

Current Advances of Nanocarrier Technology-Based Active Cosmetic Ingredients for Beauty Applications

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Abstract: Nanocarrier technology has been effectively applied to the development of drug delivery systems to overcome the limitations of traditional preparation. Its application has been extended to various pharmaceutical fields from injection preparation to oral preparation and external preparation, and now it has appeared in the field of cosmetics for beauty applications. The widespread influence of nanocarrier in the cosmetics industry is due to the fact that nanocarrier can effectively promote the percutaneous penetration and significantly increase skin retention of active components in functional cosmetics. Meanwhile, nanocarrier can effectively improve the water dispersion of insoluble active cosmetic ingredients, enhance the stability of efficacy components and achieve the codelivery of diverse cosmetics active ingredients. In this review, we summarized the current progress of nanocarrier technology in the functional cosmetics, including the types and the routes of dermal/transdermal drug delivery nanocarriers used in the functional cosmetics, the mechanism of nanocarriers promoting the percutaneous penetration of active cosmetic ingredients, the application and efficacy evaluation of different active cosmetic ingredients in nanocarriers and discussing the potential risks to human. This will provide a useful reference for the further development of nanocarriers in the field of functional cosmetics.

Keywords: nanocarrier technology, functional cosmetics, active cosmetic ingredients, skin penetration and positioning, efficacy evaluation, codelivery nanocarriers

Introduction

Nanocarriers, also known as nanocarrier drug-delivery systems, refer to a new class of pharmaceutical preparations developed by using nanometer preparation technology, which is the core technology of nanometer drugs. As one of the most industrialized and promising technologies in nanotechnology, the research and development of nanocarriers have become the current international frontier and hot spot. Recent studies have demonstrated that nanocarriers can effectively promote the penetration of cosmetic efficacy components through the stratum corneum and significantly increase the skin retention of efficacy components.¹ Meanwhile, nanocarriers can effectively improve the water dispersion of insoluble active ingredients and potentiate the stability of active ingredients.² These show a good application prospect in the solution of skin problems, treatment of skin diseases and skin care and beauty.

Since 1986, Christian Dior launched the first cosmetics (Capture) applied by liposome technology,³ and then the research of nanocarrier technology in functional

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cosmetics has been promptly developed. Functional cosmetics products using nanocarrier technology have been listed successively (Table 1), showing the broad application prospect of nanocarrier technology in the field of cosmetics.⁴⁻⁶ Studies have revealed that the application of nanocarrier technology in functional cosmetics can realize the skin targeted transportation of efficacy components, enable the efficacy components to enter target sites and target cells, and achieve the functions of sustained release, controlled release, long-term release and so on.⁵ At the same time, it can effectively augment the stability of light/heat sensitive components and improve the compatibility of efficacy components.¹

In recent years, cosmetics containing natural plant active ingredients have been favored by consumers. The application of plant active ingredients in functional cosmetics often has several problems such as poor solubility and stability, low skin permeability and skin irritation, which limit the application of plant active ingredients in functional cosmetics.⁷ Nanocarrier technology solves the above problems well and greatly expands the application of plant active ingredients in functional cosmetics (Table 2).^{8,9} In addition, skin care often needs to consider multifaceted factors,^{10,11} which lead to the need for synergistic effects of multiple efficacy components in functional cosmetics. However, at present, the active ingredients of most functional cosmetic products on the market are single, or the physicochemical properties of different efficacy ingredients are greatly different, resulting in poor compatibility and difficulty in transdermal absorption. The specially designed nanocarriers can simultaneously load multifarious efficacy components with different physical and chemical properties. By transdermal co-delivery of skincare efficacy components, the synergistic effect of multi-effect and multi-target skincare efficacy components can be realized.¹²

In this Review, we summarize the research progress of nanocarrier technology in functional cosmetics, including the types and the routes of dermal/transdermal drug delivery nanocarriers used in functional cosmetics, the mechanism by which nanocarriers promote the transdermal penetration of active cosmetic ingredients, the application and efficacy evaluation of different active cosmetic ingredients in nanocarriers and discussing the potential risks to human, which will provide reference for the further development of nanocarriers in the field of functional cosmetics.

The Types and the Routes of Dermal/Transdermal Drug Delivery Nanocarriers

The Types of Dermal/Transdermal Drug Delivery Nanocarriers in Cosmetics

The types of dermal/transdermal drug delivery nanocarriers used in cosmetics include microemulsions/nanoemulsions, liposomes, lipid nanoparticles, lipid liquid crystals, nanocrystals, polymer nanocarriers and inorganic nanocarriers. The particle size is the primary characteristic of nanocarriers, which constitutes an important material basis for the special biological effects of nanocarriers. Compared with the size of nanomaterials defined in the field of materials science (0.1 ~ 100 nm), extensive research has indicated that when the particle size of the nanocarrier is from 10 to 1000 nm, the efficacy components are distinctly different from the traditional preparations in terms of physical and chemical properties, pharmacokinetics and pharmacodynamics.¹³ When cosmetic efficacy components are loaded into nanocarriers in different ways including dissolution, dispersion, encapsulation, adsorption and coupling, its physical and chemical properties (such as saturated solubility, dissolution rate, crystal type, hydrophilic and hydrophobic, and stability) and biological characteristics (such as specific molecular affinity, cell affinity and biodegradability) are altered, thus affecting the absorption, distribution, metabolism and excretion of efficacy components (such as changing skin transdermal permeation, biological adhesive, internal stability and targeting property, slow/controlled release characteristics and cellular uptake). In this way, the bioavailability and therapeutic effect of cosmetic efficacy components can be heightened and its adverse reactions can be attenuated.

The Routes of Dermal/Transdermal Drug Delivery Nanocarriers

Based on the existing literature,¹⁴ there are three main routes by which nanocarriers can promote percutaneous absorption of efficacy components (Figure 1): (1) The nanocarriers penetrate by skin appendages including hair follicles and sebaceous glands and deliver cosmetic efficacy components to surrounding tissues, (2) Interactions between nanocarriers and the skin stratum corneum can enhance permeability of efficacy components, (3) The deformable nanocarriers in intact form penetrate the living cell layer of the skin by the intercellular route of stratum corneum.

Table 1 List of Nanocarriers Applied in Functional Cosmetic Products

Nanocarriers	Product	Proposed Use	Manufacturer
Nanoemulsions	Vitacos Vita-Herb Nona-Vital Skin Toner	Moisturizer	Vitacos Cosmetics
	Precision-Solution Destressante Solution Nano Emulsion	Moisturizer	Chanel
	Peaux Sensitivity		
	Coni Hyaluronic Acid & Nanoemulsion Intensive Hydration Toner	Moisturizer	Coni Beauty
	Phyto-Endorphin Hand Cream	Anti-aging	Rhonda Allison
	Bepanthol-Protect Facial Cream Ultra	Moisturizer/Anti-aging	Bayer HealthCare
Liposomes	Azelac Ru Serum	Whitening	Sesderma
	Seskavel Mulberry Anti-Hair Loss Foam	Anti-alopecia	Sesderma
	C-Vit Facial Serum	Anti-aging	Sesderma
	Daeses Lifting Cream	Anti-aging	Sesderma
	Acglcolic Classic Crema Hidratante SPF 15	Anti-aging	Sesderma
	Isocell™ MAP	Anti-aging	Lucas Meyer Cosmetic
	Capture	Anti-wrinkle	Christian Dior
	Eye Defense Cream	Anti-wrinkle	L'Oreal Paris
	Derma Stemness Reviving Serum	Anti-wrinkle	Kaya skin clinic
	Royal Jelly Lift Concentrate	Anti-wrinkle	Royal Jelly
	Decorte Moisture Liposome Face Cream	Moisturizer	Decorte
	Dermosome	Moisturizer	Microfluidics
	Kerstin Florian Rehydrating Liposome Day Creme	Moisturizer	Kerstin Florian
	Premier Bio Performance Liposome	Moisturizer	Dead Sea Premier
	Moisture Liposome Cream	Moisturizer	Cosme decorte
	Clinicians Complex Liposome Face & Neck Lotion	Moisturizer/Anti-aging	Clinicians Complex
Russell Organics Liposome Concentrate	Moisturizer/Anti-aging	Russell Organics	
Lumessence Eye Cream	Anti-wrinkle/Anti-aging	Aubrey Organics	
Solid lipid nanoparticles	Allure Body Cream	Moisturizer	Chanel
	Soosion Facial Lifting Cream SLN Technology	Anti-wrinkle	Soosion
	Phyto NLC Active Cell Repair	Moisturizer/Whitening	Sireh Emas
Nanostructured lipid carriers	Swiss Cellular White Illuminating Eye Essence	Whitening	La prairie
	Surmer Creme Leg`ere Nano-Protection	Moisturizer	Isabelle Lancray
	lope Supervital Extra Moist Sofner	Moisturizer	Amore Pacific
	Olivenol Anti Falten Pfegekontrat	Anti-wrinkle	Dr. Teiss/Medipharma cosmetics
	Surmer Masque Creme Nano-Hydratant	Moisturizer/Anti-wrinkle	Isabelle Lancray
Regenerations Cream Intesive Ampoules	Anti-wrinkle/Anti-aging	Scholl	
Cutanova-Cream Nanorepair Q10	Anti-wrinkle/Anti-aging	Dr. Rimpler	
Niosomes	Niosome Plus	Anti-aging	Lancome
	Niosome+ Perfected Age Treatment	Anti-wrinkle	Lancome
	Anti-Age Response Cream	Anti-wrinkle	Simply Man Match
	Niosome+	Whitening	Lancome
	Guinot deep action lightening serum	Whitening	Guinot
	Eusu Niosome Makam Pom Whitening Facial Cream	Whitening	Eusu
	Identik Masque Floral Repair	Anti-alopecia	Identik
	Identik Shampooing Floral Repair	Anti-alopecia	Identik
	Mayu Niosome Base Cream	Moisturizer/Whitening	Laon Cosmetics

(Continued)

Table I (Continued).

