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AN OVERVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM (TRANSDERMAL PATCHES)

Karthikeyan R.[1*], Kalaiselvi C.[2], Karthick D.[3], Anushya N.[3], Elavarasan E.[3] and Arunkumar D.[3]

[1,3]Students, SS Institute of Pharmacy, Sankari, Salem, Tamilnadu-637301.
[2]Department of Pharmaceutics, SS Institute of Pharmacy, Sankari, Salem, Tamilnadu-637301.

***Corresponding Author: Karthikeyan R.**
Students, SS Institute of Pharmacy, Sankari, Salem, Tamilnadu-637301.

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ABSTRACT
Transdermal drug delivery system is the type of drug delivery system in which are represented to overcome the difficulties of other routes especially oral route. Transdermal patches are medicated adhesive patches that is placed over the skin to deliver a specific dose of medication through the skin and into the bloodstream. Drug delivery through the skin to achieve a systemic effect without producing any fluctuation in plasma concentration of the drug. An advantage of therapeutic agent offers many advantages over conventional oral and invensive method of drug delivery and provides controlled release of the drug delivery system [TDDS]. This review article cover brief outline, skin pathway for transdermal, merits, demerits and its limitation, evaluation of transdermal system and recent advancements.

KEYWORDS: Transdermal, Drug delivery system, Other routes, Topical.

INTRODUCTION
Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.[1,2]

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a three-day period.[3]

ANATOMY AND PHYSIOLOGY OF SKIN
The skin can be considered to have four distinct layers of tissues including non-viable epidermis, viable epidermis, viable dermis, and hypodermis. The epidermis is the relatively thin, tough, outer layer of the skin. The epidermis has 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. The stratum corneum is the outermost portion of the epidermis, 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 is much thicker. The viable epidermis layer of the skin has a thickness ranging from 50-100 µm. The structure of the cells in the viable epidermis is physiochemically similar to other living tissues. Cells are held together by ton fibrils. The water content is about 90%. The dermis, the skin's next layer, is a thick layer of fibrous and elastic tissue that gives the skin its flexibility and strength. The dermis contains nerve endings, sweat glands, oil glands, hair follicles, and blood vessels. It is composed of loose textured, white, fibrous connective tissue containing blood and lymph Vessels.[4]

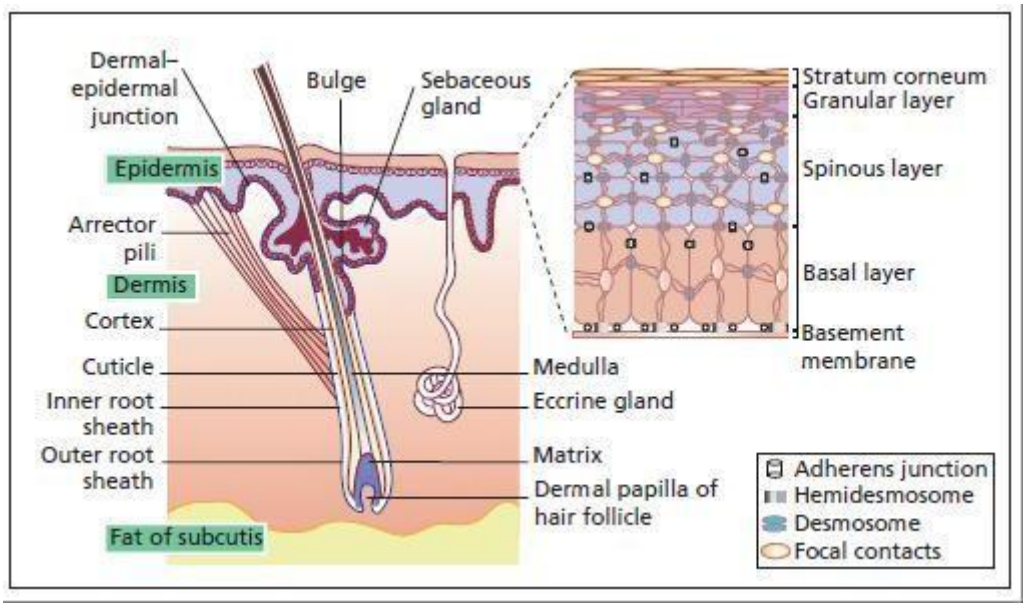

Figure 1: structure of skin.

Pathways of Skin Permeation

Drug molecules permeate through the skin surface by the different potential pathways including through the sweat ducts, through the hair follicles and sebaceous glands, or directly across the stratum corneum Since the last few years there is a point of debate among scientists for the relative importance of the shunt or appendageal route of transport across the stratum corneum and is further complicated by the lack of a suitable experimental model to permit separation of these pathways. A recent review by Menon provides a valuable resource. The stratum corneum consists of 10 to15 layers of corneocytes.[5]

TRANSDERMAL PATCH

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979 containing scopolamine for motion sickness The highest selling transdermal patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobacco smoking. The first commercially available vapor patch to reduce smoking.

