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Novel Lipid-Based Systems for Skin Enrichment

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ABSTRACT: Topical drug application has been introduced for a long time to achieve several objectives on different levels. However, several problems have been reported with the conventional topical preparations e.g. low uptake due to the barrier function of the stratum corneum and absorption to the systemic circulation. The scientific literature today provides several systems that can deliver active pharmaceutical ingredients across the skin. These include reservoir matrices, matrix diffusion-controlled devices, multiple polymer devices and multilayer matrix assemblies. Among these, topical application of the lipid based system has emerged as novel systems. The use of lipids in drug delivery is by no means a new trend. 'Old' lipid dosage forms such as suppositories, creams or emulsions have been on the market for a long time, and some of them in use for a long time. However, approaches in new designs of lipid carriers have considerably developed for the delivery of poorly soluble drugs. Lipid based drug delivery systems play a direct role in improving efficacy and drug safety, whereby new and improved therapies are possible. Lipid based formulations also protect active compounds from biological degradation which ultimately lead to an enhancement of drug potency. This article mainly focuses on various novel lipid formulations, their prominent applications in pharmaceutical drug delivery.

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INTRODUCTION:

Skin is the largest organ of the human body and provides protection against the external environment. As our age increases, our skin undergoes gradual changes that are [1,2]:

- Cells divide more slowly and the inner layer of skin (the dermis) starts to thin. Fat cells beneath the dermis begin to shrink. In addition, the ability of the skin to repair itself decreases with age, so wounds heal more slowly. The thinning skin becomes prone to injuries and damage.
- The deeper layer of the skin, which provides the support structure for the surface skin layers, loosens and

unravels. Skin then loses its elasticity (To stretch and return to position). As a result, skin sags and forms furrows.

- Glands that secrete oil shrink (atrophy). This leaves the skin without a protective layer of oil. The skin's ability to stay moisturized decreases, becoming dry and scaly.
- Frown lines (between the eyebrows) and crow's feet (lines that spread from the corners of the eyes) develop because of repetitive muscle contractions during facial expressions.
- Gravity causes skin and tissues to sag, leading to formation of jowls and drooping eyelids.

Sunlight, Ultraviolet Radiation, and Photo aging:

Sunlight exposure is the most important cause of early aging of skin (a process called photoaging). Sunlight exposure is also the main cause of skin cancers. The two types of sun rays that can injure the skin are Ultraviolet A (UVA) and Ultraviolet B (UVB). Exposure to ultraviolet radiation accounts for most of the symptoms of early skin aging. Much of the damage is underway by age 20. The effects of UV on skin are mentioned below [1,2];

- UVA affects the deep layers of skin. Most of the ultraviolet rays that reach the earth are UVA. UVA is not as intense as UVB. UVA rays are equally intense throughout the entire day and year. UVA can pass through clouds and glass.
- UVB is the main cause of sunburns. It mostly affects the outer skin layers.
- UVB is most intense in the United States between 10 a.m. and 4 p.m. from April to October. Skin damage from UVB can also occur during winter, especially at high altitudes or in places with snow and ice, which reflect rays onto the skin. Window glass filters out most UVB rays.
- Even small amounts of UV radiation trigger the processes leading to skin wrinkles.
- Long-term repeated exposure to sunlight adds up. This is responsible for the problems of aging skin, including basal cell and squamous cell cancers.
- Intense exposure to sunlight in early life is an important cause of melanoma, an aggressive type of skin cancer.

Processes Leading to Wrinkles:

Wrinkles form in the following way:

Sunlight damages collagen fibers. Collagen is the main protein that gives structure to the skin. Sunlight also damages elastin. This is another protein in the skin that helps it and the tissue below stay springy and strong. In response to sun-induced elastin damage, the body produces large amounts of enzymes called metalloproteinases. Some of these enzymes break down collagen. The result is an uneven formation of disorganized collagen fibers called solar scars. Repetition of this abnormal skin rebuilding causes wrinkles. An important event in this process is the over-production of oxidants, also called free radicals. Excessive amounts of oxidants damage the body's cells. They can even alter the genetic material of cells. Oxidation may lead to wrinkling by activating the specific metalloproteinase that degrades connective tissue [1,2].

Other Factors Responsible for Wrinkles:

In addition to sunlight, other factors can speed the formation of wrinkles.

***Cigarette Smoke*:**

Smoking produces free radicals in the body. These cause wrinkles and age-related skin problems to develop sooner. Free radicals also increase the risk of non-melanoma skin cancers. Studies suggest that smoking and resulting oxidation produce higher levels of metalloproteinases.