Nanocarriers	Product	Proposed Use	Manufacturer
Nanocapsules	Hydra Flash Bronzer Daily Face moisturizer Hydra Zen Cream Primordiale Optimum Lip Soleil Instant Cooling Sun Spritz SPF 15 Soleil Sof-Touch Anti-Wrinkle Sun Cream SPF 15 Eye Contour Nanolif	Moisturizer Moisturizer Lip treatment Sunscreen Anti-wrinkle/Sunscreen Anti-wrinkle/Anti-aging	Lancome Lancome Lancome Lancome Lancome Euoko
Nanospheres	Clearly It! Complexion Mist Fresh As A Daisy Body Lotion Cell Act DNA Filler Intense Cream Nano Salmmoisture Key Coryse Salome Competence Hydration Ultra-Moisturizing Cream Hydralane Ultra Moisturizing Day Cream Nanosphere Plus	Anti-acne Anti-wrinkle Anti-wrinkle Moisturizer Moisturizer Moisturizer Anti-aging/Anti-wrinkle	Kara Vita Kara Vita CellAct Switzerland Salvona Coryse Salome Paris Hydralane Paris DermaSwiss
Gold nanoparticles	Nano Gold Firming Treatment Chantecaille Nano Gold Energizing Cream LR Nano Gold Day & Silk Day Cream Nuvoderm Nano Gold Anti-Aging Lifting Serum Orogold 24K Nano Ultra Silk Serum Ameizii Nano Gold Foil Liquid Tony Moly Nano Gold BB Cream SPF 50 PA+++ O ³⁺ 24K Gold Gel Cream	Anti-aging Anti-aging Anti-aging Anti-aging/Anti-wrinkle Anti-aging/Anti-wrinkle/ Moisturizer Anti-aging/Whitening/ Moisturizer Whitening/Anti-wrinkle/ Sunscreen Whitening/Anti-wrinkle/ Sunscreen	Chantecaille Chantecaille LR Zeitgard Nuvoderm Orogold Ameizii Tony Moly O ³⁺
Silver nanoparticles	Cosil Whitening Mask Lancome Renergie Microlif Nano Cyclic Cleanser Silver	Whitening Anti-wrinkle Anti-wrinkle/Anti-acne/ Freckle-removing	Natural Korea Lancome Nano Cyclic
Fullerene C ₆₀	Zelens Fullerene C ₆₀ Night Cream	Anti-aging	Zelens

The Permeation of Nanocarriers via Skin Appendages

Nanocarriers can penetrate through skin appendages including hair follicles, sebaceous glands and sweat glands, which were collectively termed the transappendageal route. Nanocarriers accumulating the deep of the hair follicle generate a depot effect and slowly release the efficacy components. Hair follicles extend up to 1000 µm deep into the dermis and form a three-dimensional contact surface with the skin, which provide sufficient absorption area for the efficacy components.¹⁵ Studies have shown that the permeability behavior of hair follicles of nanocarriers is closely related to their particle sizes. Lipid-based nanocarriers of less or equal to 640 nm can penetrate into

hair follicles.¹⁶ Smaller particle size nanocarriers can penetrate into the bottom of hair follicles and show more accumulation and stronger permeability. The observations uncover that 40 nm polymeric nanoparticles may enter the perifollicular dermis,¹⁷ whereas polymeric nanoparticles of 300 nm penetrate up to 300 µm deep into the hair follicles.¹⁸ In addition, microparticles with a size of 3–10 µm may reach the orifices of hair follicles or even block them.¹⁶

Interactions Between Nanocarriers and the Skin Stratum Corneum

The skin stratum corneum-nanocarriers interactions, known as intracellular route, include increased stratum

Table 2 Applications of Phytobioactive Ingredients into Nanocarriers for Cosmetic Formulation

Phytobioactive Ingredients	Nanocarrier Type	Size (nm)	Effect	Applications	Reference
Virgin coconut oil	Solid lipid nanoparticle	608–44,265	Enhancing penetration and moisturisation, controlling the release	Moisturizer	Noor et al ⁶⁰
Argan oil	Nanostructured lipid carrier	100–200	Prolonging contact time, facilitating local application, improving skin hydration	Moisturizer	Tichota et al ⁶⁷
Rice bran oil	Nanoemulsion	69	Facilitating penetration, increasing skin water content, maintaining the normal skin pH	Moisturizer	Bernardi et al ⁶⁸
Glabridin	Nanocrystal	149.2	Enhancing permeation and retention time of skin, improving low water solubility and poor stability	Whitening	Wang et al ⁶⁹
Resveratrol	Solid lipid nanoparticle	≤200	Enhancing skin permeation and retention, reducing the cytotoxicity in high concentration	Whitening	Rigon et al ¹⁰
Paeonol	Lipid liquid crystal	85	Improving the water solubility and stability, reducing the volatility and the skin irritation	Whitening	Li et al ⁷³
Ascorbic acid	Microemulsion	256	Enhancing the solubilisation, stabilisation, penetration and protection of ascorbic acid	Whitening	Pakpayat et al ¹¹¹
Hesperetin	Microemulsion	101.5–233.0	Increasing the skin retention, improving stability, diminishing skin irritation	Whitening	Tsai et al ¹¹²
Curcumin	Polymeric micelle	172.6	Improving the solubility, stability and systemic bioavailability	Whitening	Cheng et al ¹¹³
Pomegranate peel polyphenol	Nanoemulsion	169	Promoting the penetration of pomegranate polyphenols into the deeper skin layers	Anti-aging	Baccarin and Lemos-Senna ¹¹⁴
Lutein	Solid lipid nanoparticle, nanostructured lipid carrier, nanoemulsion	150–350	Enhancing solubility and photo stability, facilitating penetration and release	Anti-aging	Mirri et al ¹¹⁵
α -Tocopherol	Nanostructured lipid carrier, nanoemulsion	67 and 586.5	Increasing photostability, release and permeation, reducing skin irritation	Anti-aging	Abla and Banga ⁷⁴
Madecassoside	Liposome	293	Promoting drugs to penetrate epidermis, remaining or releasing at dermis, maintaining long term drug storage	Anti-aging	Wang et al ⁷⁵
Quercetin	Nanostructured lipid carrier	215.2	Promoting the permeation, increasing the skin retention, enhancing the effect of anti-oxidation	Anti-aging	Guo et al ¹¹⁶
Quercetin	Mesoporous silica nanoparticle	250	Increasing the skin penetration, water-solubility and photostability, enhancing the effect of anti-oxidation	Anti-aging	Berlier et al ¹¹⁷ Sapino et al ¹¹⁸
Rutin	Mesoporous silica nanoparticle	250	Improving the physicochemical stability and skin accumulation, increasing the effect of anti-oxidation	Anti-aging	Berlier et al ¹¹⁹
Lavender	Polymeric nanoparticle	301.8	Enhancing the physicochemical stability, increasing the epidermal permeation, reducing the risks of toxicity	Anti-aging	Pereira et al ¹²⁰
Rosemary extract	Solid lipid nanoparticle, nanostructured lipid carrier	57	Improving the suitability and compatibility, increasing the skin penetration and the effect of anti-oxidation	Anti-aging	Lacatusu et al ¹²¹

(Continued)

Table 2 (Continued).

