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AN EXTENSIVE REVIEW ON NANOSTRUCTURED LIPID CARRIER (NLCs)

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ABSTRACT

The current review on Nanostructured Lipid Carrier (NLCs) become one of the most popular drug carrier technique among other carrier system. Nanostructured Lipid Carrier (NLCs) are second generation nano sized lipid-based drug delivery system which designed to overcome the limitations of conventional lipid carrier like solid lipid nanoparticles (SLNs). NLCs are colloidal drug delivery system composed of mixture of a solid and liquid lipids, surfactants offering improved drug loading capacity, controlled drug release and enhanced stability. NLCs are suitable for both lipophilic and hydrophilic drugs. These carriers provide several advantages including increased solubility of poorly water-soluble drugs (Febuxostat), protecting the sensitive drug molecules and enhanced bioavailability. NLCs can be used for various routes of administration such as oral, parenteral and topical delivery. This article highlights the formulation strategies, characterization techniques and potential applications of NLCs in modern pharmaceutical and therapeutic field, showing their promise for more effective and patient compliance drug delivery. Due to their biologically non-toxic and non-immunogenic NLCs are going to be widely explored among lipid nanocarrier system.

KEYWORD:- Nanostructured Lipid Carrier (NLCs), Solid Lipid Nanoparticles (SLNs), Solid and liquid lipid, Surfactant, Colloidal drug delivery.

INTRODUCTION

Lipid nanoparticles as drug delivery systems were considered from the beginning of the 19th century by professor R. H. Muller from Germany and Professor M. Gascon from Italy. In the last decade, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been looked upon as promising carriers for presenting several attractive features for transdermal drug delivery.[1]

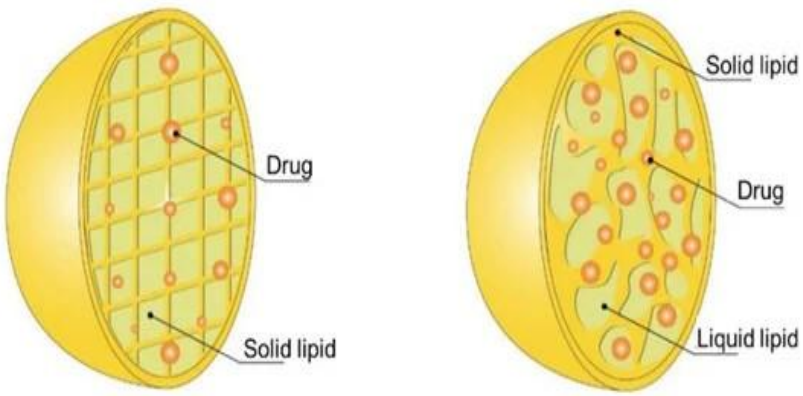


Fig. 1: SLNs and NLCs.

Many pharmaceutical companies have developed a well-established industrial processes for the manufacturing of large-scale batches of nanostructured lipid carriers, but still all major kind of parameters like choice of lipid, surfactants other essential excipients and methods of preparation varies which leads to change in parameters like particle shape and size, phase transition, solubility, bioavailability of drug etc.

Lipid nanoparticles made with a solid matrix (solid lipid nanoparticles, SLNs) are derived from oil-in-water type nano emulsion formed by replacing liquid oil with a solid

lipid. The first generation of SLNs was developed at the beginning of 1990. The advantages of SLNs are the use of physiological lipids, avoidance of organic solvents, and the applicability of large-scale production. As a drug delivery carriers, SLNs can improve bioavailability, protect sensitive drugs from a rigorous environment, and control drug-release characteristics. But SLNs show some disadvantages as drug carriers including an unpredictable gelation tendency, polymorphic transition, and low incorporation due to the crystalline structure of solid lipids. To overcome this the Nanostructured Lipid Carriers (NLCs) were developed to resolve the problems raised by SLNs.

Nanostructured lipid carrier

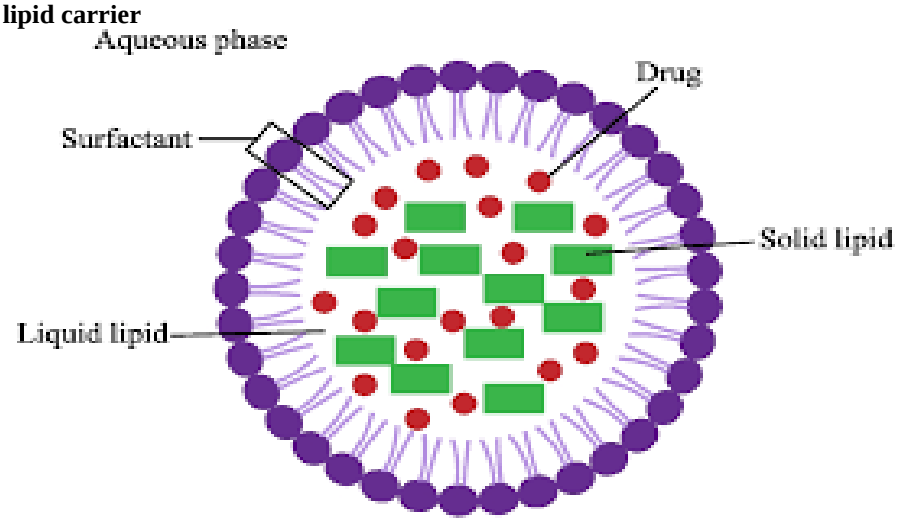


Fig. 2: Structure of Nanostructured Lipid Carrier (NLCs).

Nanostructured Lipid Carrier (NLCs) are second generation of lipid-based nanocarriers formed from mixture of solid and liquid lipids and have unstructured-matrix due to the different moieties of the constituents of NLCs. NLCs were designed in order to overcome the Solid Lipid Nanoparticles (SLNs) limitations.

NLCs have higher drug loading capacity because of imperfect crystal structure and could avoid drug expulsion by avoiding lipid crystallization during the manufacturing and storage periods. Due to the presence of liquid lipids in NLCs formulation expulsion of loaded drug after formulation and during the storage period is minimized. NLCs also can increase drug solubility in lipid matrix and they can show more controllable release profiles in comparison to SLNs. Although NLCs are solid in nature even in body temperature but they have low melting point than SLNs and due to their unstructured nature and imperfection in their crystalline behaviours provide more space for drug dissolution and payload in liquid part of the NLCs. So that the loading capacity in NLCs are more than SLNs. Previous researches also confirm on less susceptibility of NLCs than SLNs to gelation during the preparation and storage period, which is another advantage of NLCs.

