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NANOSTRUCTURED LIPID CARRIERS FOR VARIOUS DRUG DELIVARY SYSTEMS

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ABSTRACT

Lipid Nano carriers are developed as another to chemical compound nanoparticles, liposomes and emulsions. Further, Nanostructured super molecule Nano carriers are the second generation Lipid Nanocarriers developed to beat issues associated with Solid Lipid Nanoparticles and are used in varied therapeutic approaches. NLCs were primarily thought of for the delivery of lipotropic medication however their quality for hydrophilic medication is currently well established. Biocompatible nature of lipids is accountable for its development as a promising drug delivery. It was found to be having superior characteristics over different Lipid Nanocarriers formulations. this text describes the NLC with respect to structures, strategies of preparation, characterization, stability and its blessings over 1st generation lipid nanoparticles. Review primarily focuses on the varied therapeutic applications of NLCs and their specificity for different physiological proximities. because of their biologically non-toxic, non-immunogenic and compatible nature, NLCs are progressing to be the wide explored Lipid Nanocarriers r systems.

KEYWORDS:- NLC, Lipids, Topical, Pulmonary, Transdermal, Oral, Blood brain barrier, Intranasal, Drug delivary.s.

1. INTRODUCTION

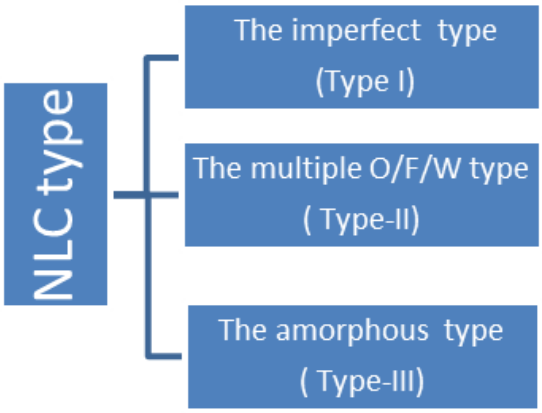
Exploration of novel lipoid nanoparticulate drug delivery system was started from the assembly of solid lipoid nanoparticles (SLNs). Incorporation of drug into numerous

biocompatible lipids developed at nano vary has become a promising approach of drug delivery as lipoid nanocarriers. This initial generation lipoid nanocarrier system was additional developed to realize the drug delivery by various routes of administrations within the treatment of physiological complications.[1] Some limitations of SLNs were determined by investigators that resulted into development of latest lipoid carrier in 1999/2000 by Muller called nanostructured lipoid carriers (NLCs). NLCs were developed by substitution a fraction of solid lipids with liquid lipids to create drug incorporated matrix. Currently, NLCs square measure thought-about as potential drug carriers thanks to their biocompatibility and superior formulation properties over SLNs.[2] Development, characterization and institution of effectualness of drug loaded NLCs is currently a current topic for the drug delivery and targeting. Since most of the medication square measure lipotropic in nature, their solubility in biocompatible liquid lipids could be a key issue for NLC development. NLCs are explored within the drug targeting in numerous diseases. NLCs square measure developed to boost the oral bioavailability of poorly aqueous soluble medication.[3] Currently, NLCs incorporated cosmetic products and dermal creams square measure marketed.[4] Formulation of medicine into NLCs for drug targeting in numerous diseases is explored wide. Drug targeting to numerous systems like pulmonic, brain tissues, anterior and posterior ocular tissues,[5] targeting cancer tissues in numerous types of malignancies, rising the bioavailability and specificity and reversal of multidrug resistance is investigated by utilizing NLCs as potential lipoid nanocarriers.[6] Carbone et al[7] enclosed the data regarding patents on the lipoid primarily based nanocarriers wherever lipoid nanoparticles were developed for the targeting and treatment of assorted ailments. Oral and topical medical aid, brain and cancer targeting, gene delivery square measure self-addressed.

Lipid nanocarriers

SLNs are the primary generation lipoid nanocarriers. These are developed to formulate drug in solid lipids ideally by cold or hot blending technique, relying upon thermal stability of the drug. Due to some discovered limitations of SLNs like drug escape through matrix throughout storage, lower drug loading potency, NLCs were developed. NLC formulation is predicated on the construct of incorporation of drug within the mixture of varied ratios of solid lipoid and liquid lipoid. NLCs were designed to get the less/no crystalline matrix with coagulated core to beat the constraints occurred thanks to crystallinity of SLNs core. Methods of preparation of SLNs and NLCs aren't a lot of completely different from one another. Cold blending, hot blending, hot emulsification - Ultrasonication are the normally used techniques

for both SLNs and NLCs preparation. The formulation parameter that shows distinction in each is nothing however the composition of core/matrix. In SLNs the medicine area unit primarily dissolved or directly incorporated within the solid lipids. NLCs contain the drug solubilized and/or dissolved within the liquid and solid lipoid mix and distributed within the liquid section containing wetter. During storage and forthwith throughout blending, the core in the SLNs tends to create a wonderfully ordered crystalline structure, permitting the escape of drug in dispersion media. Because of excellent crystalline nature of core there's less house out there for drug loading. This development is avoided within the formulation of NLCs. because of presence of liquid lipids at the side of solid lipid; matrix loaded with drug does not form excellent Bravais lattice. It forms imperfect core and doable amorphous matrix permitting higher drug loading and hindrance of drug escape. Amorphous nature of core avoids expulsion of drug into liquid section. Once drug has higher solubility in liquid lipoid used, the oilin-solid fat-in- water (O/F/W) system will be developed. Little oil globules area unit incorporated and equally distributed into solid lipoid core in which drug is slowly discharged from oil droplets.[8] Briefly, styles of NLCs will be summarized as below:



