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Veterinary drug delivery: potential for skin penetration enhancement

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Abstract

A range of topical products are used in veterinary medicine. The efficacy of many of these products has been enhanced by the addition of penetration enhancers. Evolution has led to not only a highly specialized skin in animals and humans, but also one whose anatomical structure and skin permeability differ between the various species. The skin provides an excellent barrier against the ingress of environmental contaminants, toxins, and microorganisms while performing a homeostatic role to permit terrestrial life. Over the past few years, major advances have been made in the field of transdermal drug delivery. An increasing number of drugs are being added to the list of therapeutic agents that can be delivered via the skin to the systemic circulation where clinically effective concentrations are reached. The therapeutic benefits of topically applied veterinary products is achieved in spite of the inherent protective functions of the stratum corneum (SC), one of which is to exclude foreign substances from entering the body. Much of the recent success in this field is attributable to the rapidly expanding knowledge of the SC barrier structure and function. The bilayer domains of the intercellular lipid matrices within the SC form an excellent penetration barrier, which must be breached if poorly penetrating drugs are to be administered at an appropriate rate. One generalized approach to overcoming the barrier properties of the skin for drugs and biomolecules is the incorporation of suitable vehicles or other chemical compounds into a transdermal delivery system. Indeed, the incorporation of such compounds has become more prevalent and is a growing trend in transdermal drug delivery. Substances that help promote drug diffusion through the SC and epidermis are referred to as penetration enhancers, accelerants, adjuvants, or sorption promoters. It is interesting to note that many pour-on and spot-on formulations used in veterinary medicine contain inert ingredients (e.g., alcohols, amides, ethers, glycols, and hydrocarbon oils) that will act as penetration enhancers. These substances have the potential to reduce the capacity for drug binding and interact with some components of the skin, thereby improving drug transport. However, their inclusion in veterinary products with a high-absorbed dose may result in adverse dermatological reactions (e.g., toxicological irritations) and concerns about tissue residues. These are important considerations when formulating a veterinary transdermal product when such compounds are added, either intentionally or otherwise, for their penetration enhancement ability.

Keywords: Penetration enhancers; Animal health; Transdermal drug delivery; Absorption enhancement

Contents

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1. Introduction

Many veterinary drugs are being formulated into topical products and are being applied to animals. In order to promote drug penetration through the skin these products frequently include penetration enhancers, which act on the stratum corneum (SC), the major barrier layer in the skin [1,2]. Skin is a complex, dynamic organ that has many functions that go far beyond its role as a barrier to the environment. The skin is an attractive potential route for drug administration since the first-pass hepatic metabolism of drugs intended for systemic action may be avoided (although skin metabolism may be a problem), thus offering potentially decreased drug dosages and reduced side effects [3–6]. Many of the drugs under investigation, in particular in human medicine, but also in the field of veterinary medicine, do not have the ability to cross the skin in sufficient amounts, and ways must be found to modify the diffusional barrier of the skin. Penetration enhancers are substances that can partition into, and interact with, skin constituents (mainly the intercellular lipid lamellae) and induce a temporary and reversible decrease in skin barrier properties. Much of the work on skin permeation enhancement has been directed towards improving human transdermal drug delivery and an understanding of the differences in skin morphology and transport properties between species is necessary before a reasoned appraisal of their veterinary usefulness can be made. This chapter will outline differences in species morphology and skin permeability, and the means whereby the barrier properties of the skin can be modified using chemical penetration enhancers from a veterinary point of view. The chemicals used as potential skin permeation enhancers are discussed and the chapter ends with a paragraph regarding the formulation aspects of veterinary pharmaceutics.

2. Species variation in skin anatomy

The skin of animals of veterinary medicine interest (most domestic animals, including companion animals, farmed and those used in experimental studies) is anatomically divided into the outermost layer, the epidermis, and an underlying dermis. Beneath the dermis lies the hypodermis or subcutaneous layer, which anchors the dermis to the underlying muscle or bone. Studies in dermatology, cutaneous pharmacology, and percutaneous absorption involve experiments in which skin from different animal species and body regions is used. Species–species extrapolation of dermal absorption data is difficult, and this is usually because of differences in epidermal anatomy and physiology between species (e.g., skin thickness, number of cell layers, sebaceous secretions) [7]. Laboratory animals, such as rats, mice and rabbits, have more hair follicles than humans and lack sweat glands [8]. Another example is the different hydration effect between hairless mouse and human skin [9,10]. Larger animals, including human, share more similarities in their skin anatomical features. The

most important differences in terms of barrier function, however, are the presence of hairs, the sebum and the SC.

Hair and wool can be considered to be the first absorption barrier to applied compounds in most animal species. It is possible that a permeation enhancement effect may occur within the hair follicles. It has been estimated that there are up to 10 000 follicles per square centimeter in some regions of merino sheep [11]. Accordingly, the follicular route for skin permeation may be significant, and it is likely that penetration enhancers will interact with the sebum present in the follicles and either increase or decrease the amount of applied formulation able to penetrate into the follicle, with obvious consequences for skin absorption. Sheep wool and cattle hairs are coated with an emulsion of sweat and sebum that is formed in the hair follicle infundibula [12]. The wool of the sheep has a continuous coat of this emulsion, whereas in cattle only the lower part of the hair is coated. Walters and Roberts [1] have reported that this emulsion may act as a solvent for many topically applied chemicals and that diffusion within the emulsion always competes with diffusion through the skin. The emulsion itself may also be capable of lateral movement in sheep [13]. In cattle, where no intact emulsion layer is present, the lipids on the skin act more as a surface sealant and are probably not involved in lateral transfer of topically applied drugs or pesticides.

The basic architecture of the integument is similar in all mammals. However, structural differences in the arrangement of hair follicles and hair follicle density exist between domestic and laboratory animals. The hair density in pig and human is sparse compared to that of the rodent. Hair follicles, sebaceous glands and sweat glands are often envisioned as shunt channels through the SC that facilitate absorption of topical compounds, thus bypassing the rate-limiting SC barrier. The comparative permeability of human and animal skin may be related to the diffusion of compounds through these skin appendages. One must remember that even when a compound traverses the skin via hair follicles, passage through the SC also occurs. It is probable that any increase in absorption attributed to the appendage results from the increased surface area associated with invaginations of the stratum corneum, therefore, areas covered with hair have a greater skin surface area available for transdermal absorption. Investigators have speculated that transappendageal transport of drugs in cattle and sheep may be more important than transport through the transcellular or intercellular pathway. Pitman and Rostas [12] conducted percutaneous absorption experiments that showed that levamisole, a polar drug, had a significantly higher rate of penetration in excised cattle skin than in excised human skin. This effect may be based on the difference in density of hair follicles between humans ($40–70/cm^2$) and cattle ($890/cm^2$) and the presence of emulsions on cattle skin. It should be noted that frozen skin sections were used in these studies, and the data may not represent percutaneous absorption in living skin sections. Hair follicle-rich areas have been shown to allow greater penetration of some pesticides [14]. The importance of the hair follicle in percutaneous absorption was evaluated in a model of regrown skin without hair follicles dorsally on the hairless rat. Diffusion cell studies were used to compare the absorption of tritiated hydrocortisone, niflumic acid, caffeine, and *p*-aminobenzoic acid in intact and appendage-free skin. These studies confirmed a higher rate of diffusion in intact skin and suggested that hair follicles acted as the major absorption pathway [15]. Other investigators have also studied this phenomenon [16,17].

