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Research Paper

Review: Basics of Nanostructured Lipid Carriers (NLC) and Their Various Applications

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Colloidal drug delivery systems at the nanoscale, known as Nanostructured Lipid Carriers (NLCs), are based on a lipid mixture consisting of both liquid and solid lipids. This lipid-based nanosystem was offered as a safe, non-toxic, and biocompatible way to distribute nanodrugs, as opposed to polymer or metal nanoparticles[1]. The size range of nanoparticles is 150–300 nm; in certain circumstances, they may be smaller less than 100 nm or larger up to 1000 nm[2].

Advantages of NLC

This NLC offers the advantage of a drug adsorption system because drug substances generally dissolve more easily in oil than in liquid lipids.

a. NLC is capable of increased therapeutic efficacy, increased skin hydration, increased stability of the encapsulated active ingredient, and generally extended shelf life[3].
b. Positively charged NLCs can improve the dissolution profile of water-insoluble drugs[4].
c. NLCs are potential carriers for therapeutic agents, especially hydrophobic molecules, with biocompatibility, mucoadhesion, permeation/retention, low clearance rate, controlled stability release, and protection of drug candidates from chemical degradation[5].

❖ **NLC can increase drug bioavailability**

According to Alcantara[6] NLC can increase drug bioavailability. This can be seen from the use of NLC for transporting Mupirocin to the intravascular space, where the drug can be delivered more effectively to the site of action. NLC can protect Mupirocin from degradation thereby prolonging its release in the body. In addition, NLC can increase the retention of mupirocin in blood vessels, thereby increasing the amount of drug that reaches the target location. NLC may also reduce the clearance of Mupirocin, thereby prolonging its presence in the body.

❖ **NLC can increase drug efficacy**

The amount of drug that can be added to lipid nanoparticles can be increased by NLC. This is due to the fact that liquid lipids can encourage drug dispersion in lipid nanoparticles and solid lipids have a high drug loading capacity. Because liquid lipids encourage drug diffusion and solid lipids can create a physical barrier that limits drug release, NLC releases pharmaceuticals more effectively. Liquid lipids make the medicine more stable by increasing the fluidity of the nanoparticles and reducing aggregation, whereas solid lipids offer a barrier against outside forces[7]. NLC can increase the effectiveness of drugs in skin hydration and occlusion[8]. NLC with ultrafine particle size (approximately 100-150 nm) allows deeper skin penetration and better hydration and can also increase drug retention time on the skin surface thereby increasing drug efficacy. This shows that NLC can be an effective carrier for delivering hydrating substances to the skin, improving skin occlusion so as to prevent water loss from the skin and help retain moisture in the skin.

❖ **NLC can reduce the dose required**

The synergistic impact of the medicine and the essential oil serves as the basis for the explanation of the mechanism of action of NLC comprising Clotrimazole and Mediterranean essential oil in lowering drug dosage. Clotrimazole and essential oils are both antimicrobials. When both are used together, the effects may be greater than when they are used alone. Since the increased efficacy of the NLC and medicine combination makes lesser doses of the medication still effective, this synergistic effect may result in a reduction in the amount of medication used[9].

❖ **NLC can reduce side effects**

The gastrointestinal tract (GIT) barriers that limit the solubility and bioavailability of these medications can be overcome by NLC, a potentially effective delivery method. These NLCs have the ability to move drug moieties across intestinal membranes with efficiency, shielding the medication from enzymatic breakdown and changes in intestinal pH. Via a number of channels, including transcellular absorption, paracellular transport, and M cell uptake, lipid compounds facilitate easy absorption or uptake. These processes can circumvent first-pass metabolism and improve medication solubility and absorption while also extending bioavailability and residence time[10].

NLC has been used in several preparations which have various biological activities such as anti-inflammatory, antibacterial, anticancer, antioxidant and many more.

- **Anti-inflammatory**

Ricci *et al* [11] investigated in vitro the penetration of indomethacin from gels containing NLC and gels without NLC through the stratum corneum and epidermis. In this study it was found that the anti-inflammatory effect after topical use of indomethacin was longer with NLC gel containing indomethacin. The following are several journals that discuss anti-inflammatory NLC (table 1).

