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Research Paper

Transdermal Drug Delivery System

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ABSTRACT
*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**Bharadwaj,S.et al (2011)**.It implies topical drug application to achieve systemic pharmacological effects. An appropriate proportion of drug to the desired site of action in the body; to accomplish the desired action is the trans-dermal drug delivery system.**Bharadwaj, S. et al(2011)** The topically administered medications in self-contained, discrete dosage forms of patches which when applied to the skin deliver the drug, through the skin portal to systemic circulation at a predetermined and controlled rate over a prolonged period of time in order to increase the therapeutic efficacy and reduced side effect of drug.lipid solubility is to be considered for trans dermal delivery.**Preetam Bala et al (2014).**It explains typically the diffusion and absorption routes.**)**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.**Davidson, Get al (2004)***

*Physicochemical properties of the penetrate molecule, drug delivery system and the physiological and pathological condition of the skin cannot neglected .**P.C. Mills(2006)** In Veterinary Medicine, TDDS has a great potential,being able to use for both hydrophobic and hydrophilic active substances into promising deliver-able drug.**Krotscheck, U. et al (2004)** Different components of such patches, their release mechanism is known. Trans Drug delivery strategies are complicated by species diversity, body size variations, cost constraints and level of convenience. The adhesive of the patches is critical to the safety, efficacy and quality of the product **Thomasy, S.et al (2004)** 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.**Thomas, B.et al (2004)** With efficient experimental designs and available transdermal patch technology, there are no obvious hurdles for the development of effective therapeutic agents in veterinary practice.**Partidos, C.D.,et al (2005).** A new and evolving area of Vapor patch and micro-reservoir approach, microneedles is introduced with various details of its fabrication procedures and the properly-domain is elaborated. (**Bora, P.,et al 2008)** The stimuli for release, which can also be engineered, falling under different categories such as electrically-based, ultrasound, pressure based, laser based, and so on.**Shital H. Bariyaet al (2012).**An extremely promising novel route, which introduces nanotechnology and nanomaterials to improvise the conventional transdermal drug delivery system, is then elaborated.**Karande, P,et al (2004)** Careful monitoring, communication, and documentation will increase the success of any transdermally administered therapy.**Magnusson, B.M.et al. (2001)***

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MANUSCRIPT

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 parental dosing (Riviere and Papich,2001).Transdermal drug delivery system/patches imply topical drug application to achieve systemic phar-macological 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).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 com-pounds. Significant species differences have an impact on the design of transdermal patches. In factthe 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-ion-ized 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, G.pigs, primates and humans is mouse >> rats/rabbits >humans/pigs and primates. Rats, mice and pigs are often used as models to investigate TD 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 ishigher through cattle skin than through human skin.However, the reverse is true with aqueous solution.The penetration through the appendages could bedue to emulsified sebum in the cattle skin.Molecular penetration through the skin Epidermal transport The diffusivity of the drug through the skin, includ-ing the SC, is limited by the binding of the drug tokeratinocytes, the viscosity of the intercellular en-vironment and the tortuosity of the pathway(Roberts *et a*l., 2002). Transport via a transcellularpathway is unlikely because it would require re-peated partitioning of the solute between lipophilic and hydrophilic compartments, including the almost impenetrable intracellular matrix of the keratinocytes. All solutes are transported through alipid 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 hairfollicles and sweat glands) is controversial due orelatively 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 (Mag-nusson *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 diminishesthe barrier function of skin. Extraction of intercellular lipids with various solvents causes a reductionin the barrier function of the SC (Monteiro-Riviere *et al*., 2001). Delipidation of skin by acetone in-creases transdermal penetration of salicylate (Ben-feldt *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 skinobeys Fick's first law which states that the steady state of drug flux across a membrane can be ex-pressed 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 ab-sorption rate constant (Ka) obtained in pharmaco-kinetic analyses of transdermal drug

delivery studies. Among the species, the factors that may alter drug flux include skin thickness, hair density and thus inter follicular epidermal thickness, as wellas 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

