Review Article

A Review on Novel Topical Formulations of Vitamins

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Abstract

Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have drug-like benefits. Cosmeceuticals are one of the fastest-growing segments of the personal care industry as their use has drastically increased over the years. Vitamins being one of the popular ingredients in cosmeceuticals have numerous skin benefits. Vitamins are organic micronutrients essential for the proper functioning of the body. The popular vitamins used in cosmetics are vitamin A, vitamin B_3, vitamin C, vitamin E, and vitamin K. These vitamins play an important role in treating skin conditions like acne, hyperpigmentation, and photoaging, protecting from UV, deactivating free radicals, and improving skin moisture retention levels of the skin. This review article emphasizes on the novel formulation of the vitamins-based cosmeceuticals. The novel carriers system has gained importance in cosmetic delivery due to its advantages such as enhanced skin penetration, sustained and controlled drug release profile, maintenance of the concentration within the therapeutic range, with greater safety and targeted delivery of active to the desired tissues.

Keywords: *Ascorbic acid, liposomes, microemulsion, nanoparticles, niacinamide, niosomes, retinoids, tocopherol, vitamin*

Introduction

The term "cosmeceutical" is derived from a combination of two terms "cosmetics" and "pharmaceuticals." Cosmeceutical can be defined as "a category of cosmetic that claims to produce therapeutic benefits."These hybrids are intended to enhance the beauty and health of the skin.[1] The term "cosmeceutical" was coined by Raymond Reed, founding member of the United States Society of Cosmetic Chemist in 1961 and was popularized by Dr. Albert M. Kligman in 1971. The role of cosmetics as a healing aid was ignored until the late 1970s and early 80s. In the midway of this period, Kligman designed a formulation containing retinoic acid to improve the appearance of wrinkled skin. Dr. Albert Kligman said that it would be possible to incorporate a large number of active substances such as vitamins, antioxidants, peptides, and hormones in the skincare products to achieve therapeutic benefit.[2]

Currently, cosmeceutical represents one of the largest segments of skincare products, and it is regulated by the Federal Trade Commission for accuracy with substantial scientific evidence. The Asia–Pacific cosmeceutical market is expected to reach USD 88.14 billion by 2024 and anticipated to expand at a compound annual growth rate of 6.8%. According to studies, countries like India, China, and Vietnam present increasing growth opportunities for the market players, majorly due to the growing millennial population. Cosmeceutical products such as sun care, antiaging, and hair care products are predicted to drive the market's growth trends in the near future.[3]

An intake of vitamins and antioxidants through diet and from some additional manufactured supplements is the most important to maintain the health of human beings. Skin being the largest organ and primary barrier, it is the forefront that experiences all the damage from the external sources (UV radiations, environmental pollutants) that produce free radicals. These free radicals significantly damage DNA and biomembranes of the cells. It is thought additionally using topical vitamins and antioxidants neutralizes free radicals. Vitamins are also beneficial to the skin for other effects such as collagen production, eliminating excess sebum, bruising, improving keratinization, depigmentation, and anti-inflammatory effects.[4]

Advanced technologies such as laser therapy, botox, microdermabrasion, facelifts have gained importance in recent years but are less preferred by people due to its high cost and invasive nature.

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Topical application of vitamin-based formulations is favored as it is noninvasive and provides direct contact with the skin tissues.[5] Conventional formulations like creams, gels, ointments have limited efficacy for the skin as the stratum corneum serves as a rate-limiting barrier to drug deposition and percutaneous absorption, due to which delivery of active is generally compromised.[6] Vitamins are commonly used as active agents in skincare products designed to improve skin appearance. An appropriate formulation type prevents the inactivation of vitamin through oxidation, moisture hydrolysis, and light, which promises to retain its activity and efficacy. In the past few decades, a plethora of novel carrier systems has been evolved to improve the delivery of actives into the skin as mentioned in Figure 1.

This article mainly focuses on the vitamins (A, B_3, C, E, and K) that are potentially used to treat acne, wrinkles, hyperpigmentation, photoaging, bruising, etc., along with its mechanism of action, side effects associated, and various topical novel formulations that potentially eliminate/minimize the side effects and improve drug permeation, drug retention, and stability. This review gives in-depth idea regarding the cosmeceutical formulations containing vitamins that can be used as a therapeutic adjunct and are popular among the consumer.

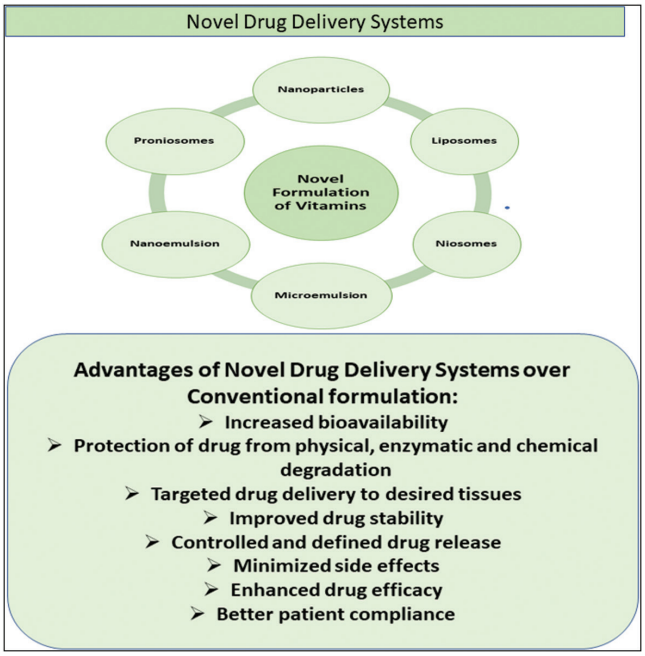

Figure 1: The novel drug delivery systems and its advantages over conventional delivery systems

Advantages of the novel drug delivery system over conventional drug delivery systems

Encapsulation techniques are most widely used in the development and production of improved drug delivery systems as described in Figure 1.