Phytobioactive Ingredients	Nanocarrier Type	Size (nm)	Effect	Applications	Reference
Lauric acid	Liposome	119.9	Enhancing the water solubility, preventing the degradation, reducing the skin irritation, facilitating the interaction with bacterial membranes	Anti-acne	Pornpattananangkul et al ⁸⁷
Curcumin	Microemulsion	< 276	Enhancing the physicochemical properties, skin accumulation and antimicrobial effect	Anti-acne	Liu and Huang ⁸⁹
Thai basil oils	Microemulsion	NA	Enhancing transdermal transport and the skin accumulation of antibacterial agent	Anti-acne	Viyoch et al ¹²²
α -Mangostin	Polymer nanocarrier	300–500	Improving hair follicle entrapment, controlling sustained release and reducing the skin irritation	Anti-acne	Pan-In et al ¹²³
Hinokitiol	Nanocapsule	55–234	Enhancing the transdermal delivery and the dermal delivery, increasing entrapment efficiency, shelf stability and solubilization in a detergent solution, promoting hair growth	Anti-alopecia	Hwang and Kim ¹²⁴
Hinokitiol	Lipid nanoparticle	<100	Enhancing the skin permeation	Anti-alopecia	Cho et al ¹²⁵
Safranal	Solid lipid nanoparticle	106 and 233	Increasing the encapsulation efficiency and skin water content, blocking ultraviolet lights and exhibiting occlusive properties	Sunscreen	Khameneh et al ¹²⁶
Safranal	Liposome	90.2–135.9	Reducing systemic absorption and adverse reactions in high concentration, increasing sun protective and moisturizing effects	Sunscreen	Golmohammadzadeh et al ¹²⁶
Rice bran and raspberry seed oil	Lipid nanoparticle	<200	Minimizing the side effects, improving the photoprotection by simultaneously co-encapsulating and co-releasing two ultraviolet A and ultraviolet B absorbers	Co-delivery for sunscreen	Niculae et al ¹²¹
Resveratrol and curcumin	Nanocapsule	201	Increasing the photostability and water solubility, facilitating penetration of resveratrol into deeper skin layers, providing an immediate as well as a sustained polyphenol release	Co-delivery for whitening	Friedrich et al ¹²⁷
Aqueous propolis and lycopene	Nanoemulsion	NA	Controlling release of dozed form, improving efficiency and skin acceptance, minimizing the skin irritation	Co-delivery for anti-aging	Butnariu and Giuchici ¹²⁸
Resveratrol, α -tocopherol and curcumin	Niosomal	471–565	Improving the stability and short half-life, increasing the skin penetration	Co-delivery for anti-aging	Tavano et al ¹²⁹

Abbreviation: NA, not available.

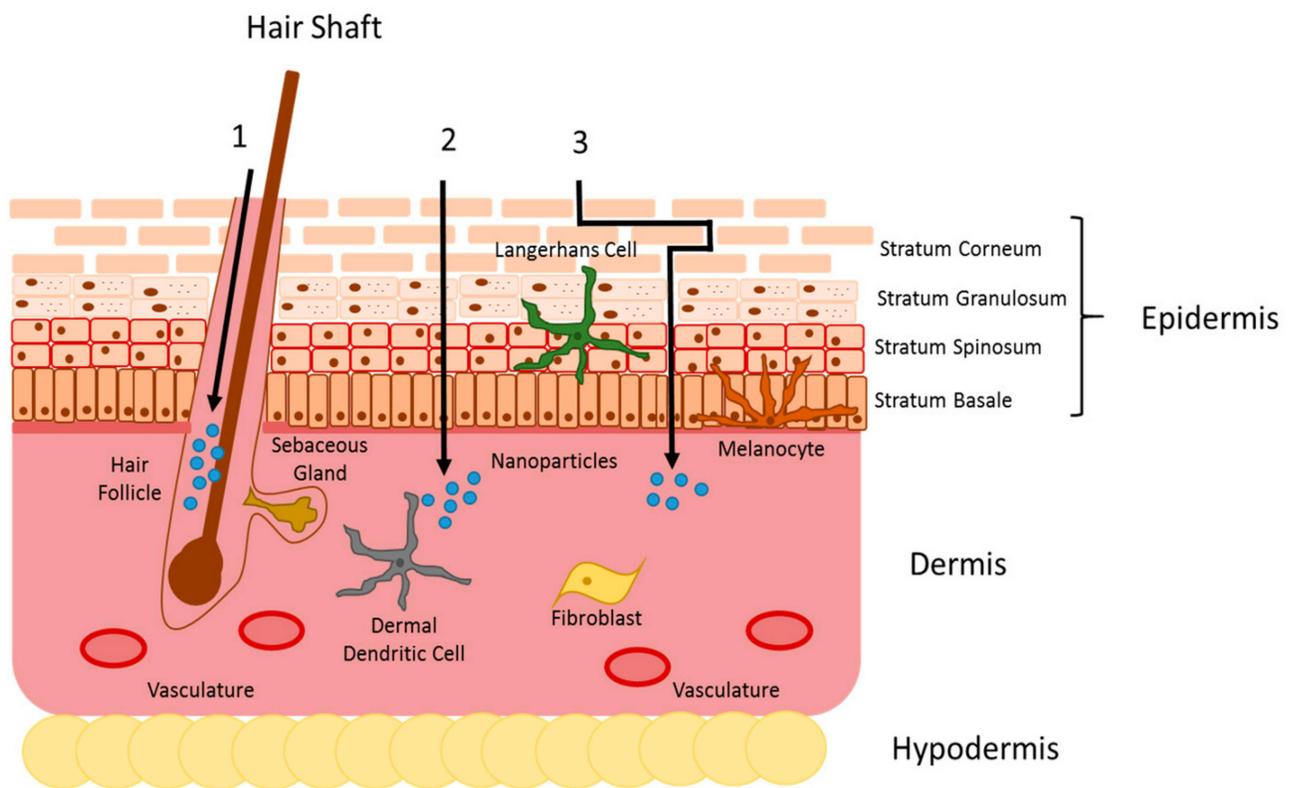


Figure 1 Mechanisms of nanocarriers promoting percutaneous absorption of efficacy components.

Notes: Reprinted from Palmer BC, DeLouise LA. Nanoparticle-enabled transdermal drug delivery systems for enhanced dose control and tissue targeting. *Molecules*. 2016;21(12):7–9.¹⁴ Creative Commons CC-BY 4.0 (<https://creativecommons.org/licenses/by/4.0/legalcode>).

corneum hydration by sticking to the skin surface, lipid exchange occurring between nanocarriers and stratum corneum, and enhanced fluidity and improved polarity of lipid bilayer of stratum corneum. The interactions can disorganize the lipid structure of stratum corneum by changing its composition of the stratum corneum lipid and tight arrangement of the bilayer, and weaken the barrier effect of the stratum corneum to increase drug penetration by increasing the mobility and permeability of lipids in the skin. Noteworthy, the effect of nanocarriers on the lipid bilayer of stratum corneum is mild and reversible, without permanent damage to its structure. However, due to the low permeability of the stratum corneum cells and the multiple hydrophilic/lipophilic distribution of drugs through the intracellular route, the intracellular route is only a minimal part of the transdermal drug delivery of nanocarriers.

Nanocarriers Crossing the Intercellular Gap of Stratum Corneum

The intact nanocarriers cross the stratum corneum by the intercellular gap, which is the main route for nanocarriers

to carry the efficacy components into the active epidermis and dermis, and then to be absorbed into the systemic circulation. The composition, structure, particle size and surface charge of the nanocarriers affect its penetration behavior and penetration depth in the skin. Solid lipid nanoparticles and nanostructured lipid carriers are mainly retained in the stratum corneum due to their strong lipophilic properties. Due to the poor membrane fluidity and elasticity, it is difficult for the conventional liposomes to cross the stratum corneum in an intact form. Considering that the modified liposomes (such as transporters, alcohols and terpene liposomes) have better deformation capacity, and modifiers (such as cholate, ethanol and terpene) have stronger disturbance to the arrangement structure of cuticle, the research have shown that such nanocarriers with suitable particle sizes can penetrate the complete skin.¹⁹ Moreover, low generation dendrimers can penetrate into the stratum corneum in intact form, but the extent and route of their penetration are influenced by its surface properties including polarity and electric charge.²⁰ Furthermore, the intact inorganic nanocarriers such as mesoporous silicon nanoparticles, gold nanoparticles and

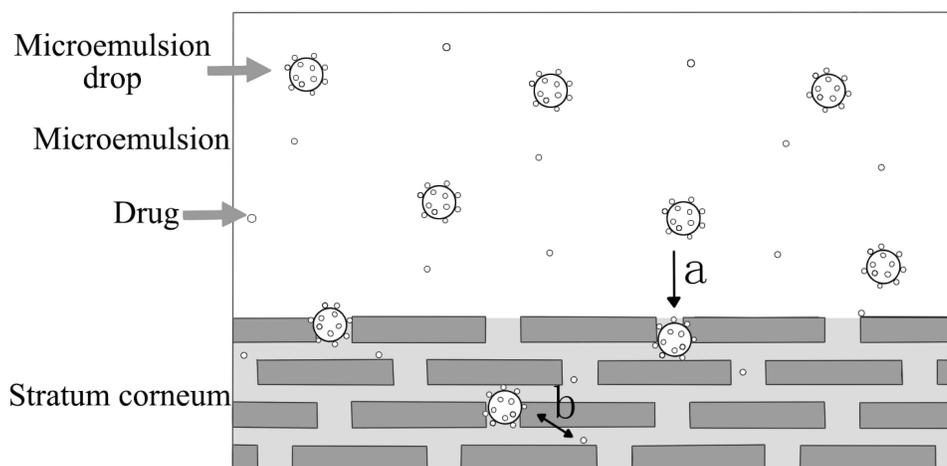


Figure 2 Schematic of the mechanism of microemulsion-mediated intercellular infiltration in the stratum corneum. In step (a) the microemulsion drop loading the drug penetrates through the porous structure of the skin. In step (b) the drug is released from the microemulsion droplet into the surrounding cell space.

quantum dots with suitable particle size and surface modification can also pass the stratum corneum.