a) NLC type I

It also can be referred as imperfect sort. Replacement of a fraction of solid lipid by liquid lipid/oil causes formation of imperfect crystal lattice/matrix. This development shows availableness of extra space for accommodation of drug and permits higher drug loading. Formation of imperfect crystal core offers extra space for drug incorporation, avoiding

formation of extremely structured or ordered matrix which might have expelled drug out of the core.

b) NLC type II

This can be multiple type and developed from the construct of w/o/w emulsion. It's primarily oil-in-solid or fat-in-water type NLC, which might be developed solely by part separation technique. When drug shows higher solubility in oil, this approach is utilized in formulation of NLCs so as to improve drug loading capacity and stability. Little droplets of oil are spread uniformly in solid lipid matrix and this technique is spread within the aqueous medium.[9]

c) NLC type III

This can be additionally called amorphous/ structureless sort. Use of solid lipids that stay in α being once hardening and storage along with liquid lipids tend to make amorphous core. This is advantageous over type I NLCs as no crystallization happens and drug remains embedded in amorphous matrix. The β being of solid lipids develop crystalline structured matrix.

The outline of all kinds of NLCs are shown in **Figure -1 :-**

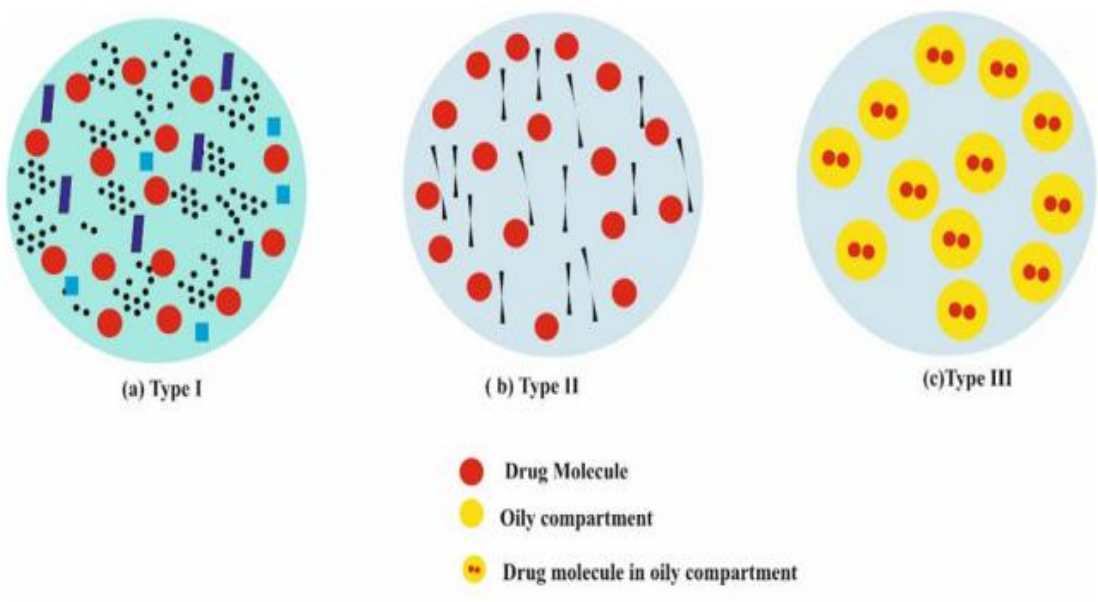
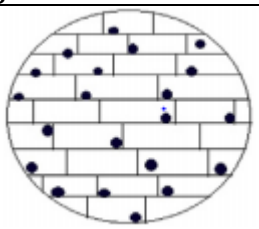
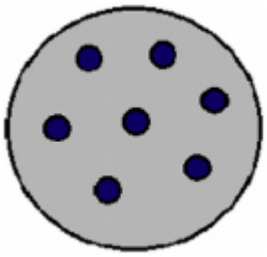
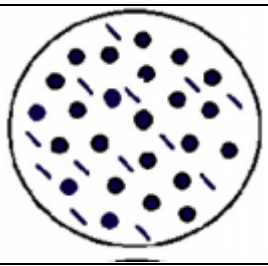


