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## TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS): AN OVERVIEW

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### ABSTRACT

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Enhancers

The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route. This review describes enhancement techniques based on drug/vehicle optimization such as physical and chemical penetration enhancers. Various novel carriers and vehicles like micro/nano and multiple emulsion, Liposomes, Niosomes, and Transferosomes etc., along with formulation strategies has also been discussed in the present review.

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**INTRODUCTION:** Transdermal delivery has received increased attention in the face of growing awareness that drugs administered by conventional means are frequently excessively toxic and sometimes ineffective. Thus conventional drugs in the form of tablets, capsules, injectables and ointments are introduced in the body as pulses that usually produce large fluctuations of drug concentration in the blood stream and tissues and consequently unfavorable patterns of safety and efficacy.

Transdermal delivery provides an improved approach to the administration of drugs by maintaining a therapeutic constant concentration of drug in the blood for desired period of time, usually between one and seven days. Transdermal drug delivery enables avoidance of gastrointestinal absorption, which is associated with pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced

pharmacological dosing due to the shortened metabolic pathway of the transdermal route versus the gastrointestinal pathway. Transdermal drug delivery system releases its active ingredient through the patient's skin providing a uniform blood level. In addition since the active ingredient moves with the blood stream directly into the targeted organ, the effective dose can be lower than that in the traditional drug type.

The transdermal drug delivery system permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medication. The transdermal route categorized with oral treatment as the most successful route and innovative research area in drug delivery, and around 40% of the drug delivery systems under clinical evaluation are related to transdermal system. The worldwide transdermal patch market <sup>1</sup> approaches about £ 2 billion. Some

marketed transdermal drug delivery systems are given in Table 1. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve a optimum concentration and the desired therapeutic effect <sup>2</sup>.

**Transdermal drug delivery approach has following advantages and disadvantages over other routes <sup>3</sup>:** The advantages of delivering drugs through the skin include:

- (i) Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.
- (ii) The ease of usage makes it possible for patients to self-administer these systems.
- (iii) In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.
- (iv) Since the composition of skin structurally and biologically is the same in almost all the humans, there is minimal inter and intra patient variation.
- (v) Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.
- (vi) Continuous, non-invasive infusion can be achieved for drugs with short biological half-lives, which would otherwise require frequent dosing.
- (vii) Due to reduced frequency of dosing there is better patient compliance.
- (viii) Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.
- (ix) The adverse effects are minimized due to a steady and optimum blood concentration time profile.
- (x) The risks, pain and inconvenience associated with parenteral therapy are evaded.
- (xi) The release is more prolonged than oral sustained drug delivery systems.
- (xii) At times the maintenance of the drug concentration within the biophase is not desired; therefore transdermal systems are suitable in this case.

- (xiii) The daily dose of the drug required is lower than that with conventional therapies.
  - (xiv) The drug release is such that there is a predictable and extended duration of activity.
- The following are some of the shortcomings of the transdermal delivery system:
    - (xv) There is possibility of skin irritation due to the one or many of the formulation components.
    - (xvi) Binding of drug to skin may result in dose dumping.
    - (xvii) It can be used only for chronic conditions where drug therapy is desired for a long period of time e.g., hypertension, angina and diabetes etc.
    - (xviii) Lag time is variable and can vary from several hours to days for different drug candidates.
    - (xix) Cutaneous metabolism will affect therapeutic performance of the system.
    - (xx) Transdermal therapy is feasible for certain potent drugs only.
    - (xxi) Transdermal therapy is not feasible for ionic drugs.
    - (xxii) It cannot deliver drug in pulsatile fashion.

**TABLE 1: MARKETED TRANSDERMAL DRUG DELIVERY SYSTEMS**

Drug	Trade name	Company
Estradiol	Estraderm	Ciba Geigy
	Climara	Berlexpharma
	Fempatuch	Parke Davies
Fentanyl	Alora	Proctor & Gamble
	Duragesic	Alza corp, N.J.
Testosterone	Testoderm	Alza corp, N.J.
	Androderm	Alza corp, N.J.
	Deponit	Schwarz Pharma
Nitroglycerin	Nitrodur	Ciba Geigy
	Nitrodisc	Robests Pharma
	Minitran	3 M
	Transderm nitro	Ciba Geigy
Clonidine	Catapress	Boehringer Ingelheim
Scopolamine	Transderm scope	Ciba Geigy
	Nicoderm	Smithkline Beecham
Nicotine	Nicotrol	Mc neol consumer products
	Prostep	Ledisle Pharma
	Habitrol	Ciba Geigy

**Skin as route of Transdermal Drug Delivery:** The transdermal permeation of a chemical involves partitioning into and transport through the cutaneous layers, namely the stratum corneum, the viable epidermis (stratum basale) and the upper dermis. A topical product is designed to deliver the drug into the skin to treat dermal disorders and therefore skin is the target organ. Non steady state transport generally characterizes a topical product.