- Retinoids used as topical agents in creams, ointments, and gels are associated with disadvantages like poor aqueous solubility, photoliability, burning, dryness, erythema, skin peeling, and itching that affects the patient compliance and obstructs the treatment. The novel drug delivery system strategies are known to improve the optimization of the therapeutic agent by either modulating their biopharmaceutical property and physicochemical property or eliminating/minimizing the side effects associated with it and thus improving patient acceptance.[7] Systems like proniosomes, microemulsions, liposomes, niosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers prevent photodegradation and facilitate the stability of the retinoids, improve the skin permeability and therapeutic response, and reduce the side effects associated with it.[8-12]
- Niacinamide/vitamin B_3 is a hydrophilic molecule with minimum side effects. In order to improve the efficacy of the drug at the target site and to achieve prolonged release effect, the incorporation of niacinamide in liposomes, microemulsions, and nanofibers is appreciated.[13-15]
- The major challenge in utilizing hydrophilic molecule vitamin C is to maintain its stability. Vitamin C rapidly degrades in the aqueous medium, at high pH, in the presence of oxygen and metal ions. The novel drug delivery system helps in controlling the degradation of vitamin C in the presence of oxygen during storage. The degradation of vitamin C from moisture can be prevented by formulating its liposomes. Reducing the water content in the formulation and achieving low pH can be done by the use of a nonaqueous formulation. For the utilization of more stable derivatives of vitamin C to enhance the delivery of vitamin C in deep skin layers, formulations like liposomes, microencapsulated and nanoencapsulated delivery systems have been appreciated in several years.[16]
- Vitamin E is lipophilic and chemically unstable and has poor skin penetration ability, which has limited its effect in the conventional formulation. In recent decades, SLNs, nanostructured lipid carriers, and liposomes have gained importance due to their advantages of compatibility with the skin, ability to enhance penetration of drugs in the stratum corneum, protection of encapsulated molecule against degradation by external medium, and control of drug release.[17,18]
- Vitamin K being lipophilic in nature encapsulated in lipid formulations and nanocarriers facilitate the enhanced penetration and accumulation of vitamin K into the skin with a prolonged release effect.[19]

Vitamins

Based on scientific evidence, vitamins are effective in treating various skin conditions. Vitamins are organic micronutrients essential for the proper functioning of the body. Vitamins A, B_3, C, E, and K are commonly used in cosmetics as they exhibit good benefits on the skin as depicted in Figure 2. Naturally occurring antioxidants such as vitamins donate electrons, neutralize free radicles, and prevent skin damage.[5]

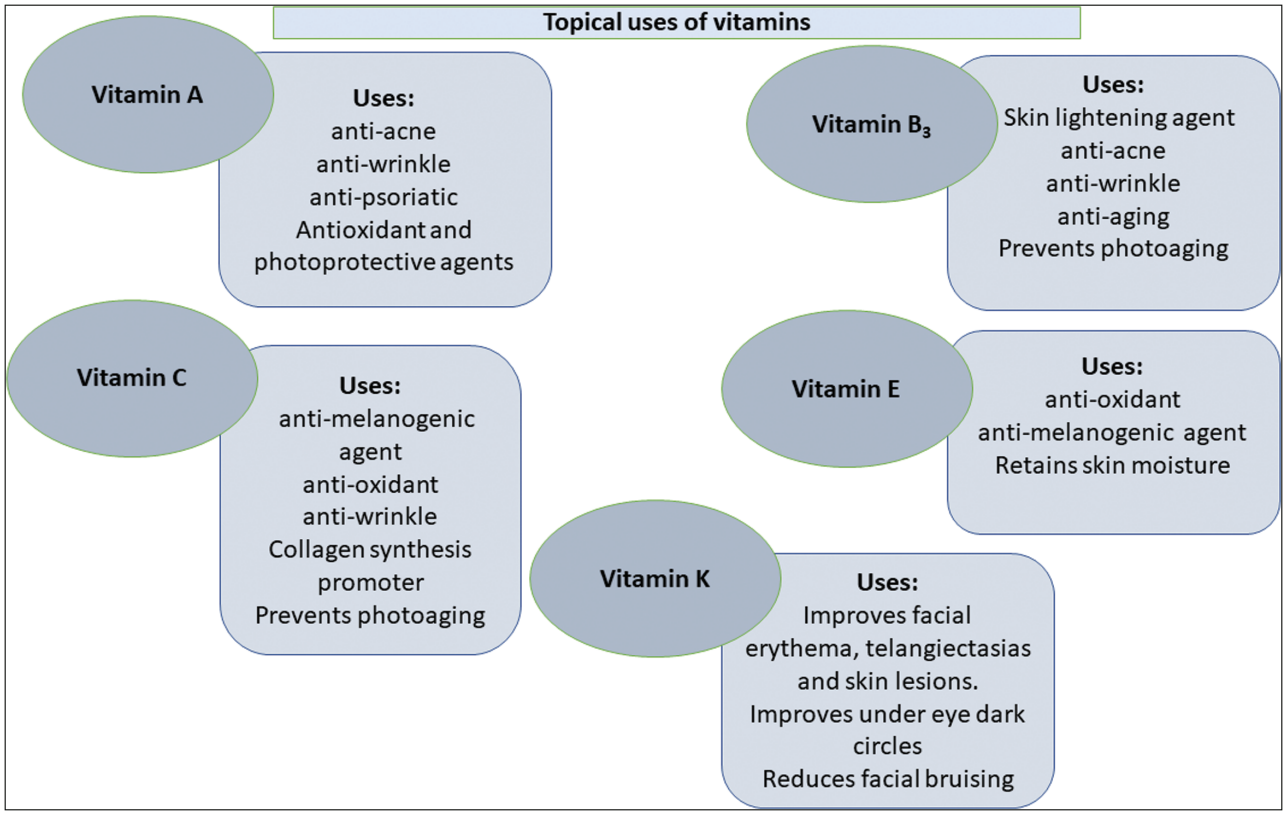

Figure 2: Topical uses of vitamins

Vitamin A

It is a group of fat-soluble vitamins and belongs to the category of retinoids. Retinoids promote keratinocytes differentiation and proliferation, protect epidermis, prevent collagen degradation, inhibit matrix metalloproteinase activity, and act as a comedolytic agent in acne. Retinoids refer to the class of synthetic and natural analogues of vitamin A, which is potent in treating acne, psoriasis, and other skin conditions. Based on the structure, retinoids are divided into three generations:

- first generation—monoaromatic compounds and natural retinoids (retinal, tretinoin, isotretinoin)
- second generation—monoaromatic compounds and synthetic analogues (etretinate, acitretin)
- third generation—polyaromatic retinoids (tazarotene, adapalene).[20]

Mechanism of action of retinoids/vitamin A

Retinoids being sparingly soluble in body fluids need special proteins to transport them intracellularly. Proteins such as cytosolic retinol binding protein (CRBP) present in the cytoplasm has an affinity for retinol, whereas cytosolic retinoic acid-binding protein (CRABP) has an affinity for retinoic acid. There are two subtypes of each protein such as CRBP I and II and CRABP I and II. The intracellular concentration of retinoids depends on the binding efficiency of retinoids to these proteins. CRABP I modulates the level of retinoic acid in different tissues, whereas CRABP II is present abundantly in the epidermis. These proteins activate specific nuclear retinoic acid receptors (RAR): RAR-α, β, and γ and the retinoid X receptors (RXR): RXR-α, β, and γ of the cells through which retinoids mediates its activity as described in Table 1.[21] The use of topical retinoids is associated with local side effects such as dryness, erythema, stinging, and itching of the skin. Topical application of tretinoin, isotretinoin, acitretin, and adapalene is contraindicated in pregnancy and lactation as abnormalities and adverse effects are reported.