Advantages of nanostructured lipid carrier

- Improved drug loading capacity
- Enhanced solubility for poorly water-soluble drugs
- Both hydrophilic and lipophilic drugs are transported at a same time
- Biocompatibility and safe for use
- Less risk of toxicity
- Sensitive drugs are encapsulated and protected from external factors
- Enhanced bioavailability
- Ease of large-scale production
- Reduced drug leakage
- Most lipids used in NLCs are biodegradable
- Enhanced permeation through biological membranes.

Types of nanostructured lipid carrier

Depending on the various production techniques and the composition of the lipid blends, different types of NLCs are obtained. The basic idea is to provide a certain nanostructure for the lipid matrix so as to increase the pay-load for active compounds and reduce the expulsion of compound during storage. The three types of NLCs can be summarised as:

- NLC type 1 also called as imperfect crystal.
- NLC type 2 also called as amorphous type.
- NLC type 3 also called as multiple type.

NLC type 1

NLC type 1 also called imperfect crystal types have a badly structured solid matrix. Different fatty acids such as glycerides can be used to improve and modify the structure. The total number of imperfections in the structure are responsible and also helpful for the property of good drug which can be easily increased. The type 1 of NLCs can be prepared by mixing spatially with different lipids which can leads to imperfections in the crystal lattice. The drug molecules lodges extra disorderly crystal as molecular form and amorphous clusters. To avoid this adding to a minor quantity of

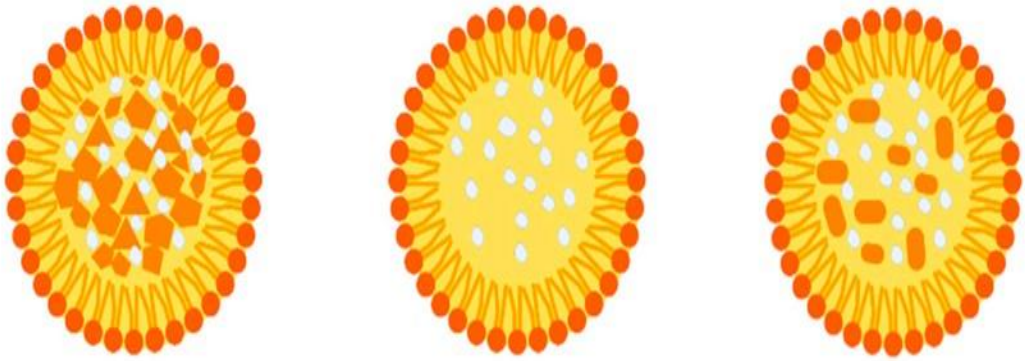
liquid lipid additional leans to increases the drug-loading. The small quality of the glycerides can be used to overcome this situation.

NLC type 2

This type of NLCs also called as amorphous type. In this technique of preparation of NLC's, the lipids are mixed in such a way that crystallizing can be prevented through mixing procedure. In type 3 method the lipid matrix remains solid but, in an amorphous state the technique and method of crystallization often leads to drug expulsion. To minimize this, NLCs can also be formulated by carefully mixing of solid lipids with special lipids such as hydroxy octacosanyl hydroxyl stearate, isopropyl palmitate or MCT. Solid non-crystalline NLCs are formed.

NLC type 3

The oil-in-lipid-in-water type NLCs is also called as multiple type. In type 2 NLCs the solubility of oil is greater as compare to solubility of solid lipids. In type 2 NLCs high amount of oil are mixed with solid lipids due to this oil molecule can easily spread into the lipid matrix at a low concentration of oil. If the added oil in excess quantity than required of its solubility can lead to separation of different phases, finally produces small oily nano compartments which are bounded by the solid lipid matrix. This kind of formulation permit controlled drug release and leakage of drug from lipid matrix. In this case, lipophilic drugs can be made soluble in oil first and type 2 method can be followed with the cooling procedure of a hot homogenization process.[4,22,23]



a) Type 1 **b) Type 2** **c) Type 3**

Fig. 3: Types of Nanostructured lipid carriers.

Components of nanostructured lipid carrier

The lipid itself is the main ingredient of NLC that influence their drug loading capacity, stability and the sustained release behaviour of the formulations. Lipid nanoparticle dispersions are based upon a variety of lipid materials including fatty acids, glycerides, and waxes. Most of these lipids, with the notable exception of cetyl palmitate, are approved as (Generally-recognised-as-safe) (GRAS) and are physiologically well-tolerated.[9] Selection of appropriate lipids is essential prior to their use in preparation of lipid nanoparticle dispersions.[9] Although there are no specific guidelines, empirical values, such as the solubility of drug in the lipid have been proposed as suitable criteria for selection of an appropriate lipid.[15,16] Wax-based NLC are physically more stable, however they exhibit significant drug expulsion cause of their more crystalline nature. To avoid such problems with lipid crystallinity and polymorphism, a binary mixture of two spatially different solid lipid matrices, i.e., a solid lipid and a liquid lipid (or oil) was used to prepare lipid nanoparticle dispersions, now known as nanostructured lipid carriers (NLC).[17,18]

Solid lipids

A combination of numerous chemical compounds which have a melting point higher than 40°C. These solid lipids are well tolerated.[19,20]

- Accepted for human use.
- Also in-vivo biodegradable.

Examples are beeswax, carnauba wax, dynasan, precifac, stearic acid, ppLfil, cutina CP 8 etc.

Liquid lipids (oil)

Liquid lipids are well tolerated and accepted for human use.

