REVIEW ARTICLE

Nano-lipid Carriers for Topical Application: Current Scenario

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Abstract

Since the beginning of the 1990s the nano-lipid carriers (NLCs) have been attracting a growing interest from the pharmaceutical technology research groups worldwide. NLCs appeared as consumer products first on the cosmetic market. The article gives an overview of the cosmetic benefits including enhancement of chemical stability of actives, film formation, controlled occlusion, skin hydration, skin bioavailability, and physical stability of the lipid nanoparticles. Solid-lipid nanoparticle as topical formulations. List of the cosmetic products currently available in the market, and bioequivalence protocol, excipients, improvement of the benefit/risk ratio of the topical therapy is shown.

Key words: Nanoparticles, novel drug delivery system, topical, polymers, excipients

INTRODUCTION

Pharmaceutical breakthrough new technologies have leads to find numerous new mighty therapeutic compounds. To assure progress in drug therapy, the development of new drugs merely is not sufficient. Poor water solubility and insufficient bioavailability of the new drug substances are very extensive issues encountered. Thus, there is an expanding need to develop a pharmaceutical carrier scheme that overcomes these matters, such a carrier should have an adequate pharmaceutical loading capability, free from cytotoxicity and the possibility of possessing pharmaceutical targeting and controlled release characteristics. The system should provide chemical steadiness to incorporate pharmaceuticals. Lipid nanoparticle different categories are shown in Figure 1.[1]

A wide range of nano-lipid carrier (NLC) can be used for topical application of drug. To illustrate, several problems have been reported with the conventional topical preparations, e.g., low uptake due to the barrier function of the stratum corneum and unwanted absorption to the systemic circulation. The literature review provides several systems that can deliver an active pharmaceutical ingredients across the skin presenting advantages in systemic treatment with minimal side effects, the absence of first-pass metabolism, and in topical treatment allowing targeting specific skin appendages.[2]. Among the carriers, solid-lipid nanoparticle (SLN) and NLC have emerged as novel systems composed of physiological lipid materials suitable for topical, dermal, and transdermal administrations. Many features, these carrier systems exhibit suggest for dermal application including cosmetics and pharmaceuticals.

NLCs are the new generation of lipid nanoparticles, attracting major attention as novel colloidal drug carriers for topical use. NLC has been developed to overwhelm the drawbacks affiliated with SLN.[3] 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. While NLC consists of a mixture of specially blended solid lipid (long chain) with liquid lipid (short chain), preferably in a ratio of 70:30 up to a ratio of 99.9:0.1. The resulting matrix of the lipid particle shows a melting point depression compared to the original solid lipid, however, the matrix remains solid at body temperature. However, some limitation of the SLN system regarding drug expulsion during storage,

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Received: 14-05-2015
Revised: 04-01-2016
Accepted: 28-01-2016

reduced particle concentration, reduced drug loading, these limitations were solved by formulating lipid particles with controlled nanostructure known as NLC. For a number of drugs, the solubility of liquid lipid is higher than that of solid lipid, which enhances drug-loading, NLC possess numerous features that are advantageous for the topical route of application. NLC are composed of physiological and biodegradable lipids that show low toxicity. The small size ensures a close contact to the stratum corneum and can increase the amount of drug penetrated into the skin. Due to the occlusive properties of lipid nanoparticles, an increased skin hydration effect is observed. Furthermore, lipid nanoparticles are able to enhance the chemical stability of compounds sensitive to light, oxidation, and hydrolysis [Figure 2].[4]

Drug incorporation model of NLC

SLN modified by incorporation of liquid lipid into the solid lipid has been proposed to NLC to overcome the some limitation of old generation SLN.[5] There are three types:

Type I (highly imperfect matrix)

In Type I NLC, low liquid lipid (oil) concentration is used compared to solid lipid. Solid lipid and oil are blended to o/w nano-emulsion that when cooled from molten state to room temperature, forms solid particle, due to crystallization process, leads to highly disordered, imperfect lipid matrix offering space for drug molecules and amorphous structure of drug.

