Galenics of dermal products – vehicles, properties and drug release

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- skin effect
- topical application

Summary
The efficiency, tolerability, and applicability of topical agents are directly related to employed vehicles. Thus to achieve optimum topical therapy, a solid knowledge of the vehicles, their composition, and their physical and dermatopharmacological actions are important. Common vehicles are complex mixtures consisting of diverse ingredients belonging to six major groups, i. e. hydrophilic and lipophilic bases, emulsifiers, gel-forming agents, preservatives, and antioxidants. This makes it possible to optimize both the cosmetic features and to adjust a vehicle to the properties of an incorporated drug and site of application. On the other hand it makes it difficult to make a proper choice between several alternatives or to use it in individual prescriptions. In order to simplify the selection of a formulation, it is useful to categorize them systemically into several groups, such as ointments, creams, gels, emulsions, and suspensions.
Within these groups some general rules can be derived for the selection of a vehicle with respect to skin conditions and the application site. When active substances are incorporated into a base the dermato-biopharmaceutical properties of the whole system (drug + vehicle) also have to be considered. If for a given vehicle drug transport into the skin does not suffice, several methods are described to facilitate its penetration, such as by hydrating the skin or by adding chemical penetration enhancers.

1. Introduction
The efficacy, tolerability, and application properties of dermatological products are clearly related to the type of base used. Interactions between the base, skin, and drug influence the effect of the preparation and release of the drug. A variety of various vehicles are available that make it possible to adapt a given therapy to the state of the skin. Yet, the criteria used to divide vehicles into different types are diverse, making orientation difficult or even impossible. Vehicles can be distinguished by their galenic properties based on the guidelines of the European Pharmacopoeia (PhEur). Criteria include rheologic properties (liquid or spreadable), polarity (hydrophilic or hydrophobic) and physicochemical features (single-phase or multiphasic) [8]. The aim of the present paper is to provide a systematic description of the galenics of these systems and to discuss special considerations associated with their use.

2. Bases and additives in dermatological products
Dermatological products are seldom pure substances, but rather often consist of highly complex mixtures [17]. Nonetheless, the base of a product and additives can be divided into a few essential groups and classified by polarity (i.e., hydrophilic or lipophilic) or intended use (Table 1).

2.1 Hydrophilic bases
The main ingredient in hydrophilic preparations is purified water. Water-soluble alcohols such as ethanol and isopropanol (2-propanol) are also used. Polyvalent alcohols - glycerol and propylene glycol, and less commonly sorbitol – act as humectants due to their hygroscopicity.
Macrogols (polyethylene glycols) are also included in hydrophilic bases. They are used in aqueous systems as co-solvents or in anhydrous systems as a hydrophilic ointment base.

2.2 Hydrophobic bases

All water-insoluble, organic compounds can be used in hydrophobic bases. The behavior of these mostly lipophilic bases is largely determined by their polarity and spreadability. [Although the terms hydrophobic and lipophilic are often used synonymously for water-insoluble substances, hydrophobic is the more precise term, while lipophilic describes a substance that dissolves in lipids. Thus (dimethyl siloxane) silicone oils are hydrophobic, but not lipophilic]. "Spreadability" describes the ease with which a substance is spread over the skin. Lipids that spread easily are quickly absorbed by the skin and do not leave a greasy feel, while those that are spread poorly over the skin are perceived as very oily and occlusive.

Lipids can be roughly divided into four chemical classes: The least polar substances are hydrocarbons such as petrolatum or soft or liquid paraffin. Moderately polar lipids include many types of wax such as yellow wax and fluid wax esters (isopropyl myristate and ethylhexyl palmitate), which typically spread over the skin very well. Among the more polar lipids are most of the glycerides such as medium-chain triglycerides (neutral fat) and olive oil [4]. Silicone oils are hydrophobic substances that spread extremely well. These include various compounds that contain a polyorganosiloxane as the characteristic functional group. Important substances include dimethylpolysiloxane (dimethicone), phenyl methyl polysiloxane, and cyclic methyl siloxane (cyclomethicone).

2.3 Emulsifiers

The presence of both hydrophobic and hydrophilic ingredients in a preparation results in a thermodynamically unstable emulsion. Emulsifiers must be added to guarantee a sufficient shelf life of the product. These are accumulated between the lipid and water phases. The most commonly used emulsifiers added for stabilization of pharmaceutical and cosmetic emulsions are classified as surfactants based on their structure and physicochemical behavior. They are amphiphilic and can form aggregates such as micelles or lamellar liquid crystals (Figure 1).

The vast array of different commercially-available amphiphilic substances can be grouped into a few basic chemical structures. An important distinguishing factor is the charge of the hydrophilic head-

Table 1: Major vehicle components used in dermatological products.

Hydrophilic base ingredients	Water Ethanol 2-Propanol Glycerol Propylene glycol Sorbitol Macrogol Dimethyl sulfoxide Acetone
Hydrophobic base ingredients	Petrolatum Hard paraffin Soft and liquid paraffin Triglycerides Wax Liquid wax ester Partial glycerides Silicone oils
Emulsifiers	Anionic surfactants Cationic surfactants Zwitterionic surfactants Nonionic surfactants
Gelling agents	Bentonite Carbomer Carmellose sodium Hydroxyethyl cellulose Hydroxypropyl cellulose Hypromellose Povidone
Preservatives	Alkyl-4-hydroxybenzoates (parabens) Sorbic acid Benzyl alcohol Phenylethyl alcohol
Antioxidants	Butylhydroxyanisol Butylated hydroxytoluene Tocopherol (acetate) Ascorbyl palmitate

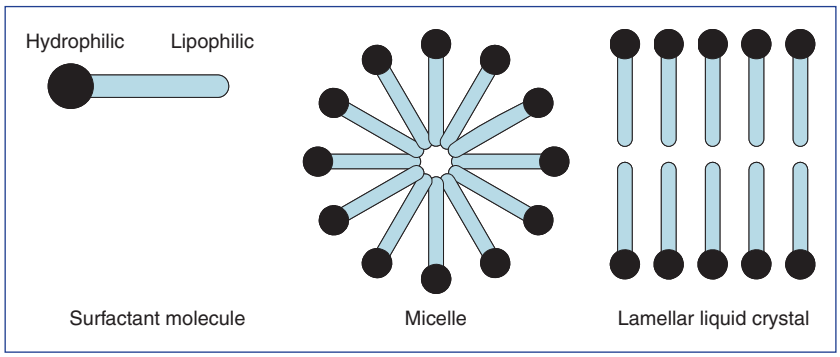


Figure 1: Schematic drawing of a surfactant, micelle, and lamellar liquid crystal.

