Review

Appl. Cosmetic Sci. & Tech. 1 (1): 1–20

Percutaneous Absorption of Cosmetics and their Ingredients

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Percutaneous absorption and skin permeation of cosmetics and their ingredients are reviewed. In this field, the definitions of related terms are often vague, and researchers sometimes use different terms. Thus, the definitions are first clarified for these terms. Next, examples of active ingredients in current medicated cosmetics in Japan are presented, for which percutaneous absorption and skin penetration are essential. Then, the skin barrier properties, especially in the stratum corneum, are summarized, and the skin penetration and permeation behaviors are explained for chemical compounds containing cosmetic ingredients. The skin permeation kinetics are also mathematically described, and factors affecting these kinetics are listed, such as lipophilicity, molecular weight, and thermodynamic activity of chemical compounds. After that, *in vitro* and *in vivo* methods for measuring skin permeability are exemplified, and finally, the future image of cosmetics and quasi-pharmaceutical products is summarized, including reader's expectations.

Key words: percutaneous absorption, skin permeation, skin permeation kinetics, cosmetics, quasi-pharmaceutical products, medicated cosmetics, future cosmetics, stratum corneum

1. Introduction

Chemical compounds that come into contact with the skin can be broadly classified into those used intentionally and those used non-intentionally. The former include topical medicines, transdermal drug delivery systems (TDDS), quasi-pharmaceutical products, makeup cosmetics, functional cosmetics, fragrances, hair cosmetics, soaps, and bath salts, together with clothing fibers, adhesive bandage tapes, and film dressings. The latter include household chemicals such as insecticides, plasticizers in building materials, environmental chemicals containing industrial emissions, environmental hormones, or endocrine disruptors, and radioactive materials, together with pollen and volcanic ashes. Thus, a wide variety of chemical compounds come into contact with the skin. These compounds are summarized in Table 1.[1)]

Do these chemical compounds permeate the skin? We expect intentionally applied pharmaceuticals to permeate the skin. Active drugs in topical formulations and TDDS must penetrate into and permeate through the skin. Do functional cosmetics or cosmeceuticals designed with active ingredients, for example, to adjust skin tone, also penetrate the skin? We intentionally apply soaps and body shampoos to the skin. Are these active ingredients designed to penetrate? Are there any skin-exposed chemicals that are permeable through the skin? Are they safe if they permeate through the skin?

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DOI: 10.69336/acst.Inv-2024-01

Table 1 Classification of chemical compounds applied or exposed to skin.[1)]

Chemical compound	Application	Application period	Percutaneous absorption	Remarks
Topical medicines	Intentional	Leave on	Skin penetration into skin tissues and surrounding sites	
TDDS	Intentional	Leave on	Percutaneous absorption into systemic circulation	
Functional cosmetics	Intentional	Leave on	Distribution to skin surface	Skin tone adjustment cosmetics, etc.
Make-up cosmetics	Intentional	Leave on	No expectation of skin permeation	
Fundamental cosmetics	Intentional	Leave on	No expectation of skin permeation	
Fragrances	Intentional	Leave on	No expectation of skin permeation	Potential for pulmonary absorption
Hair cosmetics	Intentional	Rinse off from skin	No expectation of skin permeation	
Soaps and bath salts	Intentional	Rinse off	No expectation of skin permeation	
Household chemicals (insecticides, building plasticizers, etc.)	Non-intentional	Exposure	No expectation of skin permeation	Potential for non-intentional pulmonary absorption
Environmental chemicals (chemicals discharged from industries, including environmental hormones)	Non-intentional	Exposure	No expectation of skin permeation	Potential for non-intentional pulmonary absorption
Environmental chemicals (pollen, volcanic ash, etc.)	Non-intentional	Exposure	No expectation of skin permeation	Potential for non-intentional pulmonary absorption
Radioactive materials	Non-intentional	Exposure	No expectation of skin permeation	Potential for non-intentional oral and pulmonary absorption

Are active materials in pesticides against cockroaches and mosquitoes safe for human beings? How do we understand the safety of topically exposed chemical compounds?

Generally, chemical compounds applied or exposed to the skin can be distinguished as leave-on and rinse-off materials, as shown in Table 1. Topical medicines, TDDS, and cosmetics are left on the skin usually for a few to several hours. On the other hand, soaps and body soaps are generally rinsed off. Thus, intentionally applied chemical compounds on the skin can be easily classified into leave-on and rinse-off materials. However, it is somewhat difficult to distinguish between these categories for non-intentionally exposed chemical compounds on the skin. Although we should avoid exposure to environmental chemicals, our skin may still come into contact with such compounds, and they may remain on our skin for extended periods.

In this paper, consideration is given to understanding or realizing the percutaneous or transdermal absorption of various chemical compounds, particularly cosmetics and cosmetic ingredients.

2. Terminology and Definitions

Before considering the percutaneous or transdermal absorption of chemical compounds such as pharmaceuticals and cosmetics, we first clarify and define the terminology commonly used in these fields.

2.1. Percutaneous absorption, skin permeation, and related terms

First, terms such as percutaneous absorption, skin permeation, and skin penetration (Fig. 1) are explained by referring to a manuscript by Basketter et al.[2)] The technical terms “permeability and permeability coefficient” and “diffusion,

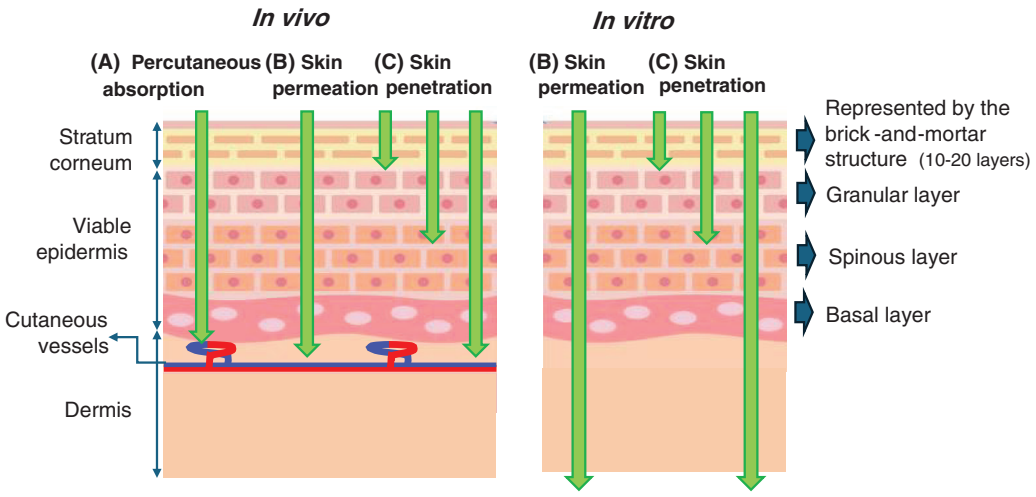

Fig. 1 Schematic illustration explaining percutaneous absorption, skin permeation, and skin penetration. The barrier function of the SC is represented by the brick-and-mortar system. (A), (B), and (C) show percutaneous absorption, skin permeation, and skin penetration, respectively.

diffusivity and diffusion coefficient in skin" are added, as they are closely related to percutaneous absorption and skin permeation.

2.1.1. Percutaneous absorption (transdermal absorption, dermal absorption, and skin absorption)

In biopharmaceuticals and pharmacokinetics, the *absorption* of a chemical compound is defined as the entry of a chemical compound into the systemic circulation (mainly the systemic blood circulation). Thus, the term *percutaneous absorption* means that a chemical compound on the skin passes through the skin barrier (both the stratum corneum and the viable epidermis below the stratum corneum) and enters the capillary blood vessels in the dermis. Therefore, this technical term should only be used in *in vivo* (in humans or animals) or *in situ* (where living tissues and cells naturally exist) studies (Fig. 1A). Technical terms such as *transdermal absorption*, *dermal absorption*, and *skin absorption* have the same meaning as percutaneous absorption. The transfer phenomenon of a chemical compound from the outside of the skin into the skin is sometimes called percutaneous absorption, transdermal absorption, dermal absorption, or skin absorption. However, considering the definition of *absorption* mentioned above, this should be changed to *skin permeation* or *skin penetration* as shown below. In the 1980s, there was a discussion that *epidermal absorption* should be used more accurately instead of *dermal absorption*. This is correct, but dermal absorption has been commonly used in these fields.

2.1.2. Skin permeation

The term skin permeation of a chemical compound is defined as the transfer of a chemical compound from the skin surface through the entire skin thickness to the back side of the skin (Fig. 1B). Because it does not contain the word *absorption*, the term can be used for *in vitro* studies as well as *in vivo* or *in situ* studies.

2.1.3. Skin penetration

As shown in Fig. 1C, *skin penetration* of a chemical compound does not depend on the depth of penetration into the skin. The term *penetration* can mean to *go through*, but it is better to use the term, *permeation* for *piercing* or *passing through*. *Penetration* can also mean to *seep in* or *into*. Therefore, the term *skin penetration* can be used not only for *in vivo* or *in situ* studies but also for *in vitro* studies. For chemicals that enhance the skin penetration of a chemical compound, it is better to call them *skin penetration enhancers* rather than *skin permeation enhancers*.

