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A REVIEW ON NANOSTRUCTURED LIPID CARRIERS AS DRUG DELIVERY SYSTEM

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Abstract:

Now-a-days, nanocarrier drug delivery systems are proved to be the most efficient drug carrier systems. Nanoparticles contribute to site specific targeting thus preventing the degradation of drug from various physiological barriers. Amongst all advancing nano drug carriers, lipidic systems are considered to be the most evident. Hence, nanostructured lipid carriers are formed. These are the safe lipidic colloidal systems made up of liquid and solid lipid mixtures. The structure of these NLCs is imperfect that provides high drug loading capacity and long-term drug stability. The system is stabilized using surfactants. This lipidic formulation provides increased drug solubility, enhanced permeation, prolonged half-life, reduced clearance and enhanced bioavailability of different class of drugs. The in-vitro drug release studies show different release kinetics of drug. The in- vivo studies showed better permeation of drug into the system and better safety profiles of drug. This ultimately leads to increased safety and efficacy of drugs causing increased patient compliance. these lipidic nano-formulations can be administered through various routes based on the therapeutic action needed. Due to their adhesive property to mucus the orally administered ones are more useful for treatment of local GIT and pulmonary infections. Also, nose to brain delivery of many drugs that do not cross blood brain barrier due to their non-lipophilic nature can be administered in the form of NLCs to increase the bioavailability of drug in brain. Due to the different applications of NLCs such as oral, topical, ocular and pulmonary the formulation is considered to be the most emerging in class of lipidic-NPs.

Keywords: Nanocarriers, nanostructured lipid carriers, high drug loading, enhanced efficacy, lipidic-nanoparticles.

INTRODUCTION:

Nanoparticles at present are considered to be a potential drug delivery platform for treatment of various chronic as well as acute diseases that improves the safety and efficacy of different class of drugs. Nanoparticulate drug delivery system enables site specific targeted drug delivery by protecting the various drug from various physiological barriers. Also, controlled drug delivery system is also achieved by encapsulating the drug into various polymers and lipids to enhanced its efficacy. From all the different nanoparticulate drug delivery systems, lipid nanocarriers are the most evident ones.[1] The lipid carriers that were first formulated were the solid lipid nanoparticles. They had an advantage over liposomes that they possess better stability, controlled release drug delivery, lesser toxicity. But the main disadvantage of SLNs is that its lower drug loading. To overcome the same disadvantage, another generation of lipid nanoparticles are the nanostructured lipidic carriers. They contain both solid as well as liquid lipid component. This leads to decreased ordered structure ultimately increased imperfections that assist increased drug loading. This leads to NLCs the better carrier systems than SLNs.[2] The NLCs are composed of the lipid phase, the aqueous phase and the surfactants. The components are selected and the ratio is defined according to the desired drug release behavior.[1]

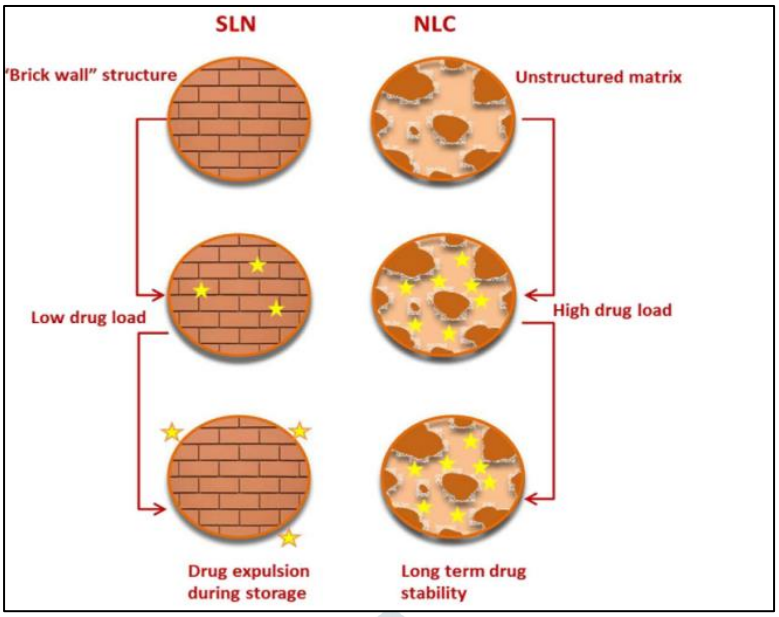

Figure 1: Structure of SLN versus NLC, (Advantages of NLC over SLN)[2]

