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REVIEW ARTICLE

Solid Lipid Nanoparticles: A Strategy to Improve Oral Delivery of the Biopharmaceutics classification system (BCS) Class II Drugs

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ABSTRACT

In drug discovery, approximately 70% of new drug candidates have shown poor aqueous solubility in recent years. Currently, approximately 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble (<100 g/mL). The aqueous solubility of a drug is a critical determinant of its dissolution rate. The Biopharmaceutics Classification System (BCS) is a useful tool for decision-making in formulation development from a biopharmaceutical point of view. BCS Class II drugs are identified as low solubility and high permeability. In general, the bioavailability of a BCS Class II drug is rate limited by its dissolution so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability. Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS Class II drugs. Solid lipid nanoparticles (SLNs) were developed in the mid-1980s as an alternative system to the existing traditional carriers (emulsions, liposomes, microparticles, and their polymeric counterparts) when Speiser prepared the first micro- and nano-particles (named nano pellets) made up of solid lipids for oral administration. SLNs are colloidal carriers made up of lipids that remain solid at room temperature and body temperature and also offer unique properties such as small size (50–500 nm), large surface area, high drug loading, and the interaction of phases at the interfaces and are attractive for their potential to improve performance of pharmaceuticals, nutraceuticals, and other materials. Moreover, SLN are less toxic than other nanoparticulate systems due to their biodegradable and biocompatible nature. SLN is capable of encapsulating hydrophobic and hydrophilic drugs, and they also provide protection against chemical, photochemical, or oxidative degradation of drugs, as well as the possibility of a sustained release of the incorporated drugs.

Keywords: Bioavailability, biopharmaceutics classification system class II drugs, solid lipid nanoparticles

INTRODUCTION

In drug discovery, the number of drug candidates defined as having low solubility has increased, and approximately 70% of new drug candidates have shown poor aqueous solubility in recent years.[1] Currently, approximately 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble (<100 g/mL).[2] There are many problems arising from the poor solubility of drug candidates in drug research and development. The aqueous solubility of a drug is a critical determinant of its dissolution rate. The limited dissolution rate arising from low solubility frequently results in the low bioavailability of orally administered drugs, and compounds with aqueous solubility lower than 100 µg/mL generally present dissolution-limited absorption.[3] The solubility and permeability of drugs can be categorized by the Biopharmaceutics Classification System.

BCS

BCS is a useful tool for decision-making in formulation development from a biopharmaceutical point of view.[4]

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The BCS categorizes drug substances into one of the four categories based on their solubility and intestinal permeability, and these four categories are defined as follows: High solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III), and low solubility/low permeability (Class IV).

For BCS Class I or III drugs, formulations are designed with a simple strategy. However, for BCS Class II or IV drugs, deliberate formulation designs based on both the physicochemical and biopharmaceutical properties of the drugs are required to obtain sufficient and reproducible bioavailability after oral administration. The viable formulation options based on the BCS are summarized in Figure 1.

FORMULATIONS FOR BCS CLASS II DRUGS

The molecular characteristics of BCS Class II drugs are identified as low solubility and high permeability. For instance, cyclosporine, griseofulvin, and itraconazole are categorized into this class.[5] In general, the bioavailability of a BCS Class II drug is rate limited by its dissolution so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability.[6] Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS Class II drugs.

Several physicochemical factors control the dissolution rate of the drugs. According to the modification of the Noyes–Whitney equation, the factors affecting the drug dissolution rate are defined as the effective surface area, diffusion coefficient, diffusion layer thickness, saturation solubility, amount of dissolved drug, and volume of dissolution media.[3] Increases in the saturation solubility and the effective surface area have a positive impact on the dissolution rate of the drugs, and these factors could be increased by efforts of pre-formulation study and formulation design.

