Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

A review of the preparation, characterization and application of nanostructured lipid carriers

Asha Spandana K M[1], Jawahar Natarajan*[2], Shailesh Thirumaleshwar[1], Hemanth Kumar S[1]

[1]Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, SS Nagara, Mysuru, Karnataka, India
[2]Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India

Article History:

Received on: 24.08.2019
Revised on: 02.11.2019
Accepted on: 11.11.2019

Keywords:

Nanostructured lipid carriers,
solid lipids,
liquid lipids,
surfactants

Abstract

Lipid Nanoparticles have gained increased attention during the last few decades. These carrier systems offer many advantages over conventional drug delivery system, including protection of the entrapped active ingredient from environmental (pH) or physiological (immune system, enzymes) degradations, improved bioavailability, prolonged circulation time, sustained release of drug and site specific drug delivery, reduced dose and side effects. Solid Lipid Nanoparticles (SLN), has been reported as an alternative carrier system to liposomes. However, SLN show some disadvantages such as drug expulsion during storage, low drug loading and aggregation of the particles. Nanostructured lipid carriers are evolved as second generation lipid nanoparticles to overcome the limitations of SLN, by modifying SLN by incorporating liquid lipid to the solid matrix for better drug accommodation to increase drug loading and prevent drug leakage while preserving the physical stability of the formulation. This article describes the features, various preparation techniques, characterization techniques and the therapeutic applications of NLCs in topical drug delivery, brain, oral and pulmonary delivery.

*Corresponding Author

Name: Jawahar Natarajan
Phone: +91-9791439545
Email: jajupharma@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i1.1946

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

In the past few decades, Lipid-based drug delivery systems gained increased attention due to their biodegradable and biocompatible property, non-toxicity, ability to improve safety, efficacy, and ability to penetrate through physiological barriers which can present challenges for drug delivery particularly blood-brain barrier (Dutta *et al.*, 2018). Additionally, improved stability and easy scale-up of nanoparticle (Sailaja *et al.*, 2011) makes lipid nanoparticle as a promising delivery system for a variety of drug molecules and other agents.

The first generation Solid lipid nanoparticles(SLN) was formulated at the beginning of 1990 as an alternate carrier system to other colloidal carrier systems (Muller *et al.*, 2007). Advantages of SLNs include enhanced bioavailability, protection of entrapped active ingredient from the outer environment (water, light), and controlled-release of a drug, use of physiological lipids, no use of organic solvents (Jores *et al.*, 2003). However, SLN show some disadvantages like low drug-loading capacity due to the crystalline structure of solid lipids, stability problems because the expulsion of active pharmaceuticals following the polymeric transition, parti-

cle growth during storage (Yoon *et al.*, 2013). To overcome these limitations of SLN, the Nanostructured lipid carriers (NLCs) are evolved as second-generation lipid nanoparticles developed by incorporating liquid lipid to the solid matrix to increase the number of imperfection in the solid matrix, thus to increase the drug loading, while preserving the physical stability of the formulation (Beloqui *et al.*, 2016).

MATERIALS AND METHODS

High-pressure homogenization method (HPH)

Hot HPH is suitable for insoluble and lipophilic drugs and rarely suitable for hydrophilic drugs, it involves the melting of solid lipid materials initially and then mixing with liquid lipid and drugs. The molten liquid thus formed is dispersed uniformly in the aqueous phase containing surfactants, later the mixture is stirred continuously until an emulsion is formed, which is further broken into nanoparticles by to high shear force (Salvi and Pawar, 2019).

In the Cold HPH, the solid and liquid lipids are melted at the temperature higher than the melting point of solid lipid. The drug is dispersed in the melted lipid, which is then subjected to high-pressure homogenization to form an emulsion, and the emulsion is rapidly cooled by using liquid nitrogen to yield solid mass. The solid mass thus obtained is size reduced to microparticles, the microparticles are distributed in the cold aqueous phase containing a surfactant, the aqueous phase is further subjected to homogenization with high shear to obtain NLCs (Salvi and Pawar, 2019).