Table 2: Emulsifiers used in dermatological products.

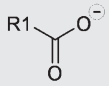
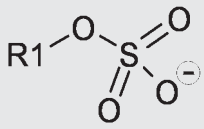
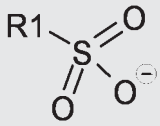
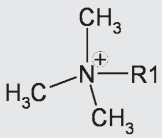
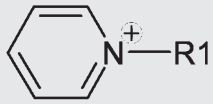
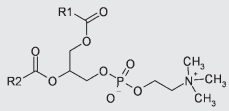
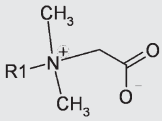
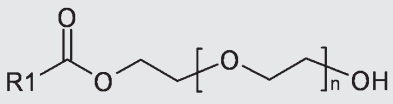
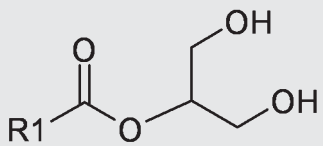
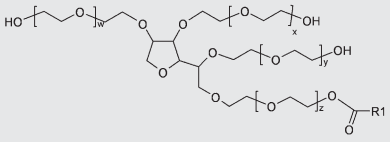
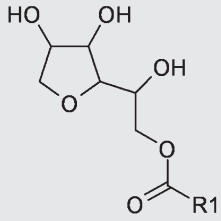
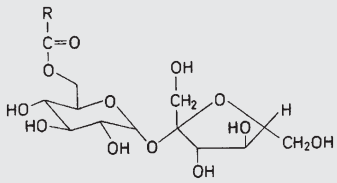
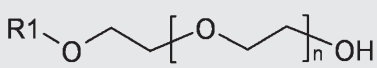
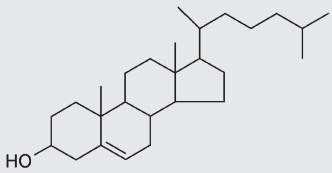
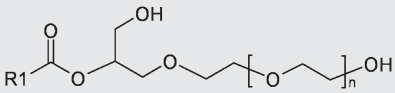
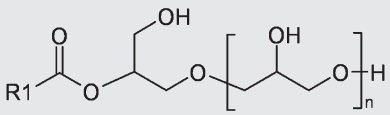
Compound class	Structure	Examples
Anionic emulsifiers		
Carboxylate		Sodium stearate Aluminium stearate
Sulfate		Sodium dodecyl sulfate Sodium cetyl stearyl sulfate Sodium lauryl ether sulfate
Sulfonate		Sodium dioctyl sulfosuccinate
Cationic emulsifiers		
Quaternary ammonium compound		Cetyl trimethyl ammonium bromide Benzalkonium bromide
Pyridinium compound		Cetylpyrdinium chloride
Zwitterionic emulsifiers		
Lecithins		Phosphatidylcholin
Betaine		Betaine monohydrate Dehyton K®
Nonionic emulsifiers		
Macrogol fatty acid esters		PEG-30 stearate
Glycerol fatty acid esters		Glycerol monostearate Glycerol monooleate Glycerol monoisostearate Partial glyceride, medium-chain
Polyoxyethylene sorbitan fatty acid esters		Tween® Polyoxyethylene (20) sorbitan monostearate

Table 2: Continued.

Compound class	Structure	Examples
Sorbitan fatty acid esters		Sorbitan laurate Sorbitan monooleate Sorbitan monopalmitate Sorbitan monostearate Sorbitan tristearate Sorbitan sesquioleate
Saccharose fatty acid esters		Saccharose monostearate; Saccharose distearate Saccharose cocoate
Macrogol fatty alcohol ethers		Cetomacrogol 1000 Macrogol cetostearyl ether Macrogol oleyl ether Lauromacrogol 400
Sterols		Cholesterol Wool fat Wool fat, acetylated Wool fat, hydrated Wool fat alcohols
Macrogol glycerol fatty acid esters		Macrogol 1000 glycerol-monooleate Macrogol 1000 glycerol-monostearate Macrogol 1500 glycerol-triricinoleate Macrogol 300 glycerol tris (hydroxystearate) Macrogol 5 glycerol stearate Macrogol glycerol hydroxystearate
Polyglycerol fatty acid esters		Triglycerol diisostearate

group of the molecule. Surfactants are classified as anionic, cationic, amphoteric (zwitterionic), and nonionic [2]. A few typical examples are listed in Table 2.

2.4 Gelling agents

Gelling agents are usually organic, rarely inorganic, macromolecules that enable formation of a three-dimensional framework by intermolecular interactions and thus form viscous solutions in aqueous systems or, in higher concentrations, gels. They have the task of enhancing viscosity of the finished product. This can improve storage of the product and give it certain sensory properties.

The most important gelling agents are synthetic polyacrylic acid (carbomer) and semi-synthetic cellulose derivatives such as sodium carboxymethyl cellulose (carmellose sodium) and hydroxyethyl cellulose. Natural gelling agents, such as xanthan or the inorganic bentonite, are used less often in dermatological products [4].

Some thickening agents, such as hypromellose (hydroxypropyl methylcellulose), also possess interfacial activity and thus can be used as macromolecular emulsifiers in surfactant-free emulsions.

2.5 Preservatives

The drugs used in dermatological practice are required to have a low bacterial count. According to the guidelines set forth in the current German Pharmacopoeia, bacterial count should not ex-

Table 3: NRF guidelines for maximum expiration dates of chemically and physically stable dermatological products, intended for repetitive uses and stored in multidose containers [14].

Drug form	Expiration date (after seal is broken)
Hydrophobic ointments, hydrophobic gels	
Jar (rarely)	6 months
Dispenser	3 years
Tube	3 years
Hydrophilic creams, hydrogels	
Jar (rarely), with preservatives	1 month
Tube, with preservatives	1 year
Dispenser, with preservatives	6 months
Jar (never), no added preservatives	–
Tube, no added preservatives	1 week
Dispenser, no added preservatives	1 week
Hydrophobic creams	
Jar (rarely), with preservatives	1 month
Tube, with preservatives	1 year
Dispenser, with preservatives	6 months
Jar (never), no added preservatives	–
Tube, no added preservatives	1 month
Dispenser, no added preservatives	1 month
Liquid aqueous solutions, emulsions, suspensions	
With preservatives	6 months
No added preservatives	1 week

ceed 10^2 colony-forming units (CFU) per gram [7]. Given the hygiene risk associated with aqueous preparations, use of the product must be limited to a certain period of time after opening (Table 3), or preservatives must be added to ensure microbiological quality [2, 14].

