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NANOSTRUCTURED LIPID CARRIER: THE ADVANCED LIPID CARRIERS

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ABSTRACT: The skin is the largest organ of the human body and easily accessible. It's potential as an alternative route for administering drugs for both systemic and local effects has attracted considerable interest. Most of the topical medications which are applied on the skin or mucous membrane to treat ailments include a wide range of creams, foams, gels, lotions, ointments, eye drops, ear drops, *etc*. Topical drug delivery provides a convenient and effective system for the treatment of local pathological conditions (dermal drug delivery) or as the site for systemic drug administration (transdermal drug delivery). Nanostructured Lipid Carriers (NLCs) are drug-delivery systems composed of both solid and liquid lipids as a core matrix. It has been shown that NLCs exhibit several advantages for drug therapy over conventional carriers including increased solubility and stability, improved permeability and bioavailability, reduced adverse effects, prolonged half-life, and tissue-targeted delivery. NLCs have attracted expanding scientific and commercial vigilance in the last couple of years as alternate carriers for the pharmaceuticals. A new generation of NLCs consisting of a lipid matrix with a special nanostructure has been developed. This nanostructure improves drug loading and firmly incorporates the drug preventing loss during storage. The present review provides insights into characteristics of NLCs as colloidal carriers including production techniques, stabilization methods, formulations, and pharmaceutical applications of NLC. The potential of NLCs to be used for various routes of administration is also highlighted.

INTRODUCTION: New drug delivery systems can be developed to overcome the problems of poor water solubility and insufficient bioavailability. There is an expanding need to develop a pharmaceutical carrier system that overcomes these difficulties.

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Systems as an alternative to an emulsion, liposome, and polymeric microparticulate systems include lipid nanoparticles such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLCs).

This review describes several systems that can deliver active pharmaceutical ingredients across the skin with added advantages in systemic treatment with less side effects, absence of the first-pass metabolism, and allowing the targeting of specific skin appendages for dermal applications including cosmetics and pharmaceuticals. Such a carrier should have an adequate loading capability, freedom from cytotoxicity and the possibility of

possessing pharmaceutical targeting and controlled release characteristics. These particulate carriers include liposomes, transfersomes, lipid-based nanoparticles, polymeric nanoparticles, ethosomes and niosomes.

SLNs and NLCs have emerged as novel systems composed of physiological lipid materials suitable for topical, dermal and transdermal administration. These carrier systems exhibit many features of lipid nanoparticles attracting major attention as novel colloidal drug carriers for topical use. SLN has gained a lot of popularity amongst researchers due to their applicability for various routes, site-specificity and controlled drug delivery with less side effects. Some challenges with these include low drug loading, drug expulsion during storage. These limitations can be overcome with NLC which are the second generation lipid carriers offering advantages of improved drug loading capacity and better release properties of poorly soluble drugs mainly due to their imperfect structure, the stability of bioactive compounds, enhanced shelf-life, functionality, consumer acceptability and controlled release of encapsulated materials. SLNs use only one form of lipid which is a solid lipid that orients the drug between the fatty acid chains of glycerides [1]. NLC has been developed to overcome the drawbacks associated with SLN. SLN is produced by replacing the oil of an o/w emulsion by a solid lipid or a blend of solid lipid, i.e., the lipid particle-matrix being solid at both room and body temperature. NLCs are systems that have been successfully used for topical, dermal, transdermal administration. NLC consists of a mixture of specially blended solid lipids (long-chain) with liquid lipid (short-chain) preferably in a ratio of 70:30 up to a ratio of 99.9:0.1.

These systems consist of aqueous dispersions of solid nanoparticles stabilized by one or two surfactants. NLCs improve skin hydration due to their physiological lipid composition and occlusion properties. Biomaterials with nano-scale organizations have been used as controlled release reservoirs for drug delivery. They can be synthesized with controlled composition, shape, size, and morphology. Their surface properties can be manipulated to increase solubility, immune compatibility, and cellular uptake.

Advantages and Disadvantages of NLCs: NLCs are one of the carriers of choice for topically applied drugs because their lipid components have an approved status or are being used as excipients in commercially available topical, cosmetic or pharmaceutical preparations. The advantages include [2].

1. Improve physical stability.
2. Control and targeted drug release.
3. High drug content compared to other carriers.
4. Feasibility of carrying both lipophilic and hydrophilic drugs.
5. Most lipids are being biodegradable and biocompatibility.
6. Organic solvents can be avoided.
7. It is less expensive than polymeric/ surfactant-based carriers.
8. Easier to validate and to gain regulatory approval.

Disadvantages: These include [3].