2.1.4. Permeability and permeability coefficient

Permeability is a term that describes the nature of permeation. Skin permeability is the ability to allow chemical compounds to pass through the skin. The *permeability coefficient* is an evaluation index of permeability. The permeability coefficient for the skin permeation of a chemical is an essential index to show the skin permeation rate of the chemicals. Its dimension is length/time, and it is expressed in cm/s or cm/h for skin penetration. On the other hand, the permeation rate of a chemical through the skin is usually expressed by $\mu g/cm^2/h$ or $mg/cm^2/h$. One must distinguish the permeation rate from the permeability coefficient. In this paper, the symbol for the permeability coefficient is denoted as *P*. In pharmaceutical sciences, the term *clearance* expresses the excretion and metabolic capacity of the kidney and

liver, respectively, and is described in mL/s, cm^3/s, mL/h, or cm^3/h. Similarly, the permeation clearance of a chemical compound can also be defined as the product of *P* and skin area.

2.1.5. Diffusion, diffusivity, and diffusion coefficient in skin

The *diffusion* of a chemical compound in the skin spreads the compound throughout the skin. The permeation rate of a chemical compound across the skin is usually expressed by its *diffusion coefficient* or diffusivity in the skin or skin barrier times the negative value of its concentration gradient in the barrier. The diffusion coefficient or diffusivity can be defined by Fick's law of diffusion (details below). The dimension of the diffusion coefficient is length^2/time, and it is expressed in cm^2/s or cm^2/h. Its symbol is denoted as *D*.

2.2. Terms to apply medicines and cosmetics to the skin

Next, the methods of administering medicines and cosmetics to the skin and the formulation terminology are explained.

2.2.1. Transdermal administration (skin administration)

Transdermal administration refers to a method where active ingredients are delivered across the skin for systemic distribution. Formulation examples include patches or tapes used for medicine delivery. *Skin administration* is also used in the same sense. As mentioned above, the more term is *trans-epidermal administration*, but it is commonly referred to as *transdermal administration*.

2.2.2. Topical application (skin application)

Topical application is done on the body surfaces such as the skin for medications or cosmetics. *Skin application* is also used in a similar sense. It can be done by liquids, semisolids, or gases using several formulations like lotions, gels, creams, ointments, and sprays. They can also be applied using plasters, tapes, masks, and cataplasms. Recently, microneedle patches (patches with a microneedle array) have been developed both for transdermal administration and topical application.

2.2.3. TDDS or transdermal therapeutic systems (TTS)

TDDS or *TTS* are dosage forms developed to deliver medications directly through the skin into the bloodstream. The term TTS was used in the late 1970s or early 1980s, but the term TDDS became mainstream around 2000. Due to their ease of administration, excellent patient convenience, and adherence, TDDS (TTS) offer an advantageous alternative to oral drug delivery systems like tablets, capsules, and syrups. They find applications in pharmaceuticals, skincare products, and cosmetics. Their formulations are mainly tapes and patches.

2.3. Pharmaceuticals, quasi-pharmaceutical products, and cosmetics

Furthermore, the terms used to classify cosmetics, functional cosmetics, and related compounds are explained. In Japan, general skin care products are classified as either *pharmaceuticals*, *quasi-pharmaceutical products*, or *cosmetics* according to the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as the Pharmaceuticals and Medical Devices Act for brevity),[3] and the range of effects and efficacy is clearly divided.

2.3.1. Pharmaceuticals

Pharmaceuticals are medicines intended to treat illnesses or diseases. They contain active drugs that are approved by the Ministry of Health, Labor and Welfare, Japan. These include *medical prescription drugs* that require a doctor's prescription and non-prescription drugs, or the so-called over-the-counter drugs, which can be purchased at drugstores. For treatments not covered by health insurance, a prescription may also be given for cosmetic purposes.

2.3.2. Quasi-pharmaceutical products

Quasi-pharmaceutical products contain effective ingredients approved by the Ministry of Health, Labor and Welfare, Japan, at a certain concentration. They are made for prevention and hygiene rather than treatment. These products contain effective active ingredients against rough skin, acne, blemishes, freckles caused by sunburn, and skin hygiene. In addition, the term *medicinal* is often used interchangeably with *quasi-drugs*.

2.3.3. Cosmetics

Cosmetics have milder efficacy and effects than quasi-pharmaceutical products and are used for purposes such as cleaning, beautifying, increasing attractiveness, altering appearance, or keeping the skin or hair in good condition. Cosmetics include makeup products, skincare products, and haircare products (i.e., fundamental cosmetics). The main purpose of cosmetics is to improve appearance and provide basic moisturizing and protective functions for the skin. Under the Pharmaceuticals and Medical Devices Act in Japan, these products are not permitted to claim specific therapeutic or improving effects, such as alleviating rough and chapped skin, preventing acne, or sterilizing the skin.

Table 2 Existing medicated and functional cosmetics in Japan.

Category	Types of cosmetics
Medicated cosmetics: can claim efficacy within a defined category	Skin-tone adjustment cosmetics (old term: whitening cosmetics: prevents pigmentation caused by sunburn)
	Cosmetics to prevent rough skin
	Hair growth and nourishing products
	Cosmetics for acne
	Antiperspirant cosmetics
Functional cosmetics	Sunscreen
	Anti-wrinkle and anti-sagging cosmetics
	Whitening cosmetics expected to improve age spots
	Pore care cosmetics
	Slimming cosmetics

2.3.4. Medicated cosmetics

Among quasi-pharmaceutical products, there are *medicated cosmetics* that are similar to cosmetics. Eight types of medicated cosmetics are identified: shampoo, conditioner, lotion, cream/lotion, shaving cream, sunscreen, face mask, and soap. Medicated cosmetics contain active ingredients in addition to cosmetic ingredients, and therefore have both efficacy and effects derived from the cosmetic and active ingredients. Medicated cosmetics include skin-tone adjustment cosmetics that prevent pigmentation caused by sunburn, cosmetics to prevent rough skin, hair growth and nourishing agents, cosmetics for acne, and antiperspirant cosmetics, as listed above among quasi-pharmaceutical products. Table 2 summarizes the types of medicated cosmetics. They usually claim skin-tone adjustment, rough skin, hair growth and nourishing products, acne, and antiperspirants.

2.3.5. Functional cosmetics

Functional cosmetics are cosmetics that claim to provide specific beauty effects or functions. They generally contain ingredients that suggest specific efficacy, but the classification of functional cosmetics is not officially recognized under the Pharmaceuticals and Medical Devices Act. The effects are not as specific as those of quasi-pharmaceutical products, and therapeutic effects like those of pharmaceuticals cannot be expected. Functional cosmetics include sunscreens, cosmetics to prevent wrinkles and sagging, skin-tone adjustment cosmetics that are expected to improve existing age spots, pore care cosmetics, and slimming cosmetics. Cosmetics with moisturizing functions may also be called functional cosmetics. Table 3 summarizes the functional cosmetics as well. Sunscreen, anti-wrinkle and anti-sagging cosmetics, improving cosmetics against age spots, pore care cosmetics, and slimming cosmetics are typical examples of functional cosmetics.

2.3.6. Doctor's cosmetics

Doctor's cosmetics are only sold at medical institutions, and one must visit a medical institution to purchase them. Doctor's cosmetics are not officially recognized under the Pharmaceuticals and Medical Devices Act.

It is important that these terms are clearly defined, and these defined terms should be used for scientific discussions.

3. Active Ingredients in Medicated Cosmetics

Recently, "well-being" has been attracting attention. The World Health Organization states that "well-being is a positive state experienced by individuals and societies. Similar to health, it is a resource for daily life and is determined by social, economic, and environmental conditions".[4] Cosmetics and skincare are linked to a sense of happiness and well-being. Therefore, they will become even more important in the future, and it is necessary to increase the effectiveness and functions that can be claimed for the above-mentioned medicated cosmetics and functional cosmetics.

Regarding active ingredients in medicated cosmetics, a notice was issued by the Pharmaceuticals and Food Safety Bureau of the Ministry of Health, Labour and Welfare of Japan on December 25, 2008. However, a new notice was subsequently issued regarding medicated shampoos and conditioners, and furthermore, the section on "medicated soaps (including facial cleansers)" in the 2008 notice was deleted.

Table 3 summarizes active ingredients in medicated cosmetics (quasi-pharmaceutical products) used in the Japanese market. Medicated cosmetics have roughly 6 categories: anti-inflammatory, blood-circulation promotion and metabolic

Table 3 Active ingredients in medicated cosmetics (quasi-drugs).

