Active pharmaceutical substances are usually applied to the skin in the form of semisolid formulations for topical treatment of dermatological diseases or for improvement of the skin condition. The skin may also be recognized as an alternative port of entry for systemically acting drugs. For the effectiveness of the formulations applied to the skin, the active compounds incorporated into the semisolid base must reach the site of action. However, the skin acts as a barrier controlling the entry of molecules from the administered medications.[1]

Transport of active substances through the skin may be described as a series of consecutive steps, each of which can potentially be rate limiting[2]. First, the drug needs to diffuse from the formulation to the skin surface[2]. This process is characterized by the release rate. The release requires dissolution of the active substance and may be rate limiting process for skin delivery[3,4] due to the fact that only small molecules can penetrate into the skin.

After being released, the active substance partitions into and diffuses through the stratum corneum, the principal skin barrier, which represents the thin outer layer (10 µm) of the epidermis and is typically comprised of about 10-25 corneocyte cell layers[1,2]. The stratum corneum structurally composed of tightly packed alternating hydrophilic and lipophilic layers organized as “bricks and mortar”[1-5]. Human stratum corneum consisted of corneocyte “bricks” composed primarily of aggregated keratin filaments encased in a cornified envelope that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers serving as mortar[5].

There are different potential pathways for permeation through the stratum corneum. These pathways include: appendageal, transcellular or intercellular route[1]. The route to be followed by any active substance depends on its physiochemical characteristic, although more than one route may be used at the same time[1]. The appendageal route along hair follicles, sebaceous follicles and sweat glands is considered to be of minor importance because of their relatively small area (less than 0.1% of the total surface)[1]. Substances that are preferentially transported via the transcellular route have also to cross the intercellular spaces[1]. Therefore, the intercellular route through the extracellular milieu of lipids is considered to be the main pathway for any molecule moving through the stratum corneum. Lipid extracellular matrix is continuous, yet very convoluted[1,5]. This results in long and tortuous pathway for any molecule moving through the stratum corneum[1,5]. The extreme hydrophobicity and the
composition and highly rigid ordered distribution of the three key species of intercellular lipids (ceramides, cholesterol and free fatty acids) contribute for the \textit{stratum corneum} barrier function\cite{1,5}. Although these structured lipids prevent entry of most topically applied active substances (other than those which are lipid soluble and of low molecular weight), the lacunar domains, which represent the likely aqueous pore pathway and aqueous pores within the extracellular matrix of the \textit{stratum corneum} provide the opportunity for the delivery of active substances that are lipid insoluble. However, these lacunar domains are discontinuous and only under certain conditions (e.g. occlusion, prolonged hydration) may form a continuous but collapsible network\cite{5}.

After overcoming the \textit{stratum corneum}, the active substance permeates into and diffuses through the viable epidermis, which is situated beneath the \textit{stratum corneum}\cite{1,2,5}. The cellular structure of the viable epidermis is predominantly hydrophilic throughout its various layers and substances can be transported in its intercellular fluids\cite{1}. Especially for polar substances, the resistance to permeation is considerably lower than in the \textit{stratum corneum} and the active substance permeates easily to the dermis, which consists of connective tissue and contains blood vessels, lymph vessels and nerves\cite{1}. Chemicals reaching the dermis are readily absorbed into the bloodstream and may act systemically\cite{1,6}. Finally, the dermis is located on the subcutis, which is made of a network of fat cells\cite{6}.

The percutaneous absorption process may be divided into three steps: penetration, which is entry of the active substance into a particular layer or organ and diffusion within that layer or organ; permeation, which is the penetration through one layer to another, which is both functionally and structurally different from the first layer; absorption, which is the uptake of the active substance into the vascular system\cite{1,6}.

Transport of active substances through the skin (release from a formulation, skin penetration and skin permeation) is mainly investigated \textit{in vivo} but may be also studied \textit{in vitro} conditions. The \textit{in vitro} study of the release is performed with a diffusion cell as a process of permeation of the active substance from a semisolid formulation through an artificial membrane to an acceptor fluid (aqueous buffer pH 5-8 or aqueous ethanol mixture)\cite{7,8}. \textit{In vitro} drug release studies are particularly useful in the early stage of the development of dermatological formulations as they help to identify interactions between the active substance and the semisolid base\cite{7}.

The penetration through the \textit{stratum corneum} may be characterized experimentally by a tape-stripping method\cite{9,10}. Skin permeation studies may be performed \textit{in vitro} in diffusion cells with the skin as a membrane. The rate of the skin permeation process may be expressed as the amount of the active substance appearing in the acceptor fluid, similarly as in the release studies\cite{11}.

From the perspective of topical products (cosmetic or dermatologic), it is necessary to achieve an appropriate active substance concentration in the skin tissue (skin retention). However, permeation of active substance through the skin from topical products should be limited to prevent the occurrence of side effects related to the entering into the bloodstream. Skin retention and permeation may not be correlated so these processes must be characterized separately\cite{12}.

A base type of a semisolid dosage form affects dermal and transdermal delivery of an active substance and thus its therapeutic efficacy. This impact is well illustrated using the example of topical glucocorticosteroid formulations. Topical semisolid formulations of betamethasone dipropionate at the same glucocorticosteroid concentration (0.05%) belong to four different classes in terms of potency (I, II, III, V) depending on a base type (Table 1)\cite{13}. As is apparent from Table 1, betamethasone dipropionate formulations with the highest potency (class I: super potent) are Diprolene Gel 0.05% and Diprolene Ointment 0.05%, while the least potent formulation is Dipsone Lotion 0.05% (class V - lower mid-strength)\cite{13}.

