy Input, theoretical stability.	Extremely sensitive to change, labor intensive formulation process
2	Contact Ultrasonication	Reduced shear stress, effective at lab scale	High metal contamination potential, energy intensive process, unproven scalability.
3	High pressure Homogenization	Scalable, well developed technology, continuous operation, commercially demonstrated.	Extemely energy intensive process, polydisperse distribiutions, biomolecule damage
4	Hot Homogenization Technique	Applicable to lipiphilic And insoluble drugs, Exposure time to high temperature is short.	Low entrapment efficiency for hydrophilic drugs
5	Cold Homogenization Technique	Best for Hydrophillic drugs and thermolabile and thermosensitive drugs.	Exposure to heat can not be Completely avoided.
6	Solvent Evaporation Technique	No dilution solidification step, monodisperse distributions	Residual organic solvent

rapidly sprayed in a larger volume of water maintained at a temperature between 2°C-10°C. This leads to rapid solidification of the lipid nanodroplets present in the microemulsion thus forming solid nanoparticles. The nanoparticles formulated by this technique should ideally yield particles having an average diameter from 50-800nm, preferably between 100 and 400nm, and a polydispersity index from 0.06 to 0.90, preferably between 0.10 and 0.70 (Gasco and Antonelli, 1993).

5.2. Membrane Contractor Technique

As per this method, the lipid phase is pressed through a membrane, at a temperature above the melting point of the lipid allowing the formation of droplets. The aqueous phase, which circulates inside the membrane chamber, transfers the droplets formed at the membrane pore outlets to the bulk. SLN are formed by the subsequent cooling of the bulk at the room temperature. This technology allows the preparation of SLN with a mean SLN size between 70 and 250 nm. The advantages of this new process include its ease of use, the control of the SLN size by an appropriate choice of process parameters, and its scaling-up abilities (Trotta et al., 2001: 119-128).

5.3. High Pressure Homogenization

High pressure homogenization offers the advantage that the use of organic solvent is avoided (Casadei et al., 2006: 140-146; Kalariya et al., 2005: 233-240; Liu et al., 2007: 191-195; Zhang et al., 2005: 54-57). In this production technique, the liquid is forced under high pressure (about 500 bar), through a narrow orifice. Due to high shear stress and cavitation forces, size reduction of particles to the submicron range takes place. High pressure homogenization yields dispersion with an average particle size below 500 nm and low microparticle content (Mehnert and Mader, 2001: 165-196). High pressure homogenization can be classified as: Hot Homogenization and Cold Homogenization Technique

5.3.1. Hot Homogenization Technique

Lipids selected for the formulation are melted by heating them to about 10°C above their melting points (Muller et al., 2000: 161-177). The drug is then dispersed in hot lipid melt (Gohla and Dingler, 2001: 61-63; Mao et al., 2005: 273-277)which is further dispersed in a hot aqueous surfactant solution to form a pre-emulsion. This is then homogenized at high pressure and at a temperature at least 10°C above the melting point of the lipid.

5.3.2. Cold Homogenization Technique

As in hot homogenization, the drug is added to the melted lipid, followed by rapid cooling by liquid nitrogen or dry ice. The cold drug lipid matrix is then milled to form microparticles of about 50-100 µm. Then these microparticles are dispersed in the cold aqueous dispersion medium. Disadvantages of cold homogenization include the formation of larger particles with a higher polydispersity index , as compared to hot homogenization (Vyas and Khar, 2002: 331-386).