Table 1 : Anti-inflammatory NLC

Active compound	Reference
Lornoxicam	[12]
Meloxicam	[13]
Aceclofenac	[14]
Naproxen	[15]

- **Anti-cancer**

The purpose of the study was to assess the pharmacokinetic, biodistributive, and in vitro anticancer efficaciousness of tamoxifen NLC based on long-chain lipids (LCTT NLC). LCTT NLC demonstrated better pharmacokinetics compared to tamoxifen, with a longer half-life and slower elimination. It has the potential to be a viable drug delivery method for the treatment of breast cancer in breast cancer models. The biodistribution analysis revealed a substantial difference between the accumulation of NLC in the tumor and free tamoxifen. Studies on the in vitro anticancer effectiveness of LCTT NLC demonstrated increased cytotoxicity and induction of apoptosis in comparison to tamoxifen (Shete et al., 2013). Several journals that discuss NLC for anticancer can be seen in table 2 below.

Table 2 : Anti-cancer NLC

Active compound	Reference
8-cyano-6-phenyl-7-methyl-3-(para-chlorophenyl)-[2,1-d]-pyrrolo-[1,2,3,5]tetrazine-4-one 8-cyano-3,6-diphenyl-7-methyl-[2,1-d]-pyrrolo-[1,2,3,5]tetrazine-4-one	[16]
Chrysanthemum cinerariifolium	[17]
all-trans retinoic acid	[18]
Citral	[19]
Ribociclib	[20]
Thymoquinone	[21]

- **Antioxidant**

In antioxidant research , lipid nanoparticles filled with tocopheryl acetate and idebenone showed synergistic benefits. The nanoparticles showed improved in vivo topical efficacy, increased antioxidant activity in vitro, and enhanced penetration and retention (EPR) effects. The fact that treated animals did not have any adverse effects suggests that these lipid nanoparticles are non-irritating and biocompatible[22]. Several journals that discuss NLC for antioxidant can be seen in table 3 below.

Table 3 : Antioxidant NLC

Active compound	Reference
Jasminum officinale L	[23]
Resveratrol	[24]
Retinyl palmitate	[25]
Hesperetin	[26]
Camellia sinensis L.	[27]

- **Antimicrobial**

This study examined the antimicrobial activity of amikacin (AMK) and sodium colistimethate (SCM), which were added to the NLC formulation through high pressure homogenization, both in vivo and in vitro, against the resistance of Acinetobacter baumannii (AB), Klebsiella pneumoniae (KP), and Pseudomonas aeruginosa (PA). It has been demonstrated that SCM and AMK work well against this infection. This study advances the subject of antibiotic resistance by offering a possible novel therapeutic approach[28].

Antibacterial agents can be directed to the infection location using NLC.

NLCs can be used to transport antibacterial drugs to the site of infection. Drugs can be packed and distributed to specified areas including diseased areas more successfully[29]. When it comes to antibacterial drugs, NLC can improve the medication's ability to get to the infection site. It is possible to build the NLC so that the medication is released only at that location. This can increase the treatment's effectiveness and decrease any potential side effects in the surrounding tissues. Various NLC anti-bacterial products can be seen in the table 4 below.