The components of semisolid base can influence active substances as well as properties of a skin

<table>
<thead>
<tr>
<th>Product</th>
<th>Potency group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diprolene gel 0.05%</td>
<td>Super potent-I</td>
</tr>
<tr>
<td>Diprolene ointment 0.05%</td>
<td>Super potent-I</td>
</tr>
<tr>
<td>Diprolene cream AF 0.05%</td>
<td>Potent-II</td>
</tr>
<tr>
<td>Dipsone ointment 0.05%</td>
<td>Potent-II</td>
</tr>
<tr>
<td>Maxivate ointment 0.05%</td>
<td>Potent-II</td>
</tr>
<tr>
<td>Dipsone cream 0.05%</td>
<td>Upper mid-strength-III</td>
</tr>
<tr>
<td>Maxivate cream 0.05%</td>
<td>Upper mid-strength-III</td>
</tr>
<tr>
<td>Maxivate lotion 0.05%</td>
<td>Upper mid-strength-III</td>
</tr>
<tr>
<td>Dipsone lotion 0.05%</td>
<td>Lower mid-strength-V</td>
</tr>
</tbody>
</table>

Classification according to potency by the National Psoriasis Foundation\cite{14}.
barrier function and thereby affect release of active substances from the formulation and their delivery to the skin (retention) and through the skin (penetration, permeation)\cite{2,13,14}. The composition of the semisolid base impacts parameters of the active substance that are important from the point of view of the release, skin and transdermal delivery such as: concentration of dissolved form, thermodynamic activity, skin/base partition coefficient as well as diffusion coefficient in stratum corneum (skin permeability)\cite{2,15-19}. The values of these parameters should be as high as possible to maximize the rate of release and skin and transdermal delivery\cite{2,15-19}.

Semisolid formulations can be classified with respect to physiochemical properties of a base as: hydrophobic formulations (oleaginous ointments, anhydrous absorption ointments, oleogels), hydrophilic formulations (hydrogels, water-soluble ointments) or emulsions that are mixtures of hydrophilic and hydrophobic phase (creams, emulgels, bigels, microemulsion gels)\cite{20-22}.

The present article presents the properties of different types of semisolid bases (hydrophilic, hydrophobic, emulsions) that are crucial for the rate of release, skin and transdermal delivery of an active substance from the formulation intended for the application to the skin. The results of studies on the release, penetration, permeation and skin retention of active substances from different types of semisolid formulations are also discussed.

**TYPES OF BASES USED IN SEMISOLID FORMULATIONS**

**Hydrophobic bases:**

Hydrophobic bases are single-phase systems consisting of lipophilic components. Hydrophobic bases include lipophilic ointments, anhydrous absorption ointments and oleogels. Lipophilic ointments contain components such as hydrocarbons (petrolatum jelly is most often used as a simple base or as an ingredient of a base), vegetable oils, animal fats, synthetic glycerides, waxes, polyalkylsiloxanes\cite{21}. Anhydrous absorption ointments additionally contain w/o emulsifiers\cite{21,22}. Oleogels usually consist of liquid lipophilic components gelled with agents forming three-dimensional network\cite{21}. Oleogels may also contain w/o or o/w emulsifiers\cite{23}.

Substances that are susceptible to oxidation may have an increased stability in anhydrous hydrophobic bases\cite{21}. Hydrophobic bases have many characteristics limiting active substance release rates in *in vitro* studies. Poorly water soluble ingredients of hydrophobic bases cannot penetrate into the acceptor fluid whereby they cannot change the value of acceptor fluid/semisolid base partition coefficient for the active substance\cite{24}. The aqueous acceptor fluid poorly penetrates into the hydrophobic semisolid formulation. In consequence, the release of an active substance from a hydrophobic base is two-step process. While the active substance is easily released from the surface of the semisolid formulation contacting directly with the membrane, the next stage of release is a very slow process as it requires diffusion of the active substance from deeper layers of the hydrophobic base to the surface of the formulation\cite{25}.

Active substances of highly lipophilic nature may be usually dissolved in hydrophobic bases whereas moderately lipophilic or hydrophilic substances form suspensions\cite{21}. However, the release of lipophilic active substances from hydrophobic bases is limited, even if they are dissolved in the base because of their strong affinity to the lipophilic components (low values of acceptor fluid/semisolid formulation partition coefficients)\cite{24}.

A high viscosity of hydrophobic base reduces the rate of the diffusion of the active substances within the formulation and thus their release\cite{24}. The rate of the release from lipophilic ointments and oleogels may be increased by the addition of emulsifiers to the hydrophobic base\cite{21,26}. Anhydrous absorption ointments usually provide higher rates of the release than lipophilic ointments\cite{26}.

Some hydrophobic components of a base may penetrate into the lipids of the stratum corneum intercellular cement and thus impact properties of skin barrier (stratum corneum permeability, values of skin/semisolid formulation partition coefficients for active substances may be changed) but the rate of this process is usually limited\cite{27}. For vegetable oils and liquid paraffin a deeper penetration than into the first 2-3 upper layers of the stratum corneum could be excluded when they are applied for 30 min at once\cite{27}. However, under the influence of the systematic application of the hydrophobic formulations, lipophilic components of a base may be incorporated into the lipids of the stratum corneum. Twice daily application of Vaseline petroleum jelly within three days leads to its presence within the interstitials at all levels of the stratum corneum, where it replaced intercellular bilayers\cite{28}.
Lipophilic components of the base tend to form an occlusive layer on the surface of the skin and thus prevent water from evaporation. It can provide transepidermal water loss reduction and increase in the hydration state of the stratum corneum\cite{21,27}. The skin hydration may improve the penetration of active substances\cite{20}. Petroleum jelly is more effective occlusiver than oils\cite{27}. Hydrophobic bases, especially Vaseline petroleum jelly, provide prolonged contact of the formulation with the skin as they tend to remain on the skin surface\cite{21,27,28}.

