Potential and problems of developing transdermal patches for veterinary applications

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Abstract

A new frontier in the administration of therapeutic drugs to veterinary species is transdermal drug delivery. The primary challenge in developing these systems is rooted in the wide differences in skin structure and function seen in species ranging from cats to cows. The efficacy of a transdermal system is primarily dependent upon the barrier properties of the targeted species skin, as well as the ratio of the area of the transdermal patch to the species total body mass needed to achieve effective systemic drug concentrations. A drug must have sufficient lipid solubility to traverse the epidermal barrier to be considered for delivery for this route. A number of insecticides have been developed in liquid ‘pour-on’ formulations that illustrate the efficacy of this route of administration for veterinary species. The human transdermal fentanyl patch has been successfully used in cats and dogs for post-operative analgesia. The future development of transdermal drug delivery systems for veterinary species will be drug and species specific. With efficient experimental designs and available transdermal patch technology, there are no obvious hurdles to the development of effective systems in many veterinary species.

Keywords: Veterinary drug delivery; Transdermal drug delivery; Fentanyl; Iontophoresis

Contents

1. Introduction ................................................................................................................. 176
2. Overview of comparative cutaneous anatomy and physiology .................................................. 176
   2.1. Structure and function of skin .................................................................................. 176
   2.2. Species and regional differences .............................................................................. 180
   2.3. Quantitating percutaneous absorption ..................................................................... 181
       2.3.1. Fick’s law of diffusion .................................................................................... 181
       2.3.2. In vivo methods ............................................................................................ 183
       2.3.3. In vitro methods ........................................................................................... 184
   2.4. Transdermal pharmacokinetics .................................................................................. 186
3. Transdermal drug delivery .............................................................................................. 187
   3.1. Topical formulations versus patches ......................................................................... 187

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1. Introduction

The primary routes of drug administration utilized in veterinary medicine include oral, intramuscular, subcutaneous and intravenous dosing. Over the last decade, great strides have been made in using topical 'pour-on' and 'spot-on' applications of pesticides and antiparasitics (e.g., fenthion, ivermectin, levamisole, fipronil) for transdermal delivery in veterinary species. In this article, the term transdermal implies use of a topical drug application to achieve systemic pharmacological effects. In human medicine, there has been an increase in marketing and in acceptance of transdermal patches (e.g., scopolamine, nitroglycerin, estradiol, testosterone, nicotine, clonidine, fentanyl) as an alternate method for systemic drug delivery. 'Patches' differ from other topical formulations developed for systemic delivery by virtue of the fact that the patch controls the rate of drug delivery from these systems, rather than the drug's permeability through the skin that occurs with topical formulations. Finally, electrically driven transdermal iontophoretic delivery systems are currently being developed to provide a more controlled systemic delivery of peptide drugs not easily delivered by other routes. The literature describing the development of transdermal patch systems for humans is extensive, but there is little development and even less literature in the veterinary field.

In order to probe the application of transdermal patch technology for veterinary medicine, it is imperative to understand relevant dermal anatomy and physiology that interacts with drug transport through the skin. Surprisingly, there is a great deal of information on chemical and drug absorption in some veterinary species, often because select species (pigs, dogs) serve as models for human drug delivery. However, these studies and those conducted in rodents mainly for toxicological risk assessment purposes, have taught that significant differences exist in the barrier functions of different mammalian species. In order to interpret drug delivery data in veterinary species, as well as to consider the design constraints in developing patches for animal health, a thorough knowledge of the mechanism of chemical absorption across the skin barrier and criteria for selecting appropriate model systems is needed.

2. Overview of comparative cutaneous anatomy and physiology

One of the most obvious factors, which would impact the design of transdermal patches for veterinary species, is the anatomical difference in the skin structure among species. Even from a cursory visual inspection, it is obvious that pig, dog and sheep skin have very different appearances which would impact the design of transdermal patches. Therefore, prior to a discussion on patch design and function, the comparative anatomy and function of skin must be briefly reviewed.

2.1. Structure and function of skin

Skin is one of the largest organs of the body having a complex structure that reflects its myriad of biological functions. Recent reviews of this topic [1–3] will serve as the basis for this synopsis. The...
function most pertinent to its role in transdermal delivery is that of being a barrier to the outside environment. The skin is considered to be an efficient barrier to prevent penetration, and thus systemic absorption, of most hydrophilic and ionic compounds. It may be relatively permeable to compounds of moderate lipophilicity as will be discussed below. A second function of the skin which impacts our topic, is the skin’s role in thermoregulation manifested by the presence of hair and fur for insulation, sweat glands for evaporative heat loss, and a wide range of blood perfusion for modulating heat transfer to the environment. All of these functions may affect the rate and extent of absorption of topical chemicals across the skin. Additional functions of skin include mechanical support, neurosensory reception, endocrinology (e.g., activation and metabolism of Vitamin D), immunology, and glandular secretion.

The histological structure of skin is depicted in Fig. 1. This heterogeneous organ is composed of three layers and a number of distinct appendages.
The outermost layer, and the one responsible for the skin’s barrier properties, is the avascular epidermis which is structurally and functionally divided into the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and the innermost stratum basale which rests on the basement membrane or epidermal–dermal junction. The most metabolically active layer is the stratum basale, primarily composed of keratinocytes which actively divide, undergo differentiation and migrate outward to populate the other epidermal layers. Interspersed among these basal keratinocytes are other non-keratinocytes which include the pigmented melanocytes, the immunologically important Langerhans cells, and the sensory Merkel cells; all three of which have minimal involvement in the skin’s physical barrier properties.

As basal keratinocytes divide and move upward, they lose their cuboidal shape and prominent nucleus. Their metabolism changes to synthesize the structural protein keratin and the enzymes necessary to produce a variety of lipids. The stratum granulosum layer is named for the presence of keratohyalin granules in histological sections. They are depicted as flattened with an almost nonexistent nucleus and cytoplasm being primarily occupied by keratin and membrane coating granules. The stratum corneum, the outermost layer, is where all of the skin’s chemical barrier properties reside. The cells are extremely flat and consist entirely of keratin ‘cemented’ to adjacent cell layers by an intercellular lipid matrix derived from the contents of the exteriorized membrane coating granules. This forms a ‘brick and mortar’ structure [4] that has been used to conceptualize the barrier property of skin. The intercellular lipid ‘mortar’ component of the structure is the primary route of penetration of all topical chemicals studied to date. The stratum corneum is composed of numerous layers of stratified, highly organized keratinized cells embedded in a lipid matrix primarily composed of ceramides, sterols, and other neutral lipids. The stratum corneum layers are continually sloughed off to the external environment by friction and are replaced by the migration of differentiated cells from layers below. This cycle takes approximately 4 weeks in humans.

The stratum corneum is the primary barrier to chemical penetration. When the stratum corneum is removed by successive stripping with adhesive tape, all but a superficial barrier to chemical penetration remains. For hydrophilic compounds, the stratum corneum has been estimated to provide 1000 times the diffusional resistance to penetration as the cellular layers beneath it. Stratum corneum’s barrier function can be assessed by measuring how easily dermal water can traverse to the outside of the body in the process of normal insensible water loss. This process termed transepidermal water loss (TEWL) can be noninvasively measured on the skin surface and is often employed as an estimate of epidermal barrier function. Tape-stripping dramatically increases TEWL. However, for very lipophilic compounds with lipid/water partition coefficients greater than 400, the aqueous dermis may provide a significant barrier to systemic absorption. After lipophilic drugs are absorbed across the intact stratum corneum, further absorption of exceedingly lipophilic drugs is limited by their tendency to partition into the stratum corneum and not diffuse further into the epidermis, forming a stratum corneum reservoir. Ultimately, drugs can be eliminated in this fashion as corneum cells are sloughed off into the environment.

There are a number of other factors that can modulate stratum corneum permeability. Hydration of the stratum corneum increases its permeability to many compounds. Thus, at high relative humidity (e.g., greater than 80%), compound penetration may drastically increase as is seen in Fig. 2 with para-thion absorption dosed under different degrees of relative humidity [5]. Complete hydration of the barrier, obtained by using an occlusive dressing which prevents insensible water loss, drastically increases penetration. Most transdermal delivery devices, by their very nature, function as occlusive systems.

The dermis is a highly vascular tissue arising from its role in thermoregulation via modulation of blood flow. The dermal vasculature provides oxygen and nutrients to the avascular epidermis above it. This blood supply is under complex neural and local humoral control. Cutaneous blood flow may be shunted away from perfusing capillary beds through non-exchanging shunts when the mammal is in a mode of heat retention. In contrast, when heat exchange with the cooler skin is desired, shunts are closed and exchanging capillaries closer to the
Fig. 2. Effect of relative humidity on the percutaneous absorption of parathion using in vitro porcine skin (mean±S.E.M.).

epidermis are perfused. Dermal perfusion has been estimated to change by a factor of 100 depending on thermoregulatory status. For certain compounds, modulation of dermal perfusion may alter transdermal drug delivery. Vasodilation decreases dermal perfusion and traps drugs which have penetrated the epidermal barrier, thereby decreasing systemic absorption but enhancing the local activity. In contrast, vasodilatation would promote systemic delivery but minimize local accumulation. Fig. 3 depicts this later scenario where lidocaine absorption into the systemic circulation was increased when cutaneous vasculature was dilated with co-administered tolazoline, an α-adrenergic receptor antagonist [6]. The subcutaneous tissue is composed of adipose cells which provide shock-absorbing functions, acts as thermoinsulation, and provides a reserve depot of energy. However, relative to transdermal delivery, this lipoidal layer may also serve as a depot for lipophilic drugs that have penetrated to the dermis.