Topical formulations of retinoids/vitamin A

Tretinoin

Brisaert, *et al.* developed liposomes to improve the comedolytic activity and local tolerability of tretinoin used to treat acne. Tretinoin liposomes were prepared by the thin-film hydration method using egg phosphatidylcholine and cholesterol. The chemical stability of tretinoin in the liposomes, evaluated during 1 year, revealed no remarkable loss in tretinoin content, even when stored at 25°C. The photodegradation of tretinoin in the liposomes was about two times slower than the tretinoin in castor oil, but tretinoin degraded to approximately 25% of its initial content. The chemical evaluation of the lipid fraction showed no oxidative degradation of the polyunsaturated fatty acids in egg phosphatidylcholine. The *in vitro* release profile of liposomes evaluated with a dialysis technique has shown prolonged release effect of tretinoin liposomes.[8]

Table 1: Effects of retinoids/vitamin A in dermatology

Retinoids	Application in dermatological conditions	Mechanism of action	References
Retinol	Improves wrinkle, dyspigmentation, texture and fine lines	Inhibits MMP and collagenase, gelatinase and stromelysin; promotes GAG synthesis and GAG synthesis	[22,23]
Retinoic acid (tretinoin, isotretinoin)	Acne, psoriasis, chronic inflammation of hair follicles and sebaceous glands	Stimulates human epidermal cell proliferation, eliminates excess sebum from ducts, inhibits the secretion of interleukins, interferon-γ, and production of free radicles, thus reduces inflammation in the sebaceous gland and inhibits keratosis	[24-26]
Retinyl esters (retinyl palmitate and retinyl acetate)	Anti-wrinkle, antioxidant	Initially gets converted to retinol by cleavage of the ester bond and then into retinoic acid, stimulates cell proliferation and differentiation, and regulates sebum secretion	[21]
Retinaldehyde	Improves wrinkles and skin texture	Enzyme retinaldehyde dehydrogenase converts retinaldehyde into retinoic acid and then stimulates cell proliferation	[21]
Tazarotene	Treats acne, photodamaged skin, psoriasis and provides photoprotection	Receptor-specific retinoid downregulates keratinocyte differentiation, proliferation, and inflammation	[27,28]
Adapalene	Acne, keratosis, and inflammation	Changes gene expression and mRNA synthesis, strongly modulates keratinization of hair follicles, modifies keratinocytes metabolism and proliferation, thus provides keratolytic effects	[29]

MMP = matrix metalloproteinase, GAG = glycosaminoglycan

Tretinoin-loaded SLN were fabricated by Ridolf, *et al.* in order to improve its chemical stability and side effects so that it can be efficiently used in the treatment of acne and psoriasis. Ridolf, *et al.* developed tretinoin SLNs, with and without the addition of biopolymer chitosan. The SLNs were prepared by the hot high-pressure homogenization technique. The hydrodynamic diameter and zeta potential for tretinoin SLN and tretinoin SLN–containing chitosan was found to be 162.7 ± 1.4 nm, −31.9 ± 2.0 mV and 284.8 ± 15.0 nm, 55.9 ± 3.1 mV, respectively. The tretinoin SLNs–containing chitosan exhibited high encapsulation efficiency, high physical stability in the tested period (1 year), was not cytotoxic to keratinocytes, and showed high antibacterial activity against *P. acnes* and *S. aureus*. Thus, tretinoin SLNs–containing chitosan has shown promising results in the topical treatment of acne.[9]

To improve the skin irritation of tretinoin, Rahman, *et al.* developed tretinoin proniosomes by the slurry method using cholesterol and Span 60. The factorial design approach was used to optimize the tretinoin proniosomal formulations. The proniosomes had a vesicle size of 0.33 nm, Polydispersity Index (PDI) of 0.46, and entrapment efficiency of 94.15%. The tretinoin proniosomes were embedded in carbopol gel base to produce proniosomal gel. The prepared tretinoin proniosomal gel was evaluated for skin irritation test and clinical study in acne patients. The skin irritancy study conducted on human volunteers demonstrated that tretinoin proniosmal gel had the least skin irritation compared with free tretinoin gel and marketed gel. The clinical study population comprised 12 Egyptian patients (two males and 10 females) with acne on their face. The study results demonstrated that there was overall lesion improvement after 4 weeks with reduced side effects showed by tretinoin proniosmal gel compared with marketed formulation.[10]

Isotretinoin

Patel, *et al.* developed isotretinoin microemulsion using caprylocaproyl macrogol-8-glyceride and polyglyceryl oleate as lipids and isopropyl myristate as surfactant. The microemulsion had a particle size of 45 nm and PDI of 0.145. Encapsulation of isotretinoin in microemulsion matrix prevented its photodegradation. After the light irradiance, the concentration of isotretinoin in methanolic solution was 16% and in microemulsion was 75%. Further degradation kinetics suggested that there was an increase in the half-life of isotretinoin about five times in microemulsion matrix compared with isotretinoin methanolic solution.[11]

Liu, *et al.* developed isotretinoin SLNs using precirol ATO 5, soy lecithin, and Tween 80 by the hot homogenization method. The optimized formulation had a particle size of 42.7 nm, PDI of 0.258, zeta potential of −13.73 mV, and encapsulation efficiency of 82.62%. The optimized formulation showed enhanced skin targeting with 30% more uptake of isotretinoin in the skin than 0.06% tincture used as control.[30]

Raza, *et al.* prepared SLNs of isotretinoin by the microemulsification method using phosphatidylcholine, compritol 888 ATO, and Tween 80. The nanoparticles (NPs) exhibited drug entrapment of 89.49% and a size range of

75.53 ± 2.4 nm. The isotretinoin SLNs were found to be stable as per ICH guidelines. The SLNs were capable of transporting the drug to the various layers of the skin and showed a significant anti-acne potential and tolerability on mouse skin compared with marketed formulation. The isotretinoin SLNs showed promising results in reducing dermal irritation and increasing therapeutic efficacy.[31]