***Air Pollution*:**

Ozone is a common air pollutant. It may reduce the body's vitamin E level. Vitamin E is an important antioxidant that protects cells against the effects of free radicals [1,2].

Topical drug application has been introduced for a long time to achieve several purposes on different levels (skin surface, epidermis, dermis and hypodermis). However, several problems have been reported with the conventional topical preparations e.g. low uptake due to the barrier function of the stratum corneum and absorption to the systemic circulation. The scientific literature today provides several systems that can deliver active pharmaceutical ingredients (APIs) across the skin. These include reservoir matrices, matrix diffusion-controlled devices, multiple polymer devices and multilayer matrix assemblies. Among these, topical applications of the Solid lipid nanoparticles (SLN) and Nano Structured lipid carriers (NLC) have emerged as novel systems composed of physiological lipid materials suitable for topical, dermal and transdermal administration. Many features, which these carrier

systems exhibit fordermal application of cosmetics and pharmaceutics, have been pointed out. SLN and 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 [3,4].

Increase of skin occlusion:

The lipid film formation on the top of the skin and the subsequent 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 cystallinity have been most effective. It was found a higher occlusive factor for SLN in comparison to NLC of the same lipid content. Comparing NLC with different oil content showed that an increase in oil content leads to a decrease of the occlusive factor [5].

Increase of skin hydration and elasticity:

The reduction of trans-epidermal water loss (TEWL) caused by occlusion leads to an increase in skin hydration after dermal application of SLN, NLC or formulations containing them.

An *in vivo* study showed that the SLN-containing o/w cream increased the skin hydration significantly more than the conventional o/w cream. A study shows that the skin hydration effect after repetitive application of an o/w cream containing SLN and a conventional o/w cream was investigated for 28 days. A significant higher increase in skin hydration was found by Müller et al. for an NLC containing cream compared to conventional cream [6].

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 coenocytes packing and an increase in the size of the coenocytes gaps. This will facilitate the percutaneous absorption and drug penetration to the deeper skin layers [7].

Improve benefit/ risk ratio:

Skin atrophy and systemic side effects that occurred after applying conventional Predinicarbate cream could beavoided when this drug was formulated as SLN. Predetermine uptake was enhanced and it was accumulated in the epidermis with a low concentration in the dermis. In another study Joshi, *et al*. compared a Valdecoxib loaded NLC carbopol gel with a valdecoxib market product. The NLC containing gel showed no skin irritation while the market gel showed slight irritation after 48 h. Moreover, the NLC based gel showed prolonged activity up to 24 h while the activity of the market gel was shorter. This indicates a better skin tolerability and a longer activity of the NLC formulation compared to the marketed formulation. Tretinoin loaded-SLN formulation was studied by Shah, *et al*. concerning skin irritation. One of the major disadvantages associated with the topical application of Tretinoin is the local skin irritation such as erythema, peeling and burning as well as increased sensitivity to sunlight. In the *in vitro* permeation studies through rat skin they found that SLN based Tretinoin gel has a permeation profile comparable to that of the market tretinoin cream. But on the other hand, Draize patch test showed that SLN based tretinoin gel resulted in remarkably less erythremic episodes compared to the currently marketed tretinoin cream and hence, a better benefit/risk ratio is expected for the formulations containing tretinoin-loaded SLN. Conclusively, applying SLN or NLC can enhance skin penetration of incorporated activities, promote the epidermal targeting and minimize the systemic side effects and therefore, the benefit/risk ratio is improved [8].

Enhancement of 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. It was found that incorporating benzophenone in SLN not only improves the UV blocking activity evaluated using *in vitro* photoprotection assay but also reduces the absorption of the benzophenone into the skin in comparison to a conventional nanoemulsion. Improving the UV blocking activity allows the reduction of the concentration of the UV blocker while maintaining the protective level of the conventional formulation. These findings were confirmed by Song and Lui comparing UV absorption

properties of 3,4,5-trimethoxy benzochitin-loaded SLN and SLN free systems. Furthermore, a significant increase in 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 [9].

Enhancement of chemical stability of chemically labile compounds:

Enhancement of chemical stability after incorporation into lipid Nanocarriers was proven for many cosmetic actives e.g. coenzyme Q 10, ascorbyl palmitate, tocopherol (Vitamin E) and retinol (Vitamin A) [10].

