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Review Article

LIPOSOMES AS CARRIERS IN SKIN AGEING

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ABSTRACT

Ageing is an inevitable phenomenon. Similar to other organs, skin is also subject to an intrinsic ageing process. Additionally, skin ageing is also influenced by various environmental factors. Existing conventional formulations have limited efficacy because skin serves as a rate limiting barrier for percutaneous absorption of drugs. This has led to the evolution of various novel drug delivery systems. Among these liposomes have received considerable attention due to the numerous advantages they offer. Liposomes, submicroscopic spherical vesicles, were discovered in 1960's. Since then, they have gained popularity as potential carriers for drugs, diagnostics, nutrients, vaccines and other bioactive agents. Liposomes find applications in pharmaceutical, cosmetics and other industrial fields. Various topical actives that have been found to be efficacious in delaying the signs of ageing have been formulated as liposomes resulting in enhanced delivery, biocompatibility, and reduced toxicity. This review focusses on therapeutic use of liposomes in skin ageing.

Keywords: Liposome, Ageing, Topical application, Antioxidants.

INTRODUCTION

As the global population's median age is increasing, ageing is a major concern among people worldwide. Consumers' desire to maintain appealing look has led to the emergence of ever-expanding cosmetic market. Anti-ageing products are flourishing as a lot of emphasis is laid on youthful appearance[1]. Ageing is unpreventable and thus it has aroused the interest of researchers across the globe to curb it to some extent. Various advanced technologies such as facelifts, laser, botox, microdermabrasion etc. have gained an impetus in recent years but are less preferred by the local masses due to the associated drawbacks, high cost and invasive nature. Topical application of anti-ageing formulations has been adopted as an important strategy as they serve as a non-invasive alternative to slow the effects of ageing on the skin. The main hurdle in topical administration of actives is the barrier nature of the skin. The stratum corneum or horny layer has been identified as the principal barrier for penetration of most drugs[2]. The delivery of actives from conventional formulations is generally compromised. Thus there arises the need for a suitable carrier to increase drug deposition. A plethora of microparticulate carrier systems have evolved which improve drug delivery to skin. Recently, Liposome based formulations have been found to be extremely promising for topical delivery[3]-[4].

Intrinsic and extrinsic factors of ageing

A comprehensive grading scale for skin ageing has been validated, which categorizes skin ageing as: laxity (sagging), rhytids (wrinkles) and photoageing which is further sub-classified as erythema (redness), dyspigmentation (brown discolorations), solar elastosis (yellowing), keratoses (abnormal growths) and poor texture[5]. Ageing is due to both genetic and environmental factors popularly termed as intrinsic (chronological) and extrinsic factors of ageing. Various theories have attributed intrinsic skin ageing to factors such as oxidative stress, genetic mutations and decrease of several hormone levels. The deficiency in oestrogens and androgens cause dryness, wrinkling, epidermal atrophy, collagen breakdown and loss of elasticity[6]. Collagen, a natural protein present in dermis, imparts elasticity to the skin. With advancing age, the production of collagen decreases leading to loss in elasticity and production of wrinkles. When young, epidermis of the skin stretches and holds large amount of moisture due to the presence of fibers called elastin and also a layer of fat in the subcutaneous level of skin. Elastase is the only enzyme that is capable of breaking down elastin (an insoluble elastic fibrous protein). Elastin together with collagen is responsible for the mechanical properties of connective tissue[7]. All this is lost with advancing age leading to sagging appearance of epidermal layer of skin. Among all extrinsic factors i.e. environmental factors, solar ultraviolet (UV) radiation is a prominent causative factor for skin ageing, termed as photoageing. From studies it is now clear that both UVB (290–320 nm) and UVA (320–400 nm) radiations contribute to photoageing. UVB acts preferentially on the epidermis where it damages DNA in keratinocytes and melanocytes and causes production of proteolytic enzymes which affect the dermis. UVA radiation penetrates far more deeply on average and hence exerts direct effects on both the epidermal and the dermal compartments[8].

Oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses leads to cellular and tissue damage[9]. According to the free radical theory of ageing, reactive oxygen species, primarily arising from oxidative cell metabolism, play a major role in both chronological and photoageing. Several anti-oxidative mechanisms operate in body to combat the harmful effect of free radicals.