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 thepatch together along with adhering the patch to the skin e.g. Acrylic, Polyisobutylene (PIB), and Sili-cone. 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 onthe principle of diffusion while the latter, though based on the same principle, consists of different penetration technologies ranging from electrica lcurrent, iontophoresis, electroporation, micropo-ration, 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 re-lease 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 nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspen-sion, 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 animpervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.
ii. Matrix-dispersion system: In this type the drugis 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 imper-meable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form astrip 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 un-reachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using crosslinking agents. Transdermal penetration ennhancement Chemical enhancers Penetration enhancers partition into, and interac twith 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 leachingout 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 irrita-tion (Karande *et al.*, 2004). Early penetration en-hancers (dimethyl-sulfoxide and dimethylform-amide) tend to be disruptive keratolytic agents thatdestroy the SC and are non-specific in their pene-tration enhancement. These accelerate the penetra-tion of drugs such as antibiotics, steroids and local anaesthetics (Franz *et al.,* 1995), but have practicaldrawbacks like toxicity, irritancy and odour (Chat-taraj and Walker, 1995). Newer penetration enhancers with fewer drawbacks include propyleneglycol (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 thedrug (Insulin, Erythropoitin, Interferon) penetration through human and rabbit skin (1000-fold) by dis-turbing 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 effi-ciency depends on the polarity, valency and mobil-ity 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 hairfollicle 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 poresthrough the SC (Jadoul *et al.*, 1999), permitting drugs (Vaccines, Liposomes, and Microspheres) to penetrate more readily (Prausnitz, 1999). Electro-poration has been used to enhance the transport ofvaccines (Misra *et al.*, 1999), liposomes (Badkar *et al.*, 1999) and microspheres. It has simplified physostigmine delivery as therapeutic agent fororganophosphate 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 a*l., 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 be-come transfected and then express and secrete anti-gen which is picked up by resident APCs (Dean *et al.*, 2005). PMED has been successfully used inveterinary medicine against Influenza A virus in pigs (Macklin *et al.*, 1998), bovine herpesvirus-1in cattle and cancer immunotherapy in dogs usingcytokine DNA (Keller *et al.*, 1996).Other Enhancement Techniques (Kumar and Philip, 2007)Transfersomes: The device penetrates the skin barrier along theskin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfer-somes 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 trander-mal 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 – Mi-croscissuining) 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 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 member-ane. 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 thereis no pain sensation during the microneedles insertion into the skin (Bora *et al.*, 2008). There are anumber 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.

Polymer	**Physical property**
Poly urethanes	Elasticity
Poly siloxanes or silicones	Insulating ability
Poly methyl methacrylate	Physical strength and transparancy
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, poly-meric microneedles, which are then inserted intothe skin.Hollow microneedles-Involves injecting the drugthrough 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 TDDS. Controlled drug release in TDDS can be achieved by embedding the drug onto a polymeric material and then releasing it in a pre designed controlled manner from the polymer into the systemic circulation Polymers can be used as adhesives, as back-ing layer for the transdermal patch, or to create agel that would help embed the drug for its con-trolled 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 car-rier matrix (in a homogenous manner) that is rate controlling e.g. NitroDur designed for consistent transdermal infusion of nitroglycerine.2: Microreservoir partitioned controlled drug de-livery system:It involves dispersion of micro particles of suspen-sion of drug (aqueous in nature) in a polymer usinghigh energy dispersion e.g. Syncromate implant en-gineered to deliver subdermal administration of norgestomet (Bharadwaj *et al.*, 2011).The polymers that are currently used in the for-mulation of the transdermal patches includePoly(2-hydroxy ethyl methacrylate), Poly(N-vinylpyrrolidone), Poly(methyl methacrylate),Poly(vinyl alcohol), Poly(acrylic acid), Polyacry-lamide, Poly(ethylene-co-vinyl acetate), Poly(eth-ylene glycol), Poly(methacrylic acid).

Veterinary Medicine -Transdermal Drug Devel-opment (Riviere and Papich, 2001)There are a number of variables that may affecttransdermal patch design in veterinary medicinewhich could modulate drug release from the patch,penetration across the stratum corneum, and/or absorption into the systemic circulation. These in-clude: 1.Reduced permeability through stratum corneumresulting in a rate-limiting diffusion2. Improper patch adhesion on animal skin and its interaction with surface lipids3. 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 dermis6. Different skin and body temperatures7. Anatomical skin differences, differing rates ofcutaneous blood flow and/or patterns of dermal perfusion.8. Species-specific cutaneous biotransformation9. Wide range of body sizes both within and amongspecies (Patch area:Total body mass is important variable).10. Systemic clearance of the compound which determines the steady-state concentrations11. Formulation factors.

Experimental studies that need to be conducted for the development of a trans-dermal patch for veterinarian 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 flunixin 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 poooral 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, in-sufficient 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.

SKIN AND DRUG PERMEATION:

For understanding the concept of TDDS, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access into the body via skin.