Importance of lipid as drug delivery:

Lipid carriers form a protective barrier, make the skin water resistant, reduce the transepidermal water loss and thus protect the skin against dehydration. By filling up microscopic indentations in the skin they lead to a noticeable smoothening of the skin which simultaneously also reduces minor wrinkles [11]. It is also being proved that the unique properties of lipids viz their physiochemical diversity, biocompatibility, which reduces local irritancy, make them ideal carriers for topical usage [12]. Besides these common features there are also some specific properties for these innovative systemsLipid based carriers have been more and more explored in pharmaceutical technology, showing superior advantages for topical purposes over conventional colloidal carriers. The development of lipid based drug carriers has attracted increased attention over the last years. Lipid-based delivery systems are an accepted, proven, commercially viable strategy to formulate pharmaceuticals, for topical, oral, pulmonary or parenteral delivery. Lipid based formulations can be tailored to meet a wide range of product requirements dictated by disease indication, route of administration, cost consideration, product stability, toxicity, and efficacy. The proven safety and efficacy of lipid-based carriers make them attractive candidates for the formulation of pharmaceuticals, as well as vaccines, diagnostics and nutraceuticals.

Lipid carriers are equally important for transdermal systems as they form a protective barrier, make the skin water resistant, reduce the trans-epidermal water loss and thus protect the skin against dehydration. By filling up microscopic indentations in the skin they lead to a noticeable smoothening of the skin which simultaneously also reduces minor wrinkles. It is also being proved that the unique properties of lipids viz., their physiochemical diversity, biocompatibility which reduces local irritancy, make them ideal carriers for topical usage [13].

Increasing interest in lipid-based delivery systems is due to following reasons like [14]:

- Versatility of lipidic excipients.
- Formulation versatility and the choice of different drug delivery systems.
- Low risk profile.
- Enhanced oral bioavailability and reduced plasma profile variability.
- Enhanced permeation of these systems when used topically.
- Formation of the vesicular system which is passive, non-invasive and is available for immediate commercialization.
- Better characterization of lipidic excipients.
- High market attractiveness for products with proprietary technology.

Improved ability to address the key issues of technology transfer and manufacture scale-up.

INNOVATIVE LIPID BASED DELIVERY SYSTEMS:

Emulsions:

Following are the different emulsion delivery systems used in cosmetics.

***Micro-emulsions*:**

They are stable, transparent dispersions of oil and water stabilized by an interfacial film of surfactant molecules and having diameter < 100 nm [15]. Since micro-emulsions were discovered approximately six decades ago, their applications in cosmetics have increased because of their good appearance, thermodynamic stability, high solubilization power, and ease of preparation. Penetration of vitamin E and Quercetin was enhanced when employed in a micro-emulsion. Quercetin encapsulated in micro-emulsion did not cause skin irritation and was effective against UVB induced damage. Micro-emulsion containing ascorbic palmitate effectively prevents UVA induced lipid peroxidase ion [16]. A study on development of a curcumin encapsulated in oil-in-water phospholipid based microemulsion showed that its degradation was prevented with increase in concentration in aqueous phase [17].

***Liquid crystals*:**

Liquid crystalline phase is the intermediary state between solid and liquid, representing a state of

incomplete melting. Emulsions containing liquid crystals have been observed to release activity at much slower rate than those without this stabilizing component. For example, timed release of vitamin A palmitate containing liquid crystals dispersed in water-based gel [18].

***Multiple emulsions*:**

Multiple emulsions are a type of polydisperse system, in which the dispersion phase contains another dispersion phase. They are of two types: W/O/W type and O/W/O type. These are excellent and exciting potential systems for slow or controlled release of active constituents. O/W/O multiple emulsions have potential applications because of more occlusivity on skin and acceptability. Moreover higher amounts of active substances can be retained in epidermis and dermis using these systems. Ascorbic acid and vitamin A formulated in O/W/O emulsion illustrated multiple emulsions to be effective carriers for stabilizing and improved release profile [19].

***Nanoemulsions*:**

These systems are fine oil-in-water dispersions, having droplet diameter smaller than 100 nm with aesthetic properties i.e. low viscosity and transparency, making these systems suitable for their application in cosmetics. But, in comparison with microemulsions, they are in a metastable state and are very fragile systems by nature [34]. The nanoemulsion of CoQ10 and vitamin E acetate was proven to be a promising cosmetic ingredient to prevent premature skin aging by protecting the mitochondrial DNA against UV-induced mutations [35]. A study on antioxidant synergy formulation nanoemulsion (ASF) containing different tocopherol isomers indicated that preparations containing gamma, alpha, and delta tocopherol enhanced anti-inflammatory properties and increased bioavailability compared to their suspensions [20].