Chemical name	Comments (containing molecular formula and weight)
1. Anti-inflammatory	
Glycyrrhizic acid dipotassium salt	Glycyrrhizic acid: $C_{42}H_{62}O_{16}$ = **899.12**, used in many cosmetic formulations
Stearyl glycyrrhetinate	$C_{48}H_{82}O_4$ = **723.18**, used in many cosmetic formulations
Allantoin	$C_4H_6N_4O_3$ = 158.12, used in many cosmetic formulations
2. Blood circulation promotion and metabolic activation	
dl-*α*-Tocopherol acetate	$C_{31}H_{52}O_3$ = 472.75, used in many cosmetic formulations
Vitamin A oil	*β*-Carotene*:* $C_{40}H_{56}$ = **536.89***,* used in creams, etc.
Retinol palmitate	$C_{36}H_{60}O_2$ = **524.86**, used in creams, etc.
dl-Camphor	$C_{10}H_{16}O$ = 152.23, used in lotions
3. Skin tone adjustment or whitening	
Placenta extract	Inhibits melanin production and promotes melanin excretion, highly recognized
Ascorbic acid and its derivatives	Ascorbic acid: $C_6H_8O_6$ = 176.12, inhibition of tyrosinase activity and reduction of melanin, highly recognized
Kojic acid	$C_6H_6O_4$ = 142.11, inhibition of tyrosinase activity and TRP-2 activity
Arbutin	$C_{12}H_{16}O_7$ = 272.25, inhibition of tyrosinase activity
4-*n*-Butylresorcinol (Rucinol)	$C_{10}H_{14}O_2$ = 166.22, inhibition of tyrosinase activity and TRP-1 activity
m-Tranexamic acid and cetyl tranexamate HCl	*m*-Tranexamic acid: $C_8H_{15}NO_2$ = 157.21, inhibition of plasmin production
4-Methoxysalicylic acid potassium salt	4-Methoxysalicylic acid: $C_8H_8O_4$ = 168.15, inhibition of tyrosinase activity
Adenosine monophosphate disodium	$C_{10}H_{12}N_5Na_2O_7P$ = 391.19, promotes melanin excretion (promotes cell turnover)
5,5′-Dipropyl-biphenyl-2,2′-diol (Magnolignan)	$C_{18}H_{22}O_2$ = 270.37, inhibition of tyrosinase maturation
Nicotinamide	$C_6H_6N_2O$ = 122.13, has anti-wrinkle effects too
4. Antibacterial and anti-dandruff	
Isopropyl methylphenol	$C_{10}H_{14}O$ = 150.22
Benzalkonium chloride	$[RN(CH_3)_2CH_2C_6H_5]Cl$
Eucalyptus oil, peppermint oil	
Hinokitiol	$C_{10}H_{12}O_2$ = 164.20
Miconazole nitrate	$C_{18}H_{14}Cl_4N_2O{\cdot}HNO_3$ = 479.14
Pyrithione zinc	$C_{10}H_8N_2O_2S_2Zn$ = 317.70
5. Stratum corneum peeling	
Salicylic acid	$C_9H_8O_4$ = 180.16, used in many cosmetic formulations
Sulfur	S = 32.06, used in many cosmetic formulations
Urea	CH_4N_2O = 60.06
6. Anti-wrinkle	
Retinol	$C_8H_9NO_2$ = 151.17, promotes skin turnover and hyaluronic acid production, increasing collagen density in the dermis
NEI-L1: neutrophil elastase inhibitor-license 1	$C_{26}H_{32}F_3N_4NaO_7$ = **592.54**, inhibits the activity of neutrophil elastase to improve wrinkles

Molecular weights more than 500 Daltons are shown in the bold numbers.

activation, skin tone adjustment or whitening, antibacterial and anti-dandruff, stratum corneum peeling, and anti-wrinkle. Most of the active ingredients have a molecular weight of less than 500 Daltons, as shown in this table. The relationship between the skin permeability and molecular weight of chemical compounds is explained later.

4. Skin and Skin Barrier[5)]

The skin is composed of the epidermis and the dermis, as shown in Fig. 1. Subcutaneous tissues are located under the dermis. The basal layer is at the very bottom of the epidermis. Keratinocytes in the basal layer divide to form new cell layers, such as the spinous layer and granular layer, which move up 1 layer at a time, eventually reaching the uppermost layer of the epidermis, the stratum corneum in about 2 weeks, where the keratinocytes become dead cells called corneocytes. After that, it takes another 2 weeks to form the complete stratum corneum.

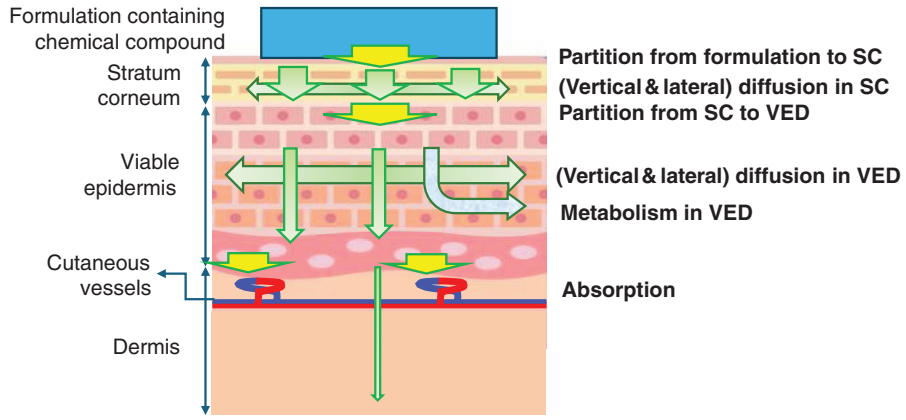

Fig. 2 Schematic illustration explaining the disposition of chemical compounds in the SC and VED. The term distribution can be used interchangeably with partition. The width of the arrow indicates the amount of chemical compound. Although adsorption or retention of chemicals may occur in the stratum corneum, these processes are not depicted in this figure.

The viable epidermis, from the basal layer to the granular cell layer, has metabolic activity against several chemicals. The dermis contains the locus of capillary blood vessels, sensory nerves, and lymphatics in the skin, and provides physiological support for the epidermis. The skin also includes appendages, such as hair follicles, sweat glands, and sebaceous glands.

The functions of the skin, especially the stratum corneum, include protecting against the entry of exogenous chemical substances and pathogens, and preventing the severe loss of endogenous compounds like water and essential lipids and amino acids. The skin also regulates our homeostasis, such as body temperature, and repairs harsh changes in the dermatological environment. Thanks to the stratum corneum, we can survive in this inorganic air. If it takes 20 to 30 min for a chemical compound to permeate the stratum corneum, it will pass through the living epidermis and dermis in just a few seconds. In this way, the stratum corneum acts as the largest barrier. The stratum corneum varies in thickness from approximately 10 to several 100 μm, depending on the region of the body. It is composed of layers of dead, flattened keratinocytes surrounded by a lipid matrix, which together act as a brick-and-mortar system that is difficult to penetrate.

5. Permeation of Chemical Compounds through Skin

5.1. Percutaneous absorption progressed by partitioning and diffusion[1)]

When a chemical compound comes into contact with the skin, it is distributed from the vehicle in which it is dissolved (such as an ointment or tapes in the case of pharmaceutical preparations, or a lotion or cream in the case of cosmetics) into the stratum corneum, and then diffuses through the stratum corneum. As shown in Section 4, the diffusion rate of chemical compounds in the stratum corneum is the slowest in the entire process of percutaneous absorption, and this is the rate-limiting step for the overall skin permeation. The chemical compound is then distributed and diffused from the stratum corneum into the living epidermis (epidermis excluding the stratum corneum) to diffuse into the dermis. However, since there are capillaries in the upper part of the dermis, most of the chemical compounds that have penetrated up to this point are absorbed into the blood. In addition, some of the chemical compounds that have not been absorbed into the blood penetrate the subcutaneous tissue. Each of these processes of percutaneous absorption is summarized in Fig. 2. It has been pointed out that some compounds may bind to components in the stratum corneum and remain in the skin, although not shown in Fig. 2.

Figure 3A shows a typical concentration *vs*. distance profile of a chemical compound in the stratum corneum and viable epidermis (except for the stratum corneum) at a steady state after application to the skin.[6)] A model in which the skin barrier is divided into the stratum corneum, viable epidermis, and dermis is called the 2-layered skin model. In addition, the viable epidermis and dermis (VED) have metabolic activity, and some ratio of compounds may be metabolized in the viable epidermis and dermis.

5.2. Skin Permeation pathway and skin permeation models[5)]

The skin surface has pores, sweat glands, and other openings, where some chemical compounds may easily penetrate. However, these only account for 0.1% of the surface area of the entire skin (approximately 99.9% is the

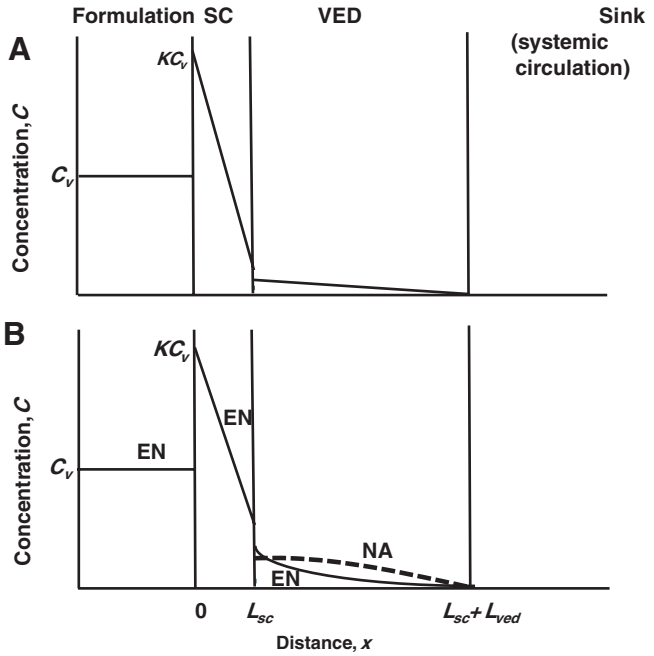

Fig. 3 Schematic concentration *vs*. distance profile of a chemical compound (A) and EN and NA (B) in the SC and VED.[6,20] The skin barrier can be expressed by this 2-layered model. Steady-state profiles are shown in (A) and (B). EN is metabolized to NA by esterase in the VED.