The skin is a barrier to topically administered drugs. Topical formulations usually contain several excipients, which also partition into the skin according to their physicochemical properties. Certain excipients change the integrity of stratum corneum. Stratum corneum can exhibit swelling by water. Thus, the permeability of drugs depends on the degree of hydration. Cosolvents may alter the barrier properties of the skin. Some substances having considerable polarities also enhance the permeability of the horny layer.

It is known that use of oleaginous vehicles enhances the skin permeation. Topical preparation applied to the skin may be designed for surface, local or systemic effects. In order to understand these effects, a brief review of the skin structure is provided.

**A brief review of skin structure:** The skin can be considered to have four distinct layers of tissue.

- Non-viable epidermis (stratum corneum)
- Viable epidermis
- Viable dermis
- Subcutaneous connective tissue (hypodermis)

**Epidermis:** The epidermis is the relatively thin, tough, outer layer of the skin. The epidermis is keratinocytes. They originate from cells in the deepest layer of the epidermis called the basal layer. New keratinocytes slowly migrate up toward the surface of the epidermis.

**Non-viable epidermis (stratum corneum):** The outermost portion of the epidermis, known as the stratum corneum, is relatively waterproof and, when undamaged, prevents most bacteria, viruses, and other foreign substances from entering the body. The epidermis also protects the internal organs, muscles, nerves, and blood vessels against trauma. The outer

keratin layer of the epidermis (stratum corneum) is much thicker.

**Viable Epidermis:** This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100  $\mu\text{m}$ . The structure of the cells in the viable epidermis is physiochemically similar to other living tissues. Cells are held together by tonofibrils. The water content is about 90%.

**Dermis:** The dermis, the skin's next layer, is a thick layer of fibrous and elastic tissue (made mostly of collagen, elastin and fibrillin) that gives the skin its flexibility and strength. The dermis contains nerve endings, sweat glands and oil glands, hair follicles, and blood vessels.

**Subcutaneous Connective Tissue:** The subcutaneous tissue also known as hypodermis is not actually accepted a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, where the fatty tissue serve as a depot of the drug.

**Mechanism of Skin Penetration:** Drug molecule penetrate through skin surface with the following three potential pathways: through the sweat ducts, through the hair follicles and sebaceous glands or directly across the stratum corneum<sup>4-6</sup>, since the last few years there is a point of debate among scientists for the relative importance of the shunt or appendageal route vs transport across the stratum corneum and is further complicated by the lack of a suitable experimental model to permit separation of the these three pathways<sup>7,8</sup>.

A recent review by Menon provides a valuable resource<sup>9,10</sup>. *In vitro* experiments tend to involve the use of hydrated skin or epidermal membranes the lipid phase behavior is different from that of other biological membranes<sup>11</sup>. The stratum corneum consists of 10 to 15 layer of corneocytes<sup>12-14</sup>.

## Carriers and Vehicles:

**Micro or nanocapsules:** Nanocapsules are submicroscopic colloidal drug carrier systems composed of an oily or an aqueous core surrounded by the thin polymer membrane<sup>15</sup>. It consists of a shell and a space, in which desired substances may be placed. Dispersed polymer nanocapsules can serve drug carriers to achieve controlled release as well as efficient drug targeting. Their release and degradation properties largely depend on the composition. The nanocapsules can be prepared by four principally different approaches: interfacial polymerization, interfacial precipitation, interfacial deposition, and self assembly procedures<sup>16</sup>.

**Microemulsions:** These systems are transparent mixtures of water, oil, and surfactants. They are thermodynamically stable and optically isotropic. Microemulsion are spontaneously produced in a narrow range of o/w surfactant composition, they are dynamic system with continuously fluctuating interface. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilizing properties<sup>17</sup>.

**Nanoemulsions:** These are oil in water emulsions with an average droplet size ranging from 100 to 500 nm. They have a very good stability and they do not undergo phase separation during storage. Many studies showed reduced trans-epidermal water loss, which means support to the barrier function of the skin<sup>18</sup>. Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays. The preparation of nanoemulsions requires high-pressure homogenization. The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids<sup>19</sup>.

The concentration range of components of nanoemulsion composed of isopropyl myristate (IPM) as an oil phase, tween 85 as surfactant, ethanol as cosurfactant, water as aqueous phase. The effects of the content of IPM as an oil phase and n-methyl pyrrolidone (NMP) as transdermal enhancer on rat skin permeation of granisetron hydrochloride nanoemulsion were studied *in vitro*<sup>20</sup>.

