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RECENT APPROCH IN TRANSDERMAL DRUG DELIVERY SYSTEM: AN OVERVIEW

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Abstract: Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs through the skin. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. This review article covers a brief outline of the trasdermal drug delivery system, advantages over conventional drug delivery system, Layers of the skin, various components of transdermal patch, penetration enhancers, and evaluation of transdermal system and applications of Transdermal patch.

Keywords: Permeation enhancer, Structure of skin, Trandermal patches, Patents.



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INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively [1]. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy. [2] The common ingredients which are used for the preparation of TDDS are as follows [3].

Drug:

Drug is in direct contact with release liner.Ex: Nicotine, Methotrexate and Estrogen.

Linners: Protects the patch during storage. Ex: polyester film.

Adhesive:

Serves to adhere the patch to the skin for systemic delivery of drug. Ex: Acrylates, Polyisobutylene, Silicones.

PERMEATION ENHANCERS:

Controls the Release of the drug.

Ex: Terpenes, Terpenoids, Pyrrolidones. Solvents like alcohol, Ethanol, Methanol. Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

Backing layer:

Protect patch from outer environment. Ex: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber

Advantages of Transdermal drug delivery system [4,5, 6]

1. Avoidance of first pass metabolism of drugs.
2. Transdermal medication delivers a steady infusion of a drug over a prolonged period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
3. The simplified medication regimen leads to improved patient compliance and reduced the side effects, inter and intra-patient variability.
4. No interference with gastric and intestinal fluids.
5. Maintains stable or constant and controlled blood levels for longer period of time.
6. Comparable characteristics with intravenous infusion.
7. It increases the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
8. This route is suitable for the administration of drugs having very short half life, narrow therapeutic window and poor oral availability.
9. Improved patient compliance and comfort via non-invasive, painless and simple application.

Disadvantages [7, 8, 9]

1. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
2. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

3. Only small, lipophilic drugs can be delivered currently through the skin.
4. Drug molecule must be potent because patch size limits amount that can be delivered.
5. Not suitable for high drug doses.
6. Adhesion may vary with patch type and environmental conditions.
7. Skin irritation and hypersensitivity reactions may occur.
8. Drugs that require high blood levels cannot be administered.
9. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

Skin [10,11-14]

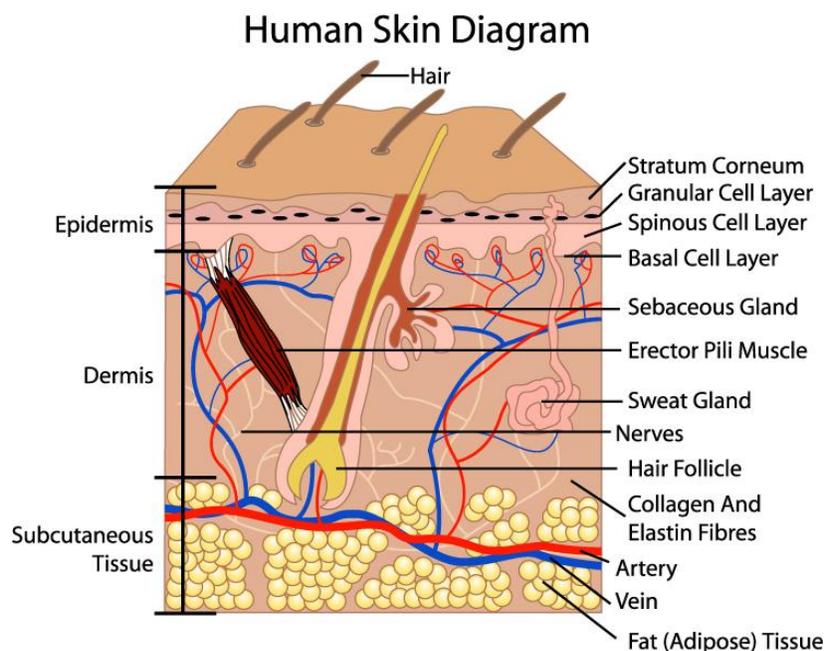


Figure-1 Human skin diagram

The skin of an average adult human covers a surface area of nearly 2m^2 and receives about one-third of the blood circulating through the body. Microscopically skin is composed of three main histological layers: epidermis, dermis and subcutaneous tissues. The epidermis is further divided into two parts- the nonviable epidermis (stratum corneum) and the viable epidermis. The viable epidermis is divided into four layers, viz., stratum lucidum, stratum granulosum, and stratum spinosum and stratum germinativum.