***Pickering emulsions*:**

These are lipid-based emulsions with internal nanostructures stabilized by solid particles such as silica, clays, calcium carbonate, titanium dioxide, latex and many others. The ultra-fine amphiphilic particles are defined as having particle sizes <200 nm. Pickering emulsions are new drug penetration vehicles with specific behavior; they are well-suited either for targeting the stratum corneum or aimed at slow release of drug from stratum corneum used as a reservoir to the deeper layers of skin [20]. The skin absorption of caffeine from silica stabilized pickering emulsion was three fold higher than emulsifier stabilized emulsion attributed to the higher adhesion potential of pickering emulsions [21].

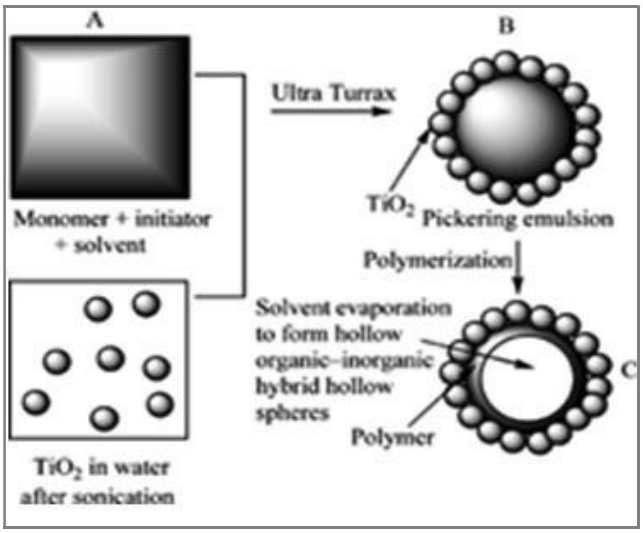

Fig 1. Pickering emulsion stabilized by TiO_2.

Vesicular systems:

In several studies, the diffusion of a drug was facilitated or achieved certain selectivity into human and nonhuman skin by vesicle encapsulation. Only a few papers (5 %) claimed that the vesicles have no effect on the skin [21].

***Liposomes*:**

Liposomes are the most widely known vesicular cosmetic delivery systems. These vesicles contain from one to several concentric lipid bilayers with intercalated aqueous sections. Topically, liposomes offer a wide array of advantages including biodegradability, nontoxicity, moisturizing and restoring action, sustained dermal release and similarity to biological membranes enabling penetration into epidermal barrier compared to other delivery systems [22]. Liposomes are nanosized artificial vesicles with lipid bilayer composed of phospholipids and cholesterol. Liposomes have many drawbacks like tendency to be taken up by the RES system, modification of system for delivery to special sites, cost, etc., lead to development of newer drug delivery systems like transfersomes, ethosomes, etc [24]. Also cholesterol commercially available is derived from egg or wool grease. These animal sources are potentially not suitable for human pharmaceuticals due to the potential viral contamination. Also, cholesterol is readily oxidized creating a stability problem for lipid based drug products. Some of these oxidation by-products like 25-hydroxy cholesterol, 7-keto-cholesterol, 7a- and 7ß-

hydroxycholesterol, cholestane-3ß,5a,6ß-triol and the 5- and 7-hydroperoxides, were found toxic causing aortic smooth muscle cells to die. Liposomes act as vesicles to target anticancer drugs resulting in reduced side effects but prolonging their circulation time through pegylation and thus improving effectiveness in the body. Liposomes help in the biopreservation of RBCs. Liposome-encapsulated hemoglobin (LEH) has evolved to carry oxygen, capable of surviving in the circulation and can be produced in large-scale production. Topically liposomes has several advantages including biodegradability, non-toxicity, moisturizing and restoring action, sustained dermal release and similarity to biological membranes enabling penetration into epidermal barrier compared to other delivery systems.

Table 1. Different modifications in liposomes for improver drug delivery.

Modified liposomes	Application
Immuno-liposomes	Adsorb DNA non specifically on their surface and transfer it directly to cytoplasm,without being presented to lysosomes for degradation
Genosome	Complex formulations of DNA with various cationic liposomes which is used as a form of non-viral gene therapy as the complex does not require any components of virus in order to transport genetic material
Marinosome	Based on a natural marine lipid extract containing a high polyunsaturated fatty acid(PUFA) which are not present in normal skin epidermis like ecosapentanenoic acid etc which are metabolized by skin epidermal enzymes into anti-inflammatory and anti-proliferative metabolites that are beneficial in treating inflammatory skin disorders
Ultrasomes	Specialized liposomes encapsulating an endonuclease enzyme extracted from micrococcus luteus; the enzyme recognizes the sun damage to the skin and initiates removal of damaged DNA
Asymmetric oxygen carrier system (AOCS)	Designed to carry oxygen into the skin, are composed of perflurocarbon core surrounded by a monolayer of phospholipids,followed by a bilayer system