Emulsification-ultrasonication method

The method involves mixing of a drug, liquid, and solid lipids and melting at a temperature higher than the melting point of solid lipid. An aqueous phase is prepared by heating distilled water along with surfactants at the same temperature of lipid melt. The aqueous phase is slowly added into lipid phase to get a pre-emulsion, which is further homogenized at high shear followed by ultrasonication, the emulsion is added to a specified quantity of water, cooled, solidified at room temperature to form NLCs (Salvi and Pawar, 2019).

Solvent diffusion method

In this method, the NLC's are prepared by incorporating the drug in organic solvents along with lipid mixture and lipophilic surfactant at elevated temperature, then the resulting organic solution containing drug is instantly dispersed with high mechanical agitation at 25 °C until the NLC's are obtained. The residual organic solvent from the prepared dispersion is evaporated by placing the dispersion in vacuum desiccators for 24 hours (Salvi and Pawar, 2019).

Solvent emulsification evaporation method

The method involves the preparation of NLC by dissolving the polymer in an organic solvent and then dispersing the drug in the polymer solution to form an organic phase. The organic phase is then slowly poured to the aqueous phase and emulsified by using an emulsifier or surface-active agent to form an oil-in-water system. The organic solvent is evaporated form the prepared emulsion by heating under reduced pressure (Salvi and Pawar, 2019).

Film-ultrasonication method

This method involves the preparation of NLCs by probe ultrasonication in which the melted lipid, polymer, and drug are dispersed in an aqueous solution containing a surfactant. The resulting dispersion is allowed to cool and then solidified to get NLCs (Salvi and Pawar, 2019).

Microemulsion method

In this method, the drug, emulsifier, auxiliary emulsifier, and deionized water are added to previously melted lipid to form a thermodynamically stable transparent microemulsion. The obtained microemulsion is immediately dispersed in ice water (0-4 °C) to form an NLC dispersion (Salvi and Pawar, 2019).

Hot-melt extrusion technology

Hot-melt extrusion with twin-screw extruder is a new technology for NLC preparation. The extruder has three feeding ports, the first to add lipid drug mix, the second to add liquid lipid, and the third to add aqueous phase. Solid lipid and drug mix are added in first port through a volumetric feeder, the heated liquid lipid is added through the second port by using a peristaltic pump. As the solid lipid, drug, and liquid lipid is introduced into the extrusion barrel, it undergoes melting and mixing. The Third port is selected for inclusion of preheated aqueous phase containing surfactant by using a peristaltic pump and mixed at the optimum speed to form pre-emulsion. That obtained pre-emulsion is extruded into a vessel attached with probe sonicator to obtain NLCs (Salvi and Pawar, 2019).

RESULTS AND DISCUSSION

Lipids and surfactants used in nanostructured lipid carriers production

The major components of NLC are lipids, surfactants, and water. Lipid core comprises of a blend of

solid lipid and liquid lipid. The surfactant is added to stabilize the system. Table 1 indicates the various formulation ingredients used in the NLC formulation

Characterization of nanostructured lipid carriers

Particle size and Polydispersity index

Particle size and the polydispersity index indicates the quality of nanoparticle with respect to size distribution. Rate of drug release, bio distribution profile, mucoadhesion, cellular uptake of water and buffer exchange to the interior of the nanoparticles, and protein diffusion affected by particle size (Bahari *et al.*, 2016). And also the particle size is a crucial factor in producing nano-sized particles, which describes the stability of the formulation, narrow size should be maintained during storage, increased size indicates agglomerates during storage (Suhaimi *et al.*, 2015). The delivery of some therapeutic agent to specific sites of the disease and their release profile is also affected by particle size (Naseri *et al.*, 2015). Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the widely used methods for the particle size measurements (Iqbal *et al.*, 2012).

Polydispersity index describes the degree of non-uniformity of a size distribution of particles. Value of less than 0.5 are considered to be acceptable in practice for lipid nanoparticles, indicates monodisperse and homogenous. Values greater than 0.7 indicate that the sample has a very broad size distribution. PDI of nanoparticles measured using the Microscopy method, diffraction and scattering techniques, and hydrodynamic techniques (Danaei *et al.*, 2018).