Table 4 lists the most common preservatives used in dermatological products.

The concentration of the drug must be sufficiently high in the water phase in order to ensure its efficacy. This depends on pH value, solubility, and distribution coefficients.

Protection against bacterial growth can also be adequately provided by ethanol, 2-propanol, and propylene glycol, given a high enough concentration in the water phase (about 20 %). It should be noted that these substances are not considered "true" preservatives, and that at this level of concentration they can have a considerable influence on drug penetration.

2.6 Antioxidants

Lipids containing non-saturated fatty acids or fatty alcohols can be broken down by oxidation reactions and become rancid when exposed to light, air, and heat. The addition of antioxidants serves to prevent this and is expressly permitted by PhEur. Table 5 presents a summary of frequently used substances.

3. Liquid preparations

Liquid preparations for cutaneous application are defined by PhEur as "liquids of a variety of viscosities intended for local or transdermal delivery of active ingredients. They are solutions, emulsions or suspensions that may contain one or more active substances in a suitable vehicle. They may contain suitable antimicrobial preservatives, antioxidants and other excipients such as stabilisers, emulsifiers and thickeners.

Emulsions may show evidence of phase separation but are readily redispersed on shaking."

Liquid dermatological products can be distinguished in terms of polarity and whether they are single or multiphasic preparations.

3.1 Solutions

Single-phase liquid preparations are considered solutions in terms of physicochemical properties.

Usually water and/or alcohol are used as the solvent in **hydrophilic solutions**; the use of ether or acetone is very rare. Ethanol and isopropanol are examples of suitable alcohols. The addition of humectants, such as glycerol, help retain moisture. The addition of small amounts of dissolved castor oil or isopropyl myristate can help avoid excessive drying of the skin. Antifungal solutions often contain short-chain macrogol (PEG 400) as a hydrophilic solvent.

Medicinal *lipophilic solutions* for use on the skin are very uncommon. Suitable solvents include fatty oils such as olive oil, fluid wax, or liquid paraffin.

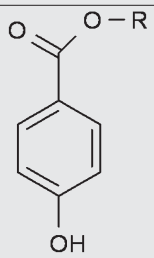
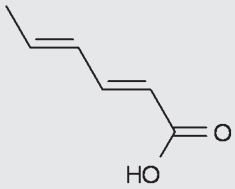
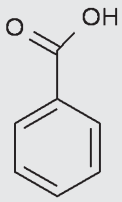
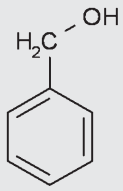
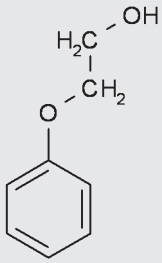
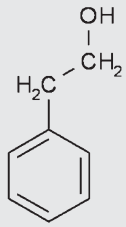
3.2 Liquid emulsions

Emulsions consist of two immiscible liquids. One phase is hydrophilic and the other lipophilic. The base of the hydrophilic phases is usually water, or a fluid that is miscible with water. It is thus known as the water phase (W). The lipophilic component of an emulsion can be a fat, oil, mineral oil, or other organic fluid. This is generally known as the oil phase (O).

In an emulsion, one immiscible liquid is dispersed in the other form a dispersion medium in which various states of distribution are possible depending on which component forms the dispersed phase and which forms the continuous phase [11]. Different types of emulsions are shown in Figure 2 [3].

The droplet size in the dispersed (internal) phase is usually 1 to 40 µm and is thus within the coarsely dispersed range (0.5–200 µm). Colloidal dimensions (< 500 nm) are less common. The majority of emulsions have a white, milky appearance due the fact that the dispersed and continuous phases have different refractive indexes, and thus as light striking the droplets is diffusely scattered.

Table 4: Preservatives used in dermatological products.

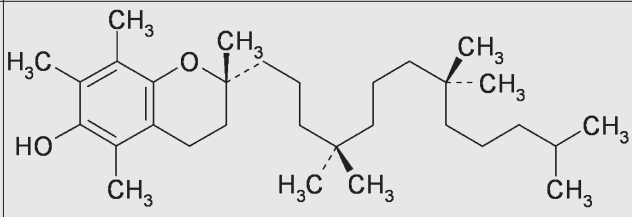
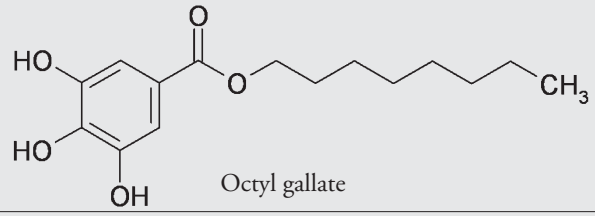
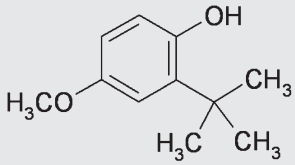
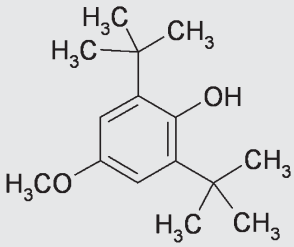
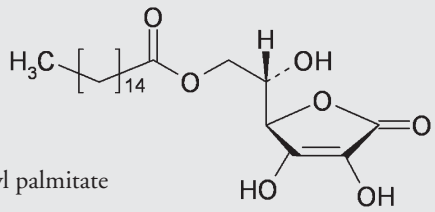
Preservative	Structure	pH range	Usual concentration
Alkyl-4-hydroxybenzoates (methyl, ethyl, propyl, butyl parabens)	 R= Methyl Ethyl Propyl Butyl	4–8	0.01–0.2 %
Sorbic acid		< 5	0.1–0.2 %
Benzoic acid		< 5	0.15–0.5 %
Benzyl alcohol		5–6	0.5–2.0 %
Phenoxyethanol		4–9	0.5–1.0 %
Phenyl ethyl alcohol		4–5	0.3–0.5 %

For sufficient stabilization, emulsions require the addition of appropriate emulsifiers, i.e., surface active agents, or macromolecules [18].

3.2.1 Lipophilic emulsions

In lipophilic emulsions the aqueous phase is dispersed in a lipid phase; such emulsions are water-in-oil (W/O) emulsions. Generally, hydrophobic skin emulsion bases are emulsions with a high proportion of the water phase (up to about 70 %). Lipophilic emulsifiers, e.g.,

Table 5: Antioxidants used in dermatological products.