Some of the differences between epidermis and dermis layers of skin. The skin is one of the most extensive organs of the human body covering an area of about 2m2 in an average human adult. This

multilayered organ receives approximately one third of all blood circulating through the body (Guy *et al*., 1987). Epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards skin surface (Flynn, 1985). Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. Together, these other layers constitute the viable epidermis. Dermis is foundation of firm connective tissue upon which epidermis is laid and is of mesoderm origin. The dermis or corium consists of a dense felt work of connective tissue in which bundles of collagenous fibres predominate, mingled with a certain proportion of elastic tissue in superficial levels. Dermis contains fine plexuses of blood vessels, lymphatics and nerves, hair follicles, sweat glands and sebaceous glands (Gros and Clark, 1980).

Drug penetration pathways:

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin the appendages (shunt routes); through the intercellular the other layers of the epidermis the stratum lucilipiddomains; or by a transcellular route. A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule (Reinhold, 1989).

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skins surface area) therefore limiting the area available for direct contact of the applied drug formulation (Gandhi *et al*., 2012).

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrate keratin, provide an aqueous environment for which hydrophilic drugs

Intercellular route:

Skin condition: Skin age: Blood supply: can pass. The diffusion path- way for a drug via the transcellular route requires a number of partitioning and diffusion steps (Gandhi *et al*., 2012). The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons. Recalling the 'bricks and mortar' model of the stratum corneum, the inte rdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which in contrast to the relatively direct path of the transcellular route. The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin (Gandhi *et al*., 2012). **FACTORS INFLUENCING TRANSDERMAL DRUG**: The effective transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and the vehicles. So the factors affecting can be divided in to classes as biological factors and physicochemical factors. **5.1. Biological factors:** Acids and alkalis, many solvents like chloroform methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration. The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS. Changes in peripheral circulation can affect transdermal absorption. **✓ Regional skin site: ✓ Skin metabolism: ✓ Species differences: Physicochemical factors: ✓ Skin hydration: ✓ Temperature and pH: ✓ Diffusion coefficient:** Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significantly penetration. Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin. The skin thickness, density of appendages, and keratinization of skin vary species to species, so affects the penetration (Deshwal and Verma, 2012). In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin.The permeation of drug increase ten fold with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration. Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them. ✓ Drug concentration: ✓ Partition coefficient: ✓ Molecular size and shape. The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier. The optimal K, partition coefficient is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated. Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known (Deshwal and Verma, 2012). **TYPES OF TRANSDERMAL PATCHES: Single layer drug in adhesive:** In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and

this type of layer is responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing. (Willams and Barry, 2004) **Multi -layer drug in adhesive:**

This type is also similar to the single layer but it contains a immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. The

Drug-in-adhesive system:

adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing (Pellet *et al*., 2003).

Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions (Pellet *et al*., 2003).

Reservoir system:

In this system the drug reservoir is embedded between the two layers; 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 (Pellet *et al*., 2003).

Matrix 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 on an impervious

Matrix-dispersion system

backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose (Brown and Jones, 2000).

.In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is 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 (Brown and Jones, 2000; Tsai *et al*., 1998).

Microreservoir Controlled TDDS:

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer

Polymer matrix.

. Drug.

. Permeation enhancers.

. Pressure sensitive adhesives (PSAs).

. Backing membrane.

. Release liner.

. Other excipients (Hanumanaik et al., 2012)and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross linking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc Positioned at the center and surrounded by an adhesive rim (Patani and Chien, 1999). .

Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.

. Natural polymers:

. Synthetic polymers:

Physicochemical properties:

Polymer matrix / Drug reservoir:

Polymer matrix, prepared by the dispersion of a drug in a suitable polymer, controls the release of the drug from the device. Polymers used in TDDS should be stable, compatible and non-reactive with the drug and other components of the system, should provide effective release of the drug throughout the device. They should be easily fabricated to the desired product. Polymers and their degradation products must be non-toxic and non-antigenic to the host (Mishra, 2002).

The polymers used for TDDS can be classified as:

Hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (sodium CMC), cellulose acetate, methyl cellulose, ethyl cellu-lose, gelatin, chitosan, sodium carboxymethylguar, sodium alginate, polymerized rosin etc (Bagyalakshmi *et al*., 2007; Kulkarni *et al*., 2004; Satturwar *et al*., 2005).