Table 4 Permeation pathway of chemical compounds through the skin barrier.[5]

Permeation pathway		Comments
Stratum corneum pathway	Transcellular pathway	Passing through corneocytes
	Intercellular pathway or paracellular pathway	Passing through the intercellular lipid
		Primary pathway for most chemical compounds
		Follow the 500 Daltons rule[10]
Appendicular pathway	Hair follicles	Penetration of polymers and nanomaterials has been confirmed
		Primary pathway when applied iontophoresis
		High-molecular compounds may penetrate
	Sweat glands	Primary pathway when applied iontophoresis
	Sebaceous glands	The same opening sites as hair follicles

stratum corneum), so the main route of penetration is through the stratum corneum. Furthermore, the stratum corneum contains corneocytes and intercellular lipids (phospholipids that fill the spaces between corneocytes in the stratum corneum), and the main route of penetration of chemicals applied to the skin is the intercellular pathway (or paracellular pathway). Therefore, by perturbing these intercellular lipids, chemical compounds can more easily penetrate the skin. These penetration pathways of chemical compounds into the skin are summarized in Table 4.

The skin permeation pathways shown in Table 4 can be simply expressed by a parallel skin permeation pathway model.[7] In other words, the biggest skin barrier, the stratum corneum, has hydrophilic and lipophilic domains, and water-soluble chemicals can be considered to permeate mainly through the hydrophilic domains, while lipid-soluble chemicals can permeate mainly through the lipophilic domains. Using this parallel permeation pathway model, the permeability coefficient, P_{sc}, of a chemical through the stratum corneum becomes:

$$P_{sc} = P_{lip} + P_{aq} \tag{1}$$

where P_{lip} and P_{aq} are permeability coefficients across the lipophilic domain and aqueous domain, respectively.

Furthermore, as shown in Fig. 3, the skin is represented as a 2-layered model consisting of the stratum corneum and the VED below it due to differences in barrier function. The reciprocal of the permeability coefficient of the entire skin,

$1/P_{tot}$, is the sum of the reciprocal of the permeability coefficient of the stratum corneum, $1/P_{sc}$, and that of the viable epidermis and dermis, $1/P_{ved}$, as follows:

$$\frac{1}{P_{tot}} = \frac{1}{P_{sc}} + \frac{1}{P_{ved}} \tag{2}$$

Combining Eqs. (1) and (2), we finally obtain the following equation:

$$\frac{1}{P_{tot}} = \frac{1}{P_{lip} + P_{aq}} + \frac{1}{P_{ved}} \tag{3}$$

6. Skin Permeation and Skin Concentration of Chemical Compounds

6.1. Kinetics showing skin permeation and skin concentration of chemical compounds[1)]

The kinetic equations for skin permeation rate and skin concentration change depending on how the skin barrier is considered. In Section 5.2, the parallel permeation pathway model and the 2-layered model were presented as skin barrier models. However, to allow readers to understand intuitively, analysis using the simplest single permeation and single-layer model, expressed only by the stratum corneum barrier, is presented.

In general, diffusion phenomena of chemical compounds in the skin can be explained by Fick's 1st and 2nd laws of diffusion as follows:

$$J = -D\frac{dC}{dx} \tag{4}$$

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{5}$$

where J, C, and D are skin permeation rate (per unit application or exposed skin area), concentration, and diffusion coefficient, respectively, of the chemical compound in the skin barrier (stratum corneum), and t and x show time after skin application or exposure and depth of the stratum corneum from the skin surface, respectively. The 1st law can be used when $C(x)$ is not affected by t, and J is proportional to the concentration gradient of the chemical compound in the stratum corneum, dC/dx. The 2nd law can be used when $C(x)$ changes with t, and indicates that C is determined by t and x. When analyzing this partial differential equation, initial conditions (i.c.) and boundary conditions (b.c.) are required. Here, i.c. and b.c. are shown for the so-called infinite dose system, where a sufficient amount of chemical compound is present on the skin and the skin concentration does not decrease

$$\begin{array}{lll} \text{(i.c.)} & C = 0 & \text{at } t = 0 \\ \text{(b.c.)} & C = KC_v & \text{at } x = 0 \\ & C = 0 & \text{at } x = L_{sc} \end{array} \tag{6}$$

where K, C_v, and L_{sc} are the partition coefficient of the chemical compound from vehicle to stratum corneum, i.c. of chemical compound in the vehicle, and thickness of the stratum corneum, respectively. Skin permeation rate, J, and cumulative amount of skin permeation, Q, can be determined as a function of time, t, using Eqs. (6)–(8) as follows:

$$J = \frac{dQ}{dt} = \frac{KC_v D}{L_{sc}}\left[1 + 2\sum_{n=1}^{\infty}(-1)^n \exp\left(-\frac{D}{{L_{sc}}^2}n^2\pi^2 t\right)\right] \tag{7}$$

$$Q = KL_{sc}C_v\left[\frac{D}{{L_{sc}}^2}t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp\left(-\frac{D}{{L_{sc}}^2}n^2\pi^2 t\right)\right] \tag{8}$$

Bold lines in Figs. 4A and 4B shows the time course of J and Q, respectively.[8)] Furthermore, the concentration and amount of the chemical compound in the skin barrier, stratum corneum per unit area, C and A, are expressed as functions of time, t, and depth of the stratum corneum, x, as follows:

$$C = KC_v\left[\left(1 - \frac{x}{L_{sc}}\right) - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\left(\frac{n\pi x}{L_{sc}}\right)\exp\left(-\frac{D}{{L_{sc}}^2}n^2\pi^2 t\right)\right] \tag{9}$$

$$A = KC_v L_{sc}\left[\frac{1}{2} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp\left(-\frac{D}{{L_{sc}}^2}n^2\pi^2 t\right)\right] \tag{10}$$

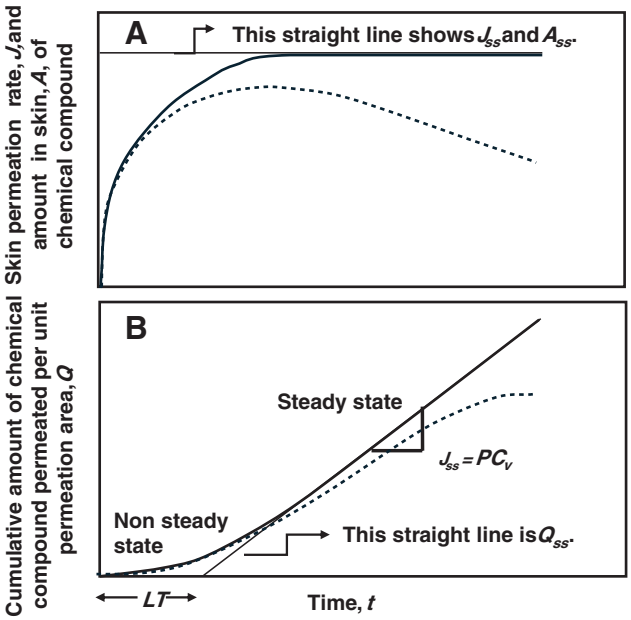

Fig. 4 Schematic diagram of time courses of Q, J, and A of a chemical compound.[1)] Refer to the equations for J, Q, A, J_{ss}, Q_{ss}, A_{ss}, and LT in Eqs. (7), (8), (10), (7'), (8'), (10'), and (11), respectively. Bold and dotted lines represent infinite and finite dose systems, respectively. The vertical and horizontal axes in (A) and (B) show relative values.

As shown in Eqs. (7) and (10), the time course of A and J show similar shapes. The time course of A is also represented by the bold line in Fig. 4A. When a sufficient amount of chemical compound is applied or exposed, the values of J, Q, C, and A quickly reach their steady-state values. These steady-state values, abbreviated as J_{ss}, Q_{ss}, C_{ss}, and A_{ss} are expressed as follows:

$$J_{ss} = \left(\frac{dQ}{dt}\right)_{ss} = \frac{KC_vD}{L_{sc}} = PC_v \tag{7'}$$

$$Q_{ss} = \frac{KC_vD}{L_{sc}}\left(t - \frac{L^2}{6D}\right) \tag{8'}$$

$$C_{ss} = KC_v\left(1 - \frac{x}{L_{sc}}\right) \tag{9'}$$

$$A_{ss} = \frac{KC_vL_{sc}}{2} \tag{10'}$$

Lag time (LT) calculated by extrapolating the $Q - t$ profile onto the time axis, as shown in Fig. 4B. In addition, the permeability coefficient, P, is obtained by K, D, and L_{sc} as follows:

$$LT = \frac{{L_{sc}}^2}{6D} \tag{11}$$

$$P = \frac{KD}{L_{sc}} \tag{12}$$

The LT is usually about 30 min to 1 h for chemical compounds with molecular weights of 500 Daltons or less. When a chemical solution is applied to the skin, the skin swells as the solvent penetrates it. Such changes in the skin over time can result in LTs higher than those obtained by diffusion of the chemical compound alone. Therefore, when measuring the skin permeation of a chemical compound from aqueous solution, the solvent should be applied to the skin to swell it, and the water should be removed before applying the chemical solution. The equations (J, Q, J_{ss}, and Q_{ss}) related to the skin permeation rate and amount in the single-layered model shown here can also be used to analyze the 2-layered model using the same equations; however, D and L_{sc} are adjusted values rather than actual values.