Antioxidant	Structure	Concentration
Alpha-Tocopherol		0.05–0.075 %
Gallates (ethyl-, propyl-, octyl-, lauryl-, decyl ester)	 Octyl gallate	0.05–0.1 %
Butylhydroxyanisol		0.005–0.02 %
Butylated hydroxytoluene		0.005–0.02 %
Ascorbic acid esters (myristin, palmitin, stearin acid esters)	 Ascorbyl palmitate	0.01–0.015 %

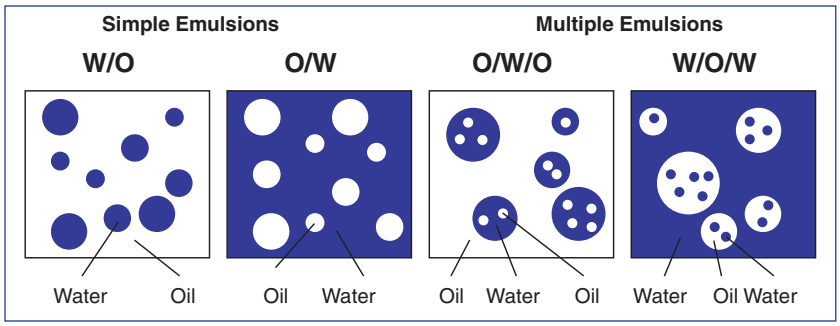


Figure 2: Schematic drawing of various types of emulsions.

diglycerol dipolyhydroxystearate and triglyceryl diisostearate, are good stabilizers for such emulsions.

Emulsions whose external, continuous phase is formed by lipids, tend to leave an oily film on the skin.

Unlike the numerous hydrophilic preparations, hydrophobic emulsion bases which are cosmetically acceptable are barely documented in officinal regulations.
An example of a typical formulation is given in Table 6.

3.2.2 Hydrophilic emulsions

In hydrophilic emulsions the internal, dispersed phase consists of an organic liquid (an "oil") and the external, coherent phase consists of water; these are known as oil-in-water (O/W) emulsions. If the internal phase has a low concentration and no thickening agents are added, such preparations will have a watery consis-

Table 6: Example of a formula for a hydrophobic skin emulsion.

Triglycerol diisostearate DAC	5.0 g
Isopropyl palmitate	10.0 g
Soft paraffin	23.0 g
Magnesium sulfate heptahydrate	0.5 g
Glycerol 85 %	10.0 g
Potassium sorbate	0.14 g
Anhydrous citric acid	0.7 g
PEG-6 cetyl stearyl ether	2.0 g
Sterile water	Up to 100.0 g

tency. Liquid O/W emulsions are customarily referred to as lotions or milks.

3.3 Suspensions

Liquid suspensions are referred to as shake lotions or often simply lotions. Their low viscosity causes them to settle quickly, and they must therefore be shaken before use. In a fluid vehicle, suspensions consist of up to 50 % suspended agent or base.

Lipophilic suspensions are usually dispersions of inorganic pigments (zinc oxide, talc, titanium dioxide) in oil. They can also contain dissolved or suspended drugs.

Hydrophilic suspensions consist of water with insoluble powder components such as zinc oxide, talc, or titanium dioxide. After the water or water/alcohol mixture evaporates, a layer of pigment remains on the skin – hence the name "liquid powder". The addition of polyols, such as glycerol or propylene glycol, which do not evaporate upon application, improves adhesion. Hydrogel-forming agents, such as bentonite or cellulose ether, increase viscosity and reduce sedimentation. As viscosity is increased, such preparations become hydrophilic pastes.

3.4 Special liquid preparations

In addition to the traditional liquid preparations, there are now newer formulations such as liposome dispersions, nanoemulsions, microemulsions, and multiple emulsions. Although they are used to a limited extent in cosmetic products, their use is still virtually unheard of dermatological products.

Bath additives also deserve mention. Bath oils are liquid preparations that are not applied directly to the skin. The two main types are cosmetically and bath oil emulsions. Bath oils achieve their effect by leaving a coating of lipids (soybean oil, olive oil, almond oil, and paraffin) on the skin. Oil dispersion baths demonstrate the best moisturizing effect and reduction in transepidermal water loss (TEWL) [8]. Unlike oil dispersion baths, they do not contain emulsifiers; after bathing they leave a lipid film on the skin (and coating the bathtub). Bath oils with small amounts of surfactants are an acceptable compromise.

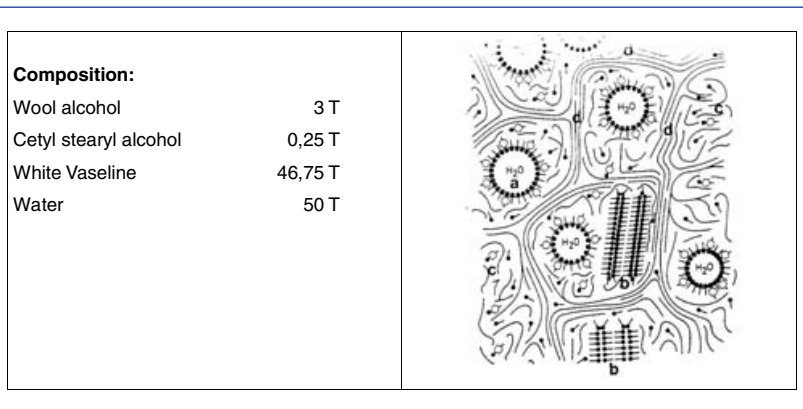


Figure 3: Composition and structure of aqueous wool fat ointment (from [12]). a) Water droplet, stabilized by mixed emulsifier system, b) Crystals of excess emulsifiers, c) Lipophilic liquid with dissolved emulsifier, d) Lipophilic gel phase.

4. Semi-solid preparations

In the monograph "Semi-solid preparations for cutaneous application", PhEur distinguishes between ointments, creams, gels, pastes, and poultices.

4.1 Ointments

Ointments are non-aqueous semi-solid preparations. They consist of a single-phase basis in which solids or liquids may be dispersed.

4.1.1 Hydrophobic ointments

Hydrophobic ointments can absorb only small amounts of water. Typical bases used for their formulation are petrolatum, hard, liquid and light liquid paraffins, vegetable oils, animal fats, synthetic glycerides, waxes and liquid polyalkylsiloxanes [4].

Bases can also be distinguished by chemical structure into hydrocarbon gels (containing petrolatum or paraffin) and lipogels (vegetable oils, animal fats, synthetic glycerides, or wax).

Hydrophobic ointments as finished drug products are commonly termed fatty ointments. The basis include, along with hydrocarbon gel components, other fatty components which may be considered lipogels.