**Hydrophilic bases:**

Hydrophilic bases consist of water-miscible components. Hydrophilic bases include macrogel ointments (PEG ointments) and hydrogels. PEG ointments consist of mixtures of liquid and solid polyoxyethylene glycols (PEGs)\cite{21}. Hydrogels are composed of a liquid phase (water, ethanol, isopropanol, propylene glycol, glycerol, sorbitol, PEGs) and gelling agents forming a coherent three-dimensional network\cite{20,21}. The consistency of the hydrophilic bases may be easily optimized by a proportion of liquid and solid PEGs (PEG ointment)\cite{29} or a type and a concentration of gelling agents (hydrogel)\cite{20}. Hydrogels are not proper bases for substances that are susceptible for oxidation in aqueous media (e.g. ascorbic acid)\cite{30}. In contrast, anhydrous PEG ointments may provide increase in the stability of these substances (e.g. ellagic acid)\cite{24}. The solubility and concentration of dissolved form of the active substance in hydrophilic bases may be easily adjusted by a proper selection of solvents, which are contained in the liquid phase. Active substances insoluble in water may be dissolved in ethanol, isopropanol, propylene glycol or PEGs before its introduction into a hydrophilic base. PEGs are especially capable of dissolving many substances\cite{21}. However, highly lipophilic substances cannot be put into the hydrophilic bases in dissolved form.

Hydrophilic bases usually provide high rates of release in vitro, as they are easily penetrated by the acceptor fluid\cite{31}. Low molecular-weight components of hydrophilic bases (alcohols, PEGs) can easily permeate into the acceptor fluid and if they are good solvents for the active substance they may increase the value of acceptor fluid/base partition coefficient and thus the rate of the active substance release. However, high release rates of active substances from hydrophilic bases (especially PEG ointments) observed in vitro usually does not correlate with increased skin delivery so they must be interpreted with caution. PEGs penetration into the skin is very poor due to their highly hydrophilic nature\cite{18}. Poor penetration of PEGs into the skin as well as their solubilizing capacities may contribute to decrease in the value of skin/base partition coefficient of substances dissolved in PEG ointments and thus decrease in skin penetration. PEGs hygroscopic properties may contribute to the stratum corneum dehydration and thus decrease in active substances penetration\cite{32}. Moreover, PEGs are incompatible with many active substances\cite{21}.

Many studies show that PEG ointments do not provide skin delivery of active substances at rates necessary to achieve therapeutic effects. PEG ointment of acyclovir was ineffective in the treatment of herpes virus skin infections because of the poor skin retention of the active substance\cite{33}. The permeation of idoxuridine through the guinea pig skin as well as the human skin from PEG ointment was negligible\cite{31}. Ellagic acid\cite{24}, nonivamide\cite{34}, sodium acetate nonivamide\cite{34} did not permeate the rat skin from PEG ointment.

Some components of the hydrophilic bases may be considered as permeation enhancers. Water, a main component of hydrogels, is able to increase the hydration of the stratum corneum and acts as a natural penetration enhancer\cite{35}. However, the tendency of hydrogels to rapid drying after application to the skin limits their moisturizing properties\cite{36}. Solvents of the active substance that are the components of the liquid phase of the hydrogels (e.g. ethanol, propylene glycol) are able to penetrate into the lipid intercellular cement of the stratum corneum and thus increase the value of skin/base partition coefficient\cite{4,21}.

The pH of the liquid phase of the hydrogels may be easily adjusted to the specific value\cite{37}. This pH value should provide compatibility of the formulation with the skin as well as active substance stability within the formulation\cite{38,39}. The pH value may affect solubility and ionization of the active substance and hence, its ability to permeate the skin\cite{1,37,40}. The increase in the pH value causes ionization and increase in the solubility of weak acids and the decrease in the pH value causes ionization and increase in the solubility of weak bases\cite{1,21}. On the one hand, this increase in the solubility may cause increase in the concentration of the dissolved form in the semisolid base and thus increase in the skin permeation\cite{37}. On the other hand, this increase in the solubility is due to the increase in
the degree of ionization, ionized species are considered to have lower intrinsic permeability than parent molecules\textsuperscript{[1,40,41]}.  

\textbf{Emulsion bases:}  

Emulsion bases consist of an oil phase and an aqueous phase. Emulsion bases contain emulsifiers stabilizing a dispersed phase in an external phase. Emulsifiers determine also a type of the emulsion. Emulsions may be two-phase systems (o/w or w/o) or multi-phase systems (w/o/w or o/w/o)\textsuperscript{[20-22,42]}. Among emulsion bases, creams, emulgels, bigels, microemulsion gels can be distinguished\textsuperscript{[20-22,42]}. The cream is a conventional semisolid preparation. The modern type of the cream is lamellar liquid crystal formulations characterized by an ordered, layered arrangement of the emulsifiers in the formulation resembling lipid bilayers present in the cell membranes. The emulgel base is an emulsion that contains gelling agents in the external phase. The gelling agents increase the viscosity of the external phase and thus stabilize the emulsion and adjust the consistency of the semisolid base\textsuperscript{[20]}. The use of gelling agents may enable to obtain stable emulsions without using typical emulsifiers\textsuperscript{[30]}. Bigel is a mixture of a hydrogel and an oleogel and may be obtained without using emulsifiers\textsuperscript{[20]}.  

The modern type of semisolid formulations is a microemulsion gel obtained by the addition of gelling agents to the liquid microemulsion\textsuperscript{[41]}. The droplet size of the microemulsions is usually under 100 nm\textsuperscript{[21]}. The small droplet size is achieved with the use of high concentration of emulsifiers and co-surfactants\textsuperscript{[21]}.  