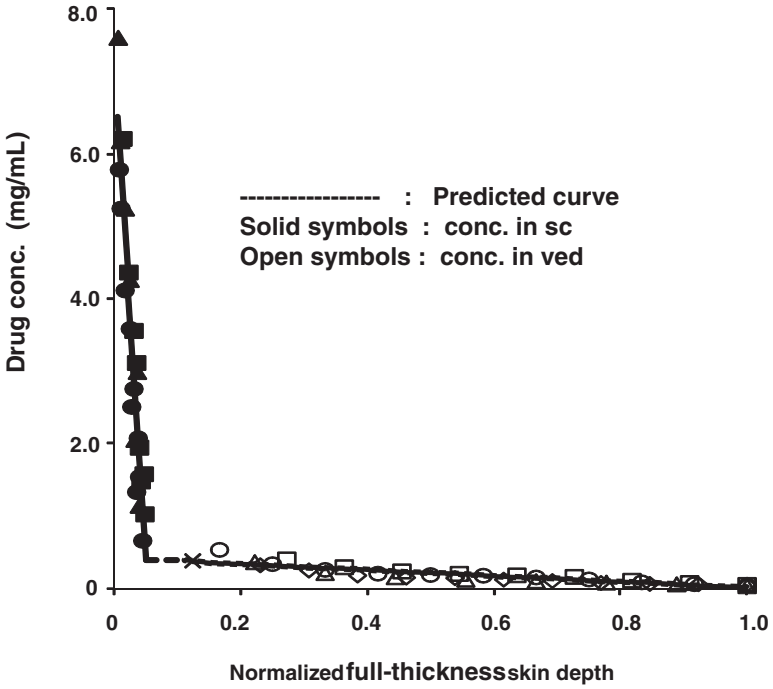

Fig. 5 Estimation of skin concentrations of topically applied lidocaine at each depth profile.[9)]

6.2. Differences in the rate (amount) of drug absorption (skin permeation) and skin concentration

As is clear from Eqs. (7), (8), (7'), and (8'), the skin permeation rate and amount of a chemical compound increase with an increase in the partition coefficient, K, from the vehicle to the skin (stratum corneum), and the diffusion coefficient, D, in the skin (stratum corneum). On the other hand, as shown in Eq. (9), the chemical concentration in the stratum corneum increases with an increase in K, but it does not change regardless of whether D is high or low. In other words, it is important to recognize that the skin permeation rate and amount are related to the $K{\cdot}D$ product, while the concentration in the skin (stratum corneum) is determined only by K.

We investigated whether the calculated values of the lidocaine concentration at each skin depth using Fick's 2nd law of diffusion matched the observed values.[9)] Each stratum corneum layer was tape-stripped, the thickness was determined, and the amount of lidocaine was measured for each tape. Then, the VED were sliced using a dermatome, and the amount of lidocaine was also measured. The results are shown in Fig. 5. A calculated line was first drawn in the figure. Then, the observed data were plotted. As a result, the observed values were exactly on the calculated line. In other words, the calculated values of the lidocaine concentration in the stratum corneum and the VED using Fick's 2nd law of diffusion matched extremely well with the observed values. In addition, it was clear the lidocaine concentration gradient in the stratum corneum (closed symbols in Fig. 5) was much greater than that in the VED (open symbols in Fig. 5).

7. Various Factors Affecting Skin Permeation of Chemical Compounds

7.1. Effect of lipophilicity or hydrophilicity and molecular weight of chemical compounds on their skin permeation coefficients

The important factors affecting the skin permeability coefficient of a chemical compound are its lipophilicity and molecular weight. First, the effect of a chemical compound's lipophilicity on skin permeability is shown. Figures 6A and 6B show the relationship between the logarithm of the permeability coefficient of a chemical compound through human and hairless rat skin, log P_{tot} (units of P_{tot}: cm/s), and the logarithm of the skin permeation rate, log J (units of J: mg/h/cm^2), as well as the logarithm of the n-octanol/water partition coefficient, log K_{ow}. A higher K_{ow} indicates higher lipophilicity. Figure 6A also shows experimental data for human skin permeability (symbol: open circle) and hairless rat skin permeability (symbol: closed circle). Note that all data shown here are for low-molecular-weight chemicals with a molecular weight of 500 Daltons or less, and water was used as the vehicle.[7)]

In a zone of log K_{ow} <− 1 (Zone 1), human and hairless rat skin showed similar log P_{tot} values despite different K_{ow} values. This is because water, the solvent, penetrates the skin, and chemical compounds dissolved in water penetrate at

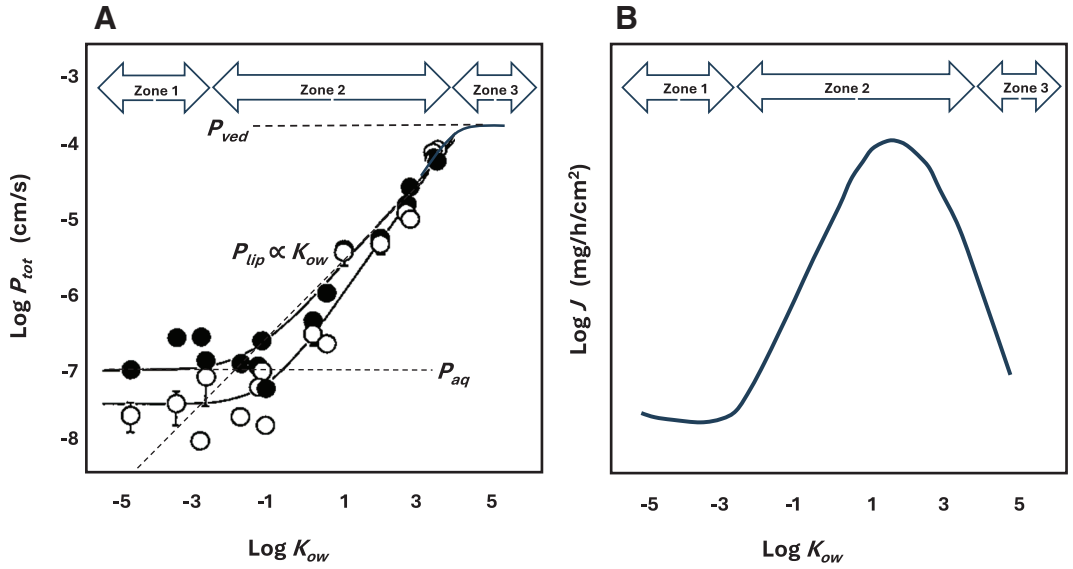

Fig. 6 Schematic diagram of relations between log P_{tot} *vs*. log K_{ow} (A) and log J *vs*. log K_{ow} (B) of chemical compounds with a molecular weight less than 500 Daltons.[7] Symbols in (A): ○, human skin; ●, hairless rat skin. P_{tot}, permeability coefficient through whole skin; J, skin permeation rate; K_{ow}, partition coefficient of the chemical compound between *n*-octanol and water; P_{ved}, permeability coefficient through viable epidermis and dermis; P_{lip}, permeability coefficient through the lipophilic pathway in the stratum corneum; P_{aq}, permeability coefficient through the hydrophilic (or aqueous) pathway in the stratum corneum.

almost the same rate, that is, $P_{tot} \fallingdotseq P_{aq}$ in Zone 1. In addition, the hairless rat skin permeability was 5 to 6 times higher than that of human skin, because the hair follicle area of rat skin is larger than that of humans. In a zone of $-1 < \log K_{ow} < 4$ (Zone 2), the higher the lipophilicity of the permeating substance (larger log K_{ow}), the higher the permeability (log P_{tot}). This is because the lipophilic domain dominates in the stratum corneum barrier rather than hydrophilic domains, and the logarithm of the permeability coefficient through the lipophilic pathway is almost proportional to log K_{ow}. However, when log $K_{ow} > 4$ (Zone 3), the P_{tot} is almost the same (data not shown). This is because P_{tot} is very close to P_{ved} in this zone.

Figure 6B shows the relationship between log K_{ow} and the logarithm of the skin permeation rate (e.g., mg/h/cm^2), log J. When preparing a chemical solution using water as a solvent, the chemical concentration decreases as the chemical lipophilicity increases (log K_{ow} increases). Therefore, even when K_{ow} and P_{tot} increase, the chemical concentration decreases. Consequently, the skin permeation rate J reaches a maximum value between log K_{ow} values of 2 and 3. The considerations when using vehicles other than water will be shown later.

Next, the effect of the molecular weight of chemical compounds on the skin permeability is shown. Potts and Guy have shown the relationship between P_{tot} and molecular weight,[10,11] but this explanation uses a report by Bos and Meinardi.[12] They proposed the 500 Daltons rule based on the experience of scientists up to that point. In other words, they stated that chemical compounds with molecular weights up to 500 Daltons can penetrate through healthy skin. As shown in Fig. 7, they noted that many chemical compounds suddenly stop penetrating the skin once their molecular weight exceeds 500 Daltons. On the other hand, chemical compounds can penetrate the atopic dermatitis skin up to a molecular weight of around 700–800 Daltons.

It is clear from Figs. 6 and 7 that chemical compounds with moderate lipophilicity and small molecular weight have high skin permeability.

Recently, there has been discussion about the skin application of nanomaterials, similar to that of high-molecular-weight pharmaceutical and cosmetic ingredients. Solid nanomaterials may penetrate if there are scratches or cracks in the stratum corneum. However, they are not usually absorbed through the skin because they do not diffuse through skin tissue. In Japan, ultraviolet scattering agents using titanium dioxide nanomaterials are used for sunscreen purposes. Since the purpose of these agents is to scatter ultraviolet rays, it makes sense from a safety standpoint that they are not absorbed through the skin. Titanium dioxide nanomaterials do not decompose in the environment, so their use is prohibited in Western countries for environmental conservation.

