International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(6): November-December 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 26-10-2015; Revised: 31-10-2015; Accepted: 01-11-2015

A REVIEW ON NANOSTRUCTURED LIPID CARRIER (NLC)

Baliram D.Khandekar*, Moreshwar P.Patil, Amol C Jahagirdar, Balasaheb Targe

Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik-422003, India

Keywords:

Nanostructured lipid carrier,Homogenization, SEM,TEM

For Correspondence:

Baliram D.Khandekar

Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik-422003, India

E-mail:

balikhandekar19@gmail.com

ABSTRACT

We are amidst a nano-era. Nanotechnology,for that matter,has emerged as a contemporary discipline with novel applications in drug delivery research as well. Literally, the Greek word, "**nano"** signifies "a billionth" (i.e., of a meter). It verily implies tiny particles, even much smaller than a living cell. Nano-sized particles range form nano-liposomes, to dendrimers, to self nano-emulsifying systems, to quantum dots, to carbon-based nanoparticles like nano-tubes and nano-fibers.The present study aimed to evaluate influences of mixed lipids and their proportions on formation andproperties of nanostructured lipid carriers (NLCs).The physicochemical parameters of drug-free NLCswere characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM), differ-ential scanning calorimetry (DSC), X-ray diffraction (XRD) and rheological measurements. In addition,a drug incorporation model was introduced into the NLCs for the application.

INTRODUCTION

A new generation of nanostructured lipid carriers (NLCs) consisting of a lipid matrix with a special nanostructure has been developed. This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high- pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%.Carrier system. However, the NLC system minimizes or avoids some potential problems associated with SLN.

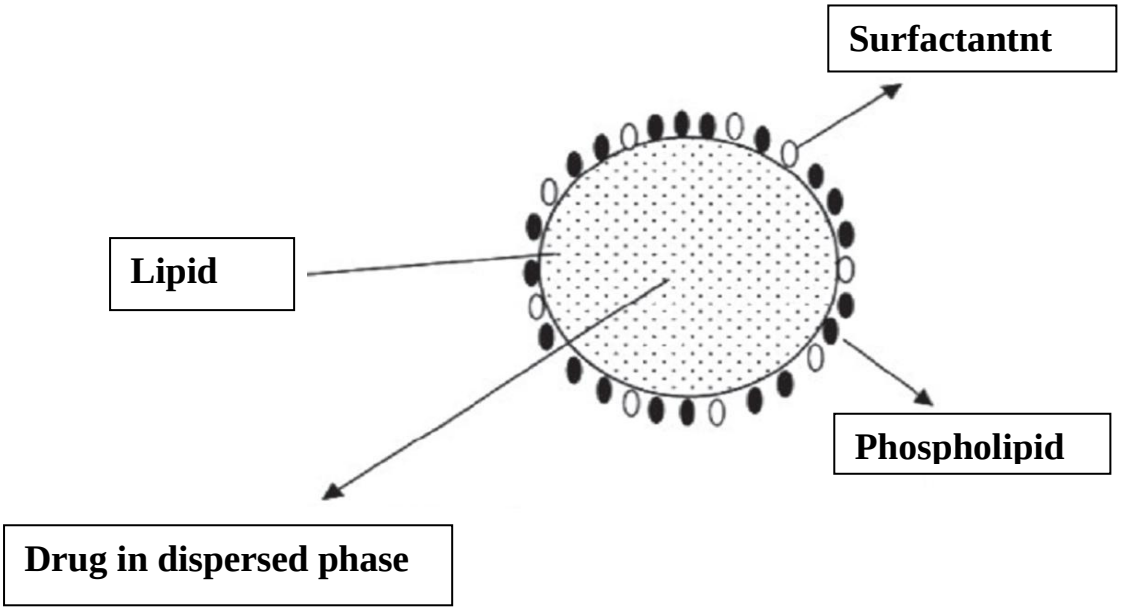
The review by Mehnert and Mader14 high lights these aspects:

1. Pay-load for a number of drugs too low
2. Drug expulsion during storage
3. High water content of SLN dispersions.[1,2,3]

The new concept for the production of NLC, spacially very different lipid molecules are mixed, i.e. blending solid lipids with liquid lipids (oils). The resulting matrix of the lipid particles shows a melting point depression compared to the original solid lipid but the matrix is still solid at body temperature. Depending on the way of production and the composition of the lipid blend, different types of NLC are obtained. The basic idea is that by giving the lipid matrix a certain nanostructure, the pay-load for active compounds is increased and expulsion of the compound during storage is avoided. New and improved generation of SLNs and are made of a solid lipid matrix entrapping liquid lipid nanocompartments, 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, long-term physical stability of the suspension, *etc.* Subsequent to these first-generation lipid pellets, the second-generation "lipid nanopellets" were developed for oral administration in the mid-eighties. This system, however, could not be further developed, primarily due to non-existential patent protection in many countries then. At the beginning of the nineties, the third generation products were evolved as "solid lipid nanoparticles" (SLNs). These submicron size range (50–1000 nm) particles, made up of biocompatible and biodegradable materials, and capable of incorporating lipophilic and hydrophilic drugs, have withstood the test of time till date.