5.4. Solvent Emulsification Technique

Preparation of SLN by the solvent emulsification/evaporation process involves dissolving the lipid matrix in water immiscible organic solvents (such as chloroform or cyclohexane), which are subsequently

Table 4: Characterization methods for SLN

S. No	Parameters	Characterization method	Reference
1	Particle size & size Distribution	Photon correlation spectroscopy, scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Atomic force microscopy (AFM), Mercury porositometer, Laser defractrometer	(Douglas et al., 1987: 233-261; Gref et al., 1994: 1600-1603)
2	Charge determination	Laser droplet anemometry, zeta potentiometer	(Sestier et al., 1998: 1220-1226)
3	Surface Hydrophobicity	Water contact angle measurements, rose bangle (dye) binding, hydrophobic interaction chromatography, X-ray photoelectron spectroscopy	(Carr et al., 1991: 565-568; Scholes et al., 1999: 261)
4	Chemical analysis of Surface	Static secondary ion mass spectrometry	(Sarbak et al., 2004: 82-87)
5	Carrier drug Interaction	Differential scanning calorimetry	(Sarmento et al., 2006: 1-7)
6	Release profile	In-vitro release characteristic under Physiologic & sink condition	(Magenheim et al., 1993: 115-123; Kreuter, 1983: 196-207; Kreuter, 1991: 169-179)
7	Drug stability	Bioassay of drug extracted from Nanoparticles, chemical analysis of drug	(Santander-Ortega et al., 2006: 522-529)

emulsified in an aqueous phase (Trotta et al., 2003: 153-160). Evaporation of the organic solvent results in precipitation of the lipid in aqueous medium, to form a nanoparticle dispersion. Westesen et al (Westesen et al., 1993: 189-199) have prepared 30-100 nm SLN using this technique using various lecithin/co-surfactant blends.

5.5. Solvent Diffusion Method

The solvent diffusion method is a novel approach to prepare organic suspensions. It uses a partially water miscible solvent, which is extracted from an O/W emulsion by adding water. The process is based on the water miscibility of these solvents (Trotta et al., 2003: 153-160). Particles with different characteristics can be obtained by controlling the key formulation parameters. Trotta et al have prepared drug nanosuspensions from emulsions containing partially water miscible solvents with low toxicity, such as benzyl alcohol or butyl lactate, by a solvent diffusion technique.

6. Characterization of SLN

Various parameters for characterization of SLN involves particle size analysis, charge determination, surface hydrophobicity, chemical analysis of surface, carrier drug interaction, release profile, and drug stability. Various methods reported for the characterization of SLN are enlisted in Table IV.

6.1. Particle size analysis

Particle size distribution is one of the most important physical characteristic of a colloidal suspensions as of sedimentation tendencies of a nanoparticulate drug carriers during long term and accelerated stability studies can be determined by measuring the changes in the particle size distribution of the colloidal suspensions (Kreuter, 1983: 196-207).

6.1.1. Photon correlation spectroscopy

Photon correlation spectroscopy (PCS), also known as Dynamic light scattering (DLS) or Quasi –elastic light scattering (QELS), is routinely used for size analysis of particles in submicron range. PCS has been used for size analysis of lipid nanoparticles (Bargoni et al., 2001: 497-502; Cavalli et al., 2003: 1085-1094; Ugazio et al., 2002: 341-344; Cavalli et al., 2000: 305-309; Hong et al., 2006: 312-315; Jores et al., 2004: 217-227; Oyewumi and Mumper, 2002: 317-328; Scholer et al., 2001: 57-67). The PCS apparatus consist of a laser, a temperature controlled sample cell and a photomultiplier for detection of the light scattered at a certain angle. PCS is a non-invasive and non-destructive technique, that helps in avoiding artifacts associated with particle isolation, sample drying and sample loss (Phillies, 1990: 1049A-1057A). PCS measures the Brownian movement of the particles, and therefore the particle size determination can get influenced by the hydration layer from surrounding medium, temperature, type and concentration of electrolyte (Kreuter, 1983: 196-207).