In addition, various other patches are available in the market including fentanyl, an analgesic for severe pain, nitro-glycerine patches for angina, lidocaine patches, marketed as Lidoderm, relieve the peripheral pain of shingles Buprenorphine, marketed as Bu Trans, as analgesia for moderate to severe chronic pain. It is also now commonly used off-label, for pain from acute injuries and chronic pain. Flector (Diclofenac Epolamine) patch is an NSAID topical patch for the treatment of acute pain due to minor strains, sprains, and contusions. It is also being used in the treatment of pain and inflammation for chronic conditions.

NSAIDs including fibromyalgia and arthritis. Hyperactivity Disorder (ADHD), the FDA announced that they are investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control.[6]

MERITS OF TRANSDERMAL PATCHES

- Improved bioavailability and longer duration of action resulting in a reduction in dosing frequency · Steady permeation of drug across the skin, allowing consistent serum drug level; often a goal of therapy.
- Reduced side effects and in addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch.
- Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug degradation effects.
- Topical patches are a painless, noninvasive way to deliver substances directly into body.
- This is an effective route to deliver drugs that are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver.
- Transdermal patches are alternative to oral route for people who cannot, or prefer not to take medications or supplements orally. It is of great advantage in patients who are nauseated or unconscious.
- Topical patches are cost-effective, convenient; especially notable parameter in some patches is that it requires only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

DEMERITS AND LIMITATIONS OF TRANSDERMAL PATCHES

- Many drugs especially those with hydrophilic structures permeating the skin too slowly, may not achieve therapeutic level.
- The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.
- The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.[7]
- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma.
- TDDS cannot be developed for drugs of large molecular size.
- TDDS cannot deliver drugs in a pulsatile fashion.
- TDDS cannot be developed if drug or formulation causes irritation to skin.

TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM

- **Single-layer Drug-in-Adhesive System**

In this type of patch the adhesive layer of this system contains the drug. The adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but it is also responsible for the releasing the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Figure 2: Single-layer Drug-in-adhesive.

- **Reservoir-Drug in-adhesive**

In this System the drug reservoir is kept in between backing layer and a rate controlling membrane. And drug releases through microporous rate controlled or gel or dispersed in a solid polymer matrix in the reservoir compartment.

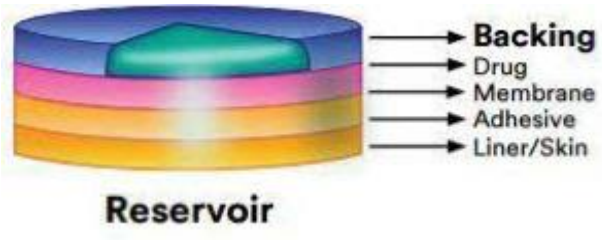

Figure 3: Reservoir System.

- **Matrix System**

This system is of Two type

a) Drug-in-Adhesive System: For the formation of drug reservoir, the drug dispersed in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) on to an impervious backing layer.

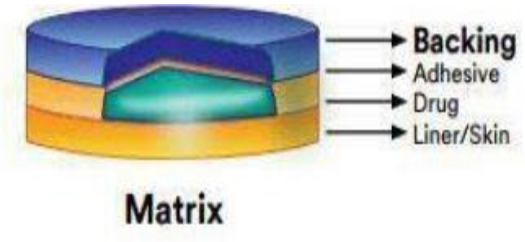

Figure 4: Matrix drug-in-adhesive.

b) Matrix-Dispersion System: In this system the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. And this containing polymer along with drug is fixed onto an occlusive base plate in a compartment fabricated from a drug- impermeable backing layer. In this system the adhesive is spread along the circumference instead of applying on the face of drug reservoir to form a strip of adhesive rim.[8]

- **Micro-Reservoir System**

This system is a combination of reservoir and matrix-dispersion systems. In which drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.[9]

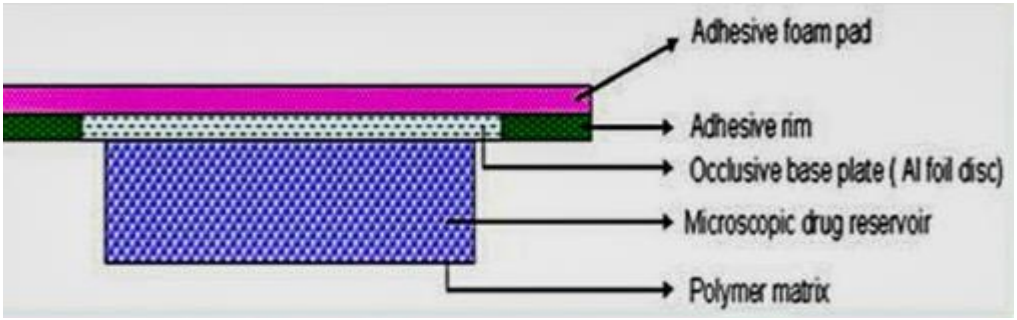

Figure 5: Micro-Reservoir System.

COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

Drug is in direct contact with release liner. The selection of drug for TDDS is based on physicochemical properties of drug. Transdermal drug delivery system is much suitable for drug having.

Physicochemical properties[10,11]

- 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.
- Hydrogen bonding groups should be less than 2.
- Low molecular weight (less than 500 Daltons).

Biological properties

- Drug should be very potent, i.e., It should be effective in few mg per day (ideally less than 25 mg/day).
- 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
- Narrow therapeutic window.

POLYMER MATRIX / DRUG RESERVOIR

The polymers used for TDDS can be classified as.

Natural polymers: e.g. cellulose derivatives, zein, gelatine, starch and chitosan, etc.

Synthetic elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, butylrubber etc.

Synthetic polymers

- e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, epoxy, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, hydroxypropylcellulose etc.[12,13] List of polymer given in table 1.

Table 1: List of Polymers used in Transdermal Drug Delivery System.[14]

Polymer	**Type of System**
EthylCellulose T-50	Matrix
BIO PSA	Adhesive in Matrix
Scotch Pak	Backing/Release Liner
Eudragit	Matrix
MDX -4-421 (a silicone)	Matrix
Acrylic PSA emulsion	Drug-in-adhesive
Acrylic adhesives	Drug-in-adhesive
Polyisobutylene solutions(Vistanex LM-MH, Vistanex MML-100)	Drug-in-adhesive
Silicone PSA	Drug-in-adhesive
Silcone Oil	Reservoir
EVA	Membrane
Polyisobutylene	Adhesive
ScotchPak 1006	Backing Film
2-Ethylhexyl acrylate	Drug-in-adhesive
Acrylic acid copolymer	Matrix
PIB	Matrix
MDX4-4210 silicone elastomer	Matrix
Acrylate copolymer (Gelva-737)	Matrix
Silicone-2920 and 2675	Matrix
2-Ethylhexyl acrylate and acrylic acid copolymer	Drug-in-adhesive

PERMEATION ENHANCERS

The penetration enhancer should be pharmacologically inert, non toxic, non allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogeneous materials.[11,15] List of penetration enhancers given in table 2.

PRESSURE SENSITIVE ADHESIVE (PSA)

The pressure-sensitive adhesive (PSA) affixes the Transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy and exert a strong holding force.[11,16]

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally.

The three major classes of polymers evaluated for potential medical applications in TDDS include.
Polyisobutylene type pressure sensitive adhesives.
Acrylic type pressure sensitive adhesives.

Silicone type pressure sensitive adhesives.[10,11,16,17]

BACKING LAMINATES

Backing materials must be flexible while possessing good tensile strength.[18] While designing a backing layer, the consideration of chemical resistance of the material is most important.[14] List of baking membranes given in table 3. Examples of some backing materials are vinyl, polyethylene and polyester films.[14,19]

RELEASE LINER

Protects the patch during storage. The liner should be removed before its use.[21] The release liner has to be removed before the application of transdermal system, and it prevents the loss of the drug that has migrated into the adhesive layer during storage. It also helps to prevent contamination. It is composed of a base layer, which may be non-occlusive (e.g. paper fabric) or occlusive(e.g. polyethylene, polyvinylchloride), and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metallized laminate.[8]

Table 2: Types of chemical classes that act as penetration enhancers.

CLASSES	EXAMPLE
Alcohols	Alkanol: ethanol, propanol, butanol, pentanol, hexanol, octanol, Fatty alcohol: caprylic, decyl, lauryl, stearyl
Alkanones	N-heptane, N-octane, N-nonane, N-decane, Nundecane
Amides	Cyclic amide: 1-dodecylazacycloheptane-2-one (Azone) Pyrrolidone derivate: 1-methyl-2- pyrrolidone Urea, dimethylacetamide, diethyltoluamide, dimethylformamide
Fatty acids	Linear: heptanoic, lauric, myristic, oleic, stearic, valeric Branched: isovaleric, isostearic, neoheptanoic, neopentanoic
Fatty acid Esters	Alkyl: butyl acetate, ethyl acetate, ethyl oleate, methylvalerate Aliphatic-isopropyl n-butyrate, isopropyl n-decanoate
Organic acids	Citric and succinic acid, salicylic acid and salicylates
Polyols	Butanediol, glycerol, hexanetriol, propylene glycol
Sulfoxides Surfactants	Decylmethylsulfoxide, dimethylsulfoxide Anionic: sodium laurate, sodium lauryl sulfate Cationic: benzalkonium chloride, cetyltrimethyl ammonium bromide, tetradecyltrimethylammonium bromide Nonionic: polyoxyethylene alkyl ethers, poloxamers, polysorbates. Bile salts: sodium cholate, glycholic
Terpenes	Alcohols: a-terpineol, carvol, terpinene-4-ol Hydrocarbons: a-pinene, b-carene, D-limonene Ketones: carvone, menthone, piperidone, pulegone Oils: anise, Chenopodium, eucalyptus, ylang ylang Oxides: 1,8-cineole, cyclohexene oxide, limonene oxide

The material properties to be considered for a release liner are as follows:

- The material must be chemically inert.
- The material should be such that it should not permeate the drug.
- Affinity towards water should be null.