Mechanism of Nanocarriers Promoting Dermal/Transdermal Delivery of Active Cosmetic Ingredients

Skin penetration and positioning of efficacy components are important conditions for functional cosmetics to play their role in protecting skin. However, it is still difficult to accurately evaluate the behavior of nanocarriers in the skin and the exact process of promoting the penetration of efficacy components through the skin barrier. Therefore, the elucidation of the promoting permeability mechanism of nanocarriers provides theoretical support for the design of ideal nanocarriers of functional cosmetic and the effective improvement of skin efficacy components' percutaneous permeability efficiency.

Microemulsions/Nanoemulsions

Microemulsions are a thermodynamically stable isotropic dispersive system formed spontaneously by oil, water and surfactant. Nanoemulsions are considered as a kind of conventional emulsion containing very small droplets and is a thermodynamically unstable colloidal dispersion system.²¹ The surfactant interface between the oil phase and the water phase of the microemulsions and nanoemulsions creates additional solubility region, which improves the drug loading capacity of the emulsion.²² For example, incorporation of resveratrol into microemulsions resulted in improved solubility (over 23-fold) compared to

crystalline resveratrol.²³ The percutaneous absorption route of most drugs in microemulsion and nanoemulsion is through the intercellular gap. For instance, microemulsions mediated intercellular infiltration in the stratum corneum (Figure 2).²⁴ The microemulsions loading the drug enter the intercellular gap from the skin surface (Step a) and then release the drug into the surrounding cell space (Step b), allowing the drug to penetrate into the deeper tissues of the skin. In the process of transdermal absorption, the water in microemulsions is rapidly absorbed into the skin to form supersaturated solution, which increases the drug diffusion pressure and thus significantly potentiates the rate of transdermal absorption.²⁵

In additional, there are also small amounts of free drug uptake via intracellular route.²⁶ The surfactants, cosurfactants and oil phases used in the preparation of microemulsions and nanoemulsions usually have a certain permeability promoting effect, which can reverse and temporarily destroy the double layer structure of the lipid in the stratum corneum, increase the fluidity of the lipid in the stratum corneum, and thus fortify the transdermal permeability of drugs. Meanwhile, surfactants, cosurfactants and oil phases, as permeability enhancers, can perform a "diffuse-distribution-dissolution" effect in the skin, thereby elevating the percutaneous absorption of drugs.²⁷ Furthermore, skin hair follicles are closely related to drug percutaneous penetration, which is an important storage of drugs in the skin and also a channel for particles to percutaneous penetration.²⁸ The W/O nanoemulsion is compatible with the lipophile sebaceous environment of hair follicles and promotes the effective transport of the hydrophilic drug in the skin.²⁹

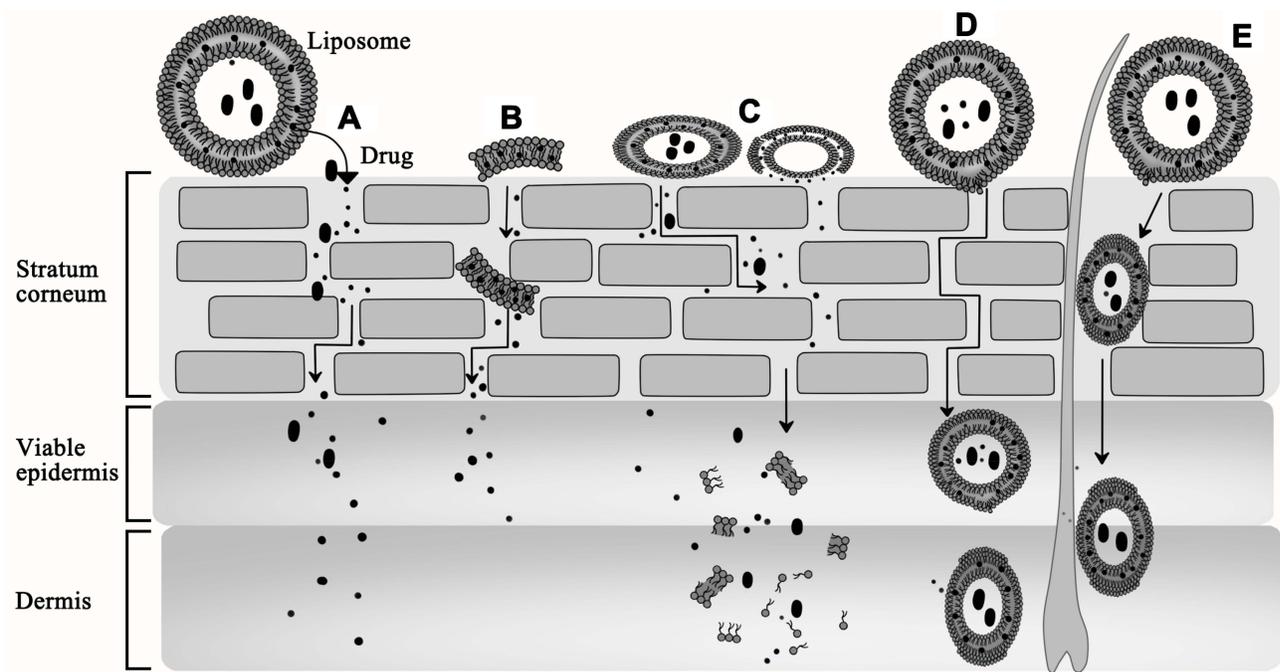


Figure 3 Different mechanisms of percutaneous infiltration of liposomes. (A) Liposomes release drugs outside the stratum corneum by the hydration; (B) Lipid flakes after rupture of liposomes play a role in promoting permeability; (C) Liposomes fuse with the stratum corneum; (D) Some deformable liposomes pass through the stratum corneum in their intact form; (E) Liposomes enter the skin via hair follicles and/or sebaceous glands.

As dermal/transdermal drug delivery nanocarriers, microemulsions and nanoemulsions are characterized by strong skin permeability, large load, good wettability, spreading and stability on the skin surface. Therefore, the colloid delivery system based on microemulsions or nanoemulsions is applied more and more widely in the field of cosmetics.^{22,30}

Liposomes

Liposomes, also known as lipid vesicles, are similar to the stratum corneum in structure and composition and can deliver the efficacy ingredients to the target site of the skin through fusion (Figure 3C). Lipid exchange resulting from this fusion can also form lipid flakes in the intercellular gap of stratum corneum, loosening the cuticle and facilitating drug penetration (Figure 3B).³¹ By significantly improving the hydration of the skin stratum corneum, liposomes can change the arrangement and structure of the hydrophobic part in the lipid bilayer of the stratum corneum so that drugs can easily penetrate the stratum corneum (Figure 3A). Lipid composition contained in liposomes also forms a lipid film on the skin surface, which can decrease skin moisture loss, improve the water content of the stratum corneum, and promote drug penetration.

Of note, the improved liposomes such as transfersomes, ethosomes, niosomes and so on have deformable ability, which enables them to penetrate the stratum corneum by the intercellular gap and deliveries drugs into the deep tissues of the skin (Figure 3D).^{32,33} For example, transfersomes can cross the intercellular space of the stratum corneum by deformable ability and widen the space between keratinocytes to promote the percutaneous penetration of efficacy components by osmotic pressure.³⁴ By changing the lipid structure of the stratum corneum, ethosomes can accumulate in the deep layer of the skin to significantly enhance the penetration depth and skin retention of efficacy components.³⁵ Besides, ethanol contained in the ethosomes is a skin penetration enhancer that enhances percutaneous penetration by affecting the physicochemical properties of the ethosomes (such as particle size, zeta potential, membrane fluidity and solubility). Niosomes promote transdermal absorption of efficacy components and increase its retention in the stratum corneum and active epidermis to prolongate action time by reducing skin tension.