6.1.2. Transmission electron microscopy

Electron microscopy provides valuable information on topography, morphology and crystallography. Transmission electron microscopy (TEM), can provide valuable information on particle size, shape, structure and the presence of different types of colloidal structures within the dispersion (Bunjes, 2005: 41-67). The TEM

functions on the same basic principles as the light microscopy but uses electrons instead of light (Williams et al., 1996). Analysis of nanoparticles using electron microscopy techniques requires sophisticated sample preparation techniques and expertise in image analysis, which can lead to artifacts (Bunjes, 2005: 41-67). SLN have routinely been imaged by employing heavy metal stains such as phosphotungstic acid (Liu et al., 2007: 191-195; Yang et al., 2007: 123-132; Zhang et al., 2006: 5821-5828; Hu et al., 2002: 121-128) or uranyl acetate (Sznitowska et al., 2001: 159-163). The nanoparticles are usually placed on a carbon mesh by passive adsorption or the sample is sprayed onto the grid and then dried prior to observation (Wong et al., 2004: 1993-2008).

6.1.3. Scanning Electron Microscopy

The first true scanning electron microscopy (SEM) was described and developed in 1942 by Zworykin, has been increasingly used to study the surface characteristics of the lipid nanoparticles (Dubes et al., 2003: 279-282; Iscan et al., 2006: 315-327). The sample is usually prepared by passive adsorption onto the surface of carbon stubs followed by air or infra-red aided drying of the dispersion medium (Vigneshwaran et al., 2006: 55-59; Liu et al., 2006: 304-308). The dried sample is then coated with gold and placed in the vacuum column of the SEM (Casadei et al., 2006: 140-146). The sample requirements for SEM analysis include the sample's ability to withstand vacuum environment and a conductive nature. Conductivity may be induced in a non-conductive specimen by coating it with a thin metal film (Partner et al., 1987: 51-90).

6.2. Entrapment efficieny (EE%)

Entrapment efficieny of drug is calculated with the help of equation 1 (Hou et al., 2003: 1781-1785)

$$EE\% = \frac{W_{\text{initial drug}} - W_{\text{free drug}}}{W_{\text{initial drug}}} \times 100\% \quad \text{Equation 1}$$

6.3. In-vitro Drug Release

Release mechanism, the diffusion coefficient, and the biodegradation rate are the main factors influencing the drug release (Cappel and Kreuter, 1991: 389-401). Release rate of drug from nanoparticles is strongly affected by the biological environment. The enzymatic interaction is one of the important factors that may modify in-vivo drug release (Amselem et al., 1993: 219-237). As a consequences, the in-vitro drug release may not have much in common with the in-vivo delivery and/or release (Amselem et al., 1993: 219-237; Hermina et al., 1986: 187-198). Nevertheless, the determination of in-vitro release of colloidal drug carrier is important for characterization purpose and quality control reasons,

The characterization of the in-vitro drug release from colloidal drug carrier is technically difficult to achieve due to the inability to effectively and rapidly separate nanoparticles from the dissolved or released drug in the surrounding solution (Magenheim and Benita, 1991: 221-241)

6.3.1. Separation Technique

This technique involves mainly the use of filtration or ultracentrifugation to separate the drug released from the nano-sized carrier (Seijo et al., 1990: 1-7; Brasseur et al., 1991: 129-135). The carrier is diluted in a media with sink conditions and this is sampled at given time intervals. The continuous phase of the sample is then separated from the carrier phase, usually by filtration or centrifugation. Released drug is then assayed. As the particle size decreases, the separation becomes more problematic and the release becomes faster (Seijo et al., 1990: 1-7).

6.3.2. Dialysis Bag Diffusion technique

A certain volume of colloidal drug carrier is placed in the dialysis bag, sealed and dropped into the media with sink conditions. Samples are withdrawn from the receptor compartment at predetermined time intervals and drug content is quantified by appropriate analytical methods (Malaiya and Vyas, 1988: 243-254; Levy and Benitas, 1990: 29-37). The dialysis bag technique has been criticized by Washington (Washington, 1989: 71-74), since the carrier suspension is never diluted, and the experiment cannot be practically performed under sink conditions even if such conditions are constantly maintained in the receptor compartment where sampling is performed. Therefore, the method does not measure the release rate but rather the partition of a drug between the various phases of a dispersed system. Other experimental factors affecting the appearance rate of drug in the sampling compartment include drug/excipient interaction, formation of micelles and osmotic effects which are usually difficult to keep constant (Ammoury et al., 1990: 763-767). This method is therefore considered to be unsuitable to evaluate the true release rate of a drug from a nanoparticulate drug carrier (Levy and Benitas, 1990: 29-37; Ammoury et al., 1990: 763-767).