Due to the fact that emulsion base contains different types of components (hydrophobic and hydrophilic), it combines the properties of hydrophobic and hydrophilic base\textsuperscript{[20]}. However, a predominance of the external phase properties may be seen (the emulsion is hydrophilic, if its external phase is aqueous and hydrophobic, if its external phase is oil)\textsuperscript{[20]}.  

The presence of the hydrophilic components, hydrophobic components and emulsifiers in the emulsion bases enables to dissolve both hydrophilic and hydrophobic active substances\textsuperscript{[44]}. The solubility of the active substance in the emulsion base may be increased by emulsifiers or solvents that may be easily incorporated into the formulation\textsuperscript{[16,21,43]}. Emulsion bases enable to incorporate both hydrophilic and hydrophobic solvents of active substances\textsuperscript{[16]}. The active substance may be localized in the external phase or in the dispersed phase (depending on its solubility in the oil phase and in the aqueous phase as well as the emulsion type). The release rate of active substances from emulsion bases \textit{in vitro} is largely determined by the penetration of the acceptor fluid into the formulation and is usually higher when external phase of emulsion is aqueous. The release of active substances from hydrophilic emulsions is usually higher than from hydrophobic emulsions. The emulsifiers, especially these with high HLB values, may increase the penetration of acceptor fluid into the emulsion base\textsuperscript{[18]}.  

Emulsion bases influence the skin barrier and thus have a significant impact on the skin delivery of active substances. Emulsion bases, especially emulgels and lamellar liquid layer crystal formulations, may increase the rate of the \textit{stratum corneum} hydration\textsuperscript{[36]}. Hydrophilic emulsions act similarly to hydrogels. The increase in hydration of the \textit{stratum corneum} is provided by the direct contact of the external aqueous phase of hydrophilic emulsion with the skin. Hydrophobic emulsions act similarly as hydrophobic bases and increase the rate of the \textit{stratum corneum} hydration indirectly, thanks to their occlusive properties\textsuperscript{[21]}.  

Some emulsifiers contained in emulsion bases may penetrate into the intercellular lipids of the \textit{stratum corneum} and act as penetration enhancers by increasing the \textit{stratum corneum} permeability and/or the value of active substances partition coefficient skin/base\textsuperscript{[2,45-47]}.  

\textbf{COMPARISON OF RELEASE OF ACTIVE SUBSTANCES FROM DIFFERENT TYPES OF SEMISOLID BASES}  

The physiochemical nature of the semisolid base influences the release rates of active substances \textit{in vitro}. The type of the semisolid base determines the ability of the acceptor fluid to the penetration into the formulation\textsuperscript{[31]}. The release rate of hydrophilic and moderately hydrophilic active substances usually increases when more hydrophilic bases are used (hydrophobic<emulsion<hydrophilic).  

The high rate of the release from hydrophilic bases may be attributed to the readily dissolution of water-miscible components of the base in the acceptor fluid penetrating into the formulation\textsuperscript{[16,31]}. Hydrophilic components of the base may penetrate into the acceptor fluid and thus change the value of partition coefficient acceptor fluid/base of the active substance\textsuperscript{[31]}.  

When hydrophilic base is used, the active substances diffuses directly from the aqueous phase of the hydrophilic base to the aqueous acceptor fluid\textsuperscript{[48]}. The
release rate from hydrophobic and emulsion bases is usually slower than from hydrophilic bases, owing to the partitioning of the active substance between aqueous and oil phase\[48\]. Examples in Table 2\[48-58\] show the advantage of the hydrophilic bases over the hydrophobic and emulsion bases in providing the high release rate of active substances.

Hydrophilic emulsions release active substances usually faster than hydrophobic ones. The release of local anaesthetics through the hydrophilic membrane was higher from o/w cream than from w/o cream\[57\]. Similarly, the release rate of hydrocortisone from o/w cream was two-fold higher than from w/o cream\[58\].

The use of hydrophobic bases, immiscible with the acceptor fluid, results in low release rate of active substances\[31\]. The results of studies summarized in Table 3\[59,60\] indicate that hydrophobic formulations show lower release rate of active substances than hydrophilic and emulsion bases.

However, highly lipophilic active substances, in contrast to hydrophilic and moderately lipophilic active substances, may be released faster from hydrophobic bases than from hydrophilic ones. The release of hydrophilic and moderately lipophilic active substances from hydrophobic bases is limited, as they are usually suspended in the formulation and they cannot diffuse easily within vehicle. The highly lipophilic substances are often partly dissolved in the hydrophobic base and their molecules may directly penetrate into the