Various approaches to overcome the poor aqueous solubility of drug candidates have been investigated in drug research and development. Changing the chemical structure in the lead optimization phase is considered to be an option to increase the solubility of drug candidates. Prodrug approaches might also enhance the aqueous solubility of drug candidates by introducing a polar functional group into the structure of a molecule.[7]

In recent years, it has become more and more evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. Exciting experimental data obtained *in vitro* are very often followed by disappointing results *in vivo*. Main reasons for the therapy failure include insufficient drug concentration due to poor absorption, rapid metabolism and elimination (e.g., peptides and proteins), drug distribution to other tissues combined with high drug toxicity (e.g., cancer drugs), poor drug solubility which excludes i.v. injection of aqueous drug solution, and high fluctuation of plasma levels due to unpredictable bioavailability after peroral administration, including the influence of food on plasma levels (e.g., cyclosporine).[8] A

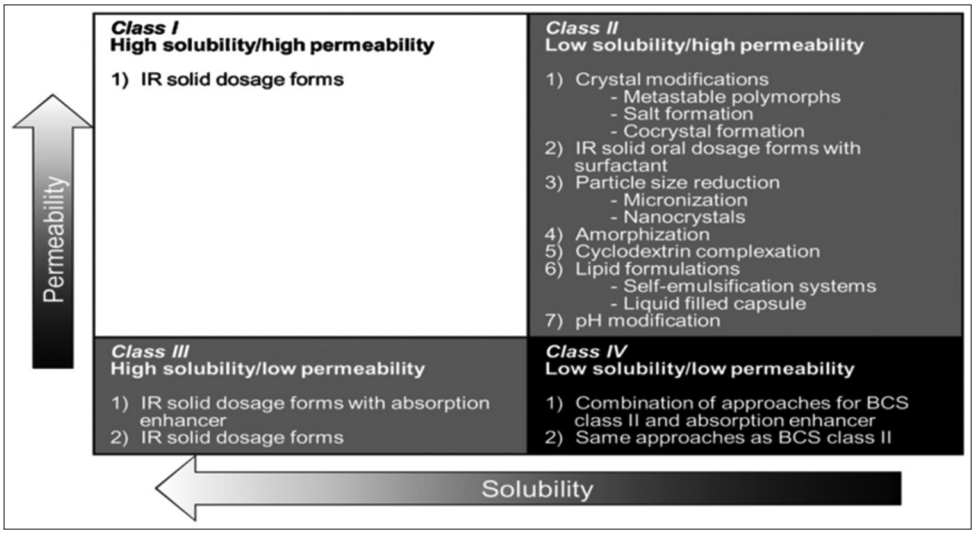

Figure 1: The Biopharmaceutics Classification System and viable formulation options

promising strategy to overcome these problems involves the development of suitable drug carrier systems. The *in vivo* fate of the drug is no longer mainly determined by the properties of the drug but by the carrier system, which should permit a controlled and localized release of the active drug according to the specific needs of the therapy.[9] The size of the carrier depends on the desired route of administration and ranges from few nanometers (colloidal carriers) to the micrometer range (microparticles) and to several millimeters (implants). Implants and microparticles are too large for drug targeting and intravenous administration. Therefore, colloidal carriers have attracted increasing attention during recent years [10,11] Investigated systems include nanoparticles, nanoemulsions, liposomes, nanosuspensions, micelles, and soluble polymer–drug conjugates. Polymers from natural[11,12] and synthetic sources[13] have been used. Polymer-based systems in the submicron size range include water-soluble polymer-drug conjugates,[14] polymer nanocapsules, and nanospheres.[15] Problems of polymer-based nanoparticles derive from residues from organic solvents used in the production process, polymer cytotoxicity, and the scaling up of the production processes.[16]