The appendages including hair, sweat and sebaceous glands provide another potential route for drug transport from the skin surface into the dermis, bypassing the stratum corneum barrier. Most recent studies suggest that this is not an important route of entry for topically applied drugs since the surface area of their orifices are very small compared to that
of the interfollicular epidermis. However, drug particles that lodge in the openings of hair follicles or glandular ducts, may slowly release drug into these appendages. A similar mechanism occurs with some topical flea products in dogs and cats. The drug fipronil for dogs and cats has its advantage over other topical flea products in that animals can be bathed after topical administration. The drug collects in the sebum and oils of the follicles and is slowly released. This results in a 30-day effect after a single treatment.

Hair follicle density and arrangement is a major variable when comparing drug absorption across species. Species with high hair density, tend to have attenuated interfollicular epidermis, which may provide a reduced barrier to drug penetration. Additionally, some drugs may physically bind to hair further preventing absorption. The secretions of sweat and sebaceous glands also provides another variable, both by providing a mechanism to hydrate skin via sweat or decreased water loss due to a layer of sebum on the skin’s surface. Similarly, sebum may serve as a vehicle for drugs that are soluble in it.

The final factor which must be considered is the ability of the epidermis to metabolize drugs before being absorbed by the systemic circulation [7]. Studies have demonstrated that the skin possesses both phase I and II biotransformation pathways, allowing first pass cutaneous metabolism of compounds. In addition to cellular enzymes, soluble esterases are also present which have been used in transdermal drug delivery studies. In these cases, pro-drugs are formulated as esters which promote stratum corneum transport. As these pro-drugs reach the epidermis, soluble esterases cleave off the ester groups and release active parent drug into the systemic circulation.

2.2. Species and regional differences

As can be appreciated from the above discussion, there are significant species differences which could impact on the design of transdermal delivery patches for veterinary species. In fact, significant differences exist among different body regions within a species. For example, in humans it is accepted that the rate of penetration for most non-ionized compounds is: scrotal > forehead > axilla/scalp > back/abdomen > palmar and plantar [8]. The palmar and plantar regions are highly cornified due to their functions which involve constant abrasion. In addition to thickness, hair follicle density, structure and arrangement varies greatly across different body regions [3]. Because of this factor, in humans the scalp should be viewed differently than other body regions. Finally, cutaneous blood flow varies among the different body regions [9,10].

These differences are exacerbated when diversification among species is considered. Table 1 lists the comparative skin thickness and blood flow determined using laser Doppler velocimetry, across three different body sites in various veterinary species [9,10]. As one can appreciate, there are significant differences in all parameters across body sites and species. The ear and abdomen generally have the highest rate of blood flow while the buttocks has the thickest epidermis and stratum corneum. The hair and sweat/sebaceous gland density, as well as anatomical structures, between these sites and species is also significantly different. Another anatomical variable which has been reported to significantly affect percutaneous absorption is the size of an individual corneocyte, although this parameter has not been evaluated across veterinary species. The primary site used for transdermal patch delivery in veterinary medicine is the back, because this is one of the few locations that they cannot lick, chew, or scratch. However, in sick or debilitated animals, other sites such as the lateral thorax or inguinal area are used. It is important if drug delivery from patches applied to different sites is compared, these anatomical and physiological factors may impact the drug flux observed.

There have been a number of studies comparing the percutaneous absorption of chemicals across laboratory animal species, pigs, primates and humans focused on evaluating animal models for human drug development and chemical risk assessment. These are extensively reviewed elsewhere [11–13]. For most compounds, the rank order of the extent of absorption is mouse > rats/rabbits > humans/pigs/primates. In general, pigs and monkeys have similar absorption characteristics as humans. This is due to similar anatomy, relatively sparse hair coats (abdomen of monkeys), and biochemically similar compositions of stratum corneum lipids. Unfortunately,
similar studies have not been conducted in veterinary species except for one excellent review on topical delivery to cattle and sheep [14]. In fact, this literature is heavily skewed toward studies conducted in pigs due to their use as an accepted animal model for humans. Studies are also available in dogs due to their occasional use in biomedical research as well as studies of human transdermal patches utilized in the veterinary clinic.

2.3. Quantitating percutaneous absorption

In order to quantitate the delivery of drug across the stratum corneum and epidermis, a framework must be developed to relate transdermal flux to applied surface concentration. In most cases, transfer across the skin is similar to transfer across any membrane and thus these techniques have been extensively applied to dermal transport [15–18]. These approaches will be reviewed briefly.

2.3.1. Fick’s law of diffusion

The movement of chemicals across the stratum corneum barrier into the epidermis occurs primarily by passive diffusion driven by the applied concentration of drug on the surface of the skin. This is best expressed using Fick’s Law of Diffusion which states that the steady state of drug flux across a membrane can be expressed as:

\[
J = \frac{D P}{h} (\text{Concentration Gradient}) (\text{Surface Area})
\]

where \( D \) is the diffusion coefficient or diffusivity of the drug in the intercellular lipids of the stratum corneum, \( P \) is the partition coefficient for the drug between the stratum corneum and the dosing medium on the skin surface, and \( h \) is the skin thickness or actual path-length through which the drug diffuses across the diffusion barrier. The driving force for this process is the concentration gradient that exists.
between the applied dose and the blood-perfused dermal environment. The term \( \text{DP/h} \) is often called the permeability coefficient. Kinetically, this is a first-order rate constant that is the basis for the absorption rate constant \( (K_p) \) obtained in pharmacokinetic analyses of transdermal drug delivery studies. Transdermal flux is expressed in terms of skin surface area, making the two important properties of dosage in a transdermal system the concentration of drug applied and the surface area of application. Finally, Fick’s law expresses the steady-state flux of drug that occurs when this rate becomes constant. In skin diffusion studies, this occurs after passage of a lag time which is a function of the drug ‘loading’ the stratum corneum and dermis, diffusivity, and thickness of the skin. Because of the differences in skin thickness seen between body sites and species, this is a major variable in comparative transdermal delivery studies.

The diffusivity of a drug is a function of the molecular weight, molecular size or more specifically volume, molecular interactions with skin constituents (e.g., hydrogen bonding, hydrophobic interactions, etc.), the drug’s solubility in the membrane milieu, and the degree of ionization. Large molecular weight drugs (approximately greater than 400 Da, e.g., proteins) have extremely low diffusivities, thus effectively preventing them from being absorbed across the skin barrier. These properties are often correlated to a drug’s melting point. For compounds that are partially ionized, diffusivity is decreased, indicating that only the non-ionized fraction of a weak acid or base is available for diffusion across the stratum corneum. This is a function both of the pH of the dosing medium as well as the pH of the skin that normally ranges from 4.2 to 7.3 depending on species and environmental conditions.

The partition coefficient determines the ability of the drug to gain access to the diffusion pathway. Partition coefficient is usually determined in experimental systems by measuring octanol/water or lipid/water partitioning. The higher the ratio, the greater the lipophilicity. Dermal formulations may significantly modify percutaneous absorption. For a lipid-soluble drug, a lipid base formulation would tend to decrease absorption by retaining applied drug at the skin surface. In contrast, an aqueous base would promote absorption solely by this partitioning phenomenon which would favor drug movement out of the formulation into the more favorable lipid environment of the stratum corneum. The reverse scenario would be operative for a hydrophilic drug. Independent of these formulation effects, the penetrating drug must have some propensity to partition into the intercellular lipids of the stratum corneum. It is generally accepted that the optimal log octanol/water partition coefficient for a drug to penetrate the stratum corneum is approximately two. In other words, the drug is partitioned in the lipid phase approximately 100-fold. For hydrophilic drugs with low partition coefficients, pro-drugs can be formulated (e.g., by esterification as discussed above) which increases the drug’s permeability across the stratum corneum. The lipophilic moiety (e.g., ester) is then cleaved in the epidermis, dermis or even plasma and active parent drug is then distributed throughout the systemic circulation. If the partition coefficient is too great, drug may have a tendency to sequester into the stratum corneum and not enter the more aqueous dermis, thereby decreasing systemic delivery. If it does penetrate into the dermis, the high lipid partition coefficient may favor formation of a dermal depot. It must be noted, that the drug must also have partitioning properties which are favorable for entering into solution into the aqueous plasma, or be able to bind to plasma proteins for systemic absorption to occur. These characteristics which promote stratum corneum permeability and plasma uptake are confounding and impact on the ability of using pure physicochemical properties to predict in vivo drug delivery.

Vehicle or formulation effects in themselves may become very complex. In addition to their primary role in determining the functional partition coefficient for the system, they themselves may also be absorbed into the stratum corneum and alter the permeability properties of the lipids. This is the mechanism of many absorption enhancer molecules that are intentionally incorporated into a formulation to promote transdermal delivery. These include substances such as ethanol, oleic acid, terpenes, and a host of other lipophilic chemicals. As they diffuse into the lipid barrier, the physical chemical properties of the lipid are altered which in turn changes the permeability coefficient of the lipid relative to the penetrating drug. Occlusion and hydration of the
stratum corneum, as was discussed in the context of Fig. 2 above, operates by this mechanism. There are a number of excellent technical reviews describing these mechanisms which are beyond the scope of this review [19,20]. The vehicle may also extract the intercellular lipids, thereby reducing barrier function and enhancing absorption.