Type II multiple types

In Type II NLC, there is a high oil concentration. During crystallization process, phase separation of the two lipids occurs. At certain temperature, they have miscibility gap leading to precipitation of tiny oily nano-compartment. When lipids lack drug solubilities, the addition of higher amount of liquid lipid to the lipophilic phase display the advantages of the solid matrix which prevented drug leakages while liquid lipid shows high solubility for lipophilic drug.

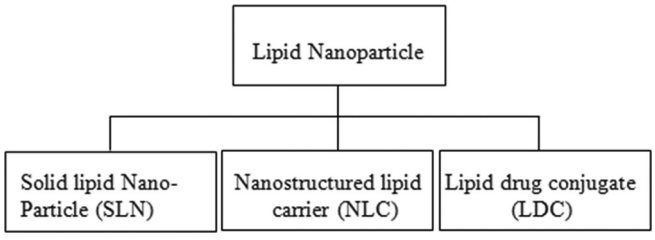

Figure 1: Lipid based drug delivery system

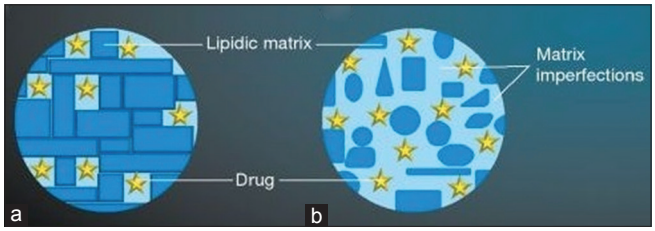

Figure 2: Drug loading in solid-lipid nanoparticle matrix (a) versus nano-lipid carriers matrix (b)

Type III amorphous type

In this type of NLC, by controlled mixture of lipids, particles were created which were solid, not crystalline but in an amorphous state. This amorphous state needs to be preserved [Figure 3].[6]

INTENTION OF TOPICAL PREPARATION

To formulate an effective and efficient topical preparation, i.e., directly concerned with the site of action and the desired effect of the preparation, this preparation may be used for;

Transepidermal water loss (TEWL)

Bioactives penetration into the stratum corneum can be enhanced by occlusion caused by the product, which enhances hydration of the stratum corneum due to the inhibition of water evaporation. Application of NLCs on the skin helped to reduce water loss from the skin when compared to the untreated control. This could be due to the small size of particles in NLCs having larger surface area, which give greater adhesive properties. They form a uniform compact layer on the skin surface, thus preventing water evaporation from the skin.[7]

Increase of skin occlusion

The occlusion effect was reported for lipid nanoparticles. By using very small lipid particles, which are produced from highly crystalline and low melting point lipids, the highest occlusion will 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

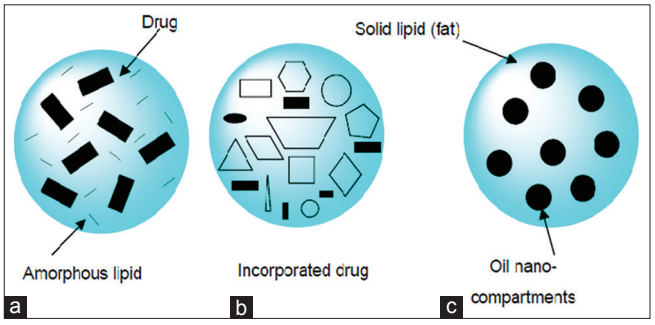

Figure 3: Different type of nano-lipid carriers: (a) Amorphous type, (b) highly imperfect, (c) multiple O/FW type

showed that an increase in oil content leads to a decrease of the occlusive factor.[8,9]

Enhancement of skin permeation and drug targeting

The stratum corneum in healthy skin has typically a water content of 20% and provides relatively an effective barrier against percutaneous absorption of exogenous substances skin hydration after applying SLN or NLC leads to a reduction of corneocytes packing and an increase in the size of the corneocytes gaps. This will facilitate the percutaneous absorption and drug penetration to the deeper skin layers.[10]

Enhancement of ultraviolet (UV) blocking activity

Some side effects of organic UV blockers were reported due to the penetration of these compounds into the skin causing skin irritation and allergic reaction. This penetration can be reduced by incorporating these compounds in lipid nanoparticles; furthermore, a significant increase in sun protection factor (SPF) up to about 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.[11]

IMPROVE BENEFITS/SKIN RATIO

Skin atrophy and systemic side effect occurred after applying conventional prednicarbate cream could be avoided when this drug was formulated as SLN. Prednicarbate uptake was enhanced and it was accumulated in the epidermis with a low concentration in the dermis.

