www.sphinxsai.com

PharmTech
International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.1, pp 68-77, Jan-Mar 2010

RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM

***[1]Debjit Bhowmik,Chiranjib ,[2]Margret Chandira, [2]B.Jayakar, [3]K.P.Sampath**

[1]Rajiv Gandhi college of Pharmacy, Uttar Pradesh,India
[2]Vinayaka missions college of Pharmacy, Vinayaka mission University, Salem,India
[3]Coimbatore medical college, Coimbatore
Tamilnadu, India
****Email-debjit_cr@yahoo.com***

ABSTRACT :Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form . It delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system .A sophisticated complex drug delivery system difficult to formulate. It requires specialized manufacturing process/equipment. Formulated to meet specific biopharmaceutical and functional characteristics. The materials of construction, configuration and combination of the drug with the proper cosolvent, excipient, penetration enhancer, and membrane are carefully selected and matched to optimize adhesive properties and drug delivery requirements. Transdermal drug delivery - an approach used to deliver drugs through the skin for therapeutic use as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Various transdermal drug delivery technologies are described including the use of suitable formulations, carriers and penetration enhancers. The most commonly used transdermal system is the skin patch using various types of technologies. Transdermal technologies may be applied for several categories of pharmaceuticals used for the treatment of disorders of the skin or for systemic effect to treat diseases of other organs. Several transdermal products and applications include hormone replacement therapy, management of pain, angina pectoris, smoking cessation and neurological disorders such as Parkinson's disease. Formulated to deliver the drug at optimized rate into the systemic circulation should adhere to the skin for the expected duration should not cause any skin irritation and/or sensitization ,Enhancing bioavailability via bypassing first pass metabolism ,Minimizing pharmaco-kinetic peaks and troughs , Improving tolerability and dosing Increasing patient compliance in Continuous delivery.
KEY WORDS: Transdermal Drug Delivery System

INTRODUCTION

Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application (topical delivery) or to have an effect after distribution through the circulatory system (systemic delivery). While there are many advantages to delivering drugs through the skin the barrier properties of the skin provide a significant challenge. By understanding the mechanisms by which compounds cross the skin it will be possible to devise means for improving drug delivery.

Some of the many factors that influence the rate of delivery of drugs across the skin include; the thermodynamic activity of the drug in the formulation; the interaction of the drug and the formulation with the skin; variations in skin with age, race, anatomical region and disease. Research in transdermal drug delivery needs to address all of these factors. 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 vapour patch to reduce smoking was approved in Europe in 2007. The patches release essential oils that help the smoker to reduce gradually the number of cigarettes instead of stopping the smoking abruptly. Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and eventhe most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs

and avoid partial first-passin activation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms. These advantages are offered by the currently marketed transdermal products. One of the most successful, the nicotine patch, releases nicotine over sixteen hours, continuously suppressing the smoker's craving for a cigarette. The scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the needto swallow tablets periodically. The fentanyl patch acts for seventy-two hours, providing long-lasting pain relief. And an estrogen–progestin contraceptive patch needs to be applied only once a week, a boon for women who find it onerous to take one pill every day.The transdermal route is indeed desirable, but there is one small obstacle: whereas the function of the GI tract is to render ingested material suitable for absorption, the skin's function is to keep things out of the body. The major barrier within the skin is the stratum corneum, the top layer ofthe epidermis. The stratum corneum consists of keratinized, flattened remnants of once actively dividing epidermal cells. Hygroscopic, but impermeable to water, it behaves as a tough, flexible membrane. The intercellular space is rich in lipids. The stratum corneum is about ten microns thick, but on the palms and soles it ranges up to 600 microns in thickness .Although the stratum corneum is an efficient barrier, some chemical substances are able to penetrate it and to reach the underlying tissues and blood vessels. These "successful" substances are characterized by low molecular weight (≤500 Da), lipophilicity, and effectiveness at low dosage. The largest daily dose of drug in patch form is that of nicotine: twenty-one milligrams Transdermal absorption occurs through a slow process of diffusion driven by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin. Thus, the delivery system must be kept in continuous contact with the skin for a considerable time (hours to days).

Advantages and disadvantages of transdermal drug delivery[1,2,4]

Transdermal drug delivery systems offer several important advantages over more traditional approaches, including:

- longer duration of action resulting in a reduction in dosing frequency
- Increased convenience to administer drugs which would otherwise require frequent dosing
- improved bioavailability
- more uniform plasma levels
- reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval
- flexibility of terminating the drug administration by simply removing the patch from the skin
- Improved patient compliance and comfort via non-invasive, painless and simple application

Some of the greatest disadvantages to transdermal drug delivery are:

- possibility that a local irritation at the site of application
- Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

TRANSDERMAL PATCHES[3.5,6,7,8,9]

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. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament into the patient. A disadvantage to development however, stems from the fact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches. At the forefront of innovation, Aveva and Nitto Denko produced the first and only marketed transdermal patch using a revolutionary gel matrix adhesive system for an unequaled balance of adhesion reliability and gentleness. Because the gel matrix adhesive doesn't cause a disruption of the stratum corneum (skin) during removal, these patches can be removed and reapplied with minimal skin irritation and a desirable patient experience is achieved. One of the most successful advancements in transdermal drug delivery systems, our crystal reservoir technology has resulted in smaller patches with a more controlled and sustained drug release. This efficient drug delivery technology may minimize the amount of active pharmaceutical ingredients required.