### TABLE 2: RELEASE OF ACTIVE SUBSTANCES FROM HYDROPHILIC, HYDROPHOBIC AND EMULSION BASES

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Results/observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolic acids from propolis extract</td>
<td>Release of phenolic acids through a cellulose membrane from hydrogel (20% of Poloxamer 407 and 1.5% of carboxymethylcellulose sodium) containing propolis extract was almost total within 8 h. In contrast, the release of phenolic acids from absorption ointment (petroleum, lanolin and glycerol) and from w/o cream (Pionier PLW, Span 80 and water) was after 8 h, 8 and 22%, respectively Faster release from hydrogels than from emulsion-based and hydrophobic vehicles</td>
<td>10</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>Faster release from hydrogels based on carboxymethylcellulose sodium than from commercially available emulgel (Voltaren Emulgel) carboner hydrogel released 74.8% of diclofenac within 24 h while w/o cream consisted of 90% of hydrophobic phase only 1.5% of diclofenac at the same time 60 to 70% of fluconazole released from hydrophilic ointment with PEG vs. 25 to 45% from o/w cream</td>
<td>49</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Higher amount of fluconazole released from carborner hydrogels than from a hydrophilic cream with stearyl alcohol and sodium lauryl sulphate as emulsifiers Cumulative amount of ascorbic acid released through the nitrocellulose membrane from hydrogel based on xanthan gum with ceteareth-20 was approximately 3-fold and 10-fold higher than from cream o/w or cream w/o, respectively</td>
<td>46</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Faster release from hydrogels than from cream o/w</td>
<td>30</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Faster release from 5% hydrogels than from creams or absorption ointment</td>
<td>48</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Higher release from hydrogels with carborner or poloxamer than from cream</td>
<td>52</td>
</tr>
<tr>
<td>Dexpanthenol</td>
<td>Carborner hydrogel released 22.0% of indomethacin within 24 h, while w/o cream consisted of 90% of hydrophobic phase, only 1.4% of indomethacin</td>
<td>52</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Release rate was significantly higher from hydroxyethylcellulose hydrogel than from microemulsion (1.3-fold), microemulsion+silica (1.9-fold), emulgel+alginate sodium (2.1-fold) and cream+carborner (2.9-fold)</td>
<td>53</td>
</tr>
<tr>
<td>Diphenhydramine hydrochloride</td>
<td>4 to 5-fold higher release rate through the cellulose acetate membrane from 10% carborner hydrogels and PEG ointment than from hydrophobic cream or white petrolatum ointment</td>
<td>54</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Release rate from 1% semi-solid formulations through the cellulose acetate membrane or cellulose acetate membrane soaked with isopropyl myristate increased in the following order: o/w cream&lt;lyotropic liquid crystal&lt;hydrogel</td>
<td>55</td>
</tr>
<tr>
<td>Ketamine hydrochloride</td>
<td>Release rate through the cellulose acetate membrane soaked with isopropyl myristate increased with the following order: lyotropic liquid crystal&lt;o/w cream&lt;hydrogel</td>
<td>55</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>17.3-fold, 23.9-fold and 155.5-fold higher release from 2% carborner hydrogel than from o/w cream, w/o cream and absorption ointment, respectively</td>
<td>56</td>
</tr>
<tr>
<td>Tiaroprofenic acid</td>
<td>Faster release from 0.5% hydrogels than from creams w/o or o/w</td>
<td>57</td>
</tr>
<tr>
<td>Tetrapeptide AcPPYL</td>
<td>Release from hydrogels was faster than from emulsions and hydrophobic bases</td>
<td>58</td>
</tr>
</tbody>
</table>

Studies indicated that release of active substances from hydrophilic bases is faster than that from hydrophobic and emulsion bases.
acceptor fluid. Moreover, lipophilic substances can easily diffuse from deeper layers of the formulation to the surface directly contacting with the membrane (diffusion coefficients of lipophilic substances within hydrophobic bases are usually high). The release rate of hydrophobic benzophenone-3 ($\log P_{o/w} = 2.01$) from white petrolatum was higher than from o/w cream, w/o cream or hydroxyethylcellulose-based hydrogel. The higher release of hydrophobic prednicarbate ($\log P_{o/w} = 3.82$) from hydrophobic and hydrophobic emulsion bases than from hydrophilic ones was observed (o/w cream < absorption ointment < w/o cream < hydrogel). An interaction between the active substance and the components of the base is another factor affecting the release rate. Terpinen-4-ol was readily released from a hydrophobic base (absorption ointment) and a hydrophilic base (hydrogel) but poorly released from an amphiphilic cream. The possible reasons for reducing release rate of terpinen-4-ol from the cream are: formation of complexes between terpinen-4-ol and emulsifiers used in the base (cetostearyl alcohol, cetostearyl sulphate sodium), incorporation of terpinen-4-ol molecules into the droplets of the internal oil phase and lengthening terpinen-4-ol diffusion pathway.

The next factor influencing the release rate is a stability of the semisolid base system. Phase-separation of the formulation, which allows a direct contact between a phase with dissolved substance and membrane may cause increase in the rate of the release. This phenomenon was observed in the case of emulgels containing terpinen-4-ol as well as absorption ointment with flufenamic acid.

The viscosity of the semisolid formulation may affect the release rate as it determines the value of the diffusion coefficient of the active substance within the formulation. However, no correlation between the base viscosity and the release rate may be observed when different types of semisolid bases are compared. The release of diphenhydramine hydrochloride from a hydrogel based on hydroxyethylcellulose was two-fold higher than from a cream containing carbomer, even though the viscosity of the hydrogel was several times higher than that of the cream.

**IMPACT OF SEMISOLID BASE TYPE ON DERMAL AND TRANSDERMAL DELIVERY OF ACTIVE SUBSTANCES**

The release rate of the active substance from the base impacts skin penetration, permeation and retention. However, dermal and transdermal delivery of the active substance is much more complicated than its release. The skin structure is much more complex than that of an artificial porous membrane and the results of the release studies must be interpreted with caution. Although the release rate through an artificial porous membrane is usually highest when hydrophilic bases are used, the rate of the skin penetration, permeation and retention achieved with hydrophilic bases may be lower than that provided by emulsion or hydrophobic bases. The main reason of that observation is that the penetration of the acceptor fluid through the membrane into the semisolid base loses importance when the skin as a membrane is used. While the acceptor fluid readily penetrates through the porous artificial membrane...
into the semisolid preparation in release studies, it encounters the stratum corneum being a barrier for water and thus cannot achieve the formulation in skin permeation studies.

The stratum corneum is a selectively permeable barrier whose properties depend on many endogenous factors as well as are influenced by components of the topical formulations. The impact of semi-solid base components on the skin, in particular on the stratum corneum, includes: hydration and incorporation of some semisolid base components into the intercellular cement lipids leading to increased disordering of lamellar and lateral packing of lipids and/or increased solubility of the active substance within the stratum corneum lipids. These interactions may alter the stratum corneum permeability (influence on skin penetration and permeation rate) or change the value of skin/base partition coefficient (influence on the rate of the skin retention). The degree of the interaction between the base components and the skin can be assessed by a comparative analysis of the release rate and the skin permeation rate of the active substance. The stages of skin permeation once the active substance overcomes the stratum corneum are similar to the in vitro release through the artificial membrane whose properties resemble these of the deeper layers of the skin. These layers are more hydrophilic and permeable than the stratum corneum.