Examples are Cetiol V, miglyol, castor oil, oleic acid, davana oil, palm oil, olive oil etc.[19-21]

Emulsifying agents (Surfactants)

Surfactants are the compounds which are adsorbed at interfaces and reduce the interfacial tension. When a surfactant is present in small amount it improves the stability by decreasing the rates of surfactants also termed as surface-active agents.[9,22] At low concentrations, surfactants adsorb onto the surface of a system or interface.[9,23] Surfactant decreases the surface or interfacial free energy and decrease the surface or interfacial tension between the two phases.[2,9,24]

The selection of surfactant for NLCs based upon a number of multiple factors like route of administration of NLCs, HLB value of surfactant. The combination of

solid and liquid- lipid mixtures will not help much for the doing the perfect crystallization in case if formulation of NLC's. To overcome this problem reducing the probability of expulsion of the encapsulated drug upon storage.[9,14] The addition of polysorbate 80 possibly provided more interfacial area than polysorbate 20.[9] As a result, the average size of NLC's 80 was smaller than NLC's 20. The properties of NLCs can be influenced by the type of surfactant used in the formulation.[25] The type of stabilizer significantly affected the average size and charge but not the size distribution of the NLCs.[25,26]

Surface modifiers

- Dipalmitoyl-phosphatidyl-ethanolamine conjugated with polyethylene glycol 2000 (DPPE-PEG2000).
- Di-stearoyl-phosphatidyl-ethanolamine-N-poly (ethylene glycol) 2000 (DSPE-PEG2000)
- Stearic acid-PEG 2000 (SA-PEG2000).
- α-methoxy-PEG 2000-carboxylic acid-α-lipoamino acids (mPEG2000-C-LAA18).
- α-methoxy-PEG 5000-carboxylic acid-α-lipoamino acids (mPEG5000-C-LAA18).[9,14,19,27,28]
- Ionic polymers: Dextran sulphate sodium salt.

Excipients for NLCs

The solid lipids commonly used for NLCs include glyceryl behenate (Compritol® 888 ATO), glyceryl palmitostearate (Precirol® ATO 5), fatty, steroids and waxes. These lipids are solid at room temperature. They melt at higher temperatures (e.g. > 80ºC) during the preparation. Liquid oils typically used for NLCs consist of digestible oils obtained from natural sources.[9,10,14]

Drug release

The controlled or sustained release of the drugs from NLCs can result in the prolonged half-life and retarded enzymatic attack in systematic circulation. The drug release behaviour from NLCs is dependent upon the production temperature, particle size, drug solubility, surfactant composition, and oil percentage incorporated in the lipid matrix.[11]

The drug amount in the outer shell of the nanoparticles and on the particulate surface is released in a burst manner, while the drug incorporated into the particulate core is released in a prolonged way. Sustained release of the drugs can be explained considering both drug partitioning between the lipid matrix and water, as well as the barrier function of the interfacial membrane.[29] The dialysis method and the utilization of the Franz cell are the modes for measuring in vitro drug release from nanoparticle. Enzymatic degradation of lipid nanoparticles may be influenced to a relevant extent by the composition of the particles.

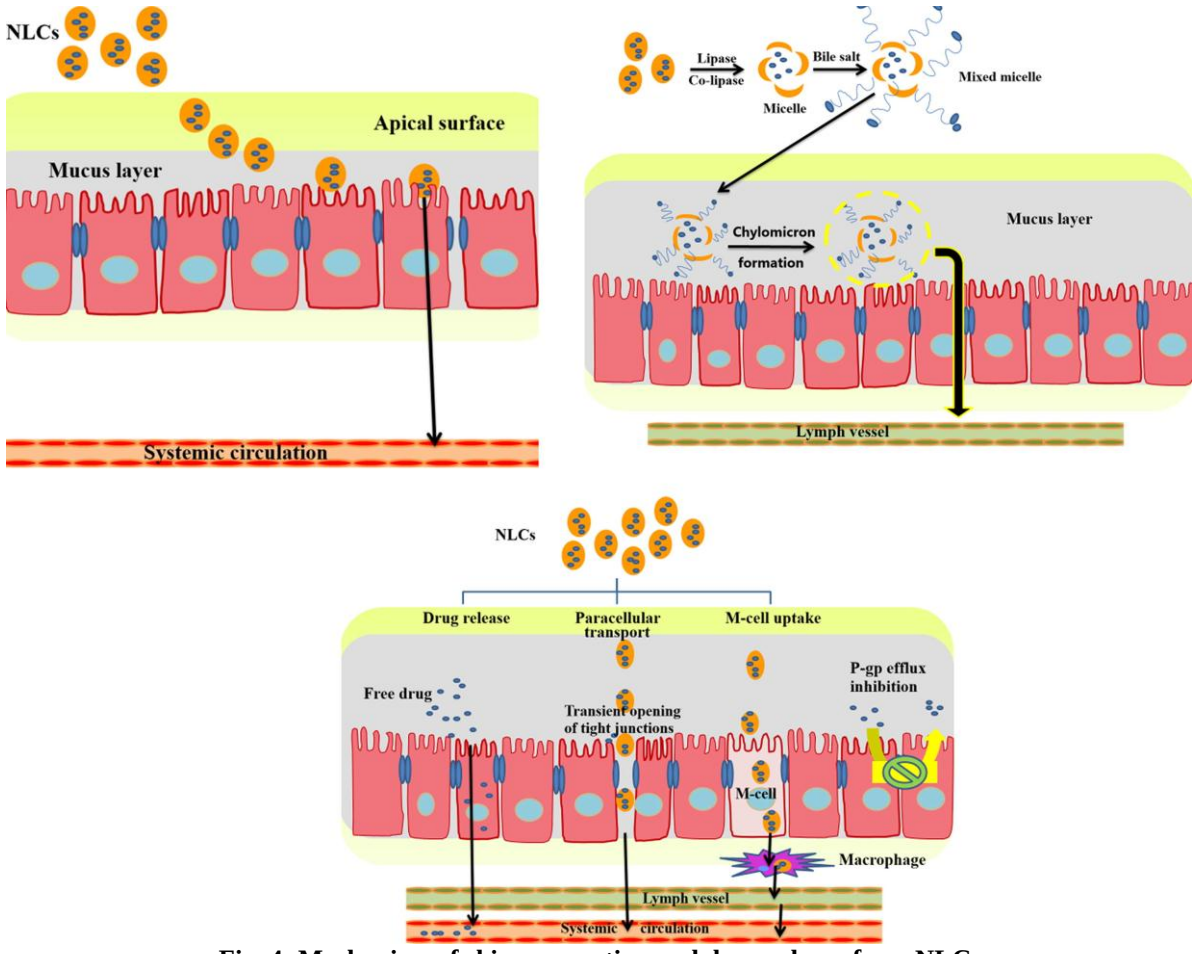


Fig. 4: Mechanism of skin permeation and drug release from NLC.