Adapalene

Kumar, *et al.* prepared adapalene liposomes by the thin-film hydration method using phospholipon 90H® and cholesterol as lipids. The prepared liposomes had a size of less than 100 nm, PDI of 0.24, and entrapment efficiency of 97.01 ± 1.84%. *In vitro* skin permeation studies and confocal laser microscopy evaluated permeation of adapalene liposomes in pig ear skin and hair follicles, wherein liposomal formulation of adapalene delivered more drug (6.72 ± 0.83 mg/cm^2) in hair follicles compared with adapalene gel formulation (3.33 ± 0.26 mg/cm^2) and adapalene drug solution (1.62 ± 0.054 mg/cm^2).[32]

Harde, *et al.* developed a topical adapalene–loaded SLNs–based gel to improve skin irritation behavior adapalene. Adapalene-SLN was produced by the hot homogenization method and optimized using Box-Behnken design. The optimized showed a mean particle size of 102 nm and entrapment efficiency above 85%. The adapalene-SLNs were dispersed in carbopol gel base. The prepared semisolid formulation exhibited a viscosity of 24.57 ± 0.27 Pa·s with a spreadability of 12.39 ± 2.62 cm^2 optimum for skin application. *In vitro* dermatokinetic studies revealed that enhanced dermal bioavailability by 4.69-fold and 3.19-fold for adapalene-SLN gel and adapalene-SLN compared with gel containing free adapalene. The confocal microscopy studies demonstrated significant follicular localization of NPs by their diffusion into the dermis. Transepidermal water loss (TEWL) studies and skin irritation studies conducted on Episkin (reconstituted human epidermis) exhibited higher tolerance of fabricated nanogel. Histological and visual findings further reinforced the enhanced anti-acne potential of the novel adapalene-SLN gel compared with the gel containing free adapalene.[33]

Shah, *et al.* developed a topical adapalene–loaded niosomal gel to improve its therapeutic efficacy in the treatment of acne. Adapalene-loaded niosomes were produced using Span 60 and cholesterol using a modified ethanol injection method and optimized using the design of experiment approach. The developed adapalene niosomes showed the mean particle size of 278 nm, zeta potential of −17.99 mV, and entrapment efficiency of 86%. The prepared niosomes were embedded in the carbopol gel base and studied for its skin irritation. The *in vitro* release studies and *ex vivo* skin permeation studies demonstrated that niosomes showed controlled release up to 12 h, whereas the niosomal gel exhibited controlled release up to 24 h with the reduction in skin irritancy in wistar rats. An *in vivo* skin deposition study showed 2.5-fold higher adapalene retention in the stratum corneum layer as compared to commercial adapalene formulation. The adapalene-loaded niosomal gel would be a safe and valuable alternative to the conventional delivery systems with anti-acne potential.[34]

Tazarotene

Aggarwal, *et al.* developed nanosponge and niosomes to improve skin irritation behavior and bioavailability of tazarotene. Tazarotene nanosponges were developed using ethylcellulose, dichloromethane, and polyvinyl alcohol (PVA) by the emulsion solvent evaporation technique, and tazarotene niosomes were developed using Tween 20, chloroform, and cholesterol by the thin-film evaporation technique. The prepared formulations were characterized for particle size distribution, zeta potential, drug content, PDI, % swelling, viscosity, and *in vitro* permeation. The nanosponges and niosomes were dispersed into carbopol gel matrix to form nanosponge- and niosome-based gel. The nanosponge- and niosome-based gel showed pH of 6.3 and 6.4, drug content of 95.13% and 92.23%, spreadability of 6.39 g·cm/s and 6.89 g·cm/s, and viscosity of 13766 mPa·s and 15480 mPa·s, respectively. The *in vitro* permeation studies conducted on Franz diffusion cell using wistar rat skin revealed 56.02% and 48.03% of tazarotene release from nanosponge and nanosponge-based gel and 50.87% and 52.65% of tazarotene release from niosomes and niosome-based gel, respectively, after controlled drug permeation up to 12 h. The *in vitro* drug retention studies suggested that 31.2 ± 0.21 µg/cm^2 of drug retained into skin after 12 h with nanosponge-based gel and 27.2 ± 0.05 µg/cm^2 of drug retained into skin after 12 h with niosome-based gel compared with 3.81 ± 0.14 µg/cm^2 of plain drug gel and 9.2 ± 0.63 µg/cm^2 of marketed formulation. The results clearly depicts that the tazarotene nanosponge and niosome-based gel provides prolonged drug penetration across the skin and enhances drug retention within the skin compared with plain drug gel and tazarotene-marketed formulation.[35]

Nasr and Abdel-Hamid developed tazarotene microemulsion using jojoba oil, Tween 80, Span 85, and water. A Qbd tool such as experimental design was employed in preparing tazarotene microemulsion. This study revealed that the deposition of highly lipophilic drug tazarotene in the skin is directly depended on surfactants/cosurfactants and water ratios of the microemulsion, respectively. The surfactant/cosurfactant ratio influenced the lipophilicity of the system and water ratio increased the skin hydration. The optimized formulation had a combination of 40% oil and 45% surfactants/cosurfactants with a particle size of 51.3 ± 4.76 nm, viscosity of 222 ± 15.86 cp, and drug deposition of 75.1% in the skin. Thus, tazarotene microemulsion formulation is found to be promising in dermal treatment of psoriasis with improved high skin tolerability.[36]

Acitretin

Acitretin nanostructured lipid carriers (NLCs) developed by Aggarwal, *et al.* by the solvent diffusion method using Oleic acid, Precirol ATO5, and Tween 80. The NLCs showed entrapment efficiency of 63.0%. The NLCs were incorporated into carbopol gel base to form NLC-based gel. *In vitro*

skin permeation studies conducted on human cadaver skin confirmed that drug deposition of acitretin NLC gel (81.38 ± 1.23%) was significantly higher than that of acitretin plain gel (47.28 ± 1.02%). Double-blinded clinical studies conducted using NLC-based gel on psoriatic patients demonstrated a significant effect in reducing the side effects and improving the therapeutic response in treating psoriasis.[12]

Hashim, *et al.* developed acitretin niosomes by thin-film hydration using Span 60 and cholesterol. The niosomes had a particle size of 369.73 ± 45.45 nm and entrapment efficiency of 90.3%. The formulated niosomes were dispersed in hydroxypropylmethylcellulose gel matrix to produce niosome-based gel. Encapsulation of the drug in the nanovesicles was further focused by differential scanning calorimetric and powder X-ray diffraction studies. After 3-month storage at 4°C, the optimized formula preserved its stability. Acitretin niosome-based gel showed enhanced *ex vivo* permeation profile up to 30 h and significant drug deposition in the viable epidermal–dermal layers compared to free acitretin gel. The anti-psoriatic activity of the acitretin niosomes was proved by *ex vivo* HaCaT cells. Topical application of acitretin-loaded niosomal gel to mouse tail model further established its distinct *in vivo* anti-psoriatic superiority in terms of significantly drug activity, higher orthokeratosis, and reduction in epidermal thickness compared with the control and other gel formulations. Also, negligible skin irritation and better skin tolerability of acitretin-loaded niosomal gel were revealed by primary irritation index and histopathologic examination.[37]