Stratum corneum and Epidermis:

The main barrier to percutaneous absorption:

The SC consists of multiple layers of horny dead cells, which are compacted, flattened, dehydrated and keratinized. The horny cells are stacked in highly interdigitated columns with 15-25 cells in the stack over most of the body. It has a density of 1.55g/cc. The SC has a water content of only 20% as compared to 70% present in physiologically active stratum germinativum. It exhibits regional differences over most of the body and is approximately 10-15µm in thickness. However, the thickness may be several hundred micrometers (300-400µm) on friction surfaces such as the palms of the hand and soles of the feet. Keratin present in the cells of the SC is a fibrous protein, which is poor in sulphur and forms a filamentous network to assure cohesion, flexibility and recovery. The unique properties of stability, insolubility and resistance observed in the SC are due to the thick cell membrane and cell matrix, which consists of amorphous proteins rich in sulphur content and lipids with many disulphide linkages. The SC is described as the only rate-limiting barrier of the skin with regard to the viable epidermis and dermis. The SC is a heterogeneous membrane consisting of alternating lipophilic and hydrophilic layers. The pH of the skin surface is between 3 and 4, which is about the isoelectric point of keratin in the SC layer. Below the SC remains the viable epidermis, which is more accommodative of permeant molecules. The viable epidermis is an aqueous solution of protein encapsulated into cellular compartments by thin cell membranes, which are fused together by tonofibrils. The viable epidermis has a density near that of water. The germinal (proliferative) layer above dermis undergoes cell divisions producing an outward displacement of the cell towards the surface. As the germinal layer moves upwards, it changes shape into a more rounded form with spiny projections and appears as a stratum spinosum. After the germinal layer has raised 12-15 layers above its point of origin, it becomes flattened and the basophilic nuclear material is dispersed throughout the cells as granules. The layer is referred to as stratum granulosum. The stratum lucidum layer, which lies just below the SC, is the site where nuclei disintegrate and keratinization and sulphahydril-rich matrix formation takes place. Eventually it moves upwards to form the SC. It should be pointed out that the epidermis contains no vascular elements. The cells receive their nourishment from the capillary beds located in the papillary layers of the dermis by diffusion of plasma and serum components.

Dermis:

The site of systemic absorption: The dermis is 0.2-0.3 cm thick and is made of a fibrous protein matrix, mainly collagen, elastin and reticulum embedded in an amorphous colloidal ground substance. It is divided into two distinct zones: a superficial finely structured thin papillary layer adjacent to the epidermis and a deeper coarse reticular layer (the main structural layer of skin).

The dermis is also the locus of the blood vessels, sensory nerves segments of the sweat glands and pilosebaceous units. The blood vessels supply blood to the hair.

Subcutaneous fatty tissue:

Cushioning the epidermis and dermis is the subcutaneous tissue or fat layer where fat is manufactured and stored. It acts as a heat insulator and a shock absorber. It essentially has no effect on the percutaneous absorption of drugs because it lies below the vascular system.

Transdermal Permeation:[15,16-19]

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and really accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows.

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary later.
5. Effect on target organ.

Care taken while applying Transdermal patch: [20,21]

1. The part of the skin where the patch is to applied should be properly cleaned.
2. Patch should not be cut because cutting the patch destroys the drug delivery system.
3. Before applying a new patch it should be sure that the old patch is removed from the site.
4. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.
5. The patch should be applied accurate to the site of administration.

TRANSDERMAL PATCHES:

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981 by FDA. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness,

clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation. Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once weekly application. Such a simple dosing regimen aids in patient adherence to drug therapy [22]

The main components to a transdermal patch are:

Polymer matrix– backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydri rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate.

- **Drug**- The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life. eg fentanyl, nitroglycerine etc.
- **Permeation enhancers**- increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug. These are of three types-lipophilic solvent, surface active agents and two component systems. E.g. DMSO
- **Adhesive**- increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug.

CHARACTERIZATION OF TRANSDERMAL PATCHES

(A) Physical evaluation

(i) Drug content uniformity [23]

It is determined by taking specific no. of patches and completely dissolving then in specific media. Resulting solution is filtered out through membrane filter. The samples so obtained is analyzed by HPLC or U.V. spectrophotometer.

(ii) Determination of surface pH

Specific number of patches are kept in contact with distilled water and excess water is drained and pH noted by pH meter.

(iii) Holding endurance [23]

It is calculated by cutting the patch in specific size by using sharp blade. Folding endurance was determined by repeatedly following a small strip of the patch at the same place till it broke. The no. of time the patch could be folded at the same place without breaking gave the value of folding endurance.

(iv) Thickness of patches

The thickness of transdermal patches is measured using micrometer screw gauge.

(iv) Weight of patches

Specific number of patches of each formulation are weighed individually in digital balance and calculated standard deviation.

(v) Moisture content [24]

The prepared patches are cut into strips of specific size. The strips are then weighed individually and kept in a dessicator containing activated silica at 300C for 12 hours. The films are reweighed individually until a constant weight is obtained.