Finally, for compounds that are absorbed across the stratum corneum by passive diffusion, other properties of the skin may modulate the rate and amount of compound which is absorbed into the systemic circulation. We have already shown in Fig. 3 how the extent of blood flow may directly effect the amount of drug which has crossed the stratum corneum that is ultimately absorbed into the systemic circulation. In general, blood flow is not rate limiting for topically applied drugs unless the normal rate of dermal perfusion is not sufficient to absorb the amount of drug entering the dermis [21]. This occurs when the drug is not soluble in the blood, or when the rate of transdermal flux exceeds the capacity of the blood to clear it from the dermis. The latter is only seen in transdermal systems which deliver a relatively high flux of drug. A second factor which may modulate the amount of drug absorbed into the systemic circulation is the extent of first-pass cutaneous biotransformation. We have discussed this in terms of ester pro-drugs, however if any drug is a substrate for epidermal enzyme systems, a fraction of drug, which has diffused through the stratum corneum, may be metabolized prior to absorption into the systemic circulation. Our laboratory has demonstrated this phenomenon with topically applied pesticides [22–24]. Finally, environmental and skin temperature may alter drug flux across the skin. There are two components to this effect. The first, even documented evidence using avascular in vitro systems, relates to an increased diffusivity of the penetrating drug in the stratum corneum arising from thermodynamic effects [25]. The second mechanism is due to an increase in dermal blood flow secondary to systemic temperature regulation.

In conclusion, transdermal drug flux occurs primarily by passive diffusion through the intercellular lipid domain of the stratum corneum. Its rate is dependent upon the permeability coefficient of the drug, applied concentration and surface area. Unlike other routes of drug administration, dosimetry for a transdermal preparation is expressed in terms of concentration per unit of applied surface area. An examination of Fick’s law also illustrates how the comparative anatomical differences among species may alter drug flux. These include skin thickness, hair density and thus interfollicular epidermal thickness, as well as differential lipid composition which would change the permeability coefficient. Further modulating factors include different rates of cutaneous blood flow and capacity or mechanisms of first-pass cutaneous biotransformation. Similarly, environmental or clinical factors such as occlusion, high relative humidity, temperature (which could increase permeability as well as increase dermal blood flow), disease-induced changes in skin structure or function, or abrasion (which would remove the stratum corneum barrier) may alter the transdermal flux.

2.3.2. In vivo methods

The target of most transdermal delivery systems is the intact animal, making in vivo methods the preferred approach for assessing feasibility and patch design. In many ways, these methods are no different than those employed for evaluating the absorption of drugs from any route of administration. The goals are to determine the fraction of topically applied dose that leaves the delivery device and enters the systemic circulation, as well as the concentrations of delivered drug relative to efficacy and safety in the target animal.

The primary method used to assess transdermal absorption in the intact animal, is to compare the area under the concentration versus time (AUC) curve after topical dosing to that obtained after intravenous administration (bioavailability) or via another route (bioequivalence). These techniques have been extensively reviewed elsewhere for veterinary scenarios [26–28] and transdermal/topical preparations in humans [29–31].

The basic approach for assessing bioavailability (compared to intravenous route) or bioequivalence (compared to existing product route) is to calculate the following ratio:

\[
\frac{(\text{AUC}_{\text{transdermal}})}{(\text{AUC}_{\text{route}})} \times \frac{(\text{Dose}_{\text{route}})}{(\text{Dose}_{\text{transdermal}})}
\]
If bioavailability ($F$) is being determined, then the value cannot exceed 1.0 since by definition an injected dose is totally available systemically. If bioequivalence is being determined, then the ratio can vary from almost zero to any number since this approach is essentially comparing the bioavailability of two formulations. If the goal is to develop a transdermal system which is bioequivalent to another already approved formulation, then the above ratio must be within the range of 0.8–1.25 relative to the pioneer formulation, estimated from a specific study design with sufficient statistical power and level of confidence ($\alpha$). Other metrics of bioequivalence, such as $C_{\text{max}}$ and partial AUC may also be appropriate. The use of partial AUC (e.g., AUC$_{0-T_{\text{max}}}$) is often suggested to insure that ‘dose dumping’ from the patch does not occur.

A simple approach often employed is to assay the drug remaining on the skin, or in the delivery device for patch studies, and compare this to the amount originally applied. The difference is the amount of drug that was delivered by the formulation. The limitation to this approach is that no information is available as to the biological fate of the delivered drug.

Another approach that has been used to assess absorption of topical formulations, relative to the actual percent of drug dose which has been absorbed into the systemic circulation and distributed to the animal, is to use the above equation but substitute recovery in urine and feces for AUC. This is preferred when the blood or plasma concentrations obtained after topical dosing are too low to adequately quantitate with existing analytical methodologies. Such studies are often used to quantitate systemic absorption of topically applied pesticides. If the drug undergoes tissue binding or sequestration in the animal’s body, a mass balance study is often performed where drug recovered in the carcass is also factored into this equation.

A problem that plagues all of these approaches is when drug is absorbed across the stratum corneum but does not reach the dermal circulation. This occurs when drug forms a depot in the stratum corneum or subcutaneous tissue. These drug concentrations could be related to local irritation of the applied drug. Mass balance studies will detect these when the total dose recovered from the dosing site, added to the amount of drug recovered from urine, feces and carcass, is less than the applied dose.

The final in vivo strategy employed is to assess absorption by measuring how much drug is absorbed into the skin under the application site. This is usually done simultaneously with assessing absorption in plasma or excreta in order to assess the cutaneous distribution of the applied dose. After removal of the formulation or device, the skin surface is swabbed to remove non-penetrated dose and a core biopsy is then taken and assayed for drug. Alternatively, the biopsy may be quick-frozen in liquid nitrogen and cryostat sections collected to determine the penetration profile in the skin. Other workers have used cellophane tape to strip off the stratum corneum and measure drug profile in this tissue. Rougiere et al. [32,33] have suggested that the amount of drug remaining in the stratum corneum 30 min after removal of a topical formulation correlates to its systemic absorption. This is based on the fact that this measurement relates to the driving force for diffusion of drug as presented earlier in Fick’s Law. The utility of this approach is in comparing formulations using a non-invasive technique, although vehicle effects that alter the stratum corneum permeability, may confound the correlation. To completely describe the absorption of a topically applied transdermal dose, a mass balance study should be conducted which assesses systemic delivery by measuring blood concentrations, mass balance and systemic distribution from total recovery in urine, feces, and internal organs; as well as skin biopsies and stratum corneum samples to measure local skin distribution under the application site. Such a study defines the total disposition of the drug and greatly facilitates the design of subsequent studies aimed to assess bioequivalence or clinical efficacy. The drawback to in vivo studies is that the pattern of percutaneous absorption is confounded with the variability inherent to systemic distribution and elimination. This impacts on the precision of in vivo data analysis to identify formulation-specific factors that alter drug delivery. This problem has led to increased reliance on and use of in vitro methods early in the development cycle.

2.3.3. In vitro methods

A significant amount of studies are conducted using various in vitro techniques. Before these are
presented, a distinction must be made between in vitro studies used to assess dissolution or release from a transdermal device, and those used to assess absorption across the skin. The former are very similar to techniques used in assessing dissolution of oral drug tablets and measuring the rate of drug release from the formulation. Unlike compendial oral dissolution methods, there are standards developed for transdermal systems such as those described in the US Pharmacopeia [34]. However, it must be stressed that they do not assess the absorption of drug across the stratum corneum barrier [29].

The primary connotation of the term in vitro in transdermal studies is the use of skin sections removed from an animal to assess transport in diffusion cell systems. These have been extensively described elsewhere [30,35]. In these systems, a section of skin is obtained from an animal donor either using a dermatome, which is a slicing apparatus that cuts sections of skin parallel to the surface, to produce a split-thickness preparation or by simply dissection to obtain a full-thickness preparation. This membrane is then mounted in a two chambered diffusion cell apparatus. The donor half faces the epidermal surface of the membrane while the receiver half of the cell faces the dermis. In many cases where only penetration through the rate limiting stratum corneum is being studied, frozen skin may be thawed and mounted in the cells. Freezing does not appear to effect the integrity of the stratum corneum barrier.

The receiver solution may be contained in one of two configurations: static where the cell is filled with a fixed volume solution and samples are taken from a port; or flow-through where the receptor solution is constantly perfused under the dermis and samples collected after they exit the system. The donor compartment may be left open to the environment and drug deposited onto the surface (finite dose), or alternatively the donor half of the cell may be also filled with liquid containing dissolved drug (infinite dose). In the latter case, the skin is fully hydrated since it is being bathed in donor solution. Receptor solutions generally consist of saline in pharmaceutical studies assessing hydrophilic drug absorption, or buffered albumin or cell culture media in toxicological studies where lipophilic drugs are being studied. Some investigators have added other solvents to the receptor phase to promote solubility of lipophilic penetrants in the perfusate. If viability of the skin membranes is desired for cutaneous metabolism studies, an energy source such as dextrose and O₂/CO₂ gas is fed into the perfusate to maintain some degree of metabolism. These systems have a regulated temperature at 32–37°C to mimic skin surface temperature or core-body temperature.

In both static and flow-through systems, drug flux is monitored in the receptor cell. The data plotted in Fig. 2 above was obtained using split-thickness porcine skin mounted in a finite-dose flow-through diffusion cell system. In vitro systems are used to obtain parameters for solving Fick’s Law. The surface concentration is known and receptor concentrations are monitored until steady-state fluxes are obtained. Knowing the partition coefficient and thickness of the skin, and by measuring the steady-state flux, the equation can now be solved for the diffusion coefficient.

