The Influence of Emollients on Dermal and Transdermal Drug Delivery

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5.1 Introduction

The word "emollient" is derived from the Latin *emollire*, meaning to soften (from *ex*, out and *mollis*, soft). According to the *Oxford English Dictionary*, an emollient is a substance "that has the power of softening or relaxing the living animal textures," with the first use of the name being

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Table 5.1 The nature, uses, and various definitions of emollients over time

Source	Date	Definition
Oxford English Dictionary	1643	Substance "that has the power of softening or relaxing the living animal textures"
Edwards (1940)	1940	"Since oils, fats and glycerin when applied to the skin tend to soften the epidermis they are termed emollients…"
		"An adhesive coat is produced which prevents the irritation of drying, and the access of bacterial, chemical and mechanical irritants"
Blank (1957)	1957	Any material that tends to prevent or alleviate the symptoms and signs of dry skin
Idson (1982)	1982	Emollients – substances lubricating and/or occluding the skin with water-insoluble material (Moisturizers – substances actively increasing the water content of the skin)
Wilkinson and Moore (1982)	1982	Emolliency is only associated with imparting smoothness and general sense of well-being to the skin, as determined by touch
Wehr and Krochmal (1987)	1987	Emollients – systems that smooth the roughened surface of the SC, but do not occlude the skin. No effect on TEWL after application
Loden (1992)	1992	Similar action to moisturizers
Dederen et al. (2012)	2012	Emollients – oily ingredients used for skin care formulations

recorded in 1643. In general, emollients are lipid in nature and are ingredients in a product, which when applied to the skin deposit a lipid film that can also replenish any lost skin lipids. The resultant effect is improved skin lubrication, a smoother skin surface, a soothing effect as it protects the exposed viable epidermis, and hydration of the stratum corneum (by moisturizing the skin through reduced transepidermal water loss). Overall, the skin treated with an emollient is described as being soft and supple, whereas that treated with a humectant (a substance that attracts water to the skin (Idson 1992), improving its hydration) has the sensory feel of softness due to moisturization of the stratum corneum, but without the sensorial suppleness feel associated with the "oily" film. A moisturizer usually refers to a product, and it may contain an emollient and/or a humectant and/or water to provide direct hydration of the stratum corneum. In practice, however, the term "emollients" has been interchangeable with "moisturizers" and "lubricants," and being used as "bases," "vehicles," or to make "vanishing creams," "revitalizing creams," or "regenerating milk" (Nola et al. 2003). Regrettably, the nature and actions of an emollient, a humectant, and a moisturizer often have become blurred in the press over the years, leading to the terms often being used interchangeably, although the sensory responses are different.

With a history of several thousands of years, the nature, uses, and various definitions of emollients have changed with time (Table 5.1). Many of the earliest emollients were derived from animal fats. Marks refers to Egyptians and ancient Greeks using "oils and pleasant smelling fatty concoctions on the skin," the use of wool fat by the Greeks in about 700 BC, the processing of lanolin from sheep's wool by a Greek physician in a *Materia Medica* in 60 AD, and the patenting of petrolatum (also known as petroleum jelly, white soft paraffin, and Vaseline) in 1872. As he points out, lanolin is a complex emollient in being a two-phase liquid and wax system consisting of multiple complex sterols, fatty alcohols, and fatty acids, dependent on the nature of the sheep sourced, its manufacturing, and its storage (Marks 2001). Interestingly, goose grease and even human fat have been used as emollients, and emolliency has also been referred to in the soothing of the throat (Coxe 1825). A prevailing view is that "lipids (fats, waxes, and oils) are seen as the essential components of emollients" and that the total lipid content in an emollient formulation is usually 20–40 % (Marks 2001).

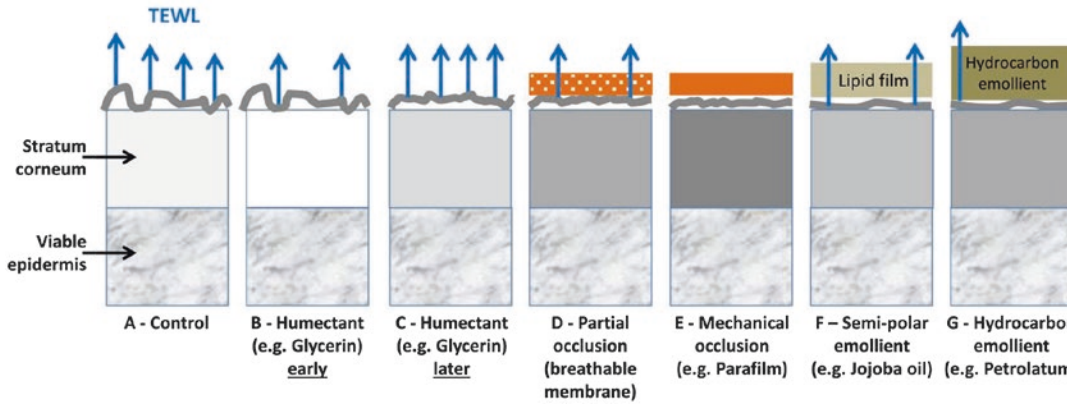


Fig. 5.1 The effect of various products on the stratum corneum, ranked in order of increasing lubrication of the stratum corneum surface after several hours of application (except B) for: (**a**). Control; (**b**). Humectant, early times only; (**c**). Humectant, later times; (**d**). Partial mechanical occlusion with a breathable membrane; (**e**). Mechanical occlusion, for example, with a plastic covering; (**f**). Semipolar emollient; (**g**). Hydrocarbon emollient. The figure also shows (i) the effect of products on stratum corneum hydration (the *darker the box*, the higher the skin hydration) and (ii) the transepidermal water loss (TEWL), with the number of arrows indicating the magnitude of the TEWL

Other definitions of emollients have included the preparations themselves (Ray and Blank 1940; Harry 1941), and ointments designed for deeper skin penetration (Wild 1911). Confusion has arisen, in part, from the early emphasis on the emollient lipid film interactions with skin lipids and scales and the more mechanistic approach advocated by Blank, in 1957, which emphasized the skin hydration associated with emolliency. He defined an emollient as "any externally applied material that tends to prevent or counteract the symptoms and signs of dryness of the skin" (Blank 1957). An occlusive dressing is also often used to increase skin moisturization.