Percentage (%) of moisture content = Loss in wt./ Initial wt. x 100

(vi) Water absorption studies

Transdermal films are into strips of specific size. A strip is weighed and kept in a dessicator at 400 C for 24 hours, removed and exposed to 75% RH (Containing saturated solution of sodium chloride) at room temperature weight is taken until a constant weight is obtained.

Water absorption capacity = Increase in weight / Initial weight x 100

(vii) Drug carrier Interaction [23]

Thin layer chromatography (TLC) or HPLC method is used for the drug carrier interaction studies.

(viii) Tack properties[25]

Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It depends on the molecular weight and composition of polymer. Test of tack includes.

(a) Thumb tack test [25]

This is a subjective test in which evaluation is done by pressing the thumb briefly into the adhesive.

(b) Rolling ball tack test [25]

This test involves measurement of the distance that a stainless steel ball travels along an upward – facing adhesive. The less tacky the adhesive the for they will travel.

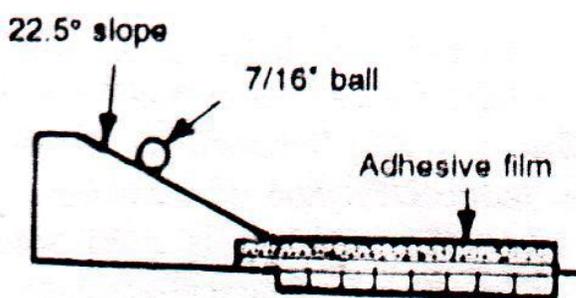


Figure Rolling ball tack test for adhesive evaluation

Ideal characteristics of chemical penetration enhancers

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells [26,27]. Some of the more desirable properties for penetration enhancers acting within the skin have been given as:

1. They should be non-toxic, non-irritating and non-allergenic
2. They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
3. They should have no pharmacological activity within the body.
4. The penetration enhancers should work unidirectionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
5. When removed from the skin, barrier properties should return both rapidly and fully to normal.

6. They should be cosmetically acceptable with an appropriate skin feel. Not surprisingly, no such material that possesses the above ideal properties has yet been discovered although some chemicals demonstrate several of the above attributes

Mechanism of chemical penetration enhancement

Penetration enhancers may act by one or more of three main mechanisms [28]:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer or solvent into the stratum corneum.

The enhancer act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and nonpolar pathway by altering the multilaminar pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product [29]. A useful way to consider factors affecting drug permeation rate through the stratum corneum is via the simple equation given below for steady state flux [28]. If we plot the cumulative mass of diffusant, m , passing per unit area through the membrane, at long time the graph approaches linearity and its slope yields the steady flux,

$$\frac{dm}{dt} = \frac{D C_0 K}{h} \text{----- (1)}$$

Where C_0 is the constant concentration of drug in donor solution, K is the partition coefficient of the solute between the membrane and the bathing solution, D is the diffusion coefficient and h is thickness of membrane. From the above equation, we deduce the ideal properties of a molecule that would penetrate stratum corneum well. These are:

1. Low molecular mass, preferably less than 600Da, when D tends to be high.
2. Adequate solubility in oil and water so that membrane concentration gradient may be high.
3. High but balanced (optimal) K (if too large, may inhibit clearance by viable tissue)
4. Low melting point, correlating with good solubility as predicted by ideal solubility theory.

Chemical penetration enhancers

Chemical substances temporarily diminishing the barrier of the skin and known as accelerants or sorption promoters can enhance drug flux. Several types are known

Sulphoxides and similar chemicals

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hygroscopic and is often used in many areas of pharmaceutical sciences as a "universal solvent". DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact urticaria, stinging and burning sensation [30]. Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as an accelerant. DMAC and DMF are similarly powerful aprotic solvents. However, Southwell and Barry, showing a 12-fold increase in the flux of caffeine permeating across a DMF-treated human skin, concluded that the enhancer caused irreversible membrane damage [31]. DMF irreversibly damages human skin membranes but has been found *in vivo* to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay [32,33].

DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels [34]. The mechanism of the sulphoxide penetration enhancers is widely used to denature protein and, on application to human skin, has been shown to change the intercellular keratin conformation, from α helical to β sheet [35,36].

Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of -7°C and it possesses a smooth, oily but yet non-greasy 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 enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1- 5% but more often between 1- 3%

13. 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 [37.]

Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-fluorouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2- pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch [38] . The pyrrolidones partition well into human stratum corneum within the issue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods [39].

Fatty acids

Percutaneous drug absorption has been increased by a wide variety of long-chain 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 have been drawn from the extensive studies of Aungst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone [40,41]. Shin et al [42] studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonic surfactant

(polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen [43]. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold through human skin membrane Vitro [44]. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a longchain fatty acid with cis- configuration [45 .]