Methods of preparation for SLN and NLC[12,13]

1. Homogenization method
   - Hot homogenization
   - Cold homogenization.
2. Solvent evaporation method
3. Solvent emulsification-diffusion method
4. Microemulsion-based method
5. Supercritical fluid method
6. Spray drying method
7. Double emulsion method
8. Precipitation technique
9. Film-ultrasound dispersion
10. High-speed homogenization followed by ultrasonication method.

Below some excipients and polymers used in preparation of NLC are shown in Table 1. Table 2 shows Overview of drug and method for topical agents incorporated in NLCs

Modulation of drug release

The common principles of drug release from lipid nanoparticles can be explained below; drug release is inversely proportional to the partition coefficient of the drug. Surface area increases due to smaller particle size in 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, such a desired burst drug release can be initiated. NLCs of certain structures can be triggered this way for example, when applying the particles to the skin incorporated in cream. Increase in temperature and water evaporation leads to an increase in drug release rate [Figure 4].[14,15] and some of the polymers used in topical are show in Table 4

Factors affecting drug release

Many factors that could affect the release profile of the drug from the NLC system.

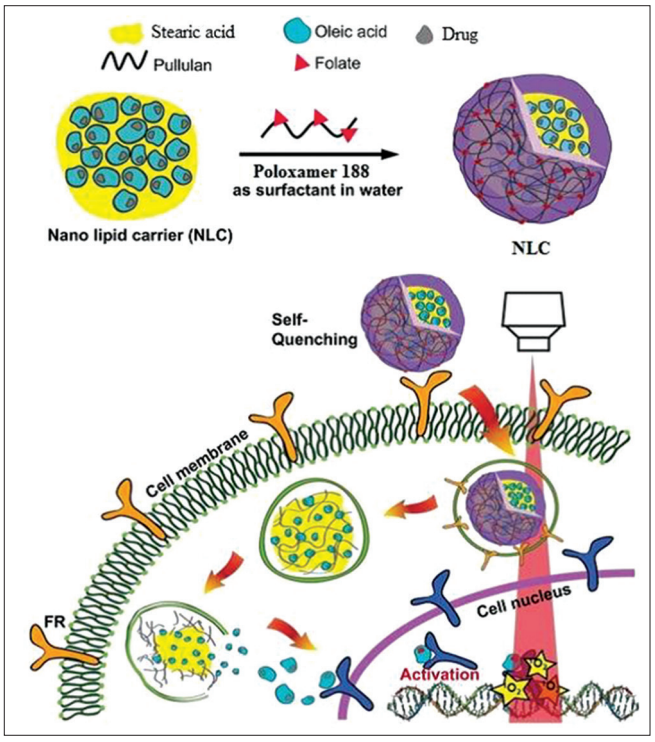

Figure 4: Modulation of drug release

- Particle size
- Lipid matrix
- Surfactant
- Drug loading
- Drug type.

Stability

During long-term storage of dispersions, element aggregation can happen. Aggregation and case formation were described for SLNs. In the highly intensified, NLC dispersions the particles pattern a "pearl-like network," thus the particles are in a repaired place and will not undergo collision and perikinetic flocculation [Figure 5].[16,17]

Characterization of NLC dispersion

- Particle size
- Zeta potential
- Scanning electron microscope
- Determined % drug entrapment efficiency
- % $EE = Wa - Ws/Wa \times 100$

Where, *EE* is entrapment efficiency, *Wa* stands for the mass of drug added to the formulation and *Ws* is the analyzed weight of the supernatant.

- Differential scanning calorimetry.