These mechanisms deteriorate with increasing age causing damage to cellular components leading to cellular ageing. The superoxide radicals and H_2O_2 formed by the mitochondria in the course of normal metabolism, causes damage to nucleic acid, lipids and proteins including collagen. This cumulative collagen damage, disrupts the structural integrity of skin and contributes to wrinkle formation[10].

Anti-ageing remedies

There are several facial treatments available that promise to cure the above mentioned problems. These include facelifts, botox, derma-abrasion, facial peels, growth hormones, collagen injections etc. These techniques have their own pros and cons. Mainly due to their invasive nature, risk of adverse effects and cost, these procedures have not reached the common folks. Thus the focus has shifted to topical anti-ageing products. Over the counter (OTC) anti-ageing products are a billion-dollar industry to which even young patients who wish to prevent the ageing process contribute[11].

The common ingredients in anti-ageing products include antioxidants, moisturisers, sunscreen agents, topical peptides, hydroxy acids and retinoids. As the root cause of skin ageing is oxidative stress, the use of antioxidants has attained priority. Naturally occurring antioxidants such as Vitamin A, C, E, squalene, coenzyme Q-10 donate electron and neutralize free radicals. Thus various OTC products claiming to be anti-ageing products are rich in such antioxidants. Antioxidants are promising in photoprotection with negligible side effects at physiological concentrations[12]. For effective photoprotection, it is necessary that desirable amount of antioxidant reaches the site of action. However, delivery of drugs

through conventional topical preparations like gels and creams is compromised due to barrier properties of the skin. Skin has been described as a waterproof barrier which does not allow hydrophilic substances or high molecular weight substances to pass through it. Thus the formulation of dermatologic cosmetics is difficult when high concentration of such actives is required in cutis. The skin's brick and mortar structure hinders drug deposition. Moreover vitamins have poor stability and lose their potency on exposure to UV light. Thus selection of proper carrier is of paramount importance so that there is increase in drug deposition and drug is protected from photodegradation[13]. Various novel drug delivery systems have been explored to overcome above mentioned problems. Of which colloidal carriers called Liposomes have received considerable attention.

Liposomes

Liposomes were first described by British haematologist Dr. Alec D Bangham FRS in 1961(published 1964), at the Babraham Institute, in Cambridge. They were discovered when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. They observed clear resemblance of the lipid structures to the plasmalemma and the microscope pictures served as the first real evidence for the cell membrane being a bilayer lipid structure[14].

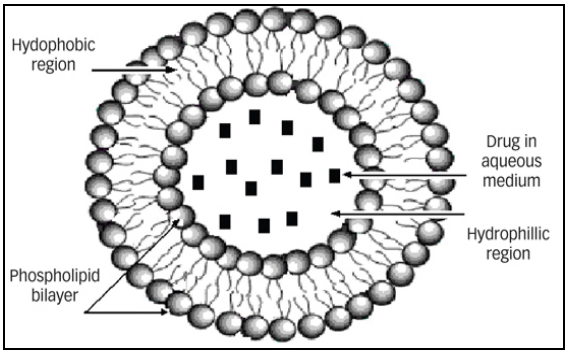

Fig.1: Structure of Liposome

The term liposome was coined from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. Liposomes are highly organized structures, consisting of concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membraneous lipid bilayer[15].Therefore both hydrophobic (in the bilayers) and hydrophilic substances (in the aqueous compartment) can be entrapped in liposomes. Liposomes thus protect the entrapped molecule from degradation. Moreover they offer sustained and targeted release[16]. The main objective of using liposomes as drug carriers is to achieve selective and sufficiently high localization of active drug at disease sites. In this respect, the liposomes differ from other controlled release systems, in which drug release occurs either in plasma or at the site of administration. Owing to their biological origin they are nontoxic in nature and are easily re-absorbed from the epidermis into the deepest layers. The encapsulation of drugs into liposomes, for topical use, gives a higher drug concentration at the intended site of action, thereby enhancing the localized effects but at the same time minimizing unwanted systemic side effects[17]. Thus the topical application of liposomes offer a wide range of advantages including increased moisturization, restoring action, biodegradability, biocompatibility and extended and slow dermal release[18].