**Multiple emulsions:** These are novel drug delivery system in the field of emulsion technology. These emulsion system involves the dispersed phase contain smaller droplets that have the same composition as the external phase<sup>21</sup>. These may be w/o/w or o/w/o type emulsion system. W/O/W emulsions consist of an aqueous phase separates internal and external oil phase where as w/o/w involves an organic phase which separate internal and external oil phase. These systems can have highly phase contents and thus present good hydration. Their efficacy has been dermatology to treat stretch marks.

**Solid lipid nanoparticles (SLN):** It is aqueous carriers for enhanced delivery for sunscreens, vitamins A and E triptolide and glucocorticoids<sup>22-29</sup>. Its enhanced skin penetrating ability is generally due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN. A 31% increase in skin hydration has been reported following 4 weeks application of skin enriched cream<sup>30</sup>.

**Liposomes:** Liposomes are colloidal particles drug delivery system involve concentric biomolecular layers that are capable of encapsulating drugs. The skin delivery of tri-amcinolone acetonide was four to five times for liposomal lotion than an ointment containing the soybean or egg<sup>31-36</sup>. Recent studies have tried to deliver macromolecules such as interferon, gene delivery, and cutaneous vaccination as liposomes.

**Niosomes:** Niosomes are obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are similar to liposomes and used as carriers of amphiphilic and lipophilic drugs. Niosomes are excellent vehicle for drug delivery as it is less toxic and improves the therapeutic index of drug by restricting its action to target cells<sup>37</sup>.

**Transfersomes:** This enables the transfersomes to cross various transport barriers efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents<sup>38</sup>.

**Ethosomes:** A form of Liposomes with high alcoholic content which have capability of penetration to deep tissues and the systemic circulation called ethosomes

<sup>39-41</sup>. It is due to the presence of alcohol, fluidized the ethosomal lipids and the stratum corneum bilayer lipids.

**Aquasomes:** Aquasomes are spherical 60–300 nm particles used for drug and antigen delivery. It is a successful carrier system as they provide protection and preservation of fragile biological molecules, and surface exposure for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites. These Three main types of core materials are mainly used for producing aquasomes: tin oxide, nanocrystalline carbon ceramics and brushite (calcium phosphate dihydrate) <sup>42</sup>.

**Formulation Strategies:** Overcoming the barrier status of skin is of prime concern for the success of a transdermal patch. A product development scientist often uses permeation enhancer(s) that increase the rate of transfer of drug(s) across the skin. In addition, adequate adhesiveness seems to be essential to ensure intimate contact of the formulation with skin for intended duration. Furthermore, choice of the rate controlling membrane is critical as it controls the release rate of the drug from the formulation.

**Adhesives:** The use of hormones for preventing ovulation as a means of contraception as well as for female hormone replacement therapy is not new. Transdermal delivery of these hormones is advantageous due to the controlled input it can offer over a long period. However, due to large molecular size, weight and high lipophilicity there is a need to include suitable ingredients for enhancing their permeation across skin.

It is important to note that the permeation of hydrophobic drug (alprazolam) was greater from polymer adhesive blends containing a higher proportion of hydrophilic polymer. On the contrary, permeation of hydrophilic drug (nicardipine hydrochloride) was greater from polymer blends containing higher proportion of hydrophobic polymer. Further, matrixes containing hydrophobic- hydrophilic polymer blends gave substantially higher drug flux as compared to those containing only hydrophilic or hydrophobic polymer <sup>43</sup>.

Similarly, in vitro permeation of estradiol and norethindrone across human cadaver skin by using different types of pressure-sensitive adhesive systems without permeation enhancer were observed to be comparable to the commercial patches. Higher permeation of drugs from these systems was proposed to be due to the presence of greater thermodynamic activity, which could be achieved with less drug concentration in the absence of permeation enhancer <sup>44</sup>.

**Enhancers:** For many years, clinical investigators and chemical welfare experts have suggested that substances must exist which could temporarily diminish the impermeability of skin. Such materials, if safe and non-toxic, could be used in dermatology to enhance the permeation rate of drugs and even to treat patients systemically by the dermal route. Such materials appear to increase skin permeability by reducing the diffusional resistance of the stratum corneum, by reversibly damaging it, or by altering its physicochemical nature.

Ideal penetration enhancers should possess the following properties

- (i) Pharmacologically inert, Inexpensive and cosmetically acceptable
- (ii) Nontoxic, nonirritating, and non-allergenic
- (iii) Rapid onset of action; predictable and suitable duration of action for the drug used
- (iv) Reversible effect of the chemical penetration enhancers on the barrier property of stratum corneum
- (v) Chemically and physically compatible with the delivery system
- (vi) Readily incorporated into the delivery system

**Physical Enhancers:**

**Ultrasound:** Ultrasound uses the ultrasonic energy to enhance the transdermal delivery of solutes, through pretreatment, and is frequently referred to as sonophoresis. The mechanism involves the increase

skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound, resulting in disruption of the stratum corneum<sup>45</sup>. Ultrasound enhancers such as treatment duration, intensity, and frequency affect percutaneous absorption, with the latter are being the most important<sup>46</sup>. Although frequencies between 20 kHz to 16 MHz have been reported to enhance skin permeation, the significant effect on transdermal drug delivery, with the delivery of macromolecules of molecular weight up to 48 kDa being reported<sup>47</sup>.