Liposomes are spherical vesicles composed of one or more phospholipid bilayers (in most cases phosphatidylcholine). Lipophilic drugs can be incorporated into the lipid bilayers while hydrophilic drugs are solubilized in the inner aqueous core.[17] Drug release, *in vivo* stability, and biodistribution are determined by size, surface charge, surface hydrophobicity, and membrane fluidity.[18] Nanosuspensions are colloidal particles which are composed of the drug and the emulsifier only. Possible production procedures include ball milling or high-pressure homogenization (HPH).[19] Lipid nanoemulsions were introduced during the 50s for the purpose of parenteral nutrition. Fatty vegetable oils (e.g., soy oil) or middle chain triglycerides are used for the lipid phase, which amounts to typically 10–20% of the emulsion. Further ingredients include phospholipids (stabilizers, 0.6–1.5%) and glycerol (osmolarity regulation, 2.25%). During recent years, it has been recognized that these systems might also be used as drug carriers for lipophilic drugs and several formulations are commercialized. The possibility of controlled drug release from nanoemulsions is limited due to the small size and the liquid state of the carrier.[20]

The use of solid lipids instead of liquid oils is a very attractive idea to achieve controlled drug release, because drug mobility in a solid lipid should be considerably lower compared with a liquid oil. Nanopellets developed by Speiser[21] were produced by dispersing of melted lipids with high-speed mixers or ultrasound. The products obtained by this procedure often contain relatively high amounts of microparticles. This might not be a serious problem for peroral administration, but it excludes an intravenous injection. Higher concentrations of the emulsifier not only result in a reduction of the particle size but also increase the risk of toxic side effects. In the following years, it has been demonstrated that HPH is a more effective method for the production of submicron-sized dispersions of solid lipids compared to high shear mixing or ultrasound.[22] Most solid lipid nanoparticle (SLN) dispersions produced by HPH are characterized by an average particle size below 500 nm and a low microparticle content. Other production procedures are based on the use of organic solvents (HPH solvent evaporation) or on dilution of microemulsions.[23]

SLN

SLNs [Figure 2] were developed in the mid-1980s as an alternative system to the existing traditional carriers (emulsions, liposomes, microparticles, and their polymeric counterparts) when Speiser prepared the first micro- and nano-particles (named nanopellets) made up of solid lipids for oral administration.[24] SLNs avoid some of their major disadvantages such as cytotoxicity of polymers and the lack of a suitable large-scale production method for polymeric nanoparticles.[16] SLNs are colloidal carriers made up of lipids that remain

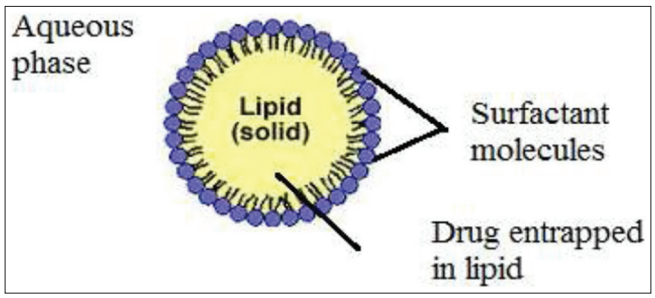

Figure 2: Schematic representation of solid lipid nanoparticle dispersion stabilized with surfactant molecules showing entrapment of drug

solid at room temperature and body temperature and also offer unique properties such as small size (50–500 nm), large surface area, high drug loading, and the interaction of phases at the interfaces and are attractive for their potential to improve performance of pharmaceuticals, nutraceuticals, and other materials.[23] Moreover, SLN is less toxic than other nanoparticulate systems due to their biodegradable and biocompatible nature. SLN is capable of encapsulating hydrophobic and hydrophilic drugs, and they also provide protection against chemical, photochemical, or oxidative degradation of drugs, as well as the possibility of a sustained release of the incorporated drugs.[25]

SLN is colloidal particles composed of biocompatible/biodegradable lipid matrix that is solid at body temperature and exhibits size in a range of 100–400 nm. SLN offers several advantages such as controlled drug release, targeted delivery, increased drug stability, high drug payload, least biotoxicity, large-scale production, and ease of sterilization. General ingredients used in the preparation of SLN are solid lipid(s), emulsifier(s), and water. The term -lipid has a broader sense here and includes triglycerides (e.g., tristearin), fatty acids (e.g., stearic acid), partial glycerides (e.g., Imwitor), steroids (e.g., cholesterol), and waxes (e.g., cetyl palmitate).[26]