Preparation methods for nanostructured lipid carrier[5]

High pressure homogenisation

HPH has been used as a reliable and powerful technique for the large-scale production of NLCs, lipid drug conjugate, SLNs, and parenteral emulsions. The lipid is pushed with high pressure (100–2000 bars) through a very high shear stress, resulting in disruption of particles down to the sub-micrometer or nanometer range. Normally the lipid contents are in the range of 5–10%. In contrast to other preparation technique, high pressure homogenisation does not show scaling up problem. Homogenisation may be performed either at elevated temperature (hot homogenisation) or below room temperature (cold homogenisation) (Schwarz *et al*. 1994).

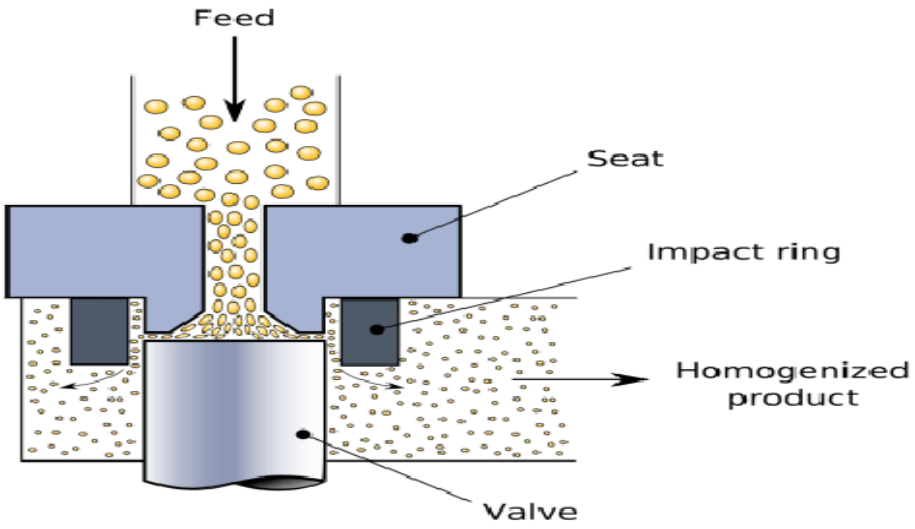


Fig. 5: High pressure homogenisation technique.

Hot homogenisation technique

In this technique the drug along with melted lipid is dispersed under constant stirring by a high shear device in the aqueous surfactant solution of same temperature. The pre-emulsion obtained is homogenised by using a piston gap homogeniser and the obtained nano-emulsion is cooled down to room temperature where the lipid recrystallises and leads to formation of nanoparticles (zur Mühlen *et al*. 1998).

Cold homogenisation technique

Cold homogenisation is carried out with the solid lipid containing drug. Cold homogenisation has been developed to overcome the problems of the hot homogenisation technique such as, temperature mediated accelerated degradation of the drug payload, partitioning and hence loss of drug into the aqueous phase during homogenisation. The first step of both the cold and hot homogenisation methods is the same. In the subsequent step, the melt containing drug is cooled rapidly using ice or liquid nitrogen for distribution of drug in the lipid matrix. Cold homogenisation minimises the thermal exposure of the sample (Gasco 1993).

Microemulsion technique

In this technique, the lipids are melted and drug is incorporated in molten lipid. A mixture of water, co-surfactant(s) and the surfactant is heated to the same temperature as the lipids and added under mild stirring to the lipid melt. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratios for microemulsion formation. Thus the microemulsion is the basis for the formation of nanoparticles of a requisite size. This microemulsion is then dispersed in a cold aqueous medium under mild mechanical mixing of hot microemulsion with water in a ratio in the range 1:25–1:50. This dispersion in cold aqueous medium leads to rapid recrystallisation of the oil droplets (Moulik and Paul 1998).

Solvent emulsification-evaporation technique

In solvent emulsification-evaporation method, the lipophilic material and hydrophobic drug are dissolved in a water immiscible organic solvent and emulsified in an aqueous phase using high speed homogeniser. The efficiency of fine emulsification is improved by immediately passing the coarse emulsion through microfluidizer. Further the organic solvent is evaporated by mechanical stirring at room temperature and reduced pressure (e.g. rotary evaporator) leaving lipid precipitates nanoparticles (Shahgaldian *et al*. 2003).

Solvent emulsification-diffusion technique

This technique can be applied both for the aqueous and oily phase where solvent used must be partially miscible with water. Initially, both the solvent and water are mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquids. During the heating process in order to solubilise the lipid, saturation step is performed at the same temperature. Then the lipid

and drug were dissolved in water saturated solvent and this organic phase is stirred using mechanical stirrer. After the formulation of o/w emulsion, water in typical ratio from 1:5 to 1:10, is added to the system in order to allow solvent diffusion into the continuous phase, thus leading to the aggregation of the lipid in the nanoparticles. Both the phases have to be maintained at the same elevated temperature while the diffusion step is performed at room temperature (Hu et al. 2002, Trotta *et al*. 2003).

Solvent injection

The basic principle of the solvent injection method is similar to the solvent diffusion method. In case of solvent injection method, lipids are dissolved in a water-miscible solvent (e.g. acetone, isopropanol and methanol) or water-miscible solvent mixture and quickly injected into an aqueous solution of surfactants through an injection needle (Schubert and Müller-Goymann 2003). The advantages of this method are the easy handling and fast production process without technically sophisticated equipment (e.g. high-pressure homogeniser). However, the main disadvantage is the use of organic solvents (Müller *et al*. 2002).

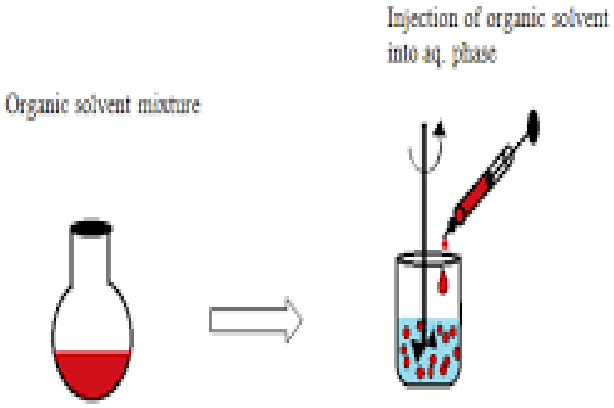


Fig. 6: Solvent injection method.