The endpoint of epidermal differentiation is the formation of the SC, a matrix of keratinized cells (corneocytes) surrounded by lipids. The SC has an exceptionally low permeability and one explanation (at least in part) may be the highly tortuous nature of the extracellular lipid domain through which most compounds are believed to permeate. The SC thickness in most domestic animal species is reasonably uniform, at approximately 30 μm (Table 1). In the pig, epidermal and SC thickness are almost twice that in cattle and horses. Stratum corneum thickness in sheep is similar to that in cattle, while the epidermis in sheep is only half as thick [7]. The SC is primarily a lipophilic barrier, which prevents excessive water loss to the environment and protects against the penetration of chemicals applied either accidentally or deliberately to the skin. The distribution and types of lipid present in SC has not been fully investigated. During mammalian epider-

Table 1
Acetone-extracted skin surface lipids and stratum corneum thickness for several species

Species	Lipids ($\mu g/cm^2$)	Stratum corneum thickness (μm)
Hairless mouse	212.4[a]	8.8[a]
Hairless rat	273.3[a]	15.4[a]
Guinea pig	224.7[a]	18.6[a]
Dog	NR	19.9[a]
Pig	130.0[a]	17.5[a]
Human	60.5[a]	18.2[a]
Sheep	NR	31.4[b]
Cattle	NR	30.9[b]

NR, not reported.
[a] Sato et al. [24].
[b] Pitman and Rostas [12].

mal differentiation, characteristic changes in lipid composition occur, consistent with the requirement for cutaneous waterproofing. In porcine, murine and human epidermis, these changes include a deletion of phospholipids and glycosphingolipids, and enrichment in the ceramide, cholesterol, and free fatty acid fractions [18,19]. Of the major SC lipids, it is the sphingolipids that are of major importance for the epidermal barrier [20,21]. Sphingolipids constitute the majority of long-chain, saturated fatty acids [22]. Cetaceans (dolphins, whales), which have far less stringent barrier requirements than do their terrestrial counterparts, display much shorter chain-length, *N*-acetylated fatty acids [23].

3. Penetration enhancers

For many yeras, scientists thought that the skin formed an impervious barrier to the outside world. Now we know that the complexity of the dermal barrier is only beginning to be understood by researchers. The highly organised structure of the SC forms an effective barrier to the penetration of a diverse range of substances which must be modified if poorly penetrating drugs are to be administered. The transdermal route for systemic drug delivery has received considerable attention in recent years [25–34]. However, a major problem encountered using this route of administration is the low permeability of the skin. One way to reduce this problem and improve the bioavailability following topical application of drugs is to include a penetration enhancer in the formulation. Penetration enhancers, accelerants or promoters are thought to interact with some components of skin causing increased fluidity in the intercellular lipid lamellae, the SC to swell and/or leach out some of the structural components and thus increase drug penetration through the barrier membrane [3,35–41]. These substances may also reduce the capacity for drug binding to the skin, thereby improving drug transport. Consequently, penetration enhancer use has become more prevalent and is a growing trend in transdermal drug delivery. Ideal penetration enhancers should have the following characteristics [3,42]:

1. be both pharmacologically and chemically inert and chemically stable;
2. have a high degree of potency with specific activity and reversible effects on skin properties;
3. show compatibility with formulation and system components;
4. be nonirritant, nonsensitizing, nonphototoxic, and noncomedogenic;
5. be odorless, tasteless, colorless, and cosmetically acceptable;
6. have a solubility parameter that approximates that of the skin.

Despite the wide range of materials proposed as penetration enhancers, no chemical has yet been found which possesses all of the above attributes. Some substances have shown sufficient promise for a limited clinical use. However, a more cautious approach now tempers the initial enthusiasm for some enhancers.

The first recognized penetration enhancers were simple disruptive, keratolytic agents that permanently destroyed the integrity of the SC and were generally nonspecific in the penetration enhancement of all chemicals. The most widely used penetration enhancers were aprotic solvents such as dimethylsulfoxide (DMSO), dimethylformamide, and dimethylacetamide [43]. They accelerated the permeation of many drugs, including antifungal agents, antibiotics, barbiturates, steroids, and local anaesthetics. However, initial optimism for these solvents was reduced because of toxicity, irritancy, and odour [44]. Several diverse chemical groups have been shown to act as

penetration enhancers. Many known and newly developed chemicals have been investigated for their ability to enhance the percutaneous penetration of drugs (Table 2). Examples are solvents such as water, alcohols, propylene glycol [67,68], Azone and its derivatives [69,70], dioxolane derivatives [71], surfactants [72,73], fatty acids [74,75], terpenes [76], sugar esters, and miscellaneous materials such as urea and its derivatives [77,78]. The literature reveals that numerous classes of chemical compounds have been used or assessed for their ability to promote or enhance the permeation of molecules through the skin. Table 3 provides an overview of some of the different chemical classes and examples of materials within specific classes.

4. Mechanisms of action of penetration enhancers

The basic requirements of a transdermal drug delivery system is for the drug to penetrate the SC, the outermost layer of the skin, which is comprised of keratin-rich cells embedded in multiple lipid bilayers. In general, the drug has three potential routes of entry to the inner tissue of the skin. The

Table 2
Diverse chemical groups that have been shown to act as penetration enhancers

Enhancer	Permeant	Species	References
Ethanol	Testosterone	Human	Mazer et al. [45] Yum et al. [46]
Ethanol, sucrose laurate	Oestradiol	Human, hairless mouse, snake, rabbit	Pershing et al. [47]; Liu et al. [48]; Megrab et al. [49]; Vermeire et al. [50]
Ethanol	Nitroglycerin	Human	Berner et al. [51]
Ethanol, terpene	TRH	Human	Magnusson et al. [52]
Ethanol, fatty acids	Acyclovir	Human, hairless mouse, rat	Cooper et al. [53] Okamoto et al. [54]
Ethanol, polyethylene glycol	Ibuprofen	Hairless rat,	Hatanaka et al. [55]
Ethanol	Nicardipine	Rhesus monkeys	Yu et al. [56]
Ethanol	Ketorolac	Rhesus monkey	Yu et al. [56]
Propylene glycol	Lidocaine	Hairless mouse	Sarpotdar and Zatz [57]
Azone, propylene glycol, polyethylene glycolon	Trifluorothymidine	Human, rat	Sheth et al. [58]
Fatty acids, fatty alcohols, surfactants, sulfoxides, amides	Nalaxone	Human	Aungst et al. [59]
Azone, DPY, DPI, DMEA, terpene, *N*-methyl-2-pyrrolidone, polyethylene glycol, 1-(*N*,*N*-dimethylamino)-2-propanol dodecanoate	Hydrocortisone	Human, hairless mouse, hairless rat, snake	Michniak et al. [60] Buyuktimkin et al. [61] Fuhrman et al. [31] El-Kattan et al. [41]
Propylene glycol, Azone	Dihydroergotamine	Human, hairless mouse, rat, rabbit, guinea pig	Niazy [62]
Ethanol, propylene glycol, Azone, *n*-decylmethyl sulphoxide, dodecyl *N*,*N*-dimethylamino acetate, *N*,*N*-dimethylamino isopropionate, oleic acid, lauryl alcohol	5-Flurouracil	Human, hairless mouse, snake, rabbit	Goodman and Barry [63] Touitou and Abed [64] Hirvonen et al. [65] Turunen et al. [66]

Table 3
Types of chemical classes that act as penetration enhancers[a]