Polyvinyl alcohol, polyethylene, polyethylene glycol, polyvinylpyrrolidone, eudragits, ethylene vinyl acetate copolymer, ethyl vinyl acetate, silicon rubber etc (Satturwar *et al*., 2005; Gondaliya and Pundarikakshudu, 2003; Schroeder *et al*., 2007).

Drug:

Drugs, having the following properties, are selected for TDDS

The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml) The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible (Jayaswal and Sood, 1987).

Substances having a molecular weight of less than 1000 units are suitable.

A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.

- Hydrogen bonding groups should be less than 2 **(**Finnin and Morgan, 1999). **Biological properties:**
- Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day)
- The drug should have short biological half life
- The drug should be non irritant and non allergic to human skin
- The drug should be stable when in contact with the skin
- The drug should not stimulate an immune reaction to the skin
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery
- The drug should not get irreversibly bound in the subcutaneous tissue
- The drug should not get extensively metabolized in the skin (Mishra, 2002). **. Chemical permeation** enhancers:

Permeation enhancers:

They disrupt the highly ordered intercellular lipid bilayers of the stratum corneum by inserting amphiphilic molecules or by extracting lipids, reversibly decreasing the barrier resistance and allowing better permeation of the co-administered drugs (Prausnitz and Langer, 2008). An ideal en-hancer should be inert, non-toxic, non-allergenic, non-irritating, work unidirectionally and compatible with the excipients and drugs. Their potency appears to be drug, skin and concentration dependent (Williams and Barry, 2004).

Physical permeation enhancers:

Some examples of permeants are ethanol (the most common permeation enhancer), essential oils or terpenes (cineole, carveol, menthone, citral, menthol, d-limonene), dimethyl sulfoxide, propylene glycol, N-methyl-2-pyrrolidine, ethyl pyrrolidine, polyethylene glycol 400, isopropyl myristate, myristic acid, succinic acid, laurocapram (azone), methyl laureate, lauric acid, sodium lauryl sulfate, non-ionic surfactant (spans, tweens), pluronic, oleic acid, diethylene glycol monoethyl ether, urea etc (Dubey *et al*., 2010; Schroeder *et al*., 2007; Kulkarni *et al*., 2004; Gondaliya and Pundarikakshudu, 2003; Suwanpidokkul *et al*., 2004; Chakkapan *et al*., 1994; Williams and Barry, 2004).

Iontophoresis enhance and control drug penetration through the skin by applying low density electric current. Electroporation applies high voltage pulses across the skin for a fraction of second, creating new aqueous pathways in the stratum corneum for drug diffusion (Jadoul and Preat, 1997). Erbium: yttrium-aluminium-garnet (Er:YAG) laser applies single pulse of low energy to ab-late the stratum corneum layers (Lee *et al*., 2008). Ultrasound or micro needle

Other permeation enhancers:

application breach the stra-tum corneum and create micro channels for the drug permeation (Lanke *et al*., 2009). Ethanolic liposomes, niosomes, protransferosome gel and prodrug approach are reported to increase permeability by increasing the drug solubilization and partitioning into the skin (Dubey *et al*., 2010; El-Laithy *et al*., 2011; Puglia *et al*., 2006).

Pressure sensitive adhesives (PSAs):

PSAs affix TDDS firmly to the skin on applying light pressure. They should be skin-compatible, non-irritant, easily removable without leaving a residue or inflicting pain. They ensure intimate contact between the drug releasing area of TDDS and the skin surface which is critical for the controlled release of drug. Commercially available PSAs include polyacrylate, polyisobutylene and silicones (Murthy *et al*., 2001; Dimas *et al*., 2000; Ho and Dodou, 2007).

Backing membrane:

Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear, pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability (Foco *et al*., 2004; Paranjothy and Thampi, 1997).

In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate. Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate. (Foco *et al*., 2004; Paranjothy and Thampi, 1997; Bhaskaran and Harsha, 2000; Aqil *et al*., 2006; Dey *et al*., 2007; Satturwar *et al*., 2005).

Release Liner:

Release liner is a protective liner for the TDDS patch that is removed prior to the application on the skin. Typically, it consists of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer of silicon (Aqil *et al*., 2006; Dimas *et al*., 2000).