Double emulsion technique

In double emulsion technique the drug (Mainly hydrophilic drugs) is dissolved in aqueous solution, and further emulsified in melted lipid. The primary emulsion is stabilised by adding stabiliser that is dispersed in aqueous phase containing hydrophilic emulsifier, which is followed by stirring and filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilise them by means of the incorporation of lipid-PEG derivatives (Date *et al*. 2007).

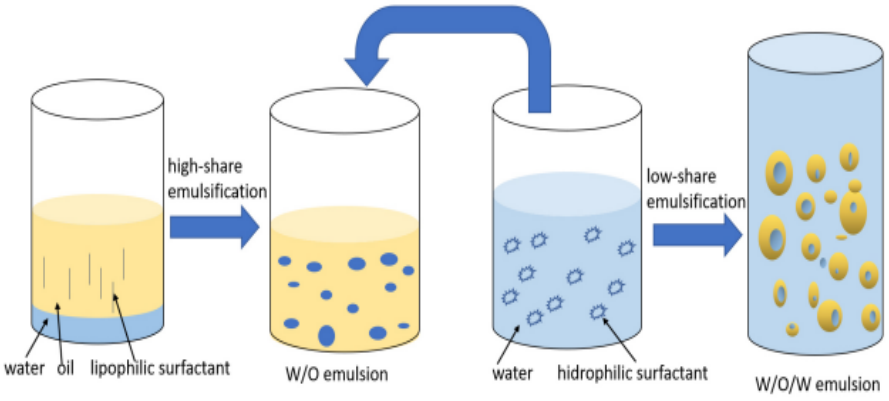


Fig. 7: Double emulsion technique.

Ultrasonication technique

This technique is one of the less frequently studied methods for the production of lipid nanoparticles. First, the core material is melted followed by the addition of phospholipids along with an aqueous medium, and finally dispersing the melted material at increased temperature by mechanical stirring or ultrasonication. Particle size reduction of the core lipid emulsion with soya lecithin is carried out with the help of ultrasonic energy (Puglia *et al*. 2008).

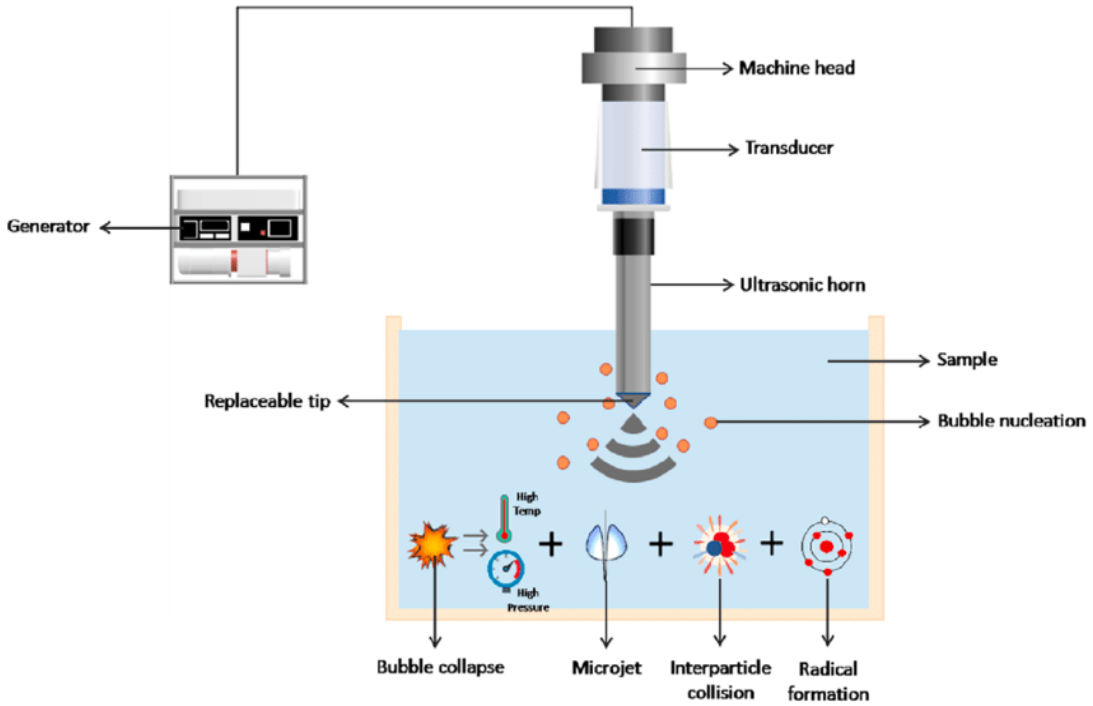


Fig. 8: Ultrasonication.

Characterization and Evaluation of NLCs

Characterization of NLC may be a serious challenge because of the small size of the particles resulting in the complexity of the system that also incorporates dynamic phenomena. Therefore characterization of the NLC may be an essential requisite for the management of the quality of the product. Many parameters need to be considered that have direct impact on the stability and release kinetics like particle size, particle size distribution, zeta potential (ZP), degree of crystallinity and lipid modification, co-existence of additional colloidal structures (micelles, liposomes, supercooled melts, drug-nanoparticles) and the dynamic phenomena.

Particle size

Photon correlation spectroscopy (PCS) and laser diffraction are the most powerful methods for routine measurement of particle size. PCS is also known as dynamic light scattering. It measures the fluctuation of the scattered light intensity produced by particle movement. This technique covers a determined size range from several nm to 3 µm.[30] The larger size can be detected by laser diffraction. This determination is based on the dependence of the diffraction angle on a particle radius. The types and ratios of lipid and emulsifier used in NLCs greatly influence particle size. The addition of more emulsifiers always facilitates more complete emulsification and more rigid structure thus the size can be reduced.[31]

Zeta potential

The measurement of surface charge is used to assess the dispersion and aggregation processes affecting particle stability in application. In general, particle aggregation or fusion is less likely to occur for charged particles because of the electrostatic repulsion. A positively charged surface of NLCs is efficient for entering the blood brain barrier (BBB) because of binding to the paracellular area of the BBB, an area rich in anionic sites.[32] Zeta potential determination is helpful for formulation design to check if the cationic surface is achieved. Sometimes a negative charge of particulate surface is needed to stabilize the nanoparticulate systems during storage.

