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Transdermal Drug Delivery System in Veterinary Practice: An Overview

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Abstract

In veterinary practice drug delivery strategies are complicated by species diversity, body size variations, cost constraints and level of convenience. A new frontier in the administration of therapeutic drugs to veterinary species is transdermal drug delivery system. It implies topical drug application to achieve systemic pharmacological effects. Its efficacy is primarily dependent upon the barrier properties of the targeted species skin, as well as the ratio of the area of the patch to the species total body mass needed to achieve effective systemic drug concentrations. The candidate drug must have sufficient lipid solubility to be considered for transdermal delivery. The adhesive of the patches is critical to the safety, efficacy and quality of the product. This novel drug delivery system offers many advantages over conventional oral and invasive methods of drug delivery like reduction in hepatic first pass metabolism, enhancement of therapeutic efficiency, maintenance of steady plasma level of the drug and improved owner compliance. With efficient experimental designs and available transdermal patch technology, there are no obvious hurdles for the development of effective therapeutic agents in veterinary practice.

Keywords: Drug delivery; Transdermal; Veterinary Practice

Introduction

A diverse range of drug delivery systems has been developed for animal welfare (The Merck Veterinary manual, 2010). In veterinary practice drug delivery strategies are complicated by the species diversity, breeds treated, body size variations, different husbandry practices, seasonal influences, cost constraints, food and fiber drug persistence, level of convenience etc.

The primary routes of drug administration utilized in veterinary medicine include oral and parentral dosing (Riviere and Papich, 2001). Transdermal drug delivery system/patches imply topical drug application to achieve systemic pharmacological effects (Kumar *et al*., 2010). Great strides over the last decade have been made in using topical 'pour-on' and 'spot-on' drug applications for transdermal delivery in veterinary practice (e.g. application of fenthion, fipronil, ivermectin, levamisole). Advantages of topical application of veterinary pharmaceuticals include reduction in first pass metabolism, non invasiveness, gastric route avoidance, continuous inputs of drugs with short half lives, elimination of pulsed entry into the systemic circulation and improved owner compliance (Roberts *et al*., 2002).

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Factors affecting transdermal drug movement

Species differences in skin structure

Skin being the largest organ of the body performs a myriad of biological functions. It is an efficient barrier to prevent penetration, and thus systemic absorption, of most hydrophilic and ionic compounds. Significant species differences have an impact on the design of transdermal patches. In fact the differences exist among different body regions within a species due to variations in thickness, hair follicle density, structure and arrangement and the cutaneous blood flow. Significant differences in transdermal penetration have been observed owing to marked species differences in skin structure. In humans, the rate of penetration for most non-ionized compounds is scrotal >foresheed > axilla/scalp > back/abdomen > palmar and planter. In veterinary medicine the primary site used for transdermal

patch delivery is the back because animals cannot like, chew or scratch. However, in sick or debilitated patients lateral thorax or inguinal areas are used. The percutaneous absorption of chemicals across laboratory animals species, pigs, primates and humans is mouse >> rats/rabbits > humans/pigs and primates. Rats, mice and pigs are often used as models to investigate transdermal drug penetration in development of formulations for human use. The extrapolation of these data to humans is controversial due to marked species differences in the transdermal penetration of a number of drugs, with the pig emerging as the model of choice to investigate potential topical formulations for human use. Functions of the skin in domestic animals (Cattle/Sheep/Goat) is affected by factors such as surface temperature, sebum output, variability in skin thickness, seasonal variations, breed differences, density of hair follicles, body weight, age and sex (Pitsman and Rostas, 1981). The penetration of levamisole with organic solvents is higher through cattle skin than through human skin. However, the reverse is true with aqueous solution. The penetration through the appendages could be due to emulsified sebum in the cattle skin.

Molecular penetration through the skin

Epidermal transport

The diffusivity of the drug through the skin, including the SC, is limited by the binding of the drug to keratinocytes, the viscosity of the intercellular environment and the tortuosity of the pathway (Roberts *et al*., 2002). Transport via a transcellular pathway is unlikely because it would require repeated partitioning of the solute between lipophilic and hydrophilic compartments, including the almost impenetrable intracellular matrix of the keratinocytes. All solutes are transported through a lipid pathway with resistance to passage of lipophilic solutes arising from the dermis and not the keratinocytes. The permeability of very polar solutes through the SC is almost constant, while permeability for lipophilic solutes changes with the degree of lipophilicity (Matsuzaki *et al*., 1993). The intercellular pathway for polar solutes may be predominantly the aqueous regions surrounding polar intercellular lipids. The ideal solutes for topical delivery include as non-ionic, reasonably lipophilic and, particularly, of small molecular weight (Magnusson *et al*., 2004).