Other excipients:

Various solvents such as water, ethanol, isopropylmy-ristate, isopropyl alcohol, and dichloromethane are used alone or in combination to prepare the drug reservoir (Suwanpidokkul *et al*., 2004; Bagyalakshmi *et al*., 2007; Aqil *et al*., 2006). Propylene glycol, ethanol are used as co solvents along with the permeation en-hancer (Magnusson *et al*., 1997; Ruland *et al*., 1994). Plasticizers like diethyl phthalate, dibutylpthalate, glycerol, triethyl citrate, polyethylene glycol 400, eudraflex and propylene glycol provide plasticity to the trans-dermal patch (Rajendran *et al*., 1997; Dey *et al*., 2007; Gondaliya and Pundarikakshudu, 2003; Aqil *et al*., 2006; Panigrahi *et al*., 2005; Bhaskaran and Harsha, 2000).

IDEAL REQUIREMENTS FOR TDDS:

Shelf life up to 2 years
Small size patch (i.e., less than 40 cm2)
Convenient dose frequency (i.e., once a day to once a week)
Cosmetically acceptable (i.e., clear, white colour)
Simple packaging (i.e., minimum number of pouches and steps required to apply the system) Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
No residue i.e., cold flow, around the edge of the patch in storage or after application to skin or beneath the patch after removal)

COMPOSITION OF TDDS:

No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.)

• Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same inividuals over time (Ghosh and Pfister , 1997).

✓✓ **Thickness of the Patch:9. EVALUATION PARAMETERS:** The evaluation methods for transdermal dosage form can be classified into following type Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters (Singh *et al*., 1993). **Folding Endurance: Percentage Moisture Content: ✓ Percentage Moisture Uptake: ✓ Water Vapour Permeability (WVP) Evaluation:** meter and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights. A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without

breaking gave the value of the folding endurance. The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula. Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100 The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula. Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100 Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following **formula: WVP=W/A ✓ Drug Content: ✓ Content Uniformity Test: ✓ Uniformity of Dosage Unit Test: ✓ Polariscope Examination:** Where, **WVP** is expressed in gm/m per 24hrs, **W** is the amount of vapour permeated through the patch expressed in gm/24hrs and **A** is the surface area of the exposure samples expressed in m2. A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples (Rhaghuram *et al*., 2003). 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. Bu if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test (Aggarwal and Dhawan, 2009). An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculate (Shaila *et al*., 2006). This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch **Shear Adhesion Test:**

Tack Properties: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer (Aarti *et al*., 1995).

Thumb Tack Test: It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

Peel Adhesion Test: In this test, a length of tape is adhered to a surface and then the tape is removed by lifting away from the surface in a specified manner. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. The results are reported as the force required for a given width of tape. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured (Aarti *et al*., 1995).

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength (Aarti *et al*., 1995).

Flatness Test: Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness. % constriction = I1 – I2/ I1X 100

Rolling Ball Tack Test: This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch (Lec *et al*., 1991).

Quick stick (peel-tack) Test: In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

Probe Tack Test: The Experimental technique known as probe tack is designed to test the adhesive properties of film for very short contact times. In this test, a flat- ended cylindrical probe is bought in contact with the adhesive film which is deposited on a rigid substrate. The probe is then maintained in contained under a controlled pressure for a certain contact time. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams (Karande *et al*., 2005).

Percentage Elongation Break Test: The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

Shear strength properties or creep resistance: Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. The test performed with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification (Karande *et al*., 2005).

Elongation percentage = L1-L2/L2 ×100

Where, **L1**is the final length of each strip and **L2** is the initial length of each

In vitro skin permeation studies:

In Vitro Evaluation:

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated (Singh *et al*., 1993).

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with

Horizontal-type skin permeation system: This has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64cm2). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermo stated water through a water jacket surrounding the two compartments (Patel *et al*., 2012).

Franz diffusion cell: The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment (Patel *et al*., 2012).

Flow-through diffusion cell: Flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to aloe appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates (Patel *et al*., 2012). the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or H LC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated mg cm2 vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load mg cm (Singh *et al*., 1993).

***Animal models Human volunteers Biophysical model**s • **Animal models:** Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man (Aggarwal and Dhawan, 2009).

In Vivo Evaluation Studies:

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using:

Human models: The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug (Aggarwal and Dhawan, 2009).

Biophysical Models: Models based on steady-state mass balance equation, solution of Fick's second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature. It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward there is scope for further refinement. Some of the unresolved issues include the barrier function of the skin with age, skin metabolism, in-vivo functioning of penetration enhancers etc (Aggarwal and Dhawan, 2009).

Skin Irritation study:

Stability studies:

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury (Shaila *et al*., 2006).

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content (Singh *et al*., 1993).