Liposomes have been widely used as drug carriers for their innumerable utilitarian aspects. But their major limitation is instability[19]. The vesicles are prone to fusion, aggregation, poor retention and drug leakage with time. According to recent research, liposomes break into pieces the moment they hit the skin's surface, or very soon after that. Liposomes cannot be transported into deeper layers. Experiments using amphiphilic and hydrophilic fluorescently labeled molecules show that the diffusion of liposomes in stratum corneum is very heterogeneous on a microscopic scale and that the penetration of intact liposomes is highly compromised by the skin barrier[20].

Composition of Liposomes

Liposome composition includes natural and/or synthetic phospholipids. Phosphatidylcholine (lecithin) and phosphatidylethanolamine constitute the two major structural components of most biological membranes. Liposome bilayers may also contain other constituents such as cholesterol or surfactants. Cholesterol has been largely used to improve the bilayer characteristics of the liposomes. It improves the membrane fluidity, bilayer stability and reduces the permeability of water soluble molecules through the membrane. A clear advantage of liposomes is the fact that the lipid membrane is made from physiological lipids which decreases the danger of acute and chronic toxicity[21].

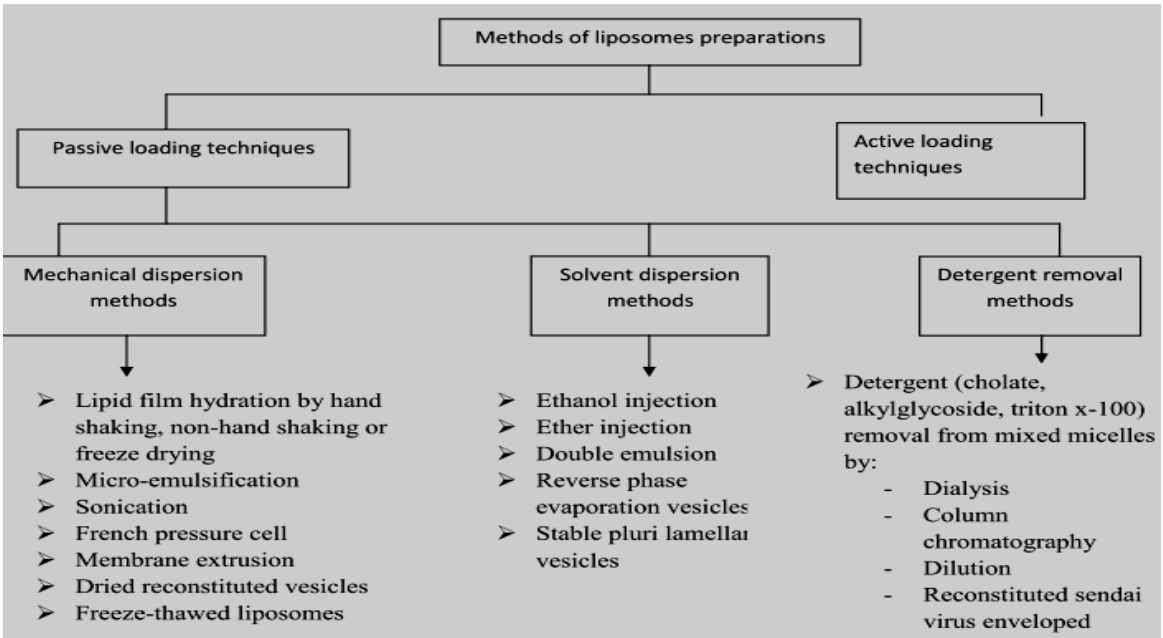

Fig. 2: Methods of liposome preparation [14]

Mechanism of action of liposomes

The activity of liposomal formulations in ageing is attributed to its occlusive action, enhanced bioavailability, protection of active ingredients, reduction of systemic absorption and reduction of side effects. The exact mechanism by which the liposomes work is highly debated but the occlusive effect of topical liposomes is already proven. Dehydrated skin loses elasticity and becomes rough and flaky. Moisturizing products constitute one of the largest and most important skin care product category.