Appendageal transport

In TDDS, the appendageal transport (through hair follicles and sweat glands) is controversial due o relatively sparse hair cover in animals (Pig) and smaller contribution to the total surface area (Roberts *et al*., 2002). As the hair follicle density increases, the follicular route of drug penetration becomes more significant (Hueber *et al*., 1994).

Molecular considerations

The ideal characteristics of pharmacological agents for TDD include low molecular weight (6500 Da), few atoms available for hydrogen bonding, lipophilicity < 2.6 and a low melting point (Magnusson *et al*., 2004).

Vehicle and formulations

Vehicles must be sufficiently soluble to contain the active drug in an aesthetically acceptable form (i.e., no granules), and the drug must simultaneously be sufficiently soluble in the SC lipids and be able to diffuse through these intercellular lipids to reach the site of intended action (Kaplun-Frischoff and Touitou, 1997).

Integrity of the skin

The progressive loss of the SC greatly diminishes the barrier function of skin. Extraction of intercellular lipids with various solvents causes a reduction in the barrier function of the SC (Monteiro-Riviere et al., 2001). Delipidation of skin by acetone increases transdermal penetration of salicylate (Benfeldt *et al*., 1999). Altering lipid content and fluidity is one strategy to enhance transdermal permeability. Similarly, lipid composition that varies with diseases of the epidermis dramatically affects drug movement through the SC.

Mechanism of Drug Delivery

The principle mechanism for drug delivery in TDDS is “a slow process of diffusion driven by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin”. The drug permeation across the skin

obeys Fick's first law which states that the steady state of drug flux across a membrane can be expressed as Flux (J) = DP / h (concentration gradient) (surface area), Where D is the diffusivity of the drug in the intercellular lipids of the stratum corneum, P is the partition coefficient for the drug between 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 DP/h is often called the permeability coefficient. Kinetically, this is first-order rate constant that is the basis for the absorption rate constant (Ka) obtained in pharmacokinetic analyses of transdermal drug delivery studies. Among the species, the factors that may alter drug flux include skin thickness, hair density and thus interfollicular epidermal thickness, as well as differential lipid composition. Factors like different rates of cutaneous blood flow, capacity of mechanisms of first pass cutaneous biotransformation, occlusion, high relative humidity, temperature, and disease induced changes in the skin structure or function, and/or abrasion, may also alter the transdermal flux.

