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An insight to NLCs in topical Delivery of Bio-actives in Pharmaceutical Industry

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Abstract:

Skin delivery is one of the most frequently method used for drug application. But due to rough and tough nature of skin there is always been a search of a carrier that easily penetrate the uppermost layer of skin hence provide significant therapeutic effect. In recent years researchers focus on potential of nanocarriers as drug delivery system in various routes of dug administration. Liposome, niosomes, polymeric nanocarriers, carbon nanocarriers, SLN, NLC are some of the recently used carriers. The safety and toxicity of some nanocarriers is always a matter of conflict so limits their use as drug carriers. NLCs are second generation lipid carriers and due to its structural integration has wide opportunity in topical drug delivery. In this article we review the utilization of NLC and the work done on recent advancement in this field. Review mainly focus on the delivery of NLC in various topical diseases and applicability as drug carrier.

Keywords: NLCs, composition, types, advantages, drug delivery, drug penetration mechanism, and topical purpose

Introduction:

Nanostructured lipid carriers (NLC) are second generation of lipid nanoparticles developed by R.H.Muller to overcome the limitations of SLNs. SLNs have been studied in various route of administration as drug delivery system as a drug carrier but due to limitations like Limited drug loading, instability at room temperature and drug expulsion NLCs are preferred carrier of choice. To overcome these limitations, it is required to use blend of lipid used that do not form crystalline arrangement. NLCs are capable of firmly immobilizing drug and prevent particle from coalescing as compared to nano emulsion. They also serve as an alternative carrier for the polymeric nanoparticles which has certain advantages like low toxicity, biodegradable, drug protection, control release and use of organic solvents is avoided. NLCs in topical delivery seems to be efficient carrier as the similarity of skin lipid with that of lipid used in the preparation of carrier. It is also a suitable carrier for the loading of hydrophilic and lipophilic drugs. Nano repair Q10 cream (Dr. Rimpler, Wedemark, Germany) was the first marketed product of NLC since than many formulations are available worldwide mostly cosmetics. NLC is one of the nanocarriers with the shortest time between invention and market introduction. The NLCs were built with a view to satisfy industrial need in terms of qualification and validation, scale up, simple technology, easy engineering, low cost etc.

1. Structural features of NLCs:

The main composition of SLNs is solid lipid, whereas the NLC made up of lipid phase that contains both solid and liquid lipids. NLC contains more amount of liquid lipid so that the nanoparticles form an irregular shape and in intact form, resulting lattice and forming an amorphous structure. Müller *et al*. [1] provides update of NLC structures: disordered, amorphous, and multiple types. The first one is disordered structure, which composed of mixed solid and liquid lipids that form irregular shape which appears between the crystal and liquid lipid, thus improved drug penetration capacity through the lipid layer [2]. The second one is amorphous non-crystalline state. Less crystalline structure significantly reduces drug leakage (addition of a mixture of lipids reduce crystal formation). Third type multiple structure that contains a higher liquid lipid concentration than the other two structure. Solubility of drug is more in liquid than in solid. Therefore, the NLCs slow down drug release and enhanced drug loading, thus avoid loss of bio actives. **Figure 1** described the macromolecular structure of NLCs.

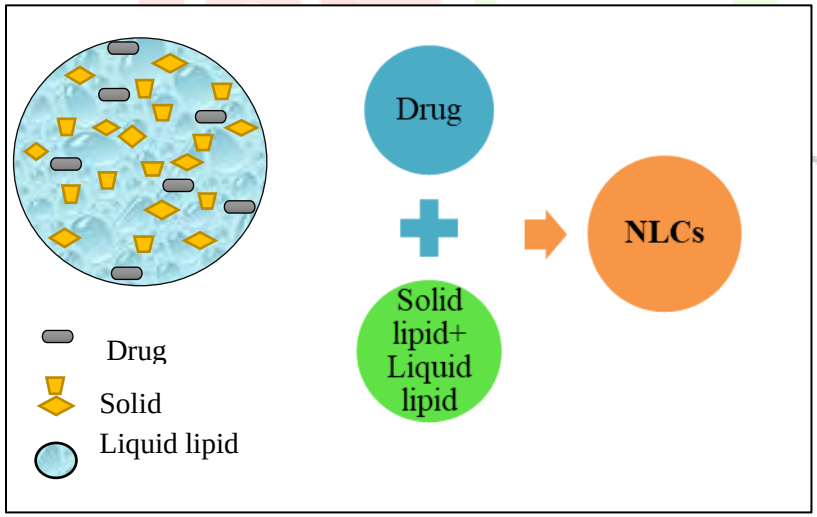

Figure 1. Macromolecular structure of NLC

2. Role of NLCs in Drug Delivery System:

NLCs, as a new drug delivery system, appeared in the late 1990s [3]. Both lipophilic and hydrophilic drug moieties can be encapsulated into the NLCs for delivery. Drug loaded NLCs provides high encapsulation efficiency, biodegradable, non-toxic *in- vivo* results. NLCs can also be used in drug targeting purpose and physicochemical properties of the NLC particles are stable [4]. **Table 1** describes the application of NLCs in drug delivery system through several route of administration.