Vitamin B_3/niacinamide/nicotinamide

Vitamin B3 is water soluble substance. It is a precursor to the endogenous cofactor such as nicotinamide adenine dinucleotide phosphate (NAD(P)) and its reduced form nicotinamide adenine dinucleotide phosphate hydrogen (NADP(H)).[38] It is widely used in dermatology as it treats many skin conditions such as acne, rosacea, photoaging, photoimmunosuppresion, and hyperpigmentation. Some reported side effects of niacinamide include mild burning, pruritus, erythema, and skin flushing, and these side effects can be improved with the continuous use of the drug.[39]

Mechanism of action of vitamin B_3

As depicted in Figure 3, niacinamide blocks poly ADP-ribose polymerase-1 (PARP) and transcriptional factors like tumor necrosis factor-α (TNF-α) interleukin-8, and interleukin-10 that are activated due to the exposure of skin to UV radiation.

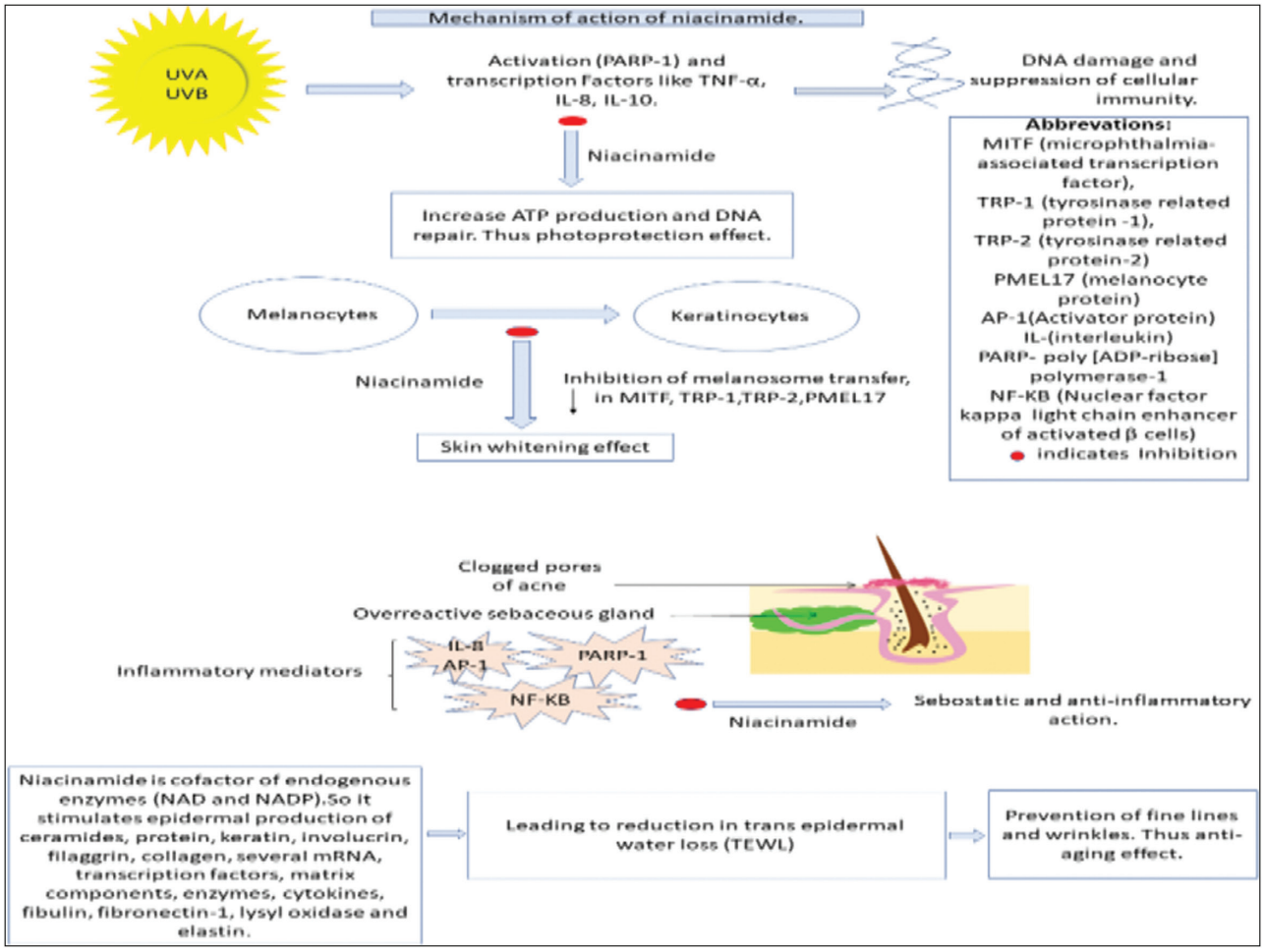

Figure 3: Mechanism of action of niacinamide as photoprotective, skinwhitening, anti-acne and antiaging

These transcriptional factors damage the DNA and suppress cellular immunity. Blocking of these factors by niacinamide increases ATP production and repairs the DNA in the cell, thus providing photoprotective effect.[40] Niacinamide is also known to be an excellent depigmenting agent as it blocks the transfer of microphthalmia-associated transcription factor, tyrosinase-related protein 1, tyrosinase-related protein 2, PMEL17 (melanocyte proteins) from melanocytes to keratinocytes, which results in skin lightening effect.[41] It is reported that an overreactive sebaceous gland in acne produces interleukin-8, PARP, nuclear factor kappa light chain enhancer of activated β cells. All these inflammatory mediators cause inflammation and overproduction of sebum in acne prone skin. Niacinamide inhibits these mediators providing sebostatic and anti-inflammatory activity.[42] Niacinamide is a cofactor of endogenous enzymes like NAD and NADP. It stimulates epidermal production of ceramides, proteins, keratin, involucrin, filaggrin, collagen, several mRNA transcriptional factors, and extracellular matrix components like elastin, fibronectin-1, fibulin, and lysyl oxidase. Stimulation of such epidermal components leads to the reduction of TEWL. Thus, retaining skin moisture levels prevents fine lines and wrinkles and delays signs of aging.[43]