4.1.2 Water-emulsifying ointments

Like all ointments, water-emulsifying ointments are anhydrous. However, they can absorb larger amounts of water and thereby produce water-in-oil or oil-in-water emulsions depending on the nature of the emulsifiers: water-in-oil emulsifying agents such as wool alcohols, sorbitan esters, monoglycerides and fatty alcohols, or oil-in-water emulsifying agents such as sulphated fatty alcohols, polysorbates, macrogol cetostearyl ether or esters of fatty acids with macrogols may be used for this purpose. Their bases are those of the hydrophobic ointments. Similar to hydrophobic ointments, water-emulsifying ointments available as finished drug products are usually termed to as fatty ointments.

4.1.3 Hydrophilic ointments

Hydrophilic ointments are preparations having bases that are miscible with water. The bases usually consist of mixtures of liquid and solid macrogols (polyethylene glycols). Unlike other ointments, they may contain appropriate amounts of water.

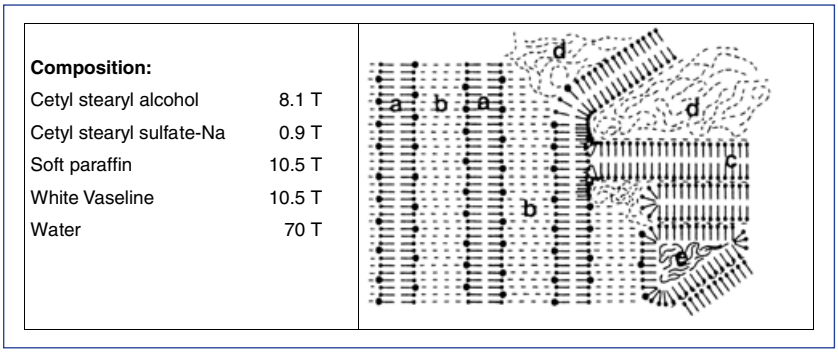


Figure 4: Composition and colloidal-chemical structure of the aqueous hydrophilic ointment (from [12]). a) Liquid crystal, lamellar gel structure of emulsifying cetyl stearyl alcohol, b) interlamellar fixed water, c) Cetyl stearyl alcohol-semihydrate-gel structure, d) Bulk water phase, e) Lipophilic, disperse phase.

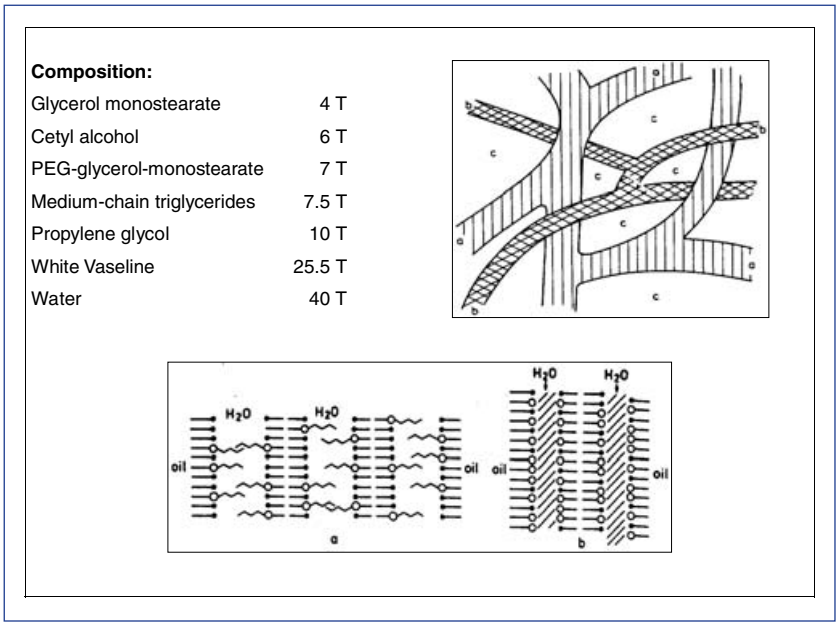


Figure 5: Composition and structure of Basiscreme DAC (from [12]). a) Partly swollen gel structure (emulsifier phase), b) Completely swollen gel structure (water phase), c) Coherent lipid phase.

Hydrophilic ointments as finished drug products are known as ointments or fat-free ointments.

4.2 Creams

Creams are multiphase preparations consisting of a lipophilic phase and an aqueous phase. They are formed by incorporating water into a water-absorbing ointment; alternatively, they can be understood as emulsions with a thickened, i.e., gelled, external phase.

4.2.1 Lipophilic creams

The external phase in lipophilic creams is lipophilic, i.e., it contains the typical components of hydrophobic ointments. They also contain water-in-oil emulsifiers such as wool wax alcohols, sorbitan esters, and monoglycerides.

W/O creams are emulsions in which the external phase is a lipophilic gel (hydrocarbon gel, oleo gel, or lipogel). This gives these creams their spreadable character.

An example of a typical lipophilic cream is the aqueous wool fat ointment in the German Pharmacopoeia (DAB) (Figure 3).

In finished drug products, these are referred to as ointments or rich creams.

4.2.2 Hydrophilic creams

In hydrophilic creams the external phase is aqueous. Hydrophilic cream preparations contain oil-in-water emulsifiers such as sodium soaps or trolamine soaps, fatty alcohol sulfates, polysorbates, or esters of polyoxyl fatty acids and fatty alcohols.

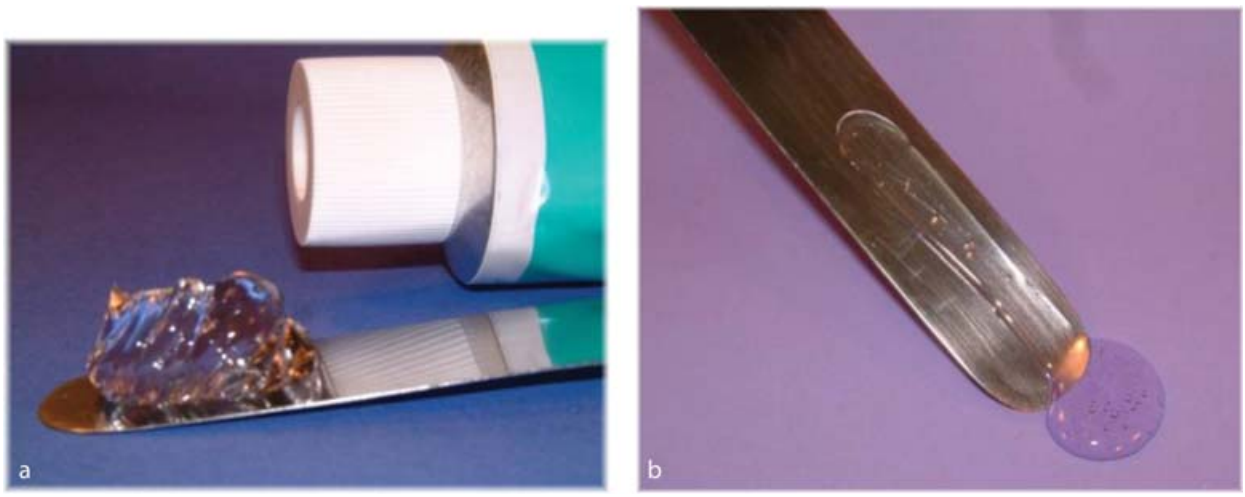


Figure 6: Thermoreversible surfactant gel. (A) Spreadable gel at room temperature, (B) Fluid preparation, cooled.