Classes	Examples	References
Alcohols	Alkanol: ethanol, propanol, butanol, pentanol, hexanol, octanol Fatty alcohol: caprylic, decyl, lauryl, stearyl	Aungst et al. [59]; Berner and Puchun [67]; Tsuzuki et al. [79]; Friend et al. [80]
Alkanones	*N*-heptane, *N*-octane, *N*-nonane, *N*-decane, *N*-undecane	Hori et al. [81]
Amides	Cyclic amide: 1-dodecylazacycloheptane-2-one (Azone) Pyrrolidone derivate: 1-methyl-2-pyrrolidone Urea, dimethylacetamide, diethyltoluamide, dimethylformamide	Hoogstaate et al. [69]; Hadgraft et al. [70]; Williams [77]; Wong and Rytting [78]; Feldman and Maibach [82]; Wong et al. [83]; Sasaki et al. [84]
Fatty acids	Linear: heptanoic, lauric, myristic, oleic, stearic, valeric Branched: isovaleric, isostearic, neoheptanoic, neopentanoic	Aungst et al. [59]; Tanojo and Bodde [74]; Kandimalla et al. [75]; Aungst [85]
Fatty acid esters	Alkyl: butyl acetate, ethyl acetate, ethyl oleate, methylvalerate Aliphatic-isopropyl n-butyrate, isopropyl n-decanoate	Sato et al. [24]; Friend et al. [86]
Organic acids	Citric and succinic acid, salicylic acid and salicylates	Sugibayashi et al. [87]
Polyols	Butanediol, glycerol, hexanetriol, propylene glycol	Bendas et al. [68]; Mollgaard and Hoelgaard [88]
Sulfoxides	Decylmethylsulfoxide, dimethylsulfoxide	Scheuplein and Blank [89]
Surfactants	Anionic: sodium laurate, sodium lauryl sulfate Cationic: benzalkonium chloride, cetyltrimethyl ammonium bromide, tetradecyltrimethylammonium bromide Nonionic: polyoxyethylene alkyl ethers, poloxamers, polysorbates. Bile salts: sodium cholate, glycholic	Carelli et al. [38]; Black [72]; French et al. [73]; Shen et al. [90]; Chowhan and Pritchard [91]; Aoyagi et al. [92]; Tan et al. [93]; Mahajour et al. [94]
Terpenes	Alcohols: α-terpineol, carvol, terpinene-4-ol Hydrocarbons: α-pinene, β-carene, D-limonene Ketones: carvone, menthone, piperitone, pulegone Oils: anise, chenopodium, eucalyptus, ylang ylang Oxides: 1,8-cineole, cyclohexene oxide, limonene oxide	El-Kattan et al. [41]; Magnusson et al. [52]; Haschida and Yamashita [76]; Williams and Barry [95]; Obata et al. [96]; Cornwell and Barry [97]; Kayama et al. [98]

[a] Adapted from [5].

different pathways are through the hair follicles with their associated sebaceous glands, via the sweat ducts, or across the stratum corneum between these appendages (intracellular- or transcellular route). Initially the drug must be delivered from an appropriate vehicle from which the substance can partition into the skin. The drug must then diffuse through the hydrophilic and/or lipophilic environment of the SC to the deeper epidermal layers and to the dermis. For the molecules reaching these highly permeable vascular regions would then be absorbed into the systemic circulation. However, for many drugs the transdermal fluxes are reported to be low. Consequently, it is advantageous to facilitate the transdermal transport by the use of penetration enhancers. The domain mosaic model proposed by Forslind [99] account for both the barrier function of the skin and the hydrophilic and hydrophobic pathways of solute transport through the skin barrier. This model depicts the bulk of the lipids as segregated into crystalline/gel domains bordered by 'grain borders' where lipids are in the liquid crystalline state. Such an arrangement is said to provide for an effective 'watertight' barrier that allows corneocytes to take up water in amounts sufficient to keep them moistened and to maintain the necessary mechanical properties permitting bending and stress imposed on the skin surface. The liquid character of the 'grain border' represents areas where hydrophilic and hydrophobic molecules may diffuse through the membrane on downhill gradients. Solutes are thought to diffuse through the fluid 'grain borders'.

The exact mechanisms by which many penetration enhancers function have not been clearly elucidated;

it is almost certain that they will have multiple effects once absorbed into the SC. Williams and Barry [95] introduced the lipid protein partitioning (LPP) theory to describe the modes of action of penetration enhancers. According to the theory, enhancers would act by one or more of three main mechanisms: (1) disruption of the highly ordered structure of SC lipid with an increase in intercellular diffusivity; (2) interaction with intracellular protein to enhance penetration through the corneocytes; (3) improvement in partitioning of a drug, coenhancer, or cosolvent into the SC.

Menon et al. [100] and Roberts et al. [101] extended the LPP model to recognise: (4) disruption of the corneocyte envelope by caustic agents such as phenol, in high concentrations and in certain vehicles and hydrocarbons; (5) effects on proteic junctions, such as desmosomes, involved in squamae cohesion; (6) alteration of the partitioning between SC components and the lipid in the diffusion pathway.

The model of the possible process of solvent enhancement of solute penetration through SC is shown in Fig. 1 [100]. The initial effect of the vehicle is the entry into intercellular and/or corneocyte envelope lipids with the enhancer/solvent determining the chemical potential of solute to partition from the vehicle into the lipids (1). Solute and/or solvent diffuse through the lipid region (2) and will then increase the fluidity of the intercellular or corneocyte envelope lipids by interaction with the lipid tails (lipophilic enhancer (i) and/or, with the polar head groups (polar enhancers (ii)). This leads to extraction of lipids (iii) and/or change in polarity (iv) of the intercellular and/or corneocyte envelope lipids. These effects may then result in formation of pools/vesicles through associations of polar solvents,

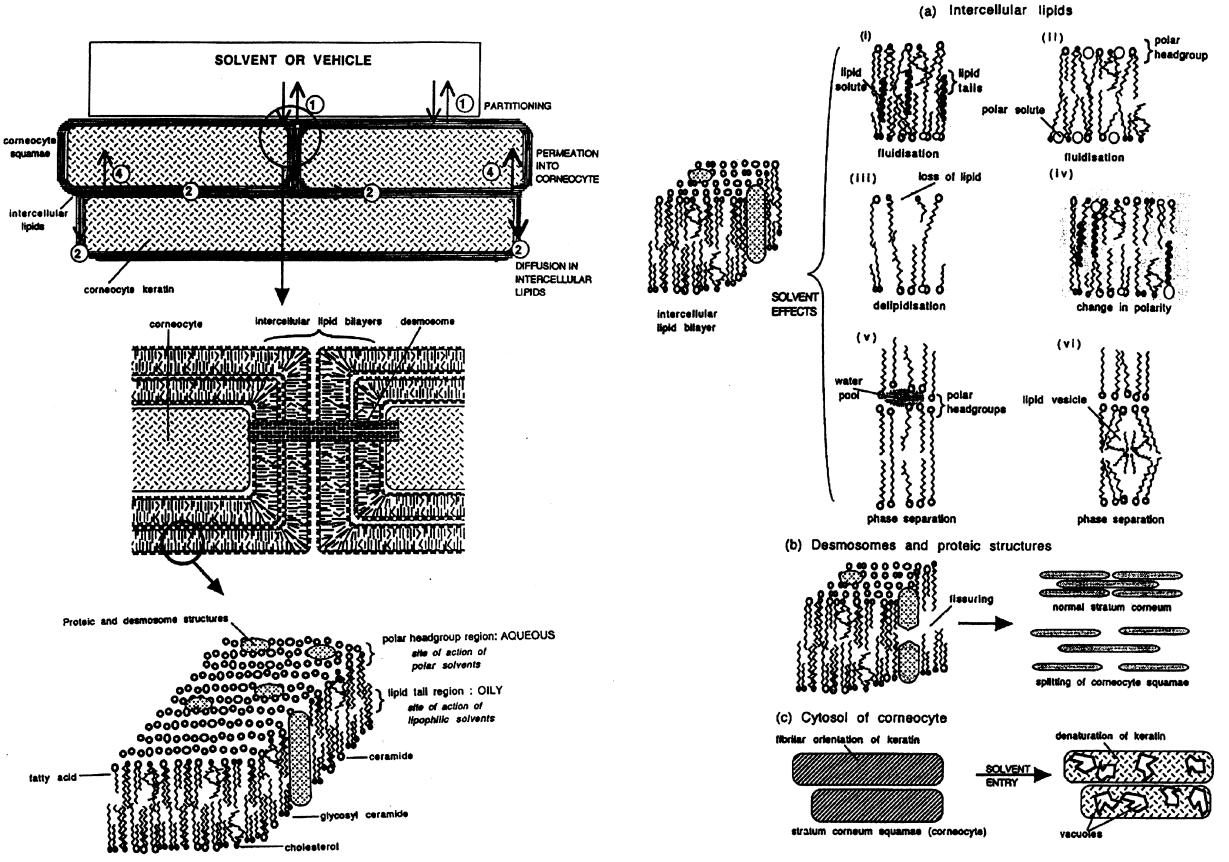

Fig. 1. Process of solvent enhancement of solute penetration through stratum corneum [100].

