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Main Cosmetic Vehicles

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INTRODUCTION

The aim of this chapter is to treat the topic of cosmetic vehicles in a conceptual way. It is not the purpose to present a lot of formulations or types of vehicles that are used for all the different cosmetic products and sites of application. Neither will the topic be presented in a comprehensive way, because of its complexity. There are many good examples of formulation compositions described in cosmetic literature and brochures of companies offering cosmetic excipients. In this chapter an overview of various selected aspects is given that should be taken into account when cosmetic preparations are to be formulated. The critical issues for formulation development will be pointed out.

FUNCTION OF VEHICLES

Direct Intrinsic Effect

The term vehicle is used in pharmaceutics as well as in cosmetics in the area of formulation. In general, this term implies differentiation between active and inactive principles. The active principle is embedded into a matrix, the vehicle. With the aid of the vehicle the active principle is delivered to the application site or to the target organ, respectively, where the desired effect is achieved. As a matter of fact, however, when dermatological and cosmetical preparations are applied, sharp differentiation between active and inactive principle is generally not possible because of the so-called vehicle effect.

The aim of application of both a pharmaceutical preparation as well as a cosmetic topical care product is to achieve a desired effect. Pharmaceutical preparations are effective because of a pharmacologically active compound delivered with the aid of a vehicle, whereas cosmetic formulations are not allowed to contain such compounds. Nevertheless, an effect is also achieved by a cosmetic preparation—not any systemic or central or curative effect—but a caring or preventing effect mainly on skin, hair, or nails. This effect may be achieved either by cosmetically active ingredients or by the vehicle itself on the site of application, i.e., on the skin in most cases. In contrast to pharmaceutics, in cosmetics the vehicle is of greater importance.

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Depending on the composition, a vehicle is used to exert mainly five types of effects on the skin, briefly described in following sections.

Cleansing

The most common and probably oldest use of cosmetic preparations is to clean the human body. In our modern time and society, not just soap but a variety of sophisticated cosmetic cleansing products are available.

Decoration

Decoration serves to produce a pleasing appearance by minimizing facial defects of color or shape and unobtrusively enhancing and directing attention toward better points [1]. Decorative cosmetic preparations are not the main object of this chapter on vehicles, although similar principles have to be considered for decorative cosmetic preparations.

Care

Probably more cosmetic preparations are applied to care for the outermost organs of the body, i.e., skin, hair, and nails, than to decorate these organs. Care of skin, hair, and nails and improvement of their state is an important function of an applied cosmetic product. Application of an appropriate vehicle may be fully sufficient for care of the body.

Hydration

The state of dry skin may be treated by applying a cosmetic product. In this case the skin is hydrated by application of an appropriate vehicle containing specific components that are able to reduce the transepidermal water loss. This results in an increase in water in the stratum corneum and a smoother surface of the skin.

Protection

A further important function of cosmetic vehicles is to build up a protective layer against external potentially damaging factors that could come into contact with the body. Especially in recent years the protective and preventive function of vehicles has become increasingly important, because of an increase of various external harmful factors or at least higher awareness about them (e.g., air pollution, UV radiation).

Delivery of Actives

From a stringent medicinal and legal point of view, a cosmetic preparation must not contain any (pharmacologically) active substance or ingredient that treats or prevents disease or alters the structure or function of the human body [2]. That means just the vehicle is effective directly at the site of application. This is in contrast to pharmaceutical vehicles, which in principle should serve as pure vehicles delivering active substances to the target organ and showing no effect on the body. However, in reality there are no such distinct but floating boundaries. Therefore, cosmetic vehicles can also be considered as means containing cosmetic actives that are applied to the outermost layer of the body. Furthermore, many cosmetically used substances are bifunctional: first they constitute the vehicle structure and second they show a positive effect on the skin status when applied.

Carrying Actives to Target (Targeting)

Going even one step further, cosmetic vehicles can also be considered and used as carriers for cosmetic actives which, after application, are carried and delivered to the specified

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target sites, i.e., to legally allowed targets in deeper regions of skin. However, this is only allowed if no systemic, physiological, or pharmacological effect is achieved and the product has shown to be safe.

Delivering active substances to these targets requires the right concentration of actives in the formulation to achieve the optimal release rate and desired distribution of active substances between the vehicle and the target site. That means the vehicle should penetrate (superficially) into the stratum corneum and release the active substance at the optimal rate (immediate or sustained for depot effect) at the target site where the desired effect is achieved.

CLASSIFICATION SYSTEMS OF VEHICLES

There are many types of classification systems based on various principles described in the literature. But one has to be aware that cosmetic preparations are rather complex systems. Most of the various classification systems are unsatisfactory and it is difficult to set up a comprehensive system. In most cases, it is problematic to make clear distinctions for classifying the vehicles in a proper and unambigous way. This is because of various possible points of view and characterization criteria used. The state of matter, e.g., depends on temperature, and therefore a lipid-based vehicle might exist either in liquid or semisolid form.

A few systems are discussed in this chapter. For modern formulation development the physicochemically based systems have been found to be the most useful and practical for understanding and explanation of formulation issues.

Appearance

The most obvious and simple classification may be performed according to the appearance of the preparations or vehicles, respectively. Based on the macroscopic physical state of matter, three types of preparations are distinguished: liquid, semisolid, and solid forms. This classification is not of great interest for rational formulation design and development. However, for many practical issues it is quite useful, e.g., for manufacturing, packaging, and application on the body.

A further classification system is based on state of matter and optical discrimination, be it macroscopically or microscopically. That means vehicles can be classified into monophasic, isotropic systems on one hand and into anisotropic heterophasic systems on the other. For example, the term ''solution'' is commonly used to describe a liquid form with isotropic appearance. However, solutions also occur in solid form, so-called solid solutions. With regard to macroscopic appearance, colloidal systems (e.g., mixed micellar solutions, microemulsions) are also isotropic, whereas e.g., coarse dispersions belong to the anisotropic systems. Unlike solutions, most cosmetic vehicles are anisotropic, heterophasic systems (mixtures). Thus, a more sophisticated system is needed to describe and classify the heterogeneity of possible vehicle forms in a satisfactory way (see Table 1).

Application, Use

Classification of vehicles may also be performed as a function of their use and application site, i.e., preparations used for the following:

TABLE 1 Junginger's Physical-Chemical Classification System

System	Brief description (examples)
Liquid systems	
Monophasic systems	
Aqueous solutions	Molecular disperse systems of solute in solvent (water, alcohol); liquid, transparent
Alcoholic, alcoholic-aqueous solutions	
Oily systems	Solutions based on (mixtures of) liquid lipids as solvent, e.g., oils for massage
Micellar systems	Solubilisates of low soluble substances due to aggregation formation of surfactants in solution
Microemulsions	Optically isotropic liquid: gel composed of water, lipid, and surfactant in distinct ratio
Multiphasic liquid systems	
O/W emulsions	Internal lipid phase dispersed in the external (continuous) aqueous phase stabilized by surfactants
W/O emulsions	Internal aqueous phase dispersed in the external (continuous) lipid phase stabilized by surfactants
Suspensions	Solid particles dispersed in a liquid phase
Aerosols	
Semisolid systems	
Water-free systems, ointments	
Apolar systems, hydrocarbon gels	Petrolatum
Polar systems	
Polar systems without surfactants	
Lipogels	E.g., hydrogenated vegetable oils
Oleogels	Colloidal silica in oils
Polyethylene glycol gels	
Polar systems with surfactants	
W/O absorption bases	Simple ointment (British Pharmacopoeia 1993): emulsifying system (cetostearyl alcohol, wool fat) in paraffin-petrolatum base
O/W absorption bases	Cetomacrogol emulsifying ointment (British Pharmacopoeia 1993): cetomacrogol 600, cetostearyl alcohol in paraffin-petrolatum base
Water-containing systems	
Monophasic systems: hydrogels	
Hydrogels with anorganic gelating agents	Colloidal silica in water (high concentration, labile gel structure)
Hydrogels with organic gelating agents	Hydroxyethylcellulose gel Polyacrylate gel
Multiphasic water-containing systems: creams	
O/W creams	
W/O creams	
Amphiphilic systems	
Amphiphilic systems with crystalline gel matrix	*
Amphiphilic systems with liquid crystalline gel matrix	*
Liposomes	Phospholipid vesicles in aqueous medium
Niosomes	Nonionic surfactant vesicles (analogous to liposomes) in aqueous medium
High-concentrated suspensions, pastes	
Powders	

* See discussion on mesophases, p. 161.
Source: Modified from Ref. 3.

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- hairs, e.g., shampoo, depilatory agents, hair colorant
- nails, e.g., polish, lacquer
- mouth, e.g., toothpaste, lipstick, lip-protection stick
- skin, e.g., moisturizing product, body lotion, aftershave, deodorant, antiperspirant, sunscreen

It is obvious that for the different application sites and modes different vehicles and forms with appropriate characteristics are needed. On the other hand, different types of vehicles may also be used for the same purpose, e.g., an aqueous-alcoholic solution or a balm for application after shaving.

Physical Chemical

In the development of cosmetic care products, a practical physical-chemical classification system that describes the principal properties and structural matrix of vehicles is preferred. Of course, there is no perfect and comprehensive classification system. A good example

TABLE 2 Definitions of Selected Vehicle Systems

Systems	
Aerosol	Dispersion of liquid or solid in gas.
Colloidal	Colloidal systems are dispersions with particle size range of 1–500 nm. They may be classified into the following three groups: 1. Lyophilic colloids: particles interact with the dispersion medium (e.g., gelatin) 2. Lyophobic colloids: composed of materials that have little attraction (e.g., gold in water) 3. Association colloids: amphiphiles or surfactive agents aggregated to micelles [4].
Dispersion	Dispersed systems consist of particulate matter (dispersed phase) distributed throughout a continuous, or dispersion, medium [5].
Emulsion	According to IUPAC (International Union of Pure and Applied Chemistry), emulsion is defined as liquid droplets and/or fluid crystals dispersed in a liquid. The dispersed phase is also called the internal phase, in contrast to the external or continuous phase. If the internal phase is lipophilic, e.g., vegetable oil or paraffin oil, and dispersed in the external hydrophilic aqueous phase, an emulsion of type O/W is obtained. On the other hand, there are W/O emulsions with the hydrophilic aqueous phase dispersed in the continuous lipophilic phase. For formation and stabilization of emulsions, emulsifiers are required. Emulsions may show liquid or semisolid consistency. Further related aspects are treated in p. 151.
Foam	Dispersion of gas in liquid phase, i.e., structure of air pockets enclosed within thin films of liquid, stabilized by a foaming agent [6].
Gel	A gel is a solid or semisolid system of at least two constituents, consisting of a condensed mass enclosing and interpenetrated by a liquid [7].
Solution	A true solution is defined as a mixture of two or more components that form a homogeneous molecular dispersion, a one-phase system [8].
Suspension	A suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium [9].

of a physical chemical system is described by Junginger [3] and slightly modified in Table 1. Although not comprehensive, such a system is a useful tool for rational formulation design and development, in particular when controlled and targeted delivery of active principles has to be achieved. Such a vehicle classification system is also a practical basis for production, use, and understanding of cosmetic vehicles. However, the boundaries between the different classes are flexible, and changing with the state of art and science. More important than pure classification of a cosmetic vehicle is its exact characterization, based on physical, chemical, and biological principles that may eventually lead to a variety of classification possibilities.

In a physical chemical classification system, various characterization criteria are used for classification of the vehicles:

- Polarity: hydrophilicity, lipophilicity
- State of matter: solid, semisolid, liquid, gaseous
- Size/dimensions of particulates dispersed in the mixtures (dispersions)
  true solution, molecular dispersion: particle size <1 nm
  colloidal dispersion: particle size 1 nm–500 nm
  coarse dispersion: particle size >500 nm
- Solubility characteristics
- Rheology, viscosity
- Composition: physical chemical characteristics of the main vehicle components
  waterfree, oily
  aqueous
  hydrophilic, nonaqueous solvents

For clarification of the terminology, a selection of definitions or descriptions of the major systems is given in Table 2. (See also Refs. 4–9.)

DESCRIPTION AND DEFINITION OF MAIN VEHICLES

Solutions

The term ''solution'' may be used in a narrow sense, describing true solutions (molecular dispersions; see Table 2), or in a broader sense, also comprising colloidal solutions, i.e., more or less transparent liquids, e.g., micellar solutions and vesicular systems (media containing liposomes, niosomes).

In general, true solutions used in cosmetics are either based on aqueous, or aqueous-alcoholic, media or on inert oily vehicles. Most organic solvents cannot be used because of their local or systemic toxicity, which causes skin irritation or permeation across the skin barrier into the body, respectively. Although good solvents for lipophilic substances, oils may not be used in every case because of their grassy characteristic, low acceptance, and exclusion for hairy application sites. However, for special applications oils are preferred, e.g., for massage. ''Massage oils'' contain essential oils and fragrances, compounds that are easily dissolved in the oily vehicle because of their lipophilic properties.

Prerequisite for solution formulation is a sufficiently high solubility of the solute in the solvent. Classical examples for solutions used in cosmetics are ''eau de parfums'' and ''eau de toilettes.'' In order to enable solubilization of the lipophilic fragrances, alcohol or aqueous-alcoholic solutions are prepared. The addition of alcohol to water, or other suitable hydrophilic but less polar solvents (e.g., glycerol, polyethylene glycol), decreases

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the polarity of the solvent and thus increases the solubility of the lipophilic solutes. Frequently, a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as cosolvency, and the solvents that in combination increase the solubility of the solute are called cosolvents [10].

Another classical example is preparations for mouthwashes. They usually contain essential oils or liquid plant extracts like peppermint or myrrh extract, which are kept in solution by the added ethanol (ca. 70%). When used for application, these concentrates are diluted with water. Then turbidity occurs because of overstepping saturation solubility. In order to prevent turbidity, solubilizing agents (surfactants, e.g., PEG-40 hydrogenated castor oil) may be added. The solubilization effect is attributed to aggregation formation of surfactants when in solution. In aqueous solutions surfactants form micelles, small aggregates, when the concentration of the surfactant exceeds the critical micelle concentration (CMC) [11]. With the aid of those micelles, the solubility of low soluble, apolar compounds may be increased because of an association or incorporation of the apolar compounds with the apolar region of the micelle. Thus, solubilization or formation of micelles is a favorable means for formulation of solutions.

Finally, salt formation or adjustment of pH also results in improved solubility of originally low soluble, ionizable solutes. Thus, e.g., addition of sodium hydroxide may be used to improve the solubility of hyaluronic acid or preservatives such as sorbic or benzoic acid. Accordingly, appropriate acids, e.g., lactic acid and citric acid, may be added when solubility of a basic substance must be increased. Although not the main type of formulation used in cosmetics, solutions have the following advantages:

1. They remain physically stable (if true solution and not oversaturated),
2. Are easily prepared: simple mixing, under heating if necessary,
3. Are transparent, clear, and have a ''clean'' appearance, and
4. Are especially suitable for rinsing and cleaning body surfaces.

However, it must be kept in mind that many compounds are chemically less stable when in a dissolved state.

In summary, whenever a solution has to be formulated, the optimal solvent must be selected, that (1) guarantees sufficient solubility and stability for the solute(s), and (2) is acceptable and safe for application to the body. Solubility may be improved by (1) adaptation of the solvent's polarity with regard to the solute, (2) salt formation/pH adjustment (ionizable compounds), (3) using mixtures of suitable solvents and cosolvents, and (4) solubilization with the aid of surfactants.

Emulsions: Lotions and Creams

Out of the range of cosmetic care products, the emulsion is the form that is probably the most used. For reasons of skin feeling, consumer appeal, and ease of application, emulsions are preferred to waterless oils and lipids along with gels. The main components of emulsions are lipids (lipophilic compounds) and water (and/or hydrophilic compounds). These two immiscible phases are allowed to remain in a metastable mixed state by an amphiphilic component, an emulsifier. This biphasic system may be regarded in analogy to the skin or even to the skin cells, which, simply put, consist of lipophilic and hydrophilic components. Emulsions can either be of the water-in-oil (w/o) or oil-in-water (o/w) types. Showing very similar structural principles, both lotions and creams are discussed in this chapter. If emulsions are liquid, they are generally called lotions. Creams are emulsions

occurring in semisolid form. Under gravitation, creams do not flow out through the orifice of reversed containers because of the heavier consistency in comparison with lotions.

Emulsions are prepared by dispersion of the internal in the external phase. For this energy-consuming process, emulsifiers that decrease the interfacial tension between the two immiscible phases are required. Emulsifiers are not only used for formation but also for stabilizing emulsions. Emulsions are metastable systems and the two phases tend to separate because of coalescence, i.e., when the dispersed droplets fuse. This process may be slowed by the addition of appropriate emulsifiers, which are ionic or anionic surfactants. The emulsifiers are thought to be located at the interfaces between the two phases, the hydrophilic part of the molecule in contact with the water phase and the lipophilic domain of the emulsifier contacting/touching the lipid phase. Large molecules may even dig into the lyophilic phase and serve as stabilizing anchors. Being adsorbed at the interfaces, the emulsifying substances form a film—monomolecular or multimolecular, depending on the substances' structures—that stabilizes the emulsion [12]. The addition of viscosity-increasing substances further results in an improved consistency and consequently more stable emulsions.

Except for the emulsifiers, the following types of ingredients are usually added to cosmetic emulsions:

- *Emollients*: They improve the sensory properties of the emulsions. Addition of an emollient results in better spreading when the emulsion is applied to the skin. Examples: isopropyl myristate, silicon oils.
- *Moisturizers and humectants*: They increase and control the hydration state of the skin. Examples: glycerol, urea.
- *Viscosity-increasing agents* are added to increase the viscosity of the external phase, if desired. Examples: xanthan gum, cellulose esters.
- *Active substances* such as UV sunscreens and vitamins.
- *Preservatives* to prevent microbial growth, particularly in o/w emulsions.
- *Perfumes and coloring agents* for aesthetic purposes.

Oil-in-Water Emulsions

The high acceptance of o/w emulsions is based on the following reasons:

- They feel light and not greasy when applied.
- They show good skin spreadability and penetration and an active hydration effect by the external water phase.
- They cause a cooling effect because of the evaporation of the external aqueous phase.

However, o/w emulsions show a lower effect in preventing dry skin in comparison with w/o emulsions. A typical o/w emulsion is composed as follows:

1.	Lipid(s) + lipophilic thickening agent (optional, e.g., microcrystalline wax)	10–40%
2.	Emulsifier system with optimal HLB-value (approx. 9–10 [13])	5%
3.	Co-emulsifier (e.g., cetostearyl alcohol, behenyl alcohol)	2%
4.	Preservatives (antimicrobial, antioxidants)	q.s.
5.	Water + hydrophilic thickening agent (optional, e.g., carbomer) ad	100%

Depending on the desired product effect, different types of lipids may be used for formulation. Addition of nonpolar, occluding lipids (e.g., paraffin oil) improves retention of moisture in the skin but lowers spreading on the skin. A good spreading effect is achieved by formation of a low-viscosity emulsion containing polar oils that show a high spreading coefficient (e.g., macadamia nut oil, wheat germ oil, isostearyl neopentanoate) [14].

Selection of the lipophilic ingredients and the excipients of the water phase determine the emulsifier system to be used and additional adjuvants, e.g., viscosity-increasing thickening agents. There is no universal emulsifier system, and a huge variety of combinations might be used. Today, complex emulgator systems that consist of one or more surfactants and a cosurfactant are commonly used. That means at least two surfactants with different HLB-values are combined. For example, steareth-21 (HLB = 15.5) may be combined with PEG-5-glyceryl stearate (HLB = 8.7). The latter emulsifier is especially suitable when nonpolar oils are to be incorporated. In recent years selected polymeric excipients have been used for emulsion stabilization, e.g., crosslinked and linear polyacrylates, polyacrylamides, and derivates of cellulose.

In selecting a co-emulsifier, the following general guidelines apply:

- For the same fatty residue, the viscosity decreases if the degree of ethoxylation increases.
- For the same degree of ethoxylation, the viscosity increases if the fatty carbon chain length increases [14].

The degree of viscosity (consistency) of o/w emulsions depends on various factors [15]:

- Volume ratio of internal to external phase: increasing lipid percentage results in higher viscosity, but not necessarily in a semisolid cream.
- Type of lipid: incorporation of high melting lipophilic compounds, e.g., solid paraffin and petrolatum, may result in soft semisolid o/w creams.
- Presence of thickening agents in the lipid phase: addition of cetostearyl alcohol generally results in (''hard'') semisolid creams.
- Presence of thickening agents in the external aqueous phase: the ultimate mean to increase the consistency of a thin o/w emulsion. Addition of hydrocolloids, e.g., carbomers or hydropropyl guar (Jaguar 8600, Rhodia Inc., Cranbury, NJ), is the most efficient method to increase the viscosity of o/w emulsions. However, depending on the properties of the added polymer, the skin feeling of the emulsion may become negatively influenced because of the stickiness.

An interesting phenomenon is the occurrance of liquid crystal structures (mesophases) in emulsions under certain conditions. This has been investigated and has become of interest more and more during the last 10 to 20 years. This subject is treated on p. 161.

Water-in-Oil Emulsions

Water-in-oil (w/o) emulsions may still be regarded as heavy, greasy, and sticky although during recent years great progress has been achieved in the preparation of pleasant w/o emulsions. Therefore, the w/o emulsion type is not only the basis for water-resistant sun protection, baby creams, or night creams, but also for protective day creams. This is because during recent years better excipients have become available. The advantages of w/o emulsions are:

- Close resemblance to the natural protective lipid layer in the stratum corneum
- Efficient skin protection attributable to formation of a continuous layer of lipids on skin after application
- Sustained moisturization because on skin a continuous semiocclusive barrier is formed that reduces evaporation of skin water and that in addition actively releases the incorporated water from the internal phase, generally several times more efficient than o/w emulsions
- Improved penetration into the lipophilic stratum corneum coupled with improved carrier function of lipophilic active substances, and even of hydrophilic substances incorporated in the internal aqueous phase
- Lowered risk of microbial growth
- Liquid at very low temperatures (beneficial for winter sport products)

A typical w/o emulsion is composed as follows:

1.	Lipid component	20%
2.	Lipophilic thickening agent (e.g., wax, optional)	1%
3.	Emulsifier system with optimal HLB-value (3–8)	7–10%
4.	Preservatives (antimicrobial, antioxidants)	q.s.
5.	$MgSO_4 \cdot 7H_2O$	0.5%
6.	Water (+ hydrophilic thickening agent, optional) ad	100%

In order to avoid the heavy feel of w/o emulsions, appropriate excipients must be selected to get products with well-accepted sensory properties. This heavy feel of w/o emulsions is directly related to the spreading characteristics of the external oil phase. Therefore, polar oils with a high spreading coefficient [16] are preferably used, e.g., macadamia nut oil, isopropyl isostearate, isostearyl neopentanoate. Addition of low-viscosity silicone fluids or volatile cyclomethicone also improves the spreading effect. The physicochemical nature of the lipid components not only determines the spreading on the skin, the degree of occlusivity, and skin protection, but also influences the selection of the emulsifier system. Therefore, choosing an optimal emulsifier system is crucial. For example, glyceryl sorbitan unsaturated fatty acid ester (Arlacel 481) and glyceryl sorbitan saturated fatty acid ester (Arlacel 986) are better suited to emulsify apolar lipids, whereas more hydrophilic emulsifyers like the analogous ethoxylated sorbitan fatty acid esters (Arlacel 581, saturated, and Arlacel 582, unsaturated) or fatty acid esters of polyols (Arlacel 1689, saturated, and 1690, unsaturated) are designed for more polar lipids. A combination of PEG-7-hydrated castor oil and polyglyceryl-3-diisostearate may also be used. Skin feel may be improved by causing thixotropic behavior of the product, which is achieved by addition of a thixotropic agent or by reduction of the emulsifier content.

Multiple Emulsions

Multiple emulsions are triphasic systems or emulsions of emulsions. That means there is a primary emulsion dispersed in an external phase, e.g., water-in-oil-in-water (w/o/w). The dispersed phase in the resulting system contains smaller droplets having the same composition as the external phase [17]. The inner aqueous phase is separated from the outer aqueous phase by the oil phase, and therefore the composition of the two aqueous phases may be different, at least after preparation and for a certain storage time. Preparation and stabilization of multiple emulsions is a challenging task. They may either be prepared by a two-step method or by the relatively new one-step process ''Partial Phase

Solu-Inversion Technology PPSIT'' [18]. The two-step method includes preparation of the primary emulsion, which thereafter is dispersed in the external phase. In the PPSIT the lipid and electrolyte-containing water phase are heated and mixed above the phase inversion temperature (PIT), where the hydrophilic emulsifier forms w/o emulsions. By cooling down, a w/o/w system occurs at the PIT for a short time period. Then the system is immediately fixed by salting out and forming a lamellar matrix structure based on the emulsifier [19]. The advantage of w/o/w emulsions is that they comprise both the light feeling and positive sensory characteristics of o/w-emulsions and the skin hydration effect of w/o-emulsions.

Gels

Gels are dispersed systems, originally liquids (solutions) that have a certain consistency useful and practical for topical application. In contrast to emulsions, gels generally do not comprise two immiscible phases of opposite lyophilicity. Therefore, the polarity and solubility characteristics of the incorporated substances are either hydrophilic—in hydrogels—or lipophilic—in lipogels (or oleogels). The consistency of gels is caused by gelling (thickening) agents, usually polymers, building a three-dimensional network. Intermolecular forces bind the solvent molecules to the polymeric network, and thus the reduced mobility of these molecules results in a structured system with increased viscosity. Pure gels are transparent and clear or at least opalescent. Transparency is only achieved if all ingredients are dissolved or occur at least in colloidal form, i.e., the size of particles is in the submicron range. Transparency in particular is an attractive property of gels. Gel products have positive aesthetic characteristics and are thus becoming more and more popular in cosmetic care products today. Gels can also serve as the basis for more complex formulations:

- Solid particles can be incorporated, resulting in stabilized suspensions
- Incorporation of oily lipids results in so-called hydrolipid dispersions or quasi-emulsions (see p. 156).