From the last decade, oral drug delivery has taken a new dimension with the increasing application of lipids as carriers for the delivery of poorly water-soluble drugs.[12,13]

The general structure of NLC is shown in Fig. 2[14,15]



Methods of Manufacturing of NLC/SLN

Different methods of SLN/NLC formulation are described here-

1. Homogenization techniques

i. Hot high pressure homogenization technique

ii. Cold high pressure homogenization technique

iii. Melt emulsification ultrasound (ultrrasonication) homogenization technique

(High shear homogenization and/or ultrasound technique)

2. Microemulsion technique

3. Emulsification-solvent evaporation technique

4. Solvent displacement or injection technique

5. Emulsification-solvent diffusion technique

6. Phase inversion technique

Methods of Preparation of NLCs

Hot High Pressure Homogenization Technique

For hot homogenization, a pre-emulsion of the drug loaded lipid melt and the emulsifier solution is prepared with a high-shear mixing device (such as Ultra-Turrax). Pre- emulsion is then passed through high pressure homogenization cycle at temperatures above the melting point of the lipid. Lipid nanoparticles are formed by the following cooling of the sample to room temperature or to temperatures below. The active compound-containing melted lipid is

dispersed in the hot surfactant solution at the same temperature applying high-speed stirring. The obtained hot pre-emulsion is passed through a high pressure homogenizer applying number of homogenization cycles. A nanoemulsion is formed which is upon cooling yield aqueous dispersion of lipid nanoparticles.[16,17]

Hot HPH technique is the most frequently applied. It can be used for the entrapment of lipophilic and insoluble drugs in the lipid. Temperature sensitive compounds can also be processed by hot HPH as exposure time to high temperatures is relatively short. However, for hydrophilic drugs this procedure is not the most appropriated one. During the homogenization of the melted lipid phase the drug will partition to the water phase resulting in a too low encapsulation rate. Figure 1 describes the schematic procedure for the preparation of lipid nanoparticles by this method.

Cold High Pressure Homogenization Technique

In contrast to hot homogenization, the cold homogenization is carried out with the solid lipid without melting as done in hot process. Drug along with lipid in solid state is milled to form microparticles, and further dispersed in a solution containing emulsifier. The pre-suspension formed is then subjected to high pressure homogenization at or below room temperature.

In the cold HPH technique, lipid is melted above its melting point and drug is dissolved or dispersed in it. The system is cooled down by means of dry ice or liquid nitrogen. After solidification, the lipid mass is grounded using ball or mortar milling to yield lipid microparticles in a range between 50 and 100 μm. Then a microemulsion is formed by adding these microparticles into cold surfactant solution with stirring. This suspension is passed through a high pressure homogenizer at/or below room temperature and the microparticles are broken down to nanoparticles.

The cold HPH technique minimizes the thermal exposure to the drugs and active substances. Therefore, this technique may be applied for temperature sensitive compounds. Hydrophilic compounds can also be incorporated by this method which might partition from the liquid lipid phase to the water phase during the hot HPH. To further minimize the loss of hydrophilic compounds to the aqueous phase of the suspension, water can be replaced by liquids with low solubility for the drug, such as oils and polyethylene glycols of low molecular weight. Lipid particles prepared using the cold HPH technique possess a slightly higher PI and mean particle size compared to the ones obtained by hot HPH technique. Homogenization cycles can be increase to further reduce the particle size and to minimize the polydispersity. Figure 1 has shown the schematic chart of this procedure. [18,19]