e.g., water in the polar head group region (v) or the more lipophilic solvents in the lipid tail region (vi). With some enhancers, especially hygroscopic agents, the integrity of the desmosomes or other proteic junctions involved in the SC cohesion may be affected (3), resulting in a fissuring and splitting of the corneocyte squamae (b). Under severe conditions, especially with polar solvents and surfactants, solutes may also enter into the corneocyte cytosol (4) with disruption of keratin and vacuolization as the result (c). As previously stated by Forslind [99], multiple domains exist in the lipids, and it is possible that a single solvent concurrently acts on several domains. It is also likely that most solvents exert their effects by multiple mechanisms.

Many penetration enhancers have a molecular structure and charge density suitable for interacting with polar head groups of the lipids. They may therefore disturb hydrated regions and head group interactions and fluidize this region, increasing the penetration of polar (hydrophilic) compounds. More aqueous fluid may enter the tissue, increasing interlamellar volume and thus the volume available for polar diffusion. Disruption of interfacial structure may lead to increased disorder of lipid chains, resulting in an increased permeation of nonpolar (hydrophobic) compound [102]. Barry and Bennett [103] suggested that penetration enhancers such as propylene glycol plus Azone, 2-pyrrolidone, *N*-methylpyrrolidone, *N*-methylformamide, enhance the permeation of polar and nonpolar compounds. Decylmethylsulfoxide plus propylene glycol affects the polar route, and accelerants, e.g., propylene glycol plus oleic acid, propylene glycol alone, and, to a limited extent, water mainly modify the nonpolar route.

4.1. Examples of lipid interactions

Many penetration enhancers exert some, if not most, of their activities by modifying the organization of the intercellular lipids. Terpenes act as enhancers mainly through interactions with intercellular SC lipids [95]. The high partition coefficient between octanol and water implied that there would be little terpene–keratin interaction within the corneocyte. Thus, protein modifications as a possible mechanism could be discarded. Azone provides a second example of a class of accelerants, which interacts with the SC lipids to increase the degree of fluidity of the hydrophobic regions of the intercellular lamellar structure, explaining its ability to decrease the diffusional resistance of the skin [70]. Hydrocarbons appear to dissolve some of the lipids [100].

4.2. Examples of protein modifications

Surface active molecules, particularly ionic substances organic acids and phenols tend to denature the keratin filaments in the corneocyte. Small polar enhancers such as dimethylsulfoxide, dimethylformamide, and the pyrrolidones have effects on proteins as well as on lipid structures [43,101,104]. Other polar solutes/solvents such urea, natural moisturising factor, polyols and water may solvate or hydrate proteins in both the corneocytes and in the intercellular region causing swelling and enhanced penetration [100].

4.3. Examples of partitioning promotion

The LPP theory proposes that one action of a penetration enhancer may be to increase the concentration of a penetrant, or a co-enhancer, in the SC [95,104]. The increased level of the drug in the membrane would then promote permeation by raising its concentration gradient and thus increasing the flux. A raised level of co-enhancer may further increase the concentration of the drug in the membrane, or reduce the barrier resistance of the tissue by lipid or protein interactions [3,5]. Small polar penetration enhancers such as dimethylsulfoxide, ethanol, and propylene glycol, may accumulate in the horny layer to such an extent that they change the solubility of the penetrant in the SC [43,105]. Synergism is often shown by propylene glycol combined with many accelerants such as Azone, long chain alcohols and terpenes. This may depend to a large extent on a mechanism by which the propylene glycol increases partitioning of the main promoter into the SC [67].

5. Normal skin permeability in different species

Veterinary topical medicine and toxicology involves the study of both therapeutic drug and

xenobiotic absorption through a range of species. In recent years different animal models have been used (e.g., skin from rat, guinea pig, snake, mouse, rabbit) [31,34,41,49,62,65,106–111]. It is noted that most studies of specific absorption are not concerned with a veterinary application but rather with defining a suitable animal model for human skin [112–114]. In general, as anticipated, human skin is the best model for the human permeability studies [115].

Reifenrath et al. [116] investigated the skin permeability of various animals by comparing the percutaneous penetration of nine radiolabeled compounds. Of the various skin weanling pig and human skin-grafted nude mouse models, permeability penetration data were close to that of human skin. Hairless dog, pig skin-grafted nude mouse, and nude mouse were not good surrogates for human skin. Scott et al. [117] reported the absorption of the herbicide paraquat through eight different animal skins. The observed permeability coefficients for paraquat relative to water are shown in Fig. 2. The hairless mouse was particular susceptible to paraquat penetration and human skin was much less permeable than any other species examined. The permeability coefficients for water in each of the species studied varied by, at the most, 5-fold. As previously discussed, laboratory animals lack sweat glands, but have more hair follicles than human skin. The different permeability coefficients probably reflect differences in follicular transport for the compounds.

Table 4 summarizes some of the in vivo data reported on the percutaneous penetration of several solutes through the skin of various species. The difference in skin permeability between the species was less than 5-fold with the rank order of rabbit > rat > pig > monkey > human.

Table 4
Relative in vivo absorption of several chemicals through human and animal skin

Penetrant	% Dose absorbed				
	Human	Pig	Monkey	Rabbit	Rat
Acetylcysteine	2.4[a]	6.0[a]	NR	2.0[a]	3.5[a]
Butter yellow	21.6[a]	41.9[a]	NR	100.0[a]	48.2[a]
Caffeine	47.6[a]	32.4[a]	NR	69.2[a]	53.1[a]
Cortisone	3.4[a]	4.1[a]	NR	30.3[a]	24.7[a]
DDT	10.4[b]	43.4[c]	1.5[c]	46.3[c]	NR
Haloprogin	11.0[a]	19.7[a]	NR	113.0[a]	95.8[a]
Lindane	9.3[b]	37.6[c]	16.0[c]	51.2[c]	NR
Malathion	8.2[b]	15.5[c]	19.3[c]	64.6[c]	NR
Parathion	9.7[b]	14.5[c]	30.3[c]	97.5[c]	NR
Testosterone	13.2[a]	29.4[a]	NR	69.6[a]	47.4[a]

NR, not reported.
[a] Bartek et al. [118].
[b] Feldmann and Maibach [119].
[c] Bartek and LaBudde [120].