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 [46]. Cornwell et al [47] 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 [48] as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin [49,50]. 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 [45].

Oxazolidinones

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 [51,52]. 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 [53]. 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 be occur.

Urea

Urea 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 non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism [54].

PATENT ON TDDS

Antimicrobial agents

Bristol-Myers Squibb has claimed topical administration of lipid formulations to prevent skin adherence of micro-organisms, including *Candida albicans*, *Staphylococcus* spp. and other

bacteria. These formulations further reduce the amount of antimicrobial agents required and replenish skin lipids. Several formulations have been discussed and the preferred choice contained 0.1 - 0.5% of the specified compound, 5 - 10% alcohol and/or 6 - 99% component copolymer. One of the three specified compounds claimed was palmitoleic acid [55]. Ganeden Biotech has claimed topical administration of a formulation containing a fructo-oligosaccharide (FOS) and the spores or viable dry cell mass of *Bacillus* spp. to prevent or treat infections of the skin or mucous membranes, including *Pseudomonas* and *Staphylococcus B. coagulans*. These formulations may be applied as a cream, lotion, gel, ointment etc., or be impregnated into a diaper, skin-wipe, dermal patch, or tampon. Formulations containing 100 - 500 mg/g FOS with viable bacteria or spores of either *Bacillus coagulans*, *B. subtilis*, *B. laterosporus* or *B. laevolacticus* were specifically claimed [56].

Analgesics and anti-inflammatory agents

Russinsky has claimed the esters of cyclooxygenase (COX) inhibitors and terpene derivatives to treat inflammation, including the specified compound, (-)-menthyl 4,5-diphenyl-2-oxazolepropanoate. These compounds are stated to have increased lipophilicity and are easily cleaved by hydrolases after penetration through the skin. Analysis with melting point, IR, ¹H-NMR, a process for manufacture and a transdermal patch including the compound were also claimed [57].

Minnesota Mining & Manufacturing has claimed an adhesive transdermal delivery device for the transdermal application of flurbiprofen. Topical use of flurbiprofen, a potent NSAID, has been applied for the treatment of gingivitis or inhibition of mitosis during cataract. This device comprises a backing and an adhesive layer containing 1 - 25% of (S)-flurbiprofen, isopropyl myristate, polyvinylpyrrolidone and co-polymers of N-vinyl-2-pyrrolidone and vinyl acetate plus acrylate and acrylamide. The device was found to demonstrate good skin adhesion and to penetrate effectively as determined in mouse, or human skin [58]

Agents for neurologic/psychologic diseases

SmithKline Beecham has claimed transdermal delivery formulations of the centrally acting dopamine D2 agonist ropinirole, in a free base form, to treat Parkinson's disease. The use of ropinirole in free base form improved skin penetration by 20- to 40-fold more than hydrochloride, with a target skin flux of 5 - 25 µg/cm²/h [59].

Alza has claimed the delivery of pergolide or its pharmaceutically acceptable salt, such as pergolide mesylate, through a body surface or membrane at a therapeutically effective rate to treat Parkinson's disease. This method allows virtually constant blood plasma levels of pergolide to be maintained in an individual over extended periods of time. The average baseline

skin flux of the pergolide base and mesylate through human cadaver epidermis was approximately 0.3 and 1.1 $\mu\text{g}/\text{cm}^2/\text{h}$ over a 52 h period, individually. The most preferred device for the transdermal administration of pergolide comprises a reservoir consisting of pergolide mesylate, glycerol monolaurate, methyl laurate, mineral oil and ethylene vinyl acetate [60]

Mucolytic and antitussive agents

Pharmacia & Upjohn AB has claimed a transdermal delivery device to administer N-acetylcysteine at concentrations between 1 and 4 mg/cm^2 with β -cyclodextrin for mucolytic use. Previously approved transdermal delivery of N-acetylcysteine [61,62] has been suggested to be ineffective for mucolytic use. The diffusion of N-acetylcysteine through pig skin or artificial membranes was measured using Franz cells. Several delivery devices comprising different drug-inadhesive and multilaminate types were also claimed. They were stated to be suitable for drug delivery over periods of 8, 12 and 24 h [63]. Pharmacia & Upjohn AB has also claimed a transdermal delivery device used to administer 0.5 - 2 mg/cm^2 dextromethorphan with β -cyclodextrin for antitussive use. Topical administration of this medication has been claimed [64] for other indications. Through bypassing the cytochrome P450 2D6 enzyme, transdermal administration of dextromethorphan reduces the degree of hepatic metabolism. The diffusion of dextromethorphan through pig skin or artificial membranes was measured using Franz cells [65].

CONCLUSION-

Transdermal drug delivery systems have been used as safe and effective drug delivery devices.

A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. This article provides valuable information regarding the transdermal drug delivery systems and its evaluation process in details.

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