Characterization of topical[42-44]

Parameters	Method
Diffusion	Franz diffusion cell
Viscosity	Brookfield viscometer
Refractive index	Abbe's refractometer
Spreadibility	Glass plate method
pH	Digital pH meter

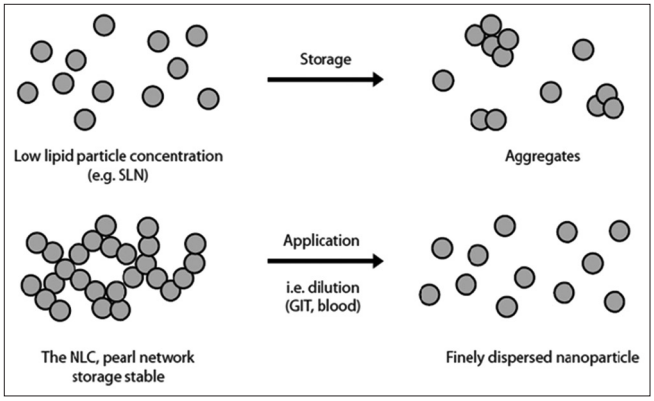

Figure 5: Aggregation process in low concentrated dispersions (upper) and pearl-like network in nano-lipid carriers dispersions with stabilizing effect

REGULATORY CONSIDERATION OF TOPICAL

Bioavailability and bioequivalence issues

The issues of bioavailability and bioequivalence were given considerable, since the target organ for topical products is skin, it seems logical that determining drug concentrations in the skin layers should provide an assessment of topical bioavailability. More work in this area is needed to establish procedures for assessing bioavailability of topical dermatological products. Using the skin stripping technique, only stratum corneum is readily accessible and the deeper tissues. At present, there are no accepted non-clinical models or approaches to predict or determine the bioavailability and bioequivalence of dermatological drugs. Consequently, bioequivalence assessment of test and reference product is based on studies with clinical end points or pharmacodynamics measurements.

Quality control issues

At present, no recognized quality control procedure is available for assessing batch-to-batch uniformity of dermatological products in terms of drug release. A simple procedure to determine the drug release rate from the cream formulations using commercially available diffusion cell and the synthetic membrane has been suggested as a means of accomplishing this, but it is clear that this approach needs to be carefully validated before it can be recommended and widely implemented. Since drug must first be released from the formulation and then permeate through the stratum corneum for therapeutic effect, it may be appropriate to use drug release properties employing synthetic membrane techniques as a quality control test to ensure batch-to-batch uniformity. The quality control test should be able to detect formulation or process factors which may affect the bioavailability and bioequivalence of the drug product.[45]

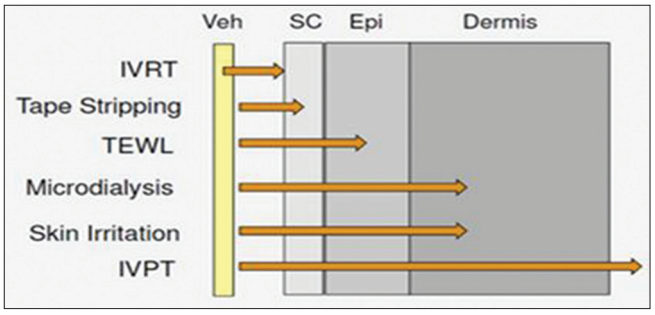

Figure 6: Systematic approach to selecting an appropriate surrogate test to establish bioequivalence of topical dermatological drug products; IVRT: *In vitro* release testing, TEWL: Transepidermal water loss, IVPT: *In vitro* permeation testing

Table 1: Excipients used in NLC topical[18-21]

Solid lipid	**HLB**	**Melting point**	
Apifil	9.4	59-70°C	
Beeswax	12	62-64°C	
Compritol 888 ATO	Above 2.0	69-74°C	
Dynasan 116	6-10	62-64°C	
Glycerylmonostearate	3.8	55-60°C	
Stearic acid	15	68-70°C	
Gelucire 44/14	14	42-44°C	
Liquid lipid	**HLB**	**Melting point**	**Boiling point**
Oleic acid	17	13-14°C	194-195°C
Ethyl oleate	10.7-14	–32°C	216-218°C
Miglyol 812	15	<0°C	240-270°C
Capmul MC	3-4	25-30°C	145-149°C
Seasame oil	7-5	–5°C	230-233°C
Cetiol V	5-6	18.2°C	494-495°C
Emulsifiers*	**Co-emulsifiers**	**HLB (*emulsifiers)**	**Melting point**
Cremophor RH40	Transcutol	13	16-26°C
Labrasol	Butanol	14	44-48°C
Span 20	N-Methyl 2-pyrrolidone	8.6	>200°C
Tween 20		16.7	21°C
Span 80		4.3	45.2°C
Solutol HS		14-16	30°C
Pluronic F-127		22	52-57°C
Tegocare 450		12	60-62°C

HLB: Hydrophilic-lipophilic balance, NLC: Nano-lipid carrier

Bioequivalence study protocol[46,47]

- Protocol and subject selection
- Application and removal of test and reference products
- Sites and duration of application
- Collection of sample
- Procedure for skin stripping.