Differences in the permeation of nicorandil, a coronary vasodilator, were determined in six different species (hairless mouse, hairless rat, guinea pig, dog, pig and human), with the pig and human being similar [121]. This study also attempted to relate the percutaneous absorption of nicorandil to the amount of surface lipid in these species. It was suggested that the difference in permeation could be explained by the differences in species-specific skin surface lipids that may also affect the partitioning of nicoran-

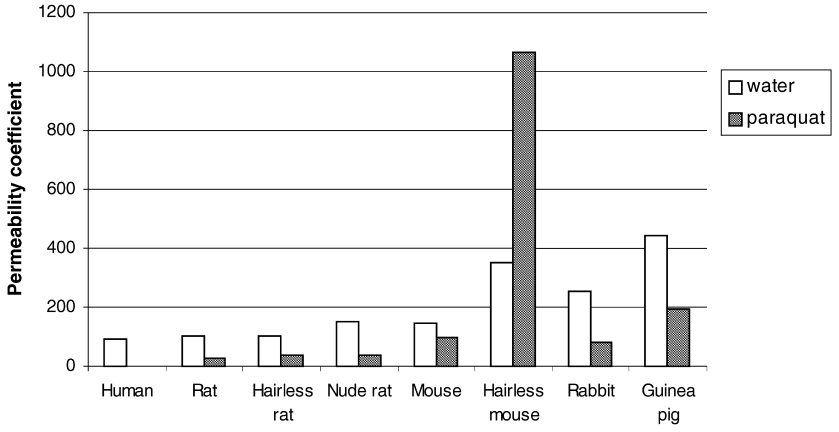

Fig. 2. In vitro permeability coefficient ($cm/h \times 10^5$) of water and paraquat through human and animal skins [117].

dil from the vehicle to the SC. The amounts of skin lipids extracted by acetone are shown in Table 1. There was a correlation between the extracted lipid data obtained using hairless mouse, hairless rat, and guinea pig and a similar pattern was seen for the permeability studies. In summary, for polar solutes such as water the magnitude of difference in skin permeability between the species is less than 5-fold, with a rank order of guinea pig > rabbit > mouse > rat > human. In general, for nonpolar solutes the corresponding rank order is guinea pig (200) > mouse (100) > rabbit; rat (10) > pig; monkey (5) > human (1). In all cases it should be noted that small laboratory animals always present a skin barrier which is more permeable than that of larger animal species including man. These results show that there is a difference in permeability between different animals, which is due to their different skin properties. This issue is of importance for development of formulations in veterinary practice for different species.

6. Effect of enhancers on permeability in different species

Niazy [62] investigated the species difference in the percutaneous absorption of dihydroergotamine (DHE) from propylene glycol formulations, using rabbit, rat, hairless mouse, guinea pig and human skins. As part of this study the influence of the penetration enhancer laurocapram (Azone) on DHE permeation was also investigated (Fig. 3). The skin permeability of DHE in the different species decreased in the following order: hairless mouse > guinea pig > rat > rabbit > human. Human skin was much less permeable to DHE than any other species examined and the hairless mouse was particularly susceptible to DHE penetration. Catz and Friend [122] reported a similar observation for permeability of the contraceptive drug levonorgestrel from a saturated solution in ethyl acetate through four skin types, which showed the following trend: hairless mouse skin > hairless guinea pig skin > rat skin > human skin. As previously stated, the main barrier to percutaneous absorption is the SC and its thickness increases with animal size. For these studies, it appears that as the SC thickness increased the transport of drugs across the skin decreased. Niazy [62] showed that Azone increased DHE penetration through excised skin of various species in the following order: rabbit skin > human skin > rat skin > guinea skin > hairless mouse skin (Fig. 3). Stoughton and McClure [123] reported enhancement factors for transdermal delivery of 8-bromo cAMP across hairless mouse skin using Azone, and showed similar results to those found for DHE. A similar enhancement effect using Azone was also reported by Okamoto et al. [124] for the transport of 6-mercaptopurine through guinea pig skin.

Fuhrman et al. [31] examined enhancer activity using occluded hairless mouse skin, hairless rat skin

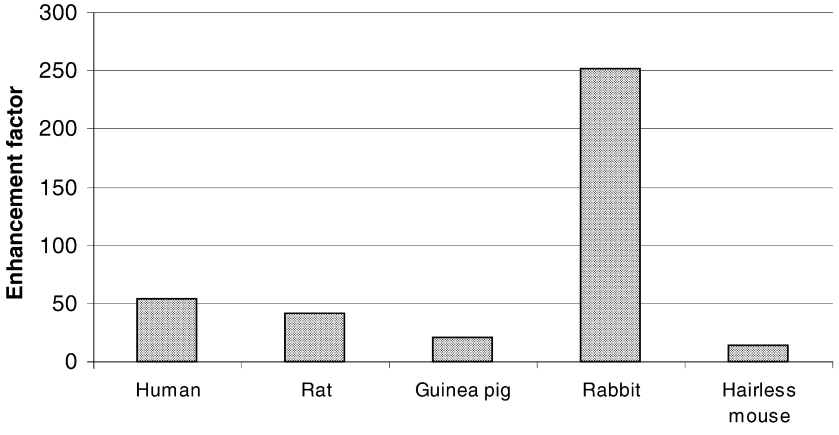

Fig. 3. Effect of Azone (6%) on the permeation of dihydroergotamine (DHE) through skin from different species [62].

and human cadaver skin using hydrocortisone (HC) as the model drug. The effect of Azone and its three analogues; *N*-dodecyl-2-pyrrolidinone (DPY), *N*-dodecyl-2-piperidinone (DPI), and *N*-dodedyl-*N*-(2-methoxyethyl)acetamide (DMEA) on the permeation parameters of HC is illustrated in Fig. 4. The results show that the Azone analogue, DPY produced the highest increase of hydrocortisone permeability coefficient in all three animal species. Decrease in the ring size of the lactam derivatives appeared to increase enhancer activity. The rank order of enhancer activity for each animal model was: DPY (five-membered ring) > DPI (six-membered ring) > Azone (seven-membered ring) (Fig. 4).

The percutaneous permeation of hydrocortisone (HC) across hairless mouse skin was determined by El-Kattan et al. [41]. The formulations used in these investigations included an alcoholic hydrogel (HPMC) containing one of 12 terpenes, the selection of which was based on an increase in lipophilicity. The permeation experiments revealed that the terpene enhancers varied in their ability to enhance the flux of HC (Table 5). The results indicated that hydrophilic terpenes, capable of hydrogen bonding,

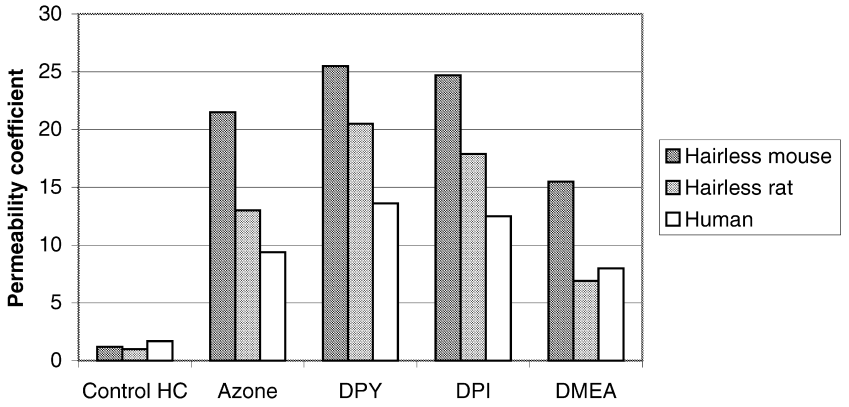

Fig. 4. Effect of Azone, DPY, DPI, and DMEA on the permeability coefficient (cm/h × 104) of hydrocortisone through skin of different species [31].