1. Less cytotoxic effects due to the nature of the matrix and concentration.
2. Irritation and sensitizing action of some surfactants.
3. Application and efficiency in case of protein and peptide drugs and gene delivery systems need to be better exploited.
4. Lack of sufficient preclinical and clinical studies of these nano-carriers.

Types of NLCs: [4]

Type I: Highly Imperfect Solid Matrix: In type, I low concentration of liquid lipid is used as compared to the solid lipid. Solid lipids and the oils are blended to form an o/w nano-emulsion which when cooled from a molten state to room temperature to form solid particles. The difference in the structures of the lipids and special requirements in the crystallization process leads to a highly disordered, imperfect lipid matrix structure

offering space for drug molecules and amorphous clusters of drugs **Fig. 1, I**.

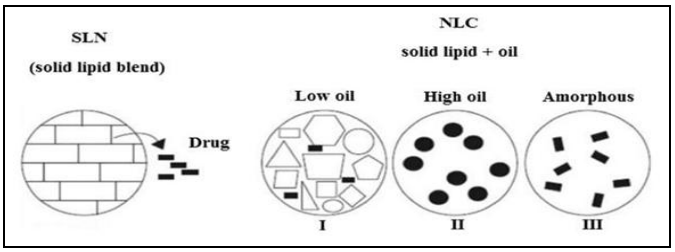

FIG. 1: TYPES OF NLCs

Type II: Multiple Oil/Fat/Water Carrier: In this case, particles are produced with a high content of liquid lipids (oils). At high oil concentration, a miscibility gap between the two lipids (solid lipid and oil) occurs. During the cooling phase, phase separation occurs, which is precipitation of tiny oily nano compartments **Fig. 1, II**. In this multiple oil/fat/water system, the drug can be accommodated in the solid with increased solubility in the oily parts of the lipid matrix.

Type III: Amorphous Matrix: Lipids are mixed to prevent them from crystallizing. The lipid matrix is solid, but in an amorphous state **Fig. 1, III** the absence of crystallization avoids drug expulsion.

NLCs Ingredients: NLCs are a nano-particulate carrier system derived from o/w nanoemulsions. The major ingredients of NLCs are solid and liquid lipids, surface active agents and water [5, 6].

Emulsifiers: The emulsifiers are used to stabilize the lipid dispersions. Hydrophilic, lipophilic or amphiphilic emulsifiers are used for fabrication of NLCs. It has been found that a combination of emulsifiers can prevent particle aggregation more efficiently.

Lipids:

Solid and Liquid Lipids: Both solid and liquid lipids are included in NLCs for constructing the inner cores. These lipids are in a liquid or solid state at room temperature. They would melt at higher temperatures (>80 °C) during the preparation process. Liquid oils typically used for NLCs consist of digestible oils from natural sources.

TABLE 1: INGREDIENTS USED IN NLCs

Emulsifiers	Examples
Hydrophilic emulsifier	Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20, Tween 40, Tween 80, Polyvinyl alcohol, Solutol® HS15, Sodium deoxycholate, Sodium glycocholate, Sodium oleate, Polyglycerol methyl glucose distearate
Lipophilic emulsifiers	Myverol® 18-04K, Span 20, Span 40, Span 60
Amphiphilic emulsifiers	Egg lecithin, Soya lecithin, Phosphatidylcholines, Phosphatidylethanolamines, Gelucire® 50/13
Solid lipids	**Examples**
Hard fats	Stearic acid, Palmitic acid, Goat fat, Theobroma oil
Triglycerides	Trimyristin (Dynasan 114), Tripalmitin (Dynasan 116), Tristearin (Dynasan 118), Trilaurin
Waxes	Beeswax, Cetyl palmitate, Carnauba wax
Mono, di and triglycerides mixtures	Witepsol bases, Glyceryl monostearate, Glyceryl behenate (Compritol 888 ATO), Glycery palmitostearate, (Precirol ATO 5), Softisan 142 and Softisan 154
Liquid lipids	**Examples**
Liquid lipids	Medium chain triglycerides, Paraffin oil, 2-octyl dodecanol, Oleic acid, Squalene, Isopropyl myristate, Vitamin E, Miglyol® 812, Transcutol, Labrafac® PG, Lauroglycol® FCC, Capryol® 90
Oils	Soya bean oil, Palm oil, Coconut oil, Corn oil, Olive oil, Almond oil

Methods of Preparation of NLCs: There are several methods for the preparation of colloidal carriers [7-12].

High-Pressure Homogenization Technique: This is a reliable technique for larger-scale production. In this technique lipids are pushed under high pressure (100-200 bars) through a narrow gap of a few microns. Shear stress and cavitation cause the disruption of particle to submicron range. Normally the lipid contents are in the range of 5-10%. In contrast to other preparation technique high-pressure homogenization has the advantages of improved texture and consistency of product with minimum scaling up problems.