Figure 5.1 summarizes our current view of the effects of humectants, semipermeable or impervious occlusive films, semipolar emollients, and hydrocarbon emollients on stratum corneum (SC) roughness, hydration, and transepidermal water loss (TEWL). It is evident from this figure that emollients differ in their actions on normal skin, compared with other skin treatments such as application of humectants and occlusive dressings. As shown in Fig. 5.1, emollients affect both the transepidermal water loss and the roughness of skin surface through the oily film that they create. The lipid surface film on the stratum corneum and its resulting lubrication of the surface gives a feel of suppleness. The reduction in transepidermal water loss (TEWL) promotes skin hydration. The application of a semipolar emollient like vegetable oil is likely to reduce TEWL to promote skin hydration to a lesser effect than the more occlusive hydrocarbon emollient.

We now describe the emollients used in practice, their potential effects on percutaneous absorption, and some practical examples of products containing emollients. In recognizing that the stratum corneum is the main barrier for both dermal and transdermal absorption, we have focused this chapter on the effects of emolliency on skin function and the skin penetration of the active.

5.2 Current Emollients, Their Modes of Action, and Their Use in Practice

5.2.1 Sebum

Sebum is the natural emollient of skin. It is produced from the sebaceous glands adjacent to the hair follicle and consists predominantly of squalene, wax esters, triglycerides, cholesterol esters, and possibly free cholesterol (Stewart 1992). The sebum provides a pliable film on the skin surface that lubricates the skin, inhibits percutaneous absorption of unwanted substances, and impairs

TEWL, leading to increased skin hydration (Stoughton 1959). As well as providing lubrication and hydration of the skin, the sebum can also provide immunological and antimicrobial protection through its surfactant proteins and peptides, especially when their expression in human skin is upregulated (Mo et al. 2007). In addition, the sebum can also act as a buffer, impairing adverse irritation from acidic or basic compounds.

Regular washing of the skin, however, can remove the sebum and result in greater skin roughness and reduce stratum corneum hydration. Low sebum levels have been regarded as a contributing factor in the development of dry skin (Clarys and Barel 1995). Emollients are widely used to provide the desired lubrication and skin hydration that is normally supported by the sebum. In addition, a number of common skin care ingredients, including mineral oil, white petrolatum, and isopropyl myristate, have been shown to enhance sebocyte counts, and hence, potentially, sebum production, in a hairless mouse model (Lesnik et al. 1992).

Sebum has been shown to contribute to stratum corneum hydration by a glycerol-dependent mechanism. Based on the identification of glycerol as the putative product of triglyceride hydrolysis in sebaceous glands, Fluhr et al (2003) treated asebia mice, showing profound sebaceous gland hypoplasia, with glycerol, and were able to restore normal stratum corneum hydration. Urea, another commonly used humectant, had no effect.

5.2.2 Emollient Classes and Properties

Members of the different classes of emollients have different physicochemical properties that result in a range of functional and sensorial effects when left as a lipid film after being applied to the skin in a cosmetic or dermatological product. Traditionally, emollients have been regarded as having a number of common properties: (i) fat solubility, (ii) the ability to soften the skin, and (iii) an oily feel. However, they can differ quite markedly in their physicochemical properties. Some emollients are partially soluble in water (e.g., PEG-150 distearate, PEG/PPG-8/3 laurate) and are used not only for skin but also for hair (e.g., PEG-7 glyceryl cocoate, PPG-3 benzyl ether myristate). Others may feel dry to the touch (e.g., oleyl alcohol, C12–15 alkyl benzoate, phenethyl benzoate, cyclomethicone, and isononyl isononanoate). In general, the lipophilicities of the emollients in (Table 5.2) are such that those containing hydrogen bonding groups, such as ethers, esters, vegetable oils, and lanolin are more polar than those without these groups, for example, hydrocarbons. Today's emollients are used to meet many different functional needs and to support multiple "claims," and hence, a formulator has to select appropriate emollients to meet not only the consumer and regulatory needs but also to cater for whether the final product is designed for a cosmetic or a therapeutic application.

5.2.3 Effect of Emollients on Skin Lubrication

The choice of an emollient is often based on the tactile properties of these substances on the skin surface and is often of higher importance in cosmetology than in the formulation of topical therapeutic drugs, where sensory properties are not necessarily the main priority (Dederen et al. 2012). A plethora of imaginative terms may be used to describe these subjective properties. Words such as "tacky," "oily," "dry-velvety," or "waxy" are readily understood, whereas other more esoteric terms such as "scroopy" (the textile chemist's description of the rough, soft-draggy feel of raw silk) are less obvious (Goldemberg and De La Rosa 1971). All these terms are used in an attempt to describe the sensory responses caused by the lubricating actions of emollients on the skin. A special issue of the *Journal of Investigative Dermatology* was devoted to the effects of emollients on the mechanical properties of the skin in 1977, with articles on the viscoelastic (Christensen et al. 1977) and frictional (Highley et al. 1977) properties of human skin, as well as measurement of skin hydration (Campbell et al. 1977), among others.