Table 5
Effect of terpene enhancers on the percutaneous parameters of hydrocortisone formulated in HPMC gels

Terpene	Log *P*	Flux μg/(cm^2 h)	Q_{24} (μg/cm^2)	Lag time (h)
Control	1.43±0.25	4.5±0.6	117±19	2.6±0.8
Terpinene-4-ol	1.06±0.20	51.0±14.3	709±91	3.4±0.5
Verbenone	1.97±0.23	51.6±10.6	653±105	3.8±0.1
Fenchone	2.13±0.30	45.6±6.6	953±184	4.5±0.7
Carvone	2.23±0.25	59.1±7.9	1104±185	2.1±1.2
Menthone	2.63±0.30	84.0±13.4	817±181	1.4±0.8
α-Terpineol	2.73±0.28	60.0±4.4	829±43	3.1±0.2
Cineole	2.82±0.25	65.1±17.6	969±153	3.0±1.0
Geraniol	3.18±0.30	76.1±4.4	1134±19	3.0±0.6
Thymol	3.28±0.20	49.6±9.7	727±154	3.2±0.5
Cymene	4.05±0.25	103.0±10.8	1451±108	0
D-Limonene	4.58±0.23	128.0±9.7	1089±190	0.5±0.4
Nerolidol	5.36±0.38	159.0±23.7	1733±93	1.2±0.3

Source: El-Kattan et al. [41].

were not as effective in promoting the permeation of HC compared to hydrocarbon terpenes (D-limonene and cymene). These results differ from previously published data. Most studies suggest that hydrophilic terpenes (alcohol, ketone, and oxide terpenes) were more effective in enhancing the permeation of hydrophilic drugs, whereas, hydrocarbon terpenes (such as limonene and cymene) were more effective towards lipophilic drugs [81,125]. A linear relationship was established between the log *P* of terpenes and the cumulative amount of HC (Table 5). There was also a correlation between the flux of HC and the lag time. The lipophilicity of the enhancer was thought to play a major role in its activity. Williams and Barry [95] found a linear relationship between the log *P* of a group of epoxide and ketone terpenes and the enhancement ratio for 5-fluorouracil. The authors suggested that terpene enhancers promoted the permeation of the drug and that this was associated with disruption of the intercellular lipid packing in the SC. In summary, the enhancement factor of Azone differ between the species, with the rank order of rabbit (250) > human chest skin (50) > rat (40) > guinea pig; hairless mouse; hairless rat (20) > human thigh skin (6). In general, the enhancement effect of terpenes increases with increased lipophilicity. In conclusion, it is relatively obvious that different enhancers have different effects on different animal skins. Therefore, any veterinary enhancer study should be performed on the target species, rather than extrapolated from studies performed in a different animal.

7. Skin permeability in large animals

Very little work has addressed the parameters or mechanisms governing percutaneous absorption on food-producing animals such as the cow, sheep or goat. The barrier properties of skin in these domestic animals are not as well understood as those of skin in human, rodents, and pigs. Risk assessment of dermal absorption of veterinary topicals is difficult because there are limited published data, and data for approved drugs and pesticides is usually proprietary information. Pitman and Rostas [12] have comprehensively reviewed the early data on cattle and sheep skin permeability. Many factors can create considerable variability in the barrier function of the skin of domestic animals. These include differences in the surface temperature between black-haired and white-haired regions, climate-induced alterations in sebum output and variability in skin thickness. Animals are sensitive to changes in the ambient temperature that can result in seasonal variations in skin permeation rates [126]. Another complicating factor is that there is considerable variability in skin morphology among breeds. There can be variability in total skin thickness as well as in the thickness of the various layers. These factors, coupled with difference in the densities of hair follicles, body weight, age and sex, can lead to significant differences in skin permeability properties both inter- and intrabreed. Pitman and Rostas [127] investigated the permeation of levamisole across cattle and human skin with an aqueous borate-buffered solution (pH 8.9) containing 0.85% levamisole, and an organic solvent made up of nonaromatic hydrocarbons (15%), polyoxypropylene 15-stearyl ether (12%), and ethoxyethanol (73%), containing 10% levamisole. The penetration of levamisole through cattle skin appeared to be higher than through human skin. Interestingly, the penetration through human skin was higher from the aqueous solution compared with the organic solvent. The authors suggested that the penetration of levamisole through cattle skin might be through the appendages with facilitation by the emulsified sebum, which provided a good partitioning medium for the drug [128]. However, the organic solvent may also have been acting as penetration enhancer by removing the sebum. The many variables in the permeability properties of the skin of large domestic animals make it difficult for the approach of formulation design. More knowledge of the properties of the skin of individual species and breed is required to investigate the feasibility of penetration enhancers.

8. Allometric issues in veterinary topical drug development

As in human skin penetration, drugs in veterinary medicine may be applied topically for a local or a systemic effect [101]. In systemic delivery the blood level and the effect is determined both by its topical absorption and by its pharmacokinetics (clearance, body volume distribution). In the simplest form, the

steady-state blood concentration is defined by the constant dermal rate of absorption divided by clearance. The dermal rate of absorption is the flux, which is a function of the area of application and the concentration of applied drug. The total amount absorbed after topical application is also determined by the time of the application, the amount entering the epidermis and epidermal/dermal metabolism [6]. Another determinants of flux are condition of the skin (e.g., normal or inflamed), site of application and conditions of application [6]. Walters and Roberts [1] have considered the extent to which species is a predictor of skin permeability. If skin permeability were related to the body size and physiological life time, the species dependence in skin permeability may be expected to be in the following order: mouse > rat > guinea pig > rabbit > monkey > dog > goat > sheep > pig > cattle > human [1]. The area of interspecies differences in skin absorption is an alluring concept for allometric use. An allometric correlation between body weight and permeability absorption with the rank order of rat; rabbit ≫ monkey; pig > human is shown in Table 4.

Pitman and Rostas [12] have stressed the importance of blood level versus time profiles for drugs following dermal application, and proposed using this information as a basis for developing new formulations. Investigators have shown that interspecies scaling is applicable for certain veterinary drugs [129]. The experimental determination of the coefficients of the allometric equation for relevant pharmacokinetic parameters could be an important tool in estimating dose in species where the drug has never been studied. Schwartz and Rosenblum [130] reported the allometry of primate hair density and the evolution of human hairlessness. The results show that increasingly massive primates have systematically fewer hairs per equal unit of body surface. They proposed that, lacking a reflective coat of hair was the primary mechanism for adaptation to the increased heat of man's new environment. Militzer et al. [131] investigated the correlation between body weight of Syrian gold hamster with organ weights and skin muscle thickness. They showed that body weight correlation predominates in the case of organ weights and skin muscle thickness and this was dependent on similarities in thermoregulatory and geometric properties.

The concept of correlating pharmacokinetic parameters (clearance and volume of distribution) with body weight from different animal species has been widely studied [129,132–137]. The allometric approach is based on the power function, where the body weight of the species is plotted against the pharmacokinetic parameters of interest. Clearance, volume of distribution, and elimination half-life are the three most frequently extrapolated pharmacokinetic parameters. Over the years, many approaches have been suggested to improve the prediction of these pharmacokinetic parameters in human from animal data. A literature review indicates that there are different degrees of success with different methods for different drugs [138]. This can be due to the fact that body weight correlates better to distribution volume than to clearance. Clearance relates to the metabolic profile that differs between different species. Overall, though interspecies scaling requires refinement and better understanding, the approach has lot of potential during the drug development process.

Fig. 5 shows that the pharmacokinetic parameters defining the disposition of a solute in the body, the clearance of the solute and volume of distribution, can be directly related to the body weight of the species. It should be noted that the body weight for pig is very similar to that of the human.

The extent to which the concepts of allometry in percutaneous penetration and in clearance can be combined to predict steady-state plasma concentrations after transdermal delivery in different species appears, at this stage, to be relatively unexplored. Given that clearance increases with body weight (Fig. 5), higher levels are to be expected for the smaller animals with the higher skin permeability, should the area and time of application be the same for all species. However, as in the case of drenching, if the area concerned is proportional to the possible skin area of the species, the total absorption will be proportionately higher and the differences in plasma concentrations not so apparent.