Basically, there are two approaches for production by high-pressure homogenization, hot and cold

homogenization techniques. For both the techniques, drugs are dissolved in the lipid being melted at approximately 5-10 ºC above their melting point.

Hot Homogenization Technique: In this technique, the drug along with melted lipid is mixed with constant stirring under high shear with an aqueous surfactant solution at the same temperature. The primary emulsion obtained is homogenized. The obtained nano-emulsion is cooled to room temperature when the lipid recrystallizes and leads to the formation of nanoparticles.

Cold Homogenization Technique: Cold homogenization has been developed to overcome the problems of the hot homogenization technique such as temperature mediated accelerated degradation of the drug, partitioning and hence loss of drug into the aqueous phase during homogenization. The first step of the cold homogenization is same as hot homogenization method. In the subsequent step, the melt containing the drug is cooled rapidly using ice or liquid nitrogen for the distribution of drugs in the lipid matrix.

Micro Emulsion Based Method: Melted lipid-containing drug is mixed with a surfactant. Co-surfactant containing aqueous phase is prepared at the same temperature as the lipid in such a ratio to form micro emulsion. The hot microemulsion is then diluted by an excess of cold water. The sudden reduction in temperature causes the breaking of the microemulsion, converting into a nanoemulsion, which upon recrystallization of the lipid phase produces lipid particles.

Emulsification-Solvent Evaporation Technique: In solvent emulsification-solvent evaporation, the lipid is dissolved in a water-immiscible organic solvent (*e.g.* toluene, chloroform) which is then emulsified in an aqueous phase before evaporation of the solvent under reduced pressure. The lipid precipitates upon evaporation of the solvent, thus forming nanocarriers.

Solvent Emulsification-Diffusion Method: In this procedure, an o/w emulsion is formed comprising of an organic phase with partially water-miscible solvents (*e.g.* Benzyl alcohol, tetrahydrofuran) saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Particles with an average diameter of 30-100 nm can be obtained by this technique. Avoidance of heat during preparation is the most important advantage of this technique.

Phase Inversion Method: It involves the addition of formulation components with magnetic stirring and subsequent heating and cooling cycles with dilution under cooling conditions. Three cycles of heating and cooling from room temperature to 85 ºC and back to 60 ºC are subsequently applied at a rate of 4 ºC/min. This thermal treatment causes the inversion of the emulsion.

Displacement or Injection Method: A solution of the lipid in a water-miscible solvent or mixture of solvents is injected into an aqueous phase with or without surfactant. In this process, an o/w emulsion is formed by injecting the organic phase into the aqueous phase under magnetic stirring to form a nanoemulsion.

Multiple Emulsion Technique: This is a modified solvent emulsification-evaporation method based on a w/o/w double emulsion. The drug is dissolved in an aqueous solution and then emulsified in the melted lipid. This primary emulsion is stabilized by the stabilizer. Emulsification is followed by solvent evaporation for the preparation of hydrophilic drug substance loaded nano-carriers.

Melt Dispersion Method: In this method, drug and solid lipids are melted in an organic solvent regarded as the oil phase, and the simultaneously aqueous phase is also heated to the same temperature. The oil phase is added to a water phase and the resulting emulsion is stirred at high speed for a few hours. Finally, it is cooled down to room temperature to yield nanoparticles.

Ultrasonication: Ultrasonication is based on the mechanism of cavitation. In the first step, the drug is added to previously melted solid lipids. In the second step, the heated aqueous phase (heated to the same temperature) is added to the melted lipid and emulsified by using high-speed stirrer. The aqueous phase added to the lipid phase drop by drop with magnetic stirring. The obtained pre-emulsion is ultrasonicated using a probe sonicator. In order to prevent crystallization during the

process, the production temperature is kept at least 5 ºC above the lipid melting point.

Merits and demerits of the above methods are listed in following table.