Material should not crack, craze, or react in any way with the mechanism that are used for penetration in active transdermal drug delivery systems.[14]

Table 3: Characteristic of some commercialized baking membranes.[14]

Product	Polymer	Oxygen Transmission (cm3/m2/24 h)	MVTR (g/m2/24h)	Enhancer Resistance
CoTran9701	Polyurethane Film	-	700	Low
CoTran9702	EVA	-	52.8	Medium
CoTran9706	-	-	26.4	Medium
CoTran9720	PE	2950	9.4	Medium
9722	-	3570	7.9	High
Foam Tape 9772L	PVC foam	-	450	-
Foam Tape9773	Polyolefin foam	-	-	-
Scotchpak1006	PE, Al vapor coat, PET EVA	4.6	0.3	High-pet side
Scotchpak1109	PE, Al vapor coat, PET	4.6	0.3	High
Scotchpak9723	PE, PET laminate	100	12	High
Scotchpak9732,9733	PET, EVA laminate	80	15.5	High-pet side
-	-	80	17	High-pet side

Other Excipients like Plasticizers and Solvents

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. Plasticizers have been known to reduce the stiffness of the polymer backbone, thereby increasing the diffusion characteristics of the drug.8 In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are to provide plasticity to the transdermal patch.[11,12,20]

EVALUATION OF TRANSDERMAL PATCHES

1. Moisture content studies
2. Moisture uptake studies
3. Flatness study
4. Scanning Electron Microscopy
5. Invitro Studies

a. Invitro dissolution studies

b. Invitro permeation studies

6. Invivo studies

Moisture Content

The moisture content was determined by keeping the drug matrix patches in a desiccator contains.

Table 4: Determination of Drug–Excipient Interaction Using the TLC Method.

Formulation Code	PVP/EC	Drug	Drug-excipients
PA1	5:1	0.794	0.828
PA2	2:1	0.793	0.793
PA3	1:1	0.798	0.782
PA4	1:2	0.709	0.756
PA5	1:5	0.803	0.797

activated silica for 24 h. The percentage moisture content was calculated from the weight differences relative to the final weight (see Experimental Section). The results of the moisture content studies for different formulation. The moisture content in the formulations was found to increase with the increasing concentration of hydrophilic polymer, PVP. Moisture contents in the formulations were found to be low.

Moisture Uptake Studies

The percentage moisture uptake was calculated from the weight difference relative to the initial weight after exposing the prepared patches to 84% relative humidity (saturated potassium chloride solution). The results of moisture uptake studies for different formulations. The percentage moisture uptake was also found to increase with increasing concentration of hydrophilic polymer, PVP.

Flatness Study

An ideal patch should be formulated in such a way that it possesses a smooth surface and it should not constrict with time. Flatness studies were performed to assess the same. The results of the flatness study showed that none of the formulations had the differences in the strip lengths before and after their cuts. It indicates 100% flatness observed in the formulated patches. Thus, no amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the patches.

Scanning Electron Microscopy

The surface morphology of the transdermal patches before and after the in vitro drug release study was scanned using a scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan) (Figsure 6-9). shows the uniform distribution of drug in the polymer matrix. Figures 7 and 8 depict how the polymer–matrix (PA4) behaves after the release of drug molecules. Figure 6 indicates that the formulation maintains the elastic nature of the film after the release of drug molecule without affecting the other parts of the patch. Figure 9 shows one of the skin appendages (shown by an arrow), which are to be the main diffusion pathways of molecules.

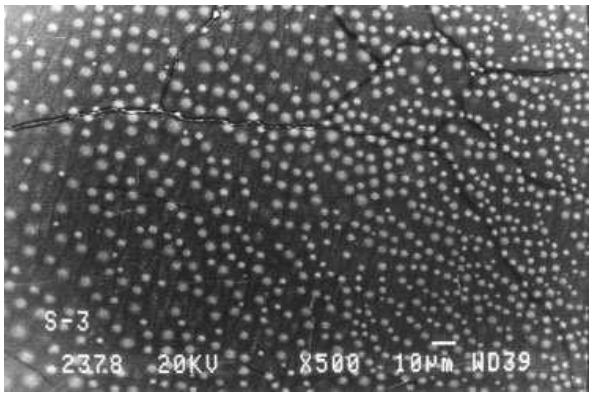

Figure 6: SEM photograph of the transdermal patch before application, shows a homogeneous dispersion of drug in the patch (original magnification ×500).