9. Formulations in veterinary medicine

Veterinary drugs can be applied using several treatment routes such as 'pour-on' products, which contain dilute solutions, or low-volume 'spot-on'

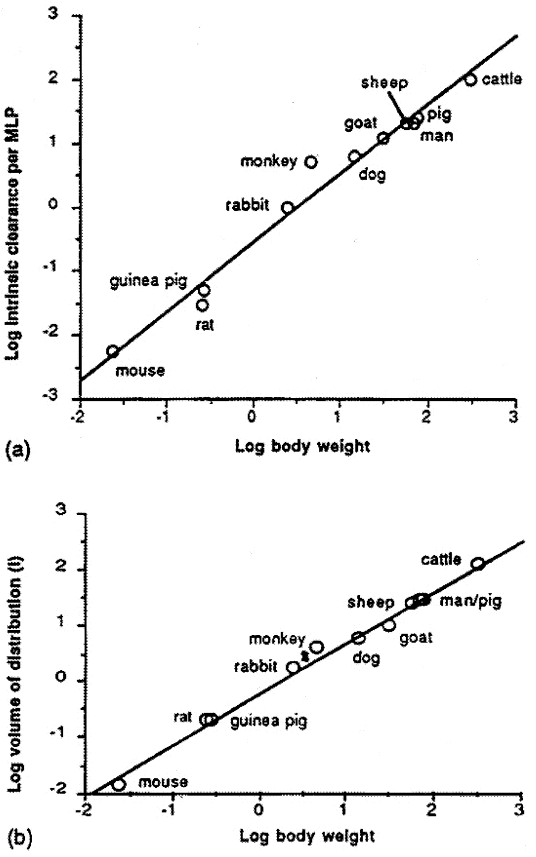

Fig. 5. Allometric relation between (a) clearance per maximum life span potential (MLP) and (b) volume of distribution for antipyrine as a function of body weight for a variety of animal species [132].

products, which contain high concentrations of the compound. Other dosage forms for veterinary use are backrubbers, dips, dust bags, whole-body sprays, and medicated ear tags that contain a small concentration of the compound and act by bringing the drug into contact with external parasites. Pour-on and spot-on formulations promote systemic drug absorption. Many pour-on and spot-on formulations contain inert ingredients (e.g., alcohols, amides, ethers, glycols, and hydrocarbon oils) that will act as penetration enhancers. The first pour-on application of an insecticide was reported in 1957 when poultry infested with the poultry body louse *Menacanthus stramineus* and sheep infested with the body louse *Damalinia ovis* were successfully treated by the application of a systemic insecticide, aldrin, to a small area of the skin [139,140]. The pour-on method was also used for the control of the cattle grub, *Hypoderma* spp., with the organophosphate compound ruelene [141] and revolutionized lice control on cattle [142–144]. Subsequently, the application of synthetic pyrethroid, deltamethrin [145,146], cypermethrin [147] and α-cypermethrin [148] via pour-on formulations became widely used in the control of *D. ovis*. In this case, a highly concentrated formulation of the active is deposited in a band along the animal's back. The insecticide is then able to spread through the fleece most likely by diffusion within the emulsion layer on the wool and skin surface. The concentration of active agents, therefore, decreases with distance from the application site [146] (Johnson et al., unpublished data). This is in contrast to the action of organophosphorous compounds which are believed to be systemically absorbed following application to the skin, distributed in the blood stream and excreted into the skin thereby reaching all areas containing sebaceous glands. Using autoradiography, Jenkinson et al. [149] found that [^{14}C]cypermethrin, applied as a pour-on formulation, spread radially across the skin within the stratum corneum at a rate which exceeded 11 cm/h. This spread was accompanied by some dermal infiltration which was most marked at the site of application. Using a similar technique, Johnson and Dixon (unpublished data) found radiolabeled cypermethrin on wool fibers both above the surface and in the follicles, extending into the dermis. Darwish et al. (unpublished data) obtained data indicating that the synthetic pyrethroid, deltamethrin, achieved higher levels on the wool compared to skin, following pour-on application. Brimer et al. [150] proposed that pour-on formulations containing parathion as the active ingredients reach ectoparasites after spreading on the surface of the skin, rather than through dermal absorption and systemic distribution. Similar results were published by Gyrd-Hansen et al. [151] for a pour-on formulation containing phosmet. In common with other pharmaceutical formulations, pour-on and spot-on products should be chemically, physically, and microbiologically stable. The products should be evaluated and optimized for drug delivery characteristics, and the formulation should minimize the risk of irritant or sensitization reactions. The use of a simple organic solvent solution of an active ingredient may not always be feasible. A water-soluble

active agent, or a combination of a water-soluble active and a water-insoluble active, may require the use of aqueous suspensions or emulsions. Many penetration enhancers are readily soluble in organic solvents but may be less soluble in aqueous based formulations.

The most commonly applied topical drugs in veterinary practice are insecticides (Table 6). Food and companion animals are often exposed to different types of insecticides to treat and control ectoparasites such as fleas, ticks, flies, lice and mites. Organophosphates (OPs) are the most commonly used topical insecticide products in domestic animals. Topical application of OPs may result in inhibition of cholinesterase activity and mild to severe neurological signs of toxicity depending on the dose absorbed [119]. Lipid-soluble pesticides such as chlorpyrifos may partition into the various skin layers and be released over a prolonged period. Other insecticides that are approved for topical applications in domestic animals include the carbamates (e.g., carbaryl), chlorinated hydrocarbons (e.g., methoxychlor, lindane) and pyrethrins (e.g., permethrin, fenvalerate) (Tables 7–9). Many of the classes of topical drugs used in veterinary medicine (e.g., antibiotics, antiseptics, and steroids) do not depend on transdermal absorption to achieve therapeutic efficacy, but act locally to treat a particular dermatological disease. Therefore, addition of penetration enhancers should be avoided for drugs that are only required to partition into the skin and not permeate through it.

An issue of bioequivalence may also arise if penetration enhancers are being used in veterinary pour-on or spot-on formulation. Both organic solvent based and aqueous suspensions have been described. Walters and Roberts suggest that nonaqueous solvent mixtures are the most widely used for pyrethroid and

Table 6
Examples of veterinary drugs

Insecticide	Compound	Treatment	Species
Organophosphates	Fenthion	Control of ectoparasites	Dog, beef cattle, dairy cattle
	Phosmet	Lice, flies, ticks, scabies mites	Dog, beef cattle, swine
	Famphur	Grubs	Beef cattle, dairy cattle
	Coumaphos	Contact insecticide	Cattle
	Chlorpyrifos	Flea collars	Cat, dog, cattle
	Trichlorfon	Lice, grubs	Beef, dairy cattle
Carbamates	Carbaryl	Ticks, fleas	Cat, dog
Organochlorines	Methoxychlor	Fleas	Cat, dog, cattle, horse
	Lindane	Screwworm	Cattle, sheep, swine, goat, horse
Pyrethrins	Fenvalerate, Permethrin, Cypermethrin	Flies, ticks, insect repellant, insect growth regulator	Cat, dog, cattle
Diamide	Amitraz	Demodicosis, mange	Dog, swine
Ivermectins		Antinematodal, antiectoparasite	Beef cattle, calves
Imidazothiazole	Levamisole	Antihelminthic	Beef cattle, calves
Steroids	Dexamethasone, Flumethasone, Hydrocortisone, Isoflupredone	Infected wounds (preparations with antibiotics)	Cat, dog
Antibiotics	Neomycin, Thiostrepton, Triamcinolone	Antibacterial (mixture of several compounds)	Cat, dog, cattle, sheep, swine, goat, horse

Source: Riviere and Baynes [2].