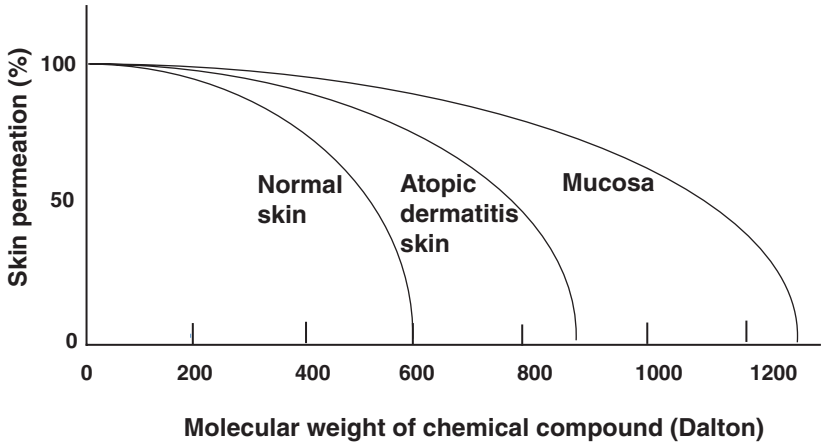

Fig. 7 Estimated permeation barrier characteristics for normal human skin, atopic dermatitis skin, and mucosa.[12)]

7.2. Effect of vehicles on the permeability coefficient of chemical compounds: Thermodynamic activity of chemical compounds and their skin permeability

The thermodynamic activity of a chemical compound in vehicles is important for evaluating skin permeability. The mole fraction concentration of a chemical compound i is expressed as x_i, whereas thermodynamic activity is usually expressed as a_i or Ai (a_i is used in this paper). The relationship between x and a is as follows:

$$a_i = \gamma_i x_1 \tag{13}$$

where γ is the activity coefficient.

Figure 8A shows the relationship between the concentration and activity of the same chemical compound in different formulation vehicles A, B, and C.[1,13)] As the concentration of the chemical compound in the vehicle increases, the thermodynamic activity also increases. However, once the chemical compound is saturated in the vehicle, the activity does not increase further. Thus, even when the concentration of the chemical compound in each vehicle is different, if a solid (crystal) chemical compound exists in the vehicle (i.e., if the chemical compound becomes a saturated solution), the thermodynamic activity of the solid compound is equal to that of dissolved chemical compounds in each vehicle. Regardless of the vehicle used, when a solid (crystal) exists, the activity will be the same, independent of the vehicle.

Figure 8B shows relationships between concentration and thermodynamic activity for different chemical compounds A, B, and C in the same formulation vehicle. Even when the same vehicle is used, the activity is specific to each chemical compound, so the maximum activity of the saturated solution differs among chemicals A, B, and C. Furthermore, the solubility of the chemical compounds in the vehicle also varies for each chemical compound, so the inflection point changes accordingly.

The steady-state skin permeation rate J_{ss} is given by Eq. (7'), but it can be rewritten using the thermodynamic activity in the vehicle a_v as follows:[13)]

$$J_{ss} = \left(\frac{dQ}{dt}\right)_{ss} = \frac{a_v D}{\gamma L_{sc}} \tag{14}$$

where γ_s is the activity coefficient of the chemical compound in the skin barrier. The vertical axis of Fig. 8 is a_v. Since J_{ss} is proportional to a_v according to Eq. (14), the vertical axis of Fig. 8 can be replaced with J_{ss}. In other words, when a chemical compound is suspended (saturated) in a vehicle, the skin permeation rate is the same regardless of the formulation vehicle used.

In addition, this concept of thermodynamic activity can be applied to compare the skin permeation of a chemical compound from w/o and o/w emulsions with the same non-saturated chemical concentration. When a lipophilic chemical is applied as a w/o emulsion, the concentration of the chemical compound in the external phase is higher than in an o/w emulsion, resulting in higher skin permeation from w/o emulsion than o/w emulsion. For hydrophilic compounds, o/w emulsion shows higher skin permeation than w/o emulsion.

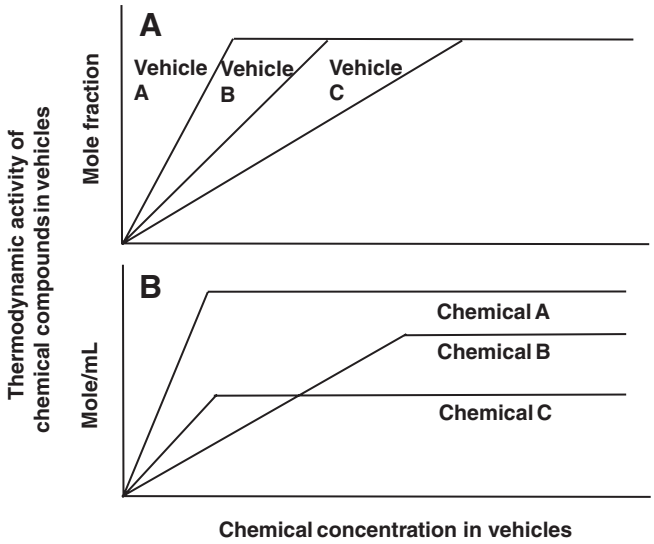

Fig. 8 Schematic diagram showing relations between the concentration of a chemical compound in different formulations and its thermodynamic activity (A) and those between the concentrations of different chemical compounds in a formulation and their thermodynamic activity (B). The vertical and horizontal axes in (A) and (B) show relative values. The bending point for the thermodynamic activity shows solubility of the chemical compound in the vehicle. Vehicle A is a poorer solvent than Vehicle C. Note that the vertical axes are parallel to the thermodynamic activity of the chemical compounds.

7.3. Finite dose system and infinite dose system

The bold line in Fig. 4B shows a typical $Q - t$ profile of a chemical compound after skin application in an infinite dose system. In contrast, the dotted line shows a profile after skin application of a small amount of the chemical compound in a finite dose system.[14–16] The chemical concentrations in the vehicle and the skin decrease with time after application. Thus, the $Q - t$ profile shows a downward curve after the linear part, as shown in the dotted lines in Fig. 4B.[1] Both the skin permeation rate and skin concentration also show a downward curve in the dotted lines in Fig. 4A.

A finite dose system is usually used when using cosmetics. In contrast, an infinite dose system is used in experiments to determine permeation parameters such as the partition coefficient K, diffusion coefficient D, and permeability coefficient P. After these permeation parameters are defined using the infinite dose system, predictions of skin permeation profiles for the finite dose system become possible. Therefore, it is recommended to determine parameters using an infinite dose system first and then evaluate the skin permeation behavior under practical conditions using a finite dose system to assess the permeation properties of effective ingredients in medicated cosmetics and functional cosmetics.

However, the formulation volume is generally large in infinite dose systems, whereas only a few microliters or milligrams are often applied in finite dose systems. Therefore, the permeation profiles in the finite system, where a small volume is applied may differ from those predicted in infinite dose systems where a sufficient amount and volume of the formulation are applied. This is because most formulations begin to penetrate the shallow skin or dry in finite dose system experiments. In the future, it will be necessary to conduct research into infinite dose system experiments with small formulation volumes and finite dose systems with large formulation volumes. This issue is summarized in Fig. 9A.

7.4. Is direct delivery of chemical compounds to the subcutaneous or muscular layer possible?

In the 1980s, there was a debate about whether the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) in poultices or tapes would be higher when applied to painful sites or similar regardless of application sites. To address this issue, we examined the topical application of the NSAID flurbiprofen in hairless rats.[17] First, drug-absorbing gel reservoirs were inserted under the left and right abdominal skin in hairless rats (as a model of muscle sites), and a drug-containing formulation was applied to only one side of the abdominal skin in this experimental model rat. *In situ* experiments were performed to determine the drug concentrations in the left and right gel reservoirs and blood over time. Figure 10A shows the estimated amount of flurbiprofen disposition 10 h after topical application. Focusing on the application site of flurbiprofen, 99.8% of the drug was absorbed into the systemic circulation, and only the remaining 0.2% permeated into the gel reservoir on the application side. On the other hand, when examining the amount of flurbiprofen in the gel reservoir, 84.0% of the drug was permeated directly from the formulation, while only 16.0% was

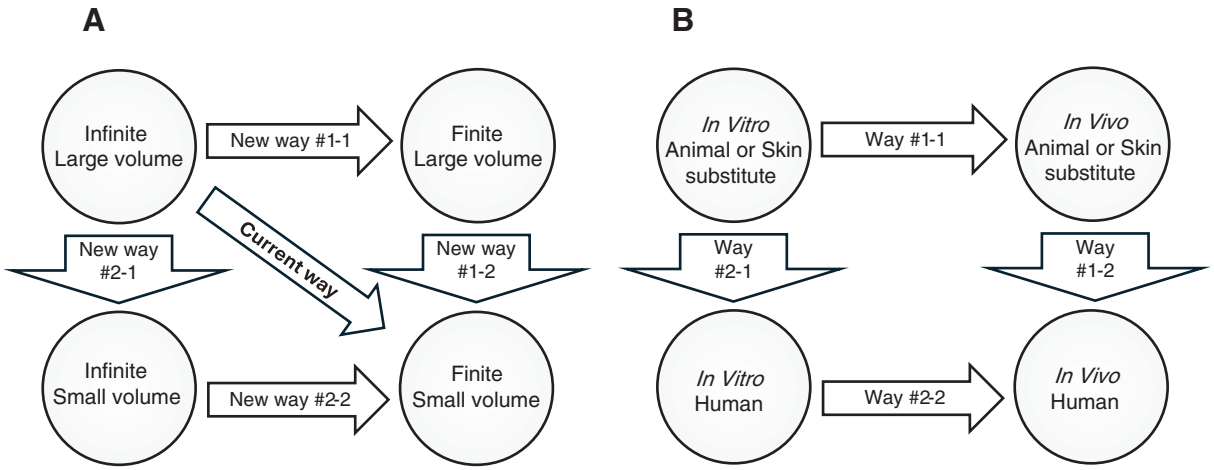

Fig. 9 Prediction of skin permeation profiles in the finite system from those in the infinite system (A) and prediction of *in vivo* human skin permeation profiles from *in vitro* animal skin or skin substitute permeation profiles (B). (A) Most studies were done using the current method. New methods #1 and 2 are needed soon. (B) *In vitro* methods are useful to predict *in vivo* skin permeation profiles.