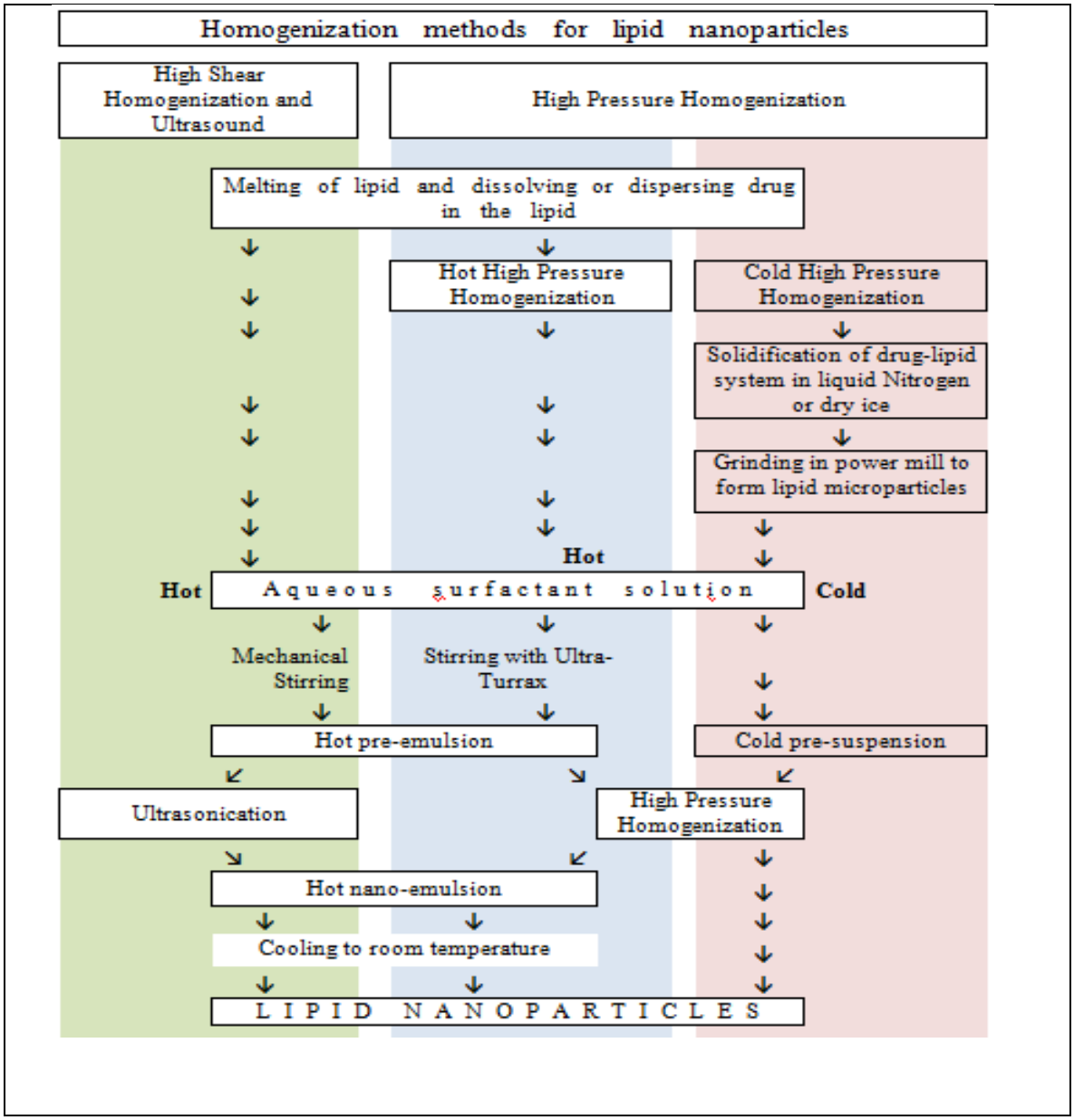


Figure 1: Schematic representation of the different homogenization techniques for the production of lipid nanoparticle.

Melt Emulsification Ultrasound Homogenization Technique

Different techniques can be employed to prepare lipid nanoparticles. Hot homogenization technique is the most commonly applied method. However, it requires the use of appropriate devices which are not commonly available in research labs. Ultrasonication instead of high pressure homogenization has been employed to produce lipid nanoparticles. This technology is based on the extreme conditions generated within the collapsing cavitational bubbles of the inner phase leading to size reduction. This method employs same procedure as hot high pressure homogenization except using ultrasonication device in place of homogenizer. Ultrasonic processing is fast and highly reproducible if the operating parameters are

optimized. These parameters are operating temperature, ultrasonication time and power. Ultrasound probes are very easy to clean; sample losses are negligible and can be used for high scale production. However, it is believed that when applying high-shear homogenizers and ultrasonication, inhomogeneous power distributions are most likely to occur as compared with high pressure homogenizers which are characterized by a homogeneous power distribution dueto the small size of the homogenizing gap.[20,21,22]

Microemulsion Technique

This method is adapted since the early start of lipid nanoparticle formulation by different research groups. In the microemulsion method, when excess amount of outer phase in cooling conditions added to a hot microemulsion the system has broken down and converting it into nanoemulsion which recrystallize internal oil or lipid phase forming particles. Briefly, the melted lipid containing drug mixed with surfactant, cosurfactant containing aqueous phase prepared at the same temperature as of the lipid in such a ratio to form microemulsion. The hot microemulsion is then diluted into excess of cold water. Sudden reduction in temperature causes breaking of the microemulsion, converting it into nanoemulsion, which upon recrystallization of lipid phase produces lipid particles. Break in microemulsion is supposed to be due to the dilution with water and the reduction in temperature narrowing the microemulsion region. The process variables affecting size and structure are microemulsion composition, dispersing device for the microemulsion dilution to the cold water, temperature condition and lyophilization of the product. Disadvantage of the microemulsion technique is the dilution of the particles suspension with water, thus removal of excess water need additional efforts. In addition, high concentrations of surfactants and co-surfactants, in the formulation raise regulatory concern. The removal of surfactants can further be performed using ultrafiltration, ultracentrifugation or dialysis adding one more step to the procedure which is time consuming and costly.[23,24]

Emulsification-Solvent Evaporation Technique

This is a method analogous to the production of polymeric nanoparticles and microparticles by solvent evaporation in o/w emulsions via precipitation. In the solvent emulsification-evaporation the lipid is dissolved in a water-immiscible organic solvent (e.g. toluene, chloroform) which is then emulsified in an aqueous phase before evaporation of the solvent under condition of reduced pressure. The lipid precipitates upon evaporation of the solvent thus forming nanoparticles.