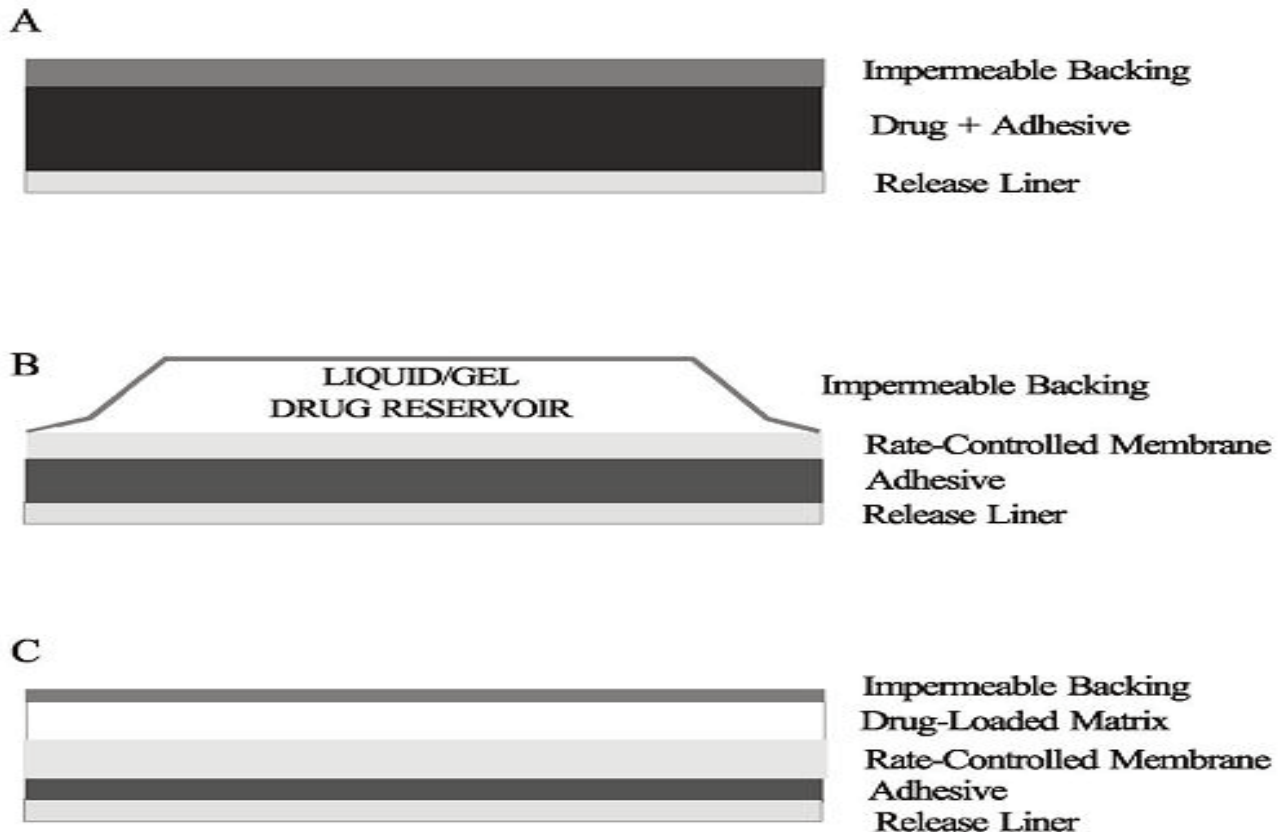


Fig. 1. Structure of Transdermal Drug Delivery Systems
A (adhesive), B (reservoir), or C (Laminated matrix) – Adapted from: Riviere and Papich (2001)

Components of Transdermal Patch

Liner:

It protects the patch during storage and should be removed before its use.

Drug:

Drug solution is in direct contact with release liner. Adhesive: It serves to adhere the components of the patch together along with adhering the patch to the skin e.g. Acrylic, Polyisobutylene (PIB), and Silicone.

Membrane:

It controls the release of the drug from the reservoir and multi-layer patches.

Backing:

The film protects the patch from the outer environment.

Types of Transdermal Drug Delivery Systems

TDDSs are classified as passive and active delivery systems. The former one relies completely on the principle of diffusion while the latter, though based on the same principle, consists of different penetration technologies ranging from electrical current, iontophoresis, electroporation, microporation, laser ablation, mechanical arrays, radio frequency, thermal/heat, and ultrasound, etc. Both these types are horizontally classified as follows (Kumar *et al*., 2010).

a) Single layer drug in adhesive: In this type the adhesive layer surrounded by a temporary liner and a backing contains the drug and not only serves to adhere the various layers together but is also responsible for the releasing the drug to the skin.

b) Multi -layer drug in adhesive: This type is also similar to the single layer but it contains an immediate drug release layer besides the other layer that allows controlled release of the drug. This patch has a temporary liner-layer and a permanent backing.

c) Vapour patch: In this patch (commonly used for releasing of essential oils in decongestion) the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour.

d) Reservoir system: In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system:

i. Drug-in-adhesive system: In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system: In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Micro-reservoir system: In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

Transdermal penetration ennhancement

Chemical enhancers

Penetration enhancers partition into, and interact with skin constituents (intercellular lipid fraction) and induce a temporary and reversible decrease in skin barrier properties (Magnusson *et al*., 2001). Their interaction with some components of the skin increases fluidity in the intercellular lipids, possibly inducing swelling of keratinocytes and/or leaching out of structural components, reducing the barrier function of the SC (Hirvonen *et al*., 1994). They may increase (100-fold) skin permeability to macromolecules (1–10 kDa) including heparin, luteinising hormone releasing hormone (LHRH) and oligonucleotides, without inducing skin irritation (Karande *et al*., 2004). Early penetration enhancers (dimethyl-sulfoxide and dimethylformamide) tend to be disruptive keratolytic agents that destroy the SC and are non-specific in their penetration enhancement. These accelerate the penetration of drugs such as antibiotics, steroids and local anaesthetics (Franz *et al*., 1995), but have practical drawbacks like toxicity, irritancy and odour (Chattaraj and Walker, 1995). Newer penetration enhancers with fewer drawbacks include propylene glycol (Bendas *et al*., 1995), alcohols and surfactants.