Nanoparticles with wettability on the surface have a good affinity with hair follicle tissue, and are easier to be absorbed by hair follicles than nanoparticles with hydrophobic surface. Liposomes just have this advantage.

Topical delivery of liposomes encapsulated gamma-interferon into hairless mouse, human and hamster skin showed that the hamster skin with the densest distribution of hair follicles had the highest cumulative skin retention.³⁶ The hair follicle uptake rate of PLGA nanoparticles coated with liposomes as drug carriers was $6.95 \pm 2.30\%$, which was significantly higher than that of PLGA nanoparticles coated without liposomes ($3.15 \pm 1.23\%$).³⁷ These results hint that transappendageal route is an important pathway for liposomes to promote drug transdermal absorption (Figure 3E).

Lipid Nanoparticles

Lipid nanoparticles, composed of solid lipid nanoparticles and nanostructured lipid carriers, are colloidal dispersion systems prepared by solid lipids or mixtures of solid lipids and lipid liquid. As the first generation of lipid nanoparticles, solid lipid nanoparticles combine the advantages of nanoparticles and liposomes. With the evaporation of water from the solid lipid nanoparticles used to the skin surface, solid lipid nanoparticles form an adhesive layer occluding the surface of skin.³⁸ Then increased hydration of the stratum corneum can diminish corneocyte packing and widen the intercellular gap of stratum corneum, which fosters efficacy components penetration into deeper skin layer.^{39,40} The smaller the size of solid lipid nanoparticles is, the stronger the hydration is and the stronger the interference effect on the lipid arrangement of skin is.⁴¹ In addition, solid lipid nanoparticles can be inserted into the lipid region of the skin stratum corneum, which destroys its bilayer structure and causes lipid rearrangement, thereby reducing the resistance of drug molecules to penetrate the skin stratum corneum. Furthermore, efficacy components dissolved in the lipid region of the solid lipid nanoparticles can be distributed directly to the lipids in the stratum corneum of skin in a high concentration gradient. These interactions between solid lipid nanoparticles with the skin stratum corneum not only promote efficacy components penetration through the stratum corneum but also enhance their passive diffusion in the skin. Noteworthy, due to their high lipophilicity, solid lipid nanoparticles can reach deep areas of the skin via transappendageal route where sebaceous glands secrete a large amount of oils, mainly short-chain fatty acids.⁴²

Nanostructured lipid carriers are a new generation of lipid nanoparticles developed on the basis of solid lipid nanoparticles. By adding liquid lipids, nanostructured lipid carriers disturb the crystal lattice formation of solid lipids,

thus notably elevating the drug loading and stability. Owing to the improvement of drug loading and stability, nanostructured lipid carriers are not only applied in the field of transdermal drug delivery but also shows good potential application in the field of efficacy cosmetics.⁴³

Lipid Liquid Crystals

Lipid liquid crystals can enhance the stability of the emulsion and be loaded with both hydrophilic and lipophilic compounds to achieve sustained and controlled release of the substance. The interactions of lipid components existing in the lipid liquid crystals and stratum corneum facilitate the flow of lipids in the stratum corneum and allow the liquid crystal to pass through the cuticle.⁴⁴ Besides, additional agents (such as surfactants and moisturizers) in the lipid liquid crystal can increase skin hydration and reduce the barrier of the cuticle.⁴⁵ Considering that both the lipid liquid crystal and the skin are negatively charged, the substances can penetrate into the skin through the channel formed by the repulsive force. Additionally, the double continuous structure of the lipid liquid crystal contains two intersecting channels, which allows hydrophilic drugs to easily penetrate the lipophilic cuticle. Similar to the structure of the stratum corneum, lipid liquid crystals can enter the skin through hair follicles. Furthermore, lipid liquid crystals have unique in situ biological adhesion and skin affinity by its high viscosity, which can not only augment the skin permeability and skin retention of drugs but also protects the damaged and susceptible parts of the skin.⁴⁴ Collectively, the structure and composition of lipid liquid crystals contribute to promote the substances through the stratum corneum. Strikingly, lipid liquid crystals applied to cosmetic products have good moisturizing effect, skin feeling and physical sunscreen effect by reflecting ultraviolet ray.

Nanocrystals

Nanocrystals, also known as nanosuspensions, refer to the colloidal dispersion system of pure drug nanoparticles obtained by controlling the particle size, which is characterized by high drug load (nearly 100%), high oral bioavailability, and good biosecurity. Nanocrystals can significantly improve the solubility and dissolution rate of water-insoluble and fat-insoluble drugs, and is suitable for transdermal administration of insoluble drugs at high dose.⁴⁶ Nanocrystals can form a higher concentration gradient on the skin surface, which facilitates the diffusion of drug molecules into the skin. In addition, nanocrystals

have good biological adhesion, which can prolong their retention time on the skin surface, help to maintain a high concentration gradient for a long time, and promote the diffusion of drug molecules into the skin. In addition to the intracellular and intercellular routes, nanocrystals can also accumulate in hair follicles to form a drug reservoir. After the nanocrystals dissolve, the drugs diffuse in a concentration-dependent manner into the skin.

Polymer Nanocarriers

Polymer nanocarriers are a kind of nanocarrier prepared by good biocompatible polymer materials, including polymeric nanoparticles, polymeric micelles, nanohydrogels, nanocapsules, nanospheres and so on. Polymer nanoparticles penetrate skin deep layers mostly through skin appendages including hair follicles and sebaceous glands and can generate a depot effect in these skin regions, where the efficacy components are diffused in a sustained manner into the skin.⁴⁷ Several observations have shown that small-size nanoparticles can penetrate deeper into the bottom of the hair follicle and show more accumulation and stronger penetration, while large-size nanoparticles can only remain at the open end of the hair follicle. In addition to particle size, polymer materials⁴⁸ and surface modification⁴⁹ can also change the permeability promoting ability of polymer nanoparticles. As a reservoir of insoluble drugs, the hydrophobic nucleus of polymer micelles can improve the concentration gradient of insoluble efficacy components in the outer skin and promote the diffusion of efficacy components in the stratum corneum.⁵⁰ The polymer micelles enter the skin in a way similar to polymer nanoparticles and cannot penetrate the stratum corneum in an intact form. The capacity of transdermal drug delivery of the polymer micelles is affected by the affinity between the drug and the hydrophobic nuclear material, and the strong affinity between the two is conducive to achieving high drug loads. However, the high solubilization ability of the polymer micelles prevents drug transfer from the hydrophobic core of the micelles to the skin. Therefore, the design of a polymer micelle system for transdermal drug delivery needs to strike a balance between high drug load and high delivery efficiency. Differing from polymeric nanoparticles and polymeric micelles, nanohydrogels can dramatically enhance skin hydration. Keratinocyte swelling in the skin treated with nanohydrogels was significantly higher than that in the skin treated with water, and the gap between the

keratinocyte cells was larger. Besides, increased mobility of the lipid bilayer of the cuticle has also been observed.⁵¹

Inorganic Nanocarriers

Inorganic nanocarriers are insoluble or biopersistent nanomaterials with a variety of compositions, structures and properties, including mesoporous silica nanoparticles, titanium dioxide nanoparticles, carbon nanomaterials (such as graphenes, fullerenes and carbon nanotubes), gold nanoparticles, silver nanoparticles and so on. These nanoparticles, characterized by large specific surface area, easy surface modification and good biocompatibility, can penetrate into the deep layer of the epidermal layer and increase its accumulation in the skin, thus being widely used in sunscreen, anti-aging and other functional cosmetic products.^{52–55} However, the mechanism of percutaneous administration of distinct inorganic nanoparticles is different. For example, the interaction between gold nanoparticles and skin cuticle lipids can induce a transient and reversible opening in the stratum corneum, which allows them to penetrate into the skin and accumulate in the active epidermis where they are captured by Langerhans cells and generate an immune response.⁵⁶ In addition, mechanism of skin permeation of drug from diverse carbon nanotubes-based formulations such as electrically tuneable carbon nanotubes films, hydrogels, and carbon nanotubes polymer composite microneedles is distinct, which is shown in detail in Figure 4.⁵⁷ The transdermal delivery mechanisms of graphenes and fullerenes is similar to the carbon nanotubes.