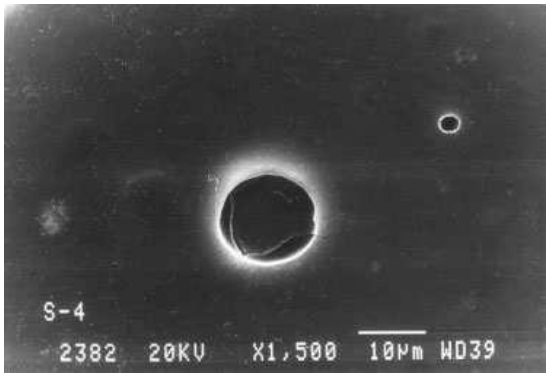

Figure 7: SEM photograph of the transdermal patch after the release of drug molecules from a zone (original magnification ×1500).

In Vitro Dissolution Studies

Dissolution studies are important for ensuring the sustained release performance and the reproducibility of rate and duration of drug release. Dissolution studies for different formulations were performed in a USP basket dissolution apparatus using phosphate buffer, pH 7.4, as dissolution media at 32℃.[22]

It was observed that as the concentration of hydrophilic polymer, PVP, increased in the formulations, the rate of dissolution increased subsequently. ‘‘Burst effect’’ was observed in formulations PA1 to PA3 (Figure 10). This may be because the hydrophilic layer might need a very little ‘‘time lag’’ to establish a concentration profile. Maximum percentage of drug released (88%) was found for the formulations PA1 (PVP/EC, 5:1) and minimum percentage of drug released (41%) was observed for the formulation PA5 (PVP/EC, 1:5).

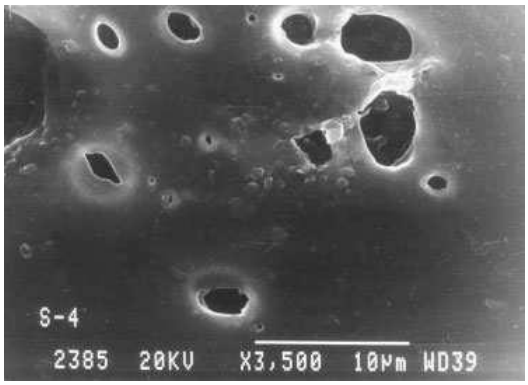

Figure 8: SEM photograph of the transdermal patch showing how the patch (PA4) behaves after the release of drug (original magnification ×3500).

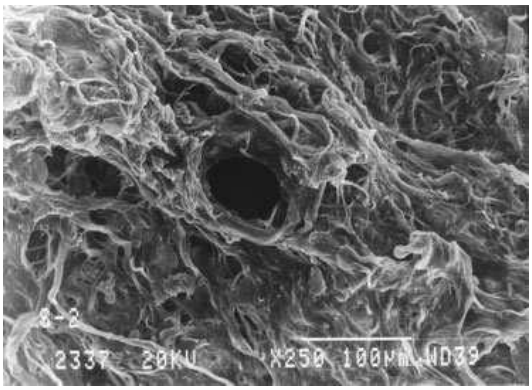

Figure 9: SEM photograph of a section of experimental skin showing one skin appendage (shown by an arrow) (original magnification × 250).

In Vitro Permeation Studies

In vitro permeation studies are predictive of in vivo performance of a drug.

Permeation studies were performed for different formulations across cadaver abdominal skin using phosphate buffer, pH 7.4, as an in vitro study fluid in the receptor compartment of a modified diffusion cell at 328C. Drug release profiles from the formulations PA4 and PA5 (Figs. 10 and 11) were more or less rectilinear and were indicative of the steady and slow release of drug in in vitro medium and formulation PA5 showed the slowest release-rate constant of all the formulations studied. It is interesting that despite the ‘‘burst effect’’ of formulations PA1, PA2, and PA3, their drug-release profiles behaved differentially during in vitro drug skin permeation study (Figs. 10 and 11). Skin permeation of drug as well as much slower exposure of PVP to phosphate buffer, pH 7.4, may be considered the reason for the same.

In Vivo Study

Variable effects of controlling paw edema induced by carrageenan were observed in the formulations PA4 and PA5. The formulation PA4 was found to provide maximum protective effect as compared with PA5 and Voveran1 gel application in the rat paw edema model.

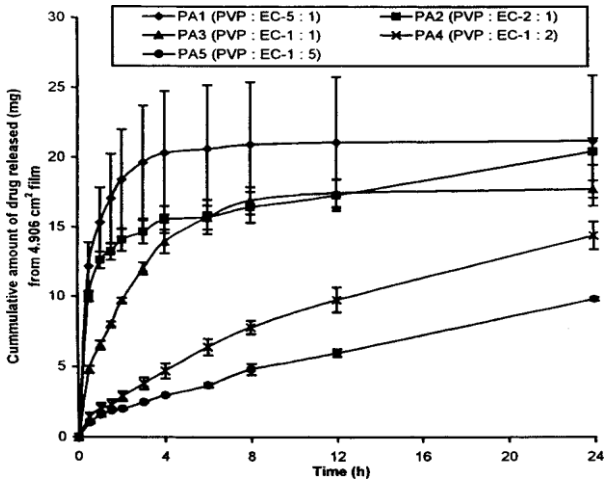

Figure 10: *In vitro* drug dissolution profile of diclofenac diethylamine from different PVP/EC drug matrix patches, using USP basket dissolution apparatus in phosphate buffer pH 7.4. Data are mean SE (*n* ¼ 6).