6.4. Zeta potential determination

Zeta potential is a key factor to evaluate the stability of a colloidal dispersion (Komatsu et al., 1995: 1412-1415). As per reported literature, zeta potential of one of drug encapsulated in SLN suspension was measured by the electrophoretic mobility of the nanoparticles in a U-type tube at 20°C (Yang et al., 1999: 299-307). The zeta potential measurement was also carried out using Zeta potential analyser (Delsa 440SX; BECKMAN COULTER). In the aforementioned example, SLN dispersion was diluted 50 fold with the original dispersion preparation medium prior to the size determination and zeta potential measurement (Luo et al., 2006: 53-59).

7. Selection of Lipids and Surfactants

Lipid and surfactant plays an important role in SLN. The nature of lipid matrix has influence on biodegradation of SLN. Triglycerides with long chain fatty acid showed delayed degradation than short chain fatty acids (Manjunath and Venkateshwarlu, 2005: 215-228). Characterization of degree of lipid crystallization and lipid modification are helpful in understanding the drug incorporation and release pattern (Venkateshwarlu and Manjunath, 2004: 627-638). The lipid crystalline structure related to the chemical nature of the lipid is a key factor to determine the loading of drug. Drug expulsion is usually seen with lipids forming highly crystalline state with a perfect lattice . On the other hand imperfection (lattice defects) of the lipid structure could offer space for drug loading (Hou et al., 2003: 1781-1785).

Although the properties of the lipids are superimposed with colloidal properties, significant differences between monoacid triglycerides and complex lipid are found. Mixed triglycerides usually have lower degree of crystalline order. Complex glyceride mixture such as hard fat may however posses a higher drug loading capacity in the crystalline state due to their lower crystallinity as compared to pure monoacid triglycerides (Westesen et al., 1997: 223-236). Factors such as rate of lipid crystallization, lipid hydrophobicity, and the self assembling properties of the lipid affecting the shape of the lipid crystals (and hence the surface area) were found to influence the final size of the SLN dispersion (Vivek et al., 2007: E1-E9).

Average particle size usually increases with increasing lipid melting temperature for both high pressure homogenization and high shear homogenization techniques (Ahlin, 1998: 257-267; Siekmann and Westesen, 1992: 123-126). Mehnert and Mader suggested this behavior is due to increased viscosity of dispersed phase (Mehnert and Mader, 2001: 165-196). When the lipid content exceeds 10% of the emulsion/dispersion, larger particles and increased polydispersity indices are observed.

Surfactant properties and concentration greatly affect the quality and efficacy of lipid nanoparticles. Few correlations are reported between surfactant composition and solid lipid nanoparticle dispersions. Optimum surfactant concentration must be determined on a case by case situation. Siekmann et al determined that 10% w/w tyloxapol stabilized 85 nm tripalmitin nanoparticles while a lower concentration of 2% w/w tyloxapol failed to stabilize the suspension (Siekmann and Westesen, 1994: 194-197). Nanoparticles quality is also affected by homogenization parameters which may vary according to choice of surfactant. An example of the beneficial role of co-surfactants is the case of SLN stabilized by surfactant mixtures, such as lecithin/poloxamer 188 and lecithin/tyloxapol, which resulted in more stable, smaller particle sizes than formulation of the same lipid and a single surfactant. When using lecithin as the surfactant with taurodeoxycholate and mono-octylphosphate as co-surfactants, Cavalli et al produced stearic acid nanoparticles having 70 ± 2 nm diameter (Cavalli, 1998: 392-396). Surfactant mixtures often reduce interfacial tension more than single surfactant formulations on a mole per mole basis, especially in cases where co-surfactant head group is significantly smaller than the surfactant head group. The phenomenon is largely due to an increased surfactant concentration at the interface, resulting from the minimization of repulsion force of closely packed, like surfactant molecules (Porter, 1994). The types of lipid and surfactant also affect the pharmacological performance of the SLN. It was reported that drug loaded nanoparticles coated by polysorbate were able to cross Blood Brain Barrier (BBB) after iv administration. These coated particles behaved as LDL particles and could interact with LDL receptors (Manjunath and Venkateshwarlu, 2005: 215-228).