The different lipids that are used in the formulation of NLCs are triglycerides, fatty acids, steroids and waxes. The different lipids and surfactants that are used in formulation of NLCs are enlisted in the following table,

Table 1: list of different lipids and surfactants used in NLCs[3]*:*

Lipid	Examples
Liquid lipids	Oleic acid, Caprylic/Capric triglycerides, a-tocopherol/ Vitamin E, Soy bean oil, Black cumin oil, Caraway essential oil, Olive oil, Sweet almond oil, Squalene, Capmul MCM C8.
Solid lipids	Compritol 888 ATO, Precirol ATO 5, Stearic acid, Glyceryl monostearate, Cetyl palmitate, Gelucire
Surfactants	Polysorabtes (Tween 20 and Tween 80), Poloxamer 108 and Poloxamer 407, Myrj52, Cremophor EL

Surfactants are used as stabilizers. These can be either used in combination or as single. The concentration of surfactants used ranges from 1.5% to 5%. These surfactants are used to stabilize the formulation of NLCs. They are absorbed onto the surface of the NLCs and reduces the interfacial tension. In most of the cases the combination or mixture of surfactants are used as they enhance the stabilization activity. The surfactant concentration mainly affects the particle size of the NLCs. Some examples of widely used surfactants are poloxamer 188, tween 80 and lecithin.[1]

NLCs are prepared using different combinations of liquid and solid lipids that are incompatible and liquid ones do not form any crystalline complex with solid lipids. Depending on the lipid content and formulation aspects the NLCs are classified into different types(structures), namely: imperfect, amorphous and multiple NLCs. The imperfect NLCs are composed using different lipid of different fatty acid chains. This forms imperfection in the NLC crystal lattice with increased drug loading. Amorphous NLCs are formed by mixing different solid and liquid lipids mixture to form different structureless amorphous matrix with enhanced drug loading. Multiple NLCs are oil in fat in water carrier systems. These are composed of solid lipid matrix enclosing multiple liquid oil nano-compartments. Hot homogenization technique is used to mix solid lipids with large amount of liquid lipids.[1,3]

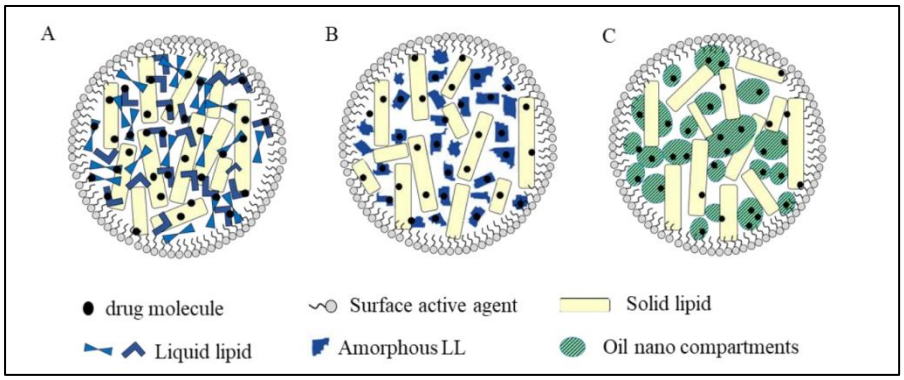

Figure 2: Different types of NLCs: A. Imperfect B. Amorphous C. Multiple[3]

Methods of preparation:

These different methods through which the NLCs are prepared are as follows:

I. High pressure homogenization:

This is the most commonly used method for preparation of NLCs. There are no solvents used in the preparation process. The particles formed are very stable and there are no organic solvent residues. There are two types of high-pressure homogenization techniques.[1] These are as follows:

1. Hot homogenization process:

   This technique is used for thermostable drug molecules. The lipid mixture is heated and molten and dispersed into the aqueous phase using surfactant. The drug is incorporated into the mixture and final emulsion is prepared. This emulsion is then subjected to high pressure homogenization. The obtained NLCs are recrystallized at room temperature. Main drawbacks to this method are degradation of thermolabile substances, lesser encapsulation efficiency, decrease in surfactant activity of many surfactants at high temperature.[1]

2. Cold homogenization process:

   In this technique drug is dissolved in molten lipid. It is rapidly solidified using liquid nitrogen or dry ice. It is dispersed in cold aqueous surfactant solution. The obtained dispersion is then subjected to homogenization. The particles possess high particle size and heterogenicity.[1]

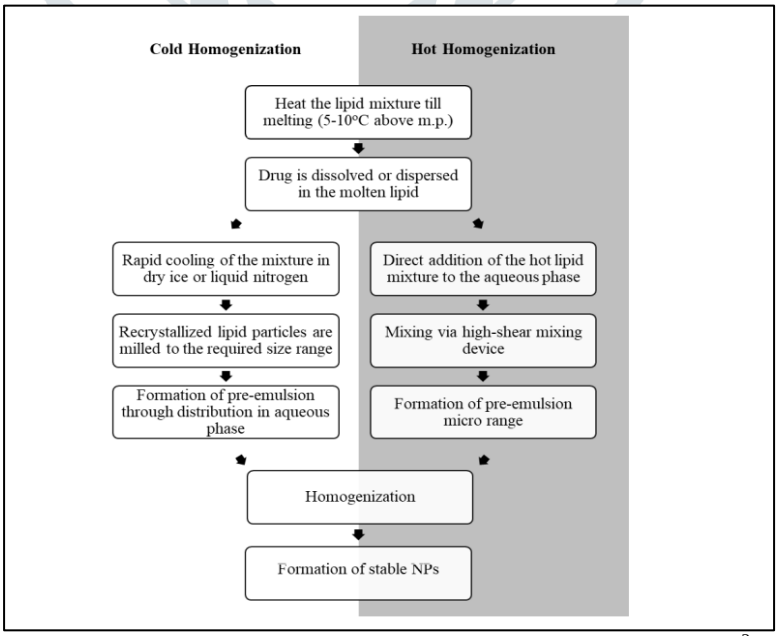

Figure 3: Difference between hot and cold homogenization process[3]

II. High shear homogenization/ sonication:

This method is generally used for lipophilic drugs. The drug is dissolved/ dispersed in molten lipid mixture. The temperature should be greater than the melting point of the solid lipid. The aqueous surfactant solution of same temperature is added to the mixture solution. The obtained dispersion is then subjected to high shear homogenization followed by probe sonication.[1]

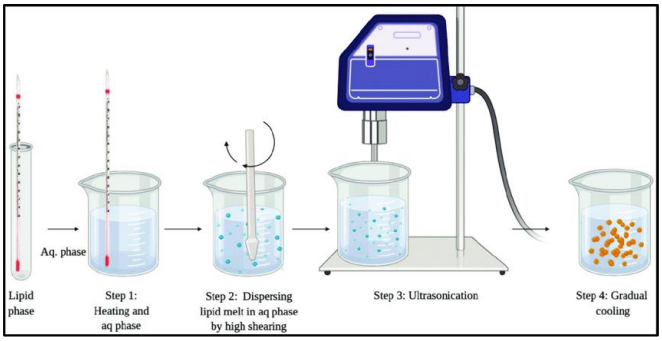

Figure 4: High shear homogenization.[4]

III. Microemulsion:

An emulsion is prepared using same technique to that of high shear homogenization. The hot microemulsion is then added to the cold water to form nano-emulsion. It is then recrystallized to form NLCs.[5]