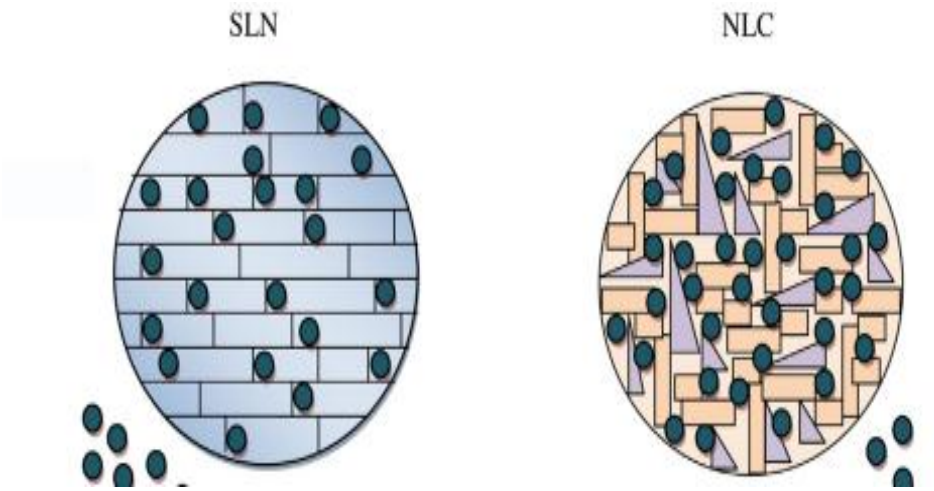
Fig. 1: Drug molecule, Oily Compartment and Drug molecule in oily compartment model of NLC's.

Table 1: Lipid nanocarriers: a summary.[9]

Lipid nanoparticles	Diagrammatic illustration[9]	Description
Solid Lipid nanoparticles		SLN is a perfect crystal lattice structure. There is less space for accommodation of drug inside the lipid core, resulting in the less drug loading and expulsion of drug out of the system.
Nanostructured Lipid Carriers NLC Type I		It is an imperfect crystal core. More space is available for drug accommodation inside the lipid core. Hence, higher drug loading is possible and reduced/no possibility of drug expulsion from core.
NLC Type II		This is multiple model known as O/F/W model. Drugs having higher solubility in liquid lipids/oils than solid lipid can be formulated into this type. It can be prepared by phase separation method. Drug is present in the dissolved state inside tiny oil droplets and uniformly distributed in the solid core.
NLC Type III		This type is also known as structureless type. Instead of conversion into a crystalline structure, solid lipids incorporated into this get converted into an amorphous form.

The stability profile of SLNs and NLCs are shown in Fig. 2. During storage, SLN and NLC dispersions behave otherwise. SLN is composed entirely of solid lipids; thus once crystallization it forms a rigid core proscribing the movement of medicine at intervals the core. This leads to expulsion of drug into dispersion media. Because of this development entrapment potency of the system is lowered.

Composition of NLCs is that the mixture of solid and liquid lipids. During rigidization of NLC in media, because of presence of liquid lipids imperfect core is made. Such core permits the upper drug loading and sufficient space for accommodation of drug. thus throughout storage, drug isn't expelled out of the core.



Expulsion of drug from the rigid core **No or very less drug expulsion from core**

Fig. 2: Illustration of stability of SLN and NLC during storage.

Comparison between SLNs and NLCs

Lipid nanocarrier systems square measure among the foremost loved analysis topics for the drug delivery and targeting. As mentioned earlier, NLCs are the second generation supermolecule nanocarriers whose development took place thanks to determined limitations of the SLNs. The improved effectuality of SLNs was incontestable by some researchers by formulating SLNs and NLCs and coincident characterization of each.

Atorvastatin -loaded SLNs and NLCs were developed and relatively evaluated by Das et al. each square measure ready by emulsificationultrasonication technique. Parameters like particle size, defense potency (EE), drug unleash and stability were influenced by concentration of lipids and quantitative relation of lipids used. At higher drug load, each NLCs and SLNs were stable at lower temperatures, whereas at the space temperature NLCs were comparatively additional stable than SLNs. In vitro drug unleash studies conducted throughout storage showed no important changes in drug unleash from NLCs. This study terminated that NLCs were superior within the desired drug unleash and stability profile as compared to SLNs.[10]

Drug delivery to the posterior phase of ocular tissues was investigated by formulating and characterizing nonsteroidal anti-inflammatory loaded SLNs and NLCs. supported the parameters like drug loading, nerve compression potency and ocular tissue penetration of drug NLC formulation was thought of as an acceptable supermolecule carrier as compared to SLN.[11]

Co-delivery system of Oncovin and temozolomide victimization 2 sorts of supermolecule nanocarriers within the treatment of deadly brain tumor was developed by Shanghai dialect et al. The in vivo tumour inhibition study was with success concluded the best effectuality of NLC formulation over SLN and different formulation counterparts. Success of this study was incontestable by the in vivo tumour repressing effectuality and NLC as a good carrier for dual and synergistic drug therapy.[12]

The summarized info of all variety of supermolecule nano carriers primarily based on their properties is delineate in table 2

Based on the investigations,[8–10,12] The lipid nano carriers can be distinguished in their properties as following.:-

Parameters	**Solid lipid nanoparticles**	**Nanostructured lipid carriers**
Nature of lipids	Solid	Blend of solid and liquid lipids
Possible drug accommodation	Low	High
Degree of crystallinity	Higher (ordered matrix)	Lower (Amorphous/imperfect crystalline matrix)
Drug escape from matrix in dispersion media	Comparatively higher	Lower
Stability	Lower	Comparatively Higher

Structures of NLCs

When SLNs are ready from solid lipids, the matrix tends to make a comparatively excellent crystal lattice; going restricted area to accommodate the active ingredients shows the projected structure of the inner cores of SLNs. In distinction, the use of a macromolecule mix as well as solid and liquid forms will distort the assembly of an ideal crystal. The particle matrix contains imperfections, providing area to accommodate the drug molecules in amorphous clusters. It's additionally been projected that NLCs are composed of oily droplets embedded in a very solid macromolecule matrix. The morphology of particles of NLCs isn't necessary spherical. Jores et al have hypothesized that the particulate structure is solid platelets with oil gift between the solid platelets and also the surface-active agent layer.