As can be appreciated, in vitro systems are economical to conduct and generate ‘clean’ data amenable to quantitative analysis since the confounding variability inherent to the in vivo setting is absent. If absorption through the stratum corneum is the rate-limiting step in percutaneous absorption, these methods are appropriate. However, if the drug’s pattern of absorption is dependent upon other biological functions such as blood flow, dermal distribution, etc., then these systems may generate misleading results. Another concern is that in full-thickness and split-thickness preparations, significant dermis remains that may be a barrier to lipophilic drugs and even serve as an artificial reservoir. To overcome this, some investigators have used techniques that split the epidermal–dermal junction (heat separation, enzyme digestion). However, if the skin being studied has significant hair density, then the resulting epidermal membrane may have holes from where the hair once exited to the surface. Another limitation is that prolonged perfusion may result in membrane degradation due to cellular death. This generally does not occur until after 24 h, however histological examination of in vitro skin sections demonstrates epidermal changes as early as 8 h [36].

Recent developments in this field have been the use of artificial skin membranes to assess absorption across human skin. Such systems are organ cultures which possess intact stratum corneum but no appendages [37]. Studies conducted to date suggest that
Permeability through these systems compared to split-thickness human skin may be ten or more fold greater. However, they may be useful to assess the ability of human cells to metabolize applied drugs.

In vitro techniques are amenable to study absorption from transdermal patches. In these configurations, a finite dose flow-through diffusion cell system is used and the patch is sandwiched against the epidermis before mounting in a diffusion cell. Drug flux is then monitored as described above.

Our laboratory has developed an alternate in vitro/ex vivo technique, the isolated perfused porcine skin flap (IPPSF), which more closely reflects the anatomical and physiological state of skin in the intact animal [38]. The IPPSF is a fully vascularized, viable model which has been shown to closely predict the absorptive flux profile seen in vivo [39–41], and because of the similarity of pig and human skin, to predict in vivo human percutaneous absorption [42,43]. A single pedicle, axial pattern tubed skin flap is created on the abdomen of a pig [44]. Two days later, the flap is harvested and the perfusing superficial epigastric artery is cannulated and the preparation transferred to a specially designed isolated organ perfusion chamber. The flap is maintained in a temperature and humidity controlled environment, and the flap perfused with a Krebs–Ringer-buffered solution containing physiological levels of albumin and glucose. The drug or transdermal patch is placed on the surface of this tubed flap and venous effluent collected over the course of an experiment. At the termination of a study, the surface is wiped, stratum corneum tape strips collected, and a core biopsy taken to allow for a complete mass balance analysis.

The advantage of this model over other in vitro approaches is that the anatomical structure of the skin is maintained and drug-induced alterations in blood flow or epidermal metabolism will affect drug absorptive flux as it does in vivo. Two flaps can be raised from a single pig. This model also allows simultaneous monitoring of the venous effluent for production of inflammatory cytokines (e.g., TNFα, interleukins, prostaglandins) to be used as early biomarkers of drug-induced irritation. Relative to predicting systemic absorption, the venous effluent is considered as input into the circulation making the IPPSF conceptually a biological infusion pump. The IPPSF is well suited to assess formulation development since transdermal flux can be measured without confounding systemic interference. This increases the power of detecting differences between drug delivery systems.

### 2.4. Transdermal Pharmacokinetics

Many workers in transdermal delivery use techniques that have been developed for other routes of administration to quantify drug flux as described above when AUC is monitored. However, when the concentration versus time profile is to be predicted from in vitro flux data, or the rate of drug absorption must be obtained from plasma concentration versus time profiles, the techniques of pharmacokinetics becomes useful.

There is no fundamental difference between the application of pharmacokinetics to transdermal delivery as compared to other routes and a general pharmacokinetics text should be consulted for approaches [28,45,46]. If the absorption of drug is first order and described by Fick’s Law, standard modeling techniques may be used to estimate $K_a$ using classical compartment-based ‘sum-of-exponential’ curve stripping or feathering techniques; or the mean absorption time (MAT) using statistical moment analysis. In many topical preparations, applied dose saturates the absorptive capacity of the skin and a significant fraction of dose is not available for absorption. When expressed as a fraction of dose absorbed, fluxes will be smaller with higher doses since all of the topically applied dose is not available for absorption. However, when expressed as permeability coefficients, rate constants such as $K_s$, or MATs, these will be constant and independent of dose. Many workers estimate flux from the in vitro systems described above and calculate $K_s$ from these data. With a knowledge of the systemic pharmacokinetic model from an intravenous study, plasma concentration profiles can then be estimated. An excellent reference describing the myriad of approaches possible is the text by Gosh et al. [29].

These approaches are applicable for topical drug preparations, however some modifications must be made when transdermal delivery patches are employed. As will be discussed in the next section, most transdermal systems control the rate of drug
release and result in constant flux expressed as mass released per unit time. In this case, absorption is now a zero-order rate and not a first-order fractional rate constant. These data should be treated as if delivered from a constant-rate intravenous infusion. For example, when statistical moment techniques are used, the rate of input is now not a MAT defined as \(1/K\); but is rather one-half the total patch release rate. Similarly, compartmental-based curve feathering techniques may not be appropriate to estimate a \(K\). Instead, methods such as nonlinear deconvolution, Wagner–Nelson or Loo–Riegelman methods may be more appropriate.

It must be stressed that the sources of variability due to flux across the skin and systemic disposition are independent. We have explored the sources of variability in transdermal systems using the IPPSF model discussed earlier. Accurate estimates of the mean plus variance of plasma concentration versus time profiles observed in vivo in pigs may be obtained using so-called boot-strap or full-space methods of combining IPPSF and in vivo intravenous pharmacokinetic parameters [47]. In this approach, all possible combinations of IPPSF efflux profiles (\(X\)) are combined with all observed intravenous disposition profiles (\(Y\)) to generate \(XY\) possible transdermal concentration versus time profiles. The statistical properties of these \(XY\) profiles closely matches observed experimental studies conducted using the same transdermal systems on in vivo pigs.

Since transdermal patches deliver a constant rate of drug release once steady-state (\(C_{ss}\)) concentrations are achieved, it is relatively straightforward to determine the actual rate of patch delivery in an in vivo experiment if one knows the total body clearance (\(Cl_B\)) of the drug after intravenous administration:

\[
\text{Delivery rate (mass/time)} = C_{ss} \text{(mass/volume)} \times Cl_B \text{ (volume/time)}
\]

This rate of delivery from the patch can then be compared to its manufacturer's stated rate. However, this requires that \(Cl_B\) be obtained from an intravenous study, ideally at the same dose that the patch should have delivered. Systemic effects on \(Cl_B\) due to metabolism or unique distribution or recycling phenomenon would be detected in the intravenous study, making this simple relationship a relatively robust tool in designing transdermal patches as well as in utilizing them in the clinic. By rearranging this relation, one can calculate the \(C_{ss}\) obtained with a specific delivery rate as:

\[
C_{ss} = \frac{\text{Delivery rate}}{Cl_B}
\]

Similar equations can be developed if stochastic methods are used to analyze the observed concentration versus time profiles. These methods calculate pharmacokinetic parameters using area under the curve (AUC) and area under the moment curve (AUMC). Since \(Cl_B = \frac{D}{AUC_{IV}}\), one can obtain this parameter after intravenous dosing and use the above formulae. The observed mean residence time (MRT = AUMC/AUC) after application of a transdermal patch system is:

\[
\text{MRT}_{\text{Transdermal Patch}} = \text{MRT}_{\text{IV}} + \left(\frac{\text{Patch Duration}}{2}\right)
\]

As can be appreciated, these techniques are powerful tools to assess the function of transdermal patches in veterinary species. To be properly applied, intravenous studies should be conducted to independently obtain estimates of \(Cl_B\), AUC\(_{IV}\) and MRT\(_{IV}\) so that the actual patch delivery rate and systemic bioavailability can be unambiguously determined.

### 3. Transdermal drug delivery

Use of the skin provides an alternative approach to systemic delivery of drugs in veterinary species. The problems which arise are due to the large differences in skin structure and function among the animals which must be targeted. However, these differences could actually be considered as a prime motivation for developing transdermal patch systems.

#### 3.1. Topical formulations versus patches

The primary difference between a topical liquid or gel formulation and a transdermal patch is that the rate of drug absorption in a formulation is controlled by diffusion through the stratum corneum, while in a patch the rate is controlled by release from the system itself. As discussed above, there are many sources of variability inherent to passive absorption by Fickian diffusion. In a transdermal preparation, such variability in absorptive flux will translate to
variability in the systemic concentration versus time profile obtained. However, this variability can be eliminated if the rate of release from the topical delivery system is controlled to be less than the diffusive flux across the stratum corneum. In this scenario, which is operative in transdermal patches, delivery across the skin is now truly a zero-order constant rate process controlled by the specific design of the patch. It must be stated that controlled release from gel formulations is also possible, however this approach has not been extensively utilized due to the other attributes of patch delivery described below.

The rate of control required for systemic effects is an important variable when selecting whether a controlled patch or normal formulation is required [29]. This is directly related to the nature of the pharmacodynamics of the process being targeted. For example, if the targeted process requires that serum concentrations be maintained within a relatively well defined ‘therapeutic window’ for either safety or efficacy endpoints, patch technology may be important. However, if the therapeutic process being targeted only requires that a minimum effective rate of delivery occurs, and intermittent high peak blood concentrations do not result in adverse effects, then liquid formulations which are capable of delivering this minimal flux may be satisfactory.