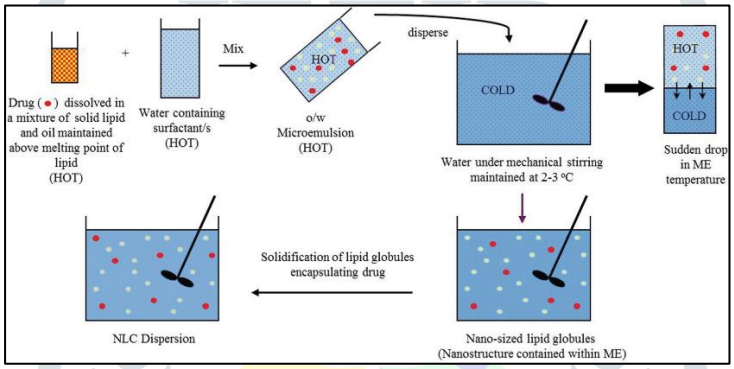

Figure 5: Microemulsion technique.[6]

IV. Double emulsion:

The microemulsion prepared is added to form cold water to cause precipitation of uniformly distributed NLCs. [1]

V. *Emulsification solvent evaporation technique*:

The drug and lipids are dissolved in water immiscible solvent. The solution is emulsified with aqueous surfactant solution. The solvent is evaporated using continuous stirring resulting in NLCs.[5]

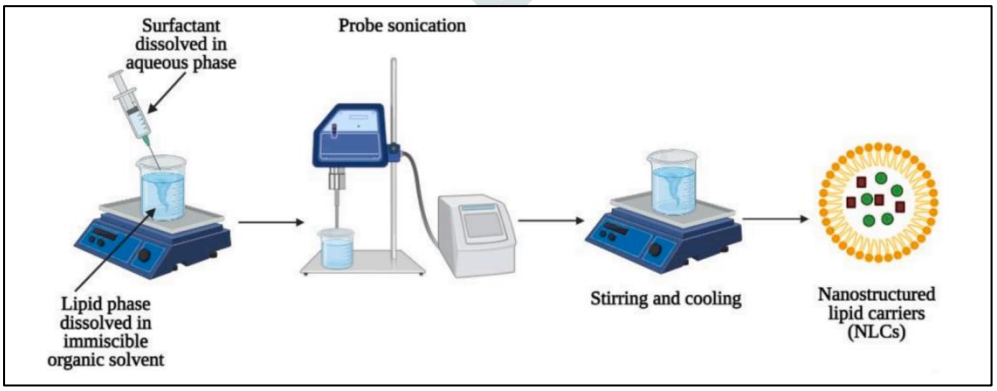

Figure 6: Emulsification solvent evaporation technique[5]

VI. Emulsification solvent dispersion technique:

The drug and lipid is dissolved in the organic solvent. It is saturated in water. The resultant o/w emulsion is distributed in water under continuous stirring until the dispersed phase is solidified.[1]

VII. Solvent injection technique:

This is a very simple and considered to be fastest method of production. In this technique, the lipids are dissolved into water miscible solvent and then is added to the aqueous solution of surfactant through needle injection.[1]

VIII. Phase inversion technique:

In this technique, the drug, lipid, water and surfactant are mixed and heated slightly above the phase inversion temperature of surfactant. The surface of the surfactant is dehydrated in order to form a hydrophilic-lipophilic balance. On cooling the surfactant again becomes hydrophilic to form NLCs.[1]

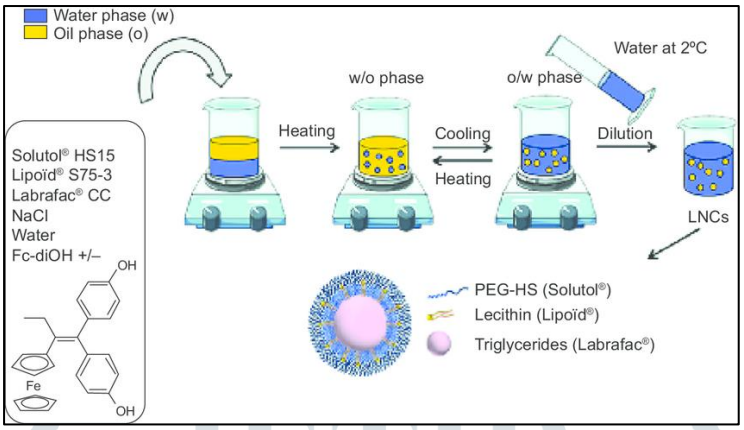

Figure 7: Phase Inversion Technique[7]