Hydrogels

Hydrogels are hydrophilic, consisting mainly (85–95%) of water or an aqueous-alcoholic mixture and the gelling agent. The latter is usually an organic polymeric compound such as polyacrylic acid (Carbopol), sodium carboxy methylcellulose, or nonionic cellulose-ethers. Hydrogels have to be preserved against microbial growth.

After application, hydrogels show a cooling effect caused by evaporation of the solvent. They are easily applicable and humidify instantaneously, but if applied over a long time they desiccate the skin. For that reason, humectants such as glycerol may be added. After evaporation, the polymer residue may cause a sticky or ''tearing'' feel on the skin if inappropriate thickening agents have been used. Careful selection and testing of the needed adjuvants is therefore recommended.

Hydrophobic Gels

Lipogels or oleogels are obtained by adding a suitable thickening agent to an oil or liquid lipid. For example, colloidal silica may be used for that reason. A special type of hydrophobic gels is silicone-based systems.

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Hydrolipid Dispersions

Hydrolipid dispersions are a special type of emulsion and are therefore treated separately in this chapter. They are disperse systems with a hydrophilic continuous phase and a lipophilic internal phase. The concentration of lipids lies between 2 and 20%. In principle, such a system is thermodynamically unstable. For stabilization, suitable large polymers are added, which are hydrated lyophilic colloids in the aqueous medium. Because of their molecular structure these polymeric emulsifiers are able to form mono- to multilamellar films at the interfaces and hence stabilize the emulsion. Typical examples are acrylates/C10-30alkyl acrylate crosspolymers. These polymers must have a sufficient surface activity that enables them to interact between the two different phases, resulting in a ''quasi-emulsion,'' alternatively called balm, costabilized by hydroxypropyl methylcellulose or polyacrylate. The dispersed oil droplets may show a relatively large size of 20 to 50 μm, but such a quasiemulsion remains stable [20]. The great advantage of hydrolipid-dispersions is their lack of conventional emulsifiers, surfactants with skin irritation potential.

Microemulsions

According to the definition of Danielsson and Lindman [21], a microemulsion is defined as a system of water, oil, and amphiphile, which is a single optically isotropic and thermodynamically stable liquid solution. ''This definition should be widened, however, to include metastable states, spontaneous emulsions of long-lived kinetic stability [22].'' The term microemulsion may be a misnomer, because microemulsions consist of large or ''swollen'' micelles containing the internal phase, much like that found in a solubilized solution [23]. Microemulsions contain oil droplets in a water phase or water droplets in oil with diameters of about 10 to 200 nm. Therefore they appear as isotropic, optically clear liquid or gel-like systems. Unlike micellar solubilized systems, microemulsions may not be thermodynamically stable; nevertheless, they are more stable than ordinary emulsions. They are a type of ternary system composed from water, lipid, and surfactant mixture in a distinct ratio. The latter is usually a surfactant, such as Brij 96 [polyoxyethylene (10) oleyl ether] combined with a cosurfactant such as propylene glycol or ethylene glycol. Microemulsions may be used to incorporate or dissolve active substances and have been found to improve skin penetration and permeation [24].

The disadvantage of microemulsions is their rather high concentration of surfactants, which is a risk for increased skin irritation and sensitization. Nevertheless, modern microemulsion formulation is based on alkyl polyglycosides which are regarded to be milder than conventional nonionic surfactants with polyoxyethylene chains.

Nanoemulsions and Nanoparticles

During the last years, special dispersion formulations have been developed and described that contain ultra small particles used as carriers for active substances. The particles have a size in the range of 10 to a few hundred nanometers. This group of formulations shows a large heterogeneity and very often various terms or trade names have been created naming the same or similar systems. Generally the particles are dispersed in an aqueous medium.

For example, solid lipid nanoparticles possess a solid matrix composed of physiological lipids or lipoids with a mean diameter in the range of approximately 50 to 1000 nm

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[25]. Active substances may be incorporated into these lipid nanoparticles serving as carriers, provided that the active substances are released after application on the skin.

Alternatively, the core of nanoparticles may either be a liquid lipid functioning as carrier or a lipophilic agent being directly effective, e.g., an emollient or occlusive agent. For stabilization, a monolayer of surfactants surrounding/covering the lipid droplet is used, e.g., phospholipids combined with a selected cosurfactant in a defined ratio [26,27]. Instead of a lipid, lipophilic active substances may be incorporated, e.g., vitamin A or E, UV filters, fragrances, etc. This type of nanoparticle is thought to be relatively insensitive toward the presence of additional surfactants in contrast to liposomes; therefore they can be mixed with conventional emulsions and the size of the nanoparticles remains in the submicron range.

Suspensions

Strictly considered, suspensions are not just vehicles but products consisting of particles, generally actives or functional excipients, that are dispersed in a liquid or semisolid medium that functions as a vehicle. Nevertheless, a suspension is also a type of formulation that may be used for application on the skin and to deliver substances to a target. In this way, a suspension can be regarded as a vehicle entity affecting the application site. Examples are sun-protection products or pearlescent nail lacquers containing pigments.

In suspension, sedimentation of unsoluble particles may happen because of difference in density. In order to guarantee a homogeneous product when applied, the particles must be redispersible by shaking before use. Alternatively, sedimentation must be hindered or at least reduced during storage. This is achieved by reduction of particle size and/or by increasing the viscosity of the vehicle, ideally creating a thixotropic system. The vehicle effect of the suspension on the skin is primarily caused by the liquid or semisolid phase of the vehicle comparable to solutions and emulsions.

Sticks

A stick is a solid delivery vehicle cast in an elongated form. By rubbing a stick onto skin, a variety of cosmetic ingredients can be delivered, such as fragrances, coloring agents, and emollients. In particular, sticks are ideally suited to deliver insoluble substances, e.g., pigments. The most popular cosmetic sticks are lipsticks and antiperspirant/deodorant sticks.

There are mainly three basic vehicle types of sticks:

1. Mixture of waxes (e.g., beeswax, carnauba) and oils (e.g., mineral, castor oil) that are cast into solid form, containing dissolved or undissolved active ingredients
2. Hydrophilic or aqueous sticks: solutions based on aqueous, propylene glycol, alcohol mixtures, solidified usually by sodium stearate, containing, e.g., aluminium chlorohydrate as antiperspirant
3. Matrix consisting of a high-boiling volatile silicone (e.g., cyclomethicone) gelled by fatty alcohol (e.g., stearyl alcohol)

In recent years, clear sticks have become popular. As a gelling agent, dibenzylidene sorbitol is used in propylene glycol or other related polyols [28].

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FUNCTIONAL DESIGN, COMPOSITION, AND RESULTING EFFECT

There is no universal cosmetic vehicle available that can simply be mixed with an active cosmetic substance to get the cosmetic care product of choice, nor is there a general principle that could be observed to perform development of such a product. But a cosmetic care product has to be developed and whenever this is the case, various issues and aspects have to be considered and many problems must be solved step-by-step. Although formulation (galenical development) of cosmetic products is still rather empirical today, a rational approach is suggested. This section discusses the main issues that are to be considered when a functionally designed cosmetic product is being developed.

Target Profile

First, a clear target profile of the product must be defined. This includes the following:

1. Site of application. Depending on the site, certain forms may not be adequate, e.g., a w/o cream is not at all suitable for application on hair.
2. Area of application. A sticky, greasy cream cannot be applied on the whole body surface.
3. Target site. For example, the uppermost layer of stratum corneum or viable epidermis.
4. Sensory properties. For example, foaming shampoo or a light, smooth, low-viscosity cream.
5. Optical aspect. Clear, transparent, or milky, mono- or multiphasic.
6. State of matter. Liquid, semisolid, or solid.
7. Basic type of form. Solution or emulsion.
8. Active substances. Selected vegetable oil, vitamins, UV screen.
9. Storage stability and conditions.
10. Packaging.
11. Comparable, competitor products.

Selection of Vehicle Type

The type of vehicle may already be determined by the product target profile. If various types are possible, the most suitable should be selected. The following selection criteria are important: function or desired effect of the vehicle on the skin, ease of formulation feasibility, and physical and chemical stability. Furthermore, solubility, polarity, saturation solubility, vehicle interactions, and formation of mesophases are subjects to be considered when dealing with development and selection of vehicles. These topics are discussed later.

True Solution Versus Disperse System

Whenever the target of an active substance lies in deeper regions of the skin or even in skin cells, the substance must be present in molecular form for successful and efficient delivery, i.e., it must be dissolved in the vehicle or it must be able to dissolve, at least, after application. In other words, dissolution of a substance is a prerequisite for its delivery to a biological viable target (e.g., cell, enzyme). It is only in the dissolved state that fast and efficient penetration and transport into the deeper skin layers and cells is possible.

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Thus, the first goal in formulation development is to dissolve the active substance in the vehicle. Therefore, the vehicle should be an ideal solvent for the active substance. If a substance cannot be dissolved in the vehicle—this may happen because of low solubility properties or stability reasons—then the substance has to be incorporated in particulate form; the smaller the size, the better. Fine particles in the order of 1 μm can be delivered onto or even into the uppermost layers of the skin, as close as possible to the target site. There they may dissolve, faster or slower, depending on their solubility in the skin. In vehicle systems containing particulate matter, homogeneous distribution of the undissolved substances must be guaranteed.

In summary, if the first goal—dissolution of active substance in the vehicle—is not achieved, the first alternative in formulation development must be targeted: the substance to be delivered must occur in particulate form as fine as possible. This is the prerequisite for fast and efficient delivery of unsoluble matter into the skin close to the target site.

Polarity

In order to achieve dissolution of a substance (solute), the adequate vehicle (solvent) has to be selected. The solubility of a substance is attributable in large measure to the polarity of the solvent, and it generally depends on chemical, electrical, and structural effects that lead to mutual interactions between the solute and solvent [29]. Polar solvents dissolve ionic solutes and other polar substances, whereas nonpolar substances are dissolved in nonpolar, lipophilic solvents. Solubility properties determine the selection of the appropriate vehicle for both, for solid as well as for liquid substances. Only nonpolar liquids are mutually completely miscible and thus can be used to make a nonpolar liquid vehicle. Accordingly, the same is true for polar liquids (e.g., water and alcohol).

Solubility characteristics of a compound used in formulation is one of the most important factors to be considered. Solubility data can be found in the literature; very often they are delivered by suppliers of the substances or they must be determined experimentally. In formulation the solubility parameter δ, according to Hildebrand and Scott [30], is a useful tool for selection of appropriate solvents. The more alike the δ-values of the compounds, the greater is their mutual solubility. A list of solubility parameters of cosmetic ingredients is given in Ref. 31. Very apolar substances have a low δ-value, and water has the highest value [23]. A rule of thumb states that mutual solubility is given if the difference between the two specific δ-values is at maximum 2 units $(cal/cm^3)^{-2}$.

Particularly in cosmetic formulation, where oils and lipids play a dominating role, polarity of oils is a factor to be considered. According to ICI Surfactants [16], the polarity may also be expressed by the polarity index based on the surface tension between the oil and water. Another interesting and simple characterization method is based on the bathochromic effect of a suitable dye dissolved in oils. The absorption maximum in the visible light—and therefore the color—of a nil-red-oil solution depends on the polarity of the oil; the higher the absorption maximum, the more polar is the oil or oil mixture [32].

In conclusion, if a monophasic system has to be formulated, only substances with mutual solubility can be combined. In contrast, if multiphasic systems such as emulsions and suspensions are made, the phase-forming components must be mutually insoluble. Nevertheless, preparation and solubilization of multiphasic systems require the addition of amphiphilic substances (emulsifiers in emulsions, surfactants for wetting and repulsing the particles in suspensions). In emulsions, polar as well as nonpolar substances can be dissolved in the hydrophilic or lipophilic phase, respectively. This is one reason for the popularity of emulsions.

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Saturation, Supersaturation

Theoretically, a solute can be dissolved in a solvent up to the saturation solubility. Beyond this concentration, precipitation of the solute or phase separation usually occurs. Some substances are able to remain transiently in solution above saturation solubility. This phenomenon is known as supersaturation, a metastable condition. Supersaturated solutions can be caused to return to saturation equilibrium by triggers such as agitation, scratching the wall of containers, or addition of seeding crystals.

The driving force for delivery of substances, i.e., release from vehicle and penetration into skin, is thermodynamic activity, which is maximal at saturation concentration [33]. Consequently, in order to achieve maximal penetration rate into the skin, a substance must be dissolved in a vehicle at saturation concentration. Moreover, saturated or supersaturated systems are necessary, but not the only prerequisites for optimal topical delivery. For example, the skin—vehicle partition coefficient of the solute also plays a role. The partition coefficient may be raised because of the vehicle—skin interaction yielding in increased skin penetration. In conclusion, achieving the highest possible concentration in the dissolved state is the second goal to be aimed for in formulation development if delivery into the skin is targeted.

Vehicle Interactions

Sun-protection products are a good example of showing interactions between vehicle, active substance, and the skin. The absorption of UV radiation not only depends on the molecular structure and concentration of the protecting agent, but on the solvent as well. Also, water resistancy may be influenced by selection and composition of the vehicle.

Vehicle components may penetrate into the stratum corneum and interact with the stratum corneum lipids. This may result in disturbance of their lamellar structures and increased and faster penetration of compounds in the stratum corneum. Alternatively, presence of vehicle components in the stratum corneum may cause a depot effect for certain compounds.

Substantivity

The term substantivity describes adherence properties of materials to keratinous substrates in the upper skin layers, in particular regarding deposition and retention capacity when in contact with water, which could deplete the material [34]. High substantivity is especially important for sun protection products. It is primarily a function of the physicochemical properties of the active molecules but may also be influenced by the vehicle. For example, addition of film-forming, skin-adherent polymeric substances to the vehicle may increase retention of sunscreens in the skin and thus result in an improved water-resistant product. Another means is creating formulations that contain phospholipids, enabling the formation of vesicular, liposomal structures in the vehicle or in the upper layers of stratum corneum and thus yielding in a depot effect.

An interesting model to assess substantivity has been presented by Ref. 34. The investigators used human callus to simulate and quantify solute sorption to human skin, which was found to be more suitable than octanol or animal keratin. However, water resistancy still has to be determined in vivo to know the true quality of the product.

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Mesophases

Not only the type of vehicle, e.g., solution or o/w emulsion, but also occurrence and type of mesophases (liquid crystal structures) determine the properties and behavior of a vehicle. At certain concentrations and combinations of specific emulsifying agents in liquids, associations may be formed, resulting in liquid crystal structures, also called mesomorphic state or mesophase. The mesophase shows anisotropy and is thermodynamically stable. Different types of mesophases have been described: middle phase (hexagonal), cubic phase, and neat phase (lamellar).

Fatty amphiphiles (e.g., long chain alcohols, acids, monoglycerides) that are dispersed in water in the presence of a high hydrophilic-lipophilic balance (HLB) surfactant form lamellar phases. They are able to swell at an elevated temperature close to the melting point of the hydrocarbon chain. These swollen lamellar liquid crystalline phases can incorporate significant quantities of water. The hydrocarbon chains are liquid-like, i.e., disordered. If the temperature decreases, the lamellar liquid crystalline phases of fatty amphiphiles are transformed to so-called lamellar crystalline gel network phases, which build complex gel networks. Such networks not only stabilize creams and lotions, but also control their consistency because of their viscoelastic properties. Such mesophases provide the following advantages to emulsions:

1. Increased stability
2. Prolonged hydration properties
3. Controlled release of active ingredient
4. Easy to formulate
5. Well-liked skin feel [35]

Metamorphosis of Vehicles

Most vehicles undergo considerable changes during and after application to the skin because of mechanical stress when spread over the surface and/or evaporation of volatile ingredients. Mechanical stress and skin temperature may influence the viscosity of the vehicle and consequently the release rate of active ingredients. Uptake of water from the skin may alter the composition of the vehicle. All these factors may also cause phase inversion or phase separation. And last but not least, as a consequence of these alterations the thermodynamic activity of an active ingredient within its vehicle will change as well. Thus, by controlling or changing the thermodynamic activity, release of a substance from the vehicle and penetration into the skin can be modulated. For example, if after application the volatile component of the vehicle, being an excellent solvent of the active substance, evaporates, saturation concentration of the active in the remaining vehicle or even supersaturation may be achieved. This results either in improved release and delivery as previously mentioned (see Section 5.2.3) or in precipitation and deposition of the active substance. Another interesting example is given by an optimally composed sun-protecting o/w-emulsion; after application the emulsion has transformed to the w/o type because of water evaporation and the mechanical stress caused by spreading. The remaining lipophilic protective film yields in improved water resistancy.

In conclusion, the optimally designed and developed vehicle not only demonstrates excellent properties after manufacturing and storage, but also after application and metamorphosis at the application site.

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Rheology

The term rheology describes the flow characteristics of liquids and the deformation of solids. Viscosity is an expression of the resistance of a fluid to flow. Rheological properties are crucial for liquid and semiliquid cosmetic formulations because they determine the product's properties meaningful in mixing and flow when produced, filled into containers and removed before use, as well as sensory properties when applied, such as consistency, spreadability, and smoothness. Furthermore, the rheology of a product may also affect the physical stability and the biological availability of the product [36].

Regarding rheological characteristics, there are two main types of systems: Newtonian and non-Newtonian. The former show constant viscosity when stressed, i.e., the rate of shear (flow velocity) is directly proportional to the shearing stress, e.g., water, mineral oil, etc. In non-Newtonian systems (most cosmetic products), however, viscosity changes with varying stress, i.e., viscosity depends on the degree of shearing stress, resulting either in plastic, pseudoplastic, or dilatant flow or in thixothropy, characteristics that are not discussed in depth here although they are of practical significance. An ideal topical product, e.g., shows optimal thixotropic properties; it does not flow out of a tube's orifice unless slightly pressed, and when on the skin it does not immediately flow and drop off unless easily spread over the application area, where under a certain stress it becomes more fluid because of the thixotropy. The rheological properties of semisolid products are determined first for general characterization in the development phase and second for quality-control reasons after manufacturing. There are various instrumental methods used to measure rheology or viscosity. Today, apparatus based on rotation or oscillation are commonly used for non-Newtonian systems.

In order to adjust the rheology of products, various means and excipients are available. If the viscosity has to be increased, addition of viscosity increasing agents is needed. Addition or increase in concentration of electrolytes may influence viscosity. Many systems, e.g., polyacrylates, are sensitive to the presence of ions and the viscosity is reduced.

In particular, emulsions are susceptible to rheological issues. Various factors determine the rheological properties of emulsions, such as viscosity of internal and external phases, phase volume ratio, particle size distribution, type and concentration of emulsifying system, and viscosity-modifying agents. However, this topic is too complex to be treated comprehensively in this context. It is further discussed in a review by Sherman [37]. It is important to realize that small changes in concentrations or ratio of certain ingredients may result in drastic changes of the rheological characteristics. Emulsified products may undergo a wide variety of shear stresses during either preparation or use. Thus, an emulsion formulation should be robust enough to resist external factors that could modify its rheological properties or the product should be designed so that change in rheology results in a desired effect.

Preservation

Antimicrobials

Most cosmetic care products must be protected against microbial growth. Not only for the protection of consumers against infection but also for stability reasons. Growth of microorganisms might result in degradation of ingredients and consequently in deterioration of physical and chemical stability. In general, presence of water in the vehicle as well as other ingredients susceptible to microbial metabolism require adequate preservation.

There are various ways to protect a product against microbial growth:

1. Addition of an antimicrobial agent, which is common practice
2. Sterile or aseptic production and filling into packaging material, preventing microbial contamination during storage and usage
3. Reduced water activity, i.e., controlling growth of spoilage microorganisms by reducing the available amount of water in cosmetic preparations [38]

It is not only mandatory to add antimicrobials but also to test their efficacy after manufacturing and after storage until the expiration date. Nowadays performance of the preservative efficacy test (PET), also known as the challenge test, is state of the art [39]. Today more and more in-use tests are performed to simulate the usage by the consumer and to show efficacious protection against microbial growth after contamination.

Addition of preservatives to complex, multiphasic systems, in particular, is a critical formulation issue for the following reasons:

1. Many preservatives interact with other components of the vehicle, e.g., with emulsifyers, resulting in change of viscosity or in phase separation in the worst case.
2. Depending on the physicochemical characteristics, preservatives are distributed between the different phases which might result in too-low effective concentration in the aqueous phase.
3. Adsorption of the preservatives to polymers in the formulation and/or packaging material; complexation or micellization might also result in too-low antimicrobial activity.

In conclusion, it is not sufficient to add a preservative at recommended concentration. To protect the vehicle sufficiently, a properly designed preservative system is required that must be tested in the formulation regarding efficacy and safety. It is a great formulation challenge to achieve sufficient protection against microbial growth in the product, especially as many antimicrobials are discredited because of their irritation and sensitization potential.

Antioxidants

Protection against oxidation may also be a formulation issue although not so relevant as antimicrobial efficacy. It is achieved by addition of antioxidants or by manufacturing and storing in an inert atmosphere. In particular, modern formulations containing oxidation-sensitive compounds, such as certain vitamins and vegetable oils with unsaturated fatty acid derivatives, must be sufficiently protected against oxygen.

Development Strategy and Rationale

Having considered the aforementioned issues, formulation development is preferably conducted according to a suitable, rational procedure. The complex formulation development process may be represented symbolically by the ''magic formulation triangle'' (Fig. 1), showing the mutual interaction and dependency of the following:

1. Feasibility of preparation or formulation of the active substance(s) in the vehicle
2. Stability (chemical and physical) of the product, and
3. Effectivity or activity of the product when applied.

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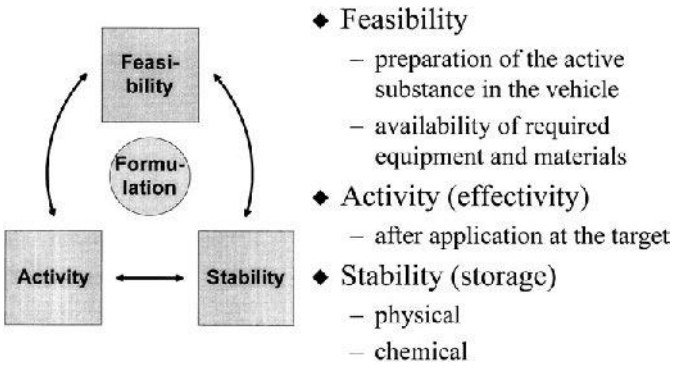

FIGURE 1 Magic triangle of formulation: mutual interaction and dependency.

First, the feasibility of preparation and formulation has to be checked. For example, if a low–water-soluble compound should be dissolved in an aqueous vehicle, solubility-enhancing studies are performed. Or if an emulsion is desired, it has to be checked whether the phases can be emulsified with the selected emulsifying system.

After having prepared the desired formulation, both stability and effect must be assessed, preferably more or less in parallel. It does not make any sense to have a stable but ineffective product, or to develop a very effective system that remains stable for a few days or that contains an ingredient that is irritating or sensitizing. Such a product cannot be marketed. For example, if a relatively unstable active substance (e.g., ascorbic acid) must be delivered in dissolved form to be effective or bioavailable at the target site, then a suitable vehicle with good solvent properties must be used. However, the chemical stability of compounds is generally lower when in solution. Therefore, not every suitable solvent can be used as a vehicle, but an optimum has to be found, a vehicle enabling both, keeping the active to remain dissolved and in a chemically stable state.

Having in mind those three cornerstones of the formulation triangle, formulation development to find the right vehicle is performed stepwise, addressing the following issues:

1. Objective, definition of target profile (See p. 158.)
2. Preformulation investigation: determination of physicochemical properties of (active) substances to be formulated, such as solubility data, partition coefficient, dissociation constant, pH, crystal morphology, particle size distribution, and assessment of their stability and incompatibility
3. Selection of appropriate excipients to be used for formulation
4. Based on the outcome of these three working steps the feasibility of preparation is checked and modifications are made if necessary, all of these together to prepare the next step
5. Formulation screening on a small-scale basis with as many as possible and feasible variations in composition, excipients, preparation methods, and so on
6. Selection of the best formulations and preparation methods from the screening program for technical scaling-up as well as for confirmation and validation of the results obtained with the formulations. The selection of the formulations is based on criteria such as physical stability or absence of precipitation in solu-

tion, no sedimentation or phase separation or recrystallization in multiphasic systems; chemical stability or degradation, respectively; preservative efficacy test (PET); biological assessment, e.g., skin-hydration effect, sun-protecting effect, and antioxidant or radical scavenger effect in cells; and

7. Safety evaluation in human beings with formulation chosen for introduction into market.

PREPARATION METHODS

It is not the intention to present a review on preparation methods and equipment for the manufacturing of cosmetic vehicles and products in this chapter. But it is common sense that the preparation method may influence a product's quality. Thus, not only the composition but also the way of preparation should be in the scope of development and preparation work. There are many types and variations of mixing, dispersion, emulsification, and size-reduction equipment that can be used to prepare vehicles that are used in cosmetics. For example, size reduction of the internal phase droplets in an emulsion depends on the mechanical principle of the used equipment, and best results are achieved with a valve homogenizer. In every case the goal is to get a homogeneous product of specified and reproducible quality. Only with a product of specified and constant quality a reproducible effect can be achieved when applied. Standard, basic operations are dissolution, blending and mixing, dispersion and homogenization, and size reduction, which may all be associated by energy transfer involving cooling or heating.