Table 7: Properties of drug-free dermatological bases applied to healthy skin (after [20]).

Dermatologic base	Moisturizing	Dryness	Oiling	Protective	Inflammatory	Antiinflammatory	Cooling	Heat accumulation
Fluid preparations								
Hydrophilic emulsions		++				+	+++	
Hydrophilic suspension (shake lotions, lotions)		+++		+		+	++	
Hydrophilic solution, aqueous		+				+	+	
Hydrophilic solution, water/alcohol (tincture)		++				+	++	
Hydrophilic solution, with acetone		+++				+	+++	
Hydrophobic solution		(+)		+	(+)			(+)
Ointments								
Hydrophobic ointment		++ +	++	++			++	
Water-absorbing ointment	+		+	+	+			+
Hydrophilic ointment		+						
Creams								
Hydrophobic cream		+				+	+	
Hydrophilic cream	+		+				(+)	
Amphiphilic cream		(+)				(+)	+	
Hydrogel								
Aqueous	++	(+)				++	++	
Water and alcohol	+	++				++	+++	
Paste								
Emulsifier-free		+	+	++		++	+	
Emulsifiers		++		+		++	+	
Powder								
Oil-free		(+)	+	+		+	++	
With oil			+	++		+	(+)	+

+++ marked, ++ moderate, + low, (+) low, with longer-term use

In terms of structure, O/W creams can be generally thought of as mixtures of a hydrogel and an emulsion. Although the hydrogel may be formed by a polymer, it is generally formed by a swollen, liquid crystal structure of a lamellar arrangement of surfactants.

For this purpose, hydrophilic creams contain a mixture of at least two emulsifiers known as "complex emulsifiers", which combine hydrophilic and lipophilic emulsifiers. The hydrophilic component determines the emulsion type and stabilizes the disperse oil phase. The lipophilic component, usually cetyl stearyl alcohol or glycerol monostearate, crystallizes at room temperature alone or together with the hydrophilic component, forming a framework that makes the cream spreadable and stabilizes it.

Typical structural features are found in the "aqueous hydrophilic ointment DAB" (German Pharmacopoeia) (Figure 4).

In finished drug products, hydrophilic creams are considered creams.

4.2.3 Amphiphilic creams

Amphiphilic creams have a bi-coherent structure, meaning that the lipophilic and

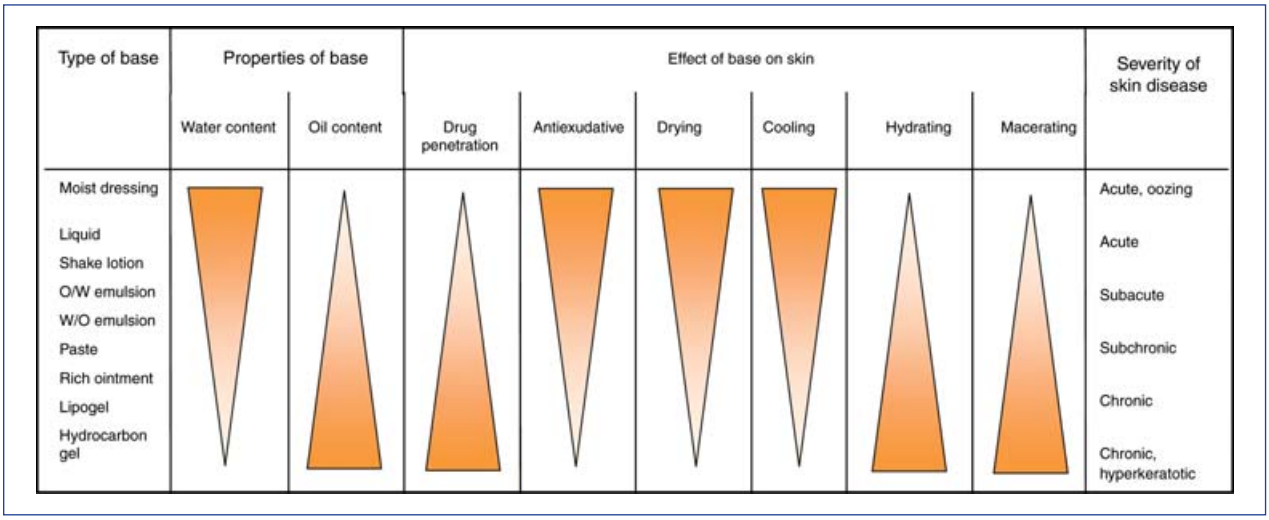


Figure 7: Use of various dermatological bases on diseased skin (after [15]).

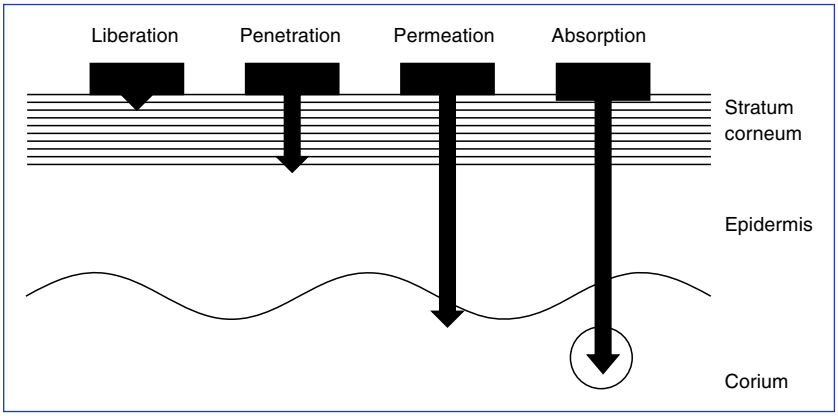


Figure 8: Transport pathways of a drug from the product to the intended site of action.

aqueous phases are continuous. They thus do not entirely conform to the definition of either a lipophilic or hydrophilic cream, but fall somewhere in between two.