Zeta potential

Zeta Potential (ZP) analysis is a technique for determining the surface charge of nanoparticles in solution (colloids), obtaining information about their stability and surface interaction with other molecules. Suitable ZP provides drug delivery to the targeted by improving the possibility of actives interaction with target cells (Honary and Zahir, 2013). Unlike particle size, ZP is a property involving not only the particles but also their environments such as pH, ionic strength, and even the type of ions (Xu, 2008). Generally, ZP values higher than positive 25 mV or less than negative 25 mV typically have high degrees of stability (Backman, 2002). Hence zeta potential is one of the important parameters to be assessed since it affects the stability and also the permeability through the membrane because of the surface charge.

Shape and morphology

Particle shape and morphology are important parameters influences various biological and processes, including biodistribution, cellular uptake, and subsequent trafficking within cells (Zhu *et al.*, 2019). It has been reported that the toxicity of the nanoparticle depends on the shape of the nanoparticles. The shape and morphology of Nanoparticles can be determined using *Scanning electron microscopy, Transmission electron microscopy, and Atomic force microscopy* (Jain and Thareja, 2019).

Drug - lipid (excipient) interaction

Fourier Transform Infrared (FTIR) spectrometer is used to identify possible interactions between the drug, lipid, and other excipients for the formulation of nanostructured lipid carriers (Zardini *et al.*, 2018). This study supports successive drug delivery design by ensuring the absences of drug interaction with the other excipients and stability of the drug in the formulation (Chandran and Prasanna, 2015).

Crystallization behaviour and lipid polymorphism

Crystallization behavior and lipid polymorphism are the two important parameters to be assessed in lipid-based nanoparticles to obtain stable NLC because crystallization behavior and lipid modification influence the entrapment efficiency and release profiles of the drug. Thermodynamic stability and lipid packing density increase, and drug encapsulation efficiencies decrease in the following order: supercooled melt; α-modification; β'-modification; β –modification (Mehnert and Mäder, 2001). Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) for the determination of the degree of crystallinity of the particle dispersion (Garud *et al.*, 2012).

Applications of NLC

NLCs can be used in a wide variety of drug delivery systems such as oral delivery, Topical delivery, Pulmonary delivery, CNS delivery because of their increased solubility, bioavailability, improved stability, protection of actives from toxicity, enhanced pharmacological activity and, sustained delivery and targeted delivery and well-established biocompatibility. Some of the NLC formulations for different routes of administration are discussed in Table 2.

CONCLUSIONS

Nanostructured lipid carrier (NLC) is the second generation of solid lipid drug carriers composed of both solid and liquid lipids as a core matrix. NLCs offer many advantages over conventional carriers for drug therapy, including increased solu-

Table 1: Various formulation ingredients used in the formulation of NLC

Formulation Ingredient	Examples	Reference
Solid Lipids	Stearic acid, cetyl palmitate Glyceryl Behenate, Glyceryl Monostearate, Gelucire Ovucire WL 2944, Grades of Softisan, Grades of Dynasans, Lauric Acid Cutina CP, Palmic acid Witepsol E 85	(Sarma and Das, 2019; Gaba *et al.*, 2015; Shete and Patravale, 2013; Pardeike *et al.*, 2011)
Liquid Lipid	Oleic acid Castor oil, Labrasol, Isopropyl myristate, Cremophore EL olive oil, soybean oil, sunflower oil peanut oil, sesame oil, corn oil, Almond oil, Cetiol, Corn oil Mygliol 812 N, Tegosoft M, and Tegosoft P	(Sarma and Das, 2019; Gaba *et al.*, 2015; Shete and Patravale, 2013; Pardeike *et al.*, 2011)
Surfactants	Pluronic F-68 and Tween 80 Tween 20, Span 80, Pluronic F 188 and Pluronic F 127 Cremophor, Solutol® HS 15, Poloxamer 188 Eumulgin SLM 20, Lutrol F68, Span 85	(Sarma and Das, 2019; Gaba *et al.*, 2015; Shete and Patravale, 2013; Pardeike *et al.*, 2011)