It is of paramount importance that in early development phases preparation is performed under well-defined and known conditions, otherwise scaling-up and reproducibility of product quality becomes a risky task. Closely related with the preparation method is testing and characterization of the product. This is treated in the following section.

CHARACTERIZATION

Physical Characterization

Appearance

Assessment and description of appearance is one of the easiest, most practical, and nevertheless powerful tests. It may be performed macroscopically, describing color, clearness, transparency, turbidity, and state of matter. In addition, microscopic investigation is recommended; taking microphotographs is useful for documentation.

Rheology

Rheological properties (viscosity, consistency) are important characteristics of most types of cosmetic care products because they have an impact on preparation, packaging, storage, application, and delivery of actives. Thus these properties should be assessed for characterization and quality control of the product.

Most disperse systems and thus cosmetic care products show Non-Newtonian flow behavior, namely pseudoplastic, plastic, or dilatant behavior. A wide variety of techniques and methods have been developed to measure viscosity properties. These procedures can be classified as either absolute or relative. The absolute either directly or indirectly measures specific components of shear stress and shear rate to define an appropriate rheological function. Methods used for absolute viscosity measurements are flow through a tube, rota-

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tional methods, or surface viscosity methods. Methods used for relative viscosity measurement are those using orifice viscometers, falling balls, or plungers. Such instruments, although they do not measure stress or shear rate, offer valuable quality-control tests for relative comparison between different materials [40]. Apparatus based on rotational or even oscillating principles to assess viscoelastic properties is state of the art.

pH

Measurement of pH value (concentration of hydrogen ions) in aqueous vehicles (solutions, suspensions, o/w emulsions, gels) is a valuable control mean. First of all, if possible, a pH value in the physiological range is generally targeted, ideally similar to that of the skin or the specific application site, in order to prevent irritation. Many reactions and processes depend on pH, e.g., efficacy of antimicrobial preservatives, stability and degradation of substances, and solubility. Thus, pH measurement is a ''must'' and it is easily performed with the available measurement systems.

Homogeneity

In many cases, at a first step homogeneity may be assessed visibly; precipitation in a solution or distinct phase separation in an emulsion is easily detected. Nontransparent, multiphasic systems are more difficult to check. In these cases, microscopic investigation of representative samples is suggested along with quantitative assays regarding active ingredients (uniformity of content).

Droplet or Particle Size and Distribution

The physical stability of colloidal systems as well as emulsions or suspensions partially depends on the particle size. In particular, preparations containing small particles with identical electrical charge are more resistant to flocculation and sedimentation than systems containing larger or uncharged entities. Similarly, reduced particle size is an indicator of improved kinetic stability of emulsions or suspensions. For that reason, determination of particle size and size distribution is an important characterization method. Various optical methods are available; A minireview is given in Ref. 41 and a selection is listed as follows:

1. Perhaps the most commonly used method today is based on laser diffraction, suitable to measure solid particles and also dispersed droplets under special conditions, size range 1 to 600 μm.
2. Dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), is used for measuring micelles, liposomes, and submicron suspensions (size range 0.003 to 3 μm).
3. Optical or electron microscopy are further methods of choice.

Chemical Characterization

Besides physical characterization, chemically based investigations are indispensable to assess the quality of a product. It is well known that the quality and composition of a vehicle can influence the chemical stability of ingredients. Many reactions, such as ester hydrolysis or other degradations, may be enhanced or sustained by change in pH, presence of catalytic or stabilizing agents, respectively. Thus, development and optimal selection of the best vehicle is supported by chemical stability investigations.

Biological Characterization

Further important assessment methods are based on biological tests. This is to evaluate and validate the desired targeted effects in vivo after application of the product. Examples include hydration of the skin, protection against sun radiation, and protection against skin irritating substances during work. This subject is treated in other chapters of this textbook.

Sensory Assessment

The sensory assessment is a useful tool for product and concept development and for quality control in the cosmetic industry. Although a very subjective and liable method, valuable data is obtained if sensory assessment is conducted in a systematic way. Terms like pick up, consistency, peaking, cushion, absorption, smoothness, stickiness, tackiness, oiliness, and greasy are used. An interesting paper on that subject has been published by Busch and Gassenmeier [42].

Barry and coworkers carried out sensory testing on topical preparations and established rheological methods for use as control procedures to maintain uniform skin feel and spreadability [43]. The consistency of a material can be assessed by using three attributes: smoothness, thinness, and warmth [44].

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15

Encapsulation to Deliver Topical Actives

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INTRODUCTION

Cosmetic technology is constantly developing raw materials and formulation with active ingredients. The new surfactant molecules, the search for original active substances and efficient combinations, and the design of novel vehicles or carriers has led to the implementation of new cosmetic systems in contrast to the classic forms such as creams or gels.

The achievements of recent extensive research has resulted in the development of controlled delivery systems. Some of these systems have been extensively investigated for their therapeutic potential while simultaneously being examined for their possible cosmetic uses. One objective in the design of novel drug delivery systems is controlled delivery of the active to its site of action at an appropriate rate. Novel polymers and surfactants in different forms, sizes, and shapes can aid in this goal. Encapsulation techniques are used in pharmaceuticals, cosmetics, veterinary application, food, copying systems, laundry products, agricultural uses, pigments, and other less well-known uses to control the delivery of encapsulated agents as well as to protect those agents from environmental degradation.

DESIGN ASPECTS OF A VECTOR

Microparticles

Microencapsulation is a process by which very thin coatings of inert natural or synthetic polymeric materials are deposited around microsized particles of solids or droplets of liquids. Products thus formed are known as microparticles, covering two types of forms: microcapsules, micrometric reservoir systems, and microspheres, micrometric matrix systems (Fig. 1).

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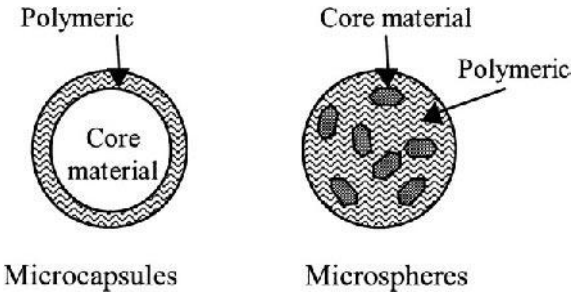

FIGURE 1 Schematic representation of microparticles.

These systems consist of two major parts. The inner part is the core material containing one or more active ingredients. These active ingredients may be solids, liquids, or gases. The outer part is the coating material that is usually of a high–molecular weight polymer or a combination of such polymers. The coating material can be chosen from a variety of natural and synthetic polymers. The coating material must be nonreactive to the core material, preferably biodegradable, and nontoxic. Other components, such as plasticizers and surfactants, may also be added.

Initially, microparticles were produced mainly in sizes ranging from 5 μm to as much as 2 mm, but around 1980 a second generation of products of much smaller dimensions was developed. This includes nanoparticles from 10 to 1000 nm in diameter [1], as well as 1 to 10 μm microspheres, overlapping in size with nonsolid microstructures such as liposomes. Commercial microparticles typically have a diameter between 1 and 1000 μm and contain 10 to 90 wt% core. Most capsule shell materials are organic polymers, but fat and waxes are also used. Various types of physical structures of the product of microencapsulation such as mononuclear spheres, multinuclear spheres, multinuclear irregular particles, and so on can be obtained depending on the manufacturing process.

Recently, a polymeric system consisting of porous microspheres named Microsponge has been developed (Microsponge System [2]; Advanced Polymer System Inc., Redwood City, CA). These systems are made by suspension polymerization and typically consist of cross-linked polystyrene or polymethacrylates.

No encapsulation process developed to date is able to produce the full range of capsules desired by potential capsule users. The methods, which are significantly relevant to the production of microparticles used in pharmaceutical products and cosmetics, are shown in Table 1. Many techniques have been proposed for the production of microparticles, and it was suggested [9] that more than 200 methods could be identified in the literature. A thorough description of the formation of microparticles are given by several reviews [4,6,10,11].

Nanoparticles

Nanoparticles can generally be defined as submicron ($<1\mu m$) colloidal systems, but are not necessarily made of polymers (biodegradable or not). According to the process used for the preparation of nanoparticles, nanocapsules or nanospheres can be obtained. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a

TABLE 1 Microencapsulation Methods

Type	Reference
Coacervation-phase separation procedures using aqueous vehicles	3
Coacervation-phase separation procedures using nonaqueous vehicles	4
Interfacial polymerization	5
In situ polymerization	6
Polymer-polymer incompatibility	3
Spray drying, spray congealing, spray embedding, and spray polymerization	4
Droplet extrusion	7 8

unique polymeric membrane; nanospheres are matrix systems in which the drug is dispersed throughout the particles.

Several methods have been developed for preparing nanoparticles. They can be classified in two main categories according to whether the formation of nanoparticles requires a polymerization reaction (Table 2) or whether it is achieved from a macromolecule or a preformed polymer (Table 3). De Vringer and Ronde [25] proposed a water-in-oil (w/o) cream containing nanoparticles of solid paraffin to obtain a topical dermatological product with a high degree of occlusivity combined with attractive cosmetic properties. Kim et al. [26] reported the encapsulation of fat vitamin series in nanospheres prepared with soybean lecithin coated with a nonionic surfactant. Müller [27,28] believes that the solid lipid nanoparticles (SLN) appear as an attractive carrier system for cosmetic ingredients—unloaded and loaded. In the case of unloaded particles, the SLN themselves represent the active ingredient, e.g., when made from skin-carrying lipids. Alternatively, the SLN can be blended with special lipids, e.g., ceramides. Finally, good reviews with methods of preparation for nanoparticles can be found in the literature, such those by Kreuter [12] and Couvreur et al. [29].

Multiple Emulsions

Multiple emulsions are emulsions in which the dispersion phase contains another dispersion phase. Thus, a water-in-oil-in-water (w/o/w) emulsion is a system in which the globules of water are dispersed in globules of oil, and the oil globules are themselves dispersed

TABLE 2 Nanoparticles Obtained by Polymerization of a Monomer

Type	Reference
Nanospheres	
Poly(methylmethacrylate) and Polyalkylcyanoacrilate nanoparticles	12
Polyalkylcyanoacrylate nanospheres	13
Nanocapsules	
Polyalkylcyanoacrylate nanocapsules	14, 15

TABLE 3 Nanoparticles Obtained by Dispersion of Preformed Macromolecules

Type	Reference
Nanospheres prepared by emulsification	
Solution emulsification	16
Phase inversion	17
Self-emulsification	18
Nanospheres of synthetic polymers	19, 20, 21
Nanospheres of natural polymers	21
Nanospheres prepared by desalvation	
Nanospheres of synthetic polymers	22
Nanospheres of natural polymers	23, 24
Nanocapsules	14, 22

in an aqueous environment. A parallel arrangement exists in oil-in-water-in-oil (o/w/o) type of multiple emulsions in which an internal oily phase is dispersed in aqueous globules, which are themselves dispersed within an external oily phase (Fig. 2).

Multiple emulsions, first described by Seifriz in 1925, have recently been studied in detail. The operational technique plays an even more important role in the production of multiple emulsions than in the production of simple emulsions [30–35]. Multiple emulsions have been prepared in two main modes: one-step and two-step emulsification.

One-step emulsification is prepared by forming w/o emulsion with a large excess of relatively hydrophobic emulsifier and a small amount of hydrophilic emulsifier followed by heat treating the emulsion until, at least in part, it will invert. At a proper temperature, and with the right hydrophilic lipophilic balance (HLB) of the emulsifiers, w/o/w emulsion can be found in the system. In most recent studies, multiple emulsions are prepared in a two-step emulsification process by two sets of emulsifiers: a hydrophobic emulsifier I (for the w/o emulsion) and a hydrophilic emulsifier II (for the oil-in-water (o/w) emulsion). The primary emulsion is prepared under high shear conditions (ultrasonification, homogenization), whereas the secondary emulsification step is carried out without any severe mixing (an excess of mixing can rupture the drops, resulting in a simple emulsion).

The composition of the multiple emulsions is of significant importance, because the different surfactants along with the nature and concentration of the oil phase will affect the stability of the double emulsion. Parameters such as HLB, oil phase volume, and the

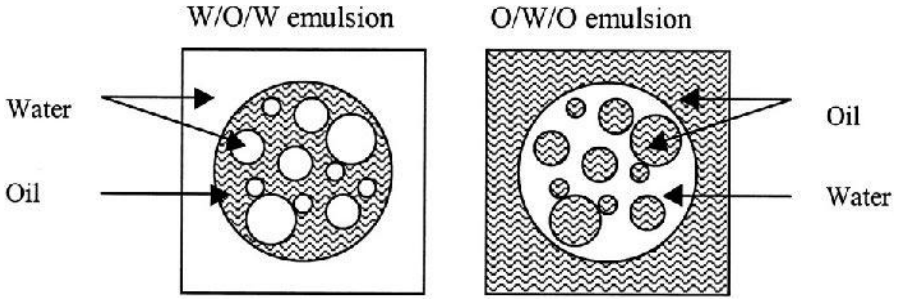

FIGURE 2 Schematic representation of multiple emulsions.

nature of the entrapped materials have been discussed and optimized. Several reviews and studies include Florence and Whitehill [36–38], Matsumoto et al. [39,40] and Frenkel [41–43].

Microemulsions

Miocroemulsions are stable dispersions in the form of spherical droplets whose diameter is in the range of 10 to 100 nm. They are composed of oil, water, and usually surfactant and cosurfactant. These systems show structural similarity to micelles and inverse micelles, resulting in o/w or w/o microemulsions, respectively. They are highly dynamic systems showing fluctuating surfaces caused by forming and deforming processes.

The main characteristics of microemulsions are the low viscosity associated with a Newtonian-type flow, a transparent or translucid appearance, and isotropic and thermodynamic stability within a specific temperature setting. Certain microemulsions may thus be obtained without heating, simply by mixing the components as long as they are in a liquid state. One of the conditions for microemulsion formation is a very small, rather than a transient negative, interfacial tension (44). This is rarely achieved by the use of a single surfactant, usually necessitating the addition of a cosurfactant. The presence of a short chain alcohol, e.g., can reduce the interfacial tension from about 10 mN/m to a value less than 10^{-2}mN/m. Exceptions to this rule are provided by nonionic surfactants which, at their phase inversion temperature, also exhibit very low interfacial tensions.

A microemulsion is usually created by the establishment of pseudoternary diagram for which a ratio of surfactant/cosurfactant is fixed, representing a sole constituent. The establishment of a ternary diagram is generally accomplished for locating the microemulsion or the microemulsion zones by titration. Using a specific ratio of surfactant/cosurfactant, various combinations of oil and surfactant/cosurfactant are produced. The water is added drop by drop. After the addition of each drop, the mixture is stirred and examined through a crossed polarized filter. The appearance (transparence, opalescence, isotropy) is recorded, along with a number of phases. In this way, an approximate delineation of the boundaries can be obtained in which it is possible to refine through the production of compositions point by point beginning with the four basic components.

Nanoemulsions (Submicron Emulsions)

Emulsions are heterogeneous systems in which one immiscible liquid is dispersed as droplets in another liquid. Such a system is thermodynamically unstable and is kinetically stabilized by the addition of one further component or mixture of components that exhibits emulsifying properties. Depending on the nature of the diverse components of the emulsifying agents, various types of emulsions can result from the mixture of immiscible liquids. The main characteristic of nanoemulsions or submicron emulsions is the droplet size, which must be inferior to 1μm.

Emulsions prepared by use of conventional apparatus, e.g., electric mixers and mechanical stirrers, show large droplet sizes and wide particle distribution. The techniques usually used to prepare submicron emulsions involve the use of ultrasound, evaporation of solvent (45), two-stage homogenizer [46,47], and the microfluidizer [48,49]. The nanoemulsion preparation process involves the following steps:

1. Three approaches can be used to incorporate the drug and/or the emulsifiers in the aqueous or oil phase. The most common is to dissolve the water-soluble

ingredients in the aqueous phase and the oil-soluble ingredients in the oil phase. The second approach, which is used in fat emulsion preparations [46], involves the dissolution of an aqueous-insoluble emulsifier in alcohol, the dispersion of the alcohol solution in water, and the evaporation and total removal of the alcohol until a fine dispersion of the alcohol solution of the emulsifer in the aqueous phase is reached. The third, which is mainly used for amphotericin B incorporation into an emulsion, involves the preparation of a liposome-like dispersion. The drugs and phospholipids are first dissolved in methanol, dichloromethane, chloroform, or a combination of these organic solvents, and then filtered into a round-bottom flask. The drug-phospholipid complex is deposited into a thin film by evaporation of the organic solvent under reduced pressure. After sonication with the aqueous phase, a liposome-like dispersion is formed in the aqueous phase. The filtered oil phase and the aqueous phase are heated separately to 70°C and then combined by magnetic stirring.

2. The oil and aqueous phases are emulsified with a high-shear mixer at 70 to 80°C.
3. The resulting coarse emulsion (1–5μm) is then rapidly cooled and homogenized into a fine monodispersed emulsion.

Vesicles

Bangham [50] clearly shows that the dispersion of natural phospholipids in aqueous solutions leads to the formation of ''closed vesicles structures,'' which morphologically resemble cells. Since 1975 [51], vesicles have been prepared from surfactants. In 1986, the first commercial product incorporating liposomes identical to those described by Bangham appeared on the market (Capture). At the same time, a synthetic one made by nonionic surfactants [52] was also launched (Niosomes). Several different compositions, for scientific, economic and business reasons, prevailed in cosmetic vesicles. None of them really resembles the liposomes we have seen in medical applications. These main groups include: (1) liposomes made from soya phospholipids; (2) sphingosomes, i.e., liposomes made from sphingolipids, and (3) nonionic surfactant vesicles (niosomes) which are a proprietary product of L'Óréal and other synthetic amphiphiles. In the 1990s, transfersomes, i.e., lipid vesicles containing large fractions of fatty acids, were introduced. Transfersomes [53–55] consist of a mixture of a lipidic agent with a surfactant. Consequently, their bilayers are much more elastic than those of most liposomes.

This chapter focuses on nonionic surfactant vesicles and transfersomes. Nonionic surfactant vesicles (NSVs or niosomes) consist of one or more nonionic surfactant bilayers enclosing an aqueous space. NSVs consisting of one bilayer are designed as small unila-

TABLE 4 Vesicles Preparation Methods

Method	Reference
Sonication	56, 58, 60
Ether injection	56
Handshaking	56
Reversed phase evaporation	61
Method as described by Handjani-Vila	52

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mellar vesicles (SUVs) or large unilamellar vesicles (LUVs). Vesicles with more bilayers are called multilamellar vesicles.

Niosomes can be prepared from various classes of nonionic surfactants, e.g., polyglycerol alkyl ethers [52,56], glucosyl dialkyl ethers [57], crown ethers, and polyoxyethylene alkyl ethers and esters [58]. The preparation methods used should be chosen according to the use of niosomes, because the preparation methods influence the number of bilayers, size, size distribution, entrapment efficiency of the aqueous phase, and membrane permeability of the vesicles [56,59]. NSVs can be formed using the same methods that are used for the preparation of liposomes (Table 4).

PROPERTIES OF A VECTOR

Microparticles

Microencapsulation has been applied to solve problems in the development of pharmaceutical dosage forms as well as in cosmetics for several purposes. These include the conversion of liquids to solids, separation of incompatible components in dosage form, taste masking, reduction of gastrointestinal irritation, protection of the core materials against atmospheric deterioration, and enhancement of stability and controlled-release of active ingredients.

For drug follicular targeting, microspheres were envisaged mainly as site-specific drug delivery systems because they present several advantages: 1) good stability of the microspheres when applied on the skin, 2) easy preparation of microspheres with a defined size in a narrow size distribution, 3) protection of the active incorporated, 4) controlled release of the active in the hair follicles from the microspheres, and 5) the possibility of incorporating either lipophilic or hydrophilic actives into the microspheres [62]. Concerning the microsponge system, each microsphere is composed of thousands of small beads wrapped together to form a microscopic sphere capable of binding, suspending, or entrapping a range of substances. The outer surface is porous, allowing the controlled flow. Microsponges can be incorporated into gels, creams, liquids, powders, or other formulations, and can release ingredients depending on their temperature, moisture, friction, volatility of the entrapped ingredient, or time.

Nanoparticles

Nanoparticles are attractive delivery systems. In most cases the advantages are 1) the solid matrix gives flexibility to modify the drug release profile, 2) the relatively slow degradation allows long release times, and 3) the protection of incorporated compounds against chemical degradation. Drug release from colloidal carriers is dependent on both the type of carrier and the loading mechanisms involved.

Nanospheres

Release from nanospheres may be different according to the drug-entrapment mechanism involved. When the drug is superficially adsorbed, the release mechanism can be described as a partitioning process (rapid and total release if sink conditions are met). When the drug is entrapped within the matrix, diffusion plus bioerosion will be involved with a biodegradable carrier, whereas diffusion will be the only mechanism if the carrier is not biodegradable. From this, it can be inferred that entrapment within the matrix of nano-

spheres may lead to sustained release, the rate of which may be related to the rate of biodegradation of the polymer.

Nanocapsules

Release from nanocapsules is related to partitioning processes within immiscible phases. The equilibrium between the carrier (loaded drug) and the dispersing aqueous medium (free drug) is dependent both on the partition coefficient of the molecule between the oily and the aqueous phases and on the volume ratio of these two phases. This means that the amount released is directly related to the dilution of the carrier and that the release is practically instantaneous when sink conditions exist. Diffusion of the drug through the polymeric wall of nanocapsules does not seem to be a rate-limiting step [63]. Coating the polymeric wall with an outer layer of phospholipids can advantageously reduce drug leakage from nanocapsules.

Multiple Emulsions

Double emulsions are an excellent and exciting potential system for slow or controlled release of active entrapped compounds. The fact that the inner w/o emulsion serves as a large confined reservoir of water is a very attractive property for dissolving it in significant amounts of water-soluble drugs. The oil membrane seems to serve as good transport barrier for the confined ionized and/or nonionized water-soluble drugs. The two amphiphilic interfaces are yet an additional barrier. The possibility to manipulate transport and release characteristics of the formulations seems to be feasible. However, despite 20 years of research, no pharmaceutical preparation using the multiple emulsion technology exists in the marketplace. It seems that the main reasons are the droplet instability and the uncontrolled release.

Although the release of the encapsulated active substance is complicated, because of the existence of different mechanisms, the multiple emulsion's behavior after application to the skin appears to be relatively simple because it is similar to the behavior observed with simple emulsions.

Microemulsions

Miocroemulsions are effective vehicle systems for dermal as well as for transdermal drug delivery because of their high drug-loading capacity of their colloidal structure. Furthermore, thermodynamic stability and simple preparation process favor them to be considered as vehicles for skin applications.

Several workers have reported studies in which the lipophilicity of the drug has been increased to enhance its solubility in the dispersed oil droplets. In this way, a reservoir of the drug is produced and a sustained-release effect is achieved as the drug continuously transfers from the oil droplets to the continuous phase to replace drug release from the microemulsion.

Nanoemulsions

Nanoemulsions have been gaining more and more attention in the last few years, mainly as vehicles for the intravenous administration of lipophilic drugs. In the skin, the patents claimed that these systems could penetrate through the skin to a greater extent compared with usual topical compositions. Nanoemulsions are so strongly compressed that they

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become ultralight and, like vesicular systems constitute a new form that could prove extremely fruitful for the release of substances.

Vesicles

Vesicles appear to be promising transdermal drug-delivery systems. The major advantages of topical vesicle drug formulations are:

- hydrophilic, lipophilic, as well as amphiphilic substances can be encapsulated in the vesicles
- for the lipophilic and amphiphilic drugs the liposomes serve as ''organic'' solvent and as a result, higher local drug concentrations can be applied
- the vesicles can act as depot, releasing their drug content slowly and controlled
- systemic effect of a dermal active compound can be reduced and the systemic effect of a transdermal drug can be increased depending on the vesicle composition
- the vesicles may serve as penetration enhancer
- the vesicles can interact with the skin because of the amphiphilic character of the bilayer
- liposomes are biocompatible and biodegradable and have a low toxicity and lack antigenicity status as well
- vesicle formulations are cosmetically accepted

There are also some disadvantages of vesicles as drug carriers:

- low encapsulation efficiencies for lipophilic or amphiphilic drugs
- no drug release from the vesicle
- low–molecular weight drugs can leak out of the vesicle
- instability of vesicles during shelf life
- sterilization of liposome formulations

DERMATOLOGICAL AND COSMETIC USES OF ENCAPSULATION

Microparticles

In recent years, numerous vectors have been proposed and used in topical formulations as drug-carrier vehicles. It has been claimed that these drug vehicles can improve and control the drug release from conventional topical formulations. Although the application of these colloidal particles in dermatology is of great interest, there are few articles about the characteristics of these vehicles for topical formulations and most of the background is based on different patents.

Miocroparticles can serve as a drug reservoir in skin products. Rolland et al. [62] investigated in vitro and in vivo the role of 50:50 poly (DL-lactic-co-glycolic acid) microspheres as particulate carriers to improve the therapeutic index of adaptalene. The percutaneous penetration pathway of the microspheres was shown to be dependent on their mean diameter. Thus, after topical application onto hairless rat or human skin, adaptalene-loaded microspheres (5 μm diameter) were specifically targeted to the follicular ducts and did not penetrate via the stratum corneum. A reduction of either the applied dose (0.01%) or the frequency of administration (every day) was shown to give pharmacological results in

the animal model comparable to a daily administration of 0.1% free adaptalene-containing aqueous gel.