The function of moisturizers is to keep the stratum corneum hydrated. Occlusive compounds promote the penetration of active compounds owing to better skin hydration[18]. As liposomes are composed of lipids, even empty liposomes have found to be useful in skin hydration. They simply contribute lipids to the stratum corneum and cosmetics containing liposomes rely on this effect[22]. Liposome as a carrier itself offers advantages because lipids are well hydrated and can reduce the dryness of the skin which is a primary cause for skin ageing[23].

Table 1: Commonly used ingredients in anti-ageing formulations[31]

Ingredient	Action	Source
Allantoin	Skin Soothing, moisturizing	Comfrey
Aloe vera	Softens skin, moisturizing	Aloe barbadensis
Ascorbic acid	Antioxidant, photoprotectant	Vitamin C (citrus fruits)
Arnica	Astringent and soothing	Arnica montane
Arjunolic extract	Antioxidant and anti-inflammatory	Terminalia arjuna
Beta-Carotene	Minimizes lipid peroxidation and cellular antioxidant	Carrots and tomatoes
Boswellia	Anti-inflammatory and anti-ageing	Boswellia serrata
Calendula	Soothes, softens skin, promotes cell formation.	Calendula officinalis
Centella	Skin conditioning agent, increases collagen production, improves texture and integrity of skin, and reduces appearance of stretch marks	Centella asciatica
Coriander seed oil	Anti-inflammatory and anti-irritant, skin- lightening properties	Coriandrum sativa
CoenzymeQ10(Ubiquinone)	Cellular antioxidant	Naturally occurring in skin
Cucumber	Refreshes and tightens pores	Cucumis sativus
Essential fatty acids	Smoothens, moisturizes and protects	Linolenic and arachidonic acid
Furfuryladenine	Improves hydration and texture of skin	Plant growth hormone
Lupeol	Antioxidant and skin conditioning agent	Cratacva nurvula
Ginkgo	Antioxidant that smoothes, rejuvenates and promotes youthful appearance	Ginkgo biloba
Green tea extract	Antioxidant	Green teas (Camellia sinensis)
Kinetin	Antioxidant	Plants and yeast
Licorice extract	Skin whitening properties,	Glycyrrhiza glabra
Oleanolic extract	Antioxidant, improves texture and integrity of skin	Olive leaf
Panthenol	Builds moisture and soothes irritation	Provitamin B5 (broccoli, calf's liver, turnip greens)
Pycnogenol	Antiageing effect, protects collagen	Grape seed extract
Retinoic acid	Promotes cell renewal and improves circulation to skin	Vitamin A(green leafy vegetables)
Sodium hyaluronate	Lubricant between skin tissues and maintains natural moisture	Natural protein
Rosemary extract	Antioxidant, antimicrobial, and anti-inflammatory	Rosemarinus officinalis
Tetrahydrocurcuminoides, turmeric oil	Antioxidant and antiageing	Curcuma longa
Tocopherol	Antioxidant, improves hydration and cellular regeneration of skin	Vitamin E (vegetable oils)
Ursolic acid	Anti-inflammatory, collagen buildup	Rosemarinus officinalis
Witch hazel	Tightens pores, tones	Hamamelis virginiana

Vegetable phospholipids like soya lecithin are widely used for topical applications in cosmetics and dermatology, since they have a high content of esterified essential fatty acids, especially linoleic acid which is believed to increase the barrier function of the skin and decrease water loss within a short period of time after application. Soya phospholipids or other vegetable phospholipids, due to their surface activity and their ability to form liposomes, are an ideal source for possible transport of linoleic acid into the skin[24].

The reports of enhanced drug delivery by liposomes have been attributed to the lipid film produced on the skin, which increases hydration[25]. Topical liposomes reduce skin roughness because of their interaction with the corneocytes and intercellular lipids resulting in skin softening and smoothening[26].

Liposomes enable better delivery of active ingredients into the deeper layers of the skin by merging with the cell membrane thus leading to enhanced bioavailability. It is supposed that upon contact with skin, molecular mixing of liposome bilayer with intracellular lipids in stratum corneum occurs which changes the hydration and thereby the structure of lipid lamellae. It is followed by enhanced permeation of lipophilic drugs into the stratum corneum and diffusion of hydrophilic drugs into the interlamellar spaces. On the other hand, it is also possible that some liposomes, which are deformable enough, pass the stratum corneum intact and disintegrate deeper in skin layer. However there is no direct evidence confirming these mechanisms[27].