Application and Efficacy Evaluation of Active Cosmetic Ingredient Nanocarriers

Skin Moisturizing Efficacy Components Nanocarriers

Skin problems and skin diseases are associated with epidermal barrier dysfunction. Epidermal barrier dysfunction can cause skin to lose a lot of water, resulting in dry, sensitive, itchy, chapped skin. Studies have shown that the nanocarriers with skin moisturizing efficacy components can effectively increase the epidermal moisture content and restore the skin barrier function, which can not only solve the skin problems but also have a preventive and therapeutic effect on chronic skin diseases such as eczema, atopic dermatitis and psoriasis.^{58–60}

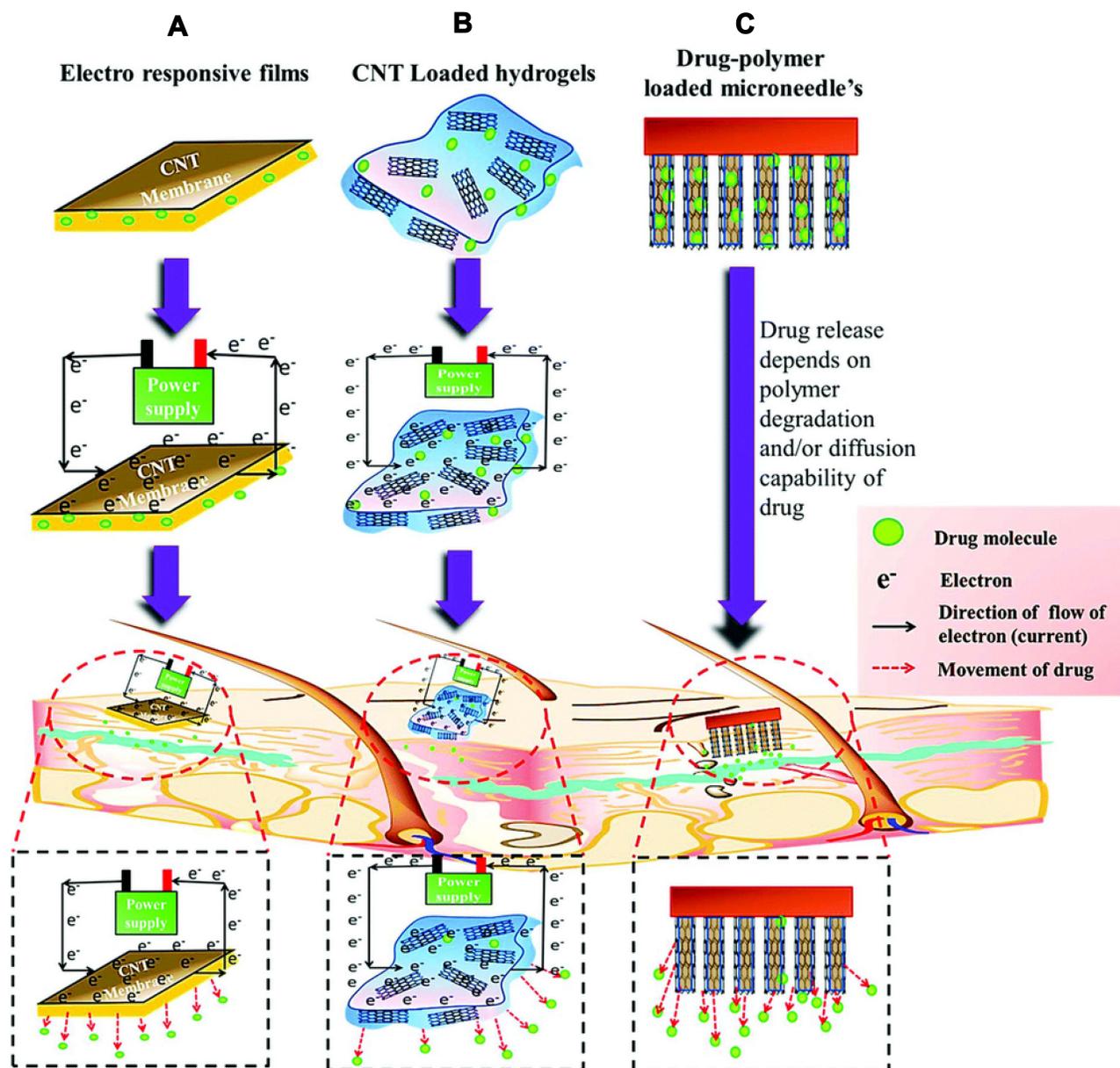


Figure 4 Mechanism of skin permeation of drug from carbon nanotubes-based formulations including electrically tuneable carbon nanotubes films, hydrogels, and carbon nanotubes polymer composite microneedles.

Notes: (A) Carbon nanotube membrane would be either covered or loaded with pure drug alone; upon application of voltage, it forces the drug to permeate through the tough stratum corneum. (B) Due to the incorporation of carbon nanotube, the conductance capacity of carbon nanotube hydrogels has been enhanced, which compels the drug to permeate through the skin to reaching the desired site of action. (C) Carbon nanotube-microneedles provide an excess mechanical strength to penetrate skin and governs the drug release profile which is completely dependent on the degradation mechanism and kinetics of the polymer. Reprinted from Kuche K, Maheshwari R, Tambe V, et al. Carbon nanotubes (CNTs) based advanced dermal therapeutics: current trends and future potential. *Nanoscale*. 2018;10(19):8911–8937.⁵⁷ Copyright (2018), with permission from Royal Society of Chemistry.

Hyaluronic acid is a major component of the extracellular matrix in the active epidermis and dermis. It has the effect of moisturizing and repairing the skin but cannot enter deep skin owing to its large molecular weight. Chen et al⁶¹ prepared an ethosomal carrier system encapsulating hyaluronic acid. Compared to PBS control, the system enhanced penetration of hyaluronic acid into the active

epidermis and dermis by disrupting the dense structure of the stratum corneum. Concentrations of hyaluronic acid in skin were about 1000-fold higher than those in blood. Ming et al⁶² developed an alcohol-free oil/water hyaluronic acid nanoemulsions with desirable skin permeable capacity. The nanoemulsions penetrated across stratum corneum and diffused deeper into dermis by follicular

and intercellular route to delivery hyaluronic acid. Its penetration mechanism be closely associated with transmembrane concentration gradient, carrier characteristics and penetration enhancers. One of the major intercellular lipid matrix of the stratum corneum is ceramide that acts as a binding agent with proteins on the cell surface through ester bonds and forms a physiological barrier in the epidermis to prevent water loss and protect against external stimuli.⁶³ As a high crystalline substance, it is difficult for ceramide to be used in cosmetics due to its low solubility, poor water dispersion and easy crystallization. Yilmaz and Borchert⁶⁴ developed a positively charged nanoemulsions containing ceramides. The stability and solubility of ceramides were significantly improved by incorporating in the positively charged nanoemulsions.

Natural vegetable oil has been widely used in cosmetics due to their antioxidant, hydration, anti-aging, and protection properties on the skin.^{65,66} Bernardi et al⁵⁸ created rice bran oil nanoemulsions using low energy emulsification methods. This formulation has no skin irritation and can significantly improve skin moisture. After 14 days of application by rice bran oil nanoemulsions, skin moisture increased by 38% in normal control volunteers and by 30% in patients with atopic dermatitis or psoriasis. Tichota et al⁶⁷ used argan oil as liquid lipid to prepare nanostructured lipid carriers and further prepared nanostructured lipid carriers-based hydrogel formulation. The formulation has high stability, firmness and adhesion, and can extend the contact time for topical application. The *in vivo* evaluation of the skin illustrated that the formulation precipitated an increase in skin hydration by a synergistic effect of nanostructured lipid carriers occlusion plus argan oil hydration and showed a tendency to enhance moisture retention over time.

Whitening and Freckle-Removing Efficacy Components Nanocarriers

The synthesis of melanin is the result of a series of oxidation reactions in which tyrosinase is the key enzyme. At present, whitening and freckle-removing efficacy components in cosmetics are mainly through inhibition of melanocyte proliferation, inhibition of tyrosinase and other related rapid-limiting enzyme activity and inhibition of melanosome migration, so as to achieve whitening and freckle-removing effect. However, there are generally the following problems in the application of these efficacy components: (i) efficacy components have poor solubility,

poor stability, and are easy to decompose and discolor when exposed to light and heat, (ii) due to the skin barrier, whitening efficacy components are difficult to penetrate into the target part (stratum basale) and unable to act on target cells (melanin cells), resulting in low whitening efficiency, (iii) certain whitening efficacy components have strong skin irritation at high doses, (iv) whitening efficacy components are single and lack the synergistic effect of efficacy ingredients of different action mechanism. The technology of nanocarriers solves the above problems well. The investigations indicate that the stability and whitening and freckle-removing efficacy of these efficacy components are significantly improved after being loaded on the nanocarriers.