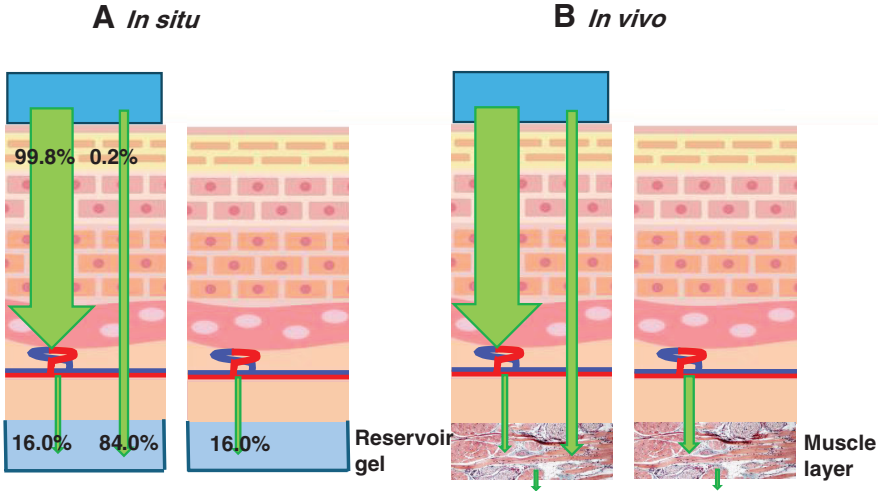

Fig. 10 Schematic diagram of the migration amount of flurbiprofen into agar gels (A) and muscle layer (B) 10 h after topical application of flurbiprofen in dual-agar gel discs-inserted rats (*in situ*) and general rats (*in vivo*), respectively.[17,18] The ratio of 99.8%:0.2% was calculated from the flurbiprofen amount distributed from the formulation into the skin, and the ratio of 16.0%:84.0% was calculated from the flurbiprofen amount entrapped in the agar gel reservoir. These ratios in the *in vivo* experiment (B) were similar to those in the *in situ* experiment (A).

transferred from the systemic circulation. As 16% of flurbiprofen was transferred from the systemic circulation to the gel reservoir on the opposite side where flurbiprofen was not applied, the concentration ratio between the left and right gel reservoirs was 100.0/16.0 = 6.25 times.[18,19] A similar study was also conducted *in vivo* (see Fig. 10B), and it was confirmed that the concentration in the muscle below the formulation was about 5 times higher than in the control site.[19] Similar results were obtained with other NSAIDs, although there were some differences depending on the drugs.

These results demonstrate the effectiveness of applying NSAID formulations to the skin above the painful muscles.

7.5. Skin metabolism of chemical compounds

As shown in Sections 4 and 5.1, VED exhibits metabolic activity against some chemicals. We applied ethyl nicotinate (EN) to the skin in hairless rats and measured both EN and its metabolite, nicotinic acid (NA) that permeated the skin over time. As a result, we found that both EN and NA permeated through the skin. By testing different amounts of EN applied, we clarified that the metabolism from EN to NA occurs in the living epidermis and dermis, and that the metabolic reaction is represented by the Michaelis–Menten equation.[20] Figure 3B shows the concentration *vs*. distance profiles of EN and NA in this case. The EN concentration profile in the VED is downward convex, while the NA concentration profile is upward convex. The diffusion equations corresponding to Eq. (5) for EN and NA are as follows:

$$\frac{\partial C_{EN}}{\partial t} = D_{EN}\frac{\partial^2 C_{EN}}{\partial x^2} - \frac{V_{max}C_{EN}}{K_m + C_{EN}} \tag{15}$$

$$\frac{\partial C_{NA}}{\partial t} = D_{NA}\frac{\partial^2 C_{NA}}{\partial x^2} + \frac{V_{max}C_{EN}}{K_m + C_{EN}} \tag{15'}$$

where C_{EN} and C_{NA}, and D_{EN} and D_{NA} are the concentrations and diffusion coefficients of EN and NA in the stratum corneum, respectively, and V_{max} and K_m are the maximum metabolic reaction rate and Michaelis constant, respectively. By inserting adequate i.c. and b.c., Eqs. (15) and (15') can be solved similarly to Eq. (5). See references[21,22] for details.

Skin metabolism also affects the safety of chemical compounds. We tested the skin metabolism and safety of phthalate esters, plasticizers found in many house-building materials, which are reproductive toxicants and endocrine disruptors. When dibutyl phthalate was applied to rat and human skin, only monobutyl phthalate was permeated from the skin, and skin permeability was higher than direct application of the monoester. In addition, di(2-ethylhexyl) phthalate was not metabolized by esterases in the skin and did not permeate the skin. In other words, moderately lipophilic phthalate esters permeate the stratum corneum and are metabolized to relatively hydrophilic monoesters in the viable epidermis and dermis. Because esterase activity varies greatly from person to person, we concluded that further research is needed to identify individual risks from dermal exposure to phthalate esters.[23]

7.6. Relation between skin permeability of chemical compounds and their safety

The safety of chemical compounds applied to or exposed to the skin should be considered separately from the safety within the skin or surrounding tissues and the systemic safety after absorption into the systemic circulation. Currently, hazard assessment is generally carried out in 3 steps: "identification of hazards," "confirmation of dose-dose correlation," and "estimation of no-observed-adverse-effect level (NOAEL)," and the NOAEL is estimated. Here, the relationship between drug efficacy, E, and drug concentration, C, is described using the following Hill equation, which is widely used in biopharmaceutics:

$$E = \frac{E_{max}C^{\gamma}}{EC_{50}{}^{\gamma} + C^{\gamma}} \tag{16}$$

where E_{max} is the maximum efficacy, EC_{50} is the drug concentration at which half (50%) of the maximum efficacy is obtained, and γ is the Hill factor ($0 < \gamma < 1$). The E in this equation can also be replaced with toxicity. If C is the concentration in the skin or surroundings, it becomes an index of local safety. If it is the blood concentration, it becomes an index of systemic toxicity. When skin permeability is low, it is sufficient to consider safety only at the local skin level. However, at a high percutaneous absorption rate, we need to evaluate systemic toxicity as well.[23,24]

In the local safety evaluation, skin irritation tests were performed in guinea pigs. However, due to animal welfare concerns, it is now recommended to use 3-dimensional cultured human skin models (3D skin models)[25] now. The barrier function of currently available 3D skin models is lower than that of human and guinea pig skin, and their metabolic capacity (e.g., esterase activity) is also low. Some ester-type chemical compounds irritate human skin but do not irritate 3D skin models. This is due to the low metabolic activity in 3D models. Conversely, in the case of metabolites of some chemical compounds that have irritation capacity, skin irritation may be observed in human skin but not in 3D skin models. Caution is therefore required.

8. Measurement of Skin Permeation of Chemical Compounds

8.1. Skin permeation experiments

Since the permeation properties of chemical compounds through the stratum corneum usually do not change even when the stratum corneum is removed from the body, *in vivo* and *in vitro* skin permeation measurements using the same chemical compounds generally show a good correlation. Vertical-type diffusion cells, such as Franz cells[26] and horizontal 2-chamber diffusion cells,[27] have been extensively used in *in vitro* skin permeation experiments. The *in vitro* methods measure the diffusion rate of chemicals through the skin or skin substitute membranes into a reservoir. Table 5 lists representative membrane models used for the *in vitro* skin permeation experiments. In addition to human skin and several species of animal skin, skin substitute membranes such as silicone membranes and Strat-M[28] can also be used. 3D skin models consisting of only the stratum corneum, the epidermis, and both the epidermis and dermis are also used.[29] Some of the 3D models are also utilized for skin irritation tests. The temperature of the test system and the composition of the reservoir fluid are key factors affecting the *in vitro* skin permeability.

Table 5 Skins and skin substitutes broadly used for the *in vitro* permeation experiments.

Skin or skin model		Comments
Human skin	Excised by surgery, etc. Cadaver skin	Full-thickness skin and tape-stripped skin were used; high variability due to individuals and body sites; need hydration before experiments
Animal skin	Mouse, rat, and guinea pig skin	Hairless animals are available; full-thickness skin and tape-stripped skin were used; higher skin permeation than human; animal welfare issues; relatively low variability
	Pig skin	Full-thickness skin and tape-stripped skin were used; close to human skin permeability
Skin substitute membranes	Silicone membrane	Very low variability; good model for lipophilic pathway, but not for hydrophilic pathway in the stratum corneum
	Strat-M	Composed of 2 layers of polyethersulfone membrane and a single layer of polyolefin membrane; no lot-to-lot variability
3-dimensional cultured human skin models (3D models)	Stratum corneum model	Representative examples: EpiDerm, Episkin, and SkinEthic
	Epidermis model	Representative examples: LabCyte EPI-MODEL, Vitrolife skin
		Good for skin irritation test; higher permeation than human skin; having metabolic activity
	Epidermis and dermis model	Representative examples: T-Skin, LSE-high
		Higher permeation than human skin; having metabolic activity

On the other hand, *in vivo* methods measure the extent of dermal absorption of the test substance and the extent of systemic absorption. This study is carried out using human volunteers and laboratory animals. The problem with using laboratory animals is that their welfare is important and that their skin permeability and whole-body properties differ from those of humans. Figure 9B shows the method to extrapolate from *in vitro* animal or skin substitute data to *in vivo* human skin data.