By virtue of encapsulating both hydrophilic and hydrophobic drugs, liposomes also protect the drug from degradation. Lee et al. investigated the effect of freeze drying on liposomes. The freeze dried ascorbyl palmitate liposomes were prepared which protected the drug from moisture attack and could be used instantly by mixing with water for anti-ageing and skin whitening therapy. The measurement of the time for reconstitution showed that freeze-dried liposomes could be changed to their initial state rapidly and short term stability test under accelerated conditions confirmed that the stability of ascorbyl palmitate was considerably enhanced as compared to freshly prepared liposomes. Freeze dried liposomes also reproduced similar skin permeation and localization properties[28].

Since the liposomal formulations provide sustained and enhanced drug levels in the strata, with increased localization, the incidence of undesirable side-effects arising from systemic administration is reduced[29]. A study conducted by Sinico et al. showed that liposomal encapsulation of trans-retinoic acid (tretinoin) helps in surmounting its side effects of skin irritation (erythema, peeling and burning) and high instability in the presence of air, light and heat[30].

Liposomal formulations in ageing

Anti-ageing formulations work mainly by reducing fine lines, visible wrinkles, pigmentation changes, blemishes and other environmentally related conditions of the skin.

Antioxidants

The term “antioxidant liposome” is relatively new and refers to liposomes containing lipid soluble, water-soluble, enzymatic or combinations of these various antioxidants. The lipid-soluble antioxidants that can be incorporated into liposomes include vitamin E, ubiquinones, retinoids, carotenoids (e.g., lutein, beta-carotene, lycopene, astaxanthin, zeaxanthin and peridinin), lipid-soluble flavonoids (e.g., quercetin, hesperedin, naringenin), soy isoflavones (genistein and daidzein). The water-soluble antioxidants that can be used in antioxidant liposomes include ascorbate (vitamin C), urate, glutathione, *N*-acetylcysteine, lipoic acid (or dihydrolipoic acid, which is its reduced form), pro-cysteine, and water-soluble flavonoids (e.g. pycnogenol)[32].

Topical application of enzymatic antioxidants has been postulated in treating oxidative stress. Superoxide dismutase, catalase, glutathione peroxidase are few endogeneous enzymatic antioxidants that serve as antioxidant defense system. The effect of a single exposure to ultraviolet radiation on skin superoxide dismutase (SOD) activity was examined in mice by Miyachi et al. A significant decrease in SOD activity was observed 24 and 48 hours after ultraviolet irradiation. The SOD levels returned to the normal level by 72 hour time period. Decreased SOD activity after ultraviolet exposure was lessened by pretreatment of skin with liposomal SOD. The authors suggested that this protective effect of the encapsulated SOD may have potential clinical application for photodermatologic reactions[24].

Sodium ascorbyl phosphate (a stable Vitamin C derivative) is an effective radical scavenger and has the greatest potential for slowing down the detrimental effects resulting from photodamage. It is cleaved by enzymes in the skin to release ascorbic acid. At physiological pH ascorbic acid is present mainly as the ascorbate anion which penetrates poorly into the skin. Thus by encapsulating into liposomes, the penetration through the stratum corneum into the deeper layers of the skin can be improved. Foco et al. performed in-vitro diffusion studies of sodium ascorbyl phosphate and ex-vivo penetration experiments on pig ear epidermis membrane in a Franz diffusion cell. They observed that sodium ascorbyl phosphate penetrated through epidermis membrane significantly better from liposome dispersions than from water solution[33].

Padamwar & Pokharkar demonstrated a factorial design approach for preparation of stable Vitamin E acetate liposomal formulation. They presented that variables such as amount of phospholipid, stabilizer and lipid: drug ratio have a profound effect on the vesicle size and drug deposition in the rat skin. Gels containing liposomal dispersion were prepared and were found to be stable for 3 months. They also proved that liposomal formulation promotes drug deposition in rat skin as compared to control drug dispersion, control gel and marketed cream[4].