Characterization of NLCs:

The characterization of any nanocarrier system is important in order to decide the quality of the product formed. The NLCs are not easy to characterize as they possess a very small particle size and complex nature of the lipids.[1]

I. Particle size, polydispersity index:

Average particle size of the NLCs ranges from 50-300nm. Various formulation parameters such as concentration and type of lipid, surfactant defines the particle size and PDI of NLCs. Different techniques can be used to measure the particle size of the NLCs. Dynamic light scattering can be used for estimation of particle size. It is a nondestructive technique based on Brownian motion of the particles in media. Here, the light intensity scattered is measured. The PDI is the size distribution of NLCs. Low (≤0.3) PDI values indicate homogeneity of the product, whereas high values (≥0.5) indicates high polydispersity, i.e. heterogeneity. [5]

II. Zetapotential:

Zetapotential measure the surface charge. It is the potential difference across the particle that decides the aggregation of system. The net positive or negative charge causes the repulsion between particles that leads to physical stability of the system. NLCs with zetapotential higher than +30 and less than -30 possess physical stability. [5]

III. Morphological studies:

The morphological study of the NLCs can be done using transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM). For examining microscopy of the NLCs, TEM is generally used. In this technique, a small drop of the NLC formulation dispersed in water is put over the carbon coated copper grids. These are stained with uranyl acetate or phosphotungstic acid. The drop is allowed to dry and then analyzed. The dark spots seen one the surface of NLCs is the liquid lipid sticked over the surface. The particles observed are generally of spherical or elliptical shape.[5]

a b

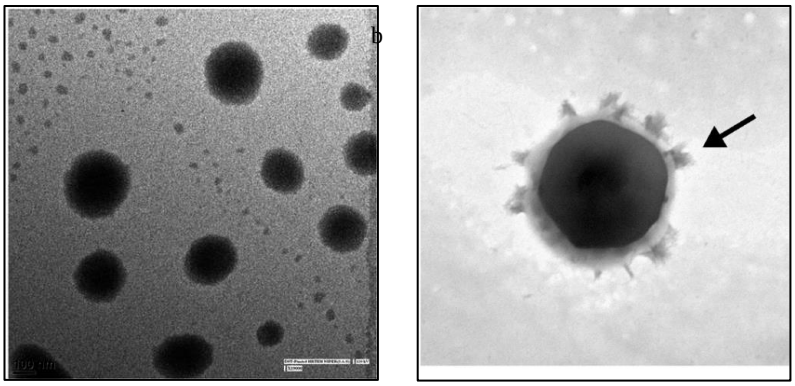

Figure 8: TEM of NLCs, (fig. b shows spots of lipid over NLC surface)[8]

IV. Entrapment efficiency:

The entrapment efficiency is the amount of drug entrapped into the NLCs that determine the efficacy of the system in encapsulating drug. As the NLCs are composed of lipids, high entrapment efficiency is seen in case of lipophilic drugs. This is observed due to the high solubilization of lipophilic drugs into the lipids homogeneously. The lipid and drug homogeneous mixture forms a solid rigid core thus preventing leakage of entrapped drug from the core ultimately leading to high entrapment efficacy. Entrapment efficiency is defined as the amount of drug observed in the particles divided by the initial amount of drug taken in formulation. The final concentration of the drug present in the estimated with the help of UV-visible spectrophotometry. The entrapment efficiency can be estimated using both direct as well as indirect method.[5] The formula for direct method is given below,

$$\%\ entrapment\ efficiency = \frac{amount\ of\ entrapped\ drug}{initial\ amount\ of\ drug\ added} \times 100$$

Entrapment efficiency using indirect method can be estimated using analysis of the supernatant obtained after centrifugation of the loaded NLC dispersion.[5] The formula for estimating entrapment efficiency by this method can be given as,

$$\%\ entrapment\ efficiency = \frac{initial\ amount\ of\ drug\ added - unentrapped\ drug}{initial\ amount\ of\ drug\ added} \times 100$$