Egg albumin microspheres of size 222 ± 25 μm, containing a vitamin A (15.7 ± 0.8%), were used to prepare o/w creams. The *in vitro* and *in vivo* drug release of a microencapsulated vitamin A cream was studied and compared with a nonmicroencapsulated vitamin A cream. The *in vitro* study showed that, during the first 3 hours, the microspheres could remain on the surface of the skin, and as a consequence, were able to prolong the release of vitamin A. The relative bioavailability of the microencapsulated formulation was 78.2 ± 7.3% [64].

Mizushima [65] reported that lipid microspheres containing prostaglandin E_1 (PGE_1), delivered preferentially to specific lesion sites, increased local action and prevented systemic side effects. Sakakibara et al. [66] evaluated the potential of topical application of lipid microspheres containing PGE_1 to treat ischemic ulcers. Nine of the 10 patients responded to the treatment, and at the sixth month of follow-up six patients had healed ulcers and recurrence was noted in three patients.

Skin absorption of benzoyl peroxide from a topical lotion containing freely dispersed drug was compared with that from the same lotion in which the drug was entrapped in a controlled-release styrene-divinylbenzene polymer system (Microsponge). The studies done by Wester et al. [67] showed the following: 1) *in vivo*, less benzoyl peroxide was absorbed through rhesus monkey skin from the polymeric system, 2) reduced skin irritation in cumulative irritancy studies on rabbits and human, and 3) when the experimental formulations were evaluated for antimicrobial activity in vivo, their efficiency was in line with that of conventional products.

A formulation containing 0.1% tretinoin was tested on 360 patients during 12 weeks for antiacne efficacy in a multicenter, double-blind, placebo-controlled study. Compared with placebo, statistically significant greater reductions in inflammatory, noninflammatory, and the total number of lesions were obtained with the entrapped retinoic acid formulation [68]. Encapsulation of deet in liposphere microdispersion resulted in improved efficacy and reduced dermal absorption. Deet-containing lipospheres (10%) were effective against mosquitoes for at least 3.5 hours. The deet absorption through skin from these formulations was a third of that from alcoholic solution for the same concentration [69].

Nanoparticles

Although cosmetic applications of nanoparticles proliferate (numerous patents have been granted), publications, studies, or reports on the skin after topical application have been rare. The incorporation of active substances in the nanospheres attempt to modulate the release of the substances in the skin. When nanocapsules are concerned, the active substances are usually of lipophilic nature, and they can be composed of an oily compound or dispersion. Here again the objective is to control the release of the actives because the molecule is protected. The release profile of the actives depends on the nature of the constituents.

Recently, Lancôme launched a cosmetic product containing nanocapsules of vitamin E (Primordiale). They claim that the vitamin is widely distributed throughout the outer layers of the skin in the form of a gradient. The effectiveness of vitamin E protection when it is incorporated into nanoparticles has been shown in vivo. Dingler et al. [70] reported that the incorporation of vitamin E into solid lipid nanoparticles enhances the stability. The ultrafine particles possess an adhesive effect. This leads to a formation of

fine adhesive film on the skin leading to occlusion and subsequent hydration. Hydration of the skin promotes penetration of actives and enhances their cosmetic efficiency. In another publication of the same research group [71], drug release of encapsulated material as well as nonencapsulated material was measured by tape stripping assay. The drug (RMAD 95) was released into the skin at approximately 53%, whereas the control (RMAD 95/isopropanol) was at 31%.

Immobilization of nanoparticles (polyamide) on the skin for prolonged periods of time has been proved feasible [72]. It has been shown to be dependent on formulation because particle retention was increased from 40% up to 98% when embedding the particles into a emulsion. Particle size, surface charge, and payload determine the properties of the nanoparticles and their application. Zülli et al. [73] encapsulated Uvinil T 150 (UV-B filter) into lipid nanoparticles. They observed an almost one-hundredfold higher affinity of Uvinil T to hair from positively charged particles compared with negatively charged particles. The same group also showed the application of a gel containing nanoparticles loaded with vitamin A and E derivatives enhances the skin humidity compared with controls.

In a 1997 patent, De Vringer [74] showed that the size of particles can change the occlusion factor. Lipoid microparticles are greatly inferior to solid lipoid nanoparticles in their occlusive effect, and the addition of solid lipoid microparticles in a cream lowers the cream's occlusivity, whereas the addition of solid lipoid nanoparticles in a cream raises the cream's occlusivity. Nanospheres containing beta carotene and a blend of UV-A and UV-B sun filters were prepared by Olivier-Terras [75]. The results clearly show the synergistic effect resulting from the combination of nanospheres and filters. They obtained with this formulation better bioavailability, better efficacy, and lastly a synergy that possesses an inhibitory effect on tyrosinase as a result of the cinnamic nature of the UV-B screening agents.

The effect of poly (methylmethacrylate) and poly (butylcyanoacrylate) nanoparticles on the permeation of methanol and octanol through hairless mouse skin was reported by Cappel and Kreuter [76]. Nanoparticles increase the permeability of methanol through hairless mouse skin and the permeability of lipophilic octanol is either unaffected by nanoparticles or decreases as a function of nanoparticle concentration depending on the lipophilicity of the polymer material. The potential use of nanoparticles as an ophthalmic drug-delivery system has been shown in numerous studies for either hydrophobic or hydrophilic drugs [77–79]. Despite the promising in vivo results, many issues must be resolved before an ophthalmic product can be developed using this technology.

Tobio et al. [80] encapsulated a model protein antigen, tetanus toxoid, into PLA-PEG nanoparticles and evaluated the potential of these colloidal carriers for the transport of proteins through the nasal mucous. The results showed that PLA-PEG nanoparticles have a great potential for delivery of proteins, either to the lymphatic system or to the blood circulation, after nasal administration. Regarding the mode of action of nanoparticles, one might hypothesize that they are associated with the skin surface, facilitating drug transport by changing the vehicle/stratum corneum partition coefficient.

Multiple Emulsions

The first commercial use of a w/o/w type multiple emulsion is Unique Moisturizing by Lancaster, which was marketed in 1991. Cosmetic application of multiple emulsions have been reported in the patents issued for their composition. One example of an application

is perfume encapsulated in the internal phase; very small amounts of it are released over a long period of time. The patents show that multiple emulsions are recommended for all kinds of cosmetic applications: sunscreens, makeup removers, cleansers, and nutritive, hydrating, and cooling products. Kamperman and Sallis [81] show that a highly charged small water-soluble molecule such as phosphocitrate can be presented in the form of a liposome or multiple emulsion and be capable of exerting a positive action against dystrophic calcification. In a rat calcergy model, both vehicles effectively reduced the formation of induced subcutaneous calcified plaques at doses for which the phosphocitrate salt alone was inactive. Three emulsions type (w/o/w, o/w, and w/o) containing a water-soluble molecule (glucose) were obtained with the same formula [82,83]. The release of glucose from the o/w emulsion was the fastest, and the w/o emulsion was the slowest, whereas the release obtained from the w/o/w emulsion was intermediate. The w/o/w emulsion showed some tendency toward steady state during the first 3 to 12 hours and the flux was found to be 1.7 times greater than that from the w/o emulsion.

In vivo release of 2.5% lidocaine hydrochloride from simple and multiple emulsion systems was compared with that from aqueous and micellar solution, and anesthetic effects such as duration of action and tolerability were also compared. The double emulsions showed a longer duration of action, less eye irritation, and improved efficacy compared with aqueous solutions [44].

Microemulsions

Over the last 15 years, many studies have been performed with the percutaneous absorption of various actives carried by microemulsions. There are numerous cosmetic products in the form of microemulsions. These products range from body care to facial and hair treatments. They include bath oils, body-thinning products, fixatives for hair, hardeners for nails, hydrating products, antiwrinkle products, seborrhea preventive products, and antiaging serums marketed principally in Europe, the United States, and Japan. In biopharmaceutics, microemulsions were used to solubilize drugs and to improve systemic and topical drug availability.

Gasco et al. [84] ascertained concentrations of timolol in aqueous humor after multiple instillation in rabbit eyes. The microemulsion, a solution of the ion-pair, and a solution of timolol alone was used. The bioavailability of timolol from the microemulsion and the ion-pair solution was higher than that obtained from timolol alone. Transport of glucose across human cadaver skin was shown [85] using microemulsions containing up to 68% water. A thirtyfold enhancement of the glucose transport was achieved. The enhancing effect for drugs contained in microemulsions in comparison to a cream gel formulation consisting of the same components was shown by Ziegnmeyer and Führer [86]. The in vitro permeation across skin membranes as well as the in vivo penetration of tetracycline hydrochloride was higher from a microemulsion than from conventional systems. Thus is can be shown that in addition to the composition, the structure of each of the typically applied vehicles may play a dominant role in the process of penetration.

Février [87] has reported in vitro experiments designed to simulate the percutaneous penetration of tyrosine when administered using an o/w microemulsion composed of a betaine derivative as surfactant, benzyl alcohol, hexadecane, and water. The release of radiolabeled tyrosine from this vehicle was compared with that from a liquid-crystal system and an emulsion using a diffusion cell equipped with rat skin. Both the microemulsion and liquid-crystal formulation enhanced the penetration of tyrosine through the epidermis

when compared with the emulsion. However, cutaneous irritation studies showed a strongly irritant effect from the liquid-crystal formulation but none from the microemulsion.

The penetration of the hydrophilic diphenhydramine hydrochloride from a w/o microemulsion into human skin under ex vivo conditions was studied by Schmalfuß et al. [88]. Modifications of the vehicle components clarified the extent to which it is possible to control the penetration of a hydrophilic drug incorporated in a microemulsion system. A standard microemulsion showed an accumulation of penetrated drug in the dermis, indicating a potential after high absorption rate. Incorporation of cholesterol into the system leads to an even higher penetration rate and a shifting of the concentration profile further towards the epidermis. The addition of oleic acid had no effect.

Wallin et al. [89] showed that high concentrations of lidocaine base included in a microemulsion produced peripheral nerve block of long duration, compared with solutions as a consequence of slow release of lidocaine. The effect of polysorbate 80 concentration on the permeation of propanolol incorporated into micelles of polysorbate 80 in water, o/w microemulsions of isopropyl myristate-polysorbate 80-sorbitol water, and o/w emulsions of isopropyl myristate-polysorbate 80-sorbitan monooleate-water has been investigated by use of an artificial double-layer membrane, composed of a barrier foil and a lipid barrier, in Franz-type diffusion cells [90]. For each system, the apparent permeability coefficient of propanolol decreased with increasing polysorbate 80 concentration. Moreover, for a given polysorbate 80 concentration, the apparent permeability coefficient of propanolol increased when the system was changed from emulsion to a microemulsion and then to a solubilized system because of the increasing interfacial area of total disperse phase.

Microemulsions may exert irritative effects, often by their high content of surfactants. It is possible to overcome this problem by the use of physiologically compatible nonionic and polymeric surfactants. The irritation potential of the formulation depends strongly on its structure. Because of an equilibrium between microemulsions and liquid crystals, when brought into contact microemulsions may dissolve skin structures that are organized in liquid crystalline form. Thus, an irritation is produced. Deduced from this, the nature of the system formed during the penetration process and the residue remaining on the skin surface are of importance in this regard.

Acute and cumulative tests were performed on human subjects in vivo with lecithin microemulsion gels using as comparison a unilamellar soybean lecithin liposome preparation and the solvent isopropyl palmitate [91]. The study showed a very low acute and a low cumulative irritancy potential for the soybean lecithin microemulsion gel. In general, microemulsions undergo structural changes after an application to the skin because of the penetration and/or evaporation of constituents and under occlusion by the uptake of water from the skin surface. The formed substances and their penetration behavior finally influences the effectiveness of the systems for dermal drug transport.

Nanoemulsions

Many formulations of nanoemulsion are available in patents. Recently, Lancôme launched a nanoemulsion rich in ceramides, Re-source. The scientific studies, however, are orientated mainly in the parenteral use of these formulations. Amselem and Friedman [92] indicated that the actives incorporated in submicron emulsions (diameter between 100–300 nm) can penetrate through the skin to a greater extent compared with the usual topical

compositions. Improved efficacy of different steroidal and nonsteroidal anti-inflammatory drugs and local anesthetics has been observed.

Anselem and Zwoznik [93] determined drug penetration through the skin, local tissue (muscle and joint), and plasma levels of ketoprofen and diclofenac after topical administration in submicron emulsion (SME) creams compared with peroral administration. Compared with peroral drugs, SME-diclofenac and SME-ketoprofen showed sixty- to eightyfold more drug in muscle tissue, about ninefold more drug in joints, and four- to sixfold less drug in plasma. The improved skin penetrative properties of the solvent-free SME delivery makes this topical carrier very promising to achieve increased transcutaneous penetration of lipophilic drugs and site specificity.

Diazepam was formulated in various regular topical creams and SMEs of different composition [94]. The different formulations were applied topically on mice. The efficacy of diazepam applied topically in emulsions strongly depends on the oil droplet size and, to a lesser degree, on the formulation and oil type. The SMEs as vehicles for transdermal delivery of diazepam generate significant systemic activity of the drug as compared with regular creams or ointments. Transdermal delivery of diazepam via SME is effective, and the activity may reach the range of parenteral delivery. A single application of diazepam in SME cream to mice skin provides pronounced transdermal drug delivery and prolonged protective activity up to 6 hours.

Using a nanoemulsion composed of lanolin, polyethylene glycol ether of lanolin's alcohol and water [95], the investigators showed the transdermal delivery of a number of pharmaceutically active ingredients (testosterone, ibuprofen, 5-fluorouracil, verapamil hydrochloride, metronidazole, vincristine sulphate, fentanyl citrate) across isolated stratum corneum. The studies indicated that nanoemulsions derived from lanolin and its derivatives are capable of being developed into useful drug-delivery systems.

Vesicles

The effectiveness of vesicles has been investigated by several research groups (Table 5). Liposomes in particular have received considerable attention [103]. In several studies the diffusion of a drug was facilitated or achieved certain selectivity into human and nonhuman skin by vesicle encapsulation. Other studies show that the influence of vesicles on drug transport is negligible. The conflicting results can be understood in terms of vesicle characteristics or in terms of protocol of investigation. Special surface characteristics of vesicle hydration and electrostatic forces, in addition to Van der Waals, can govern the short and long range of repulsive or attractive forces between vesicles and biological media.

The particle sizes, the physical state (liquid or gel) of the bilayers, the number of bilayers, the electrostatic nature of drugs and vesicles, and the stability of the vesicles face to face with biofluids in different ranges of pHs, temperatures, and degrees of dehydration can also play an important role in the phenomenon. An important contribution to the understanding of the interactions between vesicles and human skin was made by Junginger and his group [100,104]. They used freeze fracture electron microscopy and small-angle radiograph scattering to study the effects that vesicle formulations have on the stratum corneum. They identified two types of liposome-skin interactions: 1) adsorption and fusion of loaded vesicles on the surface of the skin leading to increased thermodynamic activity and enhanced penetration of lipophilic drugs, and 2) interaction of the vesicles within the deeper layers of the stratum corneum promoting impaired barrier function of

TABLE 5 Effect of Vesicles on the Permeation of Drugs Through the Skin

Reference	Year	Drug	Type of vesicle	Results
96	1995	Retinyl palmitate	NSV	Augmentation of the retention of hydrophobic substances in stratum corneum
97	1998	Gap junction	Transferosomes	Protein transported across the intact murine skin and processed immunologically
98	1998	Estradiol	Transferosomes	Augmentation of the flux in 8-fold
99	1998	Cu, Zn-superoxide dismutase	Transferosomes	Reduced local inflammation
55	1998	Insulin	Transferosomes	Transported into the body between the intact skin with a bioefficiency of at least 50% of subcutaneous penetration-enhancing effect
100	1994	Estradiol	NSV	
101	1996	Lidocaine	NSV	The flux was not influenced by the encapsulation
102	1998	Levonorgestrel	Niosomes	Penetration-enhancing effect

these strata for the drug. Recent approaches in modulating delivery through the skin are the design of two novel vesicular carriers: the ethosomes and the transferosomes. The ethosomes are soft phospholipid vesicles; their size can be modulated from tens of nanometers to microns. These vesicular systems have been found to be very efficient for enhanced delivery of molecules with different physical-chemical characteristics to/through the skin. They can be modulated to permit enhancement into the skin strata as far as the deep dermis or to facilitate transdermal delivery of lipophilic and hydrophilic molecules [105].

Transferosomes have been shown to be versatile carriers for the local and systemic delivery of various steroids, proteins and hydrophilic macromolecules [106]. The mechanism proposed by the investigator for transferosomes is that they are highly deformable, thus facilitating their rapid pentration through the intercellular lipids of the stratum corneum. The osmotic gradient, caused by the difference in water concentrations between the skin surface and skin interior, has been proposed as the major driving force for transferosome penetration [54].

THE FUTURE OF ENCAPSULATION

What can we expect from encapsulation in the future? Trying to predict what the future will be is not easy. When one addresses future developments in the field of encapsulation, one has to realize that, at present time, application-oriented research is mainly focused to solve problems. If the number of published articles on encapsulation (liposomes, nanoparticles, microparticles, microemulsions, multiple emulsions, and nanoemulsions) under the heading of drug therapy is a reliable indicator of the state of knowledge, then the field has made progress over the last two decades. Between 1975 and 1980, the Medline Data

Base registered about 20 articles per year with the term ''liposomes'' in their title in the domain of drug therapy. This number has grown to over 100 per year. Because many of these publications dealt directly with new experimental data, we must conclude that our experience has expanded dramatically.

The skin has been ''in the picture'' since Mezei and his collaborators reported around 1980 on their early work on the liposomal delivery of drugs. Through the efforts of the cosmetic industry, liposomal formulations and nanoparticle formulations on the skin have definitively been an economic success. However, many unanswered questions remain. Molecular biology has provided us with tools to identify and build genetic materials that can be used for the treatment of hereditary diseases. Developing a carrier for gene therapy is one of the main challenges that the encapsulation field faces today. With respect to gene therapy for the skin, both molecular biology and encapsulation technology are in their debut, and much progress may and should be made in the coming years.

Again, what will the future bring us? We have already indicated where, on the basis of our present knowledge, encapsulation in many vectors offer a rational advantage as active carrier systems to the skin. Therefore, efforts should be made to obtain a better understanding concerning the mechanisms of formulations of these systems at the molecular and supramolecular level. This could lead to new formulation processes and could open new prospects in the area of active delivery by means of encapsulated systems. The field will develop in a more useful fashion when appropriate well-controlled biological and percutaneous penetration studies accompany the advances in chemistry.

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Encapsulation Using Porous Microspheres

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INTRODUCTION

Encapsulation can be broadly defined as the formation of small, spherical particles that incorporate an active agent. The first commercial application of encapsulation was by the National Cash Register Company, who developed an improved copying paper using two dyes that were coated with a clay. When these capsules were ruptured by the application of pressure, a colored imprint was produced. This successful application triggered other uses in agriculture, pharmaceuticals, oil industries, food industries, and consumer products [1].

Because such spherical particles are very small, usually in the range of several to about 20 microns, the process of forming such particles is referred to as microencapsulation. However, we need to distinguish between microcapsules and microspheres. Microcapsules have a core containing the active agent surrounded by a membrane, whereas microspheres are solid particles that contain an active agent homogeneously dispersed within the solid matrix. Microspheres can be either solid or porous. These three types are shown schematically in Figure 1.

Release of agents incorporated into microcapsules can occur either abruptly, as in the National Cash Register Company product, or the ''scratch and sniff'' product manufactured by the 3M Company, where the outer membrane is ruptured by the application of pressure or can occur in a controlled manner by diffusion of the active agent from the core through the outer rate-limiting membrane. In the latter case, if the thermodynamic activity of the drug in the core reemains constant and the drug is removed rapidly from the aqueous environment surrounding the microcapsule, constant release kinetics, referred to as zero order, are obtained. No such products have been applied to the cosmetics and cosmeceutical field, but have been extensively investigated in controlled-release applications, particularly in contraception [2] and narcotic addiction [3].

Agents incorporated into microspheres are released by kinetics that are typical of matrix systems and follow $t^{1/2}$ kinetics as predicted by the Higuchi equation [4]. Thus, initial release rate is rapid and then declines as the thickness of the drug-depleted layer increases. Studies of release kinetics from biodegradable porous microspheres indicate that release kinetics similar to that noted for matrix-type microspheres are obtained [5].

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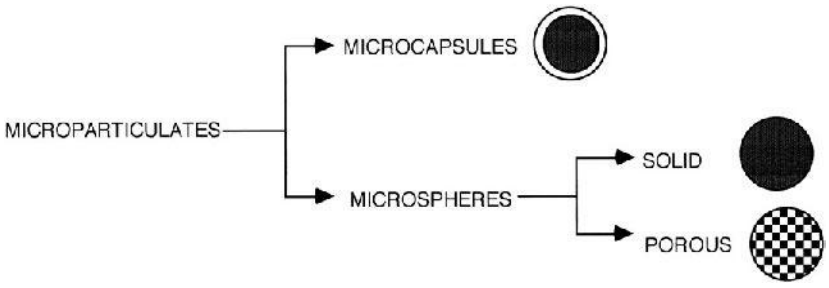

FIGURE 1 Schematic representation of various microparticulates.

Other than liposomes, which are covered in Chapter 17, only one type of microparticulate has found important applications in cosmetics and skincare technology, and these are porous microspheres. This chapter will cover the application of porous microspheres in cosmetics and skincare applications.

POROUS MICROSPHERES

Preparation

A special kind of porous microsphere is a patented [6,7], highly cross-linked polymer sphere having a size that can vary from about 3 to 3000 microns. The porous spheres are produced by an aqueous suspension of polymerization of monomer pairs consisting of a vinyl and a divinyl monomer, e.g., methyl methacrylate (the vinyl monomer) and ethylene glycol dimethacrylate (the divinyl monomer), or styrene and divinylbenzene. The divinyl monomer functions as a cross-linker, and because it is used in concentrations as high as 50 to 60%, the copolymer is a very highly cross-linked material. As a consequence of their chemical structure and the high cross-link density, the micrpsheres are totally inert and do not degrade in the body, nor do they dissolve or swell, when exposed to any organic solvent. They have been found to be stable between pH 1 and 11 and at temperatures as high as 135°C.

To prepare the copolymer, the vinyl and divinyl monomers, initiator, suspending agent (emulsifier), and a porogen, which produces the porous structure, are dispersed in water and the copolymerization started by thermally activating the initiator. The porogen must be miscible with the monomers and function as a precipitant for the polymer. Polymer particle size is controlled by the size of the suspended monomer droplets, which in turn is a function of the nature and amount of the suspending agent and the shear induced by the stirring process. When all variables are carefully controlled, a uniform batch of particles having the desired size and the desired porosity can be obtained. Typically, the surface area of such porous microspheres can be varied between 20 to 500 m^2/g and the pore volume can be varied from 0.1 to 3.4 cm^3/g.

A scanning electron micrograph of a porous microsphere magnified 5000 times is shown in Figure 2. A view of the interior, in this case magnified 6000 times and obtained by freeze fracture, is shown in Figure 3. As can be seen, the internal structure comprises small polymer particles enclosed in a porous membrane. The porosity of the microspheres

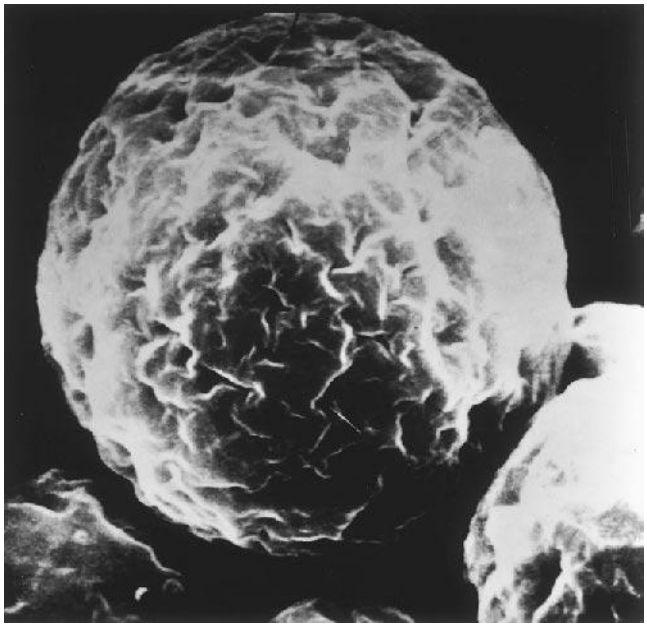

FIGURE 2 Electron scanning micrograph of porous microsphere. Magnification 5000×.

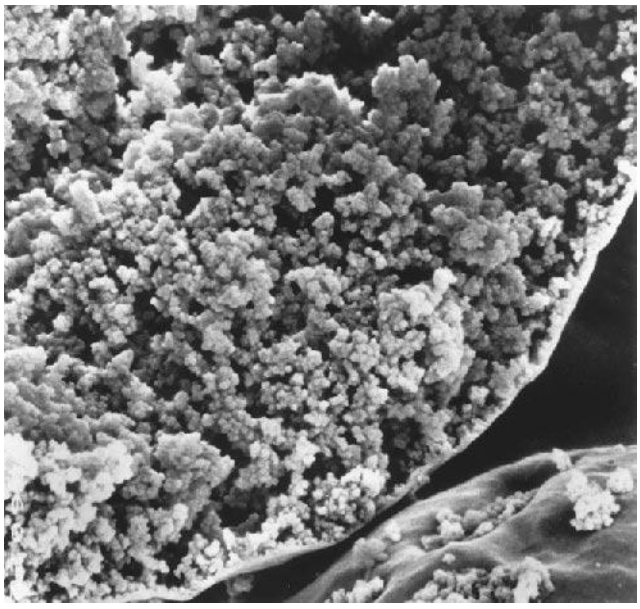

FIGURE 3 Freeze fracture micrograph of a single porous microsphere. Magnification 6000×.