Fang et al. examined the effect of liposomal composition on the efficiency of transdermal catechin delivery. Catechins which possess significant antioxidant activity were encapsulated in liposomes using anionic surfactants and ethanol. They concluded that incorporation of anionic surfactants such as deoxycholic acid and dicetyl phosphate in the liposomes in presence of 15% ethanol increased the catechin permeation by five to seven-fold as compared to the control. Skin permeation studies were conducted on mouse skin. The flexibility of bilayers was suggested as an important factor governing the enhancing effect of liposomes[34].

Various anti-inflammatory agents have been useful topically as anti-ageing remedies. Manconia et al. formulated C-Phycocyanin liposomes and proved that the protein was mainly localised in the stratum corneum, while there was no permeation through the whole skin. Two percent C-Phycocyanin liposomes showed drug accumulation higher than that of the corresponding free 2% C-Phycocyanin gel. Liposomal encapsulation also improved its anti-inflammatory activity[35].

A study conducted by Yarosh et al. demonstrated that ursolic acid incorporated into liposomes increases both the ceramide content of cultured normal human epidermal keratinocytes and the collagen content of cultured normal human dermal fibroblasts. In clinical tests, the ceramide content in human skin was increased over an 11-day period. Liposomes had effect on keratinocyte differentiation and dermal fibroblast collagen synthesis similar to retinoids[36].

Takahashi et al. prepared liposomes encapsulating aloe gel extract by Bangham method and examined for the effects on proliferation and type I collagen synthesis in normal human neonatal skin fibroblasts. Liposomal aloe gel extract clearly showed higher proliferation rate than that of aloe gel extract alone. In addition, compared to control, liposomes significantly increased the collagen synthesis by 23%, while aloe extract alone showed a small effect. Liposomal aloe gel extract was also assayed for the effect on proliferation in normal human epidermal keratinocytes. They observed that liposomal fractions containing 4 and 20 microgram/mL of the extract considerably increased the proliferation rate by 77% and 101%, respectively. In comparison, aloe gel extract fractions containing 4 and 20 microgram/mL of the extract increased the rate by 41% and 60%, respectively. Accordingly, the bioavailability and skin care properties of aloe gel extract was significantly enhanced by liposome encapsulation[37].

Resveratrol, a powerful natural antioxidant, was encapsulated in liposomes-in-alginate microbeads by using proliposome method. Diffusion studies showed prolonged release up to 5 hours[38]. In a similar study, Caddeo et al. investigated the possibility of improving the efficacy of resveratrol, on cell proliferation and photoprotection by liposomal incorporation. Oligolamellar vesicles of different lipid compositions, loaded with resveratrol, were prepared and characterized. The effect of free and liposomal resveratrol on the viability of HEK 293 cells and their photoprotection after UV-B irradiation was assessed. Photomicrographs of the treated cells from inverted light and fluorescence microscopy demonstrated resveratrol effectiveness at 10μM, as well as its toxicity at higher concentrations, based on changes in cell shape, detachment and apoptotic features. However, liposomes prevented the cytotoxicity of resveratrol at high concentrations, even at 100μM, and increased the ability of resveratrol to stimulate the proliferation of the cells and their ability to survive under stress conditions caused by UV-B light[39].

Retinoids have extensive application in cosmetics. Topical retinoid products are one of the most important drug class to reverse cutaneous ageing with clinical efficacy proven in a number of trials that included histologic evaluation. Vitamin A is the most common naturally occurring retinoid, and acts by stabilizing the oxygen radicals that are created after skin exposure to ultraviolet light[40]. However, their therapeutic use is limited due to its toxicity, poor chemical stability, and hydrophobic nature[41].

Thus antioxidant liposomes hold great potential in the treatment of many conditions in which oxidative stress plays a prominent role. Several studies have clearly indicated that the liposomal antioxidant formulations compared to that of the free non-encapsulated antioxidants exert a far superior protective effect against oxidative stress-induced tissue injuries.