3. Method of Preparation of NLCs

Various methods are available to make Nano structured drug carriers. Each process involves different approaches of critical process parameters (CPP). Different suitable methods are described in **Figure 2.**

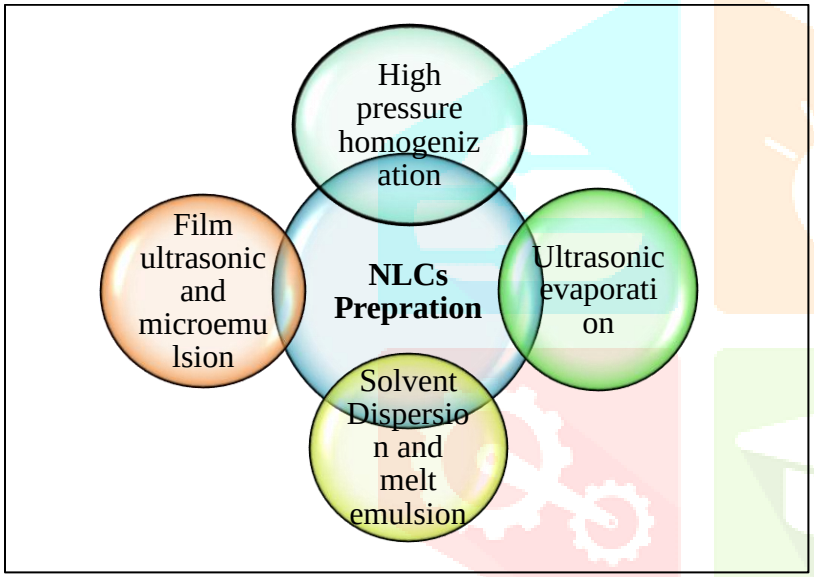

Figure 2. Various methods of NLCs Preparation.

4. Types of NLCs

NLCs are categorized into three dissimilar types depending on the type of lipid used in their assembly. The first type of structure is the disordered structure (mixed solid and liquid lipids which imitate to the disordered state). The second type is amorphous structure (non-crystalline state). The absence of a crystalline structure can avert or diminish the leakage of the loaded drug. Multiple structure is the third type which contains higher liquid lipid**. Figure 3.** Deplicts the types of NLCs.