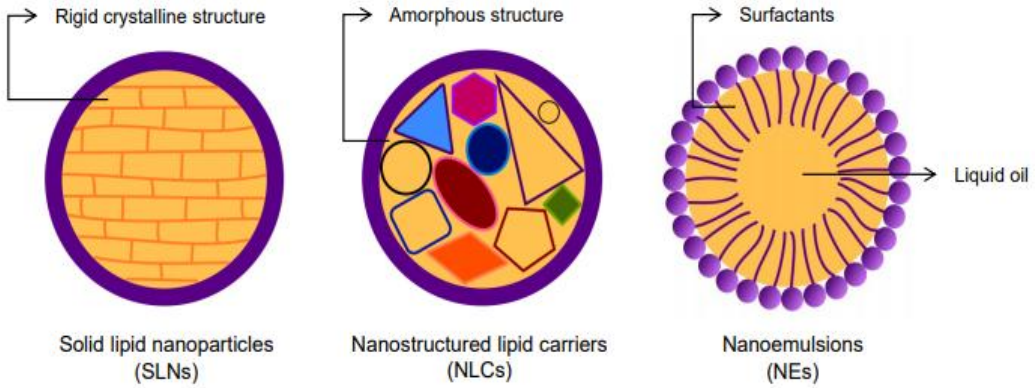
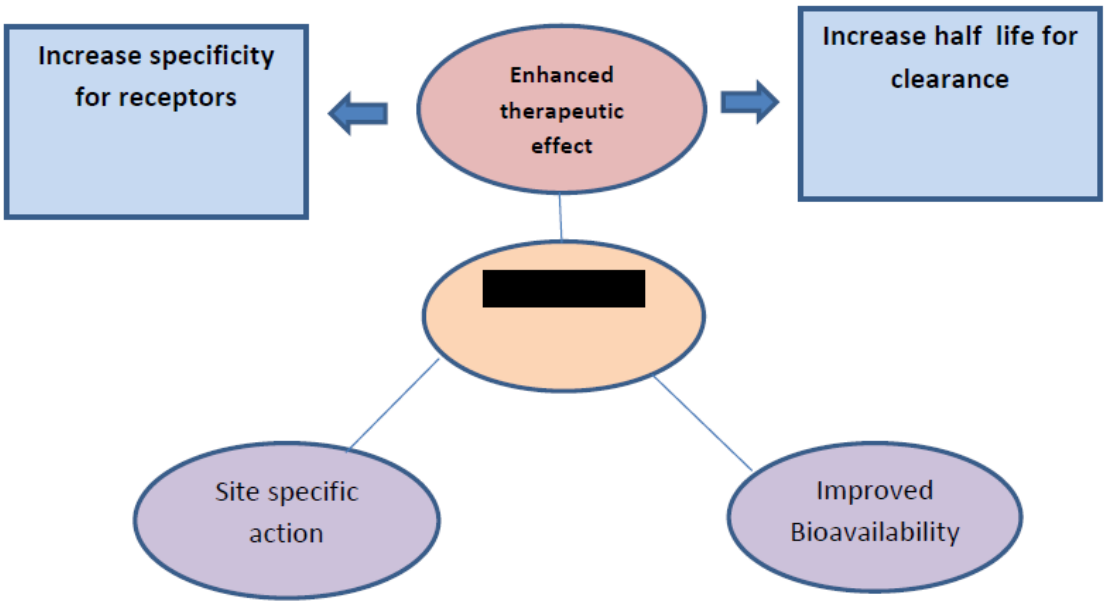


Fig. 3: Nano particulate structures of solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and Oil-in-water Nano emulsions (NEs).



Advantages of NLCs

- Better physical stability
- Ease of preparation and scale-up,
- Increased dispensability in an aqueous medium
- High entrapment of lipophilic drugs and hydrophilic drugs,
- Controlled particle size,
- An advanced and efficient carrier system in particular for lipophilic substances,
- Increase of skin occlusion,
- Extended release of the drug,

- One of the carriers of selection for locally applied medicine as a result of their super molecule elements have associate degree approved standing or are excipients utilized in commercially on the market topical cosmetic or pharmaceutical preparations,
- Small size of the super molecule particles ensures shut contact to the stratum membrane therefore enhancing drug penetration into the mucous membrane or skin,
- Improve benefit/risk quantitative relation,
- Increase of skin hydration and elasticity and
- These carriers are extremely economical systems thanks to their solid super molecule matrices, that also are usually recognized as safe or have a restrictive accepted standing
- In SLNs, the drug is mainly dispersed in molecular form, for example, located in between the fatty acid chains of the glycerides whereas in NLCs, blend of solid and liquid lipids are used and due to their differences in structure they cannot fit together very well to form a perfect crystal. This arrangement creates a lot of imperfections in matrix leading to accommodation of more drugs in molecular form and amorphous clusters.
- liquid macromolecule extra leans to increases the drug-loading. The little quality of the glycerides are often used to overcome this example. It was well documented in literature that If there's the amendment within the structure of the lipids, the issues like cluster of medicine arise and leads to disorderly imperfect macromolecule matrix and every one this happens is thanks to crystallization methodology.