TABLE 2: MERITS AND DEMERITS OF VARIOUS METHODS OF PREPARATION

S. no.	Preparation methods	Merits	Demerits
1	High-Speed Homogenisation/ Ultrasonication	• Applicable for lab scale. • Low capital cost.	• Broader range of particle size distribution. • Possibility of agglomeration of the particle after storage hence not suitable for intravenous administration. • Possibility of metal contamination. • Low stability. • Time-consuming.
2	High-Pressure Homogenisation (Hot homogenization)	• Lab-scale and large scale applicability. • Narrow particle size distribution • Low polydispersity index. • Greater stability compared to High-Speed Homogenisation/Ultra Sonication.	• Sample remains in supercooled melt state for months instead of solid-state. • Increasing the rate of homogenization leads to an increase in particle size leads to coalescence due to the high kinetic energy of particles.
3	High-Pressure Homogenisation (Cold homogenization)	• Prevents temperature-induced degradation of thermolabile drug and lipids. • Prevents complexity of the crystallization step of nanoemulsion leading to modifications in supercooled melts. • High cooling rate favors better distribution of the drug in a lipid matrix.	• Larger particle size and greater particle size distribution compared to hot homogenization. • Effective temperature control and regulation is required to ensure the un-molten state of lipid. • Costly.
4	Solvent emulsification/ evaporation	• Smallest particle size is obtained. • Lab-scale acceptability. • Higher stability. • Thermolabile drugs can be successfully incorporated without degradation.	• Use of toxic solvents. • Inconvenient for larger production scale-up. • With increasing lipid content, the difficulty arises in uniform homogenization leading to an increase in polydispersity index and particle size distribution.
5	Microemulsion based dilution method	• Particle size is intermediate between high-pressure homogenization and solvent evaporation technique. • Intermediate stability	• High thermal stress • Liable to agglomerate quicker than solvent evaporation and high-pressure hot homogenization technique. • Larger particle size is obtained.

Some case studies have been reported demonstrating that lipid based formulations exhibits better efficacy than normal formulations

TABLE 3: REPORTED NLC FORMULATIONS

S. no.	Drugs	Method	Remarks	Reference
1	Ketoprofen	Simple blending and grinding using high energy micro mill	Improved drug therapeutic efficacy and safety, allowing an improvement in the dissolution stability, high tolerability and skin permeation properties	[13]
2	Tacrolimus	Hot homogenization technique by sonication	High entrapment efficiency	[14]
3	Raloxifene	Solvent diffusion method	Increased entrapment efficiency, 3.75-fold enhancements in bioavailability with optimized NLCs formulation than plain drug suspension	[15]

4	Aceclofenac	Melt emulsification, High speed homogenization	The release rate, permeation rate and pharmacodynamics activity can be modulated upon changing the ratio of solid lipid to liquid lipid	[16]
5	Minoxidil	Ultrasonication	NLC-based gel showed faster onset and elicited prolonged activity up to 16 h. The drug release behavior from the NLC displayed a biphasic drug release pattern with burst release at the initial stage followed by sustained release.	[17]
6	Celecoxib	Microemulsion	The NLC based gel described in this study showed faster onset and elicited prolonged activity uptil 24h.	[18]
7	Nystatin	Hot homogenization and ultrasonication	NLCs represent a promising carrier for topical delivery of nystatin offering good physical stability, high entrapment efficiency, and controlled drug release.	[19]
8	Marigold extract	High speed Homogenization	Significant anti-wrinkle activity.	[20]
9	Clobetasol Propionate	Solvent diffusion Method	Improved drug loading capacity for the drug.	[21]
10	CoQ10 (anti-ageing)	Ultrasonication method	CoQ10-NLC efficiently counteract UV associated mitochondrial depolarization suggesting a potential role in anti-aging formulations	[22]
11	Lidocaine	Ultrasound dispersion method	NLC gel significantly sustained the drug release compared to that of Xylocaine® gel resulting in 5-6 fold increase in the duration of anesthesia	[23]

TABLE 4: MARKETED PRODUCTS CONTAINING NLCs

S. no.	Product name	Active ingredients	Manufacturer
1	Nano-lipid restore CLR	Black currant seed oil containing 3 and 6 unsaturated fatty acids	Special Chem. (France)
2	Nano-lipid basic CLR	Caprylic / Capric triglycerides	Dr. Kurt Richter (Germany)
3	NLC deep effect eye serum	Coenzyme Q10, Oligosaccharides	Beate Johnen (Germany)
4	Extra moist softener	Coenzyme Q10, 3 and 6 unsaturated fatty acids	Amore Pacific (Korea)
5	NLC deep effect repair cream	Q10, Titanium dioxide, highly active oligosaccharides	Beate Johnen (Germany)
6	Surmer Elixir du Beauté Nano-vitalisant	Coconut oil, pseudo-peptide, milk extract from coconut, wilder extract	Isabelle Lancray (France)
7	Surmer Masque Crème Nano-hydratantti	Coconut oil, wild ginger, pseudo-peptide, tamanut tree extract	Isabelle Lancray (France)
8	Cutanova cream nano repair Q10	Q10, polypeptide, hibiscus extract, ginger extract, ketosugar	Dr. Rimpler (France)
9	Cutanova cream nano vital Q10	Q10, TiO2, polypeptide, ursolic acid, oleanolic acid, sunflower seed extract	Dr. Rimpler (France)

Strategies to Overcome Stability Issues:

Spray Drying: It is a cheaper, alternative technique. It recommends the use of lipids with a melting point more than 70 ºC. The best results are obtained with SLN concentrations of 1% in a solution of trehalose in water or 20% trehalose in the ethanol-water mixture. The addition of carbohydrates and lower lipid amounts favor the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol-water mixtures instead of pure water [24].