This scenario is encountered in veterinary medicine where topical application of pesticides (pour-ons) for systemic control of heartworm, fleas, ticks, and other parasites only requires achieving a minimal threshold for efficacy. In fact, in these cases, the target is often the skin of the remainder of the animal.

Pour-ons provide an easy method of dosing whereby absorbed drug forms a depot in the skin at the site of application which delivers a low flux of drug to the systemic circulation, which in turn distributes back to the skin for a prolonged duration of action. Intermittent bursts of chemical flux do not lead to adverse effects and temporary breaks in delivery do not affect steady-state concentrations. These formulations are thus very effective and have been extensively utilized in the animal health market. Three of the most popular and commercially successful pour-on products are fipronil (TopSpot®, Frontline®), imidacloprid (Advantage®), and selamectin (Revolution®). They are all three distinct products. For example, selamectin is formulated in an alcohol base and is absorbed systemically to kill fleas, heartworms and intestinal parasites for 30 days. Fipronil is contained in an oily vehicle which forms a depot within the hair-follicle allowing continued release even in the face of washing. These products, and the other topical insecticides discussed below, have gained market acceptance and clearly demonstrate the potential of topical administration for delivering systemically active drugs.

Transdermal patch technology would not offer any benefits for these compounds. A similar situation exists with many hormone delivery schemes where efficacy is related to achieving a minimal effective concentration and adverse effects are not seen with intermittent high fluxes of drugs. Testosterone gel delivery systems are presently being developed in humans based on this premise.

There are some very specific limitations to the types of drugs which can be formulated in transdermal patch systems. The first is that the normal flux of drug across the stratum corneum must be great enough that patch-control to a lower rate of delivery still results in sufficient blood concentrations for efficacy. Poorly absorbed drugs are thus not amenable to incorporation into patches. However, components can be built into the patch which enhance percutaneous absorption to the point that delivery is feasible. For example, by their very nature, all patches are occlusive systems that hydrate the stratum corneum and enhance drug absorption by this means (recall Fig. 2 above with parathion). This occurs solely because the patch itself, being essentially a plastic sheet adhered to the skin, prevents water loss and thereby hydrates the underlying stratum corneum. This simple fact results in an increased rate of delivery which would not be possible with liquid formulations. Secondly, pharmacological enhancers may be incorporated into the system (e.g., ethanol) that increases diffusive flux. Finally, recalling that the rate of topical delivery of a drug is also related to the applied surface area, increased systemic concentrations can be obtained simply by making larger patches. These three approaches often increase the rate of percutaneous absorption to a degree sufficient that patch technology can then control release of the active ingredient.
It is generally accepted that under current optimized techniques in humans, approximately 1 mg of a favorable drug (molecular weight of <400 Da, melting point >150°C) can be delivered from a 1-cm² area of skin over a 24-h period [29]. Unfortunately, data do not exist to translate this working limit to veterinary species outside of the pig, which is similar to humans. In fact, these species may have higher inherent drug permeability which would allow increased rates of daily dosages.

Transdermal patches offer a number of other benefits, in addition to maintaining control when the therapeutic index is narrow, over other routes of delivery. The most obvious one is that they can be removed from the animal when one desires termination of delivery. This cannot be easily accomplished with outer routes, including topical formulations. Secondly, by virtue of entering the systemic circulation through the cutaneous vasculature, they completely circumvent the first-pass hepatic metabolism seen with many oral drugs. Although the skin has the ability to metabolize drugs, as was seen by our group with isosorbide dinitrate in porcine skin [48], it is limited and easily saturated compared to the ability of the liver to metabolize drugs presented it via the portal vein. Transdermal delivery, both as a formulation or a patch, opens up a non-invasive route of administration that is ideally suited for many drugs (e.g., nitroglycerin, scopolamine, testosterone). Third, for drugs with very short systemic half-lives that require sustained concentrations for therapeutic effects, transdermal patches provide the sustained-release delivery needed for longer periods of time. This results in a major advantage because it is more convenient for veterinary hospitals compared to intravenous infusion systems and client compliance is improved due to the reduced frequency of dosing required.

There are a number of disadvantages of transdermal delivery [29], the most obvious being that if a drug does not permeate skin, it is not amenable to transdermal delivery. This limitation is absolute unless novel enhancer technologies are developed which increase permeability to poorly absorbed drugs. Secondly, by virtue of the occlusive nature of patch systems, cutaneous irritation is often encountered which limits the duration that a patch can be worn at a single site. This is both drug specific (e.g., clonidine) and a function of the enhancers used. Some approaches to counteract this adverse effect are under development and include incorporation of anti-irritant compounds into the patch system itself. Third, the patch must have sufficient adhesion to the application site that continuous delivery of drug occurs. Also, in animals compared to people, an area of the skin to which the patch is applied must be shaved or clipped free of hair in order for the patch to adhere. Significant advances in adhesive technology over the past few years have largely eliminated this problem for humans.

3.2. Systems developed for human use

Since there have been no transdermal patches specifically developed for veterinary species, it is prudent to briefly review human patch development for insights in to design and potential candidates for veterinary applications [29]. Table 2 lists the drugs that have been developed for human transdermal drug delivery systems. A number of additional drugs are in various stages of pre-clinical and clinical development, and include albuterol, alprazolam, atenolol, buprenorphine, cytarabine, deprenyl (selegiline), dehydroepiandrosterone, dronabinol, enalapril, eptazocine, ethinylestradiol, isosorbide dinitrate, ketorolac tromethamine, ketotifen, norethindrone, prazosin, and terfenadine. Systems developed for electrically assisted transdermal delivery (e.g., iontophoresis) for compounds such as peptides (LHRH, insulin, etc.), lidocaine and other small organic molecules will be discussed below.

There are a wide number of approaches to transdermal patch design, all of which share the attributes depicted in Fig. 4 [29]. All systems consist of a method to contain the drug in a patch, either directly

<table>
<thead>
<tr>
<th>Drugs which have been incorporated into transdermal delivery systems for humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Estradiol</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Nicotine</td>
</tr>
<tr>
<td>Nitroglycerine</td>
</tr>
<tr>
<td>Scopolamine</td>
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<tr>
<td>Testosterone</td>
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</tbody>
</table>
drug is contained in a reservoir if it is in a gel or a liquid form. However, if the drug is incorporated into a laminate polymer, then a reservoir is not required and the system is a poly-laminated plastic sheet.

All systems require an adhesive layer to adhere the membrane to the skin. It is imperative in selecting the adhesive that the drug’s release from the system is not affected by passage through this adhesive otherwise the rate of delivery may be adversely affected. An advance in patch design that has further simplified these systems is the development of polymer techniques which allow the drug to be directly incorporated into the adhesive. Release from the polymer controls the rate of delivery. In such a system depicted in Fig. 4A, once the release liner is removed, the patch then consists only of the drug containing adhesive adhered to a plastic backing.

These differences in patch design have a direct implication to the use of human products in veterinary species. Since the rate of topical drug delivery is related to the area of skin application, veterinarians have used human patches in smaller species by cutting patches to the required size. Obviously, this can only be accomplished in patches where the drug is incorporated either in a matrix or the adhesive, as reservoir systems would rupture and lose their drug reservoir. Some veterinarians also remove only a portion of the protective adhesive backing ostensibly to expose a smaller surface area to the skin. However, at least in cats, this does not always seem to affect absorption.

There is an extensive literature base and patent history on the use of transdermal delivery systems in humans, which is adequately reviewed in several texts [29,49]. Many of the principles outlined in the above discussion are based on this work. These references should be consulted for details on specific systems and their applications in clinical human medicine.

3.3. Percutaneous absorption in veterinary species

The reader should now have a reasonable understanding of the mechanism of drug absorption across the skin and the factors that may modulate transdermal flux. The important aspects of comparative dermal anatomy and physiology, which could impact on transdermal drug flux, have been reviewed.
Finally, the characteristics of available transdermal patch technology, as well as the factors which make patches different from liquid topical formulations, has been presented.

The remainder of this review will focus on aspects of transdermal delivery, which highlight the unique problems caused by anatomical and physiological differences seen in veterinary species. There are two sources of information available to address these issues. The first is a reasonable body of literature on the percutaneous absorption of topically applied pesticides in veterinary species which shed light on comparative aspects of dermal absorption, and clearly demonstrate that this route of administration is efficacious for systemic targets. The second are reports on the use of human transdermal patches in veterinary species, which offer direct evidence of their efficacy as well as contrast differences between human use for which they were designed, and veterinary species.

3.3.1. Topical pesticides

There has been work done relative to the percutaneous absorption of topically applied pesticides in veterinary species, both from an animal health product perspective as well as environmental exposure. This is the only body of literature which clearly indicates that there are tissue residue concerns with topical applications that may impact food safety [50]. Recently, we have reviewed this area [51] and will highlight important concepts relative to the present topic. A large literature base exists on the comparative absorption of chemicals in laboratory animal species. However, due to the very small mass of these animals, in vivo data may be misleading when they are metabolically scaled up to larger species. As discussed earlier, chemical flux through mouse, rat and rabbit skin is much greater than that of humans and other species.

The insecticides which have been or currently are approved for topical application in veterinary species include chlorinated hydrocarbons (e.g., methoxychlor, lindane), organophosphates (e.g., fenthion, famphur), carbamates (e.g., carbaryl), pyrethrins (e.g., permethrin, fenvalerate) and antihelmethics such as ivermectin and levamisole. Most other topicals used in veterinary medicine are applied for a local dermatological effect, and not for systemic targets. Many of these products are formulated as ‘pour-on’ products which contain dilute solutions of the active ingredient; or as ‘spot-on’ low volume formulations containing concentrated active ingredients to promote systemic absorption. Three effective topical pour-on products that were discussed earlier include fipronil, imidacloprid, and selamectin. So-called ‘inert’ ingredients include glycols, ethers, alcohols, hydrocarbon oils, amides and various spreading agent that facilitate chemical delivery to the skin surface, and may act as penetration enhancers [52,53].