THERAPEUTIC APPLICATIONS OF TDDS:

- Hisetal, used in the treatment of multiple sclerosis may be formulated in TDDS using oleic acid as permeation enhancer to achieve sufficient drug delivery (Ruland *et al*., 1994).

Diclofenac sodium, celecoxib used as Non- Steroidal Anti Inflammatory Drugs (NSAIDs), formulated in TDDS may overcome the gastric lesions associated with oral dosing (Rana *et al*., 1999; Yener *et al*., 2003).

Drugs used for long term dosing in the chronic diseases like captopril, verapamil, terbutaline sulphate, pinacidil, propranolol which have a short biological half life, considerable first pass metabolism may be formulated as TDDS to achieve prolonged steady state plasma con-centration (Koteshwar *et al*., 1992; Paranjothy and Thampi, 1997; Kulkarni *et al*., 2004; Aqil *et al*., 2006; Dey *et al*., 2007).

Hydrophilic polymers like polyvinylpyrrolidone may provide faster drug release whereas hydrophobic polymers like ethyl cellulose can provide prolonged drug delivery (Dey *et al*., 2007).

Gel formulation with lipid disperse system of betahis-tine has potential for the development of an efficient controlled release transdermal system (Ogiso *et al*., 1994).

Enhancer and co-solvent may synergistically enhance the delivery of peptides like thyrotropin releasing hormone across the human skin (Magnusson *et al*., 1997).

Prazosin Hydrochloride in membrane controlled TDDS may deliver the drug enough to maintain the minimum effective concentration and can avoid hypotension associated with high initial oral dosing (Rajendran *et al*., 1997).

TDDS of indomethacin in polyvinylpyrrolidone polymer (acting as antinucleating agent) may provide better anti-inflammatory activity and lower ulcer indices compared to oral administration (Rao and Diwan, 1998).

Diclofenac sodium, existing in anionic form at skin pH may be formulated as ion-pairs with oppositely charged enhancers to enhance the transdermal deli-very compared to non-ion paired forms (Rana *et al*., 1999).

- Iontophoresis may increase the permeation rate of hydrophilic atenolol to a greater extent than permeation enhancer and overcome incomplete absorption in the gastrointestinal (GI) tract (Bhaskaran *et al*., 2000).
- Nimesulide in sodium alginate transdermal gel may provide better analgesic and anti-inflammatory activity and avoid the adverse effects associated with long term treatment with high oral dosing (Pandey *et al*., 2000).
- Terbutaline sulphate, being diamagnetic, may be incorporated in the magnetic TDDS to experience driving force to escape from the applied magnetic field and enhance diffusion across the skin (Murthy *et al*., 2001).

- Bupropion Hydrochloride, an antidepressant drug may be converted to free base to increase the lipophilicity and transdermal delivery and avoid the release of fatal metabolites associated with oral dosing (Gondaliya and Pundarikakshudu, 2003).
- Zidovudine, an anti-Human Immuno Deficiency Virus (anti-HIV) drug, formulated in TDDS may overcome toxic effects associated with frequent higher oral dose (Suwanpidokkul *et al*., 2004).
- Levonorgestrel, a potent contraceptive agent, formu-lated as transdermal protransferosome gel may provide enhanced, prolonged and controlled delivery and overcome the GI disturbances, weight gain, irregular bleeding, headache etc. associated with oral dosing (Jain *et al*., 2005).
- Polymerized rosin may be used to design the matrix type TDDS of Diltiazem Hydrochloride to prolong the drug release and avoid the variable and extensive first pass metabolism on oral dose (Satturwar *et al*., 2005).

Ester prodrug of ketorolac may provide enhanced permeation whereas nanostructured lipid carrier can act as controlled release system and avoid the gastric ulceration and renal failure associated with frequent long term oral dosing (Puglia *et al*., 2006). ✓

Micro fabricated Microneedles:

RECENT TECHNIQUES FOR ENHANCING TDDS

Structure-Based Enhancement Techniques:

Microneedles are recently used techniques for transdermal drug delivery designed to form a physical pathway through the upper epidermis to enhance skin permeability. Micro-fabricated microneedles are devices which are hybrids of the hypodermic needle and transdermal patch in this technology needles of micron dimension are inserted in to skin surface. It damages or produces pores only in SC portion so one does not feel any pain since nerve fibers are located into deeper region of the skin. Moreover distance to be travelled by drug will decrease (Kapoor *et al*., 2011).

Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique. There are 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.