A newer version of SLN called nanostructured lipid carriers (NLC), with increased drug loading, is also becoming popular recently for brain targeting which is composed of a solid lipid and a certain amount of liquid lipid (oil), maintaining the solid state at both room and body temperatures.[27]

Some other properties of lipid nanoparticles are the drug pseudo-zero order kinetics, the prolonged/sustained/controlled release obtained *in vitro* for drugs incorporated in SLN (depending on the surface properties), their rapid uptake (internalization) by cell lines (5–10 min), and also the possibility of preparation of stealth SLN using PEG molecules so as to avoid the reticuloendothelial system.[24]

Moreover, the possibility of loading drugs with differing physicochemical and pharmacological properties, no requirement of specialized instruments/apparatuses, and preparation without the use of organic solvents (in some methods like self- emulsification and HPH) make SLNs a highly versatile delivery system. Altering surface characteristics by coating SLN with hydrophilic molecules improves plasma stability and biodistribution, and subsequent bioavailability of drugs entrapped.[28]

Advantages of SLNs[25,29]

1. Controlled and targeted drug release.
2. Possible high drug loading.
3. Feasibility of carrying both hydrophilic and lipophilic drugs.
4. Water-based formulation avoids organic solvents.
5. Physiological lipids decrease the prevalence of acute or chronic toxicity; no reported biotoxicity of the carrier system.
6. Improved drug stability.
7. Most lipids being biodegradable, SLNs have excellent biocompatibility.
8. Less expensive than polymeric or surfactant-based carriers.
9. Easy to scale up and sterilize.
10. Easy to validate.
11. Easy to gain regulatory approval.

Disadvantages of SLNs

1. Poor drug loading capacity of drugs having limited solubility in lipid melt.
2. Relatively very high water content of dispersions (70–99.9%).
3. Drug expulsion after polymeric transition during storage.

The drug loading capacity of conventional SLNs is depended on the following factors:

- Solubility of the drug in lipid melts
- Structure of the lipid matrix
- Polymorphic state of the lipid matrix.

Advanced forms of SLN

NLCs

NLCs, introduced at the turn of the millennium, represent a new and improved generation of SLNs and are made of a solid lipid matrix entrapping liquid-lipid nano-compartments, the blend being solid at body temperature. This new generation of lipid carriers (NLCs) was introduced to overcome the problems associated with SLNs, such as limited drug loading capacity, drug expulsion during storage and adjustment of drug release, and long-term physical stability of the suspension.

Production procedures are identical for both lipid particles, SLNs and NLCs.[30]

Lipid drug conjugates

Lower drug loading capacity of hydrophilic actives was a major issue in SLNs due to partitioning effects during the production process. Highly potent low-dose drugs can be suitably incorporated only in the solid lipid matrix.[31]

Polymer lipid hybrid nanoparticles (PLNs)

PLNs hold great promise as a drug delivery vehicle in the treatment of a myriad of diseases such as breast cancer. A PLN comprises three distinct functional components:

- Hydrophobic polymeric core to encapsulate poorly water-soluble drugs.
- Hydrophilic polymeric shell to enhance PLN stability and circulation half-life.
- Lipid monolayer at the core and shell interface to promote drug retention inside the polymeric core.[32]

General excipients used for SLN production[32,26]

The general ingredients used for the preparation of SLNs are solid lipid(s) with relatively low melting points (solid at room and body temperature), emulsifier(s), and water. An overview of excipients, which are commonly used for SLNs, is listed here with few examples.