- **Limitations with lipid nanoparticles**

Despite the great potential of NLCs in targeted delivery, they face certain limitations like:

- Cytotoxic effects related to the nature of matrix and concentration,
- Irrigative and sensitizing action of some surfactants,
- Application and efficiency in case of protein and peptide drugs and gene delivery systems still need to be better exploited, and
- Lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair (Sch ä ferreting et al. 2007).

Oral drug delivery

Oral route is that the most convenient route of drug administration. Bioavailability (BA) of poorly water soluble drugs is reduced because of various GI barriers and organic chemistry processes like effluence by enterocyte transporters, hydrophilic surroundings, gut wall

metabolism by enzymes and resident microflora and hepatic 1st pass metabolism which can be overcome by formulating medicine in NLCs.[3]

Spironolactone (SPN), a poorly water soluble drug was developed as NLC by HPH methodology. Pharmacokinetic knowledge discovered terribly less and incomputable levels of SPN however the presence of its major metabolites 7α-TMS and canrenone answerable for result. Among these 2 metabolites, 7α-TMS was found in higher concentration in plasma. Biodistribution of radiolabelled SPN was detected within the bowel, liver and excretory organ. Formation of mixed micelles was possible to reinforce solubilization and BA of drug from micelles.[23]

Silybum marianum (milk thistle) plant extract was loaded in NLCs. In vitro lipolysis experiment has shown potential increased effectivity of drug in NLCs because of mixed particle formation. In vivo oral BA study carried out in dogs showed the less tmax than marketed formulation which was indicative of higher absorption of drug in disagreeable person.[24]

Curcumin NLCs surface was functionalized with N-acetyl-L-cysteinepolyethylene glycol(100)-monostearate (NAPG). Mucoadhesion of carrier was achieved via interaction of thiol cluster of NAPG with glycoprotein thereby increasing retention in gut that showed sweetening in curcumin absorption.[25] Chitosan coated antibiotic drug B developed as NLC showed mucoadhesion because of positive surface charge and delayed the stomachal transit thereby rising oral BA.[26]

Oral BA of tacrolimus, Associate in Nursing medication was improved once formulated as NLC. NLCs ready by HPH methodology showed higher aqueous solubility of drug as compared to NLCs ready by different method. Higher plasma drug concentration and increase in 0.5 lifetime of drug was achieved by NLCs.[27]

Vinpocetine, a genus Vinca organic compound incorporated in NLCs,[28] and in the form of co- evaporated vinpocetine-cyclodextrin-tartaric acid advanced (VP-β-CD-TA COE-NLC)[29] was found to boost oral BA than standard formulations.

NLC loaded with rosuvastatin metal showed drug permeation in deeper enteral tissues wherever superior oral BA was achieved with greater antihyperlipidemic potential than standard medical care.[30] Similarly, bioavailability of different antihyperlipidemic medicine,

lipid-lowering medication,[16] lipid-lowering medication[31] was improved by loading it in NLCs wherever sustained drug unharness with longer mean continuance and improved in vivo performance was determined.

Fang et al. developed docetaxel loaded NLCs during which surface of lipid nanocarriers was changed with amino acid mistreatment PEG 2000-monostearate as a linker. Here, improvement in BA was determined because of mucoadhesion resulting in longer continuance, inhibition of p-gp effluence because of thiomer (cysteine) and concealing properties offered by PEG.[32]

Nisoldipine[33] and Carbamazepine[34] square measure the 2 extremely metabolizing medicine whose oral BA was improved once developed as NLCs.

In vitro dynamic lipolysis experiment for lipoid nanocarriers mimick the GI surroundings i.e. digestive juice salts and numerous enzymes square measure value-added in simulated disagreeable person media that reveals the potential in vivo drug performance. The lipoid nanocarriers endure interactions with digestive juice salts forming mixed micelles, haunted by the enterocytes and humor system resulting in increased BA upon oral administration.[23–26]

The illustration represents the potential ways that of GI absorption of drugs embedded within the NLCs. Mucoadhesive materials facilitate the adhesion of NLCs to the GI animal tissue cells. This causes retention of NLCs on the GI surface and drug is discharged in sustained manner for prolonged amount of your time. Digestive juice salts gift within the GI fluids move with lipids of NLCs to make mixed micelles. These square measure simply absorbed within the systemic circulation.

Transdermal drug delivery

Some of the orally administered drugs bear degradation because of gastric acid, viscus first pass metabolism and enteric metabolism. These factors area unit answerable for drug loss and reduction in bioavailability resulting in frequent administration of dose type and subject have to suffer the varied facet effects. transdermic delivery of such drugs is another and engaging approach nevertheless possesses some difficulties. Chemistry properties of the drug molecules have an effect on the transdermal delivery. Drug must be having optimum partition coefficient so as to diffuse through hypodermic tissue; it should possess low relative

molecular mass and low freezing point. Drug delivered using chemical mediators like permeation enhancers and physical methods like EMDA and electroporation will have negative effect on the integrity and performance of skin tissues. supermolecule nanocarriers show blessings over these standard transdermic drug deliveries. Lipids area unit safe, biocompatible, non-irritant and might be developed in nano size vary.[35] Application of NLC formulation to the stratum corneum ensures the shut contact of supermolecule structures of NLC and also the skin thereby effective drug permeation is achieved. It additionally hydrates the skin by forming occlusive layer and reducing the transepithelial water loss.[36]

There area unit some studies, that counsel aggregation of negatively charged NLC at hair follicles and static interaction of completely charged NLC with negative skin surface; each resulting in permeation of drug. Clobetasol propionate loaded chitosan coated NLC[37] and fungicide HCl loaded NLC incorporated in carbopol gel[38] showed higher drug permeation and dermal retention of medicine than business formulations.

