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Nano structured lipid carrier: A promising technique for improvement of solubility and bioavailability

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Abstract:

Poor aqueous solubility and low bioavailability are major challenges in the development of many therapeutic agents, leading to reduced drug efficacy and inconsistent clinical outcomes. Nanostructured lipid carriers (NLCs) have emerged as an advanced lipid-based nanocarrier system designed to overcome these limitations. NLCs are composed of a blend of solid and liquid lipids, stabilized by surfactants, forming a nanostructured matrix that enhances drug loading capacity and prevents drug expulsion during storage.

The nanoscale size and lipid composition of NLCs significantly improve the solubility of hydrophobic drugs by promoting better dispersion and interaction with biological fluids. Additionally, NLCs enhance oral and systemic bioavailability by facilitating improved intestinal absorption, lymphatic transport, and permeability across biological membranes. They also offer advantages such as controlled drug release, improved stability, reduced toxicity, and compatibility with various administration routes including oral, topical, and parenteral delivery.

Keywords: Nanostructured lipid carriers, bioavailability, solubility, nanostructured matrix, surfactants.

Introduction:

Nanoparticle drug delivery systems have gradually become emerging technology. Nanostructured lipid carrier (NLC) is a next and advanced generation solid lipid nanoparticles consisting solid lipid and liquid lipid (oil) to form unstructured matrices, which improves drug loading and decreases the drug expulsion from the matrix during storage. NLC are lipid-based nanoparticles, has been introduced as a latest pharmaceutical delivery system.

As NLC shows excellent solubilisation and dispersing capacities, it has been turned into a promising nano carrier and has been widely investigated for oral drug delivery. [1]

Lipids as carriers in the drug delivery provide numerous opportunities due to their ability to enhance gastrointestinal solubilisation and absorption of drug by selective lymphatic uptake of poorly bioavailable drugs. Lipids in NLC possess various advantages like biocompatibility, high solubilization potential, easy manufacturing and ability to enhance oral bioavailability of poorly water soluble drug etc. Lipids eliminating various physiological barriers such as pre-systemic metabolism, gastrointestinal degradation of drug, P-gp efflux and permeability related issue, thereby enhances the bioavailability of BCS class II and IV drugs. Lipid-based nanoformulation such as nanostructured lipid carriers (NLCs) has shown great potential in delivering the active therapeutic ingredient to the intestinal lymphatic system and to avoid the first pass metabolism. After oral administration, NLC exhibits better controlled release than other lipid based formulations in gastrointestinal tract. Variable drug release mechanism can be achieved by converting the liquid lipid content in solid form. Nanostructured lipid carriers of poorly water soluble drug can maintain sufficient solubility at the intestinal absorption site on account of the small particle size and lipid solubilisation. Among the various lipid nanocarrier formulations, nanostructured lipid carriers (NLC) grabs more attention due to their unique binary lipids constituent of different chemical structure which, provides enormous scope of exploration of lipid vehicle that could improve *in vivo* release through poorly water soluble drugs. Several methods can be used for the preparation of NLC such as high-pressure homogenization, melting dispersion, microemulsion, solvent diffusion, solvent displacement- injection, solvent emulsification-evaporation, double emulsification and ultrasonification.[2]

Component of the Nanostructured lipid carriers

The lipids are the main ingredient of NLC as it influences the drug loading, stability and the drug release behaviour of the formulations. Appropriate selection of lipid is essential to prepare the stable nanostructured lipid carriers with optimum physical and chemical characteristics. The selection of solid and liquid lipids is based on the solubility of the drug in the lipids. The solid and liquid lipid should form a homogeneous stable formulation.[3]

i) Solid lipid

The solid lipids accepted and safe for the human use and *in vivo* biodegradable can be used

to design nanostructured lipid carriers. Solid lipids like glyceryl monostearate, glyceryl palmitostearate (Precirol ATO 5), glyceryl behenate (Compritol 888 ATO), beeswax, carnauba wax, dodecanoic acid, myristic acid, cetyl palmitate, palmitic acid, stearic acid, dynasan 114, precifac, etc. can be used.[4]

ii) Liquid lipids (oil)

Liquid lipids are well tolerated and widely accepted for the human use. Liquid lipids like Lauroglycol FCC, Capryol 90, paraffin caprylic- and capric triglycerides, α-tocopherol / vitamin E, squalene oil, 2-octyl dodecanol, Miglyol 812, Miglyol 810, Transcutol HP, Labrafil, lipofile WL 1349, Labrafac PG, Soya bean oil, Coconut oil, Oleic acid, medium chain triglycerides (MCT) / hydroxyoctacosanyl hydroxystearate and isopropyl myristate, Cetiol V, castor oil, palm oil, olive oil etc. can be used to design nanostructured lipid carriers.[5]

iii) Surfactants (Emulsifying agents)

Hydrophilic surfactants like polyvinyl alcohol, solutol HS15, Soy lecithin , polyglycerol methyl glucose distearate, Pluronic F68 (poloxamer 188), Pluronic F127, Tween 20,Tween 40, Tween 80 , Cremophor EL, Cremophor RH40, Cremophor RH60, d-tocopherol polyethylene glycol 1000 succinate (TPGS), Span 20, Labrafil, Labrasol, and Gelucire etc. can be used to prepare nanostructured lipid carriers.[6]

Factors influencing Nanostructured lipid carriers

i) Lipid Lipids enhance oral bioavailability and reduce plasma profile variability of drug. While screening, proper and most suitable lipid should be selected for the active ingredient, which gives the highest solubility.[7]

ii) Surfactant The concentration of the surfactant crucially affects the particle size of the NLC. It is generally observed that with increase in surfactant/lipid ratio, particle size of nanoparticles can be reduced. The decrease in surfactant concentration may result in increased particle size during storage.[8]

iii) Process parameters

Formulation temperature

The formulating temperature of the solid lipid must be 5–10 °C above its melting point. If the temperature is less than the melting point, the solid lipid will not melt and will not incorporate into the drug properly. If the temperature is higher, the lipid will get degrade.[9]

Stirring time

For the smooth and fine particle size optimum stirring rate is essential.