**Thermophoresis:** The skin temperature maintained by a range of homeostatic controls at 32°C. The effect of elevated temperature (nonphysiological) on percutaneous absorption was initially reported<sup>48</sup>. Recently, surge in the interest of using thermoregulation as a means of improving the delivery profile of topical medicaments<sup>49, 50</sup>. It has demonstrated a 2 to 3-fold increase in flux for every 7 to 8 °C rise in skin surface temperature. The increased permeation, heat treatment has been attributed to an increase in drug diffusivity in the vehicle and in the skin because of increased lipid fluidity<sup>51</sup>. The subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also play an important role in enhancing the transdermal delivery of topically applied compounds<sup>52</sup>.

**Iontophoresis:** Iontophoresis involves the application of electromotive force to drive or repel oppositely charged ions through the dermal layers into the area to be treated, either into the surrounding tissues for localized treatment or into the circulatory system for systemic treatment. Positively charged ions are driven into skin at the anode while negatively charged ions are driven into skin at the cathode. Studies have shown increased skin permeation of drugs at anodic/cathodic electrodes regardless of predominant molecular ionic charge<sup>53</sup>.

**Microneedle-based devices:** One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on the microneedle based method<sup>54</sup>. These microneedles of length 50-110 mm will penetrate the stratum corneum and epidermis to deliver the drug from the

reservoir and these reservoirs contain drug and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir<sup>55-57</sup>.

**Needleless Injection:** It is reported to a pain-free method of administering drugs to the skin. Needleless injection, avoids the issues of safety, pain, and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by applying the liquid or solid particles at supersonic speeds through the outer layers of the skin by using a suitable energy source. The latter has been reported to deliver successfully testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin<sup>58-60</sup>.

#### **Chemical Enhancers:**

**Azone:** Azone was the first molecule use as a skin penetration enhancer. Azone is a colorless, odorless liquid with a melting point of -7°C and oily but yet nongreasy feel. Azone is a highly lipophilic material with a log p octanol/water of around 6.2 and it is soluble in and compatible with most organic solvents, including alcohol and propylene glycol. Azone is most effective at low concentration. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics, and antiviral agents. Azone is most effective at low concentrations<sup>61</sup>. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone molecules may exist dispersed within the barrier lipid or separate domains within the bilayer<sup>62</sup>.

**Fatty acids:** The most popular of which is oleic acid. It is of interest to note that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains, and some structure-activity relationships, employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants, and amides as enhancers for naloxone<sup>63-65</sup>.

**Urea:** It promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and nontoxic molecules consisting of a

polar parent moiety and a long-chain alkyl ester group. As a result, enhancement mechanism may be both hydrophilic activity and lipid disruption mechanism<sup>66</sup>.

**Surfactants:** Surfactants are added to formulations in order to solubilize lipophilic active ingredients, and so they have potential to solubilize lipids within the stratum corneum. Anionic surfactants include sodium lauryl sulphate, cationic surfactants include cetyltrimethyl ammonium bromide, and both surfactants have potential to damage skin. The nonoxynol surfactants are non-ionic surfactants, and zwitter ionic surfactants include dodecyl betaine, and both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin. Nonionic surfactants tend to be widely regarded as safe. Surfactants have a low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes<sup>66</sup>.

**Essential oil, terpenes and terpenoids:** Terpenes are found in essential oils, and are compounds comprising of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Numerous terpenes have long been used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodium and ylang-ylang have been found to be effective penetration enhancers for 5-fluorouracil transversing human skin *in vivo*<sup>67</sup>.

Cornwell et al<sup>68</sup> investigated the effect of 12 sesquiterpenes on the permeation of 5-fluorouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-fluorouracil. L-menthol has been used to facilitate *in vitro* permeation of morphine hydrochloride through hairless rat skin as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin<sup>69</sup>.

One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Many terpenes permeate human skin well and large amounts of terpene have been found in the epidermis after application from a matrix-type patch. Terpenes may also modify drug diffusivity through the membrane.

During steady state permeation experiments using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity through the membrane following terpene treatment.