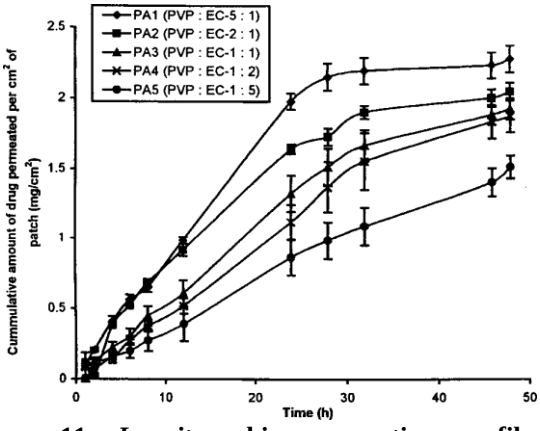

Figure 11: *In vitro* skin permeation profile of diclofenac diethylamine from different PVP/EC Matrix patches through cadaver abdominal skin, in phosphate buffer, pH 7.4. Data are mean ±SE (n=6)

CONCEPTS OF TRANSDERMAL PATCHES

Diclofenac diethylamine is a well-established nonsteroidal anti-inflammatory drug, which undergoes substantial hepatic first-pass metabolism, and thus only about 50% of the administered drug reaches the circulation.[23,24] Therefore, there is a need to search for an alternative route of administration, which may bypass the hepatic first pass metabolism. The transdermal patch delivery system may be an attractive choice of an alternative route of administration of this drug because the drug also possesses characteristics such as sparing solubility in water, short biological half-life (2–3 h), and a smaller dose range (25–50 mg).[25-28] Moreover, the logarithmic value of the partition coefficient of the drug in octanol-phosphate buffer, pH 7.4 (in vitro study fluid used by us) system, in our study showed that the value is well within the range of 0.8–3.0 required for a transdermal patch delivery system.[29] Drug–excipient interactions were studied using a silica gel G–coated TLC plate with water hydrochloric acid–glacial acetic acid-ethyl acetate system as mobile phase.[30] No distinct difference in the Rf values of both the drug and drug excipient solution used in our study indicates that the excipients do not alter the performance characteristics of the drug from the patches studied. It is already known that the common polymers such as PVP and EC are popular in controlled/sustained release matrix type patches because of their compatibility with a number of drugs.[31] In this study, various transdermal matrix type patches containing diclofenac diethyl amine of variable combinations of PVP/EC were prepared. It was desired to design a polymer matrix that allows one to control the release of diclofenac diethyl amine via the most appropriate choice of polymeric blend of EC and PVP among the formulations studied, using the different diffusion pathways of the individual polymeric composition to produce the desired overall prolonged/sustained drug release. The physicochemical performances and the release characteristics were different in the patches studied. The moisture content and moisture uptake of the various formulations showed that with the increase in concentration of hydrophilic polymer, PVP, both the percentage moisture content and moisture uptake increased. The small moisture content in the formulations helps them to remain stable and from being a completely dried and brittle film. Again, a low moisture uptake protects the material from microbial contamination and bulkiness of the patches. No amount of constriction in the formulated transdermal patches ensured their 100% flatness. Thus, these formulations can maintain a smooth and uniform surface when they are administered onto skin. Figures 7 and 8 show the electron microscopic representations of the patches after releasing the drug molecules from them. Figure 7 also shows that after the release of drug molecules, the distorted portion of the membrane had a tendency of maintaining elasticity in an affected small area with little effect on the other part of the membrane. Thus, this showed that very little or almost no constriction, that is, 100% flatness of the patches persists even after the patches were deprived of the drug molecules. Therefore, it may be suggested that the formulation of various blends of polymers used here are suitable for transdermal formulations in terms of their physical stability. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance and the reproducibility of rate and duration of drug release.[29] Initial ‘‘burst release’’ was observed in patches with PVP/EC ratios 5:1 and 2:1. This may be because of the much higher percentages of PVP in those two formulations. This hydrophilic PVP layer might need very little ‘‘time lag’’ to establish a concentration profile in the patches resulting in a ‘‘burst effect’’ in dissolution studies. The PVP/EC (1:1) patches showed the moderate ‘‘burst effect’’ pattern, whereas, the patches with PVP/EC 1:2 and 1:5 showed comparatively controlled and sustained release. It was observed that the PVP/EC 1:5 patch released only 41% of the drug incorporated in 24 h. Homogeneous uniform distribution of the transdermal patches is one of the important characteristics that also ensures the uniform reproducible sustained release of the drug molecules from the patch.[32] Electron microscopic photograph (Fig. 4) shows that diclofenac diethylamine was homogeneously dispersed in the transdermal patch formulated in our experiment. The phenomenon in this study is not a molecular dispersion; rather, drug molecules are dispersed in small (~2-mm size) aggregates. Intermolecular forces between drug molecules are stronger (ionic) as compared with those between drug and polymers (i.e., ionic drug and slightly polar polymers). Polymers known to interact physically with drug molecules through electrostatic forces[33,34] might form soluble polyion drug complex associate[35] with an individual diameter of ca. 2 mm. Polymer molecules surrounding cores of polyion complexes prevented the complexes from precipitation while they were in solution. Again, the presence of uniformly distributed about 2-mm drug aggregates indicate simultaneous precipitation of drug complexes along with polymers during solvent evaporation. In vitro release profile is an important tool that predicts in advance how the drug will behave in vivo.[36] Thus, we can eliminate the risk of hazards of drugs because of direct experimentation in the living system. In vitro skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs.[37] In our experiments, variable release profiles of diclofenac diethylamine from the different experimental patches composed of various blends of polymers, PVP and EC, were observed. Cumulative amounts of drug permeated per square centimeter of patches, through the skin into the in vitro fluid when plotted against time, showed almost a rectilinear graphic of the data obtained from the formulation PA5. It may depict the zero-order drug-release kinetic of the formulation. In the case of other formulations, PA1 to PA4, the release profiles of the drug seem to follow apparent zero-order/pseudo first-order kinetics. Initially up to 24 h, the drug released in