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is attributable to the interstitial volumes between the polymer particles, and because the membrane that surrounds the solid polymer particles is porous, the interstitial volume is open to the outside.

Loading of Active Agents

These can be incorporated by two different procedures. In one procedure, referred to as the one-step procedure, the active agent functions as the porogen and is incorporated during the polymerization process. However, this method has some limitations because the active agent has to satisfy the requirements of a porogen, it must be stable towards free radicals generated during the copolymerization process, and it must not inhibit the copolymerization process. For this reason, a procedure where porous microspheres are produced first, and subsequently loaded with the active agent, is more generally applicable. Such a process is known as the two-step procedure.

Loading is achieved by stirring empty porous microspheres in a solution of the active agent, which diffuses into the microsphere particles. The solvent is then evaporated to obtain microspheres with the active agent loaded within the pores. If the agent is soluble in the polymer, some may partition into the matrix. Should a high loading be desired, or if the active agent is only sparingly soluble in the solvent, the process can be repeated a number of times. Clearly, using such a procedure, some of the active agent will also be found on the outside of the microspheres particles.

The incorporation of an active agent into these microspheres can be investigated by environmental scanning electron microscopy (ESEM). This method has the advantage over conventional scanning electron microscopy (SEM) in that no metallic coating is required and samples can be analyzed at ambient pressures in a water vapor. Samples are sprinkled lightly onto a metallic stub, 1 cm in diameter, bearing conductive double-sided adhesive tape, and then analyzed using a Phillips XL30 ESEM FEG instrument operated with greater than 99% relative humidity [Davies, M., and Patel, N., private communication]. Using this procedure, a good visualization of the microspheres and any free drug, if present, can be achieved.

Such a visualization method is important because loading efficiency depends on the nature of the active agent, primarily its solubility and the partition coefficient between the microspheres and the solvent used in the entrapment procedure. Both lipophilic and hydrophilic materials can be loaded into such microspheres, and range from water to petrolatum to silicone oil. Extensive studies have shown that the active agent is not bound to the microspheres and can be completely extracted.

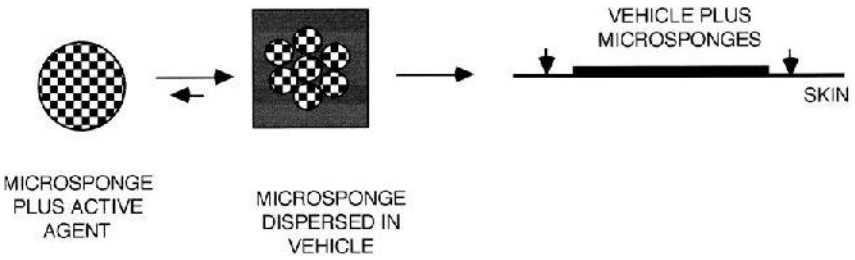

FIGURE 4 Schematic representation of controlled release of active agent from porous microspheres dispersed in a vehicle.

Release of Active Agents

Although porous microspheres can function in a limited way as a sustained-release delivery vehicle, they are best viewed as a reservoir. However, the combination of microspheres with incorporated active agents dispersed in a vehicle can function as a controlled-release device if a vehicle in which the drug is only poorly soluble is chosen. When such a formulation is applied to the skin, only that amount of the drug dissolved in the vehicle is presented to the skin. Then, as the drug diffuses from the vehicle into the skin, the saturation concentration of the drug in the vehicle is maintained by diffusion of drug from the microspheres into the vehicle. This process is shown schematically in Figure 4.

APPLICATIONS

Porous microspheres have been used in two major applications. One application takes advantage of the high porosity of the microspheres to entrap liquid materials, such as silicone oil, to convert a liquid into a free-flowing powder. This allows significant formulation flexibility, and a babywipe product has been developed where silicone in porous microspheres has been formulated in an aqueous medium.

In the other application, microspheres with incorporated active agents are dispersed in a suitable vehicle for topical applications. As already discussed, when active agents that are normally skin irritants are used and a vehicle in which the active agent is only poorly soluble is chosen, a significant reduction of irritation, when compared with ordinary formulation, is noted. Such a reduction in irritancy will be illustrated with two products, one incorporating benzoyl peroxide and the other incorporating *trans*-retinoic acid (RA).

Benzoyl Peroxide

Benzoyl peroxide (BPO) is clinically effective in acne, primarily because of its bactericidal activity against *Proprionibacterium acnes* and possibly also through its mild keratolytic effects [8–10]. The main site of pharmacological action is the pilosebaceous canal [11]. BPO penetrates through the follicular opening, probably by dissolving into sebaceous lipids, and then exerts its antimicrobial activity [12]. Skin irritation is a common side effect and a dose relation seems to exist between efficacy and irritation [13]. Thus, a controlled-release formulation would clearly be advantageous.

In vitro release kinetics were determined by applying formulations to silastic membranes mounted in static diffusion cells, and by using excised human skin. Release of BPO from two formualtions applied to a silastic membrane, one incorporating free BPO and one incorporating BPO entrapped in porous microspheres is shown in Figure 5. Initial release of BPO dispersed in the vehicle shows good linearity, but with further release would decline, as expected for $t^{1/2}$ kinetics. The calculated flux for the initial release is 0.09 mg/cm^2/h. The release of BPO entrapped in the porous microspheres shows a discontinuity. Initial flux is about 0.1 mg/cm^2/h, very close to the release from BPO dispersed in the vehicle, followed by a slower release with a flux of 0.04 mg/cm^2/h. These data indicate that not all BPO has been entrapped in the porous microspheres, and that the formulation contains some free BPO. Initial release is attributable to release of the free BPO, followed by the release of entrapped BPO.

The topical irritancy of a BPO controlled-release formulation has been determined in rabbits, in rhesus monkeys, and in human volunteers [14] using formulations with BPO dispersed in a vehicle and BPO entrapped in porous microspheres dispersed in a vehicle.

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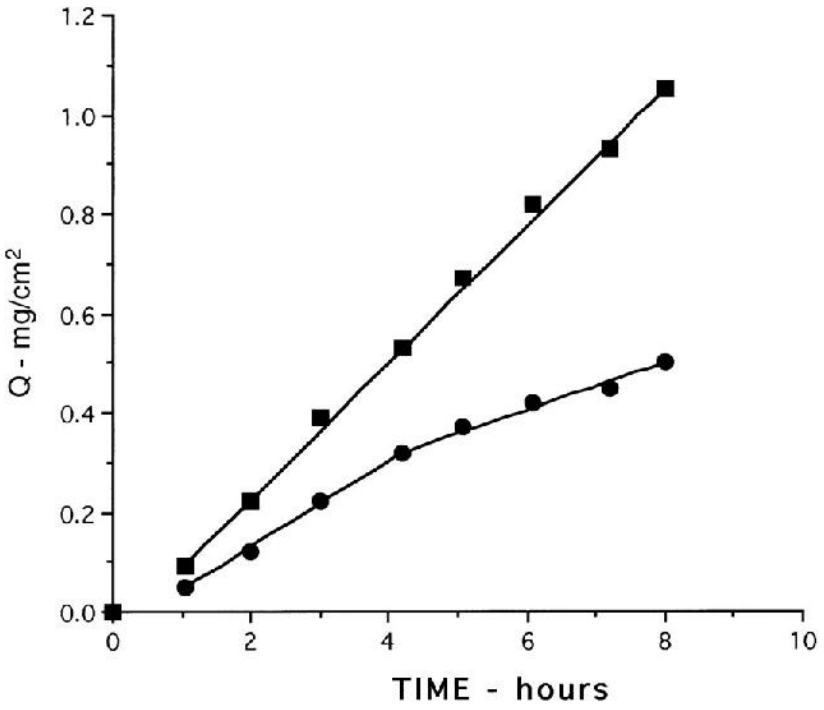

FIGURE 5 Release of BPO dispersed in vehicle (■) abd BPO entrapped in porous microspheres and dispersed in vehicle (●). Results are the average of two determinations. Formulations applied to silastic membrane. Receiving fluid 1:1 mixture of water and acetone. (From Ref. 14.)

Cumulative 14-day irritancy scores in human volunteers are shown in Figure 6 and Table 1. In this study involving 29 patients, total irritaancy of four commercial products, three containing free BPO and one containing entrapped BPO at the BPO concentrations shown, were compared. Clearly, the entrapped BPO product is significantly less irritating. A 12-week human trial, comparing the efficacy of entrapped BPO formulations at various concentrations, a placebo formulation and a free BPO formulation has also been carried out. The total reduction of inflammatory lesions shown in Figure 7 and the total reduction of noninflammatory lesions shown in Figure 8 clearly shows that the entrapped BPO is as efficacious as the free BPO. These results support evidence also obtained independently, that most, if not all, BPO entrapped in the porous microspheres is released.

Retinoic Acid

All *trans*-RA is a highly effective topical treatment for acne vulgaris. However, cutaneous irritation reduces patient compliance, and thus clinical effectiveness. A gel formulation with 0.1% RA entrapped in a porous microsphere has been developed and a single-center, double-blind, positive-controlled, randomized Phase I study carried out. The formulation with entrapped RA was designated as 0.1% TMG (tretinoin microsphere gel), and the one with free RA was designated 0.1% RA cream. Either study formulation was assigned to be applied to the right side of a subject's face on a randomized basis, the alternate formula-

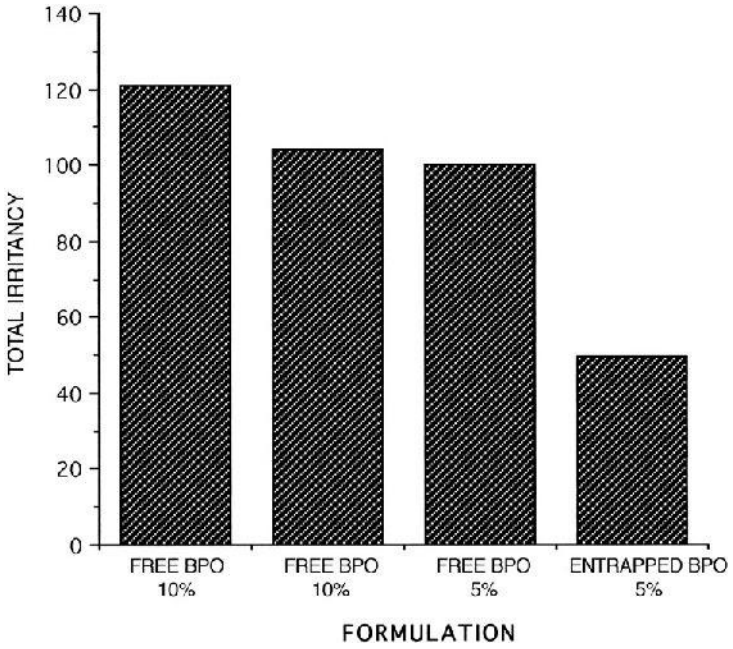

FIGURE 6 Fourteen-day cumulative irritancy test on BPO formulations in human volunteers comparing three commercial products containing BPO dispersed in a vehicle and one commercial formulation containing BPO entrapped in porous microspheres at BPO concentrations shown.

tion to the left side of the face. The dose for each formulation was 0.1 g, which was applied to the cheek areas once daily for up to 14 days. The subjects were evaluated daily by an expert grader for dryness and erythema. Results of subjects' self-assessment are shown in Table 2 and in Figure 9. Clearly, a formulation with RA entrapped in porous microspheres resulted in a statistically significant preference for the TMG formulation,

TABLE 1 14-day Cumulative Irritancy in Human Volunteers

Formulation	% Total subjects with postive response	Cumulative response index*
2.5% BPO		
Commercial product	36	1.04 (1)
Entrapped BPO	12	0.24 (2)
Vehicle	0	0.0 (3)
10% BPO		
Commercial product	52	2.59 (4)
Entrapped BPO	24	1.64 (5)
Vehicle	0	0.0 (6)

* Duncan's Multiple Range tests showed significant difference ($p < 0.05$) between (1) and (2), (1) and (3), (4) and (6), (5) and (6), but no significant difference ($p > 0.05$) between (2) and (3).
Source: Ref. 14.

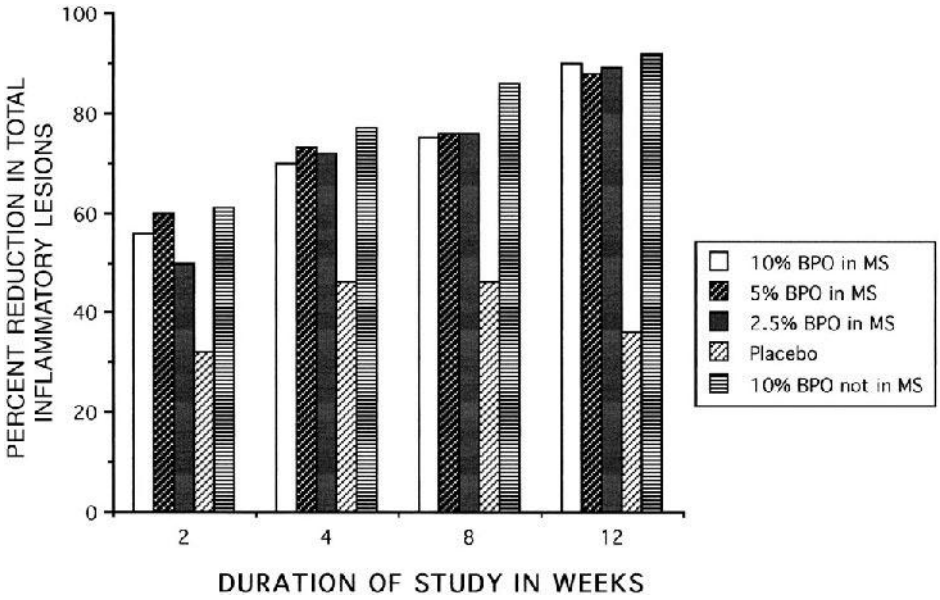

FIGURE 7 Percent reduction in total inflammatory lesions (papules/pustules) in human volunteers at 2, 4, 8, and 12 weeks, using the formulations shown.

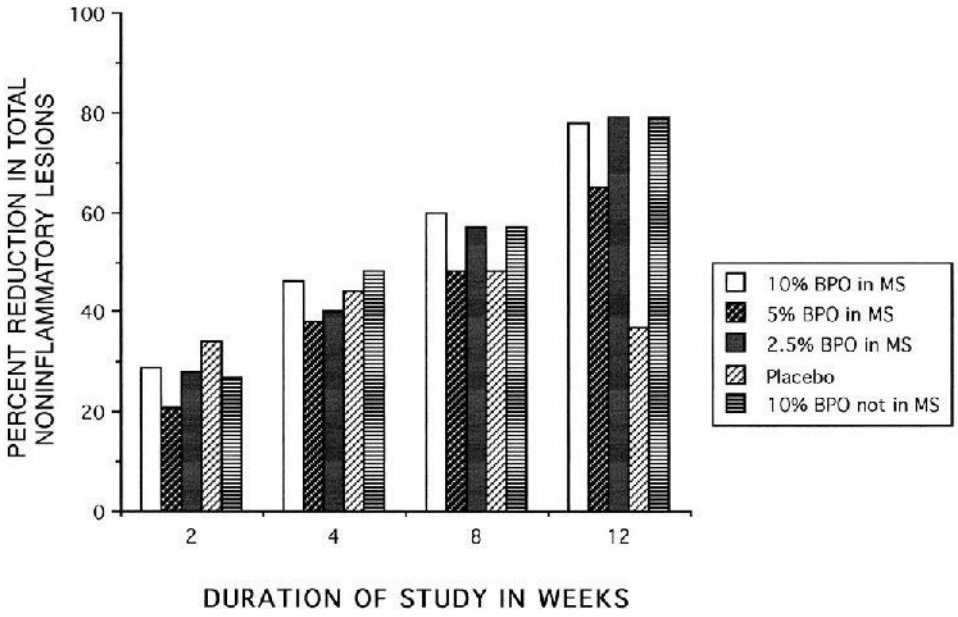

FIGURE 8 Percent reduction in total noninflammatory lesions (open and closed comedones) in human volunteers at 2, 4, 8, and 12 weeks, using the formulations shown.

TABLE 2 Subject Self-Assessment

	0.1% TMG*	0.1% RA cream	p Value
Number who prefer	23	2	
Preference score†	1.88	0.10	0.0002

* TMG is Retin-A® Micro Cream 0.1%.
† Preference score perceived as less burning and/or stinging graded on a scale from 0 (no difference) to 4 (maximal difference).

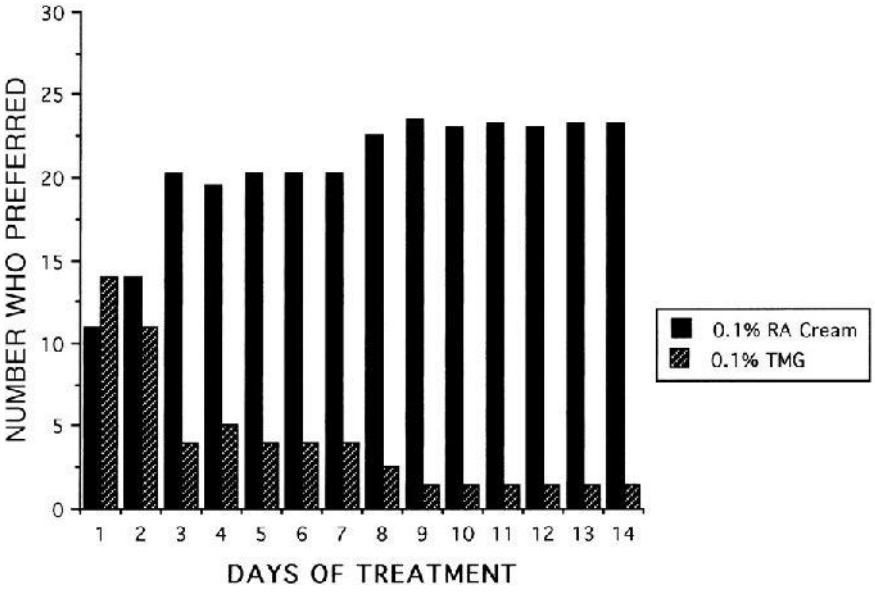

FIGURE 9 Daily self-assessment of preference for mildness. Single-center, double-blind, randomized, half-face study comprising 25 adult Caucasian women selected for having sensitive skin. 0.1% TMG is retinoic acid entrapped in porous microspheres and 0.1% RA cream in a commercial formulation. 0.1% TMG and 0.1% RA cream applied to corresponding side of subject's face, once a day for up to 14 days by a blinded technician.

which was perceived as causing less burning and stinging. In an independent, controlled multicenter trial, this TMG formulation has also proven effective for the treatment of acne and is now commercially available.

CONCLUSIONS

Porous microspheres are highly cross-linked and highly porous copolymers, which have found extensive use in the skincare arena. The nature of the polymer allows the loading of a wide range of chemical entities with subsequent release dependent on the vehicle into which the porous microspheres has been dispersed. This polymer has found widespread

acceptance as a means of reducing irritation without decreasing efficacy when used appropriately.

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Liposomes

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INTRODUCTION

Publications about and patents on liposomes, along with their different chemical components, preparation, and use in skincare products have often been reviewed [1–4]. The reviews do not need any additional comments. Of interest are general questions, such as why liposomes should be used in cosmetics, which functionalities are expected from them, and which advantages they do provide compared with alternative formulations.

The properties of the widely used main component of liposomes, phosphatidylcholine, play a key role for answering these questions. Other compounds such as niotensides and ceramides, which are naturally predestinated for the preparation of liposomes, are less important today. Niotensides do not offer superior claims, and ceramides are not available in sufficient quantities and qualities at convenient prices.

PHOSPHATIDYLCHOLINE

Looking at the horny layer, which is the barrier against external materials, phospholipids and phosphatidylcholine in particular play a minor role. The lipid bilayers contain only traces of phospholipids, and the main components are free fatty acids, cholesterol, triglycerides, hydrocarbons, and ceramides. But looking deeper into the living part of the epidermis, phosphatidylcholine is usually found as the most important constituent of all biological membranes, especially of plasma cell membranes. Over and above that phosphatidylcholine is the source of phosphocholine to transform ceramides to sphingomyelins. In this context, phosphatidylcholine stands for living tissues whereas the increase of ceramides in the cells means that their death by apoptosis is soon ahead (Fig. 1).

Human phosphatidylcholine and phosphatidylcholine of vegetable origin show a fatty acid composition, which is dominated by unsaturated fatty acids. The fatty acid content of soy phosphatidylcholine, which is readily available and mostly used in cosmetic formulas, is characterized by a ratio of linoleic acid up to 70% of the total fatty acids. Consequently, soy phosphatidylcholine has a very low phase-transition temperature of below 0°C in water-containing systems. This may be the reason for its ability to fluidize the lipid bilayers of the horny layer, which can be measured by an increase of the transepidermal water loss (TEWL) after application for a short while. The slight increase of TEWL

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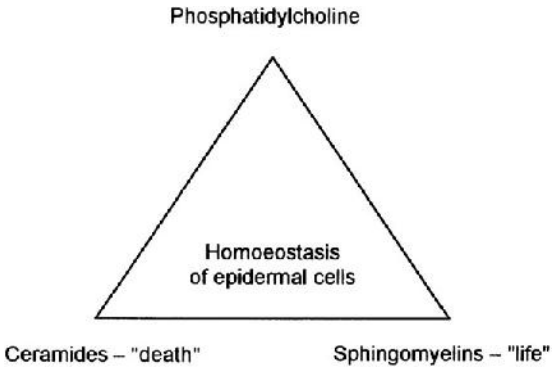

FIGURE 1 Homoeostasis of epidermal cells.

coincides with the penetration of phosphatidylcholine and active agents, which are coformulated with phosphatidylcholine. Because of its high content of linoleic acid and penetration capability, soy phosphatidylcholine delivers linoleic acid very effectively into the skin, and antiacne properties have been shown as a result [5].

By adhering very strongly to surfaces containing proteins like keratin, phosphatidylcholine shows conditioning and softening effects, which are known from the beginning of skincare products' development. So, e.g., shampoos were formulated in the past very often with egg yolk to soften hair and prevent it from becoming charged with static electricity. Egg yolk is very rich in lecithin. The main compound of egg lecithin is phosphatidylcholine.

In a given mixture it is not relevant in which form the phosphatidylcholine is incorporated. However, when phosphatidylcholine is formulated, it is practically inevitable that bilayer-containing systems like liposomes will occur, because this is the most natural form of the material. For example, phosphatidylcholine swollen by water transforms spontaneously to liposomes when ''disturbed'' by little amounts of salts or watersoluble organic compounds, like urea. On the other hand, it has been known for a long time that horny layer pretreated by phosphatidylcholine can be penetrated much more easily by nonencapsulated materials. So liposomes are not really needed to turn out the functionalities of phosphatidylcholine, but they are very convenient because the handling of pure phosphatidylcholine requires a lot of experience and sometimes patience as well.

Because phosphatidylcholine is known as a penetration enhancer, this property is usually associated with liposomes. Liposomes are the vesicles said to transport cosmetic agents better into the horny layer. That is true and, moreover, the conditioning effect causes the horny layer to become a depot for these agents. Measurements of systemically active pharmaceuticals revealed that an increase of penetration is not synonymous with an increase of permeation. Actually, permeation of active agents is often slowed by phosphatidylcholine in such a way that a high permeation peak in the beginning of the application is prevented. Instead, a more continuous permeation takes place out of the horny layer depot into the living part of the body over a longer period of time. This property makes phosphatidylcholine and liposomes very attractive for the application of vitamins, provitamins, and other substances influencing the regenerating ability of the living epidermis.

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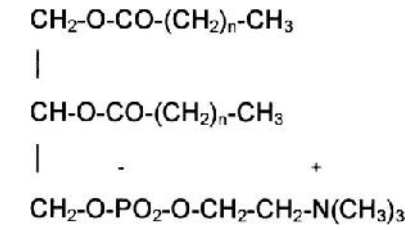

FIGURE 2 Hydrogenated phosphatidylcholine (n = 14,16).

On the other hand, liposomes consisting of unsaturated phosphatidylcholine have to be used with caution in barrier creams because they do not strengthen the natural barrier function of the skin with the exception of its indirect effect of supporting the formation of ceramide I. Ceramide I is known for containing linoleic acid and for being one of the most important barrier-activating substances. Instead of unsaturated phosphatidylcholine, a fully hydrogenated phosphatidylcholine (Fig. 2) should be selected for products designed for skin protection.

Hydrogenated phosphatidylcholine stabilizes the normal TEWL similarly to ceramides when the horny layer is attacked by hydrophilic or lipophilic chemicals [6]. Table 1 shows a summary of the properties of unsaturated and hydrogenated phosphatidylcholine. Hydrogenated phosphatidylcholine is synonymous with hydrogenated soy phosphatidylcholine, which contains mainly stearic and palmitic acid, and semisynthetic compounds like dipalmitoylphosphatidylcholine (DPPC) and distearoylphosphatidylcholine (DSPC). Because of their special properties it can make sense to combine unsaturated with saturated phosphatidylcholine in one and the same cosmetic or dermatological product.