**Cyclodextrins:** Cyclodextrins are biocompatible substances that can form inclusion complexes with lipophilic drugs with a resultant increase in their solubility, particularly in aqueous solutions. However, cyclodextrins alone were determined to be less effective as penetration enhancers than when combined with fatty acids and propylene glycol<sup>70</sup>. Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations.

This is due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers. This compound has a higher molecular weight and lipophilicity than other solvent-type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to occur<sup>71</sup>.

#### CURRENT AND FUTURE PROSPECT:

##### **Transdermal Delivery System for Anti-emetic Medication:**

The transdermal delivery system of an anti-emetic hydrophilic adhesive composition of hydrophilic polymer and anti-emetic agent, a patch containing one or two hydrophilic layer of the composition, generates hydrophilic amicro-channels in skin of a subject using the patch or composition<sup>72</sup>.

##### **Transdermal Buprenorphine to treat Pain in Sickle Cell Crisis:**

A specific dosage regimen of buprenorphine achieves pain relief from painful episodes due to sickle cell disease. The dosage used in the form of BTDS transdermal patch<sup>73</sup>.

**Transdermal Delivery of Non-Steroidal Anti Inflammatory Drugs:** Therapeutically effective amount of a non-steroidal anti-inflammatory drug; which is a safe skin-tolerant ester sunscreen ester; and at least one volatile liquid. The invention also provides a method for administering at least one systemic or locally acting non-steroidal anti-inflammatory drug to an animal <sup>74</sup>.

**Transdermal delivery system for neurobehavioral disorder:** Methylphenidate and amphetamine based stimulants are first line pharmacotherapies for attention-deficit hyperactivity disorder, a common neurobehavioral disorder in children and adults. A number of long-acting stimulant formulations have been developed with the aim of providing once-daily dosing, employing various means to extend duration of action, including a transdermal delivery system, an osmotic-release oral system, capsules with a mixture of immediate and delayed release beads, and prodrug technology <sup>75</sup>.

**Transdermal delivery system for Dopaminergic treatment:** Continuous dopaminergic treatment is considered to prevent or delay the occurrence of dyskinesia in patients with Parkinson's disease (PD). Rotigotine is a non-ergolinic dopamine-receptor agonist for the treatment of PD using a transdermal delivery system providing stable plasma levels <sup>76</sup>.

**Transdermal delivery system for rheumatic diseases:** Tenoxicam is a non steroidal anti-inflammatory drug (NSAID) widely used in the treatment of rheumatic diseases and characterized by its good efficacy and less side effects compared to other NSAIDs. Its oral administration is associated with severe side effects in the gastrointestinal tract. Transdermal drug delivery has been recognized as an alternative route to oral delivery <sup>77</sup>.

**Transdermal delivery system to increase bioavailability:** This system increase the bioavailability, maintain the concentration of drug in blood. Drug-in-adhesive transdermal patches of  $\alpha$ -asarone using Eudragit E100 as pressure-sensitive adhesives and oleic acid plus isopropyl myristate as penetration co-enhancers were developed. *In vitro* permeation, *in vivo*

pharmacokinetics in rabbits, and efficacy in asthmatic rats were evaluated <sup>78</sup>.

**Transdermal adhesive patches (capsaicin) treat neuropathic pain:** Capsaicin dermal patch is an adhesive patch containing a high concentration (8% w/w) of synthetic capsaicin. It is indicated in the Europ for the treatment of peripheral neuropathic pain in non-diabetic adults using a single 30-or 60-minute application repeated every 90 days, as required, and in the US for the treatment of neuropathic pain associated with post therapeutic neuralgia <sup>79</sup>.

**Transdermal silicone based patch (dopamine):** The nonergoline dopamine agonist rotigotine is delivered transdermally using a silicone-based patch, which promotes unidirectional drug flow from the transdermal system to the skin. Pharmacokinetic data show stable steady-state plasma concentrations over 24 h, maintained with once-daily patch administration <sup>80</sup>.

**Transdermal delivery system (isradipine) for hypertension:** Isradipine (ISDP) is an effective calcium channel blocker used in the treatment of hypertension. It undergoes extensive first pass metabolism, and bioavailability through the oral route is only about 15 to 24 %.

Hence, attempts have been made to develop a matrix type controlled transdermal drug delivery system for ISDP. Corresponding values for the cumulative amounts of drug permeated across the rat skin for the above matrix films was evaluated. It was concluded that drug release from matrix films followed Higuchi model and the mechanism of drug release was diffusion mediated may be suitable for the development of a transdermal drug delivery system of ISDP <sup>81</sup>.

## REFERENCES:

1. Barr BW: Dermatological: percutaneous absorption. Marcel Dekker. New York, Vol. 983, pp. 235-6.
2. Kanikkannan N, Kandimalla K, Lamba SS and Singh M: Structure activity relationship of chemical penetration enhancers in drug delivery. *Curr Med Chem* 1999; 6593-608
3. Barry BW and William AC: Encyclopedia of pharmaceutical technology. Marcel Dekker. New York, Vol. II, 1995, pp. 49-93.