Lyophilization: Lyophilization has been used for the long-term stability of a product containing hydrolyzable drugs. Transformation into the solid-

state would prevent Ostwald ripening and avoid hydrolytic reactions. However, when the product is lyophilized without a cryoprotectant, the final product commonly results in the aggregation of particles. Some of the most widely used cryoprotectants are trehalose, sorbitol, glucose, sucrose, mannose, and maltose.

Addition of a Stabilizing Agent:

Poloxamers: Poloxamer 188 increases the mechanical stability and contributes to the rheological effects. There is also an increase in the stability of the gel formulation by using a Poloxamer with solvents such as ethanol, propylene glycol, glycerol and PEG 400. Poloxamer 407 in the presence of organic solvents, self assembles into two liquid crystal structures, namely micellar cubic and hexagonal structures that are thermodynamically stable [25, 26].

Polyethylene Glycol: In general, surface modification of colloidal particles by coating with a hydrophilic substance like polyethylene glycol (PEG) provides benefits such as good physical stability and dispersibility of the colloid, also improving the presence of colloids in blood circulation for systemic use, increasing their stability in body fluids such as gastrointestinal fluids, acceleration of colloid transport across the epithelium, modulation of the interaction of colloids with mucus for specific delivery requirements, drug targeting, increased bio-compatibility and decreased thrombogenicity of drug carriers [27].

Skin Penetration of NLCs: The drug penetrates by three potential pathways, such as sweat ducts, hair follicles and sebaceous glands collectively called the shunt or appendages route across the stratum corneum. The molecules must have adequate solubility in water and oil, with high oil/water partition coefficients. A molecular weight less than 0.6 kDa may penetrate the skin. Therefore, topical administration is limited to hydrophobic and low molecular weight drugs. Since most drugs are hydrophilic, have low oil/water partition coefficients, high molecular weight, and ionic character, they do not easily cross the stratum corneum. The bioavailability of drugs permeating through the skin can be increased by using lipid nanoparticles. Nano-sized particles can make close contact with superficial junctions of stratum corneum and furrows between corneocytes, allowing superficial spreading of the drug. Following the evaporation of water from the nanosystems after applying on the surface of skin, particles form an adhesive layer occluding the skin. Hydration of stratum corneum increases to reduce corneocyte packing and width, inter corneocytes gaps, and also influences partitioning of the drug into the stratum corneum. Lipid nanoparticles above 100 nm do not permeate the stratum corneum due to their dimensions and rigidity. Since epidermal lipids are rich in the stratum corneum, lipid nanoparticles attaching to the skin surface would allow lipid exchange between stratum corneum and the nanocarriers. Lipid nanoparticles have the potential to deliver drugs via the follicles. Furthermore, each follicle is associated with sebaceous glands, which secrete the sebum, creating an environment enriched in lipids. This environment is beneficial for trapping of lipid nanoparticles. Sebum is a mixture of triglycerides, squalene, and waxes. Some glyceride lipids present in NLCs may accelerate entry into follicles / sebaceous glands and promote penetration [28-34].

Factors Affecting Drug Release: [35-37] Several factors such as particle size, lipid matrix, surfactants, drug concentration in the lipid matrix and drug type could affect the release profile of a drug from the NLC system.

Particle Size: The particle size of a colloidal system is a crucial factor for the release of the drug incorporated inside the matrix and affects the stability of the formulation.

Lipid Matrix: Different lipid matrices lead to different release profiles. Lipids have different crystal order, melting points, and hydrophilic-lipophilic balance (HLB) values. This varies the affinity of a drug to be entrapped within the lipid matrix from one lipid to another.

Surfactant: The physicochemical properties of NLCs are essentially influenced by the type of surfactant used. Surfactants used to stabilize particles in the dispersion media may affect the structure of the lipid nanoparticles. This happens due to an interaction between the emulsifying agent and lipid molecules.

Depending on the HLB and molecular weight of the surfactant molecules, the affinity of the surfactant for the lipid differs. Having the surfactant molecules embedded in the lipid matrix might dramatically affect the crystallization of the lipid and leave spaces in the lipid lattice. These spaces will give rise to a higher loading capacity of a drug, incorporation of imperfections inside the particle-matrix and eventually a slower release profile. Moreover, the ability of the surfactant to stabilize the oil droplets in the lipid melted state during homogenization forms smaller NLCs.