TABLE 1 Properties of Phosphatidylcholines

Parameter	Soy phosphatidylcholine	Hydrogenated soy phosphatidylcholine
Skin barrier function	Penetration enhancement; conditioning the horny layer	Stabilizing the barrier function; conditioning the horny layer
Barrier compatibility	Yes, slightly enhancing TEWL	Yes, stabilizing normal TEWL
Phase transition temperature (aqueous system)	Below 0°C	50–60°C
Fatty acid composition	Unsaturated fatty acids: predominantly linoleic acid, oleic acid	Saturated fatty acids: predominantly stearic and palmitic acid
Solubility	Soluble in triglycerides, alcohols, water (lamellar)	Insoluble in triglycerides, alcohols, and water
Toxicity	CIR-report [7]; anticomedogen	CIR-report [7]
Dispersing ability	Hydrophilic and lipophilic compounds	Hydrophilic and lipophilic compounds

Abbreviations: TEWL, transepidermal water loss; CIR, Cosmetic Ingredient Review.

LIPOSOMES

Liposomes are spherical vesicles whose membranes consist of one (unilamellar) or more (oligolamellar, multilamellar) bilayers of phosphatidylcholine. Sometimes, especially in patents, reference is made not about liposomes but about ''vesicles with an internal aqueous phase.'' The vesicles can differ in size (diameter about 15–3500 nm) and shape (single and fused particles). At a given chemical composition, these parameters strongly depend on the process of preparation. Very often the preparations are metastable. That means the state of free enthalpy is not in an equilibrium with the environment. As a result the vesicles change their lamellarity, size, size distribution, and shape with time. For example, small vesicles tend to form larger ones and large vesicles smaller ones. Fortunately this is mostly not critical for quality because the properties of the phosphatidylcholine, which the vesicles are based on, remain unchanged as a rule. Nevertheless the stability seems to be best in a range of about 100 to 300 nm. That is the case of pure aqueous dispersions of highly enriched (80–100%) soy phosphatidylcholine.

In a complete formulation together with further ingredients, other influences like compatibility, concentration of salts, amphiphilics, and lipophilics play an important role. Therefore, it is often very difficult to prove the existence of liposomes, e.g., in a gel phase or a creamy matrix. However, this is more a marketing problem than a problem of effectiveness of the formulation. Today we can assume that the effectiveness of phosphatidylcholine is based more on the total chemical composition of the cosmetic product and less on the existence or nonexistence of the added liposomes. This may seem curious, but is in fact the reality.

Of course, formulations are very effective in particular when consisting of pure liposomal dispersions bearing lipophilic additives in the membrane spheres and/or hydrophilics in the internal and external aqueous phases within the range of their bearing capacity. In this respect, there has been an intensive search to increase the encapsulation capacity of liposomes for lipids because consumers are used to applying lipid-rich creams. Efforts were made to add emulsifier to the liposomal dispersions to stabilize higher amounts of lipids. Formulators now know that the compatibility of liposomes with regard to emulsifiers is generally limited, more or less. On the other hand, additional emulsifiers have a weakening effect on the barrier affinity of phosphatidylcholine. They cause the phosphatidylcholine and the lipids to be more easily removed from the skin while washing. In this respect there is only one rational consideration: to make use of nanoemulsions consisting of phosphatidylcholine and lipids instead of liposomes. Nanoemulsions are a consequence of the observation that oil droplets can fuse with liposomes when the capacity of bilayers for lipids is exhausted [8]. Further increasing the lipid/phosphatidylcholine ratio and using high-pressure homogenizers lead to nanoemulsions. Nanoemulsions consist of emulsion-like oil droplets surrounded by a monolayer of phosphatidylcholine. The advantage of nanoemulsions is that they allow formulations to tolerate more lipids and remain stable. Also, additional emulsifiers are not needed.

Liposomal dispersions based on unsaturated phosphatidylcholine are lacking in stability against oxidation. Like linoleic esters and linoleic glycerides, these dispersions have to be stabilized by antioxidants. Thinking naturally, a complex of Vitamin C and E (respectively, their derivatives like acetates and palmitates) can be used with success. In some cases, phosphatidylcholine and urea seem to stabilize each other [9,10]. Moreover, agents that are able to mask traces of radical-forming ions of heavy metals, like iron, can be

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added. Such additives are chelators like citrates, phosphonates, or EDTA. Alternatively, the unsaturated phosphatidylcholine can be substituted by a saturated one like DPPC or hydrogenated soy phosphatidylcholine, which should be favored with regard to its price. Because of the higher phase-transition temperature, liposomal dispersions based on hydrogenated material are more sophisticated in their preparation and are reserved for pharmacological applications as a rule. An interesting new development in the field of cosmetic compositions with hydrogenated soy phosphatidylcholine is the Derma Membrane Structure (DMS)-technology [11]. DMS stands for cream bases (technically the creams are gels) containing hydrogenated soy phosphatidylcholine, sebum-compatible medium chain triglycerides (MCT), shea butter, and squalane. In addition to liposomal dispersions and nanoemulsions, DMS is a third way to formulate phosphatidylcholine with hydrophilic and lipophilic compounds free of further emulsifiers (Fig. 3). DMS is water- and sweatproof and therefore suitable for skin protection and sun creams without using silicones or mineral oil additives. It can easily be transformed into other final products by stirring at room temperature together with liquid lipids and/or aqueous phases.

As previously mentioned, DMS is predestined for skin protection, but by addition of nanoemulsions and/or liposomal dispersions DMS can easily be enriched by unsaturated phosphatidylcholine containing esterified linoleic acid. The resulting products are creamy, stable, and anticomedogenic. The effect of pure DMS basic creams on skin moisturizing, smoothing, and tightening are still significant several days after finishing the application.

Liposomes, nanoemulsions, and DMS have to be preserved. This may be a problem, because phosphatidylcholine (lecithin) inactivates most of the conventional preservatives [12]. On the other hand, preservatives should not be penetrated in the skin to prevent irritation and sensitization. Therefore, glycols like propyleneglycol, glycerol, butyleneglycol, pentyleneglycol, hexyleneglycol, sorbitol, and their mixtures are the compounds of choice. These polyols show a moisturizing effect at the same time.

One of the reasons to substitute phosphatidylcholine by polyglycerols and other synthetic derivatives at the beginning of the liposomal developments was its hydrolytic instability in aqueous preparations for longer periods of time and at higher temperatures. In fact phosphatidylcholine, like other glycerides, is attacked by water to form lysophosphatidylcholine and free fatty acids. But the cleavage of the glyceride bond occurs mainly at a pH greater than 7, so formulations in the range of pH 5.5 to 7 are sufficiently stable

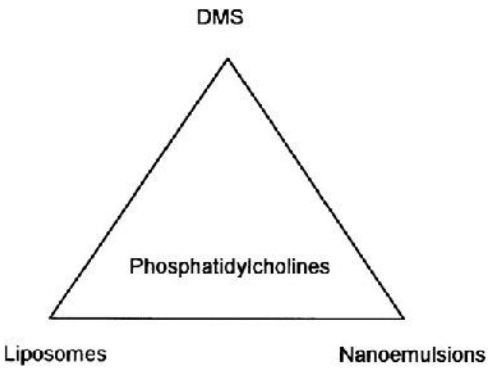

FIGURE 3 Formulations with phosphatidylcholine free of further emulsifiers.

for most purposes. It is possible that hydrolysis depends on the amount of additional surface active compounds. That is another reason to use liposomal dispersions without additional emulsifiers.

AVAILABILITY

As previously mentioned, liposomal dispersions are a very comfortable method to use to work phosphatidylcholine into cosmetic formulations to obtain its superior spectrum of multifunctionality. Preliposomal fluid phases up to 20% phosphatidylcholine and more are commercially available [13]. Also, there are references to the use of instant liposomes in combination with carbohydrates as dry powders [1]. An interesting consideration is bath oils, which form in situ liposomal dispersions free of additional emulsifiers [14]. These compositions are based on mixtures of phosphatidylcholine, triglycerides, and alcohol. By pouring the mixtures into water, liposomes are spontaneously formed. These liposomes strongly tend to adhere to the skin surface. Numerous other methods for preparing liposomes have been described [1].

APPLICATIONS

Today, most of the experts working in the field of liposomal dispersions agree that liposomes do not penetrate as intact vesicles into the skin or permeate through the skin. Liposomes are believed to be deformed and transformed into fragments as a rule. Therefore size, shape, and lamallarity are not so relevant for the application, but for the chemical composition of the total formulation.

The multifunctional properties of phosphatidylcholines lead to a number of different applications. So, formulations with unsaturated phosphatidylcholine are preferred to support skin regeneration, antiaging, acne preventing, and penetrating other active agents like vitamins and their derivatives into the skin. Formulations with hydrogenated phosphatidylcholine may be used for skin and sun protection, but it should be emphasized that in this

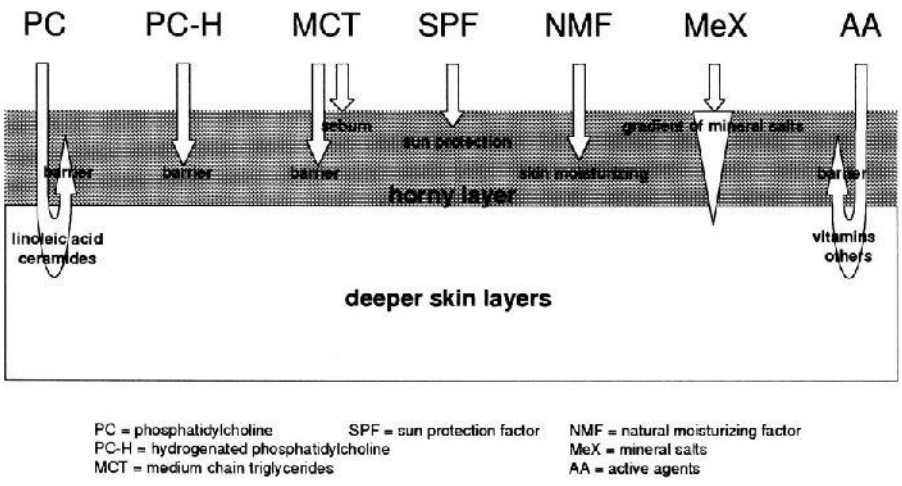

FIGURE 4 Main components of "natural" formulations.

TABLE 2 Phosphatidylcholine-Containing Formulations

Parameter	Liposomes	Nanoemulsions	DMS	Conventional emulsions
Phosphatidylcholine	++	+	Used as additive	(+)
Phosphatidylcholine hydrogenated	Rarely used	+	++	Rarely used
Lipophilic ingredients	Limited	+	+	+
Hydrophilic ingredients	+	+	+	+
Amphiphilic ingredients	Limited	Limited	+	+
Auxiliary compounds	As few as possible	As few as possible	Rarely used	++
Preparation (usual)	Usual and high pressure homogenizers	High pressure homogenizer	High pressure homogenizer	Phase conversion method
Physical stability	(+)	+	+	+
Chemical stability	Depending on pH	Depending on pH	Depending on pH	Depending on pH
Preservation	Glycols	Glycols	Glycols	Glycols
Penetration	++	+	+	(+)
Skin protection	− (Unsaturated PC)	(+)	++	(+)
Convenient particle size	100–300 nm	50–200 nm	Not detectable	Usual droplets
Cosmetic applications	Antiaging, regeneration	Versatile	Skin protection, sun protection	Versatile
Prevention of skin diseases	++	++	++	(+)

Abbreviations: DMS, derma membrane structure; PC, phosphatidylcholine.

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respect nanoemulsions and DMS are still more convenient. The main components of choice to prepare ''natural'' formulations, which are compatible with horny layer, sebum constituents, and their functions are illustrated in Figure 4. About the role of mineral salts see Ref. 15.

THE FUTURE OF LIPOSOMAL PREPARATIONS

Liposomal dispersions have proved not only to be innovative and effective cosmetic ingredients, but also to be a very convenient form to work with phosphatidylcholine. In dermatology, they will be used with success for preventing and treating several skin diseases. Complementary formulations are established where liposomal dispersions come up against limiting factors. Table 2 shows liposomal and complementary formulations in a direct comparison.

Generally, liposomes, nanoemulsions, and DMS are more compatible with the skin structure than conventional emulsions usually applied. Compatible means that formulations do not disturb the integrity of the skin lipid bilayers and are not washed out while cleaning the skin. In the sense of modern strategies of cosmetics, these formulations get by with a minimum of auxiliary compounds, which put only a strain on the skin. Moreover, compatibility means embedding lipids and hydrophilic agents in the horny layer and being in accordance with the natural situation.

Remarkably, phosphatidylcholine need not be applied in high concentrations because the experience shows that formulations are stable at lower amounts. Also, there is a cumulative effect in the horny layer with repeated application of phosphatidylcholine. In many cases, liposomes, nanoemulsions, and DMS are compatible with each other in a sense that they can be used as a sort of construction kit. So these formulations are believed to still have a great future in cosmetic science. How far new findings about the importance of the choline moiety of phosphatidylcholine [16] will impact skincare research and development cannot be estimated today.

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Topical Delivery by Iontophoresis

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INTRODUCTION

Passive permeation of drugs across the skin is limited by the low permeability of the stratum corneum. Transdermal and topical delivery of drugs are presently applicable to only a few drugs with appropriate balance hydro/lipophilicity, small size, no charge, and relatively high potency [1,2].

Strategies have been developed to increase transdermal and topical delivery across or into the skin. They consist of increasing the permeability of the skin or providing a driving force acting on the drug. Chemicals methods (e.g., penetration enhancers) or physical methods (e.g., iontophoresis, sonophoresis, or electroporation) have been shown to significantly enhance transdermal transport [2–4].

Iontophoresis is a noninvasive technique that uses a mild electric current to facilitate transdermal delivery of drugs for both systemic and local effects. Iontophoretic transport of drugs has been extensively studied [5–8]. It has the potential to overcome many of the barriers to topical drug absorption [6–13]. This chapter will focus on local delivery by iontophoresis as an aid to penetration of topically applied drugs. The mechanisms and the parameters affecting iontophoretic transport will be reviewed. The role of iontophoresis in clinical practice and cosmetics will be discussed.

IONTOPHORESIS

Iontophoresis may be defined as the administration of molecules through the skin by the application of an electric current [5–8].

An iontophoretic system has three basic components: 1) the source of electric current, 2) an active reservoir containing the active and an electrode as well as a counter electrode in a return reservoir, and 3) a control unit. The current used for iontophoretic delivery is applied for minutes or hours with current density ranging from 0.1 to 0.5 mA/cm^2. Miniaturized systems of approximately 10 cm^2 including a battery have been developed for transdermal drug delivery. For the topical delivery of actives, the current source can be an external power supply and a larger area can be treated by the current.

The principle of iontophoresis is mainly based on electrorepulsion: the electric field drives the molecules into the skin. Positive ions will be repelled from the positive elec-

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trode, called the anode, and attracted to the cathode, or the negative electrode. Negatively charged compounds will be repelled from the cathode. Neutral compounds can also be delivered by electro-osmosis [3].

Iontophoresis has been widely studied for transdermal drug delivery. It has been used to achieve systemic concentration sufficient for a desired therapeutic effect. Iontophoresis has also been successfully used in clinical medicine to achieve topical delivery of drugs for several decades. It has found widespread use in physical therapy and dermatology. Large quantities of a medication are targeted to a localized treatment region, minimizing the systemic level of the medication. The literature supports the concept that iontophoresis is a method of choice for drug application in the therapy of surface tissue [9–13].

The rationales for topical drug delivery by iontophoresis are as follows: 1) to deliver a locally high concentration of an active—the delivery of the drug is enhanced by iontophoresis by one to three orders of magnitude as compared with passive diffusion; 2) to control delivery of the active by current application—inter- and intraindividual variations can be reduced; 3) to extend transdermal transport to low and medium ($<$5000) molecular weight hydrophilic compounds [5–8,14,15].

MECHANISMS OF IONTOPHORETIC TRANSPORT

Theoretical Mechanisms of Iontophoretic Transport

The electrically induced transport of an ion across a membrane results from three mechanisms: (1) diffusion related to a chemical potential gradient, 2) electrical mobility attributable to an electric potential gradient, and 3) solute transfer attributable to a convective solvent flow, i.e., electro-osmosis [5–8,15,16].

$$J_T = J_P + J_E + J_O$$

J_T = total flux
J_P = passive diffusion flux
J_E = electrical flux
J_O = electro-osmotic flux

$$J = -D\, dC/dx - Dzc\, F/RT \cdot d\varepsilon/dx$$

D = diffusion coefficient
c = concentration
z = valence
F = Faraday's constant
R = gaz constant
T = absolute temperature
ε = electrical potential
X = distance

For ionic species, the contribution of passive diffusion is neglible. The major mechanism of active transport by iontophoresis is the electromigration or electrostatic repulsion. However, the contribution of electro-osmotic flow has been reported to be significant for neutral molecules and macromolecules. Because of its negative charges, the skin is permselective to cations, inducing a net convective solvent flow from the anode to the cathode. Hence, neutral molecules can be delivered into or extracted from the skin by cathodal iontophoresis [16–18].

Pathways for Transport

As for conventional transdermal drug delivery, the molecular transport can take place in the stratum corneum by transcellular or paracellular pathways and/or in the appendages (sweat glands and hair follicles). The major route of iontophoretic transport is believed to be the appendageal pathway because of its low electrical resistance [19,20]. However, recent evidence supports the existence of a significant paracellular route [21–23].

PARAMETERS AFFECTING IONTOPHORETIC DELIVERY

Iontophoretic delivery of compounds into or through the skin is affected by the physicochemical parameters of the active, the formulation of the active, and the electrical parameters of iontophoresis. The parameters affecting iontophoretic transport have been extensively studied and are summarized in Table 1 [5–8,24,25].

The electrical parameters allow control on drug transport. Increasing the current density and/or the duration of current application enhances the delivery of the active into or through the skin. The use of pulsed current rather than constant current can be used to avoid skin polarization, but usually decreases active transport.

The design of the electrodes is also important. Both inert and active electrodes can be used. Inert electrodes, such as platinum or stainless steel, induce electrolysis of water and consequently pH shift of the solutions requiring the presence of a buffer. Active electrodes, such as Ag/AgCl electrodes, require the presence of chloride at the anode. The polarity of the electrodes must be adapted to the charge of the active: anodal delivery for positively charged or neutral molecules and cathodal delivery for negative compounds.

The formulation of the active reservoir as well as counter electrode reservoir also affects iontophoretic transport. Increasing ionization of the active by modifying the pH or decreasing the amount of competitive ions will enhance the transport.

In order to enhance the delivery of an active in the skin, the formulation of the reservoir and counter reservoir and the electrode design have to be optimized. Once the

TABLE 1 Parameters Affecting Iontophoretic Transport

	Parameters increased	Effect on iontophoretic transport
Physicochemical properties of the active	—molecular weight	↘
	—charge	↗
	—partition coefficient	?
Formulation of the active	—pH:ionization	↗
	—competitive ions	↘
	—viscosity	↘
Electrical parameters of iontophoresis	—current density	↗
	—duration of current application	↗
	—current waveform	↘/↗
	—electrode design	↘/↗
	—area of current application	↗

Source: Ref. 24.

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formulation has been optimized and fixed, the control of active delivery can be achieved by modifying the current density and the duration of current application [5]. Hence, the prerequisites for efficient delivery by iontophoresis are 1) a good aqueous solubility, 2) a formulation with a pH allowing the ionization of the active and a low concentration of competitive ions, 3) a polarity of electrodes allowing electrorepulsion (anodal or cathodal iontophoresis for positively or negatively charged compounds, respectively) and/or electro-osmosis (anodal iontophoresis).

EFFECTS OF IONTOPHORESIS ON THE SKIN: SAFETY ISSUES

Evidence for the safety of iontophoresis comes from 1) the long clinical experience with topical iontophoretic delivery, 2) the noninvasive investigations in animals and humans, 3) the biophysical studies of the stratum corneum, and 4) the histological studies.

Effect of Iontophoresis on the Stratum Corneum

The effect of iontophoresis on the stratum corneum structure has been extensively studied by biophysical and histological methods. The effect of iontophoresis on the stratum corneum has recently been reviewed [26]. As shown in Table 2, the major modifications of the stratum corneum induced by iontophoresis include an increased stratum corneum hydration and a disorganization of the lipid lamellae.

Tolerance and Safety Issues Associated with Iontophoresis

The clinical literature on the application of low-intensity current for topical drug delivery supports the fact that iontophoresis is a safe procedure. In general, a minor erythema is observed. The redness disappears progressively within a few hours [31]. The parameters affecting the sensation of current application have been recently reviewed [32].

More recently, noninvasive bioengineering methods have been used in animals as well as in humans to investigate the effect of current application in vivo (Table 3). The barrier function of the skin is hardly modified by iontophoresis as measured by transepidermal water loss. Laser doppler velocimetry and chromametry confirm that a mild and re-

TABLE 2 Influence of Iontophoresis on the Stratum Corneum

Methods	Effect	References
Impedance	Decreased resistance	27
ATR-FTIR	Increased hydration No change in lipid fluidity	28, 29
X-ray scattering		
Small angle	Disorganization of the lipid lamellae, spacing	29
Wide angle	No change in the lipid packing in the lamellae	30
Freeze fracture electron microscopy	Disorganization of the intercellular lipid lamellae	30

Source: Ref. 26.

TABLE 3 Bioengineering Investigations of the Effect of Iontophoresis on the Skin

Methods	Effect	References
Transepidermal water loss	Transient increase (due to an increased hydration)	27, 28, 33–35
Laser Doppler velocimetry	Transient increase	28, 33–35
Chromametry	Transient increase in redness	33, 35

Source: Ref. 26.

versible erythema is induced by current application. The higher the density or the duration of current application, the higher the erythema [28].

In conclusion, the clinical use as well as experimental studies attest to the overall safety of iontophoresis and the absence of long-term side effects. Nevertheless, it should be pointed out that iontophoresis is not without potential injury if not used correctly. The major danger in all iontophoretic treatments is the occurrence of skin irritation and burns. Pain sensation can be relied on as a criterion for the prevention of skin burns as a consequence of excessive densities (>0.5 mA/cm^2). If the electrode metal touches the skin, burns can be caused by excessive current at the site of contact. The solute and the excipients in the solution being delivered can also influence the reaction of the skin [32].

TOPICAL DELIVERY OF DRUGS AND COSMETICS BY IONTOPHORESIS

Topical Iontophoretic Delivery

The main rationale for using iontophoresis for topical delivery is to achieve a higher concentration of the active in the skin. It has been shown that iontophoresis enhances the amount of permeant such as fentanyl, TRH, acyclovir, Ara-AMP, or lidocaine in the stratum corneum, epidermis, and dermis [36–39]. Confocal laser microscopy also shows that iontophoresis enhances the local concentration of fluorescent dye, oligonucleotides, or macromolecules [19,22,23].

Clinical Applications of Topical Iontophoretic Transport

Iontophoresis has been successfully used in medicine to achieve topical delivery of drugs and actives. Most of the clinical applications of iontophoresis were developed in physical therapy and dermatology. The key areas include local anesthesia, hyperhidrosis, and local treatment of inflammation. Efficacy has been shown in clinical studies. In some cases, notably for the delivery of cosmetics, the ability of the medication to penetrate the target tissue in sufficient quantities to produce a clinical effect was not studied in controlled clinical trials.

Tap-water iontophoresis has been widely used for the treatment of hyperhidrosis. It is effective in the management of hyperhidrosis for the axillae, palms, and soles by reducing sweat production with only mild and temporary side effects. The exact mechanism of action remains unknown [40,41]. Current is typically applied in a 10 to 20 min session, which needs to be repeated two or three times per week and followed by a maintenance program [9]. Commercial devices have been marketed. Iontophoresis of actives such as anticholinergic agent and aluminium chloride can increase the average remission.

The successful use of iontophoretic delivery of lidocaine for local anesthesia of the skin has been reported in a variety of situations, including painless venipuncture, painless dermatological procedures such as pulsed-dye ablation of port wine stains, and laceration repairs. The advantages of iontophoresis-induced anesthesia include the painless procedure, the adequate local and low systemic concentration, and the quick onset of action as compared with anesthesia using a eutectic mixture of local anesthetics (10 vs. 60 min) [42–46]. The first drug-iontophoresis device combination approved by the FDA is Iontocaine.

Iontophoresis can also facilitate the penetration of active molecules in the deep tissue underlying the skin. Iontophoresis of dexamethasone sodium phosphate has been reported to be effective for the treatment of patients with musculoskeletal inflammation such as tendinitis, arthritis, or carpal tunnel syndrome [47,48]. Iontophoretic delivery of pilocarpine is extensively used for the diagnosis of cystic fibrosis. It enhances sweat secretion, allowing the measure of chloride concentration in the sweat [49]. Cystic fibrosis indicators are commercially available.

Antiviral drugs such as idoxuridine, acyclovir, or vidarabin can be delivered topically by iontophoresis [10,11,39]. Iontophoresis of Ara-AMP or idoxuridine is efficient in treating HSV1 and HSV2 in mice and orolabial HSV in humans [10,11]. Antiviral-drug iontophoresis could also be useful for the treatment of active zoster lesions and postherpetic neuralgia.

Other applications for topical iontophoresis include the treatment of warts with sodium salicylate [50], calcium deposit with acetic acid [51], improvement of peripheral microcirculation by PGE1 [52,53], treatment of acne scars [54], hypertrophic scars [56,57], or photodynamic therapy with 5 aminolevulinic acid [58].

CONCLUSIONS

Iontophoresis has gained a great deal of attention during the last two decades for both systemic and topical delivery. It offers a convenient and safe means to enhance the topical concentration of drug in the skin and even in deeper underlying tissue as compared with passive diffusion or systemic delivery. Its use to treat local conditions is well known. It is particularly attractive for the delivery of low molecular weight (<1000) hydrophilic solutes at the site of action. Iontophoresis enables precise control of topical delivery by varying electrical current.

The rationales for using iontophoresis to deliver actives in cosmetics and the technology for optimized and controlled iontophoretic transport are well established. However, further double-blind clinical studies are needed to confirm the interest of iontophoresis in specific cosmetic uses.