Table 2: NLC formulations for different routes of administration

Therapeutic Applications	Therapeutic Agent	Purpose	NLC Composition	Outcome	References
Oral delivery	Exemestane	Breast cancer	Precirol® ATO 5 flaxseed oil Poloxamer 188, Tween 80, and Tween 20	3.9-fold enhancement in bioavailability	(Singh *et al.*, 2019)
Topical delivery	Flurbiprofen	NA	stearic acid glyceryl behenate castoroil Tween 80	Delayed and sustained permeation of Flurbiprofen	(González-Mira *et al.*, 2011)
Pulmonary delivery	Doxorubicin and siRNA	Lung cancer	Precirol ATO 5 Soybean phosphatidylcholine Squalene, Tween-80	Enhanced antitumor activity when compared with intravenous treatment	(Taratula *et al.*, 2013)
CNS Delivery	Protein	Neuro degenerative diseases	Precirol ATO5 and Dynasan 114) Precirol ATO5 Poloxamer 188 Tween 80 Chitosan.	Effective delivery of protein to the brain. Prolonged retention time of CS-NLCs in the nasal epithelium.	(Gartziandia *et al.*, 2015)

bility, bioavailability, improved stability, protection of actives from toxicity, enhanced pharmacological activity and intracellular uptake, improved tissue macrophages distribution, sustained delivery and targeted delivery. NLC can be easily scaled up and can be modified to alter the drug delivery rate, stability, and drug loading. NLC holds significant promise for effective therapeutic delivery of drugs administered via different routes of administration. Taking all these factors into consideration, it can be concluded that NLC could be a promising approach for the delivery of a variety of drug molecules and other agents.

REFERENCES

Backman, A.-C. 2002. Zeta Potential Analysis of Nanoparticles. *NanoComposix*, pages 23–27.

Bahari, A. S., Hamishehkar, L., *et al.* 2016. The Impact of Variables on Particle Size of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers; A Comparative Literature Review. *Advanced Pharmaceutical Bulletin*, 6(2):143–151.

Beloqui, A., Solinís, M. A., Rodríguez-Gascón, A., Almeida, A. J., Préat, V. 2016. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. *Nanomedicine: Nanotechnology, Biology and Medicine*, 12(1):143–161.

Chandran, I., Prasanna, P. 2015. Drug - Excipient interaction studies of loperamide loaded in polsorbate 80 liposomes. *Oriental Journal of Chemistry*, 31(4):2201–2206.

Danaei, M., Dehghankhold, M., Ataei, S., Davarani, F. H., Javanmard, R., Dokhani, A., Mozafari, M. 2018. Impact of Particle Size and Polydispersity Index on the Clinical Applications of Lipidic Nanocarrier Systems. *Pharmaceutics*, 10(2).

Dutta, L., Mukherjee, B., Chakraborty, T., Das, M. K., Mondal, L., Bhattacharya, S., Debnath, M. C. 2018. Lipid-based nanocarrier efficiently delivers highly water-soluble drug across the blood-brain barrier into the brain. *Drug Delivery*, 25(1):504–516.

Gaba, B., Fazil, M., Khan, S., Ali, A., Baboota, S., Ali, J. 2015. Nanostructured lipid carrier system for topical delivery of terbinafine hydrochloride. *Bulletin of Faculty of Pharmacy*, 53(2):147–159.

Gartziandia, O., Herran, E., Pedraz, J. L., Carro, E., Igartua, M., Hernandez, R. M. 2015. Chitosan coated nanostructured lipid carriers for the brain delivery of proteins by intranasal administration. *Colloids and Surfaces B: Biointerfaces*, 134:304–313.

Garud, A., Singh, D., Garud, N. 2012. Solid Lipid Nanoparticles (SLN): Method, Characterization, and Applications. *International Current Pharmaceutical Journal*, 1(11):384–93.

González-Mira, E., Nikolić, S., García, M. L., Egea, M. A., Souto, E. B., Calpena, A. C. 2011. Potential Use of Nanostructured Lipid Carriers for Topical Delivery of Flurbiprofen. *Journal of Pharmaceutical Sciences*, 100(1):242–251.

Honary, S., Zahir, F. 2013. Effect of Zeta Potential on the Properties of Nano-Drug Delivery Systems - A Review (Part 1). *Tropical Journal of Pharmaceutical Research*, 12(2).