The literature reports many studies in which the effectiveness of dermal and transdermal skin delivery of active substances from emulsion-based formulations is compared with that from hydrophilic ones. The aspects that must be taken into account when deciding which type of the base (emulsion or hydrophilic) should be chosen in a specific case are: physicochemical characteristics of the active substance, solubility of the active substance in the base, concentration of an active substance dissolved form, thermodynamic activity of the active substance in the base, the presence of base components, which can serve as solvents or solubilizers as well as penetration enhancers of the active substance.

Results of many studies demonstrated that semi-solid preparations containing dissolved form of the active substance are usually more effective than formulations in which the active substance is suspended, regardless of the base type (emulsion or hydrophilic). This aspect becomes even more important, when the active substance is hydrophobic; hydrophilic active substances are in dissolved form in both, the emulsion and the hydrophilic bases. The rate of hydrocortisone permeation through the nylon membrane, the mouse skin as well as EpiDerm was significantly higher from hydrogels (hydrocortisone in dissolved form) than from creams (hydrocortisone suspended).

Presence of base components with dual function as a solvent and an absorption promoter may provide increased solubility of the moderately hydrophobic active substances as well as the active substances insoluble in water both in the formulation and within the lipids of stratum corneum into which these components are incorporated. The use of emulsion base gives the possibility to incorporation more types of these solvents than hydrophilic base. Both water-miscible (e.g. propylene glycol) and hydrophobic (e.g. isopropyl myristate) solvents may be incorporated into emulsion bases but only hydrophilic solvents may be introduced into hydrophilic bases. The possibility of using hydrophobic solvents as well as emulsifiers that may act as solubilizing agents makes the introduction of hydrophobic substances in dissolved form easier in the case of emulsion bases than in the case of hydrophilic bases. Emulsifiers used in emulsion bases can penetrate into the stratum corneum lipids and act as penetration enhancers changing the stratum corneum lipid organization as well as increasing solubility of active substance within the stratum corneum lipids.

For these reasons, when the active substance is hydrophobic, the emulsion base may be more effective carrier than hydrophilic one not containing any hydrophobic solvents or emulsifiers. Permeation of retinol through the human skin was 4-fold higher from a cream than from an aqueous-ethanolic hydrogel. The skin retention of propolis extract components (ferulic acid, caffeic acid, vanillic acid, vanillin) was greater from w/o cream than from hydrogel. Ferulic acid as well as coumaric acid was not able to penetrate into the dermis from hydrogels. Vanillic acid showed higher penetration into the dermis from w/o cream than from hydrogel. Caffeic acid penetrated into the stratum corneum when w/o cream was used but it was not able to penetrate into the stratum corneum from hydrogel.

Liquid hydrophobic substances miscible with the stratum corneum intercellular lipids can show better penetration into the skin from hydrophilic bases in which they are dispersed than from emulsion bases. Skin retention of hydrophobic liquid terpenes: terpinen-4-ol and linalool, was higher from hydrogel than from
o/w emulsion, 3.5-fold and 3-fold, respectively. The author explains this with favourable skin/hydrophobic terpenes partition coefficient[65]. The permeation rate through human epidermis of terpinen-4-ol was almost 3-fold greater from 5% hydrogel than from 5% o/w cream[39]. The emulsifiers used in the o/w emulsion can contribute to enclose the terpenes in micelles[3]. The terpenes enclosed in the micelles cannot directly contact with the skin and thus cannot penetrate into the skin.

Higher skin penetration from creams than from hydrogels, especially in the case of hydrophilic substances, may be due to the increased level of the stratum corneum hydration provided by creams. Creams do not dry out as rapidly as hydrogels as they contain lipophilic components forming an occlusive layer preventing water from evaporation. The occlusive properties give cream the advantage over hydrogel when semisolid formulation is applied in a thin layer (finite dose) under non-occlusive conditions[36]. It was demonstrated that MetroCream containing metronidazole provided approximately 2-fold greater epidermal retention, higher retention within the dermis, and almost 10-fold higher skin permeation than MetroGel hydrogel. The formulations were applied in a finite dose manner under non-occlusive conditions[66].

The higher dermal and transdermal delivery of active substances from hydrophilic bases than from emulsion bases may be due to the higher release rates provided by hydrophilic bases. In study comparing hydrogels with emulsion bases, hydrogels provided higher release rates as well as higher therapeutic efficacy of two model drugs: ketamine hydrochloride (hydrophilic substance) and piroxicam (hydrophobic substance)[55]. The efficacy of formulations with ketamine hydrochloride in the induction of anaesthesia in rats increased in the following order: o/w cream<lyotropic liquid crystal<hydrogel[55]. The piroxicam antiinflammatory efficacy expressed as the ability to reduce edema induced by carrageenan injection was higher for a hydrogel than for an emulsion base[55]. Carboxymethylcellulose-based hydrogel provided a better permeation of diclofenac through the rat skin than Voltaren Emulgel[60].

The advantage of a hydrogel over a cream can be also provided by the use of gelling agents causing bioadhesion of the formulation to the skin as well as serving as absorption promoters. Retention of clobetasol-17-propionate was significantly higher from a gel based on sodium deoxycholate (absorption promoter) than from a cream or a chitosan gel[67].