Physical enhancers

Here electrically generated currents or energy fields are utilized in enhancing the transdermal penetration of larger polar molecules that may not normally be suitable for topical application and reducing the lag time of topically applied products like local anaesthetics.

Ultrasound:

Low frequency ultrasound (20KHz) enhance the drug (Insulin, Erythropoitin, Interferon) penetration through human and rabbit skin (1000- fold) by disturbing the SC layers by cavitation (Mitragotri *et al.*, 1995).

Iontophoresis:

Here small electrical current (0.5 mA/cm2) applied between two electrodes in contact with the skin drives a charged molecule (neutral molecules also) through the barrier (Banga *et al*., 1999). Its efficiency depends on the polarity, valency and mobility of the drug molecule besides the electrical cycle and formulation containing the drug (Naik *et al*., 2000). Iontophoresis enhances the SC delivery of proteins, and oligonucleotides (Oldenburg et al., 1995), lidocaine and fentanyl (Gupta *et al*., 1998). Electrical current induced irreversible damage to the growing hair due to least resistance of the hair follicle is its potential drawback.

Electroporation:

It involves the application of short (ms) electrical pulses (100–1000 V/cm) to the skin (Prausnitz *et al.*, 1993) which creates transient aqueous pores through the SC (Jadoul et al., 1999), permitting drugs (Vaccines, Liposomes, and Microspheres) to penetrate more readily (Prausnitz, 1999). Electroporation has been used to enhance the transport of vaccines (Misra *et al*., 1999), liposomes (Badkar *et al*., 1999) and microspheres. It has simplified physostigmine delivery as therapeutic agent for organophosphate poisoning (Rowland and Chilcott, 2000). Skin damage using electroporation is similar to iontophoresis (Prausnitz, 1999).

Particle-mediated epidermal delivery (PMED):

Here particles of gold, coated with DNA or protein are accelerated into the epidermis by a similar device used to deliver DNA and protein vaccines (Chen *et al.*, 2002), which make contact with the dense network of epidermal antigen presenting cells (APCs) resulting in antigen presentation to the systemic immune system by the transfected APCs (Dean *et al*., 2005). Local keratinocytes also become transfected and then express and secrete antigen which is picked up by resident APCs (Dean *et al.*, 2005). PMED has been successfully used in veterinary medicine against Influenza A virus in pigs (Macklin *et al*., 1998), bovine herpesvirus-1 in cattle and cancer immunotherapy in dogs using cytokine DNA (Keller *et al*., 1996).

Other Enhancement Techniques (Kumar and Philip, 2007)

Transfersomes:

The device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

Medicated Tattoos:

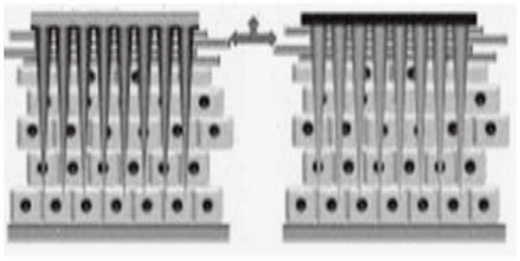
Med-Tatoos are modification of temporary tattoos which contain an active drug substance for trandermal delivery. This technique is useful in the administration of drug in patients who are not able to take traditional dosage forms.

Skin Abrasion:

This involves direct removal or disruption of the upper layers of the skin (By creating micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules – Microscissuining) to provide better permeation of topically applied drug substance.

Controlled Heat Aided Drug Delivery (CHADD) System:

CHADD system consists a small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs



Delivery site for microneedle technology (a) Hollow microneedles with applied formulation (b) Solid microneedles (Adapted from Bora *et al*., 2008)

within the unit which tends to form heat of limited intensity and duration. It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately leads to increase in microcirculation and permeability in blood vessel.