To the formulator, the tactile sensory properties of the neat oils are the first consideration in

Table 5.2 Common emollients used in topical formulations

Chemical class	INCI name	CAS number	Physical form at 25°C
Esters	Isopropyl palmitate	142-91-6	Liquid
	Isopropyl myristate	110-27-0	Liquid
	Ethylhexyl palmitate	29806-73-3	Liquid
	Octyl stearate	109-36-4	Liquid
	Cetyl palmitate	540-10-3	Solid
	Cetyl lactate	35274-05-6	Semi-solid
	Myristyl lactate	1323-03-1	Semi-solid
	C12–15 alkyl benzoate	68411-27-8	Liquid
	Ethylhexyl isononanoate	71566-49-9	Liquid
	Isononyl isononanoate	59219-71-5	Liquid
	Cetyl isononanoate	84878-33-1	Liquid
	Decyl oleate	3687-46-5	Liquid
	Diisopropyl adipate	6938-94-9	Liquid
	Diisobutyl adipate	141-04-8	Liquid
	Glyceryl stearate	123-94-4	Solid
	Propylene glycol stearate	1323-39-3	Solid
	Glycol stearate	31566-31-1	Solid
	Glycol distearate	627-83-8	Solid
Ethers	Dicaprylyl ether	629-82-3	Liquid
	PPG-15 stearyl ether	25231-21-4	Liquid
	PEG-7 glyceryl cocoate	68201-46-7	Liquid
Triglycerides	Capric/caprylic triglycerides	65381-09-01	Liquid
Fatty alcohols	Cetyl alcohol	36653-82-4	Solid
	Cetearyl alcohol	8005-44-5	Solid
	Stearyl alcohol	112-92-5	Solid
	Oleyl alcohol	143-28-2	Liquid
	Octyldodecanol	34513-50-3	Liquid
Fatty acids	Oleic acid	112-80-1	Liquid
	Linoleic acid	60-33-3	Liquid
Hydrocarbons	Liquid paraffin	8012-95-1/8042-47-5	Liquid
	Petrolatum	8009-03-8	Solid
	C9–14 isoparaffin	246538-73-8	Liquid
	Polyisobutene	9003-27-4	Liquid
	Isohexadecane	93685-80-4	Liquid
Vegetal butters	*Butyrospermum parkii* butter (Shea butter)	194043-92-0	Semi-solid
	Theobroma cacao seed butter (cocoa butter)	84649-99-0	Semi-solid
	Mangífera indica seed butter (mango butter)	90063-86-8	Semi-solid
Vegetal oils	*Prunus Amygdalus Dulcis* seed oil (sweet almond oil)	8007-69-0	Liquid
	Vitis vinífera seed oil (grape seed oil)	8024-22-4	Liquid
	Simmondsia chinensis seed oil (Jojoba oil)	90045-98-0	Liquid
	Triticum vulgare germ oil (wheat germ oil)	68917-73-7	Liquid
	Sesamum indicum oil (sesame oil)	8008-74-0	Liquid
Esterols	Lanolin	8006-54-0	Semi-solid
Silicones	Cyclopentasiloxane	541-02-6	Liquid
	Dimethicone	9006-65-9	Liquid
	Dimethiconol	31692-79-2/70131-67-8	Liquid

Table 5.3 Spreading values for selected ester emollients

High spreading values	>850 mm^2/10 min	For example, isopropyl myristate and isopropyl palmitate
Medium spreading values	501–850 mm^2/10 min	For example, ethylhexyl stearate and decyl oleate
Low spreading values	0–500 mm^2/10 min	For example, C12–15 alkyl benzoate

choosing an emollient for a cosmetic product (Goldemberg and De La Rosa 1971; Zeidler 1992). The key property of the emollient that this is reflecting is its ability to lubricate and reduce any friction between the skin surface and its environment (skin with skin, clothing with skin, etc.), as this reduces possible discomfort, irritation, and pain (Dederen et al. 2012). The lubrication intensity of the emollient on the skin can be partly explained by the properties of the emollient itself; the residual film thickness, by dynamic spreadability and the viscosity. However, the skin is not a rigid, inert surface, and emollients can directly or indirectly modify its mechanical properties. This must also contribute to the overall sensory response (Dederen et al. 2012). This important property of emollients is defined by their ability to disperse more or less quickly on the skin surface by forming a film. This can be assessed quantitatively using a parameter known as the spreading value. A common technique for determining the spreading values has been described by Zeidler (1985). Spreading values, in units of mm^2/10 min, are determined by applying 20 μl of an emollient to the center of an ashless, medium-to-fast filter paper at 25 °C and measuring the area covered by the applied material in 10 min. Examples of spreading values for some of the most widely used group of emollient for skin lubrication, the esters, are shown in Table 5.3. Esters are useful to formulators because of their versatility and the unique properties they can give to the final product, influenced by the chemical properties, including chain length, of their constituent fatty acids and alcohols. As can be seen, changes in the constituent chain lengths can alter the skin-surface spreading characteristics of ester emollients. For example, isopropyl myristate and palmitate, with short-chain alcohol components and the shortest acid chain lengths (C14 and C16, respectively) in this table, have the highest spreading values. The C16 palmitate is greasier than the C14 myristate, but the spreading values are similar. Ethylhexyl stearate and decyl oleate, with longer chain components, have medium spreading values, whereas the longer chain alcohol (C12–C15), alkyl benzoates, are low spreading esters.

Many attempts have been made to achieve a measure of sensory softness of the skin. In 2013, Nakatani suggested that conventional methods for measuring the mechanical properties of the skin, such as the elongation in response to suction, elastic responses to ballistic impact, and rheological responses to torsional stress, were restricted to measuring the properties of the whole skin and were unable to look at different skin layers separately. They developed a novel piezoelectric tactile sensor system that could simultaneously measure the mechanical properties of the whole skin and its superficial layer. Such a technique has obvious advantages to the cosmetic industry, but can also be applied clinically to the quantitative evaluation of skin disorders such as atopic dermatitis (Nakatani et al. 2013).