8. Solid Lipid Nanoparticle Stability

Lipid nanoparticle stability must be considered from two perspectives, the particle size distribution and the lipid crystalline state (Porter, 1994). The lipid crystalline state strongly correlates with drug loading, release rates, and the particle geometry, i.e. spherical versus prolate (Mehnert and Mader, 2001: 165-196).

Particles size is one of the main factors influencing the biodistribution and reticuloendothelial system (RES) clearance mechanisms (Porter, 1994). The degree of polydispersity affects the particle size growth via Ostwald ripening and can impact the overall drug release kinetics (Mehnert and Mader, 2001: 165-196).

Phase separation processes include creaming, Ostwald ripening, flocculation, and coalescence. By definition, creaming does not change the particle size and therefore is of little concern in SLN systems. Coalescence is the fusion of individual droplets to form larger droplets. Ostwald ripening is due to lipophilic molecules in smaller particles diffusing to large particles, if the lipophilic molecule has some degree of aqueous solubility. Ostwald ripening occurs because smaller particles have high energy states than do larger particles because of a higher degree of curvature than do larger particles, thus exposing more interfacial molecules to the continuous phase. This results in a lower net attractive force within the bulk lipid phase of smaller particles, hence leading to diffusion of molecules to large lipid droplets (Siekmann and Westesen, 1994: 194-197; Porter, 1994). Ostwald ripening cannot be prevented, but it can be slowed by reducing the polydispersity. Flocculation and coalescence are of concern for SLN (Porter, 1994). The potential at the surface of shear is known as the Zeta Potential, ξ, and is measured in millivolts (mV). Zeta potential is a function of the charge of the particle, any adsorbed layer at the interface, and the nature and composition of the surrounding environment (Triplett, 2004). The magnitude of zeta potential

has been correlated to the stability of particle and emulsion droplets. As Zeta Potential increases, electrostatic repulsion between two particles increases and on exceeding the attractive forces due to van der Waal's interactions, the colloidal system will become stable. If not, flocculation followed by coalescence will lead to phase separation. Zeta Potential values more electronegative than -30 mV generally represent sufficient electrostatic repulsion for stability, and stability is assured in most instances at zeta potentials between -30 to + 45 mV. Steric stabilization prevents two particles from approaching to the short distances needed for flocculation and coalescence. Nonionic surfactants operate by steric stabilization, and ethylene oxide/propylene oxide copolymers are routinely employed for steric stabilization capabilities (Porter, 1994). However, caution needs to be exercised as they are effected by temperature (Triplett, 2004).

Often, the best stabilization strategy is to use both electrostatic and steric approaches. This strategy has been widely used in liposomes science (Gregoriadis, 1998: ; Srinath and Diwan, 1994: 176-184). Several researchers have successfully applied this approach to SLN, also (Cavalli et al., 2000: 305-309; Bocca et al., 1998: 176-184; Fundaro et al., 2000: 337-343). Lipid crystallinity is another factor affecting lipid nanoparticle stability, lipid nanoparticle drug incorporation and release characteristics (Muller et al., 2000: 161-177). Despite the stability challenges, optimized SLN dispersion can be stable for more than one year (Westesen et al., 1997: 223-236; Westesen, 2000: 0608-0618). To avoid instability issues in aqueous dispersion, researchers have utilized spray drying and lyophillization techniques with successful reconstitution to attain long term stability (Freitas and Muller, 1998: 145-151; Zimmermann et al., 2000: 211-213; Heiati et al., 1998: 173-184; Lim and Kim, 2002: 135-146).