- Lipids (Triacylglycerols): Tricaprin, Trilaurin, Trimyristin, Tripalmitin, Tristearin, etc..
- Hard fats: Witepsol™ (W/H 35, H42, E85)
- Acylglycerols: Glyceryl behenate (Gelucire 50/02, 50/13, 44/14), Glycerol monostearate (Imwitor 900™), Glyceryl behenate tribehenate (Compritol 888 ATO™), Glycerol Palmitostearate (Precirol ATO 5™), Cutina CBS, Glyceryl tripalmitate (Dynasan® 116), Glyceryl trimyristin (Dynasan® 114), Cetyl palmitate, Glyceryl tristearin (Dynasan 118), etc.
- Fatty acids: Stearic acid, palmitic acid, decanoic acid, behenic acid, etc.
- Waxes: Cetyl palmitate
- Others: Hydrogenated coco-glycerides, Softisan 154.

Surfactant/Co-emulsifier • phospholipids: Soybean lecithin, egg lecithin, phosphatidylcholine

- Ethylene/propylene oxide copolymer: Polaxomer 188, 182, 407, 908
- Sorbitan ethylene/propylene oxide copolymer: Polysorbate 20, 60, 80
- Alkylaryl polyether alcohol polymer: Tyloxapol
- Bile salts: Sodium cholate, glycocholate, taurocholate, taurodeoxycholate
- Alcohols/acids: Butanol, butyric acid, ethanol, poly vinyl alcohol
- Others: Hydroxypropyl distarch, tegocare, epikuron 200, etc.

Production methods for SLNs (HPH technique)

Hot homogenization technique

In this technique, lipids are forced through a narrow gap (few micron ranges) with high pressure (100–200 bars). Disruption of particles into submicron range occurs due to the shear stress and cavitation (due to a sudden decrease in pressure) force. There are two approaches - hot and cold homogenization techniques**.** For both the techniques, a common preparatory step involves the drug incorporation into the bulk lipid by dissolving/dispersing/solubilizing the drug in the lipid being melted at approximately 5–10°C above the melting point.[27]

The melted lipid-containing drug is dispersed in the aqueous surfactant solution of identical temperature under continuous stirring by high shear device. This pre-emulsion is homogenized using a piston-gap homogenizer and the produced hot oil-in-water nanoemulsion is cooled down to room temperature. The lipid recrystallizes and leads to the formation of SLNs.[33-38]

Advantages

- Preparation without the use of organic solvent
- Feasibility of large-scale production
- High-temperature results in lower particle size due to the decreased viscosity of the inner phase
- Suitable for drugs showing some temperature sensitivity because the exposure to an increased temperature is relatively short.

Disadvantages

- Poor technique for hydrophilic drugs
- Drug and carrier degradation is more at high temperature

- Due to small particle size and presence of emulsifier, lipid crystallization may be highly retarded and the sample remains as super-cooled melt for several months
- Burst release of drugs from SLNs because during heating the drug partitions into aqueous phase and when cooled, most of drug particles remained at the outer layer of the SLNs
- Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result of the high kinetic energy of the particles.

Cold homogenization technique

In comparison to above, the cold homogenization technique is carried out with the solid lipid and represents, therefore, a high-pressure milling of a suspension. The drug-containing lipid melt is cooled, the solid lipid ground to lipid microparticles (approximately 50–100 mm), and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then, this pre-suspension is homogenized at or below room temperature; the cavitation forces are strong enough to break the lipid microparticles directly to SLNs.[39,40]

Advantages

- Avoids temperature-induced drug degradation and complexity of the crystallization step
- Minimizes the melting of lipid and therefore minimizes the loss of hydrophilic drug to aqueous phase
- Water from aqueous phase can be replaced with other media (e.g., oil or PEG 600) with low solubility for the drug
- Suitable for highly temperature-sensitive compounds.

Disadvantages

- In comparison to hot homogenization, particle size and polydispersity index are more
- Minimizes the thermal exposure of drug but does not avoid it completely
- HPH increases the temperature of the sample (10–20°C for each cycle.