Tabel 4: Antibacterial NLC

Type of preparation		Reference
Gel	The ultrasonication emulsification method was utilized to successfully manufacture NLC containing erythromycin. The lipids (stearic acid + oleic acid), surfactant (Pluronic F127), and sonication time were optimized using central composite design. EM-NLCs-opt has a high entrapment efficiency and nanometric size. EM-NLCs-opt was effectively added to an in situ gel with the use of chitosan and pH-sensitive carbopol 940. EM-NLCs-opt-IG4 demonstrated considerably increased bioadhesion, was stable for over 24 hours, and frequently gelated.	[30]
Encapsulation of essential oils	This research aims to assess the effectiveness of peppermint essential oil (PEO) integrated into a nanostructured lipid carrier (PEO-NLC) on the healing of infected wounds in a mouse model both in vivo and in vitro antibacterial activity. Similar antibacterial efficacy against S. epidermidis, S. aureus, L. monocytogenes, E. coli, and P. aeruginosa species was demonstrated by in vitro investigation using PEO and PEO-NLC. Our findings show that PEO-NLC is effective in treating infected wound models, and they could offer a practical approach to creating topical formulations	[31]
Dental Implant	Recently, an inventive method of replacing lost teeth has been proposed: immediate implant implantation. Because of their precise construction, nanocomposites can be put directly into the socket prior to restorative treatment. A better way to get positive local-regional medication effects that promote tissue healing while reducing the risk of bacterial infections, biofilm development, and oxidative stress damage.	[32]
Injection	The potential of cationic nanostructured lipid carriers loaded with Vancomycin (VCM) generated by solvent-free cold homogenization process is investigated in this article. This NLC would be a desirable alternative for the integrative treatment of bacterial endophthalmitis as well as a biocompatible carrier with improved performance for topical ocular vancomycin delivery.	[33]
Suspension	Some antibiotics that work effectively against resistant P. aeruginosa, K. pneumoniae, and A. baumannii are sodium colistimethate (SCM) and amikacin (AMK); nevertheless, their toxicity severely restricts their use. In this work, high pressure homogenization was used to include SCM or AMK into the NLC formulation. Because the SCM-NLC and AMK-NLC medications have the same in vitro activity as the free drug, the encapsulation technique does not lessen the drug's effectiveness.	[28]

Antiviral

Research on immunoregulation and immunopotentiation of Atractylodes Macrocephala Koidz (PAMK) polysaccharides was done in 2018 by Liu et al[34]. PAMK-containing NLC demonstrated significant immunopotentiation. The application of NLC as an adjuvant makes use of some of the special features of

nanotechnology, namely its capacity to target particular tissues and cells. The polysaccharides (PS) that this adjuvant contains are responsible for its characteristics. In the domains of agriculture and medicine, the adjuvant qualities of NLC from Atractylodes macrocephala Koidz have important consequences. These components may be utilized to boost the effectiveness of vaccinations and enhance a number of plant health-related issues. Several journals that address NLC for antiviral (table 5).

Table 5 : Antiviral NLC

Active compound	Reference
Remdesivir	[35]
Lactoferrin	[36]
Salinomycin	[37]

- **Anti-acne**

A new medication for acne vulgaris is NLC which contains azelaic acid. These nanostructures have the ability to minimize systemic exposure, boost therapeutic efficacy, and transport azelaic acid to the afflicted skin. The loaded nanoparticles had a mean size of less than 400 nm. A randomized controlled experiment was conducted to examine the effectiveness of 15% azelaic acid gel with 20% trichloroacetic acid peel. In terms of counting acne lesions, both the peels and the gels shown similar efficacy after eight weeks of treatment[38]. Several journals that address NLC for anti-acne (table 6).

Table 6 : Anti-acne NLC

Active compound	Reference
Tretinoin	[39]
Dapson	[40]
Tretinoin and tetracycline	[41]

- **Antileishmania**

Research from Kar [42] was to assess the antileishmanial action of cedrol produced by NLCS (lipid-binding system). The antileishmanial activity of NLCS was evaluated in vitro against the amastigote Leishmania donovani type liar and its resistance to treatment. The results indicate an increase in physical activity when compared to basal body temperature. Additionally, NLCS is evaluated in vivo in leishmanian-infected tikus. NLCS significantly reduces the length of the lesson as compared to the control group. According to the aforementioned study, NLCS containing cedrol can function as an effective medication delivery system for leishmaniasis treatment.