What is clear from an analysis of available literature, is that the solvent system used in topical formulations may have a controlling influence over the rate and extent of active ingredient absorption; in some cases acting as controlled-release systems. In the formulation of these products, it is hypothesized that systemic concentrations are required for efficacy, although there is very little information on what actually constitutes an effective blood concentration, a situation very different from biopharmaceutics. However, it is clear from a wealth of field experience with many products in many species, dermal administration is an efficacious route of administration for these products.

Organophosphates are amongst the most widely used topical insecticides in domestic animals. Dermal exposure may result in inhibition of blood cholinesterase activity and produce neurological signs of toxicosis, two clear indications that systemic absorption has occurred. It is interesting to note that in most species, there is a rapid onset of clinical signs after topical application of lipophilic organophosphates such as chlorpyrifos, except in the cat where onset is delayed [54]. Fenthion is approved in dogs, beef cattle, and non-lactating dairy cattle in concentrations ranging from 3 to 20%. In cattle, the tissue withdrawal time is 45 days which clearly proves dermal absorption and systemic distribution. Phosmet is approved for use in dogs, swine and beef cattle. In pigs, dermal bioavailability was less than 3% of the applied dose administered in three different vehicle systems [55]. This type of data is conspicuously absent from other studies making interspecies comparisons difficult. Famphur is approved in cattle with a meat tissue withdrawal time of 35 days. In a study of subcutaneous fat biopsies
following dermal application of 25, 50 or 150 mg/kg famphur in an oily vehicle, peak residues occurred at 1 day of exposure and were insignificant by 11 days for all doses. Coumaphos at a dose of 14 mg/kg given as a pour-on to goats was slowly absorbed at a constant rate for 7 days, with 45% of the dose remaining unabsorbed [56]. Chlorpyrifos is used in flea collars for cats and dogs, dips for dogs, and in ear tags for cattle. Studies tend to indicate that absorbed chemical has the highest concentration in fat which in swine results in detectable residues for 3 weeks. As discussed above, absorption in cats seems to be different from other species.

It is instructive at this point to reiterate the difference between dermal penetration into the skin and absorption into the systemic circulation. This difference is clearly illustrated from in vivo and in vitro studies of the disposition of topical piroxicam in pigs [57]. A piroxicam (anti-inflammatory drug) topical gel was applied to cranial or caudal ventral abdominal body sites, differing only by the nature of the cutaneous vasculature perfusing the skin. The cranial site is perfused by penetrating musculocutaneous vasculature while the caudal site is perfused by direct cutaneous vasculature that does not perfuse deeper tissue beds before reaching the skin. In vitro flux across skin from both sites was identical, however cutaneous deposition at the cranial sites was much greater than the caudal sites. Thus, dermal depots would be expected to be formed after topical application to cranial sites perfused by musculocutaneous vessels, despite the fact that trans-epidermal flux was equivalent. Similar phenomena occurring with other drugs could confound interpretation of data when different body sites are used.

Extensive work has been done with parathion in swine as an animal model for assessing human absorption [5,22–25,58–63]. In intact pigs and the IPPSF, approximately 7–14% of a topically applied dose is absorbed systemically. This is increased under occlusive conditions as well as with increased relative humidity as depicted earlier in Fig. 2. Increased temperature and perfusate flow increases absorption in in vitro diffusion cell studies. Dermal biotransformation to paraoxon and para-nitrophenol has been demonstrated using both in vitro and in vivo models. Both degree of absorption and extent of biotransformation are body-site specific in the pig, with greatest absorption and metabolism occurring in the back compared to abdomen. Absorption can be modulated by a number of coadministered compounds, including fenvalerate, para-nitrophenol, paraoxon, sodium lauryl sulfate, methyl nicotinate, stannous chloride and different solvent vehicles. When combinations of these are dosed, complex but reproducible patterns of absorption are seen. In some cases, systemic absorption does not parallel changes in dermal depot concentrations. Such studies clearly indicate that parathion absorption, as well as in some cases cutaneous biotransformation, can be modulated by co-administration of other compounds and changes in site of application as well as environmental conditions.

Carbaryl is the most widely used carbamate insecticide in veterinary medicine. Unlike many of the earlier compounds where percutaneous absorption was not specifically measured, studies do exist for carbaryl in rodents and domestic species. Carbaryl is extensively (50–95%) absorbed in rodents. Studies conducted in the IPPSF in pigs demonstrated 10% absorption in 8 h, with 23% of this absorbed dose being the metabolite 1-naphthol [23]. Pharmacokinetic extrapolation of the total bioavailability was 33% after 6 days, supporting the existence of a dermal reservoir that continually releases drug after absorption. Baynes and Riviere [52] studied the effects of ‘inert’ ingredients and metabolites on the absorption of carbaryl and demonstrated clear cut enhancing effects of solvents, piperonyl butoxide, and 1-naphthol. These types of studies illustrate why this literature is difficult to evaluate, since all pesticides studied are in commercial formulations of various composition, making differences in absorption difficult to correlate to drug, species or formulation.

Some interesting data pertinent to transdermal issues have been reported for the chlorinated hydrocarbon lindane absorption in veterinary species. Dermal absorption of lindane is relatively slow and occurs to a limited extent. In the IPPSF [23], 2% of the dose of lindane was absorbed after 8 h which extrapolated to a 6-day absorption of 7.6%. In a separate study, fenvalerate enhanced lindane absorption [58]. In sheep dipped in 0.025% lindane, 8–10% of the applied dose was absorbed and fat residues were violative at 28 days but finally declined to safe
levels by 70 days. Absorption was bi-phasic, with the majority of the dosed absorbed by a slower process with a half-life of 169–200 h, and the remainder by a more rapid process. A significant difference was noted in the absorption kinetics of shorn versus un-shorn sheep. A deconvolution analysis was performed on the time required to absorb 50% of the available dose. This was determined to be between 115 and 179 h and was hypothesized to be due to a slow release of lindane from the stratum corneum reservoir in the skin [64,65].

Levamisole is formulated as a 20% pour-on in diethylene glycerol monobutyl ether. Several studies suggest that this formulation achieves effective blood concentrations in cattle. The extent of absorption is influenced by environmental temperatures, with increased absorption in summer over winter. In addition to a direct temperature effect, seasonal changes in skin structure and hair coat length may be factors causing this seasonal effect.

These studies clearly indicate that systemic absorption occurs after topical application of pesticides in a wide range of veterinary species. Although clear cut quantitative studies specifically assessing absorption in multiple species are difficult to find, since the purpose of many of these published studies was food safety and not quantification of absorption, systemic exposure occurs as evidenced by efficacy in treatment and occurrence of tissue residues at slaughter. Many factors including temperature and body site modulate absorption and the formation of epidermal and dermal depots. These factors have impact on the design of transdermal systems in veterinary species.

### 3.3.2. Transdermal patches

The above review indicates that there are significant differences in topical pesticide absorption between species. Some of this difference is related to actual flux across the stratum corneum which can be assessed by in vitro techniques. However, some differences are related to dermal factors such as differential perfusion and the tendency to form dermal depots. As will be seen, these factors may play a role in transdermal patch design in veterinary species.

As indicated earlier, there is not a great deal of literature on the use of transdermal patches in veterinary medicine. The clear cut exception is the use of fentanyl patches in dogs and cats and the use of the pig as a selective animal model for human delivery systems, typified by the development of transdermal testosterone systems. Since the authors have extensive first-hand experience with both, this will be the focus of this section.

#### 3.3.2.1. Fentanyl

Human fentanyl transdermal delivery systems were investigated for their use as a convenient postsurgery analgesic in dogs. Fentanyl (N-phenylethyl-N-(1,2-phenylethyl-4-piperidyl) propanamide) is a synthetic opioid with strong μ and δ opiate receptor agonist activity. In the dog, fentanyl elimination is rapid requiring intravenous infusion to maintain constant plasma concentrations needed for effective analgesia. Kyles et al. [66] compared the disposition of fentanyl in dogs after intravenous and transdermal administration using a commercial human patch (Duragesic-50 Fentanyl System; membrane-controlled alcohol-based reservoir system) designed to deliver 50 μg/h for 72 h. When applied to the clipped back (between shoulder blades) of Beagles weighing an average of 13.5 kg, the patch delivered an average of 36 μg/h which was 72% of the stated rate of delivery. This was sufficient to maintain an average steady-state concentration of 1.6 ng/ml from approximately 24 until 72 h when the patch was removed. The AUC in these dogs was 102 ng-hr/ml per ml. After patch removal, plasma fentanyl concentration rapidly decayed at a half-life that correlated to the initial distribution half-life seen with intravenous administration. The plasma concentration versus time profile of fentanyl applied to six beagle dogs is depicted in Fig. 5.

When compared to pharmacokinetic studies conducted in humans with the same transdermal delivery system, dogs achieve effective plasma concentrations relatively rapidly apparently due to the lack of a dermal depot for fentanyl in dogs compared to humans. This hypothesis is consistent with the more rapid decline in plasma concentrations after patch removal in dogs compared to a prolongation in half-life to greater than that seen with intravenous administration in humans. This is believed secondary to a slow release of fentanyl from a dermal depot.