Firstly, an organic phase has produced containing the lipid material dissolved in a water-immiscible organic solvent, and then the drug is dissolved or dispersed in that solution. This organic phase is emulsified in an o/w surfactant containing aqueous phase by mechanical stirring. Subsequent quick removal of solvent by evaporation from the obtained o/w emulsion under mechanical stirring or reduced pressure nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The solvent evaporation step must be quickly in order to avoid particle aggregation.[26,28]

Solvent Displacement or Injection Technique

The solvent displacement technique was first described for the preparation of liposomes and polymeric nanoparticles from pre-formed polymers. Recently, this technique has also been used to prepare lipid nanoparticles. Precipitation of lipid dissolved in solution is the basis of this process. In this method, a solution of the lipid in a water-miscible solvent or a water-miscible solvent mixture is rapidly injected into an aqueous phase with or without surfactant. In this process, an o/w emulsion has been formed by injecting organic phase into the aqueous phase under magnetic stirring. The oil phase is a semi-polar water-miscible solvent, such as ethanol, acetone or methanol, lipid material is dissolved in it and then the active compound is dissolved or dispersed in this phase. Aqueous phase consists of surfactant. In this procedure solvent displacement of diffusion takes place and lipid precipitate has obtained. Solvent removal is necessary and can be performed by distillation. The lipid nanoparticles are formed after total evaporation of the water miscible organic solvent. Particle size is dependent on the preparation conditions such as amount to be injected, concentration of lipid and emulsifier.

This method offers clear advantages over the existing methods such as the use of organic solvents which is pharmaceutically accepted, high pressure homogenization not required, ease in handling and less time consuming without technically sophisticated equipment. Disadvantages clearly evident is use of organic solvent although they are pharmaceutically accepted excipients frequently used in formulations.[29,30]

Emulsification-Solvent Diffusion Technique

The emulsification-solvent diffusion technique is usually used to produce polymeric nanoparticles based on synthetic polymers via precipitation. However, it has been recently applied to prepare lipid nanoparticles. In the solvent-diffusion technique, partially water miscible solvents (e.g. benzyl alcohol, ethyl formate, tetrahydrofuran) are used. Initially, they are mutually saturated with water to ensure initial thermodynamic equilibrium of both liquids. Then the lipid is dissolved in the water-saturated solvent and subsequently emulsified

with solvent-saturated aqueous surfactant solution at elevated temperatures. The lipid nanoparticles precipitate after the addition of excess water (typical ratio: 1:5–1:10) due to diffusion of the organic solvent from the emulsion droplets to the continuous phase.

In this procedure an o/w emulsion is formed comprising organic phase of a partially water soluble solvent which is previously saturated with water to ensure the initial thermodynamic equilibrium between the two liquids (that is water and solvent). This saturated solution is used to dissolve lipid followed by the drug in the organic phase. This organic phase is then emulsified in an aqueous solution containing surfactant under mechanical stirring for the preparation of an o/w emulsion. The subsequent addition of excess water to the system causes solvent diffusion into the external phase and the lipid starts precipitating. The solvent can be eliminated by ultra-filtration or by distillation. After the complete removal of organic solvent, an aqueous dispersion of lipid nanoparticles is formed. The dispersions obtained in this procedure is fairly dilute similar to microemulsions method, and required to be concentrated by means of ultra-filtration or lyophilisation thus extra step is needed. Particle size is also small around 100 nm with narrow size distribution in this method.[32,33,34]

Phase Inversion Technique

Recently, a novel phase inversion-based technique has been described for the preparation of lipid nanoparticles. It involves two basic steps, first is addition of formulation components with magnetic stirring and subsequent heating cooling cycles and second is dilution under cooling conditions. The general procedure consists of magnetic stirring of all the components (lipid, surfactant and water) in the correct proportions optimized previously. Three cycles of heating and cooling from room temperature to 85ºC and back to 60ºC are subsequently applied at a rate of 4ºC/min. This thermal treatment (85ºC-60ºC-85ºC-60ºC-85ºC) will cause the inversion of the emulsion. It is followed by dilution with cold water. The system will break down due to an irreversible shock induced by dilution with cold water to the mixture maintained at the elevated temperature. This fast cooling dilution process with cold water leads to lipid particles in the nanometer range. Afterwards, a slow magnetic stirring is applied to avoid particle aggregation. A general procedure has been schematically represented .[35]

Multiple Emulsion Technique

This is a modified solvent emulsification-evaporation method based on a w/o/w double emulsion. It applied emulsification followed by solvent evaporation for the preparation of hydrophilic drug substance loaded SLN. 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. It has advantages and limitation of previously described method of emulsification solvent evaporation technique but it can be applied for the incorporation of hydrophilic molecules such as peptides and proteins also.[36]

Supercritical PGSS Technique (Particle from gas saturated solution)

This is a relatively new technique for lipid nanoparticle production based on the use of supercritical carbon dioxide (scCO2). It has been described as a single step method capable of encapsulating drugs into organic solvent-free lipid particles. Carbon dioxide (99.99%) is a good choice as a solvent for this method.