A number of factors must be considered in creating an NLC

i. Selection of main excipients used in the production of lipid nanoparticles are basically lipids, surfactants and water. The choice of lipid will directly influence the physicochemical characteristics of the nanoparticles obtained, namely morphology, size, polydispersity and zeta potential value. In addition, the composition of the lipid will determine its crystallinity and thus the incorporation ability of drug molecules.

ii. The choice of method for producing NLC will determine the quality of the obtained nanoparticle dispersion, in particular, the average particle size, polydispersity, encapsulation efficiency and loading capacity of a particular drug matrix. The factors that most influence the choice of method are the characteristics of the drug to be included, namely (i) solubility, (ii) molecular weight, (iii) thermolability, (iv) susceptibility to oxidation and (v) chemical structure

Lipid

Liquid lipids function to improve the encapsulation efficiency of bioactive compounds, while solid lipids help to decrease the molecular diffusion process in NLC, increasing the retention and chemical stability of bioactive components. The following elements need to be taken into account while choosing appropriate liquid and solid lipids (lipid mixtures) for NLC formulations[43].

- One of the key elements influencing the loading capacity of bioactive substances is their solubility in the lipid matrix. Many substances can be added to the liquid lipid, stirred, sonicated, centrifuged, or filtered (to remove insoluble bioactive compounds), and then the dissolved compounds can be quantified using UV Vis spectroscopy or chromatography equipment.
- Good miscibility and compatibility between liquid and solid lipid molecules are required. Liquid lipids are so prevented from joining the solid lipid crystal matrix and from dissolving in the oil phase. In order to prevent phase separation and instability at temperatures below the lipid melting point, solid and liquid lipids

must also dissolve at a specific concentration required for the creation of NLCs.Matriks lipid harus memiliki stabilitas terhadap degradasi kimia termasuk oksidasi dan lipolysis

- Food-grade lipid matrix is required. Several types of solid lipids, liquid lipids, and surfactants that used in NLC (table 7 and 8).

Table 7 : Types of solid lipids

Solid lipid		Reference
Stearic acid, beeswax and carnauba wax	Carvacrol-containing NLCs with antioxidant and antibacterial properties have been created. As solid lipids in this investigation, stearic acid, beeswax, and carnauba wax were utilized. Further sustainability benefits are conferred by using solid lipid source materials, and the resulting NLC is well-suited for the administration of carvacrol.	[44]
Glyceryl monostearate	For NLC preparations, four formulations were created to optimize the steady solid lipid concentration of glyceryl monostearate (GMS) and the liquid lipid concentration of olive oil. The active constituents in the formulation are n-Butanol Lerak Extract, n-Butanol Gotu Kola Extract, and n-Butanol Neem Seed Oil. The ratio of liquid to solid lipid concentrations greatly affected particle size, but neither dispersive power nor zeta potential had any effect.	[45]
Stearic acid or glyceryl behenate	The topical delivery of flurbiprofen, a non-steroidal anti-inflammatory medicine (NSAID), has been studied in relation to the possible application of NLC. Mixture of medium chain triglycerides and castor oil makes up NLC, which is made up of the fatty acid stearic acid or glyceryl behenate. Through enhanced drug penetration and the avoidance of the drawbacks associated with oral NSAID treatment, both optimized NLC formulations (based on a glycerol behenate or SA matrix) offer extremely efficient and non-irritating vehicles for topical delivery of FB. When applied topically as a solid lipid, NLC made of stearic acid, glyceryl behenic acid, and flurbiprofen demonstrated encouraging actions.	[46]

Table 8: Types of liquid lipids

Liquid lipid	Reference
Oleic acid	[47]
Caprylic/Capric triglycerides (Miglyol 812)	[40]
a-tocopherol/ Vitamin E	[48]
Soy bean oil	[49]
Caraway essential oil	[50]
Olive oil	[51]
Sweet almond oil	[52]
Squalene	[53]

Surfactant

Surfactants increase the surface area between lipids while preserving nanoscale particle size by reducing the surface tension between the two lipid phases and preventing aggregation. The zeta potential value will rise with the addition of surfactant[54]. Instead of using only one surfactant, a combination of water- and oil-soluble surfactants is typically employed to prepare NLCs since this often results in better functional qualities and strong physical stability.

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