Drug Loading: Drug loading might affect the release profile. It depends on the affinity of the drug to mix with the lipid and be enclosed in the matrix.

Drug Type: The drug type affects the release profile because, with the different compositions of drugs, there are different affinities to the lipid matrix. NLCs have unique characteristics that can enhance the performance of a variety of incorporated drug forms.

Bioavailability and Bioequivalence Issues: Bioequivalence assessment of the test and reference product is based on studies with clinical endpoints or pharmaco-dynamic measurements.

Studies of Topical Bioequivalence:

***In-vitro* Release Testing:** Widely accepted Franz diffusion cells are used to estimate the rate of drug release from drug products. It involves the application of a drug product onto a membrane (synthetic membrane, excised animal skin, or excised human skin) that separates the donor and receiver chambers. The receiving chamber simulates sink conditions *in-vivo*. The rate of delivery obtained from these studies is assumed to be similar to the *in-vivo* situation. The method has been widely employed in discovery research for screening formulations and understanding the mechanism of cutaneous drug transport [38].

Tape Stripping Method: It provides information on drug uptake, apparent steady-state levels and drug elimination from the stratum corneum based on a concentration-time curve. This method is also known as the dermato-pharmacokinetic (an approach similar to blood, plasma and urine analysis) for drug concentrations as a function of time [39].

Microdialysis: This is a continuous sampling technique in which the molecule of interest is collected from the target tissue, thus providing an insight into the time course of drug action or biochemical monitoring of the tissue. The technique can be imagined as an artificial capillary, in which a hollow semi-permeable probe is carefully inserted into the site of interest such as the brain, muscle, eye, and skin. Therefore, it provides valuable information about unbound drug concentrations or biomarkers on the site closer to the pharmacological action compared to the conventional plasma/blood drug concentration versus time [40].

Applications of NLCs:

Oral Drug Delivery: Increasedbioavailability and prolonged plasma levels are described for peroral administration of NLCs. The lipid nanocarriers can protect the drugs from the harsh environment of the gastrointestinal tract. Lipophilic drugs can be entrapped by NLCs to resolve insolubility concerns. Repaglinide, an anti-diabetic agent with poor water solubility has low oral bioavailability and a short half-life is suitable for loading into NLCs for improving oral delivery by using Gelucire for improving the aqueous solubility of lipophilic drugs [41-43].

Drug Delivery to Brain: NLCs of this generation is considered to be one of the major strategies for drug delivery without any modification to the drug molecule because of their rapid uptake by the brain, acceptability, and biodegradability. NLCs of Asenapine (ASN) maleate was found to have improved bioavailability and enhanced uptake of ASN to the brain [44].

Pulmonary Drug Delivery: Inhalation drug delivery represents a potential delivery route for the treatment of several pulmonary disorders. NLCs have greater stability against the shear forces generated during nebulization compared to polymeric nanoparticles, liposomes, and emulsions. NLCs are comprised of an inner oil core surrounded by an outer solid shell and hence allow the high loading of lipophilic drugs.

NLCs in pulmonary disorders seems to be a promising strategy since the lung epithelium can be directly reached, resulting in the faster onset of action. Desired dose and dosing frequency can be reduced as compared to other routes like oral and undesirable side effects of drugs can be avoided. Bio-adhesive properties of NLCs are due to their small particle size as well lipophilic character lead to longer residence time in the lungs [36, 45-46].

Cancer Chemotherapy: The function of NLC in cancer chemotherapy are reported and hot spots in research are emphasized. It is foreseen that, in the near future, nanostructured lipid carriers will be further advanced to consign cytotoxic anticancer compounds in a more efficient, exact and protected manner.

Zerumbone (ZER) loaded into NLC did not compromise the anti-proliferative effect of ZER. Both ZER and ZER- NLC significantly induced apoptosis *via* the intrinsic pathway in a time-dependent manner. The proposed mechanism of apoptosis of cancer cells induced by ZER and ZER-NLC is *via* activation of caspase-9 and caspase-3, inhibition of anti-apoptotic protein and stimulation of proapoptotic protein expressions. Loading of ZER into NLC will increase the bioavailability of the insoluble ZER in the treatment of cancers.

L-arginine lauryl ester (AL) into NLCs and then coating with bovine serum albumin (BSA), pH-sensitive membranolytic and lysosomolytic nano-carriers (BSAAL-NLCs) were developed to improve the anti-cancer effect. This renders more nanocarriers lysosomolytic capability with lower cytotoxicity, as well as an improved therapeutic index of loaded active agents [47, 48].