Formulating procedure

It is very important parameter that affects the particle size, zeta potential and polydispersity index of NLC.[10,11]

Significance of Nanostructure lipid carriers

- Simple manufacturing process without addition of any organic solvents.
- High efficiency of drug loading.
- Excellent biocompatibility and improved stability
- Easy scale up (e.g., high-pressure homogenization).
- Nanostructured lipid carriers can be administered by various route of administration like oral, parenteral, pulmonary, dermal, and ocular.
- Organic solvents can be avoided, as it is water-based methods.
- NLC shows efficient control of drug release, and can incorporate drug.
- Nanostructured lipid carriers (NLCs) have potential in delivering the agents to the intestinal lymphatic system and to avoid the first pass metabolism.
- NLCs have been proved to enhance oral bioavailability and other pharmacokinetic properties of drugs to be administered orally.[12,]

Mechanism of drug release

Active ingredients along with surfactant and cosurfactants can be fabricated as NLC, the formulation shows improved properties. The improved properties are because of change in the physical state of lipid molecules as well as the molecular interactions between the lipid molecules within the lipid core and with the aqueous surfactant environment. The reduction of particle size leads to increase in surface area and energy of interaction between the lipids, surfactant and the active ingredient. This influences the bioavailability of drug loaded NLC.[13]

Solubility and bioavailability enhancement of drug can be achieved through NLC due to the transformation of drug from crystalline to amorphous form. After oral administration of nanostructured lipid carriers, it gets absorbed from the intestine by direct uptake through the GI tract. NLC also suppress degradation of drugs in GIT. Surfactants increases drug permeation and decreases degradation and clearance. In addition to this, the NLCs can also

adhere on to the gut wall for the prolonged time, and consequently increases the absorption.[14]

Methods of Preparation

The formulation of NLC involves the nanoemulsification of a lipohilic phase composed of a mixture of solid lipid and liquid lipid in an aqueous solution of water-soluble surfactants or emulsifiers. Following techniques can be used in formulation of NLC.

i) High Pressure Homogenization:

This is the most common and suitable method used for the preparation of drug-loaded nanostructured lipid carriers as it does not require any organic solvents. High pressure homogenization is top-down method; it can reduce the large size of drug crystals by mechanical abrasion. HPH can be classified as hot HPH and cold HPH. In the hot high pressure homogenization technique, the drug is dispersed in a mixture of melted liquid lipid (eg. Miglyol®812 or soy lecithin) and Solid lipid like triglycerides, waxes, or fatty acids, such as glyceryl palmitostearate. This hydrophobic drug mixture is then mixed and blended with a heated aqueous solution of hydrophilic and hydrophobic surfactants, using a high-pressure homogenizer at the pressure range (100–2000 bar) for an average of 3–5 cycles of homogenization. This results in forcing the hydrophobic phase into small cavities in the homogenizer and formation of emulsified particles in the submicron range. Hot HPH is suitable for the large scale production of NLC. In cold HPH, the drug is mixed with the lipid phase just above its melting point followed by immediate cooling of the mixture on dry ice or liquid nitrogen, which results in rapid recrystallization of solid lipid particles. The mixture latter milled into micron range and to formulate NLC it is passed through high pressure homogenizer.

ii) Ultrasonication or High speed Homogenization:

In this technique heated lipid phase is mixed with large portion of surfactant in heated aqueous phase using ultra-sonication or high-speed homogenization. NLCs can be formulated either using water bath ultra-sonication or high-speed homogenization. NLC formulated by this method commonly shows large polydispersity and moderate product stability.

iii) Solvent Emulsification/Evaporation:

In this technique drug and lipid mixture, is dissolved in a water-immiscible organic solvent

followed by emulsification in an aqueous phase using ultrasonication or high shear homogenization. The organic solution then kept under low pressure 40–60mbar for complete evaporation of organic solvents. This method is suitable for heat sensitive drugs.

iv) Spray Drying:

The spray drying technique can be used for high melting point lipid phases. It is as an alternative approach to freeze drying. In this method due to elevated temperature and shear stress particles kinetic energy increases and it gives multiple smaller particle collisions. For the better yield, solid lipids with melting point higher than 70◦C can be used at a concentration of 1% w/v in an aqueous solution of trehalose.

Nanostructured lipid carriers (NLCs) have emerged as a highly effective lipid-based drug delivery system for improving the solubility of poorly water-soluble drugs. By combining solid and liquid lipids, NLCs create a less ordered lipid matrix that enhances drug loading capacity and prevents drug expulsion, making them superior to earlier lipid carriers.

One of the major advantages of NLCs is their ability to significantly enhance the bioavailability of active pharmaceutical ingredients. Their nanoscale size increases surface area, promotes better absorption, and facilitates improved drug transport across biological membranes, leading to more efficient therapeutic outcomes. NLCs also offer advantages such as controlled and sustained drug release, improved stability, and reduced side effects. These properties make them suitable for a wide range of administration routes, including oral, topical, and parenteral delivery systems.[15]

Conclusion

Overall, nanostructured lipid carriers represent a promising advancement in nanotechnology-based drug delivery. Their ability to improve solubility and bioavailability while maintaining safety and stability highlights their strong potential in modern pharmaceutical research and future clinical applications.

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