5.2.4 Effect of Emollients on Skin TEWL and Skin Hydration

The residual lipid film on the stratum corneum surface after the application of products containing emollients will limit the evaporation of water from the skin surface and therefore cause an increase in skin hydration. Accordingly, emollients have been described as indirect skin moisturizers (Dederen et al. 2012). In general, the presence of hydrogen bonds in emollients also facilitates the transport of water through the lipid films, so that for lipid films of similar thickness and viscosity, the semipolar emollients will be more permeable to water than the hydrocarbon emollients, resulting in a lower occlusive state than that induced by the hydrocarbon emollients. However, these findings can differ significantly,

depending on the nature of the emollient. Patzelt et al (2012) recently showed that vegetable oils (except Jojoba oil) led to a similar occlusion of the human skin surface in vivo as paraffin oil, but the semisolid, petrolatum, was the most effective occlusive. The occlusive effects of an emollient then result in a reduced transepidermal water loss (TEWL) and, in turn, an increase in the hydration of the stratum corneum relative to normal moisture conditions. By occluding the skin and providing an additional barrier to water loss, skin hydration can be increased by up to 50 % (Hafeez and Maibach 2013a). This increase in hydration as an effect of occlusion has also been seen with physical occlusives like wound dressings and bandages (Voegeli et al. 2009, 2011). Increasing the thickness of the lipid film and/or increasing the viscosity of the lipid film will reduce the TEWL and increase stratum corneum hydration, so that a wax will have a low TEWL and higher SC hydration than an oil.

The presence of water in a formulation can add to the moisturizing properties of that formulation on the skin, but generally for only a short time. Indeed, the moisturizing effect of topically applied water is often lost after 10–20 min of application (Batt and Fairhurst 1986; Paepe and Rogiers 2009). Blank showed that the main effect associated with skin moisturization was an increase in its softness and pliability (Blank 1952). The moisturizing effect of water can be prolonged when an emollient is present in the moisturizing formulation. The presence of a humectant, such as glycerol, in the aqueous phase, as well as the emollient will increase the moisturization of the skin. Indeed, Batt et al. showed that the enhanced moisturizing effect of glycerol by different emollients and oils was present even 12 h after application (Batt et al. 1988).

Nonphysiological occlusive moisturizers such as petrolatum remain on the skin surface without being incorporated into the deeper skin layers. While they may provide some benefit by improving skin hydration, they are not effective in directly treating the disordered lipid states in such diseases. For example, petrolatum treatment had no effect on the abnormal lipid organization associated with barrier defects in patients with atopic dermatitis or laminar ichthyosis (Pilgram et al. 2001). On the other hand, some moisturizers do act by penetrating the intercellular lipid regions. A novel mechanism known as “internal occlusion” (Wiechers et al. 2009) has been described, where moisturizers such as isostearyl isostearate and isopropyl isostearate cause improved skin hydration and barrier function by stabilizing the SC lipid organization in the more tightly packed orthorhombic phase (Caussin et al. 2007).

A different approach to the emollient treatment of skin diseases such as atopic dermatitis, relying on the use of emollient treatments containing ceramide-dominant physiological mixtures of the three key lipids, cholesterol, free fatty acids, and ceramides at the appropriate physiological pH, has been pioneered by Elias (Chamlin et al. 2002; Elias 2010). The mechanism leading to skin barrier enhancement is believed to involve more than a simple augmentation of intercellular lipid populations and structure. On passing through the SC, the applied lipids migrate to the nucleated cell regions, to be taken up by keratinocytes and then trafficked to lamellar bodies, where they are mixed with endogenous epidermal lipids. The augmented lipid mixture is then secreted into the SC intercellular spaces (Mao-Qiang et al. 1995; Chamlin et al. 2002) to enhance skin barrier function and normalize skin hydration. According to Elias, the effectiveness of any such treatment depends primarily on understanding the mechanism responsible for a particular skin barrier defect, in order to judge whether lipid replacement is appropriate for that condition (Chamlin et al. 2002). An alternative approach to address imbalance in the SC proteolytic cascade leading to dry skin is to use serine protease inhibitors to treat mild-to-severe barrier abnormalities (Voegeli et al. 2009; Rawlings and Voegeli 2013).

5.2.5 Emollient Substantivity

This is defined here as a measure of the retention of an emollient in and persistence of its effect on the skin after exposure to water, perspiration, and resistance to being rubbed off. Another definition of substantivity is: “the property of continuing therapeutic action despite removal of the vehicle, such as the action of certain shampoos” (Mosby

2009). (*MediLexicon* 2013), referring to *Stedman's Medical Dictionary* (Stedman's 2011), suggests substantivity is a "term comprising the adherent qualities of a sunscreen and its ability to be retained after the skin is exposed to water and perspiration. Persistence of effect of a topically applied drug or cosmetic, determined by the degree of physical and chemical bonding to the surface; resistance to removal or inactivation by sweating, swimming, bathing, and friction, among other factors." In general, emollient substantivity is poor for an aqueous gel but comparatively better for an O/W emulsion. Greater substantivity would be expected for a W/O emulsion and more particularly for an ointment. It has been suggested that silicone ingredients have a higher substantivity than the more common emollients, as silicone chains are entangled (Sene 2003).

5.2.6 An Overall Comparison of Emollient Properties

Wiechers began his pioneering work on skin care products by working with panels of human subjects. He tested a broad spectrum of materials (Wiechers 1997), quantitatively assessing moisturization by skin hydration (using a Corneometer, with glycerin as a positive control and untreated skin as a negative control), elasticity (using a Dermal Torque Meter, with water applied 30 min under occlusion as a positive control and untreated skin as a negative control), and substantivity (using a Sebumeter, with petrolatum as a positive control and untreated skin as the negative control). For each property, he then derived a relative performance index (RPI). A value of ≥70 % for a particular property indicated a good performing ingredient, while ingredients with RPI values between 30 and 70 % were regarded as medium performers. Figure 5.2 shows Wiechers' RPI values for moisturization, elasticity, and substantivity for a range of selected emollients. It is apparent that there are many more medium–good performing moisturizing and substantivity ingredients than there are elasticity ingredients, so that a good RPI for moisturization, for example, did not necessarily predict a similar result for the other parameters. This led Wiechers to conclude that multiple mechanisms were present (Wiechers and Barlow 1999) and that multiple emollients are needed for enhanced overall emollient performance (Wiechers et al. 2002). Most recently, we combined forces to use the principles described here and in his work to predict the skin penetration of actives from complex practical formulations (Wiechers et al. 2012).