V. In vitro drug release studies:

The in vitro drug release studies can be done using dialysis bag method. Drug loaded NLCs with water are placed into dialysis bag and tied at both the ends. The bag is placed into the dissolution medium. It is placed in a thermostatic shaker at 37°C and at predetermined time the samples are withdrawn. Equal amount of replenishing media is added each time. The drug concentration in the sample is estimated using uv-visible spectroscopy. Samples are analyzed in triplicate. The cumulative drug release is plotted versus time and compared to free drug profile. The drug release kinetics are determined using this.[5]

Various routes of administration of NLCs:

The prepared NLCs can be administered through various routes. For different therapeutic applications the NLCs are to be administered through different routes and undergo various pathways to employ its therapeutic activity.[2] The different route through which the NLCs can be administered are as follows,

Oral delivery:

The oral route is most widely used route of administration for any formulation. It is considered to be easiest, cheapest of all the routes. Due to its ease it leads to maximum patient compliance. But the major disadvantage of the oral route is that it is susceptible to first pass metabolism. Where the bioavailability of the drug is very low as compared to other routes of administration. The NLC preparation gives advantages over several disadvantages to oral route. The NLC preparation increases drug solubility, enhanced stability of drug over enzymatic degradation, increased circulation half-life, reduced clearance, enhanced permeability and bioavailability. The drug incorporated in NLC decreases the transit time of gut thus increasing mean residence time in stomach and intestine. Drug absorbed in small intestine gives sustained release.[2]

Nasal delivery:

The drug incorporated into NLCs provide enhanced permeation into the pulmonary interstitium. This provides better drug efficacy when drug is loaded into NLCs. Also, due to the lipophilic nature of various lipids the NLCs can be used to impart nose to brain delivery of drugs. The loading of NLC into in-situ gels helps nasal retention of drug giving local action and also enhances its permeation across membrane.[2]

Topical delivery:

Topical delivery of lipidic carrier systems is well-explored using NLCs. The increased solubility of drugs into the lipids helps into deeper penetration of drugs. NLCs provide enhanced skin targeting, faster onset of action and sustained release profile of drugs. It also assists better safety profile of drugs and reduced skin irritation of drugs. Various anti-psoriasis, anti-inflammatory and anti-fungal drugs can be loaded in NLCs to give topical action.[2]

Ocular delivery:

In ocular drug delivery, the bioavailability of drugs is very less due to various anatomical barriers. The NLCs provide enhanced corneal penetration of drugs and provides increased ocular residence time due to presence of lipids. This improves to ocular bioavailability of drugs and also reduces systemic side effects of drugs. Examples of drugs used for ocular delivery using NLCs are ciprofloxacin, amphotericin B, dasatinib, etc.[2]

Applications of NLCs:

The various routes of administration as discussed above provide highlight their applications in different pathological conditions imparting better efficacy profile of drugs. The advantage of different routes provide implication of NLCs as a better drug delivery system. Some of the remarkable applications of NLCs are discussed below.

1. *Enhancing oral bioavailability of drugs using NLCs:*

Bioavailability is defined as the rate and extent to which the active drug moiety is available into system circulation after administration. Low solubility of drug leads to low drug bioavailability. Hence, increasing the drug solubility leads to increased bioavailability which can be obtained through increased solubility of drugs in lipids. NLCs also improve the oral bioavailability of drug by intracellular uptake through M-cells of payer's patches. Adhesion of NLCs on the wall of intestine cause retention of drug in intestine to be increased. Pluronic used as surfactants cause stearic hindrance effect owing to reduced degradation of drugs.[1] Some examples are discussed further. The NLCs composed of glyceryl tripalmitate (solid lipid), castor oil (liquid lipid), Pluronic F-68 and soy lecithin (surfactants) loaded with olanzapine cause 5.5 times increase in oral bioavailability of drug in rats when compared to simple olanzapine suspension.[9] The NLCs composed of Stearic acid (solid lipid), oleic acid (liquid lipid) and PluronicF-68 (surfactant) with simvastatin as active moiety caused 4fold increase in oral bioavailability of the drug in single dose only.[10] The NLC prepared from Monosteol (solid lipid), Capryol 90 (liquid lipid), Kolliphor EL (surfactant) and Transcutol HP (Cosurfactant) and Ezetimibe (API) increased oral bioavailability of drug 2.5 times when compared to drug suspension and 1.6 times compared to the marketed formulation.[11]