Parasitic Treatment: Novel colloidal delivery systems have gained considerable interest for anti-parasitic agents to focus on three major parasitic diseases like malaria, leishmaniasis, and trypanosomiasis. Lipid Nanoparticles combine advantages of traditional colloidal drug carrier systems like liposomes, polymeric nanoparticles and emulsions but at the same time avoid or minimize the drawbacks associated with them. The delivery system should be designed in such a way that physicochemical properties and pharmacokinetic properties are modulated of the anti-parasitic agents in order to improve bio-specificity and bioavailability with minimization in the adverse effects associated with it. SLN and NLCs have the ability to deliver hydrophobic and hydrophilic drugs with more physical stability and biocompatibility. For Dihydroartemisnin (anti-malarial) loaded NLCs, the drug release behavior from the NLC exhibited a biphasic pattern with burst release at the initial stage and sustained release subsequently [49].

Ocular Delivery: SLNs have been used for ocular drug delivery in the last decades. Recently, further investigations employing NLCs as ocular delivery systems have been carried out. Cyclosporine loaded NLCs, the mucoadhesive properties of the thiolated nonionic surfactant Cysteine polyethylene glycol stearate (Cys PEG SA) and NLC modified by this thiolated agent were evaluated. Resultant NLCs provided a promising system with prolonged residence time [50, 51].

Intranasal Drug Delivery: Nasal administration is a promising alternative noninvasive route of drug administration due to rapid absorption and onset of action, avoiding degradation of labile drugs (peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers. The development of a stable NLC system as a carrier of curcumin biodistribution showed a higher drug concentration in the brain after intranasal administration [52]. In addition, NLC further enhanced the intranasal drug delivery of Duloxetine in the brain for the treatment of major depressive disorder. NLCs of Asenapine maleate showed improved bioavailability and enhanced the uptake to the brain [52].

Parenteral Drug Delivery: The nano-drug delivery systems such as nano micelles, nanoemulsions and nanoparticles have displayed great potential in the improved parenteral delivery of the hydrophobic agents since last two decades. NLC has been considered as an alternative to liposomes and emulsions due to improved properties such as ease in manufacturing, high drug loading, increased flexibility in modulating drug release profile, aqueous nature and biocompatibility of the excipients has enabled intravenous delivery of the drug with passive targeting ability and easy abolishment. Another reported example is NLCs of

artemether (Nanoject) that offers a significant improvement in the anti-malarial activity and duration of action as compared to the conventional injectable formulation. Nanoject can be considered as a viable alternative to the current injectable intramuscular formulation [53].

Cardiovascular Treatment: With Tashinone (TA) loaded NLCs the *in-vitro* incubation tests confirmed that TA- NLC could bind to apoA-I specifically. Macrophage studies demonstrated that TA- NLC incubated with native HDL could turn endogenous by association with apo-lipoproteins, which cannot trigger immunological responses and could escape from recognition by macrophages.

Nifedipine loaded NLCs nanoparticle suspensions were formulated with negatively charged phospholipids, dipalmitoyl phosphatidylglycerol in preventing coagulation to improve solubility and hence bioavailability of drug [54, 55].

Cosmetic Applications of NLC: Lipid nanoparticles, SLN and NLC can be used to formulate active compounds in cosmetics, *e.g.* prolonged release of perfumes [56]. The incorporation of cosmetic compounds and modulation of release is more flexible when using NLC. In addition, the release of insect repellents has been described. A feature of general interest is the stabilization of chemically labile compounds. The solid matrix of the lipid nanoparticle protects them against chemical degradation *e.g.* Retinol and coenzyme Q10. A recently discovered feature is the sunscreen blocking effect of lipid nanoparticles. Similar to particles such as titanium dioxide the crystalline lipid particles scatter UV light, thus protecting against UV irradiation [57].

Trans Epidermal Water Loss: Tacrolimus loaded NLCs were successfully prepared. The penetration rate of these NLCs through the skin of a hairless mouse was greater than that of Prototopic®. *In-vitro* penetration tests revealed that the tacrolimus-loaded NLCs have a penetration rate that is 1.64 times that of the commercial tacrolimus ointment [58].

Increase of Skin Occlusion: Occlusive effect is reported for lipid nanoparticles. By using very small lipid particles, which are produced from highly crystalline and low melting point lipids, the highest occlusion can be reached. Particles smaller than 400 nm containing at least 35% lipid of high crystallinity have been most effective. Comparing NLC with different oil content showed that an increase in oil content leads to a decrease in the occlusive factor [59-62].

Enhancement of Skin Permeation and Drug Targeting: An increase of skin penetration was reported for coenzyme Q 10-loaded SLN as compared to Q10 in liquid paraffin and isopropanol. The cumulative amounts of Q10 were determined to performing a tape stripping test. After five strips the cumulative amount of Q10 was 1%, 28% and 53% of the applied amount from the liquid paraffin, isopropanolol and the SLN formulation respectively. Similar results were achieved by another study for Q10 loaded NLC [63].