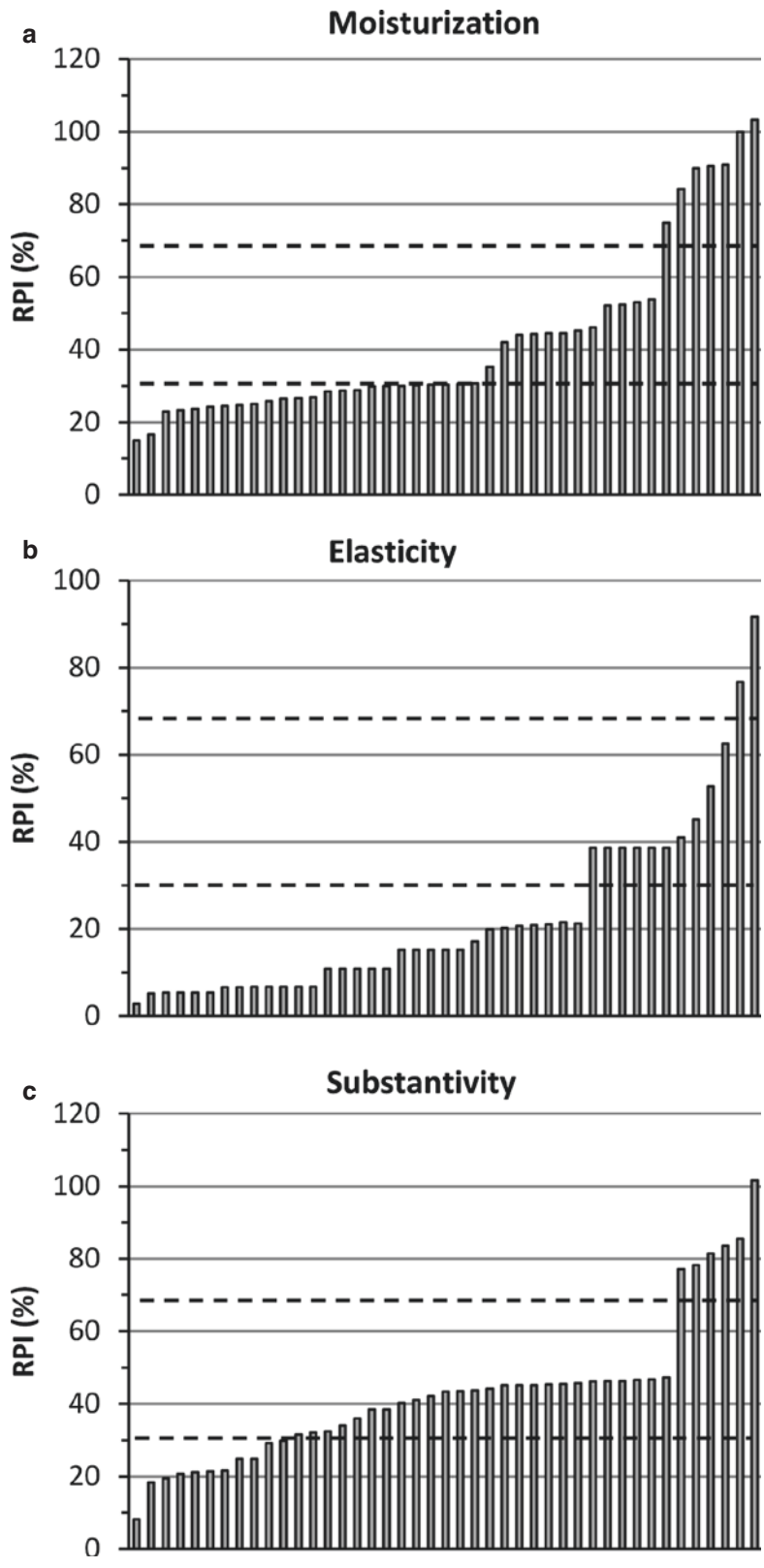
5.3 Effects of Emollients on Percutaneous Absorption

As discussed in the earlier sections, emollients can differ greatly in their properties and in their effects on the skin. These in turn can greatly affect how these emollients in formulations impact on the percutaneous absorption of actives in various formulations. We now consider each of the mechanisms by which emollients can affect percutaneous absorption in turn.

5.3.1 How Do the Various Emollients Differ in their Ability to Dissolve and Release Different Actives?

An overarching view of percutaneous absorption is that maximal penetration for an active in a stable formulation will occur at its maximum

Fig. 5.2 Relative performance indices (RPI, as %) for a range of emollient ingredients shown as individual bars. (**a**) Moisturization (by skin hydration using a Corneometer, with glycerin as a positive control and untreated skin as a negative control); (**b**) Elasticity (using a Dermal Torque Meter, with water applied 30 min under occlusion as a positive control and untreated skin as a negative control) and (**c**) Substantivity (using a Sebumeter, with petrolatum as a positive control and untreated skin as the negative control). For each property, ingredients were classified as: good-performing ingredients, RPI ≥70 %; medium-performing ingredients, RPI between 30 and 70 %; low-performing ingredients, RPI ≤30 %. The 30 and 70 % cutoffs are shown as *dotted lines* (Adapted from Wiechers et al. 1997)


a
Moisturization
RPI (%)
120
100
80
60
40
20
0
b
Elasticity
RPI (%)
100
80
60
40
20
0
c
Substantivity
RPI (%)
120
100
80
60
40
20
0

solubility in the formulation, that is, at saturation, providing the formulation does not affect the skin. Accordingly, the maximal flux for smaller actives is greater than that for larger ones, and those with the lowest melting point (Magnusson et al. 2004) and highest flux for a series of actives of similar size will occur at a lipophilicity similar to that of the skin lipids (a log *P* of about 3) (Zhang et al. 2009). There are two general principles defining the ability of an emollient to dissolve an active: "Like dissolves like" and "Oils ain't all oils"! In other words, lipid-soluble actives generally dissolve better in emollients than polar actives, AND not all emollients have the same properties. In general, actives dissolve better in semipolar emollients (e.g., esters) than in nonpolar, for example, hydrocarbon emollients. Actives can dissolve in both liquid and waxy emollients after heating, but will be released more slowly from the waxy than the liquid emollient. However, increasing the viscosity of a formulation can sometimes result in an enhanced skin penetration as a result of the formulation excipients on evaporation, leaving behind a semisolid barrier that may impede TEWL, promote skin hydration, and in turn skin penetration flux (Cross et al. 2001a).