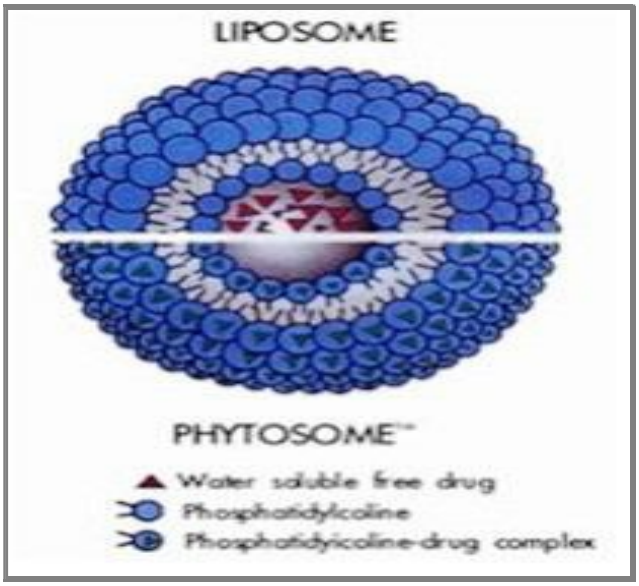

Fig 2. Difference between Phytosome and a liposome.

Several drugs and cosmetics in this form are already commercially available and successfully used, with lesser incidence of side effects [23]. The modification of liposomes is given in Table 1 with their applications.

***Phytosomes*:**

Some studies have reported that phospholipids exhibit a marked affinity for some classes of flavonoids, a new series of compounds denominated as “phytosome” has been developed by complexation with polar botanical derivatives such as catechin, quercetin, escin and glycyrrhetinic acid. Phytosomes are complexes between a pure phospholipid and pure active principles from the chemical perspective. The soothing activity of silymarin has shown to be increased by six fold in silymarin phytosomes compared to free active principles, which is proposed to be due to higher affinity of complexes for skin phospholipids. The green tea (polyphenol), grape seed, silybum marianum, hawthorn extracts and olive polyphenols were successfully commercialized as phytosomes for antioxidant, free radical scavenger, UV protectant actions [24].

***Transferosomes*:**

In the 1990s, transfersomes, i.e., lipid vesicles containing large fractions of fatty acids, were introduced. Transfersomes are vesicles composed of phospholipids as their main ingredient with 10 to 25 % surfactant and 3 to 10 % ethanol. In consequence, their bilayers are much more elastic than those of liposomes. Higher membrane hydrophilicity and flexibility both

help transfersomes to avoid aggregation and fusion, which are observed with liposomes. When applied non-occlusive, they significantly improve skin deposition of α-tocopherol and its photostability [25]. The therapeutic application of Transferosomes is given in Table 2.

Table 2. Therapeutic applications of Transfersomes.

Drug	Effects observed
Indinavir	Reduce side effects, Improved skin permeability
Propranolol	Improved transdermal flux
Insulin	High encapsulation efficiency. Transfer across the skin with an efficiency of >50%. Provide noninvasive means of therapeutic use
Interferone	Controlled release. Overcome stability problem.
Tamoxifen	Improved transdermal flux
Meletonin	Improved systemic absorption
Meloxicam	Improved biological activity
Valsartan	Improved skin permeability
Tetracaine	Noninvasive treatment by topical drug application
Lidocaine	Noninvasive treatment by topical drug application
Norgesterol	Improved transdermal flux
Oestradiol	Improved transdermal flux

***Ethosomes*:**

They are lipid vesicles containing high content of ethanol (20 to 50 %) acting as drug penetration enhancer and fluidizer for membranes. It is proposed that the alcohol fluidizes the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.These carriers transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposomes [42]. The *in vitro* release rate of azelaic acid was more rapid from ethosomal systems (plain and viscous formulations) than from liposomal systems [26].

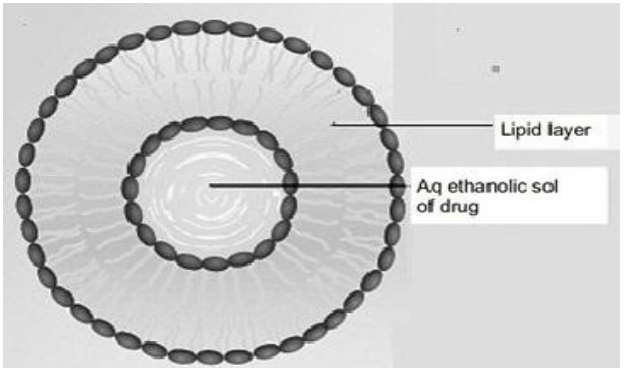

Fig 3. Ethosome vesicle.