Phenylethyl resorcinol is a new whitening agent with the ability to inhibit tyrosinase activity and has been applied in cosmetics as a whitening and brightening efficacy component.⁶⁸ However, the light instability and poor water solubility of phenylethyl resorcinol limit its application. Kim et al⁶⁹ prepared a phenylethyl resorcinol-loaded nanostructured lipid carriers by the hot-melted ultrasonic method. The incorporation of phenylethyl resorcinol into nanostructured lipid carriers conferred excellent physicochemical stability and photo stability and revealed a sustained release. Nanostructured lipid carriers could efficiently promote the uptake of phenylethyl resorcinol by melanocyte in epidermis to inhibit of melanosome migration, thus achieving the whitening effect. N-Acetyl-D-Glucosamine, a precursor of hyaluronic acid, can preserve the skin hydration and is used for topical treatment of hyperpigmentation disorders because of its inhibitory effect on tyrosinase enzymes in melanocytes, which shows a broad prospect in the application of whitening skin care products. Unfortunately, it is barely absorbed by the skin. The solid lipid nanoparticles allowed a higher N-Acetyl-D-Glucosamine permeation through the stratum corneum compared to the free N-Acetyl-D-Glucosamine to contributing to the improvement of skin properties.⁷⁰ 4-n-Butylresorcinol has an inhibitory effect on melanogenesis by directly inhibiting the activity of tyrosinase and tyrosinase-related protein-1 but can induce skin irritation, particularly in high concentrations. 4-n-Butylresorcinol can reduce melanin synthesis by directly inhibiting the activity of tyrosinase and tyrosinase-related protein-1 but can induce skin irritation, particularly in high concentrations. Liposomes improved stabilization and enhanced penetration of 4-n-butylresorcinol. Liposome encapsulating 4-n-butylresorcinol was well tolerated without any adverse

reactions such as skin irritation and significantly reduced the skin melanin content when used to treat patients with chloasma for 8 weeks.⁷¹ Except to bind directly to the tyrosinase, resveratrol can regulate various melanogenic signaling molecules to inhibit melanogenesis. Several observations illustrated that liposomes encapsulating 4-n-butylresorcinol and resveratrol have a synergistic effect the treatment of melasma with its effect appearing as early as 2 weeks.⁷²

In addition, the plant source whitening agents such as paeonol, glabridin, resveratrol and curcumin can also effectively inhibit the tyrosinase activity but are difficult to add to the cosmetic formulations in an effective dose due to their poor water dispersibility. Nanocarriers significantly increase the load of efficacy components. Using pigmentation guinea pigs as models, Li et al⁷³ found that the whitening effect of paeonol lipid liquid crystals was comparable to that of commercial hydroquinone cream, but its skin irritation was less than that of hydroquinone cream and commercial paeonol ointment.

Anti-Aging Efficacy Components Nanocarriers

Skin aging is related to the accumulation of excess oxygen-free radicals in human body. Timely scavenging of excess oxygen-free radicals is an effective means to prevent diseases and delay skin aging. At present, the anti-aging ingredients commonly used in cosmetics can effectively eliminate oxygen-free radicals, but there are some problems in practical application, such as poor stability, low bioavailability, the decomposition under light, heat, and oxygen, and difficulty in transdermal absorption. The emergence of nanocarriers with anti-aging efficacy components has provided the possibility to solve these problems.

Considering the safety of cosmetic efficacy components, the natural active ingredients with antioxidant and free radical scavenging properties such as polyphenols, flavonoids and carotenoids are widely used in cosmetics (Table 2). Tocopherol is sensitive to light and easy to be oxidized. Nanostructured lipid carriers significantly enhance the stability of tocopherol, and makes it stay in the epidermis at a high concentration to achieve efficient moisturizing and antioxidant effects.⁷⁴ Madecassoside is difficult to be absorbed by the skin due to its polarity and large molecular weight. Liposomes can promote madecassoside to penetrate epidermis and remain or release at

dermis, which prevents it from entering the blood circulation and causing systemic adverse reactions.⁷⁵ The utilization of astaxanthin, a natural pigment carotenoid with remarkable antioxidant activity, is limited due to its low water solubility and poor chemical stability. Compared with the free astaxanthin, solid lipid nanoparticles or nanoemulsions significantly enhanced the chemical stability of astaxanthin, even under a variety of external stimulation, and provided a long release in a simulated vivo environment.^{76,77}

Of note, the high antioxidant capacity of inorganic nanocarriers has attracted the attention of researchers. Lens et al⁷⁸ prepared novel organofullerenes by encapsulating fullerene-C₆₀ and synthesized fulleropyrrolidine derivatives into multilamellar phospholipid liposomes. The novel organofullerenes increased the efficiency of delivery of fullerenes to target tissues by enhancing their water solubility and showed better antioxidative characteristics for hydroxyl radical and superoxide radical compared with fullerene-C₆₀ and its derivatives. Ito et al⁷⁹ investigated the antioxidant effects of fullerene in ultraviolet B-induced disorders in mouse skin. In comparison with the control, the co-application of fullerene and ascorbic acid could effectively suppress the oxidative damage of skin and significantly decrease erythema, the reactive oxygen species index and apoptosis index in mouse skin after ultraviolet B irradiation.

Anti-Acne Efficacy Components Nanocarriers

Acne vulgaris (acne) is a common and chronic inflammatory dermatoses of the pilosebaceous units.⁸⁰ The main causes of the development of acne include hyperactivity of the sebaceous gland, follicular epidermal hyperproliferation and inflammation of pilosebaceous units caused by pathogens such as *Cutibacterium acnes* (*C. acnes*).⁸¹ Although topical therapy is considered the first option in the management of mild and moderate acne, physical and chemical properties of drugs such as skin irritation and low permeability limited their applications, which provides an enormous opportunity for the nanocarrier technology in designing of a novel, low-dose and effective treatment systems to control acne disease.⁸²

Adapalene, a chemical of third-generation retinoid, has been commercially available in the form of topical gel and cream for the treatment of mild to moderate acne. However, the therapy of topical adapalene suffers the

most common side effect characterized by scaling, dryness, erythema and a burning sensation in the area of application.⁸³ Guo et al⁸⁴ developed an acid-responsive polymeric nanocarriers encapsulating adapalene via nanoprecipitation. The in vivo and in vitro experiment revealed that the adapalene-loaded polymeric nanocarriers appear to be as efficient as the commercial product Transcutol[®]. Notably, the nanocarrier system realized the on-demand delivery and skin-irritation reduction of drug by using the acidic microenvironment of acne skin. In another study, the nanoemulsion gel formulation containing adapalene seems to be more efficacious and better tolerated than the conventional gel formulation for the treatment of patients with acne.⁸⁵

In addition to synthetic chemicals, the research and application of plant ingredients with antibacterial, anti-inflammatory and scar removing effects in anti-acne cosmetics has been gradually increasing due to the safety limitations of cosmetic hygiene standards on the anti-acne cosmetic ingredients. Lauric acid, a natural free fatty acid, have been revealed to be strong antibacterial activity against *C. acnes* but less harmful than the synthetic antimicrobial chemicals.⁸⁶ Pornpattananangkul et al⁸⁷ developed liposomal lauric acids (LipoLA) by loading lauric acids into the lipid bilayer of liposomes. LipoLA not only well preserved the bactericidal property against *C. acnes* but also readily fused with bacterial membranes, which led to more effective killing of *C. acnes* by destroying bacterial membrane structures. Subsequently, topical application of LipoLA in a gel form onto the infectious skin sites eradicated *C. acnes* bacteria in vivo and did not induce acute skin toxicity. Curcumin, isolated from the spice turmeric, can inhibit the growth of *C. acnes* but is limited in use because of low aqueous solubility and poor bioavailability.⁸⁸ Microemulsions loading curcumin significantly improved its physicochemical properties and could efficiently accumulate in the skin, which caused the formation of curcumin reservoir to suppress *C. acnes* in vitro.⁸⁹ The observations highlight the potential of harnessing nanocarriers containing plant ingredients as an alternative treatment for acne vulgaris.

Recently, oxidative stress has been disclosed to play a vital role in acne formation, hinting that oxygen radical scavengers are potential anti-acne agents.⁹⁰ Fullerene, a spherical carbon molecule with strong radical sponge activity can penetrate deep into the epidermis without causing skin irritation.⁹¹ Inui et al⁹² topically applied fullerene gel onto the skin with acne lesions twice a day in an open trial. Erythematous papules and pustules significantly

decreased by suppressing sebum in the inflammatory response and by reducing *C. acnes* lipase activity and the water content of the skin significantly increased after treatment for 8 weeks, implicating that the fullerene gel may control acne vulgaris with skin care benefit.

Anti-Alopecia Efficacy Components Nanocarriers

Hair loss is associated with different diseases, nutritional deficiency, aging, hormone imbalance, and stress.⁹³ It is generally not a life-threatening event but potentially affects social interactions and the psychological wellbeing of patients.⁹⁴ The main approach of treatment of hair loss in the clinical setting is the topical application of anti-alopecia agents. Recently, new formulation productions have been developed through nanocarrier technology, which notably alleviates the side effects of direct application of anti-alopecia agents in the affected area.