These findings have the following implications for how the solubility of an active in an emollient may affect its percutaneous absorption. Firsty, the thermodynamic activity for two equal concentrations of an active in two emollients will be higher in the hydrocarbon than in the semipolar emollient in accordance with their different relative fractional solubilities, resulting in a higher flux of the active through the skin (Wiechers et al. 2012; Roberts 2013). Hence, an active formulated with a hydrocarbon emollient will usually have a faster rate of skin penetration than the one formulated in a semipolar emollient. Accordingly, the skin flux for the sunscreen oxybenzone for petrolatum was found to be greater than that for an oil-in-water (o/w) emulsion (Kurul and Hekimoglu 2001). However, there can be a downside. As the active in the hydrocarbon emollient has a limited solubility, it will also exhaust much more quickly than in the semipolar emollient, that is, the semipolar emollient will generally deliver its active for a longer period of time. On the other hand, with a semipolar emollient, the product will be more readily washed off by water. Silicone emollients appear to offer both persistence in their retention in the skin and a high solubility, and thus substantivity, for actives dissolved in them (Sene 2003).

5.3.2 How Do the Emollients Differ in their Ability to Affect and Enter the Skin (Size and Solubility Parameter Determined) and to Promote Skin Penetration of Actives?

The primary action by which an emollient promotes skin penetration is by hydration of the stratum corneum. When the skin barrier is normal, increasing the water content by occlusion can lead to enhanced penetration of some, but not all compounds (Hafeez and Maibach 2013a). Some possible mechanisms include increased solubility of the compound in the SC, increased partitioning from the vehicle into the hydrated membrane, and structural alterations due to the swelling of corneocytes and a rearrangement of the intercellular lipid domains (Bjorklund et al. 2010; Hafeez and Maibach 2013b). Occlusion is a well-recognized strategy for enhancing skin penetration (Roberts et al. 2008). The recent reviews by Hafeez and Maibach examined literature data on the effects of occlusion on the penetration of compounds of varying lipophilicities in vivo (Hafeez and Maibach 2013b) and in vitro (Hafeez and Maibach 2013a). They concluded that occlusion tends to enhance the penetration of lipophilic compounds more than hydrophilic compounds, which would be expected, given the relatively lipophilic nature of the intercellular domains into which the compound must partition. However, there appears to be a fall-off in penetration for very lipophilic compounds, which would also be expected as the hydrated conditions under occlusion increase the water content in the intercellular regions. Additionally, the penetration of highly lipophilic compounds may be further limited, as they will not readily

partition from the stratum corneum to an increasingly hydrated viable epidermis. These findings show an interesting parallel to those of Zhang, who showed a parabolic relationship between maximum flux and lipophilicity for a series of phenols penetrating human skin in vitro. Zhang saw the greatest penetration at an octanol–water partition coefficient of about 3, with a reduced flux at higher values, and concluded that the relationship was driven by the solubility of the compound in the stratum corneum (Zhang et al. 2009). In both of these examples, stratum corneum solubility can be seen to be largely dependent on the relative lipophilicities of the penetrating compound and the intercellular lipid domain.

As we have seen, a large part of the strategy of using emollients to moisturize and soften the skin is concerned with replacing, replenishing, and reorganizing the population of intercellular lipids. At the same time, a restored lipid domain may strengthen the skin barrier and most likely lead to a reduced permeability to applied chemicals. Results from infrared spectroscopy on human stratum corneum suggested that increased lipid organization occurred as a result of increased hydrogen bonding (Kaushik and Michniak-Kohn 2010). On the other hand, petrolatum (Ghadially et al. 1992) and nonphysiological lipophilic moisturizers (Caussin et al. 2007) were shown to become localized in separate intercellular domains, with little effect on lamellar organization or barrier function.

Conversely, the application of emollients to the skin may have the effect of reducing barrier function and enhancing the penetration of applied compounds. This may occur as a result of a direct effect on intercellular lipids, where they become disrupted or fluidized (Kaushik and Michniak-Kohn 2010). Certain silicone polymers, although functioning as effective moisturizers, were shown by electron microscopy to disrupt lipid bilayers, leading to reduced barrier function (Menon and Ghadially 1997).

In the same way as active solutes will penetrate the skin according to their size, melting point, and lipophilicity, similar considerations determine how emollients enter the skin. Thus, of the ester emollients in Table 5.2, the liquid diisopropyl adipate (MW 230 Da) is most likely to enter the skin, whereas the solid, glycol distearate (MW 595 Da) is the least likely to enter. Zhang et al (2013) showed that the ester emollient isopropyl myristate (MW 270 Da) rapidly enters the skin and could change its properties, whereas the hydrocarbon emollient liquid paraffin appears not to enter the skin. Thus, isopropyl myristate is an emollient that enhanced the skin penetration of phenols, whereas mineral oil did not. The main effect of isopropyl myristate was to carry the phenols into skin lipids, increasing their overall solubility and maximum flux. However, isopropyl myristate also appeared to act as a reservoir, retarding the penetration for the more lipophilic phenols.

Limited information is available about the extent to which emollients can modify the skin reservoir effect. It seems likely that, in a similar way to occlusion, emollients may promote the release of actives from the horny layer (Roberts et al. 2004). However, there may be some waxy emollients which have a very slow release rate of actives. Therefore, such emollients, if retained in the horny layer, could potentially cause an enhanced reservoir effect. A more desirable effect is to have an enhanced substantivity as a consequence of the emollient's substantive properties, as shown for silicone esters (Sene 2003).