- **Coat and poke approach:** Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.
- **Biodegradable microneedles:** Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- **Hollow microneedles:** Involves injecting the drug through the needle with a hollow bore (Kapoor *et al*., 2011; Ritesh and Anil, 2007).
- **Dry-Coated Macro flux system:** This is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.
- **D-TRANS Macro flux system:** This is also for short duration administration that consists of a microprojection array combined with reservoir of drug.

This system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer .The main component of the microprojection patch is a titanium disk affixed to a polymeric adhesive back. The titanium disk is 8 cm2 and consists of an array of microscopic, titanium, tooth-like microprojections that are coated with medicinal substances. There are as many as 300 microprojections per cm with the length of individual micro projection less than 200ìm. They penetrate just the 10ìm to 25ìm-thin layer of dead cells of the stratum corneum, in which they create 'holes'-microchannels, large enough to permit the transport of large molecules to the physiologically active deeper layers of the epidermis. The titanium microprojections are too small to cause pain. This technology offers a needle-free and painless transdermal drug delivery of large-molecular-weight compounds such as insulin, several peptidic hormones, and vaccines. With this new system; patients can receive drugs for 12 weeks (Ahad *et al*., 2010; Ritesh and Anil, 2007). Three types of Macroflux have been designed. They include,

E-TRANS Macro flux system: This is for on demand delivery that involves a microprojection array combined with an electrotransport system (Ahad *et al*., 2010; Ritesh and Anil, 2007).

Metered-Dose Transdermal Spray (MDTS): It is a liquid preparation in the form of solution that are used topically which is made up of a

vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. 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 (Gaur *et al*., 2009; Kapoor *et al*., 2011). ✓

. Electrically-Based Enhancement Techniques:

In iontophoretic delivery devices, Drug is placed on the skin under the active electrode, and a current (< 0.5mA) passed between the two electrodes effectively repelling drug away from the active electrode and into the skin. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anaesthesia (Kapoor *et al*., 2011; Ritesh and Anil, 2007).

Photomechanical Waves:

Electro-Osmosis: Needle-Free Injections: Intraject The application of ultrasound of a suitable frequency significantly enhances the transdermal transport of drugs by means of skin system not larger than wrist watch-a phenomenon referred to as phonophoresis or sonophoresis. It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. In this technique, the drug is mixed with a coupling agent usually a gel but sometimes a cream or ointment is used which transfers ultrasonic energy from the device to the skin through this coupling agent. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier. It employs ultrasound waves ranging from 20 kHzto 10 MHz with intensities of up to 3Wcm-2 have been applied to mitigate the stratum corneum barrier property (Kapoor *et al*., 2011; Ritesh and Anil, 2007; Gaur *et al*., 2009). The mechanism of photochemical wave was found to act by producing changes in the lacunar system which results in the formation of transient channels through the stratum corneum by permeabilization mechanism (Naik *et al*., 2009). In this method, aqueous pores are generated in the lipid bilayers by the application of short electrical pulses of approx 100-1000 volt/cm. It may combine with Iontophoresis to enhance the permeation of peptide (Ahad *et al*., 2010). If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volumes flow, called electro osmosis (Soni *et al*., 2009; Ahad *et al*., 2010). ImplajectJet SyringeIject Cross jet Jet Syringe (Arunachalam *et al*., 2010; Ritesh and Anil, 2007). **Powderject Device: Skin Abrasion:** Mini-ject The powderject system fires solid particles (20-100 mm) through stratum corneum into lower skin layers, using a supersonic shock wave of helium gas (Gaur *et al*., 2009). **Other Enhancement Techniques:** Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. They are lipid vesicles that fully enclose an aqueous volume. Liposomes acts by penetrating the epidermis, carrying the drug into skin (Kapoor *et al*., 2011; Ritesh and Anil, 2007; Soni *et al*., 2009; Ahad *et al*., 2010).

Transferosomes are modified liposomes i.e. they are liposomes with edge activators (sodium cholate). Transferosomes by passes the cutaneous capillary bed because they are too large to enter the blood vessels locally and reach subcutaneous tissue. Transferosome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug (Kapoor *et al*., 2011; Soni *et al*., 2009). The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules are generally known as Microscissuining (Ritesh and Anil, 2007; Soni *et al*., 2009). Med-Tats is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children (Ahad *et al*., 2010; Snigdha *et al*., 2011). This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs (Kapoor *et al*., 2011; Soni *et al*., 2009).