Minoxidil, a pyridine-derivative, is widely used for the treatment of androgenic alopecia. Commercial products containing minoxidil are usually solutions with high percentage of ethyl alcohol and/or propylene glycol and are recommended as proper use in twice-daily applications. However, repeated applications of high ethyl alcohol and/or propylene glycol content products lead to severe adverse effects. Mura et al⁹⁵ showed alcohol-free liposomal formulations potential as minoxidil topical delivery in hair loss treatment by enhancing its skin penetration. Balakrishnan et al⁹⁶ indicated that niosomal formulations of minoxidil have a good potential for drug cutaneous targeting with regards to process variables. In another study, minoxidil-loading solid lipid nanoparticles suspensions have been shown as efficient as commercial solutions for skin penetration; and were non-corrosive while commercial solutions presented a corrosive potential.⁹⁷ These data suggested that nanocarriers would be a promising application for hair loss treatment. In addition, applications of the phytobioactive ingredients with anti-alopecia property into nanocarriers also have a good effect (Table 2).

Sunscreen Efficacy Components Nanocarriers

Sunscreen efficacy ingredients can prevent skin from damage by absorbing and reflecting ultraviolet light, thus reducing the occurrence of light linear disease and light aging.⁹⁸ Considering synthesized by chemical ultraviolet

absorbers, they generally have the disadvantages of large skin irritation and poor light stability. However, these challenges could be well solved by loading sunscreen efficacy components into nanocarriers.

Octyl methoxycinnamate is a widely used sunscreen characterized by potent ultraviolet-B absorbing properties but its applications are limited by photoinstability and potential skin permeation. Octyl methoxycinnamate in liposomes has a greater skin accumulation but a lower penetration into the deeper skin layers, which lead to a slightly better sun protection factor and more remains in the stratum corneum compared to a conventional formulation.⁹⁹ In another study, octyl methoxycinnamate was loaded into the pores of the mesoporous silicate MCM-41 and then entrapped there by plugging the pore openings. The MCM-41 inclusion product allows a remarkable improvement of sunscreen photostability, broader photoprotection range and negligible sunscreen release.¹⁰⁰ Besides, nanocapsules or transfersomes coating octyl methoxycinnamate has a similar effect.¹⁰¹ Benzophenone-3, a lipophilic chemical absorber absorbing both ultraviolet B and short ultraviolet A, is classified as a safe and effective, over-the-counter sunscreen agent by the Food and Drug Administration. It has a poor sunscreen effect at concentrations less than 5%, but can trigger photosensitivity in high dose and be absorbed by the skin leading to toxic side effects. Compared with w/o microemulsions containing benzophenone-3, the w/o microemulsions were more suitable for topical delivery of the sunscreen due to low transdermal fluxes and release rates.¹⁰² Strikingly, nanocarriers loading the sunscreen properties of herb such as safranal and similar derivatives could exert good sunscreen activity.⁵⁹

In addition to improving the properties of sunscreen ingredients, nanocarriers can also effectively improve the sunscreen efficiency. Compared with conventional sunscreen gel or emulsion formulations, the sunscreen formulation containing nanocapsules a better sunscreen effect. Sunscreen efficacy components can be quickly dispersed from the nanocapsules to the cuticle surface and the extremely high specific surface area of the nanocapsules makes it more effective in covering the skin against ultraviolet radiation.¹⁰³ Furthermore, certain nanocarriers such as solid lipid nanoparticles and titanium dioxide nanoparticles have the properties of reflecting and scattering ultraviolet rays and can act as a physical sunscreen agent, synergistic effect with the sunscreen efficacy components to enhance the sunscreen effect.¹⁰⁴

Multiple Functional Components Codelivery Nanocarriers

Skin problems and skin diseases are often not caused by a single factor. Mutual coordination or joint effect of multiple functional ingredients can play a better effect of sunscreen and skin care. 2-ethylhexyl trans-4-methoxycinnamate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate and bis-ethylhexyloxyphenol methoxyphenyl triazine are three molecular sunscreens, which can absorb different wavelengths of ultraviolet light but have the side effects in high dose. The solid lipid nanoparticles loading three molecular sunscreens improved their photostability and enhanced the sun protection factor values by more than twice in comparison with free samples. It also obtained a lower allergenic potential by using less than half of maximum admitted concentration imposed by International Agency of Food and Drug Administration regulations (10%).¹⁰⁵ The bioactive peptides such as antioxidative peptides, signal peptides and neurotransmitter inhibitor peptides can regulate many biological processes with relevance to skin aging but are different in the mechanism of action. The liposomes coating three bioactive peptides showed high encapsulation efficiency, high loading capacity and sustained release. Application of the nanoliposomes in face led to a remarkable reduction of the volume, area and area ratio of wrinkles, and an improvement of skin elasticity by reducing H₂O₂-induced oxidative stress damage, inhibiting catecholamine release and increasing their expression levels of type I collagen and hyaluronic acid.¹² In addition, the codelivery of multiple plant active ingredients has also attracted great attention (Table 2).

Intriguingly, certain inorganic nanoparticles such as fullerene-C₆₀ and gold nanoparticles have dual properties. In addition to being nanocarriers, they are regarded as special cosmetic efficacy components due to their antibacterial or antioxidant ability. Nanofiber face mask containing ascorbic acid, retinoic acid, collagen and gold nanoparticles presented a well anti-wrinkle property because of its high surface area- to-volume ratio enhancing the skin permeation of efficacy components.¹⁰⁶ In another study, LipoFullerene cream containing fullerene-C₆₀ dissolved in squalane remarkably enhanced the skin moisture and the repressive-wrinkle formation when compared with squalane blended cream (without fullerene-C₆₀).¹⁰⁷

Summary and Prospect

The application of nanocarrier technology in functional cosmetics not only improves the stability and solubility

of efficacy components but also overcomes the barrier effect of cuticle, which enables the active cosmetic ingredients to enter the target site of the skin and realize the functions of sustained release, controlled release and long-term release, thus solving various skin problems and skin diseases. Compared with conventional cosmetic preparations, the formulation and preparation process of nanocarriers are more complicated. The properties, dosage and proportion of each component in the formulation as well as the preparation process affect the surface charge, internal structure, interaction with efficacy components, stability and skin permeability of the nanocarriers. There are still many problems to be solved in the large-scale production and product application of some nanocarriers, such as Ostward ripening in the preparation of nanoemulsions and nanocrystals, drug leakage and material degradation of liposomes, and lipid crystallization and polycrystalline transformation inducing particle aggregation in lipid nanoparticles. Moreover, the nanocarriers are not the final cosmetic dosage form, but also needs to be further processed into appropriate cosmetic dosage form, such as cream, emulsion and gel. The addition of excipients required for these dosage forms increases the difficulty of quality control, and may cause problems such as nanocarrier particle size change and drug leakage, thus affecting its skincare efficacy. Therefore, the formulation optimization, quality research, preparation technology research and the development of special preparation equipment are important directions of research and development for the application of nanocarrier technology in the field of cosmetics.

The application of nanocarrier technology in the field of cosmetics presents a great prospect but also faces many challenges. Firstly, the biosafety and skin toxicity of nanocarriers in cosmetics should be paid more attention. For example, the immunogenicity of the polymer materials used to prepare nanocarriers should be concerned. Dendritic polymers rich in amino have a large amount of surface positive charge, which leads to potential cytotoxicity. The formation of microemulsions requires high concentrations of surfactants, which may irreversibly alter the stratum corneum structure for long-term application, resulting in skin irritation. In addition, with the application of inorganic nanomaterials (such as mesoporous silica nanoparticles, titanium dioxide nanoparticles, fullerenes and graphenes) in the fields of functional cosmetics, the absorption and accumulation of skin and hair follicles and metabolism and toxicology *in vivo* deserve attention.¹⁰⁸

Secondly, there are few reports on the distribution, sustained/controlled release behavior, metabolic pathways and products, and metabolic kinetics of nanocarriers in the skin. Therefore, it is necessary to carry out systematic and in-depth research on the skin toxicology and skin metabolic kinetics of nanocarriers used in functional cosmetics, and to understand their influencing factors and mechanism of action, which will provide a solid theoretical and experimental basis for the comprehensive application of nanotechnology in the field of functional cosmetics.

The application of nanocarrier technology in functional cosmetics is a new platform for dermal/transdermal drug delivery, which greatly promotes the development of dermal/transdermal drug delivery. With the breakthrough in preparation technology, quality control, promoting permeability mechanism and safety evaluation, it can be expected that there will be a new nanocarrier of functional cosmetics on the market in the future. In addition, while developing the nanocarrier technology for functional cosmetics, it is necessary to improve the construction of regulations and establish a standardized evaluation system for effectiveness and safety, which promotes the healthy development of nanocarrier technology in the field of cosmetics.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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