The efficacy of transdermal fentanyl patches in dogs was subsequently evaluated for analgesia un-
dergoing ovariohysterectomy [67]. The same 50-μg/h patch was applied to 10 dogs of an average weight of 21 kg on the dorsal area of the neck 20 h before surgery to assure that steady-state concentrations were achieved before surgery. The efficacy of fentanyl was compared to a randomized treatment group of 10 dogs given oxymorphone intramuscularly (2.5 mg/meter² every six h starting immediately pre-surgery). In this trial, steady-state plasma fentanyl concentrations of 1.2 ng/ml were achieved between 19 and 46 h after patch application. This study concluded that transdermal fentanyl delivered as effective post-operative analgesia as did the accepted injectable oxymorphone protocol, but was associated with less sedation. Similar to the previous pharmacokinetic study, steady-state concentrations were on-average well maintained but significant inter-individual animal variation was reported. Another analgesia efficacy study was conducted in dogs undergoing major orthopedic surgery [68] using 100-μg/h patches in dogs weighing an average of 23 kg. These patches were applied to a clipped area of skin between the scapulae (dorsal shoulder). Again, steady state was reached in 24 h and were approximately 0.95 ng/ml, but individual steady-state values varied. As in the first post-surgery study, analgesia was effectively maintained and in this study, was more effective then epidural morphine. In the three studies cited above [66–68], the assay was identical and performed in the same laboratory.

A final study of transdermal fentanyl administration in dogs was conducted by a different group of investigators [69] and compared plasma concentrations achieved after use of three different size patches (50, 75 and 100 μg/h) in a cross-over experimental design. Patches were applied to the clipped lateral thorax of six dogs weighing an average of 20 kg. Steady-state plasma concentrations were achieved in 24 h and averaged 0.7, 1.4, and 1.2 ng/ml with 50-, 75- and 100-μg/h patches, respectively. AUCs were 46, 101 and 80 ng-hr/ml per ml, respectively. Some skin irritations were observed in these dogs, however they were related to dose or individual animal. This study also demonstrated considerable inter-individual variability, as is also observed in humans which is purported to be secondary to differences in skin and body temperatures, hydration status, sweat gland function, ethnic group, and the state and integrity of the stratum corneum [70]. It should be noted that the core body tempera-
ture of dogs is a few degrees greater than that of humans.

These studies in dogs suggest that transdermal fentanyl is an effective analgesic for post-surgical pain. Although effective steady-state plasma concentrations are maintained, there is considerable variability in their level. This can be seen in Table 3 which compares the mean concentrations or AUCs in the above studies in dogs administered the same 50-µg/h patch. The highest concentrations and AUCs are achieved in the smallest dogs, which could be partially predicted by normalizing patch delivery rate to body weight. If actual patch delivery rates were available in all studies, further variability may be explained. Additional variables include different body sites of application and different breeds of dogs. In the study evaluating delivery from three patch sizes, there was not a linear relation between stated patch delivery rate and observed $C_{ss}$ or AUC, suggesting either saturation of percutaneous absorption at the higher fluxes or altered systemic elimination.

Lee et al. [71] compared fentanyl concentrations achieved after application of a 25-µg/h patch to the clipped dorsal cervical region of six cats with an average weight of 3.8 kg. Steady-state concentrations were achieved in 12–18 h and maintained at approximately 1.9 ng/ml for 100 h as seen in Fig. 6. Two cats in this study did not achieve measurable fentanyl concentrations. However, when they were repeated,

Table 3
Steady-state plasma fentanyl concentrations ($C_{ss}$) and AUC in dogs administered a single 50-µg/h transdermal patch

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Rate/kg (µg/kg-h)</th>
<th>Body site</th>
<th>$C_{ss}$ (ng/ml)</th>
<th>AUC (ng-h/ml)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5</td>
<td>3.7</td>
<td>Thorax</td>
<td>1.6</td>
<td>102</td>
<td>66</td>
</tr>
<tr>
<td>20</td>
<td>2.5</td>
<td>Dorsal neck</td>
<td>0.7</td>
<td>46</td>
<td>69</td>
</tr>
<tr>
<td>21</td>
<td>2.4</td>
<td>Thorax</td>
<td>1.2</td>
<td>–</td>
<td>67</td>
</tr>
<tr>
<td>23</td>
<td>2.2</td>
<td>Dorsal shoulder</td>
<td>0.95</td>
<td>–</td>
<td>68</td>
</tr>
</tbody>
</table>

Fig. 6. Transdermal delivery of fentanyl in cats (mean±S.E.M.).
delivery occurred and they were then included in the calculation of mean values. Intravenous fentanyl pharmacokinetic studies were also conducted which allowed the actual delivery rate from these patches to be estimated at only 8.5 \( \mu g/h \) using ratios of AUC to calculate bioavailability as presented in Section 2.3.2 above. In contrast to dogs, but similar to humans, plasma fentanyl concentrations did not decline after patch removal. This was not due to systemic pharmacokinetic properties, since the observed intravenous half-life in cats of 2.4 h was shorter than the 6-h half-life reported in dogs. In contrast this suggests the presence of a dermal depot in cats which prolongs elimination due to slow absorption after patch removal.

In contrast to dogs, the lower rate of delivery compared to the stated patch release rate suggests that feline stratum corneum is less permeable to fentanyl than that of canine or human tissue, or alternatively the interface between the patch adhesive and skin surface is not uniform or another interaction is present. There is not a straightforward correlation to anatomical or physiological variables tabulated earlier (Table 1). As discussed earlier, it has been postulated that the major anatomical variable relating to stratum corneum absorption is the size of individual stratum corneum cells, a metric that has not been determined for either cats or dogs. Alternatively, the structure and arrangement of hair follicles in feline and canine skin are different, which may modulate the effective delivery rates achievable with these systems. Cats also have less active apocrine sweat glands than dogs which may modify the patch–skin interface [3]. In vitro studies are not available to further probe these mechanisms.

Finally, transdermal fentanyl (50 \( \mu g/h \)) patches were applied to the clipped neck of eight goats weighing an average of 40 kg [72]. In contrast to cats and dogs, steady-state concentrations of fentanyl were not achieved in goats, however plasma half-life after patch removal was 5.3 h compared to the 1.2 h seen after intravenous administration. Similar to other species, there was significant inter-individual variations. Peak concentrations were greater than those reported in other species. Curiously, total drug delivery from the patches was calculated to be greater than the stated delivery rate by the manufacturer. The cause of this discrepancy is not clear.

In conclusion, these studies on fentanyl administration in dogs and cats suggest that transdermal patches may be an effective route of drug administration in veterinary species. Adequate plasma concentrations are obtained and effective analgesia maintained for two types of surgical procedures. The patches are now widely used clinically in dogs and cats for indications ranging from post-operative pain to cancer pain. The convenience compared to multiple injections is obvious. However, the studies also indicate significant degrees of inter- and intra-species variability. These issues will be discussed below.

3.3.2.2. Testosterone

In order to illustrate that transdermal patches may be efficacious in species other than dogs and cats, Fig. 7 illustrates the blood concentration versus time profile seen after application of two human testosterone transdermal delivery patches applied to the abdomen of four pigs. (Androderm, combined 15-cm\(^2\) surface area containing a total of 24.4 mg testosterone.) The concentrations achieved are in the physiological range for efficacy. Compared to human delivery, in vivo transdermal flux from these systems is 2–3-fold less than humans. In contrast, with radiolabelled testosterone administered as a topical solution to both pigs and humans, the fraction absorbed was closer at 9 and 15% of applied dose, respectively. As discussed earlier, absorption in pigs and humans is generally similar with no clear cut trend of over- or under-estimation evident when a wide series of compounds are studied. Thus absorption, as seen with all compounds discussed above, is compound, site, species and most likely patch/formulation specific.

3.3.3. Iontophoresis

There is another approach to transdermal delivery which is receiving attention in the literature as systems for human drug delivery are presently under development. This relates to electrically assisted transdermal drug delivery systems typified by iontophoresis. As of the date of this review, no iontophoretic systems are approved for use in humans; however, pigs have been extensively used in their development. Some systems have been marketed in veterinary medicine; however, there is no published data either on their ability to deliver drugs transder-
mally or on their clinical efficacy. The nature of the formulations used in these systems would question both endpoints.

Electrically assisted transdermal drug delivery describes systems where the drug flux across the stratum corneum is driven by an electrical gradient rather than the concentration gradient which drives diffusion. There are a number of mechanisms whereby drug flux is potentiated using electrical energy, including iontophoresis, electro-osmosis and electroporation. For the purposes of this review, iontophoresis will be presented for illustrative purposes. Reviews of this area should be consulted for further details [73,74]

The two major advantages of iontophoretic systems over passive diffusion-driven systems are the control achieved by linking drug flux to the magnitude of the applied electric current, and the ability to deliver polar molecules (including small peptides) which are not amenable to diffusion systems. Additionally, lag times do not occur making onset of drug action in the systemic circulation more rapid. Drug flux is proportional to the applied current per unit of surface area ($\mu$A/cm$^2$) as described by the Nernst–Planck equation for membrane transport of ions under an electric field. A positive current (anodal) will promote the delivery of positively charged drugs (cations), while a negative current (cathodal) will promote the delivery of negatively charged drugs (anions). Flux is directly proportional to the total charge a drug carries and inversely proportional to its molecular weight. Total drug flux is also dependent upon all of the ionic compounds included in the formulation, thus inclusion of a charged additive will decrease delivery of the target drug. Formulation and pH may also effect efficacy of transport by mechanisms very different than passive systems. If a positive charge is placed on the skin, water will move across the skin due to a process called electro-osmosis, which allows for the delivery of neutral compounds by bulk-flow. Finally, iontophoresis tends to increase permeability of the stratum corneum to large and/or charged drugs that cannot be delivered by passive diffusion. The delivery of peptides has been a major focus of this research. Like the transdermal patch technology reviewed above, the iontophoretic electrode controls the rate of delivery across the skin, not the stratum corneum. Lag times are eliminated leading to much shorter onset times than are seen with patch technology.