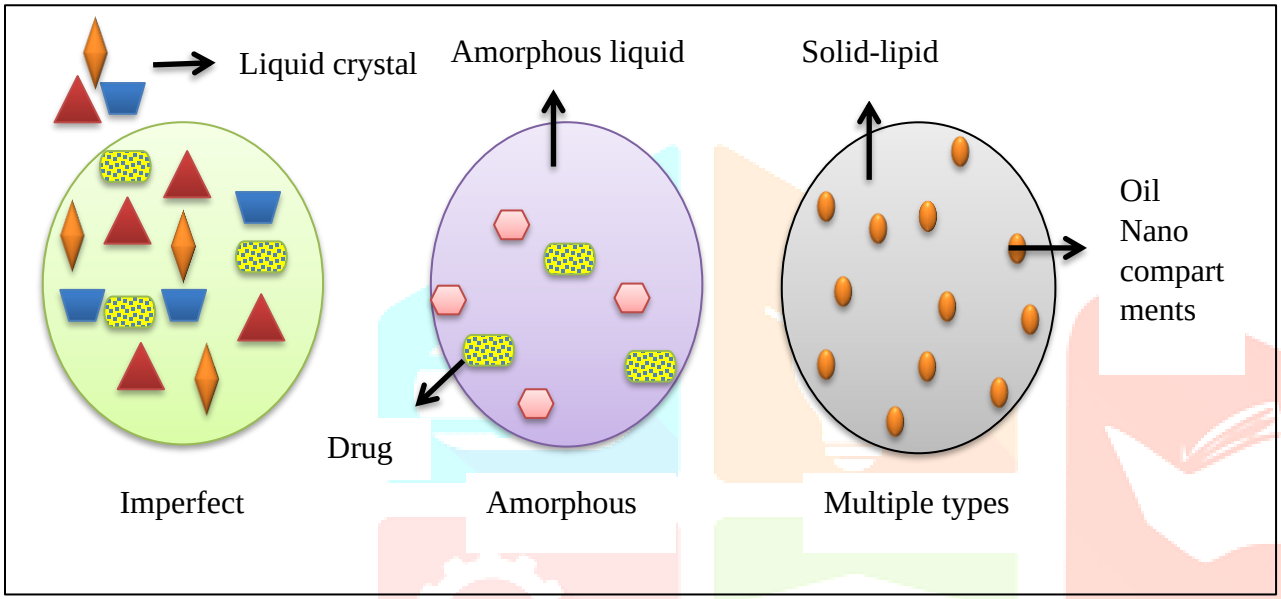

Figure 3. Types of NLCs

Table 1. Application of NLCs in pharmaceutical field as Drug Delivery Carrier

SL No.	Route of Administration	Advantages	References
1.	**Oral.**	NLCs provides various advantages such as enhanced solubility, enhanced permeability and bioavailability, improves stability by protecting the drug molecule from pH and enzymatic degradation, prolonged circulation time, reduced clearance and increased mean residence time (MRT). NLCs mainly used in oral administration to enhance oral bioavailability by increasing the uptake.	[5]
2.	**Topical**	Providing controlled release, protection of the active component, enhanced permeability into the skin and minimal skin irritation. Higher drug release rates and permeability were observed with NLCs than other conventional formulation. NLC shows better skin targeting efficiency, faster onset, prolonged release, negligible skin irritation and a good safety profile for different therapeutics. Tacrolimus – encapsulated NLCs were successfully prepared and the permeation rate of these NLCs through the skin of a hairless mouse.	[8], [18]
3.	**Transdermal**	Having small particle size, it forms a thin film on the skin, so that drugs entrapped in NLCs and avoid chemical decomposition. NCLs remotes drug release that protects the skin, and reduces skin atrophy from repeatedly taking the medication.	[6], [7]
4.	**Pulmonary**	Colloidal mainly lipid Nano-carriers shows many advantages in pulmonary drug delivery system such as a) fully uniform distribution of the drug dose in the alveoli; b) increased Solubility; c); stable from degradation d) sustained release. So, prolonging therapeutic efficacy and reduce dose frequency; e) delivery of macromolecules effectively; f) reduces side effects and g) provide better patient compliance. NLCs may be delivered to the lower respiratory tract successfully due to lower particle size (≤500 nm) leads to improve deposition in all parts of lungs.	[9]
5.	**Intranasal delivery**	Provides rapid absorption due to the high surface area, intense blood supply and porous endothelium of the nasal mucosa, avoid the gastrointestinal and hepatic metabolism, reduce side effects and dose reduction and offers better patient compliance. NLC further enhanced the intranasal drug delivery of duloxetine in the brain for the treatment of major depressive disorder. Nanostructured Lipid Carriers (NLCs) of Asenapine maleate to improve the bioavailability and enhance the uptake of ASN to the brain.	[10], [11], [12]
6.	**Parenteral**	Bufadienolides a class C-24 steroid showed effectiveness of enhanced hemolytic activity and cytotoxicity and provided less side effects when incorporated in NLCs. Nanostructured lipid carriers (NLCs) were prepared and optimized for the intravenous delivery of β-Element (β-E) β-E-NLCs showed a considerably higher bioavailability and anti-tumor efficiency than Element injection.	[13]

7.	**Brain delivery**	Due to the growing incidence of central nervous system diseases such as Alzheimer's disease, Parkinson's disease, stroke, brain tumors, epilepsy and brain infections, drug delivery to the specific brain site becomes a great challenge as about 98% of the newly discovered drugs cannot cross BBB. Nano carriers have shown promising delivery of drug molecule to the brain with higher retention time and besides enhanced capillary wall adsorption. This enhanced retention and adsorption provides a higher concentration gradient those results in an increased uptake of nanoparticles into the brain.	[19]
8	**Ocular delivery**	Recently NLC formulations widely investigated for their potential ocular delivery due to enhance corneal permeation and thus improve bioavailability in addition to being safe, non-invasive and patient compliant. Also the mucoadhesiveness of NLCs increase their interaction with the corneal membrane that results prolonged residence time, improved bioavailability and smaller systemic and local side effects.	