Topical formulations of vitamin B_3

Lee, *et al.* prepared flexible liposomes of niacinamide to treat melasma. The technique employed for preparing liposomes was the high-pressure homogenization method using lipids such as hydrogenated lecithin, cholesterol, ceramide along with the surfactant dipotassium glycyrrhizate (edge activator). The edge activator used decreased the interfacial tension of the bilayers present in the stratum corneum leading to enhanced permeation of liposomes into the skin. The formulation was stable for 6 months with a particle size of 200 nm, zeta potential of 32 mV, and PDI of 0.27. *In vitro* release studies demonstrated that prolonged release effect of niacinamide was by flexible liposomes when compared with conventional liposomes. *In vivo* skin whitening effect and safety were evaluated on 21 patients with melasma, which demonstrated a significant skin whitening effect after 4 to 8 weeks of application with no skin irritancy.[13]

Boonme, *et al.* formulated the microemulsion of nicotinamide that enhanced the penetration of active into the skin. Nicotinamide microemulsion was fabricated using isopropyl palmitate, Span 80, and Tween 80. The formulation was physicochemically stable for 3 months at refrigerated conditions and room temperature. The mean droplet size, PDI, and zeta potential values of nicotinamide microemulsion were 344.7 nm, 0.276, and 3.30 mV, respectively. The skin penetration and drug retention studies demonstrated that the formulated microemulsion has higher drug penetration and retention compared with the conventional solution. Thus, making it suitable for skin lightening treatment as the surfactants used caused easy movement of droplets across the stratum corneum.[14]

By virtue of forming niacinamide nanofiber by Nada, *et al.*, using the electrospun technique demonstrated that encapsulating niacinamide in the polymers such as hydroxyethyl cellulose (HEC), PVA, and citric acid (crosslinker) showed a sustained release profile for 24 h compared with nanofibers without crosslinker. The diameter of nanofibers ranged from 80 to 60 nm. Smooth texture of fiber was achieved due to the use of citric acid. Immortalized human skin fibroblast cells demonstrated the biocompatibility of the produced HEC/PVA/nicotinamide electrospun fibers. The cytotoxicity of matrix system against human fibroblast cells (hTERTBJ1) was very low, which proved the formulation to be safe for human use.[15]

Vitamin C

Vitamin C (L-ascorbic acid) is a water soluble substance that cannot be synthesized by humans due to the lack of α-glucono-γ-lactone oxidase enzyme responsible for vitamin C production. Thus, it has to be obtained from dietary means only. As vitamin C is prone to oxidation, it is difficult to deliver an optimum dose of vitamin C to the dermis. To overcome this issue, esterified derivatives such as magnesium ascorbyl phosphate, sodium ascorbate, and ascorbyl-6-palmitate are used in topical preparation to improve stability. Orally administered vitamin C is first absorbed internally and taken up by the vital organs making the skin the last to receive it. Thus, the bioavailability of vitamin C to the skin is lower when administered orally. Therefore, topical application of ascorbic acid is favored in dermatology. Vitamin C being potent antioxidant scavenges reactive oxygen species formed due to UV exposure and neutralizes the oxidative stress by the process of electron transfer and/or donation of electron and prevents UV-induced erythema, photoaging, and sunburn effects.[44]

Mechanism of action of vitamin C

Also, vitamin C depigments the skin by interacting with copper ions at the tyrosinase active sites and inhibits enzyme tyrosinase and reduces melanin production.[44,45] The conversion of melanin to leucomelanin (colorless) by vitamin C is known to treat mild melasma. Synergistic effect is achieved along with vitamin E.[46] Other than this, vitamin C promotes collagen synthesis by enhancing the production of lysyl and prolysyl hydroxylase, which are responsible for crosslinking and stabilizing collagen molecules as depicted in Figure 4. It also increases the production of malonaldehyde via lipid peroxidation. This stimulates collagen gene expression.[47] Rare and minor side effects of vitamin C such as erythema, rash, redness, dryness, and stinging of skin has been reported.

Topical formulations of vitamin C

To enhance the permeation of unstable ascorbic acid through epidermis and dermis, Serrano, *et al.* formulated sodium ascorbate phosphatidylcholine liposomes. The liposomes with a particle diameter in the range of 80–120 nm, polydispersity index below 0.12, and a zeta potential between 30 and 150 mV were produced. Penetration of liposomes was tested *ex vivo* in whole skin, epidermis, and dermis by means of sodium

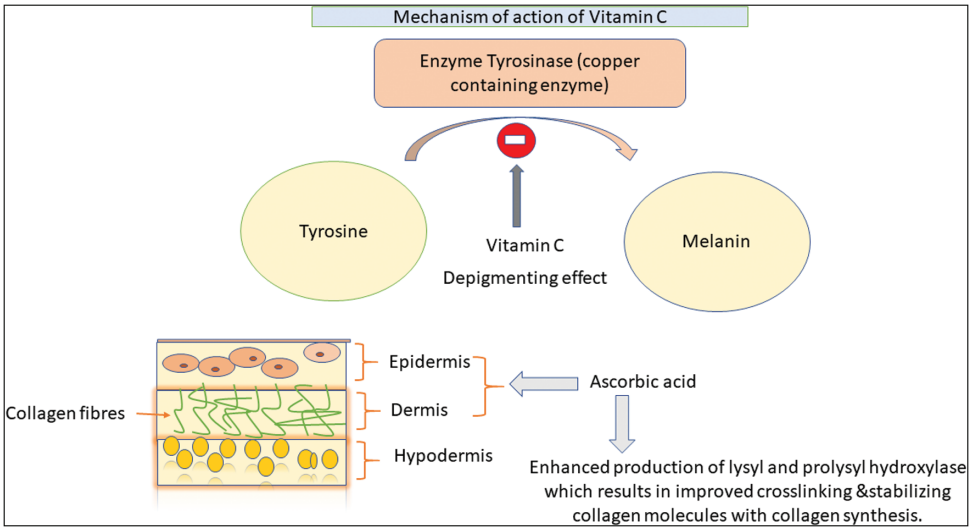

Figure 4: Mechanism of action of ascorbic acid as depigmenting agent and collagen synthesis promoter

ascorbate and fluorescein. Histology and Franz diffusion cells were used to monitor the percutaneous absorption. HPLC-UV was used to monitor the diffusion of sodium ascorbate, whereas fluorescent microscopy and spectrofluorimetry were used to monitor the diffusion of fluorescein liposomes through the different layers of the skin. UVA/UVB irradiation of whole skin was applied to analyze the antioxidant capacity by Trolox assay and anti-inflammatory effects by TNF-α and interleukin-1-β enzyme-linked immunoassay. The overall results demonstrated that the sodium ascorbate phosphatidylcholine liposomes showed significant skin penetration, antioxidant, and anti-inflammatory against UVA/UVB photodamage of the skin.[48]