Electron microscopy

The particulate radius and size distribution of NLCs can also be measured by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). In addition, the electron microscopy is beneficial in observing the shape and morphology of the particles. SEM employs electrons transmitted from the surface of the sample, while TEM uses electrons transmitted through the specimen. SEM possesses high resolution and easy preparation of the samples. TEM allows visualization of nanoparticles after freeze-drying or freeze-thawing.

Atomic Force Microscopy (AFM)[33,34]

AFM is optimal for measuring morphological and surface features that are extremely small. AFM does not use photons or electrons but a very small sharp-tipped probe located at the free end of a cantilever driven by interatomic repulsive or attractive forces between the tip and surface of the specimen. Although electron microscopy is still frequently used, the AFM technique offers substantial benefits: real quantitative data acquisition in three dimensions, minimal sample preparation times, flexibility in ambient operating conditions, and effective magnifications at the nano

levels.

Surface tension

The surface tension of water at 20°C is 72.8 dynes/cm. The addition of lipids and emulsifiers can significantly reduce the surface tension to a lower value. The surface tension decreases following the increase of emulsifier concentration due to the emulsification process of the whole system. Surface tension of the lipid nanoparticles is often measured by the Wilhemy plate method. The measurement of the contact angle is another method for detecting surface tension of the nanoparticulate systems.[35]

Differential Scanning Calorimetry (DSC)[36,37]

DSC gives an insight into the melting and recrystallization behaviour of the solid lipids from SLNs and NLCs. DSC determination uses the fact that various lipid modifications have various melting points and enthalpies. The degree of crystallinity of NLCs is calculated from the ratio of NLCs enthalpy to bulk lipid enthalpy, which is calculated on the basis of total weight taken. The crystallinity degree of nanoparticles decreases with increasing liquid lipid ratio in the particles. This result presents the evidence that the liquid oil is the main factor lowering the crystallinity and increasing the less-ordered structure of NLCs. The decline of enthalpy and reduction of the melting point of the lipids occur in the NLCs that have a smaller size, a higher surface area, and a greater number of emulsifiers. The loading of liquid oil leads to crystal order disturbance, resulting in more space to include drug molecules. DSC profiles are advantageous to suggest the preferential drug dissolution in solid or liquid lipids.

X-ray Diffraction[38,39]

Both DSC and X-ray diffraction are widely used to investigate the status of lipids. The lipid molecules composed of a long hydrocarbon chain have been known to possess polymorphism. The crystalline order of NLCs can be elucidated by wide-angle X-ray diffraction. The polymorphism status of the nanoparticles detected by X-ray can be utilized to confirm DSC results. By means of X-ray scattering, it is possible to assess the length of the long and short spacing of the lipid lattice.

Nuclear Magnetic Resonance (NMR)

Proton NMR spectroscopy is performed to investigate the mobility of the materials in the inner core of NLCs. The mobility of the solid and liquid lipids is related to the width at half amplitude of the signals.[40] Broad signals and small amplitudes are characteristics of molecules with restricted mobility and strong interactions.[41] The higher line width of NLCs compared to the physical mixture of the materials added in NLCs indicates the interaction of liquid oil with the solid lipid. Immobilization of the nanoparticles of NLCs is stronger compared to SLNs with totally crystallized cores.

Drug encapsulation efficiency

Determination of drug-loading efficiency is very important for NLCs since it affects the release characteristics.[42] The lipophilic drug molecules may homogeneously distribute in the lipid matrix or enrich the core or particulate shell. Aqueous and interfacial phases are the main locations for loading hydrophilic drugs. The prerequisite to achieving high loading capacity is sufficient solubility of the drug in the lipids. The solubility should be higher than required because it decreases when cooling down the melt and may even be lower in the solid lipids. The encapsulation percentage of the drugs in NLCs is based on the separation of the internal and external phases. To separate the dispersions, different techniques such as ultrafiltration, ultracentrifugation, gel filtration by Sephadex, and dialysis are commonly used. As compared to SLNs, the incorporation of liquid oil to solid lipid in NLCs leads to massive crystal order disturbance. The resulting matrix indicates great imperfection in the lattice and leaves more space to accommodate the drugs. The entrapment efficiency and loading capacity of the drugs are thus improved.

Entrapment efficiency can be calculated where the amount of drug in the NLCs is measured spectrophotometrically at the corresponding λmax, after addition of sufficient volume of organic solvent (e.g. methanol) to break the NLCs and release the entrapped drug.

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug entrapped drug}}{\text{Total amount of initially added drug}} \times 100$$

Applications of nanostructured lipid carrier

Now-a-days several NLCs formulations are marketed for therapeutic and cosmetic uses probably because of their well-established biocompatibility due to use of lipids. Development and characterization of NLCs exploring treatments for various diseases and disorders is an ongoing process. Teixeira et al summarized the therapeutic applications of lipid nanoparticles in the treatment of various disorders. The lipid nanoparticles are suitable for incorporation of drugs belonging to BSC class II and IV which otherwise create problems in bioavailability due to their physicochemical properties. There are several potent applications of NLC which are given below.

NLC for topical delivery

Skin is a choice for drug delivery in many localized skin diseases and infections as well as delivery of drugs in a sustained and controlled fashion for the management of pain or wound healing. Skin being an easily accessible organ with a large surface area makes drug delivery through this route achievable without pain and undesired systemic side effects. Drug delivery through this route is mainly divided into dermal for localized effect and transdermal for deep skin penetration. Skin is a metabolically active organ with the main function of protecting the body from external dangers. Skin act as a

barrier for external microorganisms, chemicals, or other molecules which try to enter the body and may create harm. This barrier function of the skin makes it difficult for therapeutically active molecules to directly enter the body. Many studies have been performed on topical application of NLCs for their unique properties. NLCs can enhance the apparent solubility of entrapped drugs, which can form high concentration gradient on skin to facilitate drug permeation. The nano-sized particles tightly adhere to the skin surface and release the drugs in a more controlled manner. Therefore NLCs are used for topical application of various categories of drugs for improvement of penetration along with sustained release.