Laser Radiation:

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. This technique improves the delivery of lipophilic and hydrophilic drugs.

Magnetophoresis:

The effect of magnetic field on diffusion flux of drug substance is enhanced with increasing applied strength.

Microfabricated Microneedles:

These are the devices which have features of both the hypodermic needle and transdermal patch and transport the drug effectively across the membrane. The systems consists of a drug reservoir and some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug. Microneedles do not penetrate deep enough into the skin to reach up to the nerve endings and thus there is no pain sensation during the microneedles insertion into the skin (Bora et al., 2008). There are a number of delivery approaches that have been employed to use the microneedles for TDDS. These include:

Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Table 1. Polymers in Transdermal Drug Delivery System

Polymer	Physical property
Poly urethanes	Elasticity
Poly siloxanes or silicones	Insulating ability
Poly methyl methacrylate	Physical strength and transparency
Poly vinyl alcohol	Hydrophilicity and strength
Poly ethylene	Toughness and lack of swelling
Poly vinyl pyrrolidone	Suspension capabilities

Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament then occurs by dissolution.

Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which are then inserted into the skin.

Hollow microneedles- Involves injecting the drug through the needle with a hollow bore.

Metered-Dose Transdermal Spray (MDTS): It is a liquid preparation used topically which is made up of a volatile cum non volatile vehicle consisting of completely dissolved medicament. The MDTS has the following potential advantages:

- It improves delivery potential without skin irritation due to its non-occlusive nature
- Increased acceptability
- Dose flexibility
- Simple manufacture

Polymers in Transdermal Drug Delivery System

Controlled drug release in TDDS can be achieved by embedding the drug onto a polymeric material and then releasing it in a predesigned controlled manner from the polymer into the systemic circu-

Table 2. Veterinary Drugs Considered for Transdermal Therapy (Davidson, 2003).

Drug	Max. Recommended Starting TD Dose	Target for Efficacy	Symptoms of toxicity
Aminophylline	4 mg/kg q 8 to 12 hr	Serum theophylline level in therapeutic range. Evidence of controlled asthma	Tachycardia, Arrythmia, Seizure, Hypothermia
Amitryptylline	1.25 mg/cat q 24 hr	Cessation of undesirable behavior, Cessation of cystitis	Dry mouth, gastric distress, constipation, ataxia, tachycardia, weakness, sedation, urinary retention
Amlodipine	0.625 mg/cat q 24 hr	Reduction in blood pressure	Hypotension
Atenolol	3.25 mg/cat q 24 hr	Reduction in pulse (140-200 bpm)	Hypotension, bradycardia, bronchospasm, cardiac failure, hypoglycemia
Buprenorphine	0.01 mg/kg cat q 8 hr	Apparent analgesia	Respiratory depression
Butorphanol	0.4 mg/kg cat q 6 hr	Apparent analgesia	Oversedation, respiratory depression
Cisapride	2.5 mg/cat q 12 hr	Resolution of Ileus	Diarrhea, abdominal pain and cramping, arrhythmia from drug interactions
Clomipramine	1.25 mg/cat q 24 hr	Cessation of undesirable behavior	Excessive sedation, dry mouth, urinary retention
Cyproheptadine	2 mg/cat q 12 hr	Stimulation of appetite, relief of pruritus, cessation of undesirable behavior	Excessive sedation, dry mouth, urinary retention
Diltiazem	7.5 mg/cat q 12 hr to q 24hr	Reduction in pulse (140-200 bpm)	Bradycardia, vomiting, heart block
Enalapril	0.25 mg/kg cat q 24 hr	Improvement of clinical signs of heart failure	GI distress, hypotension
Glipizide	2.5 mg/cat q 12 hr	Reduction in blood glucose < 200 mg/dl	GI distress, hypoglycemia, icterus, hyperglycemia from therapeutic failure
Methimazole	2.5 mg/cat q 12 hr	Reduction in serum T_4 level, improvement in clinical symptoms	Vomiting, dermal excoriations, leucopenia, hepatopathy, thrombocytopenia
Phenobarbital	2 mg/kg cat q 12 hr	Seizure free, serum concentration of 10-30 µg/ml	Ataxia, over sedation, bone marrow suppression, immune mediated reactions
Fentanyl	50 µg/hr (dogs, cats, goats)	Post-operative analgesia	Skin irritation
Testosterone (Androderm)	15 cm^2 surface area containing 24.4 mg testosterone	As anabolic steroid	----------
Luteinizing hormone releasing hormone (LHRH)	----------	Increase in LH in female pigs and FSH in male pigs	----------