NLC incorporated gel of acid was developed wherever hindrance in permeation of charged NLC was overcome by incorporation of permeation enhancers in gel. Accumulation of drug in skin was ascertained that cause the discharge of drug for prolonged amount of your time.[39] Flurbiprofen (FP) loaded NLC,[40] FP-NLC loaded carbopol gel[41] and valdecoxib NLC gel[20] showed bigger diffusion of drug through skin, winning inhibition of dropsy and prolonged action of drug while not inflicting irritation to the skin. Similar findings were reported just in case of clobetasol propionate NLCs loaded topical gel[42] and methotrexate NLC loaded carbomer gel[43] developed for the treatment of skin disorder and skin disorder, severally. Guo et al., incorporated 2 organic compounds lappacontine and ranaconitine from genus Aconitum sinomontanum in NLC that showed less toxicity than alkaloid solutions and showed higher in vivo BA in comparison with SLN.[44] Corticoid was developed as NLC and its follicular delivery and localization was ascertained which could be helpful for the treatment of sex hormone phalacrosis.[45] Topical anaesthetic and prilocaine co-loaded NLCs showed effective anesthetic analgesic activity than single drug loaded formulations.[46] A silver-nanolipid complicated was formulated for the treatment of dermatitis. Microsilver was added within the NLC dispersion ready by HPH technique and its sorption on NLC surface was confirmed by exaggerated particle size of NLCs and combination of field flow fractionation and multiple angle light-weight scattering (FFF–MALS). Silver-NLC showed pronounced antimicrobial activity against staphylococci aureus as compared to the alone

silver. Hapten-induced inflammatory animal model showed important reduction in erythroderma and ear thickness once silver-NLC formulation was applied. in vivo studies conducted in animals and human showed the significant reduction within the symptoms of dermatitis. Success of this study may be explained on the premise of medicine activity of silver at low concentrations and skin occlusion and association provided by lipids thereby prolonged contact time of formulation with affected skin.[47]

Investigators have compared 5 unremarkably used solid lipids used for formulation of NLCs so as to estimate their cytotoxic potential in human dermal embryonic cell by analyzing aerobic stress upon UVA exposure and cell viability. The results showed the comparative safety upon use of Compritol ™ 888 ATO thanks to its neutral cytotoxic behavior and gentle pro-oxidant result that wasn't aggravated by UVA exposure.[48]

Factors influencing NLCs

The major factors influencing NLCs formulation are as follows:-

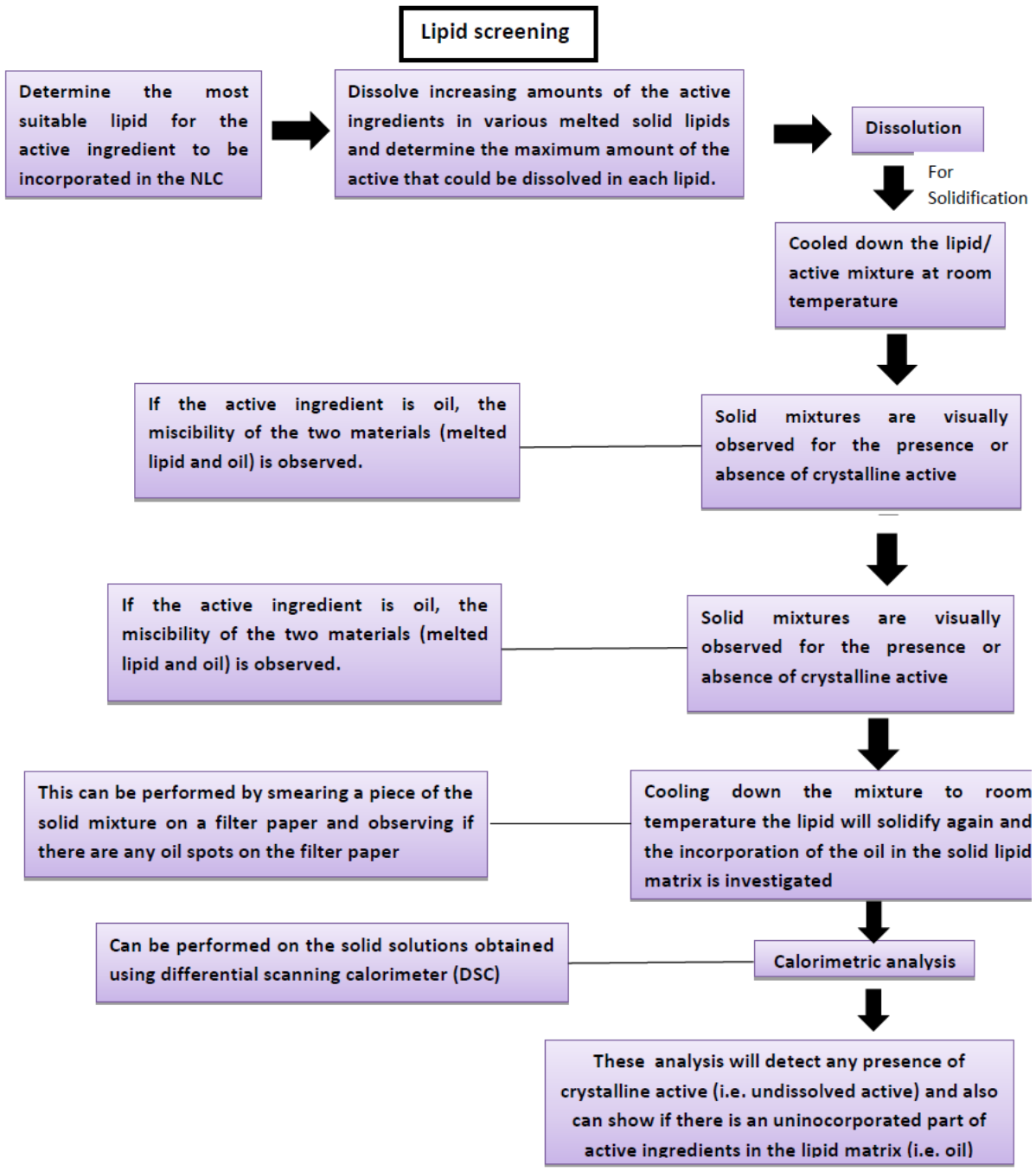
Lipid:- Lipids enhance oral BA and decrease plasma profile variability. Its screening should be performed to work out the foremost suitable lipid for the active ingredient which supplies the highest solubility.[49]