STUDIES OF TOPICAL BIOEQUIVALENCE [FIGURE 6]

In vitro release testing (IVRT)[48,49]

IVRT utilizes widely accepted Franz diffusion cells to estimate 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 receiver 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 mechanism of cutaneous drug transport.

Tape stripping (TS)

TS provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration time curve (FDA's Draft Guidance, 1998). This method is also known as the dermatopharmacokinetic approach similar to blood, plasma, and urine analysis for drug concentrations as a function of time.

Microdialysis (MD)

MD is a continuous sampling technique in which the molecule of interest is collected from the target tissue; thus providing 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 semipermeable probe is carefully inserted into the site of interest: Brain, muscle, eye, and skin. Therefore, it provides valuable information of unbound drug concentrations

Table 2: Overview of drug as topical agents incorporated in NLCs

Drugs and category	Method	Gelling agent	Remarks	References
Psoralens	High shear homogenization	Carbopol 980	Enhanced permeation and controlled release were obtained	[22]
Ketoprofen (NSAID's)	Simple blending and grinding using high energy micro mill	Xanthan hydrogel	Improved drug therapeutic efficacy and safety, allowing an improvement in the dissolution stability, high tolerability, *P* and the skin permeation properties	[23]
Tacrolimus (NSAID's)	Hot homogenization technique by sonication	Carbopol 940	Lipid modification resulted in the formation of less perfect crystals offering space to accommodate the dissolved drug leading to high entrapment efficiency and topical delivery	[24]
Miconazole nitrate (anti-fungal)	Hot homogenization method	Carbopol 940	MN-loaded NLC-bearing hydrogel to increase the encapsulation efficiency of colloidal lipid carriers with advantage of improved performance in terms of stability and provides a sustaining MN topical effect as well as faster relief from fungal infection	[25,26]
FP (NSAID's)	Ultrasonication	Carbopol 934	NLC-based gel could be a promising vehicle for topical delivery of FP	[27]
Aceclofenac (NSAID's)	Melt emulsification, Low temp solidification, High speed homogenization	Carbopol940P, xanthan gum, HPMC, chitosan	The release rate, permeation rate, and pharmacodynamic activity can be modulated upon changing the ratio of solid lipid to liquid lipid	[28]
Minoxidil (anti-hypersensitive)	Ultrasonication technique	Carbopol 934	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	[29,30]
Celecoxib (NSAID's)	Microemulsion	Carbopol (Ultrez 10)	The NLC based gel described in this study showed faster onset and elicited prolonged activity until 24°h	[31]
Nystatin (anti-fungal)	Hot homogenization and ultrasonication	Cream	NLCs represent promising carrier for topical delivery of nyst offering good physical stability, high entrapment efficiency and controlled drug release	[32]
Marigold extract (anti-wrinkle)	High speed homogenization	Cream	This study demonstrated that cream containing NLCs loaded with ME was stable at 4°C and room temperature conditions, The wrinkles parameters evaluated on 25 healthy volunteers after using creams containing ME-NLCs were significant	[33]
Clobetasol propionate (corticosteroids)	Solvent diffusion method	Carbopol	Improved drug loading capacity was observed for NLC and it enhanced with increasing the CT content in NLC	[34,35]
CoQ10 (anti-ageing)	Ultrasonication method	Cream	CoQ10-NLC, were able to efficiently counteract UVA-associated mitochondrial depolarization suggesting a potential role of this molecule in anti-ageing cosmetological formulations	[36]
Lidocaine (local anesthetic)	Ultrasound dispersion method	Polycarbophil	*In vitro* permeation studies indicated that LID SLN gel and LID NLC gel significantly sustained the LID release compared to that of xylocaine® gel. LID NLC gel resulted in 5-fold and 6-fold increase in duration of anesthesia	[37]