SOLVENT EMULSIFICATION-EVAPORATION TECHNIQUE

The solvent emulsification-evaporation technique is a widespread procedure, being first used for SLN preparation (precipitation in o/w emulsion) by Sjöström and Bergenståhl.[41] Lipid and drug are dissolved in a water-immiscible organic solvent by ultrasound and emulsified in an aqueous phase containing surfactant/emulsifier using magnetic stirrer (1000 rpm). The organic solvent was evaporated by mechanical stirring at room temperature and reduced pressure (e.g., rotary evaporator) leaving lipid precipitates of SLNs.[42-44]

Advantages

- Very small particle size
- Suitable for the incorporation of highly thermolabile drugs
- Avoids temperature-induced drug degradation.

Disadvantages

- Toxicity of solvent in the final product
- Extra step of filtration and evaporation.

Double emulsion technique

This method is based on the solvent emulsification-evaporation technique in which the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. Primary emulsion was formed by dissolving the hydrophilic drug in aqueous solution, followed by emulsification in melted lipid-containing surfactant/stabilizer. The primary emulsion then dispersed in aqueous phase containing hydrophilic emulsifier forming the double emulsion.[45]

Solvent injection/solvent displacement technique

It is a novel approach based on lipid precipitation from the dissolved lipid in solution. The solid lipid was dissolved in water-miscible solvent forming the organic phase. This organic phase was rapidly injected through an injection needle

into an aqueous phase (with or without surfactant) with continuous stirring. The resulted dispersion was then filtered with a filter paper to remove any excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent.[46,47]

Advantages

- Use of pharmacologically acceptable organic solvent
- Easy handling
- Fast production process
- No use of technically sophisticated equipment
- Suitable for thermolabile drugs
- Small and uniform particle size distribution
- Avoidance of any thermal stress
- Avoids temperature-induced drug degradation.

Disadvantages

- Extra step of filtration
- Toxicity of solvent in final product.

Influence of ingredient composition on product quality

Influence of the lipid

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids.[48] However, other critical parameters for nanoparticle formation will be different for different lipids. Examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties,[49] and the shape of the lipid crystals (and therefore the surface area). It is also noteworthy that most of the lipids used represent a mixture of several chemical compounds. The composition might, therefore, vary from different suppliers and might even vary for different batches from the same supplier. However, small differences in the lipid composition (e.g., impurities) might have a considerable impact on the quality of SLN dispersion (e.g., by changing the zeta potential and retarding crystallization processes). For example, lipid nanodispersions made with cetyl palmitate from different suppliers had different particle sizes and storage stabilities.

Influence of the emulsifier

The choice of the emulsifiers and their concentration is of great impact on the quality of the SLN dispersion.[29] High concentrations of the emulsifier reduce the surface tension and facilitate the particle partition during homogenization. The decrease in particle size is connected with a tremendous increase in surface area. The increase of the surface area during HPH occurs very rapidly. Therefore, kinetic aspects have to be considered. The process of a primary coverage of the new surfaces competes with the agglomeration of uncovered lipid surfaces. The primary dispersion must contain excessive emulsifier molecules, which should rapidly cover the new surfaces.

Different emulsifier compositions might require different homogenization parameters. For example, the maximal degree of dispersing was obtained with 500 bar and three cycles for poloxamer 188 stabilized systems.[50] Homogenization with pressures of 1000 or 1500 bar did not result in further reduction of the particle size. In contrast, pressures 1500 bar proved to be the best for lecithin (lipoid 75)-stabilized systems. A possible explanation for observation is the different velocity of the coverage of the new lipid surfaces. The particle size of the SLN dispersion produced with the ionic surfactants was considerably smaller compared to the non-ionic formulation.