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Mousses

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INTRODUCTION

The term ''mousse'' originated as the French word for foam, and this in fact is a good basic description of an aerosol mousse. A foam is defined as a two-phase system wherein a gas is dispersed in either a liquid or solid phase to form a foam structure. For the purpose of this chapter all aerosol foams will be considered mousses, although the emphasis will be placed on the more recent applications.

Aerosol mousses have wider applications and can suffer greater formulating problems than are generally recognized. One of the first questions to address is: When should consideration be given to formulating a product as a mousse? Possible reasons could include cosmetic attributes, minimization of inhalable particles, ease of dosing, ease of application, and/or ease of spreading. All of these characteristics differentiate a mousse from a lotion, cream, or spray.

MOUSSE ATTRIBUTES

The primary cosmetic attributes of a mousse are its low density and attractive, pure, white appearance. Specific densities of mousses can vary considerably depending on the type and level of propellant(s) and surfactant(s) used. For oil-in-water emulsions this variable gives an ability to produce a wide range of mousse types for any basic emulsion formula. Product characteristics can be fine-tuned from a slowly expanding, dense foam to a rapidly expanding, light, dry foam. By using a low-pressure hydrocarbon such as butane, the former is produced, whereas if propane were used the latter observation would be seen.

A further variable in tuning the cosmetic attributes of a mousse is the nature of the formulation itself. Factors that affect the nature of the emulsion or dispersion will also impact on the visual characteristics of the foam. In shave and moisturizing mousses, which are generally based on alkali or amine neutralized fatty acids, the nature and blend of the fatty acids can markedly vary the appearance of the foam. The use of mixed fatty acids as opposed to single fatty acids can produce denser, creamier foams than would otherwise be the case. Addition of foam boosters such as coconut diethanolamide will also impact on the cosmetic characteristics. Use of humectants such as glycerine and propylene glycol will also tend to produce denser, creamier foams.

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In a world that will inevitably become more safety conscious, the minimization of ingestion or inhalation of consumer chemicals is becoming increasingly important. During the late 1960s almost all aerosol hairstyling products were hair sprays. Recognition of ozone depletion led to a reduction in the propellant content of many aerosols. This, in conjunction with a need for marketing innovation, led to the hair mousse. Sales of mousse hair treatments grew over the years to take up 50% of the market in some countries, and it became apparent that many users preferred the mousse variant because it was no longer necessary to hold one's breath while styling the hair.

Quite clearly, many aspects of hairstyling could be achieved with a mousse while eliminating the inhalation of solvents, resins, plasticizers, etc. Recently, we have seen concerns expressed for aerosol spray head-lice products as a result of fears that significant quantities of insecticide could be inhaled. We solved this problem by incorporating the insecticide, synergists, and solvents into an aerosol mousse form, which, in addition to capturing the number-one market position, eliminated the inhalation risk.

Although it is not easy to use metering valves with mousses, the user can achieve reasonable dose control by estimating the volume of mousse dispensed. Consumers quickly learn how to dispense the ''right'' amount of product for daily tasks such as moisturizing the hands, styling the hair or covering the lower face for shaving. Mousses do, however, present difficulties in terms of metering valves for several reasons. First, metering valves tend to have a small capacity, anywhere between 25 μL to 5 mL. The larger-chamber metering valves are available, particularly in Europe, but are also relatively expensive. When one uses metering valves with a capacity above 1 mL, there is a tendency for residual product in the metering chamber to expand and slowly emerge from the actuator, leading to dripping and mess.

One of the great pleasures of using a mousse product is the ease of application. Even viscous lotions feel lighter and easier to apply as a result of the gas cells producing a ''thin film'' liquid structure, which collapses with pressure and heat. Variables that contribute to the application characteristics include propellant nature, pressure and quantity, emulsion or vehicle viscosity, and the nature of the formulation excipients and actives. Account must be taken for the required mousse characteristics which will be dependant on the nature of the product. For example, a hairstyling mousse needs to collapse quickly during application because the user wants the resin solution to wet the hair and dry in a controlled but rapid manner. In contrast to this, a shave-mousse user needs a long-lasting foam that will easily spread over the area to be shaved and remain stable during the process of shaving.

A further advantage of mousse systems is the ease with which the mousse can be spread over a large surface area. Again, formulation variables include the propellant type, pressure, and concentration, but, more critically, the viscosity of the product and the nature of the excipients will play an important role. Even with high viscosity, high drag oil phases, the presence of the propellant in the oil phase of oil-in-water emulsions (such as moisturizers and shave foams) tends to reduce the oil phase viscosity during rub-in. In addition to this useful attribute, the thin film nature of the expanded emulsion allows much greater spreadability when compared with an ungassed emulsion.

It is possible to use a portion of low-pressure propellent to keep some waxes and solid fatty acids and alcohols in a liquid state during rub-in. Subsequent loss of propellant leaves these materials free to recrystallize and deliver their cosmetic attributes as waxes. Incorporation of slip agents such as silicones will also help with rub-in and can also

be used to allow conventional moisturizing foams to break more rapidly and further aid spreading.

MOUSSE TECHNOLOGY

The mousse product can be defined as a colloidal dispersion of gas in liquid or gas in solid. Mousse products are typically dispensed from pressurized aerosol containers that contain a liquefied propellant (or a suitable compressed gas) that is soluble or miscible with the base formulation. Depending on the propellant concentration, a mousse product can be further classified as either dilute or concentrated. The former exists as spherical bubbles separated by thick, viscous films, whereas the latter is mostly gas phase—consisting of polyhedral gas cells separated by thin liquid films.

Further distinctions of mousse products, with respect to thermodynamic stability, are ''unstable'' mousses, where solutions of short chain fatty acids or alcohols (which are mildly surface active) drain rapidly from the liquid films surrounding the bubbles, resulting in film rupture and collapse of the foam structure. The other category is ''metastable'' mousses, where solutions of soaps, synthetic detergents, proteins, and the like form a film that achieves a minimum thickness below which no drainage of the liquid film occurs.

Most cosmetic/therapeutic mousse products contain a significant amount of water (anywhere from 5 to 95% by weight of the overall formulation) that exists in the following forms; (1) a solution with a suitable organic solvent, emulsifier, or solvent/emulsifier combination; or (2) the continuous phase of an oil-in-water emulsion. Mousses can also be prepared without water where a suitably volatile propellant is in solution with a viscous nonvolatile material; as the solution is dispensed from the pressurized container the dissolved propellant has sufficient energy to diffuse from the viscous material. This causes a rapid expansion of the nonvolatile material which then sets because of its inherent viscosity.

Although it is relatively simple to form a foamy product using a combination of water, surfactant, and propellant, there are a number of considerations that must be addressed when formulating a mousse for commercial purposes. One of the most important aspects of formulating such a product is the physical quality of the finished product. It must be consistent throughout the life of the product to ensure consumer satisfaction. That is, the color should not change, the bubble size should not significantly vary, the pH should not change, and there should be no packaging interaction. Although this seems fundamental to the process of product development, there are still large numbers of products that find their way to the market and inevitably disappoint consumers or are recalled because of a lack of thorough testing. The consequences of this can include interruptions to marketing, product launch cancellations, bad press, and even lawsuits.

LIQUID-LIQUID AND LIQUID-GAS INTERFACES

One fundamental necessity of the aerosol mousse is that it must be in the liquid state within the container. This allows the product to flow within the container and be dispensed through the valve. In the case of single-phase products, low viscosity assists with solvation of the propellant within the base formulation. Multiple-phase products, such as emulsions or suspensions, must be formulated to ensure the contents remain homogenous during

both manufacture and product application. Reproducible dosing from multiple-phase products is taken into consideration at the commencement of a product development program. A dispersion within a pressurized container is likely to show some signs of sedimentation or creaming during standing so it is important that the contents can be redispersed with gentle agitation. Through the observation of subtle physical changes in the formulation during product development, a homogeneous product that delivers a foam of consistent quality can be prepared.

Surfactants play a very important role in maintaining product uniformity. A simple representation of a surfactant is a molecule that has a hydrophilic head and a hydrophobic tail. The hydrophilic head is typically a hydroxyl group, ethylene oxide chain, or other water-soluble functional group. The hydrophobic tail can be thought of as a saturated hydrocarbon chain that may have additional oil-soluble functional groups attached to the chain. In the case of oil-in-water emulsions, surfactants are dispersed throughout the liquid medium with the hydrophilic heads aligned with the water phase and the hydrophobic tails extending into the surface of the oil droplets. A surfactant layer effectively covers each oil droplet with the hydrophilic heads protruding outward. Sufficient surfactant must be present at the water/oil interface to inhibit coalescence of the oil droplets as they collide.

The surfactant can be a single excipient or a combination of several. The use of more than one surfactant provides a means of establishing the required hydrophile-lipophile balance (HLB) and concentration of the surfactants necessary to form an emulsion with a particular oil phase. Surfactants and oil-phase ingredients have HLB values assigned to them from an empirical scale. Those surfactants that have a HLB value of greater than 10 are generally referred to as hydrophilic whereas those with HLB values below 10 are considered lipophilic. The HLB value for the oil-phase ingredients represents the optimum value a surfactant or combination of surfactants must have to produce an emulsion with the oil and water phases. The HLB for the oil phase can be experimentally determined through monitoring the separation rates of emulsions prepared using different ratios of a set pair of hydrophilic and lipophilic surfactants. The oil-phase HLB value is determined for the surfactant ratio that produces the most stable emulsion. It is calculated by multiplying the fraction of each surfactant present by its respective HLB value and adding the two new values together.

The types of surfactants necessary to produce a spontaneous emulsion are generally selected on a ''like dissolves like'' principle, where it can be assumed that a match in functional groups between the primary oil-phase ingredient and the hydrophobic tail occurs. Surfactant selection can be simplified somewhat when developing pharmaceutical products through the use of materials conforming to a pharmacopoeial monograph. The range of surfactants for cosmetic products, on the other hand, is quite extensive, so much so that it is possible to select materials from any particular origin (physical or geographical). Industry journals, cosmetic ingredient dictionaries, and literature from raw-material suppliers all represent useful sources of information to assist in narrowing down the task of surfactant selection.

Surfactants are also very important in generating and maintaining the foam structure. As the mousse product is ejected from the aerosol container, it is immediately exposed to a lower-pressure atmosphere. The propellant that has been dissolved or dispersed in the formulation rapidly dissipates and is encapsulated by thin films of the liquid phase. As a result, the foam structure expands away from the surface of the liquid. The presence of surfactant lowers the interfacial tension between the propellant vapor and the liquid

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phase, enabling thin films to flex and form a matrix of polyhedra. The liquid film comprises the primary liquid phase or continuous phase of an emulsion depending on the characteristics of the base formulation.

Surfactant molecules in the foam structure are aligned with hydrophobic tails pointing away from the surface of the foam and into the center of the individual bubbles that make up the foam structure. By increasing the surfactant concentration of the formulation, a more stable foam structure with finer bubbles can be produced. Lowering the surfactant concentration enables a formulator to prepare a product that liquefies under low shear or a change in temperature. The foam's resistance to flow and subsequent film rupture are directly related to the surfactant concentration, whereas the thickness of the film is related to the cohesive forces that exist within the liquid.

CORROSION AND AEROSOL MOUSSES

Surprisingly, corrosion is not limited to the inside of the aerosol container. There are many instances where the environment in which an aerosol product is stored has led to the packaging's demise. For example, when an exposed tinplate container is stored in a wet or humid area it is not uncommon for the outer surface to rust. Shaving foams are probably the most susceptible mousse product to suffer external corrosion problems because they are often left in the bathroom and are exposed to moisture during handling and storage. Other causes could be from warehousing or transporting products from humid or tropical areas both before and after manufacturing.

Corrosion within the aerosol container can be controlled with an informed selection of packaging and excipients. As a general rule of thumb, if a product is to be formulated between an alkaline and neutral pH, use a lined or unlined tinplate container. If the product is between neutral and acidic pH use a lined aluminium container. Some products do not follow this rule, primarily because they rely entirely on the lining or corrosion passivating ingredients to minimize corrosion. This is typical of hairstyling mousses that use amine-neutralized resins to control hold and high-humidity curl retention and yet are quite alkaline in character.

Water quality is an important issue to address in minimizing the potential for aerosol-can corrosion. Unless you have a foolproof method for controlling corrosion in water containing mousse products, always use deionized or purified water! Trace amounts of chloride ions can wreak havoc on an aqueous aerosol product, ensuring corrosion and leakage of the pressurized containers within months after production. There are many electronegative ions that can have a similar effect, the most common being anionic surfactants. Salt is sometimes added, or formed as a by-product during the preparation and isolation of surfactants and other formulation excipients. If there is an element of doubt as to the existence of chloride ions in a raw material for your mousse formulation, check with the manufacturer; it could save you a lot of time and headaches!

Because of their single-piece construction and simple elegance, aluminium containers with internal coatings are typically used for many mousse products, although there are exceptions. Disinfectant mousses and shave foams have been packaged in lined and unlined tinplate for years. The most common linings for aluminium containers are epoxy phenolic, organosol, and polyamide imide, although other linings including polyethylene are available. Each lining has specific characteristics, and this determines which applications are suitable. Epoxy phenolic and organosol linings are the most common and are

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approved by most regulatory bodies for food, personal care, and pharmaceutical product contact. Polyamide imide linings are relatively new to aluminium aerosol cans and may not be fully approved for these purposes but, unlike the epoxy phenolic and organosol linings, they are quite resilient to degradation in acidic solutions.

Tinplate aerosol cans are commonly manufactured as three separate components, the base, the dome, and the can wall. A gasket compound seals the base and dome where they join with the can wall. The only negative aspects to this type of can are that a lot of work is done to the individual components before and during the assembly, and some damage can occur in the tinplate and can lining during this process. Also, there are tiny pockets or crevices between the can rims and seam that can inhibit diffusion of product within the container. The consequence of this is that the pockets can act as centers for accelerated corrosion. This issue has been minimized recently, with a new two-piece steel can entering the international market. The potential for liquid phase crevice corrosion has been ameliorated, but it is still quite possible for crevice corrosion to occur in the vapor phase of the can. With the advent of new processing techniques, there is speculation that a single piece or monobloc steel can is not too far away. The two main advantages of tinplate cans are that they are cheaper than aluminium cans and are also magnetic. This latter feature enables tinplate cans to be transported through leak-testing baths on a magnetized conveyor rather than magnetic pucks having to be individually fitted.

TYPES OF MOUSSES

Emulsion Mousses

The use of an oil-in-water emulsion is a convenient starting point for the development of an aqueous aerosol mousse. An important consideration that must be addressed in the development of such a product is the ease with which the product's uniformity can be maintained before dispensing.

During the storage of an aerosol emulsion it is almost inevitable that some separation of the emulsion will occur. In some cases the separated layers will be low in viscosity and hence will be easily redispersed with minimal agitation. However, if the formulation contains excipients that are normally solids at room temperature, there is the possibility that these may crystallize during cold-temperature storage of the finished product. The consequences of this phenomenon are that the oil phase (or possibly water phase) could increase in viscosity to the extent that it is no longer possible to redisperse the separate phases with simple agitation. Crystals may also appear in either phase which, after redispersion is achieved, could potentially block the valve mechanism so that no product can be ejected, or alternatively, product is continually ejected after one actuation (i.e., valve does not cut off).

Shaving foams are a unique example of emulsion mousses in that they contain a very low level of nonvolatile components, yet possess remarkable stability and lubricating properties. A simple shaving foam composition can be prepared with only 5% by weight fatty acid salt, 5% by weight propellant, and the remaining 90% by weight of water. The lubricity of the foam can be enhanced by the addition of emollient oils, polymers, and humectants. In some instances, these can also improve the stability of the foam structure. The density of the foam can also be improved with the incorporation of additional fatty

TABLE 1 Aerosol Shave Foam*

CTFA Name	Function	%w/w
Water	Solvent	to 100%
Potassium hydroxide	pH adjuster	0.44
Triethanolamine	pH adjuster	2.98
Glycerin	Humectant	5.00
Polysorbate-20	Surfactant	1.00
Mineral oil	Emollient	1.50
Coconut acid	Surfactant	0.70
Stearic acid	Surfactant	8.00
Preservative	Preservative	q.s.
Fragrance	Fragrance	q.s.
Propane (and) butane (and) isobutane	Propellant	4.00

* Manufacturing Procedure: Add water, potassium hydroxide, triethanolamine, glycerin, and polysorbate 20 to main mixing vessel. Mix well and heat to 75°C. In a separate vessel add mineral oil, coconut acid, and stearic acid, heat to 75°C and mix until uniform. Add hot oil phase to hot water phase while stirring. Continue stirring and cool to 45°C. Add preservative and mix until dissolved. Add fragrance, stir until uniformly dispersed. Correct for water loss, fill product into aerosol can and secure valve. Add propellant through valve.

Abbreviations: CTFA, The Cosmetic, Toiletry, and Fragrance Association; q.s., quantum sufficiat, quantum satis.

acid salt, nonionic surfactant, and/or water-soluble polymers. A typical shave foam formulation is given in Table 1.

Quick-Break Mousses

The description ''quick-break'' mousse is a vague term that may be defined by many different parameters, but typically by physical stability and the inclusion of significant quantities of an alcohol solvent. When the mousse is dispensed onto a substrate at a temperature below 32°C, it exists as a semisolid mass that can retain its structure for hours. If the mousse is exposed to heat or shear, the foam structure is disrupted and the product reverts to a low-viscosity liquid. These characteristics are valuable when developing thermophobic skincare products.

A mousse of this type can exist as either a single- or multiple-phase system with respect to the formulation packaged in a pressurized container. The single-phase system typically contains a foaming agent, bodying agent, hydroethanolic solvent, and a hydrocarbon propellant. Without the propellant and below 32°C, the concentrate exists as a pasty sludge. If the temperature of the concentrate is raised above 32°C the concentrate becomes a clear, single-phase liquid. This is due to the nature of the solvent system, which has a certain ethanol to water ratio to dissolve the bodying agent, but only when the temperature exceeds 32°C. The temperature at which the foam breaks can be controlled by manipulating the ethanol to water ratio; to increase the melting point of the foam the water level is increased. Similarly, to reduce the melting temperature of the foam the ethanol level is increased. This is true if the bodying agent is ethanol-soluble in its own right.

TABLE 2 Quick-Break Mousse*

CTFA Name	Function	%w/w
Emulsifying wax	Surfactant/bodying agent	2.00
Alcohol	Solvent	58.06
Propylene glycol	Humectant	2.00
Water	Solvent	33.94
Propane (and) butane (and) isobutane	Propellant	4.00

* Manufacturing Procedure: Add emulsifying wax, alcohol, and propylene glycol to main mixing vessel. Heat to 35°C while stirring. Heat water in a separate vessel to 35°C. Add water to alcohol phase while stirring. Continue stirring until uniform. Fill product into aerosol can and secure valve. Add propellant through valve and cool to room temperature.

Abbreviation: CTFA, The Cosmetic, Toiletry, and Fragrance Association.

When the propellant is added, a ternary solvent system is established and the formulation reverts to a clear single-phase liquid. The advantage of this system is that, once filled, the product does not need to be shaken before use. We have used this to our advantage when developing skin-disinfectant products. The inverted pressurized container sits in a cradle and is actuated by pressing down on a lever to open the valve.

The single-phase, hydroethanolic quick-break mousse system has a low viscosity inside the pressurized container, which allows for rapid foam development during spraying. When the product is ejected from the can, a rapid change occurs as the propellant boils and diffuses to the surroundings. The pressurized liquid spontaneously foams and the bodying agent precipitates, leaving a crisp, white foam matrix. When the temperature of the foam is increased to 32°C the bodying agent, which has precipitated from the liquid to provide the foam structure, quickly redissolves and the foam begins to melt. Because of the nature of the formulation, the foam is destroyed as heat travels through the structure. A quick-break mousse vehicle is given in Table 2.

This type of formulation can be easily manufactured commercially as either a single phase which is filled warm (above the precipitation temperature of the bodying agent) or by cold-filling the alcohol and water phases separately. In the latter case, the bodying agent is precipitated from the alcohol phase as it mixes with the water. A clear, single-phase liquid forms in the aerosol container with the addition of the propellant.

Multiple-phase systems also require a foaming agent, bodying agent, solvent, and propellant to produce a quick-break foam. This type of formulation shares the characteristics of the emulsion mousse and is only different in the fact that the formulation is fine-tuned to give a foam structure that is more sensitive to heat and shear. Quick-break mousses of this type can be formulated using various approaches. Some of the more popular systems rely on an oil phase that liquefies at skin temperature, using an emulsion system that is inherently unstable, or by incorporating low levels of emulsion destabilizers such as silicone oils.

Hair-Setting Mousses

These are the most common mousse products in the marketplace. They have evolved significantly over the last 30 years and have reached a high level of consumer acceptance.

The formulations were originally based on single-phase, quick-break mousse systems, but because of the residue of bodying agents and surfactants left on the hair, other approaches were also explored. Modern hair-setting mousses rely on aqueous and aqueous ethanol solutions of hair-setting resins and surfactants for their functionality. The propellant usually remains as a separate phase and is readily dispersed in the concentrate with simple agitation of the aerosol container.

Ethanol is used in some hair-setting products at levels up to 20% w/w, and the benefits of this are twofold; first, the need to include a preservative is eliminated if ethanol is present above 10% w/w, and second, the resulting foam dries quicker when the product is applied. Another advantage of including ethanol in a formulation is that it allows fragrances and essential oils to be more effectively solubilized when a surfactant is present. A hair-setting mousse formulation containing tea tree oil is shown in Table 3.

The combination of hair-setting resin and surfactant serve to generate and support the foam structure. Quaternized polymers are included in some products to confer gentle setting properties and conditioning to hair, whereas acrylate or polyvinylpyrrolidone/vinyl acetate (PVP/VA) copolymers are used specifically for setting the hair and maintaining hold in humid conditions. There are numerous additives used in hair-setting mousses to impart sheen, color, and conditioning. Some examples include protein and lanolin derivatives, fragrances, essential oils, and herbal extracts. Many of these can be quite expensive and exotic, and are often present at subfunctional levels to support label claims.

TABLE 3 Hair-Setting Mousse with Tea Tree Oil*

CTFA Name	Function	%w/w
Tea tree (*Melaleuca alternifolia*) oil	Fragrance	1.000
Tocopherol	Antioxidant	0.002
Peg-40 hydrogenated castor oil	Surfactant	2.000
Alcohol	Solvent	20.000
30% Hydroxyethyl cetyldimonium phosphate	Hair conditioner	2.000
20% Polyquaternium-46	Hair conditioner/styling polymer	10.000
Ceteareth-25	Surfactant	0.200
Water	Solvent	54.798
Propane (and) butane (and) isobutane	Propellant	10.000

* Manufacturing Procedure: Add tea tree oil, tocopherol, peg-40 hydrogenated castor oil, and alcohol to main mixing vessel. Mix until a uniform solution is obtained. Add 30% hydroxyethyl cetyldimonium phosphate to main mixing vessel while stirring. Mix until uniform. Add 20% polyquaternium-46 to main mixing vessel while stirring. Mix until uniform. Add ceteareth-25 to main mixing vessel while stirring. Mix until uniform. Add water slowly to main mixing vessel while stirring. Mix until clear and uniform. Fill product into aerosol can and secure valve. Add propellant through valve.

Abbreviation: The Cosmetic, Toiletry, and Fragrance Association.

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Postfoaming Mousses

Of the various mousse vehicles available to the formulator, one of the most interesting forms is the hybrid postfoaming mousse. This product is typically dispensed as a gel or cream into which the propellant has been previously emulsified or solubilized. When the gel or cream is rubbed onto warm skin the propellant (postfoaming agent) boils and the product starts foaming. The most notable example of this type of product is the postfoaming shave gel that is dispensed as a translucent, colored gel which expands into a creamy white foam during application.

Postfoaming products are packaged in barrier packages of which there are several variations. The first for mention is what we call a ''bag-in-can'' package. The ''bag'' is supported by the neck-roll of the aerosol container and the product is introduced directly into it. A valve (without diptube) is placed into position and secured to seal the container and hold the bag in place. An additional propellant (of higher pressure) is then injected into the cavity between the bag and the can wall through a bung in the base of the can—this provides the driving force to squeeze the product out of the bag when the valve is opened. The second type of barrier package, the ''pouch-on-valve,'' has a laminated pouch secured to the base of the valve. The pouch/valve combination is placed into an aerosol can and the space between the pouch and can wall is pressurized before securing the valve. Alternatively, propellant can be injected through a bung fitted to the can base or around the valve through a hole and flap arrangement after the product has been filled. The formulation is introduced through the valve into the pouch. The pressure within the aerosol can increases as the pouch is filled and the free volume diminishes. It is important to keep this in mind when prepressurizing this packaging arrangement with nonliquefiable propellants.

The postfoaming agent can be selected from a group of low–boiling point liquids such as butane, isobutane, pentane, isopentane, or hexane. The choice is made with the

TABLE 4 Postfoaming Shave Gel with Tea Tree Oil*

CTFA Name	Function	%w/w
Tea tree (*Melaleuca alternifolia*) oil	Fragrance	1.00
Peg-35 castor oil	Surfactant	10.00
50% Lauryl glucoside	Surfactant	40.00
Water	Solvent	to 100%
1% FD&C Blue No. 1	Colorant	0.10
Citric acid	pH adjuster	0.40
Preservative	Preservative	q.s.
Isopentane	Postfoaming agent	10.00

* Manufacturing Procedure: Add tea tree oil and peg-35 castor oil to main mixing vessel. Heat to 40°C and mix until uniform. Heat 50% lauryl glucoside to 40°C and add to main mixing vessel while stirring. Heat water to 40°C and add slowly to main mixing vessel while stirring. Continue stirring until uniform. Add 1% FD&C Blue No. 1 to main mixing vessel and stir until uniform. Add preservative to main mixing vessel and stir until dissolved. Cool contents of main mixing vessel and isopentane to 4°C. Add isopentane to main mixing vessel slowly while stirring. Continue stirring until uniform. Fill product into ''bag in can'' and secure valve in place. Pressurize container through bung in base with hydrocarbon propellant (pressure 30–40 psig at 21°C).