In this method lipid is melted and drug is subsequently dissolved or dispersed in it. Then scCO2 is dissolved in the bulk of a melted lipid phase, followed by quick expansion through a micron cone shaped nozzle upon pressure release.[37,38,39]

Formulation Considerations of NLCs

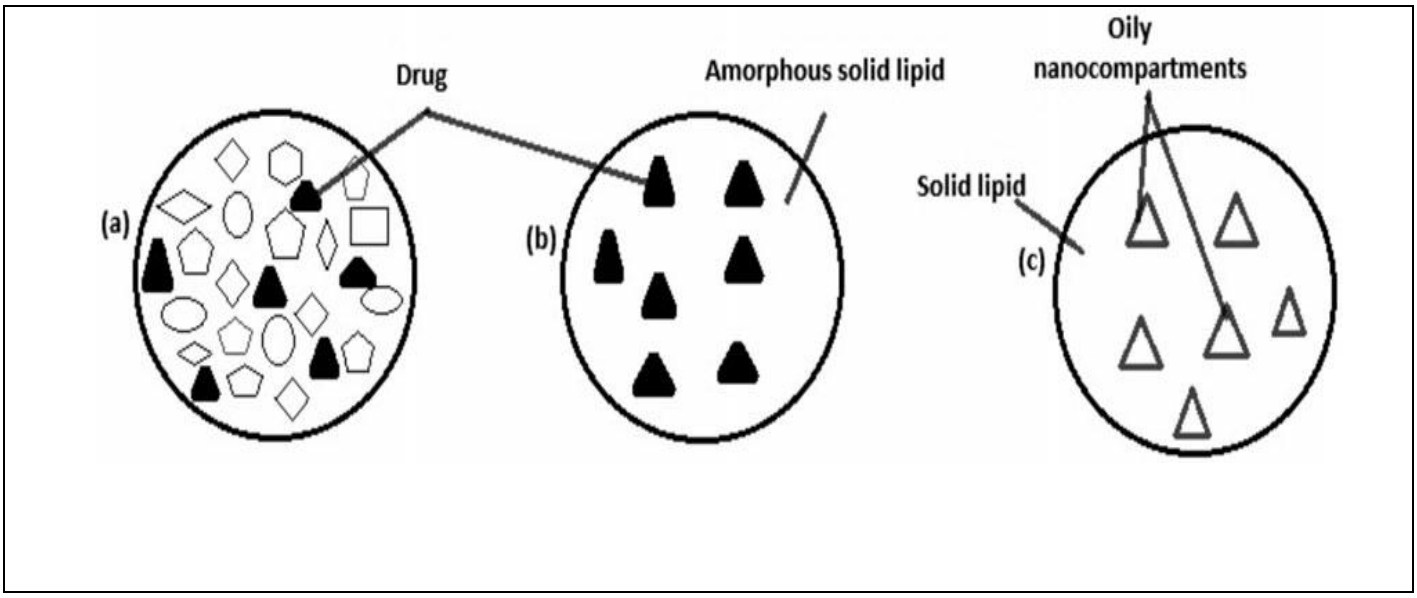
Based upon the variegated formulation strategies adopted to optimize the nanostructures, the NLCs are categorised as Type I, II, III or IV.

Type I: Imperfect type: Spatially different lipids are mixed and thus imperfections in the crystal order of lipid nanoparticles are provided (Fig. 2a). Large distances between fatty acid chains in the matrix structure of lipid nanoparticles can be increased using glycerides composed of very different fatty acids. Therefore, the matrix contains imperfections to accommodate the drug in amorphous clusters. Mixing small amounts of chemically quite different liquid lipids (oils) with solid lipids in order to achieve the highest incompatibility leads to the highest drug payload.