On the one hand creams increase the level of the stratum corneum hydration more efficiently than hydrogels, on the other hand hydrogels usually provide faster release than creams. In consequence, many studies have demonstrated that skin delivery of active substances from creams and hydrogels is comparable. (-) Epigallocatechin-3-gallate stratum corneum penetration from o/w cream and from hydrogel did not differ significantly[63]. Skin retention of mometasone furoate within the dermis from cream was not significantly higher than from hydrogels (sodium deoxycholate-based and chitosan-based)[67]. Caffeine skin permeation rates and its penetration into the subcutaneous tissue rates from cream and from gel were comparable[68]. The permeation rate of psoralen through the rat epidermis was only slightly higher for hydroxypropylcellulose hydrogel than for o/w cream, cumulative amounts of psoralen that penetrated within 3 h were as follows: 115.21±4.94 μg/cm² for hydrogel and 101.82±4.89 μg/cm² for cream[69].

The next aspect of studies on dermal and transdermal delivery of active substances from semisolid bases is an evaluation of effectiveness of hydrophobic bases. Among hydrophobic bases the most widely used in magisterial formulations is Vaseline petroleum ointment base. In general, the active substances both, hydrophilic and lipophilic, are poorly absorbed through the skin, when they are applied in Vaseline petroleum ointment base. The main reason of active substances poor skin absorption is poor release of active substances from hydrophobic Vaseline petroleum jelly ointment bases. The hydrophilic substances dissolution is not achieved when they are incorporated into the hydrophobic bases and thus release and diffusion to the surface of the skin from the hydrophobic bases is impeded in the case of these substances. In contrast, lipophilic substances may be dissolved or partially dissolved in Vaseline petroleum jelly. However, these lipophilic substances have low skin/base partition coefficient, which determines their affinity to the formulation and poor release[21]. The results of studies confirming low dermal and transdermal delivery of active substance from hydrophobic and absorption ointments are summarized in Table 4.

Although the Vaseline petroleum base do not usually provide enhanced skin and transdermal delivery, it turned out to be an effective carrier for some hydrophobic substances, which may be partially dissolved in the
petrolatum base. The retention of benzophenone-3 (log $P_{o/w}=3.6$, Pub Chem) within the epidermis and dermis was 2.5-fold higher for petrolatum-based ointment than for o/w cream.[70] Benzophenone-3 showed 2.5-fold higher permeation through the human skin from white petrolatum ointment than from hydroxyethylcellulose hydrogel and 1.25-fold higher than from o/w cream.[60].

Hydrophobic absorption ointments were found to be suitable bases for salicylic acid.[71-73]. Hydrophobic and absorption ointments with corticosteroids have higher potencies than creams and steroid lotions at the same active substance concentration (Table 1).[13]. The rate of clobetasol propionate (log $P_{o/w}=3.8$, Pub Chem) permeation through the skin was 10-fold higher from ointment than from the emollient cream and 3-fold higher than from gel and cream[74].

Vaseline petrolatum adheres strongly to the skin and thus its use provides prolonged contact of the formulation with the skin[27]. The effectiveness of petrolatum-based ointments as active substances carriers may also result from the occlusive properties of these bases. White petrolatum provides increase in the hydration of the stratum corneum and thus enhance skin penetration and permeation of active substances[1,21,27]. The modern type of hydrophobic base is oleogel, which may be an effective carrier of active substances. Oleogels were found to enhance both skin retention and permeation of many active substances[23,75,76]. A proper selection of ingredients: oils, emulsifiers, hydrophobic solvents of active substance plays an important role in the development of oleogel providing effective delivery of active substances to the skin[23,75-77]. Oleogel based on 12-hydroxystearic acid, isopropyl myristate, and oleic acid provided 4-fold higher enrofloxacin (log $P_{o/w}=3.1$) permeation through the porcine ear skin than commercial cream Pentravan[76]. The increased rate of enrofloxacin skin permeation from oleogel could arise from the presence of absorption promoters (oleic acid

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**TABLE 4: DERMAL AND TRANSDERMAL DELIVERY OF ACTIVE SUBSTANCES FROM HYDROPHOBIC BASES**

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Results/observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flufenamic acid</td>
<td>Skin retention of flufenamic acid within the stratum corneum from absorption ointment was comparable to that from w/o cream. However, the amount of the active substance delivered to the deeper layers of the skin within 3 h was approx. 1.5-fold higher when cream was applied</td>
<td>4</td>
</tr>
<tr>
<td>Sodium nonivamide acetate</td>
<td>No permeation through the skin was observed in the case of simple ointment; the skin permeation was provided by o/w creams</td>
<td>34</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Petrolatum-based hydrophobic ointment showed 10-fold lower paromomycin dermal retention than o/w cream</td>
<td>42</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>The effectiveness of the 3% white petrolatum-based ointment in reduction of carrageenan-induced edema in mice was 5-fold lower than the effectiveness of hydrophilic vehicles (3% carbomer hydrogel and 3% PEG ointment)</td>
<td>54</td>
</tr>
<tr>
<td>Sulisobenzone</td>
<td>Permeation through the human skin from a white petrolatum-based ointment was 1.5-fold lower than from o/w cream as well as from hydroxyethylcellulose-based hydrogel</td>
<td>60</td>
</tr>
<tr>
<td>Benzophenone-3, ethylhexyl methoxycinnamate, butyl methoxydibenzoyl methane, ethylhexyl salicylate, homosalate</td>
<td>White petrolatum-based ointment limited skin penetration of hydrophobic sunscreens. Approx. 4-fold higher penetration of these substances through the stratum corneum was demonstrated in vivo</td>
<td>70</td>
</tr>
<tr>
<td>Benzophenone-3, 2-ethylhexylsalicylate, 2-ethylhexyl-4-methoxycinnamate</td>
<td>Penetration the stratum corneum was lower for white petrolatum ointment base than for o/w emulgel</td>
<td>71</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Xylocaine ointment showed 2.5-fold lower penetration into the stratum corneum than Xylocaine cream (tape-stripping method). Amount of lidocaine which permeated through the skin from the ointment was 4-fold lower than from cream (microdialysis method in vivo)</td>
<td>72</td>
</tr>
</tbody>
</table>