5.3.3 What Do Other Ingredients in a Moisturizing Formulation Do to Enhance or Inhibit the Effects of Emollients on Skin Penetration?

Formulations, especially emulsions, may contain a wide range of ingredients with many different functions, including: preservants, coloring materials, fragrances, thickeners, surfactants, humectants, emollients, buffers to control the pH, chelating agents, and others. The balance between them is very important for the stability and final function of the formulation. For example, if a fragrance causes skin irritation, it may also change

skin penetration of actives. As they are major ingredients in many topical formulations, the effects of humectants and surfactants on the skin barrier may be significant.

Humectants such as glycerol, propylene glycol, or sorbitol are used to accentuate moisturization, but can also accentuate emollient effects on skin lipids by inhibiting the SC lipid phase transition. Indeed, in a 1990 study done in a dry atmosphere, Froebe et.al. (1990) showed that glycerol acts as a skin moisturizer by inhibiting the lipid phase transition from liquid to solid crystal, rather than by acting primarily as a humectant. More recently, in vitro studies using mixtures of glycerol and the powerful skin irritant and penetration enhancer, sodium dodecyl sulfate (SDS), showed that glycerol was able to attenuate the effects of SDS on the skin barrier by reducing the ability of SDS to penetrate into the SC (Ghosh and Blankschtein 2007).

Surfactants are used widely in topical formulations, usually to solubilize more lipophilic actives. As the name suggests, they interact at membrane interfaces and, in particular, are capable of modifying the structure and properties of the skin (Williams and Barry 2004). Anionic and cationic surfactants in particular may cause irritation and skin damage by strong binding and denaturing of skin surface proteins with swelling and disruption of the corneocytes, as well as disordering of the intercellular lipid structure. Nonionic surfactants tend to cause less irritation and barrier damage, with polysorbates being accorded GRAS (generally regarded as safe) status by the US Food and Drug Administration (Predmore and Li 2011). They act to fluidize lipids and bind to keratin filaments (Nokhodchi et al. 2003). As expected, alterations in SC barrier properties by surfactants may lead to enhanced permeation of topically applied materials. Most studies have examined the effects of anionic and nonionic surfactants, with the more disruptive anionic materials such as sodium lauryl sulfate and sodium dodecyl sulfate causing the greatest enhancement (Williams and Barry 2004). Nonionic surfactants like ethers and polysorbates (e.g., Tween 80) cause more modest degrees of enhancement (Som et al. 2012). Nonionic surfactants have also been incorporated into W/O emulsions which are compatible with the lipophilic sebum environment in hair follicles, in order to target the follicular route of skin penetration by hydrophilic solutes (Wu et al. 2001).

Figure 5.3 shows maximum fluxes for a series of phenols of similar molecular weight applied to human epidermal membranes from a range of simple vehicles, plotted against log *P* (Zhang et al. 2013). It is clear that the maximum fluxes for water and the occlusive emollient mineral oil

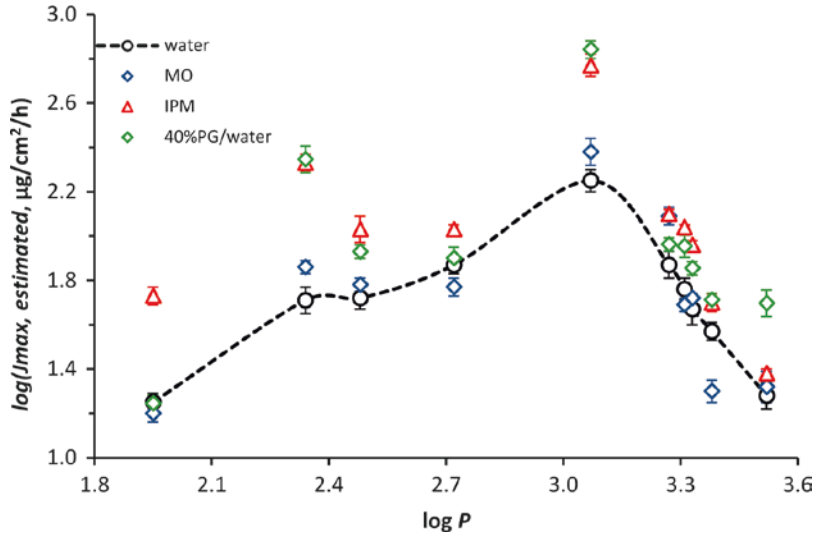


Fig. 5.3 Log (Jmax, estimated) versus log *P*. Estimated maximum fluxes ($n=5$, mean ± SD) for ten phenolic compounds of similar molecular weight from water, mineral oil (MO), isopropyl myristate (IPM), and a mixture of 40 % PG/water, plotted against lipophilicity of the phenolic compound. The *dotted line* interpolates data from the water vehicle and is included as a reference only (Adapted from Zhang et al. 2013)

(MO) are similar across this range of log *P*, as expected for "inert" solvents that do not permanently alter the properties of the skin (Barry et al. 1985; Cross et al. 2001b). In contrast, the ester emollient IPM led to increased maximum fluxes, particularly for the more polar phenols, which was due to penetration of IPM into deeper layers of the stratum corneum (Zhang et al. 2013), where it has been suggested that it integrates into the stratum corneum lipid matrix and disrupts the organization of the lipid lamellae (Brinkmann and Muller-Goymann 2005). Figure 5.3 also illustrates similar increases in maximum flux seen with mixtures of the humectant propylene glycol and water, most likely due to increased solubility of the phenols in stratum corneum lipids following propylene glycol absorption (Zhang et al. 2011). Such a mechanism was also used to explain the enhanced penetration of minoxidil into human skin from vehicles containing propylene glycol (Grice et al. 2010).