Thermodynamic activity of drug can be increased by employing supersaturated systems. In this method, when saturated formulation is used, the thermodynamic activity of the drug in the vehicle is increased above unity, thus enhancing the permeability of topically applied formulations. Skin permeation was directly related to the degree of saturation and was independent of the absolute concentration of the drug (Kapoor *et al*., 2011; Snigdha *et al*., 2011).

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength (Snigdha *et al*., 2011).

RECENT ADVANCEMENT IN TDDS: Mucha *et al*. (2013) carried out a research on controlled delivery kinetics of Ibuprofen in transdermal patch. They used chitosan (CS) based materials in a form of composite with poly (lactic acid) (PLA) granules; films and freeze-dried scaffolds also with blended form with hydroxypropylocellulose (HPC). And excellent adhesion of biopolymer matrices to PLA microspheres or hydroxyapatite (HAp) particles was proven. The Iorder drug (ibuprofen (IBU)) release kinetics from obtained films is stated (Mucha *et al*., 2013). Vitorino *et al*. (2013) carried out a research on delivering co-encapsulation of drugs as transdermal patch. In this work, a comprehensive study for the co-encapsulation of drugs with a differential lipophilicity, olanzapine and simvastatin, and their transdermal delivery in a formulation containing nanostructured lipid carriers (NLC) is presented. They found that the external medium in the NLC dispersion strongly influences permeation. He also seen that the use of NLC determines a synergistic effect with selected

permeation enhancers, thus promoting marked flux enhancement ratios (48 and 21, respectively for olanzapine and simvastatin) relative to the drugs in solution. The developed formulations can be considered non-irritant (Vitorino *et al*., 2013). Shi *et al*. (2013) carried out a research based on drug loaded nanofibers to improve the performances of transdermal patches.

They used electrospin ibuprofen (IBU)-loaded composite nanofibers for their research. Cellulose acetate/poly(vinyl pyrrolidone) (CA/PVP) blends were used to fabricate uniform nanofibers. Investigations on the physicochemical properties of CA/PVP solutions indicated that the addition of appropriate PVP improved the electrospinnability of original CA solutions. Detections on the physical states of IBU in medicated CA/PVP nanofibers suggested that IBU was uniformly distributed in nanofibers in an amorphous state. Furthermore, CA/PVP nanofibers exhibited a high water vapor permeability, which could render an improved breathability to transdermal patches. They concluded that, the electrospun drug-loaded CA/PVP nanofibers exhibited great potentials to improve the thermodynamic stability and breathability of transdermal patches, which could be used to develop new types of transdermal drug delivery system (TDDS) (Shi *et al.*, 2013). Gaur *et al*. (2013) carried out a research on developing Diclofenac sodium loaded solid lipid nanoparticles (SLNs). They used guggul lipid as major lipid component and analyzed for physical parameters, permeation profile, and anti-inflammatory activity. The SLNs were prepared using melt-emulsion sonication/low temperature-solidification method and characterized for physical parameters, in vitro drug release, and accelerated stability studies, and formulated into gel. Respective gels were compared with a commercial emulgel (CEG) and plain carbopol gel containing drug (CG) for ex vivo and in vivo drug permeation and anti-inflammatory activity. The SLNs were stable with optimum physical parameters. They found that physicochemical properties of major lipid component govern the properties of SLN. SLN made up of guggul lipid showed good physical properties with acceptable stability. Furthermore, it showed a controlled drug release profile along with a promising permeation profile (Gaur *et al*., 2013). Donnelly *et al*. (2012) carried out a research on developing Hydrogel-Forming Microneedle Arrays. They used crosslinked polymers to produce unique microneedle arrays. Crosslinked polymers rapidly take up skin interstitial fluid upon skin insertion to form continuous, unblockable, hydrogel conduits from attached patch-type drug reservoirs to the dermal microcirculation. They found, such microneedles, which can be fabricated in a wide range of patch sizes and microneedle geometries, can be easily sterilized, resist hole closure while in place, and are removed completely intact from the skin. They established that, this technology has the potential to overcome the limitations of conventional microneedle designs and greatly increase the range of the type of drug that is deliverable transdermally, with ensuing benefits for industry, healthcare providers and, ultimately, patients (Donnelly *et al*., 2012). Zhang *et al*. (2011) reported that Genetronics Inc (San Diego, California) have developed a prototype electroporation transdermal device. This device has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics (Zhang *et al*., 2011).

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 deliver-able 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 likeli hood of clinical success from using a transdermal medication, the safety of the caregiver must be the high-est priority

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