lation. Polymers can be used as adhesives, as backing layer for the transdermal patch, or to create a gel that would help embed the drug for its controlled delivery. Every layer in the transdermal drug delivery system requires properties specific for that layer only, which governs the polymer selection.

1: Polymer matrix diffusion controlled drug delivery system:

It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling e.g. NitroDur designed for consistent transdermal infusion of nitroglycerine.

2: Microreservoir partitioned controlled drug delivery system:

It involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion e.g. Syncromate implant engineered to deliver subdermal administration of norgestomet (Bharadwaj et al., 2011).

The polymers that are currently used in the formulation of the transdermal patches include Poly(2-hydroxy ethyl methacrylate), Poly(N-vinyl pyrrolidone), Poly(methyl methacrylate), Poly(vinyl alcohol), Poly(acrylic acid), Polyacrylamide, Poly(ethylene-co-vinyl acetate), Poly(ethylene glycol), Poly(methacrylic acid).

Veterinary Medicine -Transdermal Drug Development (Riviere and Papich, 2001)

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 ab-

sorption into the systemic circulation. These include:

1.Reduced permeability through stratum corneum resulting in a rate-limiting diffusion
2. Improper patch adhesion on animal skin and its interaction with surface lipids
3. Different hair, sebaceous, and sweat gland density and structure.
4. Different pH on skin surface.
5. Differential depot formation in the stratum corneum and/or dermis
6. Different skin and body temperatures
7. Anatomical skin differences, differing rates of cutaneous blood flow and/or patterns of dermal perfusion.
8. Species-specific cutaneous biotransformation
9. Wide range of body sizes both within and among species (Patch area:Total body mass is important variable).
10. Systemic clearance of the compound which determines the steady-state concentrations
11. Formulation factors.

Experimental studies that need to be conducted for the development of a transdermal patch for veterinary species include.

1.Evaluation of the candidate drug in a validated in vitro model to assess its ability to penetrate skin
2. In vitro formulation studies to optimize drug flux in a controlled environment.
3. Determination of intravenous pharmacokinetics parameters to allow stimulation of blood concentrations achievable with the drug and comparing it to drug concentrations required for efficacy.
4. In vivo absorption study to validate in vitro system.
5. Formulation of the transdermal patch based on above validated model systems.
6. Inter-site and inter-species drug delivery assessment.
7. Assessment of patch performance under varied environmental conditions and application techniques.

Potentials and Limitations

The most obvious potential for development of transdermal patches in veterinary medicine in the ease of dosing small animals and species that resist medication (cats). The best drug candidates would be those that otherwise require intravenous infusion, frequent administrations, or that have poor oral systemic availability. Cats and dogs are ideally suited for TDDS development while pigs, goats and sheep are appropriate and cattle and horses are only feasible for very potent drugs where minimal exposure (hormones) is efficacious.

Drugs that will never be appropriate for TDDS include those that are/have too large, too charged, insufficient lipid solubility, tendency to cause direct skin irritation, too rapid clearance, first pass cutaneous biotransformation, requirement of high peak or low trough blood profiles and insufficient potency. The patches must be designed which are not amenable to removal by scratching, biting or licking, and a permanent dye has to be incorporated in patches designed for food producing animals which could allow excision of the depot at slaughter.

Conclusion

The use of transdermal medications is a milestone in veterinary practice as they can be life-saving therapeutic agents for patients that cannot tolerate the administration of traditional dosage forms. In Veterinary Medicine, TDDS has a great potential, being able to use for both hydrophobic and hydrophilic active substances into promising deliverable drug. It is a realistic practical application as the next generation of drug delivery system. Careful monitoring, communication, and documentation will increase the success of any transdermally administered therapy. Regardless of the likelihood of clinical success from using a transdermal medication, the safety of the caregiver must be the highest priority.

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