Type II: Amorphous type: This kind of NLC can be achieved by mixing solid lipids with special lipids,e.g., hydroxyoctacosanylhydroxystearate, isopropylmyristate or medium chain triglycerides, such as Miglyol® 812. Therefore, drug expulsion caused by the process of crystallization to β forms during storage is prevented by the special structure of the lipid matrix, since NLC are solids in an amorphous but not crystalline state (Fig. 2b).[12,13]

Type III: Multiple type: In this multiple oil in fat in water (O/F/W) type of NLCs, drugs can be accommodated in the solid, but at increased solubility in the oily parts of the lipid matrix. The solubility of the drug in the lipophilic phase decreases during the cooling process after homogenization and the crystallization process during storage. Continuously reducing drug solubility leads to drug expulsion from the lipid nanoparticles, especially when the drug concentration in the formulation is too high. Solubility of many drugs in a liquid lipid is higher than in a solid lipid. When lipids lack appropriate drug solubilities, addition of higher

amounts of liquid lipid to the lipophilic phase displays the advantages of the solid matrix which prevente drug leakage while the liquid regions (oily nanocompartments) show comparatively high solubility for lipophilic drugs Fig.[14,15]



Factors influencing NLCs

The major factors influencing NLCs formulation are as follows

Lipid.

Lipids enhance oral BA and reduce plasma profile variability.Its screening should be performed to determine the most suitable lipid for the active ingredient which gives the highest solubility.

Surfactant

The concentration of the surfactant strongly affects the particle size of the lipid NPs. In general, smaller particle sizes were observed when a higher surfactant/lipid ratio was chosen. The decrease in surfactant concentration would result in increase in particle size during storage. Surfactants decrease the surface tension between the interface of the particles causing portioning of the particles and thereby increasing the surface area.[6,7,8]

Process parameters

Temperature

The formulating temperature of the required solid lipid must be 5–10 _C above the melting point. If the temperature is less than the melting point, the solid will not melt and it will be difficult to incorporate the drug. On the other hand, if the temperature is more, the lipid will degrade. Stirring time Time should be optimum, so that a smooth nanoemulsion wil be formed, less stirring causes the bigger particle size.

Formulating procedure

It greatly affects the particle size of the formulation which directly influences the zeta potential and polydispersity index.[10,11]

CHARACTERIZATION

Characterization of the lipid nanoparticles is critical due to complexity of the system and colloidal size of the particles. Nevertheless, proper characterization of the formulations is necessary to control the product quality, stability, and release kinetics. Hence, accurate and sensitive characterization methods should be used. There are several important characterization techniques as follows.

Particle Size

Particle size plays a crucial role in the gastrointestinal uptake and their clearance by the reticuloendothelial system. Hence, the precise determination of the particle size is very important. Particle size less than 300 nm are advisable for the intestinal transport. Photon correlation spectroscopy and laser diffraction . Are the most powerful and widely used techniques for the particle size measurement of lipid nanoparticles. PCS is also known as dynamic light scattering. The fluctuation of the intensity of the scattered light, caused by particles movement, is measured by this technique. PCS is relatively accurate and sensitive method. However, only size range from few nanometersto about 3 μ can be measured by PCS. This size range is enough to characterize lipid nanoparticles. On the other hand, LD can measure bigger particle sizes. LD covers a broad size range from the nanometer to the lower millimeter range. This method is based on the dependence of the diffraction angle on the particle radius. Smaller particles lead to more intense scattering at high angles than the larger particles. However, it is always recommended to use both PCS and LD method simultaneously as both methods do not directly measure particle sizes, rather particle sizes are calculated from their light scattering effects. This is because particles are non-spherical in many instances.

Polydispersity Index

As SLNs/NLCs are usually polydisperse in nature, measurement of polydispersity index (PI) is important to know the size distribution of the nanoparticles. The lower the PI value, the more monodispered the nanoparticle dispersion is. Most of the researchers accept PI value less than 0.3 as optimum value. PI can be measured by PCS.

Zeta Potential

The zeta potential (ZP) indicates the overall charge a particle acquires in a specific medium. Stability of the nanodispersion during storage can be predicted form the ZP value. The ZP indicates the degree of repulsion between close and similarly charged particles in the dispersion. High ZP

indicates highly charged particles. Generally, high ZP (negative or positive) prevents aggregation of the particles due to electric repulsion and electrically stabilizes the nanoparticle dispersion. On the other hand, in case of low ZP, attraction exceeds repulsion and the dispersion coagulates or flocculates.However, this assumption is not applicable for all colloidal dispersion, especially the dispersion which contain steric stabilizers. The ZP value of −30 mV is enough for good stabilization of a nanodispersion. The ZP of the nanodispersions can be determined by PCS.

Shape and Morphology

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are very useful techniques to determine the shape and morphology of lipid nanoparticles. These techniques can also determine the particle size and size distribution. SEM utilizes electron transmission from the sample surface, whereas TEM utilizes electron transmission through the sample. In contrast to PCS and LD, SEM and TEM provide direct information on the particle shape and size. Several SEM and TEM study showed spherical shape of the lipid nanoparticles. Although normal SEM is not very sensitive to the nanometer size range, field emission SEM (FESEM) can detect nanometer size range. However, sample preparation (e.g., solvent removal) may influence the particle shape. Cryogenic FESEM might be helpful in this case, where liquid dispersion is frozen by liquid nitrogen and micrographs are taken at the frozen condition. AFM technique is also gaining popularity for nanoparticle characterization. AFM provides a three-dimensional surface profile unlike electron microscopy which provides two-dimensional image of a sample. AFM directly provides structural, mechanical, functional, and topographical information about surfaces with nanometer- to angstrom-scale resolution. In this technique,

the force acting between a surface and a probing tip results in a spatial resolution of up to 0.01 nm for imaging. Direct analysis of the originally hydrated, solvent-containing samples is possible as no vacuum is needed during operation and the sample does not need to be conductive. zur Muhlen compared AFM with SEM and reported same particle size of the nanoparticles by both methods.