To treat hyperpigmentation and photoaging, topical NP-based gel of vitamin C formulated by Duarah, *et al.* by the solvent evaporation technique using polymers such as ethyl cellulose, hydroxy propyl methyl cellulose, and Pluronic F127. The NPs had entrapment efficiency of 87.3%, zeta potential of 9.30 mV, and drug content of 99.07%. The compatibility studies showed that there was no significant interaction between the drug and the polymer along with MTT assay proving that the gel was safe topically. The formulation exhibited slow and prolonged release profile up to 8 h.[49]

To protect ascorbyl palmitate from moisture attack, Lee, *et al.* investigated the effect of encapsulating ascorbyl palmitate into liposomes and freeze drying it with trehalose. Liposomes prepared by the thin-film hydration method using dimyristoyl phosphatidylcholine as a lipid had a particle size of 960 ± 50 nm. The formulation can be used by reconstituting it with water for skin whitening and antiaging treatment. The time required for reconstitution showed that freeze-dried liposomes changed to its initial state rapidly, and a short-term stability study of ascorbyl palmitate confirmed that the stability of ascorbyl palmitate was considerably enhanced in freeze-dried state compared with freshly prepared liposomes. The skin permeation and localization properties of reconstituted liposomes were not significantly different, indicating that the liposomal structures were maintained before and after freeze drying. Thus, the freeze drying method could tackle instability issue of the drug without affecting its skin permeation and localization properties.[50]

Maione-Silva, *et al.* investigated encapsulating ascorbic acid into negatively charged liposomes using cholesterol, phosphatidylcholine, and 1,2-distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol), i.e., 1,2-distearoyl-sn-glycero-3-phosphoglycerol (DSPG) by the dehydration–rehydration vesicle method. DSPG provided negative charge to the vesicles, influencing the ascorbic acid retention and its accumulation in epidermis and dermis (37 ± 12 μg/cm^3 and 74 ± 23 μg/cm^3) significantly, after 6 h. The vesicle had a diameter of 173 ± 2.0 nm, PDI of 0.11, and entrapment efficiency of 57.8%. The formulation was stable for 30 days with a seven-fold increase in flux compared with free ascorbic acid. *In vitro* efficacy studies confirmed that the liposomes effectively influenced collagen I synthesis in fibroblast and regenerated UVA-induced damage in keratinocytes that helps preventing skin aging.[51]

Vitamin E

Vitamin E is a group of fat-soluble substances that includes four tocopherols and four tocotrienols. Vitamin E is prone to oxidation. Its stability can be improved by esterifying hydroxyl group on the chromane ring of α-d-tocopherol, which resists its oxidation without affecting skin penetration power.[52]

Mechanism of action of vitamin E

Vitamin E exhibits antioxidant activity by scavenging free radical in the cells and preventing lipid peroxidation of unsaturated fatty acids present in membrane phospholipids.[53] It inhibits tyrosinase enzyme and shows anti-melanogenic activity.[54] A detailed study conducted on 98 patients with a combination of vitamin C and vitamin E demonstrated improvement in defective keratinization of sebaceous follicles.

Vitamin E also prevents skin inflammation in acne.[52] Although it does not exhibit side effects on the skin, the use of vitamin E in high doses causes rashes and bruising.[52,54]

Topical formulations of vitamin E

To prevent photodegradation of α-tocopherol, Abla and Banga formulated a NLC and nanoemulsion (NE) of alpha-tocopherol by the homogenization technique. The particle size and zeta potential for NLC was 67 nm and 32.0 mV, whereas for NE was 586.5 nm and 10 mV, respectively. Ferric reducing ability of plasma (FRAP) assay confirmed that tocopherol retained its antioxidant activity after being encapsulated into nanocarriers, and the effect of UV degradation studied using solar simulator concluded nanocarriers-protected tocopherol from UV degradation. *In vitro* release study demonstrated that the release of tocopherol from NLC was 30% as compared to release from NE, which was 4% in initial 2 h of the study. Skin permeation study performed on human cadaver skin revealed that 762.3 ng·mL^{-1} ± 184.6 of tocopherol was reached into epidermis from NLC as compared to 182.3 ng·mL^{-1} ± 52.7 from NE. The results clearly confirmed that NLCs were better nanocarriers than NE. High release of tocopherol from NLC in first 2 h confirms the potential of NLCs to be an effective carrier for cosmetic/topical delivery. *In vitro* skin permeation studies showed that tocopherol-loaded NLCs could retain significantly higher amount of drug in the epidermis, and Epiderm testing categorized NLC as a nonirritant formulation. Overall, this study supplements the evidence that tocopherol-loaded NLCs are promising nanocarriers for topical and cosmetic delivery.[55]

In order to improve skin permeation of vitamin E, Padamwar, *et al.* developed the liposomes of vitamin E acetate using factorial design approach. Vitamin E acetate liposomes were produced by the ethanol injection method using Phospholipon 80N®, cholesterol, and stearic acid. The liposomes had a particle size of 136 nm, PDI of 0.211, and entrapment efficiency of 100.95 ± 3.25%. The liposomal dispersion was incorporated into carbopol gel matrix to form liposomal gel. The liposomal dispersion and liposomal gel formulation were stable for 3 months. The drug deposition in rat skin was enhanced by four-fold and six-fold by liposomal gel formulation compared with control gel, control drug, and marketed formulation. The drug deposition studies revealed that liposomal dispersion showed a seven-fold increase in drug deposition compared with plain drug dispersion control, whereas the vitamin E acetate gel formulation demonstrated a six-fold and four-fold increase in drug deposition compared with control gel and marketed cream, respectively. Thus, vitamin E liposomal preparation demonstrates its potential for dermal use.[56]

To improve the stability and release of α-tocopherol, Ying, *et al.* developed nanolipid carrier of α-tocopherol by the high-shear homogenization method using stearic acid, lecithin, oleic acid, and Tween 80. The particles of size 200 nm, PDI of 0.2, and entrapment of above 90% were obtained. The NLCs being stored at 4°C were stable for 1 month. *In vitro* release studies showed that NLCs had a slow release of loaded alpha-tocopherol. However, the phase transition from gel-like to liquid-like of the developed gel mixture was proven to be activated by temperature changes. The rheological gelling point of the gel mixture was represented by the crossover point of storage modulus, G′ and loss modulus, G″, which was obtained in the vicinity of body temperature of 37°C. This property is useful for better spreadability of the gel on the skin and enhanced penetration of NLCs across the skin barrier. These results suggested that gel mixture of CMC and ι-C is a good candidate to be developed as a thermoresponsive gel, whereas lipid NPs are a promising carrier system for alpha-tocopherol in topical use.[57]

A novel sunscreen of α-tocopherol acetate–loaded SLN was prepared by Wissing and Müller using the high-pressure homogenization technique. The SLN composed of cetyl palmitate as lipid and polyglycerol methyl glucose distearate as surfactant. The produced dispersion was incorporated into gels and cream to form a novel sunscreen. The NPs were reported to be stable for a year with a particle size of 200 nm. The investigation of the UV-blocking capacity using different *in vitro* techniques revealed that the SLN dispersions produced are at least twice as effective as their reference emulsions (conventional emulsions with identical lipid content).The obtained data showed that incorporation of tocopherol acetate into SLN leads to an improved sunscreen and skincare formulation.[58]

Vitamin K

Vitamin K is a fat-soluble vitamin. Vitamin K is also known as phytonadione or vitamin K_1.