NLC: Nano-lipid carrier, NSAIDs: Non-steroidal anti-inflammatory drugs, FP: Flurbiprofen, HPMC: Hydroxy propyl methyl cellulose, CT: Capric triglycerides, SLN: Solid-lipid nanoparticle, LID: Lidocaine,

Table 3: Cosmetic products containing lipid nanoparticles are currently available in the market[38,39]

Product name	Active ingredients
Nano-lipid restore CLR	Black currant seed oil containing 3 and 6 unsaturated fatty acids
Nano-lipid basic CLR	Caprylic/CT
NLC deep effect eye serum	Coenzyme Q10, highly active oligo saccharides
Extra moist softener	Coenzyme Q10, -3 und -6 unsaturated fatty acids
NLC deep effect repair cream	Q10, TiO2, highly active oligo saccharides
Regenerations creme intensive	*M. ternifolia* seed oil, avocado, urea, black current seed scholl oil
Surmer crème contour des Yeux Nano-Remodelante	Kukuinut oil, Monoi Tiare Tahiti pseudo-peptide, hydrolyzed wheat protein
Surmer Elixir du Beauté Nano-vitalisant	Coconut oil, pseudo-peptide, milk extract from coconut, wilder extract
Surmer Masque Crème Nano-hydratantti	Coconut oil, Monoi Tiare Tahi, milk extract from coconut, wild ginger, pseudo-peptide, tamanut tree extract
Olivenöl anti-falten	*O. europaea* oil, panthenol, acacia senegal, tocopherylacetate
Cutanova cream nano repair Q10	Q10, polypeptide, hibiscus extract, ginger extract, ketosugar
Cutanova cream nano vital Q10	Q10, TiO_2, polypeptide, ursolic acid, oleanolic acid, sunflower seed extract

M. ternifolia: Macadamia ternifolia, O. europaea: Olea europaea, CT: Capric triglycerides

Table 4: Polymers used in topical[40-42]

Natural	Synthetic
Gellan gum (0.04-4% w/w)	PLA
Cellulose (1-2% w/w)	PACA
Starch (3-5% w/w)	Poly (acrylic acid)
Chitosan (1-3% w/w)	PVA
Xantham gum (0.5-1%)	Poly (ethylene glycol)
Carrageenan (0.1-0.5%)	

Advantages and dis-advantages

Advantages	Dis-advantages	Advantages	Dis-advantages
Less toxic	High degree of variability in natural materials derived from animal sources	Biocompatibility	Toxic
Biocompatibility	Structurally more complex		Non-degradable
Biodegradable	Extraction process very complicated and high cost		Synthetic process is very complicated and high cost
Easily available			

PLA: Poly (lactic acid), PACA: Poly (cyanoacrylates), PVA: Poly (vinyl alcohol)

or biomarkers at the site closer to the pharmacological action compared to the conventional plasma/blood drug concentration versus time.[50]

TEWL

TEWL measurements (the rate at which water vapor is lost from the body through the skin) are of great importance in evaluating barrier functionality. Often normal rates of TEWL are compromised due to injury, infection and/or severe damage as in the case of burns. Damage to the stratum corneum and superficial skin layers not only results in physical vulnerability but also results in an excess rate of water loss. TEWL is also affected by variations in sweat gland activity, temperature, and metabolism. Therefore, TEWL becomes a significant factor in dehydration associated with several major disease states.

Some Cosmetic products containing lipid nanoparticles are currently available in the market are shown in table 3

CONCLUSION

NLC were developed in 1999; the first products entered the market in 2005 just 6 years later. This is a very promising start. However, to judge the final success of a carrier system, the total number of products entering the market in the

coming years needs also to be considered, the concept of surface modification is further increasing the importance of SLN and NLC among traditional colloidal drug carrier system. SLN and NLC delivery are promising candidates that will enable efficient and targeted delivery of novel drug compound. Lipid carriers have bright future, because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility. SLN and NLC offer an economical and patient-friendly device for administration of drugs by topical routes.

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Source of Support: Nil. **Conflict of Interest:** None declared.