8.2. Variability in percutaneous absorption and influencing factors

There is considerable variability in the measurements of skin permeability of chemical compounds. Regarding the variability factors on the skin, the first is the animal species. Mouse, rat, and guinea pig skin permeabilities tend to be higher than human skin. Pig skin permeability is close to human skin permeability (see Table 5). Although the human skin structure changes with age, little is known about how age change affects skin permeability. Gender and ethnic background are not the biggest causes of variability in human skin permeability. Percutaneous absorption also depends on the anatomical site, skin condition, and hydration state of the skin. Generally, variability in human skin permeability is very large compared with animal skin permeability. Experimental factors that markedly affect *in vitro* human skin permeation include skin (stratum corneum) thickness, L_{sc}, and chemical diffusivity, D, in the stratum corneum.

Other factors that affect percutaneous absorption include the physicochemical properties of the test compound, the physicochemical properties of the formulation or medium in which the test compound is dissolved, and the interaction of the test compound or medium with the skin, the metabolic capacity of the skin, and factors specific to the test system used for measurement (such as the dose and amount of the test substance, occlusion or non-occlusion of the test skin area, *in vitro* or *in vivo* test system, and exposure period to chemical compounds).

9. Future Cosmetics and Quasi-Pharmaceutical Products

9.1. Pharmaceuticals and their modalities

Recently, the term “pharmaceutical modality” has been used to describe the different types of pharmaceutical technologies and their classifications. It also highlights the development of various new pharmaceuticals. After the Meiji Restoration, Japanese chemists learned from Western countries, extracted active ingredients from herbs, identified their chemical structures, and started creating small molecular drugs using organic chemistry.

Today, attention has shifted to biomedicines, which are derived from modifying substances like hormones, peptides, antibodies, and nucleic acids found in the body. The size of pharmaceutical molecules has increased from about 500 Daltons to several thousand or even tens of thousands. Additionally, drug delivery methods have evolved from oral tablets or capsules to injections and intravenous infusions. However, injections require medical professionals and can be inconvenient for patients. Therefore, more patient-friendly options are needed for these larger molecules.

In the realm of cosmetics and functional cosmetics, there is growing interest in medium and high-molecular-weight materials such as hyaluronic acid, proteoglycan, and collagen. To match their new cosmetic and functional cosmetic modalities, new methods for applying these materials other than topical application must be developed.

9.2. Penetration-enhancing methods for active ingredients

Since some new active ingredients in functional and medicated cosmetics, especially medium-to-high-molecular-weight ingredients, have poor skin permeability, penetration-enhancing methods are needed, as mentioned above. While chemical and formulation approaches, such as structural modifications of active ingredients and combinations with several penetration enhancers, have already been used,[30] physical penetration-enhancement methods, including iontophoresis, electroporation, thermal poration, and sonophoresis, have recently been researched as more effective approaches than chemical and formulation ones.[31] Microneedle patches are one of the most attractive physical means for increasing the skin penetration.[32] Such physical approaches have gained more attention within the past 5–10 years.

The combined use of cosmetics and beauty devices has already been put to practical use. Examples include hyperthermia, ultra-wave massage, magnetic field induction, iontophoresis, phonophoresis, and combined use of electroporation and iontophoresis, which have given rise to the term mesotherapy in the beauty field.[33] Wearable and installable cosmetics that promote the penetration of active ingredients into the skin may also be developed.

9.3. Future cosmetics

Japan has undergone significant changes in family structure and witnessed a decline in birth rates due to rapid economic development. Although there has been a rise in male cosmetic usage, the overall domestic demand for cosmetics and medicated cosmetics is decreasing. At the same time, the trend toward globalization is permeating all industries, making it imperative for cosmetics and medicated cosmetics in Japan to consider not only the domestic market but also international markets.

In Japan, medicated cosmetics are classified as quasi-pharmaceutical products, but this concept is largely absent in many parts of the world. As globalization progresses and borders blur, the notion of quasi-pharmaceutical products in Japan is becoming increasingly ambiguous, necessitating a reevaluation of what constitutes "cosmetics." The future will likely see an increase in new cosmetic ingredients and the creation of new product genres. To earn consumer trust and confidence, it will be crucial to emphasize not only the efficacy but also the safety of these products.

Skin type is greatly influenced by factors such as ethnicity, climate, and diet. Japanese cosmetics manufacturers must target the East Asian market, which shares similar climates and dietary habits with Japan, as well as other Asian regions like ASEAN, and, of course, broader global markets, including Europe and the United States. With the growing Muslim population and their increasing economic influence, there is also a heightened focus on halal cosmetics.[34] Additionally, the shift toward carbon-free, environmentally friendly ingredients for both cosmetics and medicated products is becoming increasingly necessary.

We are witnessing a parallel trend of polarization and diversification in cosmetics and makeup techniques. While some products will lose their individuality and become more uniform, interest in local cultures will grow, potentially leading to the emergence of region-specific cosmetics and makeup methods. The goal of "cleanliness," one of the purposes of using cosmetics, can be scientifically defined, which will drive uniformity. Conversely, the pursuit of "beauty" will resist uniformity even in an era of globalization. The concept of "tailor-made cosmetics," similar to personalized medicines in the medical field, will advance alongside research into its practical application.

Modern society is marked by increasing stress, leading people to seek cosmetics and makeup that offer healing effects. Women are investing more time and money into beauty products for this purpose, a trend that is also expanding into men's cosmetics. The tactile experience will play a crucial role in the future of cosmetics and makeup methods, much like it does in aromatherapy and facial massage.

As our lives become increasingly fast-paced, there is a growing demand for cosmetics that are quick and easy to use. The concepts of wearable and installable products are becoming integral to cosmetics and quasi-pharmaceutical products. Recently, mask and patch-type wearable products have gained popularity. In the future, we may see not only patch-type but also implantable cosmetics. Imagine taking a photo of your face with a mobile phone and applying makeup to the image. There could be makeup devices (see Fig. 11A)[35] that allows you to view your face in a mirror, color in the

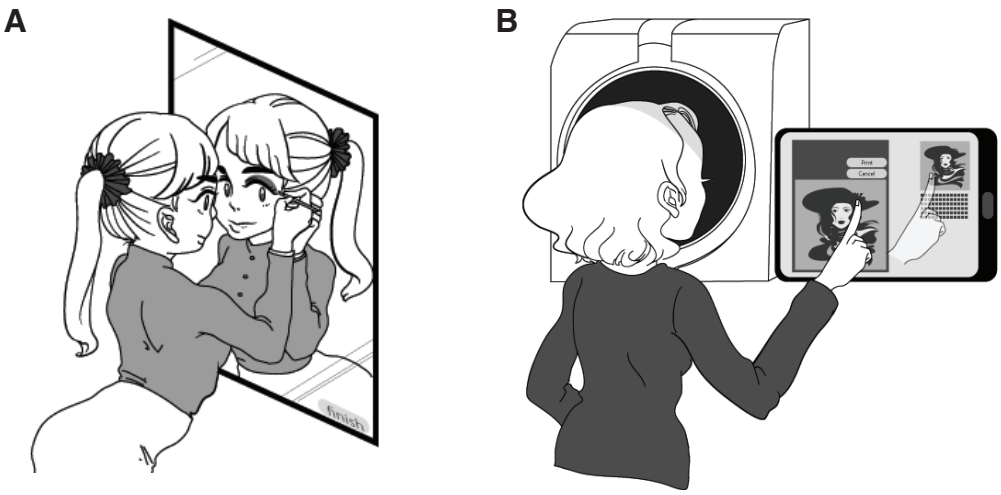

Fig. 11 Schematic diagram of 2 examples for new make-up.[32] (A) Apply makeup in the mirror, press the button, and your makeup is done. (B) Select your favorite photo and complete the inkjet makeup. Reprinted from "Future Prospects of Cosmetics and Cosmeceutics from a Viewpoint of an Academician" (JCSS Permission No. JCSS R24-008).

image instead of applying physical makeup, and press a button to complete the process. Additionally, beauty devices may emerge that enable you to select your favorite celebrity from a catalog, place your face on an inkjet printer, and achieve a similar look (see Fig. 11B).[35]

We are entering an era where the creativity of scientists and researchers is paramount. A broad perspective is essential when developing new cosmetics and medicated products. The keywords for future innovation in cosmetics will be global compatibility and creativity.

Conflicts of Interest: The author declares no conflicts of interest.

Abbreviations: 3D, 3 dimensional; b.c., boundary conditions; EN, ethyl nicotinate; i.c., initial conditions; LT, lag time; NA, nicotinic acid; NOAEL, no-observed-adverse-effect level; SC, stratum corneum; TDDS, transdermal drug delivery systems; TTS, transdermal therapeutic systems; VED, viable epidermis and dermis

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