Surfactant:- The concentration of the chemical agent powerfully affects the particle size of the lipoid NPs. In general, smaller particle sizes were determined once a better surfactant/lipid magnitude relation was chosen. The decrease in chemical agent concentration would result in increase in particle size throughout storage. Surfactants decrease the physical phenomenon between the interface of the particles inflicting portioning of the particles and thereby increasing the area.[50]

Mechanism of improvement of bioavailability by NLC:- When the lipid bulk material along with surfactant and cosurfactants is formulated as Nanoparticles, the formulation shows altered properties (Bummer, 2004).[51] The altered properties are a result of changes in the physical state of lipid molecules as well as the molecular interactions and energies involved between the physical state of lipid molecules within the lipid core and with the aqueous surfactant environment. The reduction of particle size (below sub-micrometer range) results in relative increase of surface area and higher energy of interaction between the lipid/surfactant/ Active Pharmaceutical Ingredients molecules, which in turn influences the Bioavailability of API-loaded NLCs, as the Nanoparticles dose administered is proportional

to the Lipid concentration , as well as to the number of particles per volume. It seems that small particle size of the formulation significantly improve the Bioavailability of Active Pharmaceutical Ingredients the composition, and particularly the surface properties of the NPs (Andrysek T, 2003, 2006).[52]

Methods of preparation lipid screening:- The screening of lipids stepwise, for the preparation of NLC's are shown in Figure 6[24]



Methods of preparation of NLS's

There are several methods are developed for the preparation of NLS's.[53]

The most command methods are as follows:-

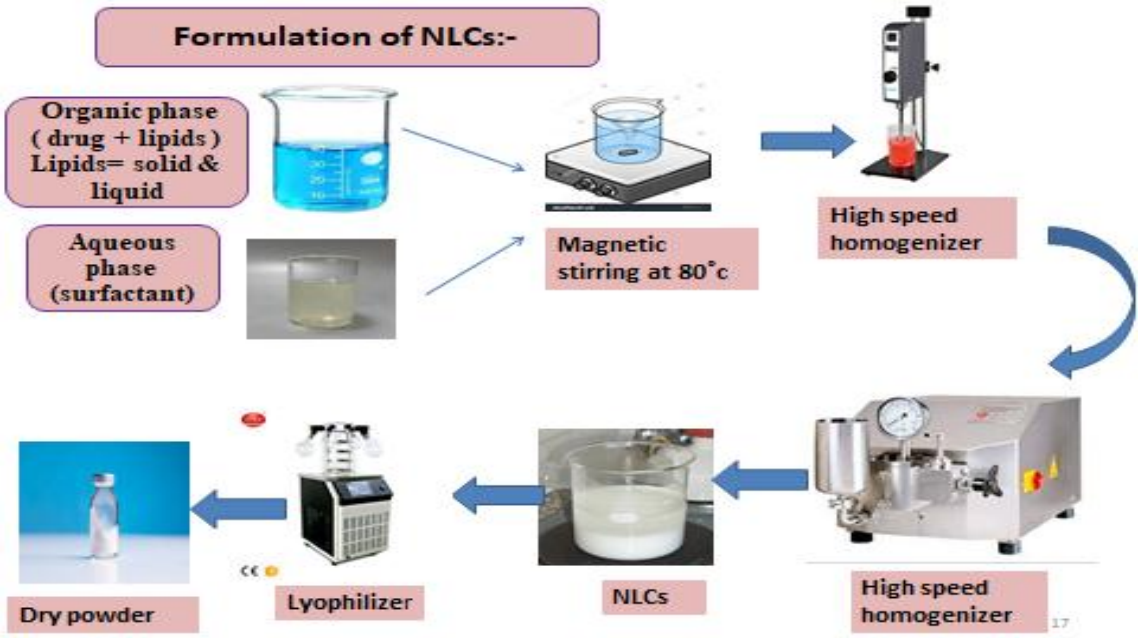
- High-pressure homogenization.
- Microemulsion technique.
- Emulsification- solvent diffusion
- Emulsification- solvent
- Evaporation solvent injection.
- Multiple emulsion techniques.
- Phase inversion.
- Ultrasonication.
- Membrane contractor technique.[53]