Table 3. Therapeautic application of ethosomes in drug delivery.

Drug	Applications	Comments
Acyclovir	Treatment of Herpetic infection	Improved drug delivery
Azelaic acid	Anti keratinizing agent used in treatment of acne	Improved transdermal delivery
Zidovudine	Treatment of AIDS	Improved transdermal flux
Lamivudin	Treatment of AIDS	Improve transdermal drug delivery
Trihexypenidyl HCl	Treatment of Parkinsoniansyndrome	Increased drug entrapment efficiency, reduced side effect & constant systemic levels
Erythromycin	Efficient healing of S. aureus-induced deep dermal infections	Improved drug penetration and systemic effect.
Insulin	Treatment of Diabetes	Improved therapeutic efficacy of drug
Diclofenac	Anti inflammatory, analgesic	Improve biological activity,Reducesideeffects
Testosterone	Treatment of male hypogonodism	Enhance skin permeation
Fluconazole	Treatment of candidiasis	Enhanced skin permeation
Cannabidol	Prevents inflammation and edema	Significant accumulation of the drug in the skin
Cyclosporin	Treatment of inflammatory skin disease	Improve oral absorption and bioavailability, protect from GIT degradatiomn
Minodixil	Hair growth promotion effect	Higher skin retention
Methotrexate	Treatment of psoriasis	Treatment of psoriasis
Salbutamol	Anti-asthmatic	Enhanced skin permeation
Bacitracin	Treatment of dermal infections	Reduced drug toxicity

***Niosomes*:**

These are essentially non-ionic surfactant based multilamellar or unilamellar vesicles. The oil spreads uniformly over the surface of the skin; vesicles penetrate the stratum corneum in fractioned form while the continuous aqueous phase evaporates.Consequently a special sensation to touch, freshness, hydration and a feeling of protection because of the oily film is experienced. If the envelope is made of sphingolipids,vesicles are named sphingosomes [26]. Manconi, *et al*. concluded that unilamellar niosomes containing Brij® 30 conferred best protection of tretinoin against photodegradation. Gopinath, *et al*. investigated the possibility of converting ascorbyl palmitate into bilayered vesicles with a view to exploit them as carriers for drug delivery. These vesicles were termed as Aspasomes and were found to possess much superiority than that of ascorbic acid. Thus, they may find applications as a drug delivery system in disorders implicated with reactive oxygen species [27].

***Nanotope*:**

Recent advancement in liposomes includes monolayered Nanotopes ™ particles, which comprises membranes having well defined ratio of a phospholipid (i.e., lecithin) and a co-surfactant. Nanotopes are formed at an optimum ratio of phospholipid to cosurfactant, which promotes intercalation of co-surfactant between the lecithin molecules to form a continuous array extending from the lipid-core into the aqueous phase. Baschong, *et al*. showed that nanotopes containing vitamin E acetate exhibited smaller size, greater uniformity, increased skin penetration of active and higher occlusion effect compared to conventional liposomal system [28].

Archaeosomes:

Archaeosomes are nano-sized vesicles prepared from total polar lipids (TPL) either extracted from the selected genera and species of the Archaea domain or synthetic archaeal lipids. Archaeal-type lipids consist of archaeol (diether) and/or caldarchaeol (tetraether) core structures wherein regularly branched and usually fully saturated phytanyl chains (20 to 40 carbons in lengths), are attached via ether bonds to the sn-2,3 carbons of the glycerol backbone [28]. There are remarkable structural differences from liposomes: the archaeosomes surface is highly entropic, possessing half the surface tension than that of liposomes and its permeability to protons and sodium cation is nearly one third of that determined for liposomes; the inclusion of macrocyclicarchaeols and

Table. 4. Novel lipid based systems explored for antioxidants.

Carrier	Active ingredient	Effects observed	Ref.
Emulsion			
Microemulsion	Quercitin and Vitamin E	Increased skin penetration and diminished skin	5
	Curcumin	Increased solubility, improved protection against degradation	11
Liquid crystals	Vitamin A palmitate	Sustained release	8,12
Multiple emulsion	Ascorbic acid and Vitamin A	Stabilizing effect and improved release profile	13
Nano emulsion	CoQ10 & Vitamin E acetate	Improved anti-aging effect	15
Pickering emulsion	Caffeine	Improved skin penetration	18
Vesicular systems			
Liposomes	(-)Epigallocatechin-3-gallate and retinoic acid	Increased drug deposition	5
Phytosomes	Green tea (polyphenol), grape seed, silybummarianum, hawthorn extracts and olivepolyphenols	Exhibit improved free radical scavenging and UV protectant action	19
Transfersomes	Alpha tocopherol	Improved skin deposition and its photo stability	5, 20
Ethosomes	Azelaic acid	Increased *in vitro*release rate compared to liposomes	22
Niosomes	Tretinoin	Protection against photo degradation	5