Internal and external phases cannot be discerned and, given their bi-coherence, amphiphilic creams can be diluted with water or lipids.

Sometimes amphiphilic creams are termed "supersaturated" O/W emulsion ointments, although this does not accurately describe their colloidal-chemical structure. A typical example is the cream base in the German Drug Codex (DAC) known as "Basiscreme DAC" (Figure 5). Most such finished drug products are referred to as creams.

4.3 Hydrogels

Hydrogels can be characterized in physicochemical terms as bi-coherent systems. They are composed of a solid component which forms a coherent three-dimensional network (matrix, texture, framework) and a fluid which is present as an immobilized coherent medium within the matrix. The liquid phase consists of water and/or alcohol and can contain additives of about 10 % propylene glycol, glycerol, or sorbitol which serve as humectants.

The network is usually formed by organic macromolecules, although it may also be formed by inorganic substances such as bentonite.

Surfactant gels are also hydrogels. The network is formed by surfactant aggregates. The use of a block polymer of polyethylene glycol (PEG) and polypropylene glycol (PPG) as the surfactant poloxamer can produce a thermally reversible gel. These have a gel-like consistency at room temperature and are viscous when refrigerated (Figure 6).

4.4 Pastes

Pastes are semi-solid preparations for cutaneous application containing large proportions of solids finely dispersed in the basis. Hydrophobic pastes contain zinc oxide and/or other inorganic pigments in a hydrocarbon gel or lipogel. Hydrophilic pastes, i.e., thickened aqueous shake lotions, are less common in dermatologic practice. Compared to traditionally-used hydrophobic pastes, their composition gives them the added advantage of having a drying effect.

4.5 Powders

Powders are described in the PhEur monograph "Powders for cutaneous application" as follows: "Preparations consisting of solid, loose, dry particles of varying degrees of fineness. They contain one or more active substances, with or without excipients and, if necessary, colouring matter authorised by the competent authority."

Powders are seldom presented as single-dose powders. Appropriate containers for multidose powders include sifter-top containers, containers equipped with a mechanical spraying device or in pressurised containers.

5. Application sites and effects of drug-free dermatological products

Dermatological products are a unique form of medicinal product in that the vehicle is expected to exert an effect of its own, even without the drug.

In addition to physical effects, such as cooling or occlusion, some bases also in-

Table 8: Influence of vehicles on hydration of the stratum corneum and permeability [after 21].

Vehicle	Examples/Components	Effect on hydration	Effect on skin permeability
Occlusive dressings	Occlusive sheets, unperforated bandages	Prevent water loss, complete hydration	Strong increase
Lipid bases	Paraffins, oils, fats, waxes, fatty acids, higher fatty alcohols, esters, silicones	Prevent water loss, can assist complete hydration	Strong increase
Absorption bases	Anhydrous lipid materials with W/O-emulsifiers Anhydrous lipid materials with O/W-emulsifiers	Prevent water loss, strong increase in hydration	Strong increase
W/O systems	W/O creams W/O emulsions	Reduce water loss, increase hydration	Increase
O/W systems	W/O creams W/O emulsions	Can deliver water to skin, small increase in hydration	Small increase
Humectants	Water-soluble bases, glycerol, glycols	Can remove water, decrease hydration	Reduction possible or effect as penetration mediator
Powders	Bentonite, Carbonate, Ultra amyl pectins, shake lotions	Support delivery of water, decrease excess hydration	Minimal effect on horny layer

Table 9: Examples of various bases used in dermatological products.

Product	Drug-free base	Extemporaneous preparation (with active ingredient)	Commercially manufactured drugs (selected drugs)
Lipophilic solution		Salicylic acid oil (NRF)	Psorimed
Hydrophilic solution		Salicylic acid –acne cleanser / (NRF); Ethanol-based chlorhexidine digluconate solution (NRF); Polyvidone iodine solution (NRF); Triamcinolone acetonide skin cleanser 0.2 % with salicylic acid 2 % (NRF)	Alpicort
Lipophilic emulsion			Excipial U Lipolotio (cosmetic)
Hydrophilic emulsion	Hydrophilic skin emulsion base (NRF)	Hydrophilic urea emulsion 5 % (NRF)	Amciderm Lotion
Lipophilic suspension		Zinc oil (NRF) Zinc oxide neutral fat 50 % with nystatin 70 000 IU/g (NRF)	

Tabelle 9: Continued.

Product	Drug-free base	Extemporaneous preparation (with active ingredient)	Commercially manufactured drugs (selected drugs)
Hydrophilic suspension		Zinc oxide shake lotion (DAC); Ethanol-based zinc oxide shake lotion (DAC)	Dercome clear
Special liquid preparations	Paraffin soy oil bath (NRF)		Linola oil bath
Hydrophobic ointments	Vaseline; Hydrophobic base gel (DAC); Simple wax ointment (FN); White almond oil ointment (FH)	Lipophilic tretinoin ointment 0.1 % (NRF)	Advantan fatty ointment
Water-emulsifying ointments	Wool fat ointment (DAB) Hydrophilic ointment Emulsifying eye ointment (DAC)	Zinc ointment (DAB); Wound ointment (NRF)	Karison rich ointment
Hydrophilic ointments	Macrogol ointment (DAC);	Povidone iodine ointment 10 % (NRF); Hydrophilic clotrimazole ointment 2 % (NRF)	Nystalocal ointment
Lipophilic creams	Aqueous wool fat ointment; Lanolin (DAB); Cooling ointment (DAB); Soft ointment (SR) 90; Hydrophobic Basiscreme DAC	Ammonium bituminosulfonate-ointment (NRF); Hydrophobe Dexpanthenol-Creme 5 % NRF; Hydrophobic triclosan cream 2 % NRF	Linola (rich) cream
Hydrophilic creams	Aqueous hydrophilic ointment (DAB); Nonionic hydrophilic cream (DAB); Hydrophilic cream (SR); anionic hydrophilic cream (SR)	Nonionic hydrophilic Chlorhexidine digluconate cream 1 % (NRF)	Mycospor cream
Amphiphilic creams	Basiscreme DAC	Hydrophilic Bethamethasone valerate cream 0.05 % (NRF); Hydrophilic dimethicone cream 10 % (NRF); Hydrophilic hydrocortisone cream 0.5 % (NRF); Hydrophilic dexpanthenol cream 5 %; Hydrophilic triamcinolone cream 0.1 % (NRF)	Linola urea

Table 9: Continued.