Sterilization is critically important to SLN efficacy. Autoclaving of SLN is investigated by Schwarz et al (Schwarz et al., 1994: 83-96). Solid lipid nanoparticle stability is a function of formulation and processing parameters, providing several options to researchers and developers.

9. In-Vivo Performance of Solid Lipid Nanoparticle systems

Lipid nanoparticles can be safely administered intravenously because of their nanoscale size. To increase circulation time, reticuloendothelial system avoidance ("stealth") can be accomplished by incorporating polyoxyethylene(Bargoni et al., 2001: 497-502; Fundaro et al., 2000: 337-343). Lipid nanoparticle drug formulations have been shown to produce improved pharmacokinetic profiles as compared to traditional drug formulations (Fundaro et al., 2000: 337-343). Drug targeting can be achieved by ligand mediated attachment, exploiting physiological conditions like the cancer's leaky vasculature, and using the immune system's affinity for hydrophobic colloidal particles.

9.1. SLN permeation across blood brain barrier

Blood Brain Barrier (BBB) penetration is most difficult and one of the critical challenges facing pharmaceutical therapeutics and imaging today.

In the late '90s SLN technology was proposed for brain drug targeting applications independently by two research groups (Yang et al., 1999: 299-307; Zara et al., 1999: 281-286) even though the first proof of lipid particle transport across the BBB had already been reported in the literature (Minagawa et al., 1996: 1016-1022). Two anticancer agents, namely camptothecin and doxorubicin, when loaded into SLN, resulted in drug accumulation into the brain after both oral and iv administration (Yang et al., 1999: 751-757; Zara et al., 1999: 281-286). Poloxamer 188 stabilized stearic acid camptothecin-loaded SLN were use for brain targeting per oral and iv administration in mice (Yang et al., 1999: 751-757). Two new SLN formulations made with biocompatible materials, such as emulsifying wax and Brij® 72, and stabilized by P80 and Brij® 78 were proposed for brain drug targeting (Koziara et al., 2004: 259-269; Koziara et al., 2003: 1772-1778; Lockman et al., 2003: 705-713). These particles showed a significant brain uptake, during a short term in situ rat brain perfusion experiment (Koziara et al., 2003: 1772-1778). Clozapine loaded tripalmitin SLN, with (+ 23.2 ± 0.9 mV;163 nm) and without stearylamine (+ 0.2 ± 0.1 mV; 233 nm), were able to significantly increase drug brain concentration in mice after iv administration when compared to clozapine suspension (Manjunath and Venkateshwarlu, 2005: 215-228). Biodistribution studies showed that idarubicin-loaded SLN were able to cross the BBB after duodenal administration (Zara et al., 2002: 1324-1333). Lipid nanoparticles accumulation in brain is suspected to be blood protein mediated. Adsorption of blood proteins such as apolipoproteins on lipid nanoparticle surface may lead to interaction with endothelial cells that facilitate crossing the BBB (Wissing et al., 2004: 1257-1272).

10. CONCLUSION

SLNs have been realized as extremely useful carrier systems in various scientific domains. Solid lipid nanoparticle drug delivery technology provides the good opportunity for improving medical therapeutics. Polymeric nanoparticle systems have some of the problems, but these problems have been overcome with the help of SLN. SLNs are also improving the formulators control over particle size, size distribution and drug loading profile through processing and material formulation variables. SLNs are good carrier systems for the targeted drug delivery. This technology would permit the delivery of the therapeutic molecules to the target site, maximizing the amount delivered and reducing the possible toxic effects from the carrier matrix. SLN will enhance the drug discovery process,

through miniaturization, automation, speed and reliability of assays. It will also allow greater selection of the right drug for the right part and enables the tests to support this decision process to be done for effective clinical control of disease conditions.

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