the in vitro study fluid followed zero-order kinetics because the dispersed drug matrix ensured constant concentration. Afterward, however, concentration-dependent release kinetic changed the system toward a first-order reaction. The process of drug release in most controlled release devices including transdermal patches is governed by diffusion[38] and the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. The alteration of the crosslinking and the modification of structural arrangements of polymers by using different blends of polymer were already reported.[39] So, different in vitro drug release profiles from the different blends of PVP and EC formulations could be attributable to the varied crosslinking networks of polymeric chains of the different blends of polymeric transdermal experimental formulations as tortuosity and diffusion pathway varied and they have thereby been reported to vary the release of drug and the duration of diffusion.[40] Moreover, the implication of skin permeation of drug on release-rate profiles of the experimental formulations should not be ignored, because the skin is known to have a substantial role in variation of release kinetic.[41] At an early stage as well as in a steady state of skin permeation, diffusion of drug through appendages (hair follicles, sebaceous and sweat ducts) (Fig. 7) are considered to be significant[42] and the variation of shunt pathways from one part of skin to the other may even be one of the causes of variation in the release-rate profiles of the experimental formulations. When the release-rate constants were compared among the formulations, almost similar values of rate constants were observed in formulations PA2 to PA4, and PA5 gave the slowest release. It is also clear that the increased amount of EC in the formulations decreased the release rate of diclofenac diethylamine. Based on physicochemical and in vitro release experiments, formulations PA5, PA4, PA3, andPA2 may be chosen for further in vivo studies. Again, when burst release as well as higher release rate were considered, formulations PA2 and PA3 may be avoided from the preparation of a physico-chemically stable and sustained-release patch type formulation. Thus, it can reasonably be suggested that the formulation PA4 (PVP/EC, 1:2) and PA5 (PVP/EC, 1:5) are best suited for further animal studies. Carrageenan-induced rat paw edema has been considered as a useful model for studying the anti-inflammatory effect of drug in rats.[43] As described by Winter et al. (1965), paw edema was induced in rats by injecting 1% w/w carrageenan solution (in double-distilled water) in our experiments to study the anti-inflammatory effect and sustaining action of diclofenac diethylamine from the two transdermal patches (PA4 and PA5 formulation) selected based on their physicochemical characteristics and in vitro release profiles. Carrageenan-induced mean percent paw edema was found to increase about 114% as compared with initial paw volume, 12 h after carrageenan injection in the carrageenan control group of animals. PA4 and PA5, respectively, half an hour before carrageenan injection. Formulation PA4 was very effective in terms of inhibiting carrageenan-induced edema as 100% inhibition, that is, no edema was observed even after 12 h of the carrageenan challenge. However, an application of formulation PA5 produced about 4% mean percentage edema within half an hour after the carrageenan injection and the value became 19.23% 12 h after the carrageenan insult. This may be because of the less percentage of drug release from PA5, which was not enough to control edema effectively for long hours. Approximately 83% inhibition was observed 12.5 h after the application of PA5 formulation. Application of Voveran1 gel half an hour before carrageenan insult showed about 3% mean percent edema value which increased eventually up to 38.28% after 12 h. As in the case of formulation PA4, there was no edema in animals after 12 h of carrageenan challenge, further study was initiated by applying the formulation 12 h before the carrageenan insult. Edema returned and mean percent edema value gradually increased with the duration. It indicates that formulation PA4 (PVP/EC, 1:2) controlled edema effectively for about up to 19 h after its application in the in vivo rat model. Thus, based on the above discussion, it is well justified to conclude that formulation PA4 has the best effective combination of polymers PVP and EC, among the formulations studied for further development of the transdermal matrix patch type delivery system of diclofenac diethylamine.