4. Flaynn CL, Bronaugh RL and Maibach HI: Percutaneous absorption. Marcel Dekker. New York, Vol. 1985, pp. 17-52
5. Kasting CB, Smith RL and Anderson BD: Topical and ocular drug delivery. Marcel Dekker. New York, Vol. 1992, pp. 117-61
6. Potts RD and Guy RH: Predicting skin permeability. *Pharm Res* 1992; 9:663-9.
7. Scheuplein RJ, Bank IH, Brauner CJ and Macfarlane DJ: Percutaneous absorption of steroids. *J Invest Dermatol* 1969; 52:63-70.
8. Scheuplein RJ and Bank IH: Permeability of the skin. *Physiol Rev* 1971; 51:702-47.
9. Higuchi WI: Analysis of data on the medicament release from ointment. *J Pharma Sci* 1962; 51:802-4.
10. Menon CK. New insights into skin structure; scratching the surface. *Adv Drug Deliv Rev* 2002; 54:3-17.
11. Scheuplein RL: Transient diffusion and the relative importance of various routes of skin penetration. *J Invest Dermatol* 1967; 48:79-88.
12. Anderson RL and Cassidy JM: Variation in physical dimension and chemical composition of human stratum corneum. *J Invest Dermatol* 1973; 61:30-2.
13. Holbrook KA and Odland CE: Regional differences in the thickness of the human stratum corneum; an ultrastructural analysis. *J Invest Dermatol* 1974; 62:415-22.
14. Bouwstra JA, Cooris CS, Vander spek JA and Bras W: Structural investigation of human stratum corneum by small angle x-ray scattering. *J Invest Dermatol* 1991; 97:1005-12.
15. National center for biotechnology information, U.S. National library of medicine 8600 Rockville pike, Bethesda, 208,94.
16. Wichting and Milano, Italie, 2005; Vol. 28, pp. 1163-71.
17. Krelgaard M: Influence of microemulsion on cutaneous drug delivery. *Adv Drug Deliv Rev* 2002; 54:77-98.
18. Muller RH, Benita S and Bohm B: Emulsion and nanoemulsion for the formulation of poorly soluble drug. *Stuttgart Med pharm* 1998; pp. 152.
19. Review of Azojono-journal of nanotechnology online-open access to leading nanotech science.
20. Zheng WU, Zhao W, Meng Wei, Ye Y and Han Xiao S: Preparation and the *in vitro* evaluation of nanoemulsion system for the transdermal delivery of granisetron hydrochloride. *Chem Pharm Bull* 2001; 58(8):1015-1019.
21. Tadros TF: Future developments in cosmetic formulation. *Int J Cos Sci* 1992; 14:93-111.
22. Satosh MC, Mehnert W, Schaller M, Korting HC and Cysler A: Drug targeting by solid lipid nanoparticles for dermal use. *Drug Target* 2002; 10:489-95.
23. Wissing SA and Muller RH: Cosmetic application for solid lipid nanoparticle. *Int J Pharm* 2003; 254:65-8.
24. Muller RH, Radtke M and Wissing SA: Solid lipid nanoparticles and nanostructured lipid carrier in cosmetic and dermatological preparation. *Adv Drug Deliv Rev* 2002; 54:131-55.
25. Wissing SA and Muller RH: Solid lipid nanoparticles as carrier for sunscreens, *in vitro* skin penetration. *J Control Rel* 2002; 81:225-33.
26. Jennings V, Cysler A, Schafer-Korting M and Cohn SH: Vit A loaded solid lipid nanoparticles for topical use; occlusive properties and drug targeting to the upper skin. *Eur J Pharma Biopharm* 2000; 49:211-8.
27. Santosh MC, Mehnert W and Schafer-Korting M: Solid lipid nanoparticles as drug carriers for topical glucocorticoids. *Int J Pharm* 2000; 196:165-8.