Crystallinity and Polymorphism

Determination of the crystallinity of the components of SLN/NLC formulations is crucial as the lipid matrix as well asthe incorporated drug may undergo a polymorphic transition leading to a possible undesirable drug expulsion during storage.Lipid crystallinity is also strongly correlated with drug incorporation and release rates. Thermodynamic stability and lipid packing density increase, whereas drug incorporation rates decrease in the following order: Supercooled melt, α-modification, β′-modification, and β-modification. However, lipid crystallization and modification changes might be highly retarded due to the small size of the particles and the presence of emulsifiers. Differential scanning calorimetry and X-Ray diffractometry are two widely used techniques to determine the crystallinity and polymorphic behavior of the components of the SLNs/ NLCs. DSC provides information on the melting and crystallization behavior of all solid and liquid constituents of the particles, whereas XRD can identify specific crystalline compounds based on their crystal structure. DSC utilizes the fact that different lipid modifications possess different melting points and melting enthalpies. In XRD, the monochromatic beam of X-ray is diffracted at angles determined by the spacing of the planes in the crystals and the type and

arrangement of the atoms, which is recorded by a detector as a pattern. The intensity and position of the diffractions are unique to each type of crystalline material. XRD pattern can predict the manner of arrangement of lipid molecules, phase behavior, and characterize and identify the structure of lipid and drug molecules. However, best results are observed when SLN dispersions are investigated directly as solvent removal may change the modification. Another two techniques, infrared and Raman spectroscopy are also useful to investigate structural properties of lipids. However, they have not been extensively used to characterize SLNs/ NLCs.

Pharmaceutical Applications

The major areas of application of NLCs are oral and topical delivery. Full range of GRAS excipients (e.g. all lipids, surfactants and other excipients used in creams, tablets, pellets and capsules) is available for the purpose. Compared to other delivery systems like liposomes and SLNs, drug loading can be markedly increased in NLCs. NLC can easily be processed to traditional dosage forms well-accepted by the patient, e.g. tablet, capsule or pellet. Because of the high particle concentration and cream-like consistency, the NLC dispersions might be directly filled into capsules. Further, the high particle concentration facilitates the use of these dispersions for granulation or as wetting agent in the pellet production. Extension of drug

release after subcutaneous or intramuscular injection is another NLC application of pharmaceutical interest. The injectable lipid nanoparticles that have been studied so far have been encapsulated with anticancer agents, imaging agents, antiparkinsonism, anti-HIV, antipsychotics, anti-rheumatoid arthritic agents, antiparasitics, antihypertensives, antibiotics and the like.There are some other niche applications too, like ocular delivery of nanoparticles to prolong the retention time. Many reports describe the prolonged retention of drugs in the eye using polymeric nanoparticles; however, up to now no product is on the market due to various reasons (e.g. toxicity problem of non-accepted polymer, polyalcylcyanoacrylate). SLNs show an increased retention time in the eye. It would be even more beneficial to use NLC with improved drug accommodation properties. Lipid nanoparticles, like SLNs and NLCs, can be used to formulateactive compounds in cosmetics, e.g. prolonged release of perfumes too. Incorporation of cosmetic compounds and modulation of release is even more flexible when using NLCs. The solid matrix of the lipid nanoparticle protects them against chemical degradation. A recently discovered feature is the sunscreen blocking effect of lipid nanoparticles. Similar to particles such as titanium dioxide, the crystalline lipid particles scatter UV light, thus protecting against UV irradiation. In addition, it was found that incorporation of sunscreens leads to a synergistic UV blocking effect of the particulate blocker lipid nanoparticle and the molecular blocker.

REFERENCES

1. Smith A, Hunneyball IM. Evaluation of polylactid as a biodegradable drug delivery system for parenteral administration. Int. J. Pharm. 1986; 30: 215– 230.

2. Siekmann B, Westesen K. Sub-micron sized parenteral carrier systems based on solid lipids. Pharm. Pharmacol. Lett. 1992; 1:123-126.

3. Muller RH. Feste lipid nanopartikel (SLN), in: Muller RH, Hildebrand GE. (Eds.), Pharmazeutische Technologie: Moderne Arzneiformen, Wissenschaftliche Verlagsgesellschaft, Stuttgart. 1997; 265– 272.