5.4 Practical Aspects

Table 5.4 shows five formulations containing different emollients and their likely effect on the skin properties and on the skin penetration of an active. The first impression that a consumer has in using a product is the sensorial feel. Formulation 1 feels light and soft, because it lacks oils but is capable of lowering TEWL sufficiently to increase hydration and potentially promote skin penetration of an active. The second formulation contains ester emollients to give a smooth and soft feel. The smoothness derives from the lubrication of the skin surface by the ester emollient's lipid film. As this film has a greater effect on TEWL and skin hydration than formulation 1, it may promote skin penetration more. On the other hand, the lipid active is probably more soluble in formulation 2, and this may inhibit skin penetration of the active. Formulation 3 contains mineral oil as an emollient, and it will feel oily and very soft, as this is

Table 5.4 Examples of some formulations containing different emollients and their effects on the skin and the likely skin penetration of an active

Raw materials	1 (control)	2 (ester)	3 (mineral oil)	4 (animal fat)	5 (IPM)
Ceteareth-20	2.0 %	2.0 %	2.0 %	2.0 %	2.0 %
Cetearyl alcohol	3.0 %	3.0 %	3.0 %	3.0 %	3.0 %
Triethanolamine	pH5.5–6.5	pH5.5–6.5	pH5.5–6.5	pH5.5–6.5	pH5.5–6.5
Carbomer	0.15 %	0.15 %	0.15 %	0.15 %	0.15 %
Caprylic/capric triglyceride (CCT)	–	5 %	–	–	–
Lanolin	–	–	–	5 %	–
Mineral oil	–	–	5 %	–	–
Isopropyl myristate	–	–	–	–	5 %
Glycerin	4.0 %	4.0 %	4.0 %	4.0 %	4.0 %
Phenoxyethanol and parabens (methyl, ethyl, and propyl)	0.8 %	0.8 %	0.8 %	0.8 %	0.8 %
Water	Qsp 100 %	Qsp 100 %	Qsp 100 %	Qsp 100 %	Qsp 100 %
Effects on skin					
Sensorial feel	Light and soft	Smooth and soft	Oily and soft	Greasy and heavy	Smooth and soft
Reduction in TEWL	↓	↓	↓↓↓	↓↓	↓↓
Skin hydration	↑	↑↑	↑↑↑	↑↑	↑↑
Change in solubility of nonpolar active	–	↑	↑	↑↑	↑↑
Potential effect on skin penetration	↑	↑/↑↑	↑↑↑	↑↑↑	↑↑↑

the most occlusive formulation of all described formulations and therefore will provide the greatest inhibition of TEWL and the greatest skin hydration. An active is also likely to have poorer solubility in formulation 3. Accordingly, this formulation is likely to provide better skin penetration of the active. Formulation 4 feels greasy, because it contains animal fat such as lanolin, and heavy because of the lanolin waxes. This formulation is expected to be occlusive and to promote the solubility of the active. However, lanolin also contains cholesterol, cholesterol derivatives, and free fatty acids, which may act as skin penetration enhancers. The overall effect is likely to be an enhancement of skin penetration. Formulation 5 is very similar to formulation 2. However, it contains the ester emollient, isopropyl myristate, a well-known skin penetration enhancer. Accordingly, formulation 5 should provide greater skin penetration of the active than formulation 2.

There are other practical considerations in the use of emollients. They can provide a number of functions, including the relief of potential discomfort and irritation caused by solvents, promotion of penetration, particle coating, stabilization of suspensions, brightness control for makeup, among others (Dederen et al. 2012). Another practical consideration is emollient stability. Ester emollient stability may be affected at low or high pH, due to the possibility of hydrolysis or saponification, respectively. While formulations are generally prepared at neutral or slightly acidic pH, care must be taken to ensure that these conditions will be maintained in a product over time. There are some raw materials that can promote stability of emollient esters at extreme pH. Additionally, it should be recognized that if the finished products are to come into contact with the mouth (e.g., in lipstick), emollients and other ingredients must not have an unpleasant taste. In summary, each product has unique physicochemical properties that can promote different interactions and reactions with the skin surface.

Another consideration is the potential irritancy of the formulations. As a general principle, in order to minimize skin irritancy, the sensitizing lanolin alcohols should be used in formulations in concentrations less than 3% (Marks 2001). Other ingredients, such as the humectant, propylene glycol (>15%), and ingredients used to stabilize emollients in products, such as surfactants (e.g., oleic acid), can also cause irritation (Marks 2001).

Conclusion

This chapter has attempted to clarify the definition of an emollient, show the range of emollients available in the market, and explore how these emollients are likely to affect skin penetration. The chapter concludes with an examination of some emollient-containing products and their effects on the skin and on the likely skin penetration of an active.

The key property of an emollient is that it softens the skin through occlusion and resultant moisturization as well as by forming a lipid film which smooths the skin by lubrication. Moisturization of the skin is well known to be the main means by which skin penetration enhancement can be achieved (Roberts et al. 2008). However, emollients can also affect the solubility of an active and penetration enhancers, and thus their effects on the skin penetration of an active may be uncertain. The final section discusses some potential outcomes for different formulations containing emollients.

It also needs to be recognized that all cosmetic and pharmaceutical products contain different ingredients, each of which can impinge on the sensorial feel and skin penetration properties of a product. One concern is the potential skin irritation caused by these ingredients. Of the emollients, lanolin and isopropyl myristate are the most likely to be associated with skin irritation. The most inert emollient is probably mineral oil and, as it is very hydrophobic, it may also promote skin penetration by inducing a high thermodynamic activity of the active as a consequence of the active's low solubility in the mineral oil.

Treatments designed to improve dry skin or treat skin diseases, such as lipid replenishment, may also enhance the skin barrier function and reduce its permeability to topical chemicals. On the other hand, emollients may

enhance the barrier's permeability by mechanisms such as increased hydration following occlusion, disruption of the intercellular lipid organization, or increasing the solubility of a chemical or active ingredient in the stratum corneum. Formulation strategies designed to enhance skin penetration can be devised by the judicious choice of emollient ingredients; however, it is important to stress that each skin characteristic varies widely between individuals. In addition, factors such as safety, cost, sensory properties, sustainability, and marketing will all be considered by a formulator in choosing a suitable emollient.

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