Iqbal, M. A., Md, S., Sahni, J. K., Baboota, S., Dang, S., Ali, J. 2012. Nanostructured lipid carriers system: Recent advances in drug delivery. *Journal of Drug Targeting*, 20(10):813–830.

Jain, A. K., Thareja, S. 2019. In Vitro and In Vivo Characterization of Pharmaceutical Nanocarriers Used for Drug Delivery. *Artificial Cells Nanomedicine and Biotechnology*, 47(1):524–539.

Jores, K., Mehnert, W., Mäder, K. 2003. Physicochemical investigations on solid lipid nanoparticles and on oil-loaded solid lipid nanoparticles: a nuclear magnetic resonance and electron spin resonance study. *Pharmaceutical Research*, 20(8):1274–1283.

Mehnert, W., Mäder, K. 2001. Solid lipid nanoparticles: production, characterization, and applications. *Advanced Drug Delivery Reviews*, 47(2-3):105–108.

Muller, R., Petersen, R., Hommoss, A., Pardeike, J. 2007. Nanostructured lipid carriers (NLC) in cosmetic dermal products☆. *Advanced Drug Delivery Reviews*, 59(6):522–530.

Naseri, N., Valizadeh, H., Zakeri-Milani, P. 2015. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation, and Application. 5:305–313.

Pardeike, J., Weber, S., Haber, T., Wagner, J., Zarfl, H. P., Plank, H., Zimmer, A. 2011. Development of an Itraconazole-loaded nanostructured lipid carrier (NLC) formulation for pulmonary application. *International Journal of Pharmaceutics*, 419(1-2):329–338.

Sailaja, A., Krishna, Amareshwar, P., Chakravarty 2011. Formulation of solid lipid nanoparticles and their applications. *Journal of Current Pharma Research*, 1(2):197–203.

Salvi, V. R., Pawar, P. 2019. Nanostructured lipid carriers (NLC) system: A novel drug targeting carrier. *Journal of Drug Delivery Science and Technology*, 51:255–267.

Sarma, A., Das, M. K. 2019. Formulation by Design

(FbD) approach to develop Tenofovir Disoproxil Fumarate loaded Nanostructured Lipid Carriers (NLCs) for the aptness of the nose to brain delivery. *Journal of Drug Delivery and Therapeutics*, 9(2):148–159.

Shete, H., Patravale, V. 2013. Long-chain lipid-based tamoxifen NLC. Part I: Preformulation studies, formulation development, and physicochemical characterization. *International Journal of Pharmaceutics*, 454(1):573–583.

Singh, A., Neupane, Y. R., Mangla, B., Kohli, K. 2019. Nanostructured Lipid Carriers for Oral Bioavailability Enhancement of Exemestane: Formulation Design, In Vitro, Ex Vivo, and In Vivo Studies. *Journal of Pharmaceutical Sciences*, 108(10):3382–3395.

Suhaimi, S. H., Hisam, R. H., Rosli, N. A. 2015. Effects of Formulation Parameters on Particle Size and Polydispersity Index of Orthosiphon Stamineus Loaded Nanostructured Lipid Carrier. *Journal of Advanced in Applied Sciences and Engineering Technology*, 1(1):36–39.

Taratula, O., Kuzmov, A., Shah, M., Garbuzenko, O. B., Minko, T. 2013. Nanostructured lipid carriers as multifunctional nanomedicine platform for pulmonary co-delivery of anticancer drugs and siRNA. *Journal of Controlled Release*, 171(3):349–357.

Xu, R. 2008. Progress in nanoparticles characterization: Sizing and zeta potential measurement. *Particuology*, 6(2):112–115.

Yoon, G., Park, J. W., Yoon, I.-S. 2013. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs): Recent Advances in Drug Delivery. *Journal of Pharmaceutical Investigation*, 43:353–362.

Zardini, A., Mohebbi, M., Farhoosh, R., Bolurian, S. 2018. Production and characterization of nanostructured lipid carriers and solid lipid nanoparticles containing lycopene for food fortification. *Journal of Food Science and Technology*, 55(1):287–298.

Zhu, X., Vo, C., Taylor, M., Smith, B. R. 2019. Non-spherical micro- and nanoparticles in nanomedicine. *Materials Horizons*, 6(6):1094–1121.