Product	Drug-free base	Extemporaneous preparation (with active ingredient)	Commercially manufactured drugs (selected drugs)
Hydrogels	Carmellose sodium gel (DAB); Hydroxyethyl cellulose gel (DAB); Methyl cellulose gel (FN); Aqueous carbomer gel (DAB); 2-Propanol carbomer gel (DAB); Ultrasound contact gel	Benzoyl peroxide gel 5 % (NRF); Zinc sulfate gel (FH)	Aknefug Oxid, mild
Hydrophobic pastes		Zinc paste (DAB); Soft zinc paste (DAB)	Nystatin "Lederle" paste
Hydrophilic pastes		Hydrophilic zinc oxide paste 40 % with ammonium bituminosulfonate 5 %	Imazol paste
Powder		Non-oily powder base (FN); Oily powder (FN); Zinc oxide talc (NRF)	Batrafen powder

NRF: New German Formulary DAC: German Drug Codex FN: National Formulary
FH: German Hospital Formulary DAB: German Pharmacopoeia DAC: German Drug Codex

teract with the skin, and thus negatively or positively influence the barrier function of the skin [10].

The effects on the skin of various bases are summarized in Table 7.

For use on diseased skin, the type of base used is determined by the acuteness of the disorder (other overriding criteria notwithstanding) rather than the preferred base (Figure 7) [15, 19]. As a general rule of thumb: "moist on moist."

If one takes into consideration the application site, selection depends primarily on criteria such as distribution over the skin and washability. For very hairy skin, a hydrophilic ointment, hydrogel, or hydrophilic solution or shake lotion is preferable.

6. Biopharmaceutical aspects

Topically applied drugs can have local, regional, or systemic effects. There are four steps in transport of the active ingredient (Figure 8):

Liberation: Release of the active ingredient from the base by diffusion

Penetration: Passage through the stratum corneum

Permeation: Diffusion in the corium and partly subcutaneous tissue

Absorption: Absorption of the active agent by the lymph and blood vessels

Extent and rate of absorption of an agent is determined by vehicle properties, the agent, and their interactions and resulting influences. For example, a given vehicle can interact with the skin and influence permeability.

In order to cross the epidermal barrier, drug molecules must possess certain characteristics including: low molecular weight (< 500 Daltons), moderate lipophilia (octanol-water partitioning coefficient between 10 and 1000) and a moderate melting point (< 200 °C) indicating good solubility. Yet, even for such agents penetration must normally be enhanced.

In general, the greatest possible activity (dissolved portion) of the drug should be achieved in the base. Optimal conditions can be achieved when galenic measures are employed to achieve supersaturation [16]. This improves skin penetration by increasing the concentration gradient which determines the rate of diffusion. Penetration is improved without disrupting the structure of the Stratum corneum.

The simplest means of penetration enhancement involves influencing the barrier function of the skin by increasing hydration of the stratum corneum. Retention of water in the horny layer loosens its compact structure, making it more permeable. The water content of the horny layer can either be increased by release of water from the vehicle or by (partial) occlusion, which blocks transepidermal water loss.

Table 8 summarizes the main effects of vehicles on the water content of the stratum corneum as well as drug penetration. Additionally, various additives can be used to enhance penetration of the active ingredient. The following are the main mechanisms [1, 6]:

- Extraction of lipids from the stratum corneum

- Altaration of the vehicle/skin partitioning coefficient
- Disruption of the lipid bilayer structure
- Displacement of bound water
- Loosening of the keratin structure in the horny cells

Chemical substances that enhance penetration can be divided into various groups. Solvents such as alcohols, alkylmethyl sulfoxide, and polyols, increase mainly the solubility and improve the distribution coefficient. In addition, some solvents, such as DMSO or ethanol, can leach epidermal lipids, making the horny layer more permeable. Oleic acid, Azone® (ϵ-laurocapram) and isopropyl myristate are typical examples of chemical accelerants that are incorporated into the lipid bilayer disrupting their densely-packed arrangement. The structure as a result becomes more fluid and diffusion is enhanced. Ionic surfactants, decylmethylsulfoxide, DMSO, and urea interact with the keratin of the corneocytes. This loosens the compact protein structure, increasing the partitioning coefficient, especially for substances that diffuse through the corneocytes.

Unfortunately, the strong interaction between potent chemical penetration enhancers and lipids or corneocytes in the stratum corneum often results in skin irritation and damage to the barrier function of the skin.

7. Magistral preparations

Most dermatological prescriptions are made by dermatologists who, during their clinical education, learned of the options and advantages offered by making individual preparations.

Recent studies suggest that the majority of prescriptions still involve extemporaneous rather than standardized preparations [13]. In addition to traditionally used bases, such as aqueous hydrophilic ointment DAB (unguentum emulsificans aquosum), a number of newer vehicles are also used, including Basiscreme DAC. Attempts at limiting prescriptions to mostly or exclusively standardized formulations have not been entirely successful.

When prescribing extemporaneous preparations, potential incompatibilities can often be determined, and suitable alternatives chosen, if the base is formulated using official sources (in Germany: DAB, DAC, Standard Prescriptions (SR), or New German Formulary (NRF)) [5, 14].

Yet, without complex studies, it remains nearly impossible to estimate long-term stability; expiration dates should be set with this in mind, especially when combinations of drugs are used.

Such problems can best be avoided by careful attention to galenics and by using standardized formulations (e.g., based on the New German Formulary) which have proven successful [14].

The situation is more difficult for finished drug products or brand-name bases. In this case the quality, for which the pharmacist is in charge, can only be ensured if adequate studies from the manufacturer are available [9].

If there are any doubts concerning their quality, such prescriptions should not be filled (§ 7 ApBetrO).

Another topic related to prescribing topical agents is the widespread practice of combining or diluting commercially made drugs with officinal or industrially manufactured bases. Especially here there is a need for special care in terms of ensuring the quality of such preparations.

A recurrent problem, for example, is the incompatibility of mixing O/W and W/O bases. This is easily avoided with proper knowledge of galenics.

8. Conclusion

A surprisingly large number of different bases (Table 9) are used in dermatological preparations for magistral preparations as well as commercially-manufactured drugs. Thus, a base can be chosen that suits the condition of the skin in various stages of disease, is appropriate for the application site, and optimizes drug penetration. Yet, prudent use of all available options requires thorough knowledge of the properties of various vehicles. Issues arising related to magistral preparations can usually be settled by communication between the dermatologist and pharmacist. <<<

Conflict of interest

None.

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