28. Dinger A, Blum RP, Niehus H, Muller RH and Gohla S: Solid lipid nanoparticles a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal product. *J Microencapsul* 1999; 16:751-67.
29. Mei Z, Chen H, Weng T, Yang Y and Yang X: Solid lipid nanoparticle and microemulsion for topical delivery of triptolidine. *Eur J Pharm Biopharm* 2003; 56:189-96.
30. Wissing SA and Muller RH: The influence of solid lipid nanoparticles on skin hydration and viscoelasticity-*in vivo* study. *Eur J Pharm Biopharm* 2003; 56:67-72.
31. Mezei M and Gulasekharan V: Liposomes a selective drug delivery system for topical route of administration. *Life Sci* 1980; 26:1473-7.
32. Toutiou E, Junginger HE, Weiner ND, Nagai T and Mezei M: Liposomes as carriers for topical and transdermal delivery. *J Pharm Sci* 1994; 83:1189-203.
33. Egbaria K, Ramachandran C, Kittayanond D and Weiner N: Topical delivery of liposomal IFN. *Antimicrob Agent Chemother* 1990; 34:107-10.
34. Birchall JC, Marichal C, Campbell L, Alwan A, Hadgraft J and Gumbleton M: Gene expression in an intact ex-vivo skin tissue model following percutaneous delivery of cationic liposomes-plasmid DNA complex. *Int J pharm* 2000; 197:233-8.
35. Babiuk S, Baca-Estrada M, Babiuk LA, Ewen C and Foldvari M: Cutaneous vaccination; the skin as an immunologically active tissue and the challenge of antigen delivery. *J Control Rel* 2000; 66:199-214.
36. Babika S, Baca-Estrada ME, Foldvari M, Baizer L, Stout R and Storms M: Needle-free topical electroporation improves gene expression from plasmids administered in porcine skin. *Mol Ther* 2003; 8:992-8.
37. Theres MA: Drugs published by Adis international Ltd.1998; 56:747-756.
38. Gompper, D and Kroll M: Driven Pores" (abstract page) physical review E 52(4) 4198-4208.doi:10, 1103, Phys Rev E.52.4198.
39. Bina G and Touitou E: Ethosomes: new prospects in transdermal delivery. *Crit Rev Ther Drug Carrier Syst* 2003; 20:63-102.
40. Touitou E, Godin B, Dayan N, Weiss C, Pilliponsky A and Levi-Schaffer F: Intracellular delivery mediated by an ethosomal carrier. *Biomaterials* 2001; 22:3053-9.
41. Dayan N and Touitou E: Carriers for skin delivery of trihexyphenidyl.HCL: ethosomes vs liposomes. *Biometrics* 2000; 21:1879-85.
42. An overview on Nano carriers tech. *Aquosomes Vol. 2, 7:209.*
43. Dunbar D and Sharma K: US20006162456A (2000).
44. Chiang CM and Tenzel RA: US20006149935A (2000).
45. Mitragotri S, Blankschtein D and Langer R: Transdermal delivery using low frequency sonophoresis. *Pharm Res* 1996; 13:411-20.
46. Mitragotri S: Low frequency sonophoresis. *Adv Drug Deliv Rev* 2004; 56:589-601.
47. Mitragotri S, Blankschtein D and Langer R: Ultrasound mediated transdermal protein delivery. *Science* 1995; 269:850-3.
48. Blank IH, Scheuplein RJ and Macfarlane DJ: Mechanism of percutaneous absorption: III. The effect of temperature on the transport of non-electrolytes across the skin. *J Invest Dermatol* 1967; 49:582-9.
49. Clarys P, Alewaeters K, Jadoul A, Barel A, Mandas OR and Preat V. *In vitro* percutaneous penetration through hairless rat skin: influence of temperature, vehicle and penetration enhancers. *Eur J Pharm Biopharm* 1998; 46:279-83.