Experimental studies have confirmed the improvements in the therapeutical response and reduction in the local side effects of the drug. Idebenone loaded nanostructured lipid carriers (I-NLCs) were prepared for topical delivery of antioxidant idebenone and evaluation of its sun protection efficacy. Sun protection factor (SPF) value for I-NLCs was found to be 23 which represents that lipid nanocarriers (LNC) have standards of blocking of 94–96% of Ultraviolet-B rays (Salunkhe et al. 2013). In another study anti-fungal drug ketoconazole loaded NLCs were physically more stable as compared to SLN as the SLN matrix was not able to protect the chemically labile ketoconazole against degradation under light exposure (Souto and Müller 2005).

NLC in cosmeceuticals

NLCs have been applied in the preparation of sunscreen and as an active carrier agent for molecular sunscreen and UV blockers. The in-vivo study showed that skin hydration will be increased after using NLC cream. Better localisation has been achieved for vitamin A in upper layers of skin when compared to conventional formulations. A prolonged release profile can also be obtained for the perfumes and insect repellents by incorporating them in NLCs (Petersen *et al*. 2006). Another product Surmer (Dr. Rimpler, GmbH, Wedemark, Germany) increases the occlusion of a day cream without changing its light character, that is, achieving higher occlusive properties without having the glossy skin appearance.

NLC as a brain targeted carrier

Brain targeting not only increases the cerebro spinal fluid (CSF) concentration of the drug but also reduces the frequency of dosing and side effects. The major advantages of this administration route are avoidance of first pass metabolism and rapid onset of action as compared to oral administration. NLC of this generation are considered to be one of the major strategies for drug delivery without any modification to the drug molecule because of their rapid uptake by the brain, bio acceptability and biodegradability. Further, the feasibility in scale-up and absence of burst effect make them more promising carriers for drug delivery. In addition, NLC further enhanced the intranasal drug delivery of duloxetine in the brain for the treatment of major depressive disorder. Bromocriptine (BC) a dopamine receptor agonist has been also incorporated in NLCs for controlled delivery of drug to provide long-lasting therapeutic effects possibly extending BC half-life in vivo for the treatment of Parkinson's disease.

NLC in pulmonary drug delivery

Drug delivery via inhalation is also a potential route of administration for the treatment of several pulmonary disease having advantages over conventional dosage forms like non-invasive, circumventing first pass metabolism systemic toxicity, reduced frequent dosing and site specificity by directly reaching to the lung epithelium. Few attempts have been made to deliver anti-cancer agents using nanoparticles and liposomes via an inhalation route, but the major limitations being instability during nebulisation, biodegradability, drug leakage and adverse side effects of drug. The lipophilic COX-2 inhibitor, celecoxib, was successfully encapsulated in the NLC nanoparticles using mixture of solid and liquid lipids where most of the nebulised nanoparticles were able to deposit in the alveolar region of the mice lungs and also enhanced the celecoxib lung residence time (Patlolla *et al.* 2010).

Gene delivery and gene therapy

Gene transfer is the most challenging task to achieve efficient and safe gene therapy. Gene delivery systems basically done by two ways, viral and non-viral vectors. Viral vectors have been extensively investigated because of their high transfection efficiency while compared to other tablets, capsules, injectables. The impact of these carrier systems is continuously increasing and thus has bright future prospects. However, their cytotoxic effects related to the nature of matrix and concentration, irritative and sensitising action of some surfactants are the areas of concern. Their application and efficiency in food, protein and peptide drugs, gene delivery systems and other fields still needs to be better exploited.

NLC in food industry

Because of its good stability and high loading capacity, the NLCs are widely applied in the pharmaceutical field. It was seldom reported that the NLC was applied as a nutritional supplement carrier in food industry for the capsule and beverage preparations. However, there are certain difficulties related to the raw material supply, availability and environmental factors due to which there is still a great risk for food industry to invest in this area. Coenzyme Q10-loaded NLCs for food application were developed to enhance the physicochemical stability and bioavailability.

CONCLUSION

Nanostructured lipid carriers (NLCs) are potential drug delivery system than the conventional delivery system. The major advantage is biocompatible, environmental friendly constituents preparation methods and that drug reaches the right site in the body, at the right time, at right concentrations. These lipid nanoparticles are

suitable carrier for both hydrophilic and lipophilic drugs. They can be administered by different routes such as topical, oral, parenteral, ocular, pulmonary, brain delivery system. Lipid nanoparticles are promising drug delivery systems for delivery of various pharmaceutically important active ingredients in future.

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All the authors have contributed equally.

Conflict of interests
Declared none.