Hydroxy acids

Alpha hydroxy acids (AHAs) derived from natural sources such as fruits are widely used in cosmetic formulations. It is suggested that AHAs reduce the calcium ion concentration in the epidermis thus promoting cell growth and differentiation giving rise to younger looking skin[42]. Glycolic acid is used in many cosmetic products as exfoliant and moisturizer. It helps in reducing excessive epidermal keratinization which in turn is useful in reduction of facial lines. But it is irritant in nature causing burning at required concentrations. This drawback can be overcome by liposomal encapsulation. Perugini et al. formulated glycolic acid liposomes with and without chitosan by reverse phase evaporation method. They investigated the interaction between liposomes and chitosan. The results showed that liposomes were suitable to modulate glycolic acid release and that the best condition to achieve this control was obtained by 5:1 glycolic acid/lipid molar ratio. Further significant release control was obtained by addition of chitosan into the liposomes[43].

Similarly, salicylic acid (beta-hydroxy acid) which is commonly used to treat acne has also been used in anti-ageing creams. Liposomes were prepared by the conventional thin film hydration technique as described by Bangham. The liposomal encapsulation of salicylic acid helped in overcoming its side effect of causing irritation[44].

Depigmenting agents

Melasma or hyperpigmentation is a common disorder observed in middle-aged women. The use of hypopigmenting / skin lightening agents have thereby received attention.

Hydroquinione has been used for decades as a skin lightening agent. It has been shown to cause reversible hypopigmentation in man and animals. However this drug is susceptible to oxidation due to its photosensitive characteristics. The liposomal formulation of hydroquinone helped improve its stability[45]. A United States patent describes a cosmetic composition containing hydroquinone and kojic acid incorporated into liposomes. The combination helps in obtaining synergistic skin-lightening effect with reduction in undesired side effects[46].

One such novel hypopigmenting agent is 4-n-Butylresorcinol; it has an inhibitory effect against tyrosinase and tyrosinase-related protein-1. Liposome encapsulation helps in improving stabilization and enhancing penetration of the product. Huh et al. conducted a randomized double blind vehicle-controlled and split-face comparison study on 23 patients with clinical diagnosis of melasma for 8 weeks. They observed that the melanin index of the 4-n-butylresorcinol-treated side showed a significant decrease when compared with the vehicle-treated side. They concluded that liposome-encapsulated 4-n-butylresorcinol 0.1% cream was well tolerated and showed significant higher efficacy than vehicle alone for the treatment of melasma[47].

In a study carried out by Shigeta et al. linoleic acid was formulated as liposomal hydrogel. Liposomal linoleic acid (0.1%) showed a whitening effect comparable to 10.0% non-liposomal linoleic acid and was far more effective than 3.0% non-liposomal linoleic acid. These results indicate that liposomal formulations are favorable for the transdermal application of linoleic acid[48].

Similarly, Wen et al. formulated arbutin liposomes for enhancing skin whitening activity. It was reported that although the permeation rate of arbutin in the liposome formulations decreased compared with arbutin solution, the deposition amount of arbutin in the epidermis/dermis layers increased in liposomal formulation. These results suggest that liposomal formulation could enhance the skin deposition of hydrophilic skin-whitening agents, thereby enhancing their activities[49].

Sunscreens

As solar radiations are detrimental for skin, use of sunscreen is highly recommended to prevent the signs of ageing. Jaafari et al. determined the influence of vehicles on the penetration of octyl methoxycinnamate (OMC) in the stratum corneum by tape stripping method. The experimental formulations consisted of a conventional o/w emulsion and multilamellar (MLV) and small unilamellar (SUV) liposomes. Various formulations were applied onto the midvolar forearms of six volunteers at a dose of 2 mg/cm. After determined time points, the stripping method was conducted and the sunscreen agent was assessed by HPLC while the SPF (sun protection factor) of the formulations was determined in human volunteers in accordance with the Australian standard. The results indicated that skin accumulation of OMC in MLVs was significantly greater than in the o/w emulsion and SUVs. Furthermore, SUV's penetration into the deeper skin layers was significantly greater than MLV's and that of a conventional o/w emulsion. Also, higher amounts of OMC were recovered from the upper layers of the stratum corneum than from the deeper layers in all the formulations tested. Finally, the SPF of the liposomes containing OMC was greater than that of the control lotions at a similar concentration of OMC[50].