Fig. 8 depicts the in vivo delivery of the peptide LHRH by anodal iontophoresis in pigs. The observed
profile is very similar to that seen in humans. Significantly, these concentrations of delivered LHRH caused an increase in LH in female pigs and FSH in male pigs, clearly demonstrating that iontophoretic peptide delivery in swine is efficacious [75]. Similar efficacious delivery of lidocaine has also been demonstrated [76], as was depicted in Fig. 3 above. Significantly, there was an exact correlation between IPPSF predicted and observed human plasma concentration profiles of iontophoretically delivered arbutamine [42]. Combining iontophoresis with electroporation, which is very short high-voltage pulsing of skin, further increased LHRH delivery, decreased onset time, and significantly reduced inter-individual variability [77].

Transdermal iontophoretic drug delivery is another potential administration strategy for use in veterinary medicine. Drugs which cannot easily be delivered by other routes have the potential to be delivered by this strategy. Unlike passive systems, drug flux only occurs when electrical current is present which opens the door to the very precise control of drugs with very narrow therapeutic windows. More importantly, peptides can also be delivered by this route.

4. Transdermal patches in veterinary species

The above review, although not comprehensive, clearly indicates the potential for this route of administration in veterinary medicine and identifies several considerations which will now be explored.

4.1. Important considerations unique to veterinary medicine

There are a number of factors that must be considered in designing transdermal patches for veterinary applications. Most of these have been alluded to in the discussions above but will now be summarized in a conceptual context.

The rate of drug delivery in a transdermal patch is designed to be controlled by the patch, and not the stratum corneum. However, based on the data from fentanyl above, it is obvious that human patches applied to dogs, cats and goats do not perform in this fashion. A similar situation occurs with testosterone. This suggests that there are a number of variables that may affect transdermal patch design in veterinary medicine which could modulate drug release.
from the patch, penetration across the stratum corneum, and/or absorption into the systemic circulation. These include, but are not limited to:

1. reduced permeability through the stratum corneum resulting in a rate-limiting diffusion;
2. improper adhesion of the patch on animal skin;
3. interaction of the patch adhesive with surface lipids changing the diffusional properties of the system;
4. different pH of skin surface;
5. different surface density and structures of hair, sebaceous and sweat glands;
6. differential depot formation in the stratum corneum and/or dermis which affects the time to steady state as well as the time for blood concentrations to decay after patch removal;
7. different skin and body temperatures, and mechanisms for their regulation, which could affect both release from patches and well as transport through skin;
8. anatomical differences in skin, differing rates of cutaneous blood flow and/or patterns of dermal perfusion (shunts, etc.) that would control delivery to the systemic circulation;
9. species-specific cutaneous biotransformation;
10. formulation factors which are important for all routes of delivery.

Another issue unique to veterinary medicine that confounds the above considerations is the wide range of body sizes seen both within and among species. Unlike humans, where body mass may only vary by a factor of 2–3-fold, domestic animals range from the few-kilogram cat to the 500-kg cow. It is obvious that a single patch could not be developed that would uniformly serve all species. Even with a species such as a dog, body sizes may range for a few to 50 kg.

The important variable in this regard is the ratio of patch area to total body mass, which sets limits on the amount of drug which can be delivered using technology available today. Assuming that the 1-mg/cm² per 24 h rule of thumb is accurate, it will be easier to develop transdermal patches for application in feline and canine medicine than in large animal practice. A relatively small patch of 10 cm² can deliver almost 4 mg/kg per 24 h to a cat and 0.5 mg/kg per 24 h to an average 20-kg dog. Equivalent patch sizes for a cow or horse would be unrealistic, even though larger surface areas of skin are available. However, if a very low effective plasma concentration is required (e.g., pesticide, growth promotant), then patch technology may be appropriate.

The potential flaw in this logic is the increased rate of drug clearance seen with animals of smaller body masses, a phenomenon that underlies the use of allometric relations to scale drug disposition across species [78]. That is, a greater dose on a mg/kg basis may be required to achieve efficacy in a cat compared to a cow. One advantage to patch technology in food producing animals would be clear demarcation of the application site for tissue residue avoidance.

An additional variable is the systemic clearance of the compound, which as described above, will determine the steady-state concentrations that could be achieved. For drugs with high clearances, high patch delivery rates are required. However, for drugs with relatively low clearances, the patch delivery rate could be low and still achieve effective concentrations. This is the situation seen with the marketed pour-on products discussed above. These issues also must be viewed in terms of the pharmacodynamics of the drug. If a steady-state blood concentration with minimal fluctuation is desired, patches may be the preferred mode of administration. In contrast, if wide fluctuations or immediately effective levels are needed, passive transdermal patches may not be appropriate. In this situation, iontophoretic systems may be ideal.

When a decision is made to explore the development of a transdermal patch for veterinary species, there are a number of experimental studies that should be conducted.

1. The ability of a drug candidate to be absorbed across the species of interest should be evaluated in a validated in vitro model. This would assess the ability of the drug molecule to penetrate the skin, a prerequisite for any transdermal delivery system; as well as generate basic parameters governing diffusion.
2. Initial formulation studies should be conducted in vitro to optimize drug flux in a more controlled environment.
3. Determine intravenous pharmacokinetic parameters to allow simulation of blood concentrations achievable with this drug. Compare these to drug concentrations required for efficacy.

4. Conduct simple in vivo absorption study to validate in vitro system with this specific drug.

5. Develop transdermal patch formulation, using the above validated model systems, to deliver desired delivery rate. In vitro drug release assays should also be used at this step to assess uniformity of delivery.

6. When a prototype transdermal patch is developed, assess inter-site and inter-species delivery and develop an understanding as to the parameters which modulate drug delivery.

7. Assess patch performance under varied environmental (temperature, activity level, etc.) and application (multiple patch placement on same and different sites, etc.) techniques.

The important concept to consider is that veterinary species are a diverse group of animals that may show differences in drug delivery rates that are not immediately obvious. These factors should ideally be known before any drug development progresses to a ‘point of no return’.

4.2. Potentials

There are a number of exciting potentials for development of transdermal drug administration in veterinary species. The most obvious is ease of dosing small animals that may be difficult to administer drugs to by other routes. The best drug candidates would be those that otherwise require intravenous infusion, frequent administration, or that have poor oral systemic availability. Owner compliance is easier to maintain due to the decreased frequency of dosing and transdermal patches would be beneficial for treating species that resist being medicated (e.g., cats). If specific veterinary patches are developed with geometries and adhesives tested in the relatively hairy skin of animals, optimal delivery may occur as compared to using a human patch designed to be adhered to glabrous skin. Because of certain animal behaviors (especially cats and dogs), patches must be formulated to be non-irritating, capable of tight adhesion to skin, and/or be placed in locations where the animal cannot reach it; otherwise they will lick, chew, and scratch the application site. Ease of dosing would be achieved if adhesive-based, rather than reservoir transdermal patches were formulated for veterinary use (e.g., Fig. 4A or C). This would facilitate obtaining correct dosing in different species of animals simply by cutting the patch material to an appropriate area.

Based on patch size to body mass considerations, it would appear that cats and dogs are ideally suited for development. Pigs, goats and sheep are similar in area to mass ratio as humans and may thus be appropriate. Patch development in cattle and horses may only be feasible for very potent drugs or compounds where minimal exposure (hormones) is efficacious.

4.3. Limitations

Some drugs will never be appropriate for transdermal patches simply because of their physicochemical properties (too large, too charged, insufficient lipid solubility, tendency to cause direct skin irritation) or unfavorable pharmacokinetic or pharmacodynamic behavior (too rapid of a clearance relative to achievable rate of skin delivery, first-pass cutaneous biotransformation, requirement for intermittent high peak and low trough blood profiles, insufficient potency). Some compounds, such as pour-on pesticides are optimally formulated with existing topical products which obviates the need to develop rate-controlled patch delivery systems. As seen with the limited experience with a single drug fentanyl, species-specific absorption occurs by mechanisms which at this point are not well understood.

The acceptability of patches in veterinary practice must overcome the potential behavioral patterns of animals that remove objects form their skin that irritate it. Thus patches must be designed which are not amenable to removal by scratching, biting or licking. The use of patches in food-producing animals would break new regulatory ground, as concerns of dermal depot formation with slow drug release might cause concern for violative tissue residues. However, if a permanent dye were incorporated in to a patch design, animals receiving patches would be marked which would allow excision of this depot at slaughter.
5. Conclusions

The development of transdermal patches for veterinary medicine appears to be a feasible scenario for the future. However, before extensive product development occurs, considerable experimental investigations are required in the primary target species to define some basic parameters of drug absorption. The data reviewed to date leave many unanswered question but very specific areas for study. Transdermal delivery is feasible as demonstrated by the use of fentanyl patches in dogs and pour-on products in all species. It is obvious that development of patches will be drug and species specific. With the rapid advancement of patch technology for humans, the know how is presently available to develop effective transdermal patches for at least canine and feline therapeutics.

References