REFERENCE

1. MuÈller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery–a review of the state of the art. Eur J Pharm Biopharm, 2000; 50(1): 161-177.
2. Beloqui A, Solinis MA, Rodriguez-Gascon A, Almeida AJ, Preat V. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Nanomedicine, 2016; 12(1): 143-161.
3. Jores K, Mehnert W, Mäder K. Physicochemical investigations on solid lipid nanoparticles and on oil-loaded solid lipid nanoparticles: a nuclear magnetic resonance and electron spin resonance study. Pharm Res, 2003; 20: 1274-83.
4. Shidhaye SS, Vaidya R, Sutar S, Patwardhan A, Kadam VJ. Solid lipid nanoparticles and nanostructured lipid carriers-innovative generations of solid lipid carriers. Curr Drug Deliv, 2008; 5(4): 324-231.
5. P. Jaiswal, B. Gidwani, A. Vyas, Nanostructured lipid carriers and their current application in targeted drug delivery, Artif. Cells Nanomed. Biotechnol, 2016; 44(1): 27–40.
6. K.W. Kasongo, R.H. Muller, R.B. Walker, The use of hot and cold high pressure homogenization to enhance the loading capacity and encapsulation efficiency of nanostructured lipid carriers for the hydrophilic antiretroviral drug, didanosine for potential administration to paediatric patients, Pharm. Dev. Tech, 2012; 17(3): 353–362.
7. Persson LC, Porter CJH, Charman WN, Bergström CAS Computational prediction of drug solubility in lipid based formulation excipients. Pharm Res, 2013; 30: 3225-3237.
8. Karunakar G, Patel NP, Kamal SS Nano structured lipid carrier based drug delivery system. J Chem Pharm Res, 2016; 8: 627-643.
9. Shah R, Eldridge D, Palombo E, Harding I Lipid Nanoparticles: Production, Characterization and Stability. Briefs Pharm Sci Drug Dev, 2015; 1: 11-23.
10. Soni K, Kukereja BK, Kapur M, Kohli K Lipid nanoparticles: future of oral drug delivery and their current trends and regulatory issues. Int J Curr Pharm Rev Res, 2015; 7: 1-18.
11. Kaur S, Nautyal U, Singh R, Singh S, Devi A Nanostructure Lipid Carrier (NLC): the new generation of lipid nanoparticles. Asian 3acLfic J Heal Med, 2015; 2: 76-93.
12. Jenning V, Schafer-Korting M, Gohla S Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release, 2000; 66: 115-126.
13. Jenning V, Gohla S Comparison of wax and glyceride solid lipid nanoparticles. Int J Pharm Sci, 2000; 196: 219-222.
14. Uner M, Yener G Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspective. Int J Nano medicine, 2007; 2: 289-300.
15. Das RJ, Baishya K, Pathak K Recent advancement of lipid drug conjugate as nanoparticulate drug delivery system. Int Res J Pharm, 2013; 4: 128-131.
16. Gaba B, Fazil M, Khan S, Ali A, Baboota S, et al. Nanostructured lipid carrier system for topical delivery of terbLnafine hydrochloride. Bull Fac Pharmacy, 2015; 53: 147-159.
17. Fang CL, Al-Suwayeh SA, Fang JY Nanostructured Lipid Carriers (NLCs) for Drug Delivery and Targeting. Recent Pat Nanotechnol, 2012; 7: 41-55.
18. Upreti T Nanostructured Lipid Carrier System for the Treatment for Skin Disease-A Review. JSM Nanotechnol Nanomedicine, 2017; 5: 1059.
19. Chen PC, Huang JW, Pang J An investigation of optimum NLC_sunscreen formulation using taguchi analysis, 2013.
20. Lasoń E, Sikora E, Ogonowski J Influence of process parameters on properties of Nanostructured Lipid Carriers (NLC) formulation. Acta Biochem Pol, 2013; 60: 773-777.
21. Joshi M, Patravale V Formulation and Evaluation of Nanostructured Lipid Carrier (NLC)–based Gel of Valdecoxib. Drug Dev Ind Pharm, 2006; 32: 911-918.
22. Chen M, Stitt A Animal Models of Diabetic Retinopathy. Curr Diab Rep, 2016; 17: 67-83.
23. Board BMA Reporting adverse drug reactions a guide for healthcare professionals. BMA Board Sci, 2006; 6: 147-158.
24. Karunakar G, Patel NP, Kamal SS Nano structured lipid carrier based drug delivery system. J Chem Pharm Res, 2016; 8: 627-643.
25. Sabtua R, Hasham R, Roslic NA, Azizd AA, Azize R Akademia baru e؈ect of high pressure homogenizer on the formation of zingiber oټcLnale- loaded nanostructured lipid carrier. J Adv Res Mater Sci, 2015; 13: 16-21.
26. Spitzer RL, Williams JBW, Kroenke K Patient Health Questionnaire (PHQ-9). J Gen Intern Med, 2001; 16: 606-613.
27. Kamble SS, Gambhire MS, Gujar KN Optimization and development of candesartan cilexetil loaded solid lipid nanoparticle for the treatment of hypertension. J Pharm Biosci, 2015; 3: 53-64.

28. Jain NK, Ram A Development and characterization of nanostructured lipid carriers of oral hypoglycemic agent: selection of surfactants. Int J Pharm Sci Revier Res, 2011; 7: 125-130.
29. Mottalib A, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, et al. Weight Management in Patients with Type 1 Diabetes and Obesity. Curr Diab Rep, 2017; 17: 92.
30. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev, 2001; 47: 165- 96.
31. Jenning V, Thünemann AF, Gohla SH. Characterisation of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. Int J Pharm, 2000; 199: 167-77.
32. Parveen S, Sahoo SK. Polymeric nanoparticles for cancer therapy. J Drug Target, 2008; 16: 108-23.
33. Hwang TL, Lin YK, Chi CH, Huang TH, Fang JY. Development and evaluation of perfluorocarbon nanobubbles for apomorphine delivery. J Pharm Sci, 2009; 98: 3735-47.
34. Sitterberg J, Özcetin A, Ehrhardt C, Bakowsky U. Utilising atomic force microscopy for the characterisation of nanoscale drug deliv_ery systems. Eur J Pharm Biopharm, 2010; 74: 2-13.
35. Forny L, Saleh K, Denoyel R, Pezron I. Contact angle assessment of hydrophobic silica nanoparticles related to the mechanisms of dry water formation. Langmuir, 2010; 26: 2333-8.
36. Hu FQ, Jiang SP, Du YZ, et al. Preparation and characteristics of monostearin nanostructured lipid carriers. Int J Pharm, 2006; 314: 83-9.
37. Castelli F, Puglia C, Sarpietro MG, Rizza L, Bonina F. Characterization of indomethacin-loaded lipid nanoparticles by differential scanning calorimetry. Int J Pharm, 2005; 304: 231-8.
38. Sato K. Crystallization behaviour of fats and lipids–a review. Chem Eng Sci, 2001; 5: 2255-65.
39. Teeranachaideekul V, Müller RH, Junyaprasert VB. Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC)–effects of formulation parameters on physicochemical stability. Int J Pharm, 2007; 340: 198-206.
40. Wissing SA, Müller RH, Manthei L, Mayer C. Structural characterization of Q10-loaded solid lipid nanoparticles by NMR spectroscopy. Pharm Res, 2004; 21: 400-5.
41. Schubert MA, Harms M, Müller-Goymann CC. Structural investigations on lipid nanoparticles containing high amounts of lecithin. Eur J Pharm Biopharm, 2006; 27: 226-36.
42. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm, 2008; 346: 124-32.