Mechanism of action of vitamin K

Dermatologists have found application of vitamin K in cosmetics due to its antioxidant effect. Vitamin K is used to treat facial skin problems like permanent erythema, telangiectasias, and skin lesions, which occurs due to the dilation of blood vessels. Initially it was considered a vitamin K-dependent enzyme (gamma-glutamyl carboxylase), exclusively active in the liver. So vitamin K was administered only orally. Due to the presence of this enzyme in the skin, the method of administration changed. Vitamin K in cosmetics has an impact on gamma-glutamyl carboxylase; vitamin K accelerates the blood coagulation process and makes dilated blood vessels less visible. Also, vitamin K strengthens blood vessel walls and decreases their fragility. Vitamin K also has anti-inflammatory and anti-clotting properties. Different derivatives of vitamin K significantly improves skin tone, skin hydration, and skin elasticity and reduces skin erythema.[59]

Vitamin K is found to be promising in treating under eyes dark circle and bruising on the face. When the fat pad beneath the eye begins to thin with age along with sluggishness of blood flow underneath the eyes contributes to appearance of dark circles, topical application of vitamin K has been found to diminish the appearance of these dark circles and reduces facial bruising. Recently, vitamin k has also been used in patients

Table 2: Few patented formulations of vitamins

Vitamins	Patent no	Benefits
Vitamin A and its derivatives	ES2447301T3	Treat acne vulgaris and psoriasis
Vitamin B_3	US6238678B1	To prevent signs of aging
Vitamin B_3	CA1074234A	Skin lightening as well as protection from sunburn and suntan
L-ascorbic acid serum	US9468597B1	Skin rejuvenation
Vitamin E acetate	EP0910367B1	Skin moisturizing effect
Vitamin K	US774549B2	Prevention from skin rash, which is secondary to anti-epidermal growth factor receptor therapy

undergoing laser treatments to lessen the appearance of spider veins on the face.[60]

Topical formulations of vitamin K

Different derivatives of vitamin K (Epoxy MQ and MQ) used in 0.5% and 0.1% concentrations significantly decreased red areas and demonstrated their antiaging effects.[59] Topical 1% vitamin K used twice a day was effective in improving vascular manifestation of aging and resolving facial bruising. Similarly 1% vitamin K in combination with retinol was proved to effective in the removal of extravasated blood under the skin by vitamin K and protection from photoaging by retinol.[61]

Nanocarriers of vitamin K formulated by Campani, *et al.* had shown to enhance the accumulation of vitamin K into the skin. Three types of nanocarriers encapsulating vitamin K were prepared viz. liposomes, transferosomes, and ethosomes. The ex *vivo* studies demonstrated that transdermal penetration was dependent on the type of formulation and the mode of administration. The nebulized form (transferosomes) showed enhanced accumulation and penetration of vitamin K into the skin. Transferosomes administered in form of aerosol (nebulized form) offered higher penetration and accumulation into skin. The diameter of transferosome after nebulization was 87.4 nm with PDI of 0.3.[19]

Topical application of vitamin k has been used for the prevention of vascular manifestation of aging, suppression of pigmentation, and the resolution of bruising. Studies conducted by Lopes, *et al.* investigated the *in vitro* skin penetration and transdermal delivery of vitamin k by lipid-based formulation. The lipid formulation used in the study contains monoolein (MO), which is structured as liquid crystalline phase, named as hexagonal phase. There were three lipid formulation used in the study namely vaseline liquid, MO-based hexagonal phase gel, and MO-based nanodispersion of hexagonal phase. The *in vitro* release study using porcine skin demonstrated in vaseline system, vitamin k was delivered mainly to the stratum corneum -9.50 ± 0.97 µg/m^2 at 12 h postapplication. The hexagonal phase gel and nanodispersion delivered two times more vitamin k than the stratum corneum than the vaseline solution. The nanodispersion (but not the gel) increased the transdermal delivery of vitamin k at 9 h (three-fold increase). These results demonstrated that the topical delivery of vitamin k incorporated in lipophilic vehicle is small, but it may enhanced by MO-based system, which might be useful for the effectiveness of topical vitamin k therapy.[62]

Studies conducted by Shah, *et al.* were double-blinded randomized placebo-controlled studies on 22 patients. The patients were divided into pretreatment and posttreatment group. Eleven patients in the former group applied vitamin k cream to half of their face and vehicle alone to other half of their face twice daily for 2 weeks before laser treatment. The latter group followed same procedure for 2 weeks after laser treatment. The results demonstrated the side of the face treated with topical vitamin k before laser therapy showed no significant difference in bruising compared to placebo. However, the side of the face treated with topical vitamin k after laser therapy showed significant lower scores of bruising severity when compared with the side treated with placebo. Although pretreatment with vitamin k did not prevent bruising, after laser treatment did reduce the severity of bruising particularly in the initial days of application [Table 2].[63]

Conclusion

This review gives information that the vitamins incorporated in cosmeceuticals can be beneficial in treating various skin conditions. Cosmeceuticals containing vitamins have an increasing demand in dermatologist's armamentarium. There has been considerable scientific evidence that the novel drug delivery system reviewed here for encapsulating vitamins suggests us that an appropriate type of delivery system may prevent vitamins from degradation due to moisture, pH, and other external factors, enhances the stability of vitamins, facilitates extended release, and also enhances the aesthetic appeal of the product. Because of increasing demand for cosmetics, it is necessary to understand the science behind cosmeceutical vitamins as they are incorporated into the skincare products and absorbed by the skin with daily use of these products.

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Conflicts of interest

There are no conflicts of interest.

Data availability

The data supporting the findings of this study are available within the article.

Ethical statement

No ethical approval was required for this article as this study did not involve human subjects or laboratory animals.

Summary of work done by the contributors

DJ carried out the major literature search and was the major contributor in writing the article. MR contributed to technically designing and writing the manuscript.

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