4. Pinto JF, Muller RH. Pellets as carriers of solid lipid nanoparticles (SLNk) for oral administration of drugs, Pharmazie. 1999; 54: 506– 509.

5. Sznitowska M, Gajewska M, Janicki A, Radwanska G. Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration to rabbits. Eur. J. Pharm. Biopharm. 2001; 52: 159–163.

6. Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv. Drug Deliv. Rev. 2002; 54 (Suppl. 1): S131–S155.

7. Muiller RH, Mehnert W, Lucks JS, Schwarz C, Miihlen A, Weyhers H, Freitas C, Riihl D. Solid lipid nanoparticles (SLN)-- an alternative colloidal carrier system for controlled drug delivery. Eur. J. Pharm. Biopharm. 1995; 41: 62-69.

8. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. Int. J. Pharm. 2002; 242: 121-128.

9. Müller RH, Souto EB, Radtke M. Nanostructured Lipid Carriers: A Novel Generation of Solid Lipid Drug Carriers. Pharmaceutical Techn. Europe. 2005; 17(4): 45–50

10.Muller RH, Radtke M, Wissing SA. (2002a). Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm 242: 121–8.

11.Muller RH, Radtke M, Wissing SA. (2002b). Solid lipid NPs (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 54:S131–55.
12. Singh B, Bandopadhyay S, Kapil R, Katare OP. Nanostructured Lipid Carriers as Novel Drug Delivery Vehicles. Pharma Buzz. 2008; 3: 38-46.
13. Doktorovova S, Souto EB. Nanostructured lipid carrier-base hydrogel formulations for drug delivery: a comprehensive review. Expert Opin Drug Deliv. 2009; 6(2): 165-176.
14. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm. 2008; 346(1-2): 124-132.
15. Pardeike J, Hommoss A, Muller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009; 366(1-2): 170-184.
16. Muller RH. Adv Drug Deliv Rev 2007; 59: 375–376.
17. Gasco MR. Ad Drug Deliv Rev 2007; 59: 377–378.
18. Jannin V, Musakhanian J, Marchaud D. Ad Drug Deliv Rev 2008; 60: 734–746.
19. Muller RH, Lucks JS. Eur. Patent No.0605497, 1996.
20.Gasco MR. US Patent No. 5250236, 1993.
21. Puglia C, Blasi P, Rizza L, Schoubben A, Bonina F, Rossi C, Ricci M. Int J Pharm 2008; 357: 295–304.
22.Yuan H, Wang L, Du Y, You J, Hu F, Zeng S. Colloids and Surfaces B: Biointerfaces 2007; 60: 174–179.
23. Jenning V, Thunemann AF, Gohla SH. Int J Pharm 2000; 199: 167-177.
24. Silva AC, Lopes CM, Doktorovova S, Santos D, Ferreira DC, Souto EB. Poster Presentation, University of Porto, Porto, Portugal, 2006.
25. Bhaskar K, Anbu J, Ravichandiran V, Venkateswarlu V, Rao YM. Lipids in Health and Disease 2009; 8: 6.
26. Hu FQ, Jiang SP, Du YZ, Yuan H, Ye YQ, Zeng S. Int J Pharm 2006; 314: 83–89.
27. Teeranachaideekul V, Boonme P, Souto EB, Müller RH, Junyaprasert VB. J Control Release 2008; 128: 134–141.
28. Borgia SL, Regehly M, Sivaramakrishnan R, Mehnert W, Korting HC, Danker K, Roder B, Kramer K.D, Schafer-Korting M. J Control Release 2005; 110: 151– 163.
29. Shen J, Wang Y, Ping Q, Xiao Y, Huang X. J Control Release 2009; 137: 217–223.
30. Shah KA, Date AA, Joshi MD, Patravale VB. Int J Pharm 2007; 345: 163–171.
31. Mandawgade SD, Patravale VB. Int J Pharm 2008; 363: 132–138.
32. Junyaprasert VB, Teeranachaideekul V, Souto EB, Boonme P, Müller RH. Int J Pharm 2009; 377: 207–214.
33. Pardeike J, Schwabe K, Muller RH. Int J Pharm 2010; 396: 166–173.
34. Teeranachaideekul V, Souto EB, Junyaprasert VB, Muller RH. Eur J Pharm Biopharm 2007; 67: 141–148.
35. Obeidat WM, Schwabe K, Muller RH, Keck CM. Eur J Pharm Biopharm 2010; 76: 56–67.
36. Garcia-Fuentes M, Torres D, Alonso MJ. Colloids and Surfaces B: Biointerfaces 2002; 27: 159-168.
37. Wissing SA, Kayser O, Muller RH. Ad Drug Deliv Rev 2004; 56: 1257– 1272.
38. Tiwari R, Pathak K. Int J Pharm 2010; doi: 10.1016/ j.ijpharm. 2011.05.044 article in press.
39.Schubert MA, Muller-Goymann CC. Eur J Pharm Biopharm 2003; 55: 125–131.