Enhancement of Ultraviolet (UV) Blocking Activity: Some side effects of organic UV blockers are reported due to the penetration of these compounds into the skin causing skin irritation and allergic reactions. This penetration can be reduced by incorporating these compounds in lipid nanoparticles. Furthermore, a significant increase in sun protection factor (SPF) up to 50 was reported after the encapsulation of titanium dioxide into NLC. Encapsulation of inorganic sunscreens into NLC is, therefore, a promising approach to obtain well tolerable sunscreens with high SPF [64].

Modulation of Drug Release: The common principles of drug release from lipid nanoparticles can be explained as follows. Drug release is inversely proportional to the partition coefficient of the drug. The surface area increases due to smaller particle size in the nanometer range, which results in higher drug release. Slow-release of the drug could be accomplished when the drug is equally dispersed in the lipid matrix. Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases, it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally, this release should be triggered by an impulse when the particles are administered. NLCs accommodate the drug because of their highly unordered lipid structures. By applying the trigger impulse to the matrix to convert into a more ordered structure, desired burst drug release can be initiated [65].

Physicochemical Characterization of NLCs: [66-70] The physicochemical characterization for NLCs is essential to confirm quality and stability. Both microscopic, macroscopic techniques are used in the development of these colloidal systems.

Particle Size: Particle size is an important parameter in process control and quality assurance because the physical stability of the vesicle dispersion depends on particle size, and as particle size decreases, surface area characteristics increase as a function of total volume. Photon correlation spectroscopy based on laser light diffraction provides an appropriate method for investigation and can be applied to particles ranging below 200 nm up to 1μm.

Zeta Potential: Zeta potential is the electric potential of a particle in a suspension. It is a parameter that is very useful for the assessment of the physical stability of colloidal dispersions. In suspensions, the surfaces of particles develop a charge due to ionization of surface groups or adsorption of ions. This charge depends on both the surface chemistry of the particles and the media around these particles. The surface charge generates a potential around the particle, which is highest near the surface and decays with distance into the medium. Zeta potential can be measured by determining the velocity of the particles in an electrical field (electrophoresis measurement).

Scanning Electron Microscopy: This technique can be used to investigate the shape of the particles prepared and to assess the particle size of these particles.

Differential Scanning Calorimetry (DSC): DSC is usually used to get information about both the physical and the energetic properties of a compound or formulation. DSC measures the heat loss or gains as a result of physical or chemical changes within a sample as a function of the temperature. It is used for the determination of the degree of crystallinity of the particle dispersion by a comparison of the melting enthalpy of the bulk material with the melting enthalpy of the dispersion.

Nuclear Magnetic Resonance (NMR): NMR can be used to determine both the size and the qualitative nature of nanoparticles. Broad signals and small amplitudes are characteristic of molecules with restricted mobility and strong interactions. The higher line width of NLCs compared to the physical mixture of the materials added in NLCs indicates the interaction of liquid oil with the solid lipid. Immobilization of the nanoparticles of NLCs is stronger compared to SLNs with totally crystallized cores.

Transmission Electron Microscopy (TEM): It is a technique where colloidal samples can be visualized at high-resolution. Sufficient contrast can be given to a thin-film of the frozen sample by the use of osmium tetra-oxide. This allows the sample to be viewed directly in the TEM. The adjustment of the temperature to -196 ºC leads to very poor pressure so that the examination of the sample is possible by preservation of microstructure despite the high vacuum.

Drug Release: The controlled or sustained release of the drugs from NLCs can result in a prolonged half-life and retarded enzymatic attack in the systemic circulation. The drug release behavior from NLCs is dependent upon the production temperature, emulsifier composition and oil percentage incorporated in the lipid matrix. The drug in the outer shell of the nanoparticles and on the particulate surface is released in a burst manner, while the drug incorporated into the particulate core is released in a prolonged way.

Sustained release of the drugs can be explained considering drugs partitioning between the lipid matrix and water, as well as the barrier function of the interfacial membrane. The dialysis method and the utilization of the Franz cell are modes for measuring *in-vitro* drug release of nanoparticles [71].

CONCLUSION: The aim of therapeutic nanotechnology is to develop a delivery system having targeted drug therapy. 'Smart' NLCs as a new generation offers much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules, and injectables. The effort to develop alternative routes and to treat other diseases with NLCs should be continued to extend their applications. Permeation *via* the gastrointestinal tract and blood-brain barrier may be a futuristic trend.

The combination of two therapeutically active agents to be included in a single nano-system is another consideration for further development. Lipid carriers have a bright future because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility and offer an economical and patient-friendly device for the administration of drugs.

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