Table 7
Marketed pour-on and spot-on formulations

Product	Active ingredient	Concentration (%)
Anthelpor 20	Levamisole	20
Citarin-L	Levamisole	10
Coopers Spot-on	Deltamethrin	1
Co-Ral	Coumaphos	4
Cypor	Cypermethrin	2.5 (40:60 *cis:trans*)
Neguvon	Trichlorfon	8
Porect	Phosmet	20
Ridect	Permethrin	4 (80:20 *cis:trans*)
Ripercol pour-on	Levamisole	20
Ruelene	Cruformate	5, 8.3, 9.4
Spotton	Fenthion	20
Tiguvon	Fenthion	3/2

organophosphorus compounds. The range of solvents used includes the enhancers, e.g., propylene glycol, ethanol, and polyethylene glycol's (Table 9). As an experience of the marked variables in formulation effects in blood levels, Walters and Roberts [1] presented blood level time curves for levamisole in heifers for two marketed pour-on formulation contained 20% levamisole. The peak levels for the two formulations were 0.73 and 0.38 μg/ml at 2 and 5 h, respectively. At 24 h after application the corresponding concentration of levamisole remaining were 0.05 and 0.12 μg/ml, respectively. The different profiles reflect the formulations used, including the potential effect of the enhancers present. These data illustrate the importance of bioequivalence studies in the evaluation of pour-on products.

10. Toxicological aspects on veterinary drug products

An important factor to be considered during the development of veterinary topical formulations is that the formulation should minimize the risk of

Table 8
Examples of some patents of topical veterinary formulations

Patent number	Date	Title	Main claim
US4479960	1984	Pour-on veterinary composition	A pour-on veterinary composition useful for the treatment of helminthic infestations in animals, which consists of tetramisole or levamisole
US4927641	1990	Veterinary liniment	Liniment for treating bowed tendons in horses comprises dimethylsulfoxide (DMSO) and sodium hypochlorite
US5391548	1995	Transdermal flux enhancing composition	A method of treating diabetes in lower animal which comprises glipizide and 0.01 to 5% of a enhancer selected from certain 1-alkylazacycloheptan-2-one
US4543247	1985	Ectoparasiticide-containing collars for pets	An ectoparasiticide-containing polyurethane collar for animals, which comprises a hydrophobic polyurethane, spreading agents and ectoparasiticides
US4879275	1989	Penetration enhancers for transdermal delivery of systemic agents	A method for topically enhancing penetration of systemically active agents through the skin of animals and into the bloodstream
US3942480	1976	Removable arthropod repellent	Device for attachment to the pinnal portion of the ear of an agricultural animal incorporating insecticide therein
US4673665	1987	Treating anestrus in ewes or beef cattle	Treatment with a gestagen having protracted action, followed by administering LH-RH
US4075353	1978	Treatment of acarid skin infections in animals	Topically administering of benzoyl peroxide to the afflicted animal
US5569461	1996	Topical antimicrobial composition and method	Method for disinfecting the skin using a propylene glycol monoester of capric acid

Table 9
Examples of solvents and spreading agents used in pour-on and spot-on formulations

Classes	Examples
Alcohols	Ethanol Isopropanol
Amides	Dimethylacetamide Dimethylformamide
Glycols	Butyl diglycol Polyethylene glycols (200–400) Propylene glycol
Glycol ethers	Butoxyethanol Ethylene glycol monoethylether Methoxyethanol
Hydrocarbon oils	Corn oil Mineral oil Vegetable oil
Miscellaneous	Dimethylsulfoxide Dimethylisosorbide
Spreading agents	Butyl oleate 2-Ethylhexyl stearate Polypropylene glycol-2-myristyl ether Polysorbate 80

irritant or sensitization reactions following application. It is possible to predict, with some certainty, the potential toxic effects of individual formulation excipients and active drugs using various in vitro methodologies. However, skin permeation characteristics of the individual components may be modified following mixing and processing of the formulation and, for this reason, it is essential to determine any adverse skin reactions to the final formulation.

The presence of antibiotic and insecticide residues in slaughtered animals has been investigated [152–154]. The fact is stressed that the persistence of residues in slaughtered animals varies, amongst other things, with the drug itself, the pharmaceutical formulation, method of topical application, presence of hair or wool, environmental conditions and the species being treated. There are marked differences between the various products as regarding the local irritation and the residual persistence in the organs. Lipid-soluble pesticides such as chlorpyrifos may partition into the various skin compartments (e.g., stratum corneum, epidermis, dermis) and be released over a prolonged period, resulting in a biphasic absorption pattern that may modulate toxicological risk [155]. For a similar scenario in food animals, slow release of these lipophilic chemicals from cutaneous depots may result in prolonged residues in meat and milk or a spike in residues in the advent of malnourishment or disease (e.g., dermatitis). The toxicity of Compound 1080 (sodium fluoroacetate) livestock protection collars (LPCs) to sheep was investigated by Burns and Connolly [156]. LPC solution poses no dermal toxicity or irritation to sheep. Under conditions of exaggerated hazard, ingesting LPC solution can poison sheep, but adverse effects from normal LPC use are rare. Fisch et al. [157] investigated the potential hazard of carbamate impregnated flea and tick collar for dogs. The dogs wearing test collars had a depression of erythrocyte and plasma cholinesterase activity. As well as miosis with decreased pupillary response and irritation of the skin of the neck. During 1975–1976 eighteen veterinarians regularly practicing organophosphate pour-on treatment of cattle for grub infestations were examined for symptoms and signs as well as enzymological and chemical evidence of organophosphate absorption [158]. Some subjects reported headache, nausea, and irritation of the face and throat during chemical application. Organophosphate absorption was not sufficient to depress blood cholinesterase activities, and only occasionally generated measurable amounts of alkyl phosphate metabolites in urine of exposed veterinarians.

The effects of anatomical site and occlusion on the percutaneous absorption and residue pattern of 2,6-parathion were investigated by Qiao et al. [159] following topical application onto four skin sites (abdomen, buttocks, back and, shoulder) in weanling swine. The percutaneous absorption from the shoulder was much lower than that from the other three sites under occluded conditions. However, if nonoccluded dosing was employed, absorption from the abdomen became the lowest, with shoulder and buttocks being similar, and the back the highest. Occlusion concealed the site difference and enhanced both the extent and the rate of parathion percutaneous absorption in vivo. The residue pattern in tissue and dosing materials was site and dosing dependent, all of which are factors which must be considered when assessing the risk of exposure to topically applied compounds.

11. Alternative methods in skin absorption

Transdermal powder delivery uses a supersonic flow of helium to accelerate drug particles to velocities sufficiently high to penetrate the stratum corneum [160]. This needle-free injection system is capable of painlessly delivering drugs and vaccines in powder form into the skin. The amount of drug delivered is related to particle size, dose level and the device operating power. Recent data demonstrated that the powder delivery system was capable of delivering salmon calcitonin across rabbit skin in a dose-dependent (but non-linear) manner [161]. A similar system (the Helios™ gun system) was used to determine the effect of the dose regimen of a model drug incorporated into poly-L-lactic acid microspheres of varying particle size [162]. It was concluded that more frequent applications containing lower amounts of the model drug generated a superior plasma profile than larger drug loading at less frequent dosage intervals. At this time, alternative methods for skin delivery in veterinary medicine are a relatively undeveloped field.

12. Concluding remarks

There are differences between different species regarding anatomy as well as skin permeability. Most of the research on interspecies percutaneous absorption extrapolation is conducted to select an animal model (e.g., mouse, rat, guinea pig, monkey, or pig) to predict absorption in humans. Percutaneous absorption studies on larger domestic animals are sparse. This review has outlined some of the possibilities and problems associated with the use of chemical penetration enhancers as well as allometric issues and development of formulations in veterinary practice. Clearly penetration enhancers offer potential advantages in delivering a broad range of agents via the transdermal route. Advantages with transdermal application of drugs in veterinary medicine are ease of administration (compare the application of a transdermal spraying versus a bolus administration), speed of administration (compare the rapidity of spraying an animals back as opposed to inserting an ear implant), sustained therapy either through specifically designed controlled release products (e.g., patches) or inherently long acting drugs. There is significant use of topicals in veterinary medicine. The field of transdermal drug delivery, with the use of penetration enhancers, has become more prevalent and has become a growing trend within animal health.

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