Nanotopes	Vitamin E acetate	Increased skin penetration of active and higher occlusion effect compared to conventional liposomal system	23
Lipid particulate systems			
Lipid microparticles	Quercitin	Improved photo and chemical stability	5
Lipid nanoparticles	Retinol, CoQ10, alpha lipoic acid, beta-cartene and alpha tocopherol	Enhanced chemical stability	7, 28, 29
SLN	Tretinoin	Diminished skin irritation	30
	Curcuminoids	Enhanced the anti-aging effects with no sign of skin irritation	31
SLN & NLC	Alpha-lipoic acid	Exhibit low cell cytotoxicity and good physical stability	29

caldarchaeols further impairs archaeosomes permeability to water and small solutes [29]. It has been shown that incorporation of polyethylene glycol and Coenzyme Q10 into archaeosomes can alter the tissue distribution profiles of intravenously administered vesicles. Omri, *et al*. (2003) had also reported that intravenous and oral delivery of nanometric-sized archaeosomes to an animal model was well tolerated with no apparent toxicity. The results of these studies are very promising for the utilisation of archaeosomes in the encapsulation and delivery of different bioactive compounds [30].

Vesosomes:

Vesosomes are multicompartment structures which have distinct inner compartments separated from the external membrane. In simple terms it can be said as a larger vesicle that deliberately encapsulates many smaller vesicles in it.

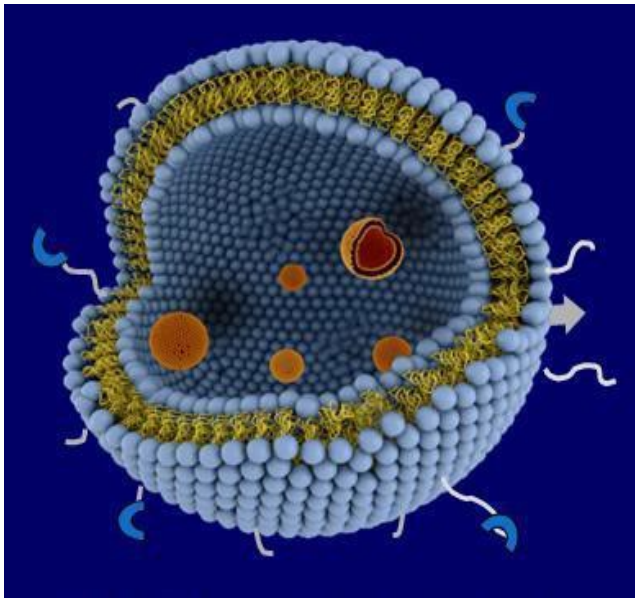

Fig 4. A vesosome – Vesicle within vesicle.

Each compartment of vesosome can encapsulate different materials and have different bilayer composition. In addition, while it has proven difficult to encapsulate anything larger than molecular solutions within lipid bilayer by conventional vesicle self-assembly, the vesosome construction process lends itself to trapping colloidal particles and biological macromolecules relatively efficiently [31]. The disadvantage of conventional liposomes is that many important drugs are released faster than optimal *in vivo*. This problem is significantly addressed by the vesosome: while small molecules are released from unilamellar liposomes in minutes, they are retained in vesosomes from hours to days, even though the liposomes and vesosomes have the same bilayer composition and size [32].

Lipid particulate systems:

Biocompatible lipid micro- and nanoparticles have emerged as potential drug carrier systems as alternative materials to polymers in recent decades. Solid lipid particles combine several advantages and avoid the disadvantages of other colloidal carriers. The following are affirmative characters of solid lipid particles as carrier systems:

- They offer the possibility of controlled drug release and drug targeting.
- They provide protection of incorporated active compounds against degradation.
- Their solid matrix is composed of physiological and well tolerated lipids.
- They allow for hydrophilic and/or hydrophobic drugs to be incorporated.
- They are stable and scale-up is easy.

The features which determine the loading capacity of drug in the lipid particles are drug solubility and

miscibility in melted lipid, chemical and physical structure of lipid materials, and their polymorphic state. Their encapsulation efficiency can vary from 1 to 5 % for hydrophilic compounds and up to 80 % for lipophilic compounds [33].