In a similar study, the photostability of avobenzone was improved in presence of UVB filter octylmethoxycinnamate, when it was encapsulated in liposomes, with a degradation percentage of 22.07 % against 32.96 % of the non-encapsulated avobenzone[51].

Peptides

Peptides have been widely used in anti-wrinkle creams. They reduce fine lines and wrinkles and result in overall improved appearance of photo aged skin. Shahi et al. encapsulated Palmitoyl hexapeptide and Vitamin E acetate in liposomes by ethanol injection method for improving topical delivery. They optimized the formulation by factorial design approach and developed stable and homogeneous liposomal dispersion and lipogel with a controlled drug release profile upto 24 hours[3].

Marketed liposomal formulations

Capture was the first anti-ageing liposomal cream launched by Christian Dior in 1987 with claims that it can reduce the sign of wrinkles. Capture liposomes penetrate beneath the stratum corneum and carry their ingredients into living cells, restoring the membrane's fluidity. Among the ingredients in Capture Complex are water, thymus extract, collagen peptides and elastin peptide[53].

Lipo C_{TM} by Lippomix is an anti-ageing liposomal cream which contains active vitamin C, vitamin E, coq10 and zinc. It claims to minimize the appearance of cellulite while helping to tone and firm sagging skin. Lipogest, a natural balancing cream, is a similar product by Lippomix[54].

In the 1980's L'oreal introduced its patented technology "Action Liposomes" in French market. It was launched as the star product costing three times the cost of a basic moisturizer. Similarly L'oreal Eye defence which is an under eye cream based on liposomal technology, claims to reduce puffiness, lines and dark circles.

Table 2: Clinical trials evaluating cosmeceuticals agents[52]

Agent	Clinical Indication	Study Type	Number of patients	Results
Oligopeptide	Wrinkles, skin ageing	OL, Cl	90	80% reduction in wrinkles
Peptide Primers	Wrinkling	OL, Cl	14	57% of patients improved
Transforming growth factor / TGF-β1 (polypeptide)	Wrinkling	DB, R	32	87% of patients improved
Pal-KTTKS (palmitoyl-pentapeptide)	Wrinkling	DB, R	49	37% less wrinkle volume
	Winkling, fine lines	OL, Cl	92	13% length reduction

Abbreviations: OL: open-label; CL: closed-label; DB: double blind; R: randomized.

Table 3: Marketed liposomal cosmetic formulations [21]·[55]·[56]

Product	Manufacturer	Key ingredients
Capture	Christian Dior	Thymus extract, collagen and elastin peptides
Effect du Soleil	L'Oréal	Tanning agents in liposomes
Liposome aktions gel	Madame Nanette Biocosmetic	Aloe vera, thymus extract
Future Perfect	Estée Lauder	Vitamin E, A, cerebroside,
Aquasome LA	Nikko Chemical Co	Liposomes with humectants like glycerine, sorbitol
Eye Perfector	Avon	Soothing cream with peptides to reduce eye puffiness
Royal jelly lift concentrate	Jafra cosmetics	Sunflower) Sprout Extract, Wintercherry and Lotus flowers, Larrea Divaricata Extract
Revitalift	L'Oréal	Pro-Retinol A
Formule Liposome Gel	Payot (Ferdinand Muehlens)	Thymoxin, hyaluronic acid
Symphatic 2000	Biopharm GmbH	Thymus extract, vitamin A palmitate
Natipide II	Nattermann PL	Preformed Liposomal gel
Inovita	Pharm/Apotheke	Thymus extract, hyaluronic acid, vitamin E

CONCLUSION

Reported literature indicates that Liposomes are efficient colloidal carriers for the delivery of therapeutics into skin. Due to the striking similarity between liposome components and skin lipids, they are safe and effective. In addition to delivering the drug in higher concentration into skin layers, they enhance skin hydration making them an ideal vehicle for anti-ageing remedies. Studies on liposomes have been widely reported over the last 30 years and, currently a wide range of liposomes varying in size, composition and surface characteristics are fabricated. Modified liposomes such as ethosomes, transferosomes, marinosomes hold a promising approach in dermatology.

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