Dermal and transdermal delivery of active substances is poor from hydrophobic bases. The retention of benzophenone-3 (log $P_{o/w}=3.6$, Pub Chem) within the epidermis and dermis was 2.5-fold higher for petrolatum-based ointment than for o/w cream[70]. Benzophenone-3 showed 2.5-fold higher permeation through the human skin from white petrolatum ointment than from hydroxyethylcellulose hydrogel and 1.25-fold higher than from o/w cream[60]. Hydrophobic absorption ointments were found to be suitable bases for salicylic acid[71-73]. Hydrophobic and absorption ointments with corticosteroids have higher potencies than creams and steroid lotions at the same active substance concentration (Table 1)[13]. The rate of clobetasol propionate (log $P_{o/w}=3.8$, Pub Chem) permeation through the skin was 10-fold higher from ointment than from the emollient cream and 3-fold higher than from gel and cream[74]. The modern type of hydrophobic base is oleogel, which may be an effective carrier of active substances. Oleogels were found to enhance both skin retention and permeation of many active substances[23,75,76]. A proper selection of ingredients: oils, emulsifiers, hydrophobic solvents of active substance plays an important role in the development of oleogel providing effective delivery of active substances to the skin[23,75-77]. Oleogel based on 12-hydroxystearic acid, isopropyl myristate, and oleic acid provided 4-fold higher enrofloxacin (log $P_{o/w}=3.1$) permeation through the porcine ear skin than commercial cream Pentravan[76]. The increased rate of enrofloxacin skin permeation from oleogel could arise from the presence of absorption promoters (oleic acid...
Microemulsion-based semi-solid preparations often provide better delivery of active substances to the skin than conventional creams, ointments or hydrogels. It is due to the high concentration of emulsifiers and co-surfactants strongly affecting the skin barrier. Emulsifiers and co-surfactants included in the microemulsions may provide enhanced solubility of the active substance e.g. solubility of pseudolaric acid B was 890-fold higher in microemulsion than in water\textsuperscript{43}. Similarly, the solubility of hydrocortisone acetate was also higher in the microemulsion than in hydrophobic ointments\textsuperscript{77}. The small size of the microemulsion droplets provides their easy penetration into the \textit{stratum corneum} lipids\textsuperscript{35}. The active substance dissolved in the lipophilic phase of the microemulsion is easily delivered into the lipids of the \textit{stratum corneum}. Hydrophilic phase of the microemulsion is responsible for hydration of the \textit{stratum corneum} and thus increased active substance penetration. The results of many studies have showed that microemulsion-based semisolid bases provide more effective skin and transdermal delivery than conventional semisolid bases (Table 5)\textsuperscript{77,79}.

The proper selection of semisolid base type (hydrophobic, hydrophilic, emulsion) as well as its components are crucial for the effective skin and transdermal delivery of the active substance. Well characterized properties of the active compound, the semisolid base and the skin barrier (especially the \textit{stratum corneum}) may help to predict the cutaneous and percutaneous absorption of the active substance. However, the difficulties in predictability of skin and transdermal delivery are usually seen due to the fact that characteristics of the active substance, vehicle and the skin should be considered as a kind of multifactorial system, not separately. The base ingredients may interact with the active substance (solubilizing effect, complexes formation) as well as with the structure of the \textit{stratum corneum} as percutaneous absorption promoters.

**Conflict of interest:**

The authors report no declarations of interest.

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Nil.

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**TABLE 5: MICROEMULSION SEMISOLID BASES AS DERMAL AND TRANSDERMAL CARRIERS**

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Results/observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudolaric acid B</td>
<td>The skin permeation rate was higher from microemulsion gel (1.844 µg/cm(^2)/h) than from a hydrogel (0.517 µg/cm(^2)/h). The skin retention after 24 h was also higher from microemulsion gel (4.46 µg/cm(^2)) than from a hydrogel (1.06 µg/cm(^2))</td>
<td>43</td>
</tr>
<tr>
<td>Caffeine</td>
<td>The microemulsion provided significantly higher delivery to subcutaneous tissue - 1.23-fold higher than cream or gel</td>
<td>68</td>
</tr>
<tr>
<td>Hydrocortisone acetate</td>
<td>The permeation rate of hydrocortisone acetate through the porcine ear skin (J) was several times higher from hydrophilic microemulsions (J= 130±10 µg/cm(^2)/h) and hydrophobic microemulsions (J= 13±5 µg/cm(^2)/h) than from hydrophobic ointment (J= 0.4±0.2 µg/cm(^2)/h) or hydrogel (J= 2±1 µg/cm(^2)/h)</td>
<td>77</td>
</tr>
<tr>
<td>5-fluorouracil,</td>
<td>Higher penetration of 5-fluorouracil (log (P_{o/w}) = -0.97) and testosterone (log (P_{o/w}) = 3.22) through the \textit{stratum corneum} of the human skin for microemulsion than for other formulations (gel, w/o emulsion, o/w emulsion, oleogel)</td>
<td>78</td>
</tr>
<tr>
<td>testosterone</td>
<td>The microemulsion provided 6-fold higher penetration of nifedipine than o/w cream. Retention of nifedipine was approx. 2-fold higher within epidermis and approx. 1.4-fold higher within the dermis from microemulsion than from o/w emulsion</td>
<td>79</td>
</tr>
</tbody>
</table>

**Microemulsion semisolid bases are better dermal and transdermal carriers** (5%) and isopropyl myristate (84%) in the base\textsuperscript{76}.