Secondary production steps

Lyophilization

Lyophilization or freeze-drying is one of the most significant secondary production steps in nanoparticles preparation, which enhances the physical and chemical stability of the formulation obtained.[51] Lyophilization aids to increase the long-term stability for a nanoparticle preparation with hydrolyzable drugs. When the nanoparticulate systems are lyophilized into solid preparation, it prevents Ostwald ripening as well as hydrolytic degradation, thereby increasing the stability. After lyophilization, NP can be more easily incorporated into different dosage forms such as tablets, capsules, parental dispersions, and pellets. In lyophilization, the NP dispersion is freezed which is then subjected to evaporation under vacuum. Cryoprotectants such as sorbitol, mannitol, glucose, and trehalose are added to

the dispersion to prevent or minimize particle aggregation and to redisperse the lyophilizates in a more efficient way.

Spray drying

Spray drying is a less frequently used method for transforming aqueous NP dispersion into a dry product. Spray dryers make use of hot gases and atomizers/nozzles to disperse effectively the NP dispersion and, therefore, sometimes result in aggregation and partial melting of NP. In case of solid lipid NP, melting can be minimized by incorporating ethanol in dispersion medium.[52]

Sterilization

Sterilization is another secondary production step which is highly desirable for NP meant for parenteral administration. Aseptic production of NP, filtration, gamma irradiation, and heating are the general methods used for sterilizing nanoparticulate systems.[53] In the case of heat-resistant drugs and nanoparticle material, autoclaving is a good method of choice. It was also found that sterilizing of nanoparticulate systems by this method could slightly increase the particle size. Sterilization by filtration requires high pressure and should not cause any change in the nanoparticulate system with respect to stability and drug release characteristics. In the case of gamma irradiation, free radicals are obtained and may undergo secondary reactions leading to chemical modifications. High molecular mobility and presence of oxygen enhance degradation reactions induced by gamma radiations.[54]

PROBLEMS ASSOCIATED WITH PREPARATION METHODS

High pressure-induced drug degradation

This problem is associated with the HPH technique. The molecular weight of polymers and the molecular structure are responsible for the drug degradation. Formation of free radical is responsible for the decrease in the molecular weight of the polymers due to shear stress. Almeida *et al*. (1997) reported that HPH -induced drug degradation will not be a serious problem for the majority of the drugs.[55]

Lipid modifications/polymorphism

The crystallized lipid may be present in several modifications of the crystal lattice. Lipid molecules have a higher mobility in thermodynamically unstable configurations with lower density and, ultimately, a higher capability to incorporate guest molecules (e.g., drugs). During storage, rearrangement of the crystal lattice might occur in favor of thermodynamically stable configurations, and this is often connected with the expulsion of the drug molecules (Muller *et al.*, 2000). Thermodynamic stability and lipid packing density increase with crystal order (supercooled melt <α-modification <β'- modification <β-modification), on the contrary to the crystallization kinetics.[56]

Particle shape

The shape of lipid nanoparticles (platelet form) may significantly differ from a nanoemulsion (sphere). Lipid nanoparticles have tendency to crystallize in the platelet form; which are having larger surface areas as compared to spheres and require higher amounts of surfactants for stabilization. As a result, much higher amount of drug will be localized directly on the surface of SLNs, which is in divergence with the general aim of the SLN systems (drug protection and controlled release due to the incorporation of the drug in the solid lipid).[48,57]

Characterization of SLNs

An adequate characterization of the SLNs is necessary for the control of the quality of the product. Several parameters have to be considered which have a direct impact on the stability and release kinetics.

Entrapment efficiency and drug loading

Entrapment efficiency describes the efficiency of the preparation method to incorporate drug into the carrier system. A very important point to judge the suitability of a drug carrier system is its loading capacity. The loading capacity is generally expressed in percentage related to the lipid phase (matrix lipid: Drug). In addition, the amount of drug entrapped also determines the performance

of the drug delivery system since it influences the rate and extent of drug release from the system. Both drug loading and entrapment efficiency depend on the physicochemical properties and the interactions between the drug, carrier matrix, and the surrounding medium.[30,58]

$$EE\ (\%) = Ws/WTotal \times 100\ DL\ (\%) = Ws/WLipid \times 100$$

Where, Ws - amount of drug loaded in the SLNs; Wtotal - total drug amount in AD-SLNs dispersion; Wlipid - weight of the vehicle.