5. Comparison between NLC and SLN respect to drug loading

Nanostructured lipid carrier (NLC) is the second generation advanced lipid nanoparticle which plays as a drug carrier system, has been developed to avoid some critical boundaries of the solid lipid nanoparticle (SLN). The core of NLCs is made up of mixture of spatially dissimilar lipid molecules; normally mixture of solid and liquid lipid that makes more imperfection in the matrix to entrap more drug molecules than SLNs. NLCs can more strongly immobilize drugs and prevent the particle from coalescing by virtue of the solid matrix compared to emulsions. Due to the lower risk of systemic side effects this carrier becomes very important in recent pharmaceutical industry. Now NLCs are used as a good substitute over other drug carriers such as liposomes, polymeric nanoparticles due to its combined advantages of other colloidal carriers. The liquid lipids having different fatty acid C-chains make the NLCs less organized crystalline structure and thus offers better loading capacity for drug loading [14], [15]. Liquid lipids offers better solubilization of drugs than solid lipids. NLCs are composed of physiological and biodegradable lipids that show low systemic toxicity and low cytotoxicity [16]. **Figure 4** compared between storage stability of SLN and NLC after drug loading.

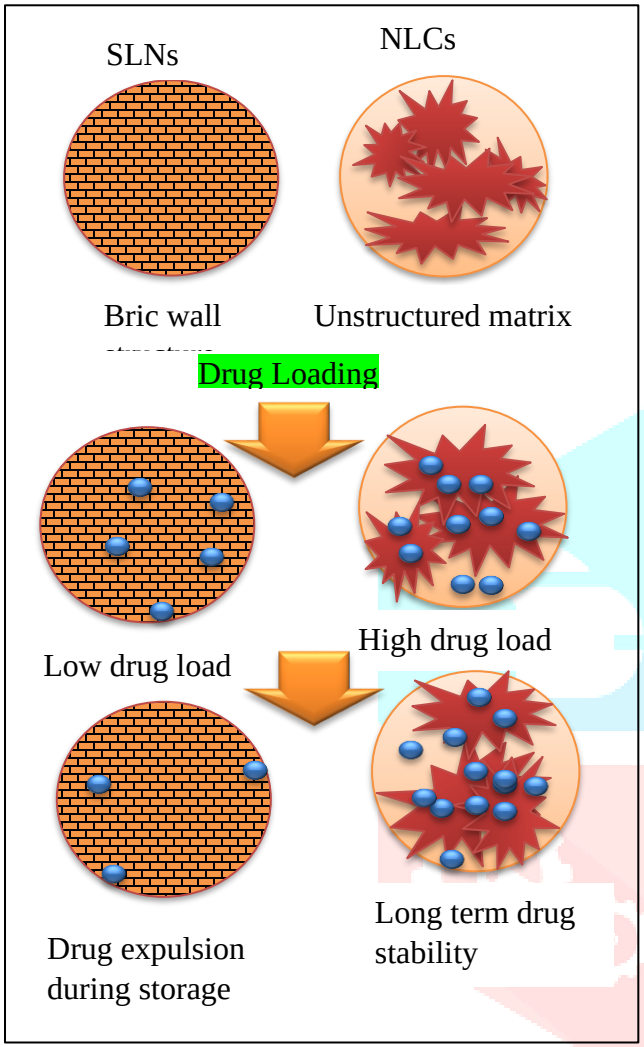

Figure 4. Comparison between SLN and NLC in terms of Drug loading

6. Mechanism of skin penetration of NLCs

The API is contacted with the skin surface, and enters by the three possible paths, like as sweat ducts, hair follicles and sebaceous gland (shunt or appendageal route.) or directly across the stratum corneum. **Figure 5** represents the mechanism of drug penetration through skin layer.