***Lipid microparticles*:**

Microencapsulation is a process in which very thin coatings of inert natural or synthetic materials are deposited around micro-sized particles of solids or droplets of liquids. Commercial microparticles typically have a diameter between 1 and 1000 mm and contain 10 to 90 % core. Microparticles with size >1 μm are retained in the skin surface or deposited on the surface of the hair follicles therefore preventing skin permeation of substances having a potential. Since microparticles are located on the skin surface forming a film, they can be used for protection against UV radiation in sunscreens. Lipid microspheres, often called lipospheres, are fat based encapsulation systems for drug delivery. These are composed of a solid hydrophobic fat core (triglycerides) stabilized by a layer of phospholipid molecules embedded in their surface. The internal core contains the bioactive compound, dissolved or dispersed in the solid fat matrix. Lipid microparticles of cosmetic ingredients such as glycolic acid have shown decreased irritation potential. While incorporation of quercetin in lipid microparticles improved photo and chemical stability of the flavonoid [34].

Lipid nanocarrier:

***Solid lipid nanoparticle (SLN)*:**

Solid lipid nanoparticles (SLN^{TM}) were developed at the midlines of the 1990s as an alternative carrier system to the existing traditional carriers, such as emulsions, liposomes and polymeric nanoparticles. Solid lipid nanoparticles (SLN) prepared either with physiological lipids or lipid molecules with a history of safe use in human medicine, which attract increasing attention as colloidal drug carriers. Under optimized conditions they can be produced to incorporate lipophilic or hydrophilic drugs and seem to fulfill the requirements for an optimum particulate carrier system. Advantages of SLN are the use of physiological lipids, the avoidance of organic solvents, a potential wide application spectrum (dermal, per os, intravenous) and the high pressure homogenization as an established production method. Additionally, improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light) and even controlled release characteristics were claimed by incorporation of poorly water soluble drugs in the solid lipid matrix [35]. Common disadvantages of SLN are their particle growing, their unpredictable gelation tendency, their unexpected dynamics of polymorphic transitions and their inherent low incorporation rate due to the crystalline structure of the solid lipid [36,37].

***Nanostructured lipid carriers (NLC)*:**

A new generation of nanostructured lipid carriers (NLCs) consisting of a lipid matrix with a special nanostructure has been developed [38]. This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high-pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30 to 80 %. Carrier system. However, the NLC system minimizes or avoids some potential problems associated with SLN. The review by Mehnert and Mader [39] high lights these aspects:

- Pay-load for a number of drugs too low
- Drug expulsion during storage
- High water content of SLN dispersions.

The new concept for the production of NLC, especially very different lipid molecules are mixed, i.e. blending solid lipids with liquid lipids (oils). The resulting matrix of the lipid particles shows a melting point depression compared to the original solid lipid but the matrix is still solid at body temperature. Depending on the way of production and the composition of the lipid blend, different types of NLC are obtained. The basic idea is that by giving the lipid matrix a certain nanostructure, the pay-load for active compounds is increased and expulsion of the compound during storage is avoided [40,41].

***Lipid drug conjugates (LDC) nanoparticle*:**

A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this limitation, the so-called LDC nanoparticles with drug loading capacities of up to 33 % have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) to a nanoparticle formulation using high pressure homogenization (HPH). Such

matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections [42-44].

Advantages of lipid based nanocarriers [45,46]:

- Control and targeted drug release.
- Improve the stability of pharmaceuticals.
- High and enhanced drug content.
- Carrying both lipophilic and hydrophilic drugs.
- SLNs have excellent biocompatibility.
- Water based technology (avoid organic solvents).
- Easy to scale-up and sterilize.
- More affordable.
- Easier to validate and gain regulatory approval.

CONCLUSION:

Lipid-based drug delivery systems are of increasing interest because of their potential to solubilize drug that may be otherwise difficult to develop .Lipid drug delivery systems offer many advantages; however, the development of these systems requires proper understanding of the physicochemical nature of the compound as well as the lipid excipients and gastrointestinal digestion. One of the major challenges of lipid excipients and delivery systems is the varying range of compounds they contain. To overcome this, proper characterization and evaluation of these delivery systems, their stability, classification and regulatory issues, which consequently have affected the number of these formulations that eventually reach the market, have to be constantly assessed. The prospect of these delivery systems looks promising. Incorporation of antioxidants or radical scavengers in suitable delivery systems is important in order to transport them as cosmetic ingredients against skin ageing, especially as curative/therapeutic in addition to their prophylactic action. Novel lipid based delivery systems reviewed here possess the potential to develop as the “new generation smarter carrier systems” for topical delivery of antioxidants.

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