Particle size and distribution

A particle size and distribution analysis is a measurement designed to determine and report information about the size and range of a set of particles representative of a material. Particle size and distribution analysis of a sample can be performed using a variety of techniques such as photon correlation spectroscopy, laser diffraction, and aerodynamic technique.

Surface charge

The surface charge of a dispersed system is best described by measuring the zeta *(ζ)* potential of the system. This parameter is a useful predictor of the storage stability of colloidal dispersions. A minimum ζ potential of ± 30 mV is considered the benchmark to obtain a physically stable system. Particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. Zeta potential helps in designing particles with reduced reticuloendothelial uptake. To divert SLNs away from the RES, the surface of the particles should be hydrophilic and free from charge.[59]

Particle morphology and ultrastructure

Particle size results are often validated by transmission electron microscopy, which provides direct information on SLN morphology and ultrastructure. In this, an electron beam is focused and directed through a sample by several magnetic lenses, with part of the beam adsorbed or scattered by the sample, while the remaining is transmitted. The transmitted electron beam is magnified and then projected onto a screen to generate an image of the specimen. The fraction of electrons transmitted depends on sample density and thickness (typically <100 nm).[60-62]

SEM uses a focused electron beam to generate a variety of signals (i.e., backscattered or secondary electrons) at the surface of solid specimens. The signals derived from electron-sample interactions reveal information about the sample including morphology, chemical composition, and potentially crystalline structure.[63,64]

In vitro assessment of drug release

In vitro release studies are generally performed to accomplish the objectives such as:

- Indirect measurement of drug availability, especially in preliminary stages of product development.
- Quality control to support batch release and to comply with specifications of batches proven to be clinically and biologically effective.
- Assess formulation factors and manufacturing methods that are likely to influence bioavailability.
- Substantiation of label claim of the product.
- As a compendial requirement.[65]

In vitro release study tells about basic information regarding the structure (e.g., porosity) and behavior of the formulation at molecular level, possible drug-excipient interactions, and about the factors influencing the rate and mechanism of drug release.[66] Such information facilitates a scientific and predictive approach to the design and development of sustained delivery systems with desirable properties. Various methods have been reported to study the *in vitro* drug release, and the most common technique is membrane diffusion techniques.

CONCLUSIONS AND FUTURE OUTLOOK

Low water solubility is widely recognized as the main reason for the poor oral absorption of many drugs. Several types of approaches have been proposed to improve the aqueous solubility of poorly water-soluble drugs. In particular, for BCS Class II drugs, increasing their solubility and/or dissolution rate would be a promising approach to enhance the oral bioavailability. Conventional solubilization approaches which include the use of surfactants, complexes, salt formations,

nanoparticles, solid dispersions, lipids, and permeation enhancers are employed in enhancing the oral absorption of drugs. However, SLN is one of the most promising approaches for improving oral delivery of BCS Class II drugs. Clear advantages of SLN include the composition (physiological compounds), the rapid and effective production process including the possibility of large-scale production, the avoidance of organic solvents, and the possibility to produce high concentrated lipid suspensions. Disadvantages include low drug-loading capacities, the presence of alternative colloidal structures, and the complexity of the physical state of the lipid which cause stability problems during storage or administration of SLN. Further work needs to be done to understand the interaction of SLN with their biological surrounding (adsorption/desorption processes, enzymatic degradation, agglomeration, and interaction with endogen). The SLNs as drug nanocarriers have the potential to achieve the broad objectives for treating various diseases. A wider collection of the lipid materials may be illustrated for SLNs in the future. The lipids from natural sources can be a major origin of the SLN lipid matrix. More patented dosage forms of SLNs can be expected in the near future.

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