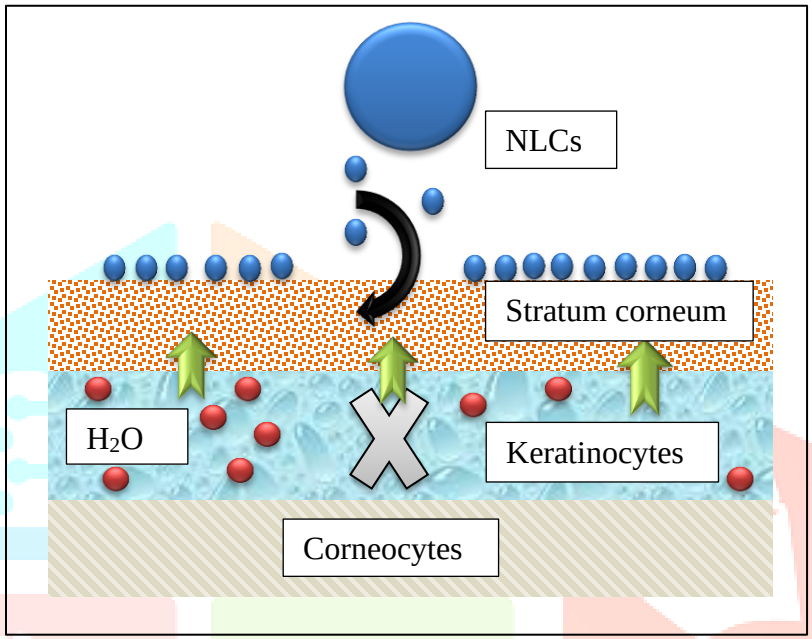

Figure 5. Drug penetration through skin layer.

7. Advantages of NLCs in Topical delivery:

Having small in size the lipid particles confirms close attachment with the stratum corneum and may help to enhance the amount of drug permeation into mucosa or skin. Due to their solid lipid matrix, drug is released in controlled manner from these carriers. This controlled characteristic plays a key role when there is need of the drug for prolonged period of time, to decrease systemic absorption, and when drug produces irritation in high concentrations. NLC provides controlled release behavior of different active ingredients such as ascorbyl palmitate, clotrimazole, ketoconazole, and other antifungal agents. I t is a preferable option for topically delivery of drugs due to their approved lipid components and excipients are widely used in commercially available topical cosmetic or pharmaceutical formulations. Drug penetration through the skin becoming challenging due to the impermeability of the SC. Nano particles improves the skin absorption and also targets the drug in the skin and/or its substructures [21]. Lipid NPs attach to the skin surface and permit lipid particles in between SC and the nanocarriers due to presence of epidermal lipids present in SC and have likely to deliver drugs through the follicles.Furthermore, every follicle is associated with sebaceous glands that release sebum, generating a lipid enriched environment [22]. Hydration of SC results reduction corneocyte packing and broadens inter-corneocyte openings and also influences partitioning of the drug into SC. **Table 2** provides the advantages and disadvantages of NLCs.

SLNO.	Advantages	Disadvantages
1	Enhanced dispersability in an aqueous medium, High entrapment of both lipophilic and Hydrophilic drugs, Controlled particle size.	Shows cytotoxic effects related to the nature of matrix and concentration.
2	Improve skin occlusion, Extended release of the drug.	Irritation and sensitising effects some surfactants.
3	These carriers are highly effective due to their solid lipid matrices, which provides safe or have a Regulatory accepted status [17].	Application and efficiency of protein and peptide drugs and gene delivery system still needs research.
4	Provides better physical stability, Simplicity in preparation and scale-up process.	Lack of adequate preclinical and clinical studies with these nanoparticles in case of bone repair [20].
5	Improve benefit/risk ratio, advanced and efficient carrier system in particular for drug moieties.	Stability of lipids and Nano toxicity.

Table 2. Advantages and Limitations of NLCs

8. Topical relevance:

For topical administration, due to the similarity of skin chemistry to that of the NLC, it shows better permeability, is non-toxic and well tolerated. NLCs can enhance the apparent solubility of entrapped drugs, which leads to high concentration gradient on skin which facilitate drug permeation. NLC dispersion on topical application forms a thin lipid film on the skin tissue which prevents the evaporation of water, maintains the moisture of the skin and ensures hydration as well provides sustain release of the drug. Loo et al. studied the effect of different ratios of ingredients on skin hydration and occlusion. The in vivo study showed that all the NLC formulations were able to significantly increase skin hydration and reduced transepidermal water loss in 7days of treatment. So, the NLCs can be efficient systems to prevent water loss from skin in dermatological conditions. Due to the negatively charged skin surface cationic NLC exhibits better drug diffusion to deeper skin and shows therapeutic effect. The Nano-sized particles closely adhere to the skin surface and release the drugs in a more controlled way. NLCs are used for topical application of various categories of drugs for improvement of penetration along with sustained release.

Conclusion

Co loading of the drugs can be achieved by using NLC as drug delivery system which means more than one drug can be loaded into it. Active targeting of various drugs which are having systemic toxicity or potent such as anticancer drugs by loading active targeting moiety on carrier surface. SLNs as pH sensitive delivery systems are already reported. In the same way, pH sensitive delivery system of NLC can be prepared and can be utilized in cancer delivery. SLN are under investigation as a pharmaceutical tool to stably carry various types of diagnostic agents such as FeO, Tc, Cu so there is possibility of using NLCs for imaging purpose. Recent studies show that NLCs had good prospective application as a new type of carriers for delivery of miRNAs in tumor gene therapy.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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