Abbreviations: CTFA, The Cosmetic, Toiletry, and Fragrance Association; q.s., quantum sufficiat, quantum satis.

product's intended use and its physical characteristics in mind. For a low-viscosity or thixotropic liquid, either the pentane(s) or hexane could be used, whereas for a high-viscosity cream or gel it may be necessary to use the butane(s) to get satisfactory expansion of the foam.

Because of the density difference between the postfoaming agent and the bulk aqueous phase, it is likely that some separation of the two phases will occur. This can be controlled with the use of thixotropic, water-soluble polymers (such as the carbomers or xanthan gum) alone, or in combination with suitable surfactants. Although most of the postfoaming shave products marketed today are based on neutralized fatty acids, it is possible to formulate totally nonionic products. An example of such a product containing Tea tree oil is shown in Table 4.

THE FUTURE OF MOUSSES

Although it is easy to describe the various characteristics and attributes of mousse products, it is difficult to entirely separate this technology from that of other product forms. There are obvious overlaps between mousse technology and the technologies pertinent to solutions, emulsions, and suspensions. The mousse product evolved from a combination of these overlaps as well as an appropriate type of packaging being available. The propellant can be considered simply as a low–boiling point excipient in the formulation. After grasping the ''contents under pressure'' concept, anyone competent in physical chemistry can successfully formulate a mousse product, although there is considerable ''art'' in formulating a product that is commercially successful.

The full potential of aerosol-mousse technology is only beginning to be exploited. Once only a form of presentation novelty, mousse formulations, where direct comparisons with ''conventional'' products have been made, are now showing important, relevant differentiators. Mousse products have in some instances shown to have better efficacy and consumer acceptance than nonaerosol formulations. Clinical studies [5,6] conducted on a scalp psoriasis-treatment mousse have shown greater clinical efficacy and patient acceptability than comparator products. The mousse product is also more likely to be used because it is effective, easy to apply, and well tolerated, thereby further increasing compliance and therapeutic efficacy. Furthermore, it has been shown [7] that an alcohol-based head-lice treatment mousse was able to exert ''a high level of direct ovicidal activity, making it effective with a single application.'' The mousse vehicle was shown to generate synergized pediculicide droplets that were small enough to penetrate the breathing pores of the louse egg shell cap and achieve a greater louse egg mortality than a commercial rinse product.

The various mousse categories previously described are by no means absolute. There are many new product forms in development that are unique in their own right. Microemulsion mousses are one such a vehicle that will offer the advantage of a single-phase system without the need for high levels of volatile organic compounds. Nonaerosol mousses have a presence in the marketplace and can be described simply as aqueous surfactant solutions. Solutions become aerated as liquid passes through a vented pump (or valve) mechanism of the dispenser and a foam with a shampoo-like consistency is formed. Facial cleansing and baby-wash products are suited to this type of mousse technology because of the wet nature of the foam.

Specialized mousse products continue to be developed for cosmetic and pharmaceutical markets, showing a willingness by consumers to try new and effective products. We

are currently exploring new ways of using mousse technology to deliver active compounds to the skin for local and systemic use. Therapeutic mousse products for topical and transdermal administration of active compounds are already in the marketplace, and new vehicles are actively being developed. As more approaches to formulating mousse products are explored, greater possibilities are being realized. Products that are cosmetically elegant and efficacious will continue to evolve as more companies explore the possibilities and opportunities of mousse technology.

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20

Cosmetic Patches

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GENERAL

The cosmetic patch is a new ''cosmetic form'' that is the result of the natural evolution of this technology in the pharmaceutical field. It appeared in the market just a few years ago, and although its applications are not too many for the time being, they have been already established as the new weapon to fight against the natural imperfections of our skin or to prevent the adverse reaction caused by environmental or other external influences. A broad spectrum of companies, including the major players, distribute at least one cosmetic-patch system. L'Oreal, Estee Lauder, Beiersdorf, Cheseborough-Ponds, Neutrogena, Lavipharm, as well as smaller manufacturers, participate in this special market.

HISTORY AND EVOLUTION

There is a close relation between topical pharmaceutical and cosmetic preparations. This relationship has its origin in the ancient years. Not only the forms (creams, ointments, solutions, liposomes, microemulsions), but also technologies and their production conditions are very close to each other. Under this rationale, the research and development of cosmetic patches started a few years ago. The influence of the pharmaceutical technology is apparent in the case of the cosmetic patches not as simple cosmetic forms but as cosmetic delivery systems. It is not the first time that such a thing has happened. Liposomes and microparticles, for example, had been transferred from other application fields to the pharmaceutical and later to the cosmetic technology fields with successful results. In Figures 1 and 2 we can see the similarities of these two categories regarding the Conventional forms as well as their delivery systems.

Cosmetic patches today, although at the beginning of their evolution and having weaknesses in some cases, represent a convenient, simple, easy, safe, and effective way for cosmetic applications, using one of the most acceptable, modern, and successful delivery technology.

BORDERS BETWEEN PHARMACEUTICAL AND COSMETIC PATCHES

By definition, cosmetic products cannot be used or claimed for the therapy of diseases. Sometimes the companies use claims exceeding the borders between pharmaceutical and

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FIGURE 1 Dosage forms ''equivalent'' for cosmetics and pharmaceuticals.

cosmetic application because the line is very thin between these major classes and/or in the past it was easier to use such terms. The patches could not be the exception to the rule.

Some patches that stand between drug and cosmetic fields, e.g., acne or acneic conditions, are included in this category, and as we will see later, in some countries the actives combining with the claims characterize the classification, although in others products like these are considered to be real cosmetics. We could synopsize some simple rules to draw a bold line between these two classes:

1. Cosmetic patches are not pharmaceutical patches (the same way cosmetic creams are not pharmaceutical creams).
2. Cosmetic patches are designed for cosmetic applications.
3. Cosmetic patches contain cosmetic ingredients only (at concentrations allowed for cosmetic applications).
4. Cosmetic claims have to be confirmed via cosmetic efficacy tests.
5. Additional tests, patch specific, have to be established for cosmetic patches (e.g., peel force, wearing tests, residual solvents).
6. Safety first and efficacy second have to characterize these new forms.

APPLICATIONS OF COSMETIC PATCHES

In theory, cosmetic patches can be applied in most cases for the same use as classical cosmetic products, e.g., wrinkles, aging, dark rings under the eyes, acneic conditions, hydration of specific areas, spider veins, looseness, and slimming. In practice, several of

FIGURE 2 Delivery systems ''equivalent'' for cosmetics and pharmaceuticals.

the aforementioned applications have been investigated, with very positive results and a high degree of acceptability from the consumers. The role of the specific form is not to cannibalize or to fully substitute the existing cosmetic forms. The main mission is to provide a breakthrough proposition for the cosmetic category as problem solvers. Someone could compare the cosmetic patches' role with the one of pharmaceutical patches. Where applicable and feasible, the pharmaceutical patches have almost substituted the classical forms because of their superiority over the conventional forms. But they did it because of, e.g., the convenience, better efficacy, less side effects, and the lessened need for use. On the other hand, they never substituted all the existing pharmaceutical forms, each one of which plays its own important role.

We could synopsize by saying that cosmetic patches are destined mainly as problem-solver cosmetic forms, i.e., they are more effective and efficient products with an absolutely and strictly localized action. Applied on the specific site, they limit their action on the specific area (acting topically), protecting at the same time the site and the active(s) itself.

DIFFERENCES BETWEEN CLASSICAL COSMETIC FORMS AND PATCHES

It is known that from the moment classical cosmetics (creams, lotions, etc.) are applied to the skin, they start changing continuously. The air, atmosphere's pollution, humid or dry environment, dust, and anything that can be transferred with it as well as any other factors alter the composition and the form of the product, which results in significant changes to the product's action. Patches, on the other hand, are systems of occlusion even if there is sometimes the need, and we have the possibility, to manufacture breathable or porous patches. Because of this, permeation is getting easier, interactions with the environment are being considerably reduced, and we can expect a more ''accurate'' and ''controlled'' overall result.

Using the term ''permeation,'' we mean the possibility that is given to several substances to reach the site of action, without of course confusing this term with the capability of a pharmaceutical patch to introduce the therapeutic substances into the systemic circulation at therapeutic levels. In many cases, this permeation makes the difference between an effective and noneffective form of administration of a cosmetic ''active.''

DEVELOPMENT OF COSMETIC PATCHES

All of the aforementioned pluses concern ''good'' cosmetic patches. As always happens with the new trends and the products following them, the low level of knowledge and experience guides several organizations to launch products without proofs of the required quality. As you will find later in the text, cosmetic patches are not pieces of Scotch tape containing one or a combination of cosmetic actives. On the contrary, it has to be an ''extremely safe and effective scientific product.'' As such a product it has to be supported with all the safety and efficacy proofs required.

As a new form or better delivery system, a cosmetic patch requires additional tests not applicable on conventional cosmetic products. Because of the occlusive or semiocclusive character, these patches require a different level of investigation concerning the percentages of the ingredients, the compatibility with the skin, the possible amplified dermal reactions, and so on. Only special people and companies can formulate cosmetic patches. First, what is required is the full and perfect knowledge of the patch technology combined

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with the same level of knowledge and experience of the cosmetically acceptable ingredients and synergistically acting combinations. Until now, the experience on the patch technology used to be a monopoly of the scientists in the pharmaceutical field. The scientists in the specific pharmaceutical field know very well the correlation between active ingredient and therapy. They used a specific active to treat a specific illness or symptom. Cosmetic technology is ''philosophically'' different. Although in recent years there have been cosmetically active ingredients with a specific action, conventional cosmetic products use several components, and it is often difficult to make the distinction between ''active'' and ''excipients.'' At the same time, because there are not real actives as we mean them in the pharmaceutical terminology or the regulations and we cannot use high concentrations of these actives, the cosmetic formulator is obliged to use, in most cases, ''its own cocktail'' of ''cosmetic actives'' to achieve the expected result. This is a big conceptual difference between the two types of formulators; the pharmaceutical and the cosmetic. This situation is also going to follow the cosmetic patches formulation. It is expected that several ''cocktails of synergistically correct combinations'' will play the role of the actives included in the pharmaceutical patches. It is obvious that the case of the cosmetic patch development and the required background cannot be found easily.

TYPES AND CONFIGURATION

There are several ways to describe and categorize a cosmetic patch. It can be characterized from the patch form (e.g., matrix, reservoir), the application purpose and the expected result (e.g., moisturising, anti-wrinkle), the type of its structural materials (synthetic, natural, hybrid), the duration of application (e.g., overnight patch, half-hour patch). Cosmetic marketing is always more inventive in finding attractive terms to characterize a cosmetic product, but even scientifically there is better flexibility regarding the terminology. In practice this category of patches covers the entire field, starting from the small or larger patch-like ''facial masques'' and finish to the cosmetic patches similar to their pharmaceutical cousins. In between, we can position some patch-like products, or strips for the removal of blackheads from the nose or other problematic areas of the face, or for the stretching of the skin. Another way to classify cosmetic patches is the duration of application, the action, and so on. Table 1 presents a different classification:

Regarding the flexibility of cosmetic patches, Figure 3 shows several and numerous combinations concerning applications as problem solvers, shape, ingredients, and site, among others.

Table 2 presents a ''map'' of cosmetic patches, covering a big part of their world.

It is obvious from all these examples of cosmetic patches that most are designed

TABLE 1 Examples of Cosmetic Patch Categories

Pore Cleansers
Blackhead removers
Stretching stripes
Short-term patch-like masks
Short-term treatment patches
Overnight treatment patches

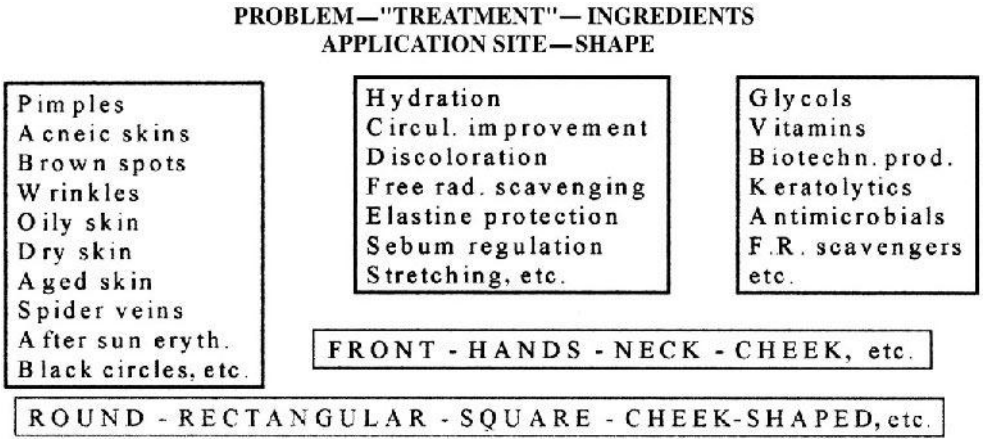

FIGURE 3 Versatility of use and applications for cosmetic patches.

TABLE 2 Categories of Functional Cosmetic Patches

Antiblemish Patch
: An extremely popular, very small and thin patch for the treatment of pimples and blemishes. Contains a balanced percentage of salicylic acid, anti-irritant, and antimicrobial agents.

Pore Cleansers
: Very popular patches applied to the nose; their role is to clean pores and remove sebum plugs.

Pimple Patch
: A relatively large and thick patch for the care of pimples and blemishes.

Eye-Contour Patch
: Mixture of several beneficial active ingredients for the fast relief of the area under the eyes after a short-term treatment (e.g., half hour).

Antiaging Patch
: One of the first cosmetic patches developed and sold. It bases its claims on ascorbic acid contained in the adhesive. Several similar patches have been developed.

Antiwrinkle Patch
: Based mainly on the antioxidant action of Vitamin C, as with the antiaging patch, this patch set is suggested for the prevention and treatment of wrinkles.

Lifting Patch
: Based on a mixture of glycolic acid, proteins, vitamins, and plant extracts, this large patch is used for the treatment of wrinkles of the neck.

Slimming patch
: Thin and transparent, this patch contains a mixture of natural extracts (Fucus vesiculosus, Ginkgo biloba, etc.) and claims a slimming effect.

according to the principle of the matrix patch. This type of patch is thin, has a light weight, has a reasonable production cost, and represents the trend in our days.

STRUCTURAL COMPONENTS OF THE COSMETIC PATCHES

Generally speaking, a matrix patch is composed of three discreet layers:

- The backing film
- The adhesive layer
- The release liner

A matrix patch has the form shown in Figure 4.

Backing Film

The backing film is one of the three layers of a matrix patch. It is the layer that is apparent after the adhesion of the patch on the specific site of the skin. Its main role is to protect the adhesive layer from the influence of external factors; it also provides such characteristics as flexibility, occlusivity, breathability, and printability. Several materials have been used as backing films. The selection of a specific film for use in a cosmetic patch may depend on the following factors:

- Cost
- Stability
- Printability
- Machinability
- Glossy or matte appearance
- Compatibility
- Anchorage to the adhesive
- Transparency
- Opacity
- Occlusivity
- Breathability

Several materials can be used for these purposes depending on the needs already presented.

One of the first and cheapest cosmetic patches used a simple paper layer.

Most of the pore cleansers use nonwoven materials. The reason is obvious: all these systems require wetting the nose before application of the patch. It means that the system has to dry out in order to be able to remove the sebum plugs that stick to the dried layer.

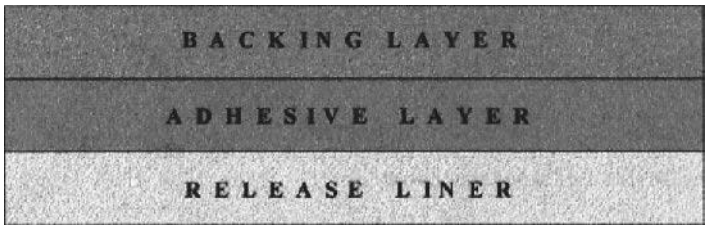

FIGURE 4 Typical structure of a matrix-type patch.

Polyethylene or polyester films are used also in most systems. They do not need to dry out after the application. Sometimes the film used is nontransparent. A white, foamy material is the backing layer of the pimple patch.

In some cases, other more expensive materials have also been tested, such as polyurethane, chlorinated polyethylenes, nylon, and saran. It is very important that the materials used as backing films for cosmetic patches have the same quality specifications with the similar films used for pharmaceutical patches to avoid any adverse reactions of the skin.

Release Liners

The main role of this layer is to protect the product, especially the adhesive layer, before the use of the product. The pharmaceutical patch development has provided a long list of release liners that can be useful for cosmetic patches as well. There are three main classes of release liners according to their composition:

1. Paper based: Glassine paper, densified Kraft super-calendered paper, clay-coated paper, polyolefine coated paper, etc.
2. Plastic based: Polystyrene, polyester (plain, metallicized), polyethylene (low and high density), cast polypropylene, polyvinyl chloride, etc.
3. Composite material based on the combination of several films

All these materials have a common characteristic: one release layer coated on one or both sides depending on the needs of the product and the system itself. This coating is, generally speaking, silicon or polyfluorocarbon. The grade, thickness, coating, and curing methods vary according to the materials and the satisfaction of specific needs.

As mentioned for backing films, this layer has to be compatible with the components of the adhesive layer and should satisfy the specific needs of the product. Sometimes this layer has to be, e.g., printed, scored, perforated, or tinted. The selection of the material and the grade are dictated from similar factors to the ones influencing the selection of the backing layer.

Adhesive Layer

This is the most important layer of a matrix cosmetic patch. The adhesive layer contains not only the adhesive that makes the patch stick to the skin, but in most of cases the cosmetic active ingredients and the additives required for correct formulation of a cosmetic product. Starting with the adhesive itself, the majority of adhesives used in cosmetic patches are taken from the general category of pressure-sensitive adhesives (PSAs). This is a class of adhesives used in several applications, and in all pharmaceutical patches. As its name shows, PSAs are adhesives which, in their solvent free form, remain permanently tacky and stick to the skin with the application of very slight pressure. There are three groups of PSAs: 1) acrylics, 2) silicones, and 3) rubbers. There are numerous members in the three main families of PSAs, but only few can be used for the formulation of cosmetic patches. The reason is that as also happens with pharmaceutical patches, there are so many restrictions on the selection of an adhesive that the useful members are relatively few. The limitations are governed by the mechanical and biomedical properties of the adhesive, as well as the characteristics of compatibility, reactivity, and stability.

The components of the adhesive are also governed by such properties as, solvents, monomers, cross-linkers, and emulsifiers.

There is also another category of cosmetic patches with similar structure, but formulated with a dry-adhesive system other than PSA. In this class we can bring the example of pore cleansers. Here the adhesive layer is created in situ, by wetting the dry adhesive layer with water the same way we stick a stamp on a letter. The components included in the composition of dry adhesives can be found in the classes of synthetic or natural derivatives, e.g., polyvinyl derivatives, starches, celluloses, and sugars.

Pouching Materials

Although this material is not a component of cosmetic patches, its importance for the integrity of the product during its shelf life makes us examine it just after the basic patch components. Almost all cosmetic patches as happens with the pharmaceutical ones, are pouched in pouches. For pharmaceutical patches, the rule is to package one patch in one pouch. With the cosmetic analogues, and in an effort to reduce cost, sometimes patches can be found in the same pouch for more than one application. In this case, it is recommended that the product has stability information for the time interval between the opening of the pouch and the use of the last patch, as well as to foresee some kind of resealable pouch. The materials used for the two categories are similar or the same. One of the differences is the number of packaged patches in one pouch. The protection of the product is the main mission of this packaging material, the role of which is critical for long-term stability of the product.

The pouching material, as has been mentioned, influences a lot of the stability of some sensitive molecules. Sometimes the phenomena of adsorption are noticed because of the affinity of some ingredients with the internal, sealable layer of the pouching laminate. In this case, e.g., AHAs can escape from the adhesive layer and, passing the edge, can be absorbed from the ionomers plastic film of the pouching material. Another protection the pouching material provides is protection from UV radiation by using at least one opaque layer in case of light-sensitive materials, along with protection from oxygen.

Production

The production of cosmetic patches depends on the type of patch, the component characteristics, and the overall configuration of the final product. Because most cosmetic patches are matrix patches, it is useful to follow the general steps of typical production concerning this type of patch. Practically, production starts from the weighing of raw materials and other components, and ends with packaging of the product in the final carton. It is not within the scope of this chapter to go into details in this field, but we can mention the basic steps of the production sequence. Some information is required regarding the critical steps of production, or better the steps that could influence the quality of the product itself. The mixing of cosmetic ingredients and adhesives has to take place under a very slight nitrogen atmosphere (pressure) to avoid oxidation of the ingredients during this phase, but not too high (to avoid inclusion of nitrogen in the mass of the mixture and bubble formation during the drying cycle). Drying is also a critical step because, during this process, the temperature of the coating goes up and the ingredients have to be stable at these conditions. During drying, some of the ingredients are evaporated and/or sublimated. An accurate validated process has to be defined to finally take the patch as it had been designed. The exposure to light has to be limited as well, and the web has to be protected and kept in the predefined conditions before packaging. Of course, all the technology for

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production of pharmaceutical patches is applicable, but found outside the scope of this chapter.

PRODUCTION STEPS

Production of Casting Solution

This involves the mixing of active ingredient(s), additive(s), and other adjuvants, in the mass of the adhesive in the appropriate size and design production vessel and in the appropriate space.

The bulk could be a solvent or waterborn system, and the basic steps are as follows:

- Weighing
- Mixing
- Deaeration
- Release
- Filtration and transfer to pressure vessel
- Final bulk release

Coating—Drying—Lamination

The casting solution is prepared, released, coated, dried, laminated, and formed to the final rolls according to the specific standard operating procedures (SOPs), and the production records as follows:

- Feeding of the dosing pump, and through this the coating station
- Casting on the release film
- Drying of the coated solution passing through the drying tunnel
- Continuous thickness control and recording
- Lamination with the backing material
- Winding in rolls
- Splitting of the rolls
- Quarantine
- Final control
- Release

Packaging

The process involved in packaging is described as follows:

- Roll feeding
- Punching
- Pouching
- Cartoning
- Boxing

REGULATORY ISSUES

As always happens with new forms, there is some confusion regarding the regulatory status of cosmetic patches. The main reason is that cosmetic patches are not included, for the time being, in the approved forms of cosmetic preparations. Considering the Directive 76/768/EEC, August 1993, which is the official regulation of cosmetic products in the

European Union, a cosmetic product ''shall mean any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours or/and protecting them or keeping them in good condition.'' According to this definition, cosmetic patches, acting similarly to conventional cosmetics, are included with cosmetic products. The confusion starts from paragraph 2 of the same article, stating that; ''The products to be considered as cosmetic products within the meaning of this definition are listed in Annex I.'' In Annex I are included all the conventional forms, but not patches because, at the time of issuing, patches did not exist. So, because cosmetic patches conceptually, according to the cosmetic definition, comply with it, and because cosmetic patches are reality in our days, Annex I has to be revised with the addition of this new category.

Another reason for this confusion is the common origin of patches and transdermal systems. As previously mentioned before, all transdermals are not patches and all patches are not transdermals.

It is true that the first patches were dedicated to transdermal delivery of actives. At the same time, it is true and correct that not all transdermal systems are patches and that not all patches are by definition transdermals. We have the case of Nitro-Bid ointment for the transdermal delivery of nitroglycerin, but at the same time we have ''patches'' stuck to the skin for diagnostic purposes or for delivering the active to the opposite direction, e.g., to the air to repel mosquitoes or for the topical treatment of pain.

To achieve transdermal delivery and effectiveness, several other factors are required:

- the intrinsic properties of the molecule,
- its concentration in the system,
- the appropriate permeation enhancers,
- the application site,
- the surface area;

and other factors play a very significant role in

- the rate and extent of absorption,
- the ability of the specific active to reach the blood stream, and
- its efficacy and toxicity.

Without forgetting the peculiarity of cosmetic patches as cosmetic delivery systems or forms, we could propose that this new system not be encountered with scepticism and to follow the rules governing other cosmetic preparation. It means that the composition of the formula qualitatively and quantitatively has to follow existing cosmetic regulations, followed by specific tests and controls required especially for patches (e.g., residual solvents, adhesion on the steel, wearability), as well as tests regarding the safety parameters of an occlusive or semiocclusive system.

FUTURE TRENDS

The evolution of cosmetic patches is something expected after the warm acceptance of new cosmetic delivery systems from consumers. There are three axes for their expansion:

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1. **The technological field**. It is expected that any new progress on patches, generally speaking, will strongly influence cosmetic patches as well. Even nonpassive cosmetic patches, like the iontophoretic ones, will find in the future several applications for the administration of more sophisticated cosmetic ingredients and actives.
2. **The applications**. For the time being, the applications of cosmetic patches cover a small part of the overall cosmetic applications. It is expected in the future to have a coverage of almost the whole spectrum of cosmetic applications.
3. **The ingredients**. The cosmetic patches, as previously explained, need to present a more potent solution for the cosmetic treatment of skin problems. For this reason, there is the need for the use of very potent ingredients or extracts, that are probably especially designed for the patches in order to achieve a very fast and effective action.

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