- **Main advantages and disadvantages of the different techniques used to prepare NLCs as drug delivery systems**

Preparation technique	Advantages	Disadvantages
Hot High Pressure Homogenization	• Low particle size and polidispersity index • Application for medium and large scale • Low cost • Absence of solvents	• Risk of drug degradation due to high temperatures and intensive energy process
Cold High Pressure Homogenization	• Application for medium and large scale • Low cost • Absence of solvents • Reduced thermal exposure of the drug	• Higher particle size and polidispersity index
Micro emulsion dilution	• No special equipment required • Low energy input • Mild operating temperatures	• Very low particle concentration
Solvent emulsification-evaporation	• Avoidance of thermal stress • Low energy input • Small particle size	• Use of organic solvents
Solvent emulsification-diffusion	• Low energy input • Small particle size and polidispersity index	• Use of organic solvents • Low particle concentration
High-shear homogenization or ultrasonication	• Small particle size	• Energy intensive process • Metallic contamination

Solvent injection	• Avoidance of thermal stress • Low energy input • Fast production	• Use or organic solvents

- **High-pressure homogenization**



High pressure homogenization (HPH), a simple and easy to scale-up technique.[55] HPH can be applied by two general approaches: hot homogenization or cold homogenization, being the hot HPH the most used. In this Figure features a schematic representation of the preparation of NLCs by hot HPH. Briefly, the melted lipids containing the PWS drug are dispersed in a hot aqueous solution of surfactant, emulsified and finally processed by HPH. Surfactant concentration and lipid composition, and operating temperature condition the distribution of the drug in the lipid matrix and the release profiles of drugs.[56] If the drug is molecularly dispersed in the lipid matrix, it is homogeneously distributed in the core, so that the drug is released by diffusion and/or by degradation of the lipid matrix. When the drug concentration is close to its saturation solubility in the melted lipid, lipid-coated core is formed principally, and the drug is retained in the core and is released slower from the nanoparticles. On the contrary, when phase separation occurs between the drug and the lipid, during the cooling process in hot HPH an outer drug-enriched shell which covers the lipid core is formed, and therefore the drug is released quickly.

In the cold homogenization technique the drug is not subjected to such high temperatures. The initial drug lipid mixture is solidified by rapid cooling using liquid nitrogen or dry ice,

then dispersed in a cold aqueous solution of surfactant, and finally HPH is applied. This technique reduces the burst effect and the thermal exposure of the drug, but the particle size and polidispersity index are higher compared to the ones in the hot technique.[58] Other classical preparation methods include microemulsion dilution,[57,59] solvent emulsification-evaporation,[39] emulsification/diffusion,[40] high-shear homogenization or ultrasonication[60, 61] and, the solvent injection.[62] Table 1 summarizes the main advantages and limitations of the mentioned techniques.

A potential limitation of NLCs has been related to the long-term storage and stability. Water elimination is an effective strategy to overcome these problems. Water elimination can be performed by spray-drying or lyophilization of the suspension. Spray-drying induces coalescence of the particles, which can be reduced by the addition of carbohydrates to the suspension prior to spray-drying.[63] Since during the lyophilization process particle aggregation may occur, the use of sugars as cryoprotectants before the freezing step is highly recommended.[64,65]

CONCLUSION

Hence, based on the above review revealed that NLC is considered being the smarter, latest generation of lipid nanoparticles possessing improved properties for drug loading, modulation of release profile and stable drug incorporation during storage. Due to the various advantages of NLC it can be easily used as a carrier for drug via oral route of administration. Over the past decade, NLC formulation has undergone a continual improvement in the biomedical field. Both amendments played a major role in the application of NLCs and achieving successful outcomes. NLCs have a number of potential industrial applications, mainly due to the many advantages, which have induced the publication of many patents for different applications. However, many of them derive from basic research, and more industrially driven studies are needed. The industrial applications for the vectorization of therapeutically relevant molecules, as well as biotechnological products such as proteins and genetic material. The production technology for highly concentrated lipid particle dispersions—developed in parallel to the NLC technology being applicable to both NLC and SLN-eases the transform of aqueous dispersions to solid products, e.g. tablets, pellets, capsules, but also powders for reconstitution. A lot of preclinical and clinical examples described in the review through clearly illustrate the promising application of the nanoformulation for the improving the existing technological drawback for the

pharmaceutical market and taking into account an increasing number of patented NLC-based formulations. These advantages are thus overcoming previous existing problems. It is also feasible to produce on large scale thus making it one of the promising deliveries, which can be seen in near future in the pharmaceutical market.

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