RECENT ADVANCEMENTS

S.NO	Recent advances	Description
1.	Formulation, development and evaluation of transdermal drug delivery system of Glimepiride	Prepared a novel matrix controlled transdermal system using glimepiride as a novel drug and chitosan as a polymer for the extended and controlled delivery of the drug for the treatment of diabetes mellitus. Optimization of the system was done using in vitro drug permeation studies through rat skin. Skin irritation tests and pharmacokinetic evaluations were carried out in healthy rats[44]
2.	Design and evaluation of pectin-based metrics for transdermal patches of meloxicam	Prepared transdermal patch using Meloxicam as a novel drug and pectin as a polymer. In-vitro release studies were carried out with modified Franz diffusion cell using pH 7.4 phosphate buffers as receptor medium and it showed controlled release of drug.[45]
3.	Design and Development of Transdermal Drug Delivery for Anti-Hypertensive Drug Using Different Polymeric System	Developed matrix type transdermal drug delivery using different polymeric system for treatment of hypertension. Atenolol is used as a model drug. Di butyl phthalate is used as a plasticizer which prolongs the therapeutic effect. The different polymers used are: Cellulose Acetate Butyrate (CAB), Cellulose

		Acetate Phthalate (CAP), Poly Methyl Methacrylate (PMM) and their combinations[46]
4.	Development and characterization of transdermal patches of metoprolol tartrate	Prepared matrix types transdermal patch by solvent casting technique using metoprolol as a model drug. Employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The permeability of Metoprolol tartrate was increased with increase in PVP content. it can be reasonably concluded that Eudragit RL100-PVP polymers are better suited than EC-PVP polymers for the development of transdermal patches of Metoprolol tartrate[47]
5.	Design and evaluation of Valsartan transdermal patch	Prepared the transdermal patch by solvent casting technique using Valsartan as a model drug. The membrane of ethyl cellulose and Eudragit RS 100 and Eudragit RL 100 along with HPMC combination was used to achieve controlled release of the drug[48]
6.	Formulation and evaluation of transdermal patches of Atenolol	Prepared a matrix type trans dermal patch using Atenolol as a model drug with different ratios of HPMC and EC. The technique used is solvent casting technique. Propylene glycol was used as plasticizer. Formulated transdermal patches were evaluated with regard to physicochemical characteristics, in-vitro permeation studies and stability studies[49]
7.	Design and development of a proniosomal transdermal drug delivery system for captopril	Developed a proniosomal carrier system for captopril for the treatment of hypertension using Captopril as a model drug. Proniosomes were characterized by transmission electron microscopy. In vitro studies showed prolonged release of entrapped captopril[50]
8.	Formulation and evaluation of matrix type transdermal patch of Glibenclamide	Prepared matrix type transdermal patches using solvent evaporation technique Glibenclamide is used as a model drug. Three different polymers were used for the formulation. PEG 400 and DMSO were used as a plasticizer and penetration enhancers respectively.[51]
9.	Lercanidipine Hydrochloride matrix type transdermal drug delivery systems: In Vitro characterization.	Developed matrix type transdermal therapeutic system containing Lercanidipine hydrochloride. The formulation using Eudragit RL and Ethyl Cellulose with Oleic acid as permeation enhancer and PEG 4000 as plasticizer showed the maximum release[52]
10.	Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate	Prepared transdermal drug delivery system using Clopidogrel bisulfate as a drug. Various polymers were used such as HPMC, PVP and Ethyl Cellulose. The technique used is solvent casting technique. The prepared formulations were evaluated for different physicochemical characteristics like thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss and weight uniformity[53]

MARKETED PREPARATION

Brand Name	Manufacturer Name	API
SonoDerm	Imarx	Insulin
Sono prep	Sontra Medical corporation	Peptides
Chadd	ZarsInc	S-caine
Powderject	Powderject Pharmaceuticals	Insulin
Macroflux	Alza Corporation	Vaccines & Therapeutic proteins
Intraject	Weston medical	Vaccines
E-Trans	Alza Corporation	Fentanyl
Testoderm	Alza corporation	Testosterone
Nicoderm	GlaxoSmithKline	Nicotine
Transderm nitro	Novartis	Nitroglycerin
Estraderm	Novartis	Estradiol
Oxytrol	Watson Pharma	Oxybutynin
SonaPrep	Echo Therapeutics	Lidocaine
Habitraol	Novartis	Nicotine
Climaderm	Ethical Holdings/Wyeth-Ayerest	Estradiol

CONCLUSION

Transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS,

many new researches are going on in the present day to incorporate newer drugs via the system. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems as a ready reference for the research scientists who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS is a realistic practical application as the next generation of drug delivery system.

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