2. *Treatment of GIT local diseases*:

The mucoadhesive property of NLCs that they stick to the walls of intestine which provides retention time and drugs can act locally. Various inflammatory bowel diseases can be treated using this. Budesonide loaded Eudragit coated NLCs were developed to treat inflammatory bowel disease. During invitro studies it was found that the colon targeting could be done efficaciously using NLCs. Also, the in vivo evaluation showed that the NLCs are non-toxic.[1]

3. *Treatment of cutaneous infections:*

Drug delivery pattern in various conventional topical preparations is different in different formulations. For example, for fast release of drug o/w emulsion-based systems were made and for prolonged release fatty acid-based ointments can be used. For local action in conditions where local action of drug is required such as, acne, dermatitis etc local cutaneous effect is seen and for systemic action transdermal effect of drug is required. The major barrier in topical drug delivery is the stratum corneum. The preparation of NLCs safeguard the drug from being degraded chemically and provides increased drug absorption. In a study, quercetin loaded NLC were synthesized. The formulation was used in treatment of reactive oxygen mediated skin damage, where the drug remained on the skin to give its local action for very longer duration. The in vivo studies showed presence of

about 3 times more retention time of the formulation compared to that of the quercetin solution. This showed increased efficacy of the drug. Similarly, the transdermal route can be used as an alternative route for systemic delivery of drugs. It can improve drug bioavailability by bypassing the first pass metabolism. The drug can be diffused through the skin and enter systemic circulation.[1] A study was performed where donepezil loaded NLCs were formed. The formulation was loaded into Carbopol 940 gel base to increase permeability of drug. The in vitro drug permeation studies showed enhanced permeation of drug through the layers and only 0.56% drug retained on to the skin. Thus, the study demonstrated enhanced efficacy of drug through enhanced permeation of drug into deeper layers using an NLC formulation.[12]

Apart from this there are various pulmonary, ocular and brain delivery applications of NLCs. Also, many studies report application of NLCs in cancer treatment.

Toxicity and Biocompatibility of NLCs:

NLCs are considered as safe colloidal systems. Many of the preparations are intended for topical use. However, some formulations containing chemotherapeutic agents can be administered through parenteral route. The toxicity of NLC can be analyzed through testing of all the components present in the formulation for their biological compatibility. In vitro cell viability studies of NLCs show cellular tolerability for positively charged lipid based nanocarriers generally prepared using cationic surfactants. In case of hemocompatibility, hemolysis assay done using NLC shows very less hemolytic effect even at high doses of lipids(1mg/ml). In Vivo animal study of NLC is done mainly to determine the pharmacokinetic parameters of the formulation. Very less or no adverse effect can be seen in case of studies on rats and mice. The safety of any NLC formulation varies from one formulation to another. The lipid content and the choice of surfactant determine the safety of the formulation. Hence proper analysis assessment should be done before designing the recipients of a formulation. The NLCs are considered to be safe nanocarriers for therapeutic agents and must be evaluated individually.[1,3]

CONCLUSION:

NLCs are considered to be the emerging in the field of lipid based nanocarrier systems. They provide wide spectrum of advantages over other conventional preparations. NLC provide high drug loading and high physical stability. They provide applications through various routes of administration such as oral, topical, ophthalmic, pulmonary and parenteral. The incorporation of active molecule in NLC provide enhanced physical and chemical stability, controlled release drug profile, prevents degradation of drug from physiological barriers and improved bioavailability. Having such wide range of advantages, NLCs are considered to be choice of formulations for topical and dermal applications. Also, the particle size of NLCs is so small that they can be easily targeted to tumor cells. This enhances drug delivery of chemotherapeutic agents and reduces its side effects. Apart from this, the in vitro and in vivo studies are evident enough to show the safety profiles of NLCs. Thus, NLCs can be optimized as the safe lipidic-nanocarrier systems that provide high efficacy and better bioavailability of various drugs.

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I wish to extend my special thanks to ‘SARAH’

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