50. Akomeah F, Nazir T, Martin GP and Brown MB: Effect of heat on the percutaneous absorption and skin retention of 3 model penetrants. *Eur J Pharm Sci* 2004; 21:337-45.
51. Ogiso T, Hirota T, Masahiro I, Hino T and Tadatoshi T: Effect of temperature on percutaneous absorption of terodiline and relationship between penetration and fluidity of stratum corneum lipids. *Int J Pharm* 1998; 176:63-72.
52. Klemsdal TO, Gjesdal K and Bredesen JE: Heating and cooling of the nitroglycerin patch application area modify the plasma level of nitroglycerin. *Eur J Clin Pharmacol* 1992; 43:625-8.
53. Henley, JL: US5658247A (1997).
54. Gerstel MS and Place VA: Drug Delivery Device. US964482 (1976).
55. Trautman J, Cormier MJ, Kim HL and Zuck MG: Device for enhancing a transdermal agent flux. US Pat 2000; 83:196.
56. Trautman J, Wong PS, Daddona PE, Kim HL and Zuck MG: Device for enhancing transdermal agent flux. US Pat 2001:322808.
57. Yuzhakov VV, Sherman FF, Owens GD and Gartstein V: Apparatus and method for using an intracutaneous microneedle array. US Pat 2001:256533.
58. Muddle AG, Longridge DJ, Sweeney PA, Burkoth TL and Bellhouse BJ: Transdermal delivery of testosterone to conscious rabbits using powderject: a supersonic powder delivery system. *Proc Int Symp Control Release Bioact* 1997; 24:713.
59. Longbridge DJ, Sweeney PA, Burkoth TL and Bellhouse BJ: Effects of particle size and cylinder pressure on dermal powderject delivery of testosterone to conscious rabbits. *Proc Int Symp Control Rel Bioact* 1998; 25:964.
60. Burkoth TL, Bellhouse BJ, Hewson G, Longridge DJ, Muddle AJ and Sarphe DJ: Transdermal and transmucosal powdered delivery. *Crit Rev Ther Drug Carrier Syst* 1999; 16:331-84.
61. Hoogstrate AJ, Verhoef J, Brusee, Ijzerman AP, Spies F and Bodde HE: Kinetic, ultrastructural aspects and molecular modeling of transdermal peptide flux enhancement by N-alkylazocyclohepton. *Int J Pharm* 1991; 76:37-47.
62. Park ES, Chang SJ, Rhee YS and Chis C: Effect of adhesive and permeation enhancer on the skin permeation of captopril. *Drug Deve Ind Pharma* 2001; 27:975-80.
63. Aungst BJ, Rogers NJ, and Shefter E: Enhancement of naloxone penetration through human skin *in vitro* using fatty acid, fatty alcohol, surfactant, sulfoxide and amide. *Int J Pharm* 1986; 33: 244-7.
64. Aungst BJ: Structure effect studies of fatty acid isomers as skin penetration enhancers. *J Pharm Sci* 2008; 6:54-6.
65. Shin SC and Lee HJ: Controlled release of triprolidone using ethylene-vinyl acetate membrane systemic agents. *J Pharm Res* 2007; 6:44-50.
66. Tupker RA, Pinnagoda J and Nater JP: The transient and cumulative effect of sodium lauryl sulphate on the epidermal barrier assessed by transepidermal water loss: inter-individual variation. *Acta Derm Venereol* 1990; 70:1-5.
67. William AC and Barry BW: Essential oil as novel human skin penetration enhancer. *Int J Pharm* 1989; 57: R7-R9.
68. Cornwell PA and Barry BW: Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. *J Pharm Pharmacol* 1994; 46: 261-269.
69. EL-Kuttan AF, Asbill CS and Michniak BB: The effect of terpenes enhancer lipophilicity on the percutaneous permeation of hydrocortisone formulated in HPMC gel system. *Int J Pharm* 2000; 198:179-189.
70. Vollmer U, Muller BW, Mesens J, Wilffert B and Peters T: *In vivo* skin pharmacokinetics of liorzole: Percutaneous absorption studies with different formulations of cyclodextrin derivatives in rats. *Int J Pharm* 1993; 99:51-58.
71. Rajadhyaksha V and Pfister WR: Oxazolidinones. *Drug Cosmet Ind* 1996; 1: 36-47.
72. <http://www.freepatentsonline.com/US7415306.html?query=P N/US7415306%20OR%...>
73. <http://www.freepatentsonline.com/US7413748.html?query=P N/US7413748%20OR%...>
74. <http://www.freepatentsonline.com/US7387789.html?query=P N/US7387789%20OR%...>
75. <http://www.freepatentsonline.com/US7395111.html?query=P N/US7395111%20OR%...>
76. Ermer JC, Adeyi BA and Pucci ML: Pharmacokinetic variability of long-acting stimulants in the treatment of children and adults with attention-deficit hyperactivity disorder. *CNS Drugs, Clinical Pharmacology and Pharmacokinetics*, Shire Development Inc., Wayne, Pennsylvania, USA. 2010, Vol. 24(12), pp. 1009-1025.
77. Grünblatt E, Schmidt WJ, Scheller DKA, Riederer P and Gerlach M: Transcriptional alterations under continuous or pulsatile dopaminergic treatment in dyskinetic rats. *J Neural Transm*, 2010 (print)
78. Ammar HO, Ghorab M, El-Nahas SA and Higazy IM: Proniosomes as a carrier system for transdermal delivery of tenoxicam. *Int J Pharm*, 2010 (print)
79. McCormack PL: Capsaicin dermal patch: in non-diabetic peripheral neuropathic pain. *Drugs*, Adis, Auckland, New Zealand. 2010, Vol. 70(14), pp. 1831-1842.
80. Borojerdi B, Wolff HM, Braun M and Scheller DKA: Rotigotine transdermal patch for the treatment of Parkinson's disease and restless legs syndrome. *Drugs Today (Barc)*, Schwarz Biosciences GmbH, UCB Pharma Group, Monheim, Germany. 2010, Vol. 46(7), pp. 483-505.
81. Tirunagari M, Jangala VR, Khagga M and Gannu R: Transdermal therapeutic system of isradipine: Effect of hydrophilic and hydrophobic matrix on in-vitro and ex-vivo characteristics. 2010, Vol. 33(7), pp. 1025-1033.

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