This efficient way of releasing a drug is based on the over saturation of an adhesive polymer with medication, thus forcing a partial crystallization of the drug. The presence of both molecular solute and solid crystal forms allow for a considerably higher concentration and consistent supply of drug in each patch. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact. This technology is employed in the commercial production of the world's only Asthma Patch, which is sold in Japan and is one of the most successful patches in the world . The transdermal (through the skin) drug delivery approach serves to illustrate "Fuzzy Front End" problems encountered with all the other new drug delivery approaches. For centuries, topical products (creams, gels, lotions, etc.) have been used to

treat local skin disorders. The idea of using the skin as a route for systemic drug delivery, however, is of fairly recent origin. The further idea of incorporating drugs in a "patch" that supplies them by transdermal means is even more recent. The most important issue in the development of new transdermal drug delivery systems is to modulate the transport of penetrates through the skin on demand. Skin patches hold promise for transdermal administration of a broad scope of medical treatments. Patches control the release of drugs and avoid peaks and valleys associated with multiple-dose oral medication, combining extended duration of delivery with patient comfort, while significantly enhancing patient compliance. Patch delivery is easier than injection, and eliminates the risk of infection. A number of drugs may be administered transdermally. Transdermal drug absorption significantly alters drug kinetics. Success depends on a variety of biological physiological, biochemical, and biophysical factors including the following:

1. Body site of application
2. Thickness, composition and integrity of the stratum corneum epidermis (a skin layer)
3. Size and structure of the molecule (related to molecular weight), which is an indicator of diffusivity)
4. Permeability of the membrane in the transdermal drug delivery system
5. State of skin hydration
6. pH and other physicochemical drug properties
7. Drug metabolism
8. Lipid solubility
9. Degree of partitioning of the drug and associated components into the skin
10. Depot (reservoir) of/for drug in skin
11. Alteration of blood flow in the skin by additives and body temperature
12. Interactions between and among the factors listed above

The main components of a transdermal patch are:

Transdermal patch may include the following components:

- Liner - Protects the patch during storage. The liner is removed prior to use.
- Drug - Drug solution in direct contact with release liner
- Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin
- Membrane - Controls the release of the drug from the reservoir and multi-layer patches
- Backing - Protects the patch from the outer environment

The future of transdermal drug delivery[10,11,16,17,18]

Transdermal drug delivery is theoretically ideal for many injected and orally delivered drugs, but many drugs cannot pass through the skin because of skin's low permeability. Pharmaceutical companies develop new adhesives, molecular absorption enhancers, and penetration enhancers that will enhance skin permeability and thus greatly expand the range of drugs that can be delivered transdermally.Two of the better-known technologies that can help achieve significant skin permeation enhancement are iontophoresis and phonophoresis (sonophoresis). Iontophoresis involves passing a direct electrical current between two electrodes on the skin surface. Phonophoresis uses ultrasonic frequencies to help transfer high molecular weight drugs through the skin.A newer and potentially more promising technology is micro needle-enhanced delivery. These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug transport. The structures are small enough that they do not reach the nerve endings, so there is no sensation of pain. These systems have been reported to greatly enhance (up to 100,000 fold) the permeation of macromolecules through skin.

LIMITATIONS OF CURRENT TRANSDERMAL DELIVERY SYSTEMS[12,13,14.15]

Only a few drug candidates are currently available in dosage forms for transdermal drug delivery. One of the earliest applications was scopolamine patches used to prevent motion sickness and treat nausea.

Another highly popularized use was Nicotine patches worn on the upper arm to resolve the nicotine "fixes" for smoking cessation.

A third application is hormone replacement - for example, estradiol for estrogen replacement in post-menopausal women.

Fentanyl patches are used to treat cancer pain or chronic pain syndromes.

Testosterone patches for men are currently worn on the abdomen, back, thighs, or upper arms.

Nitroglycerin patches are administered for alleviating angina.

Various contraception patches have also been developed.

Oxybutynin transdermal patches have been under development for the treatment of urinary incontinence, a bladder disorder that results in uncontrolled release of urine (the oral form of the drug has several adverse side effects including dry mouth, dizziness and constipation).In the cosmetics industry, vitamin C patches are promoted to improve facial-line appearance and to de-emphasize wrinkles. Other ingredients such as sea kelp are also delivered through the skin. Certain topical compositions could also be

applied in patch form: a cream-like eutectic mixture of local anesthetics (EMLA) to reduce the surgical procedural pain; corticosteroid cream administered for its local effect on skin maladies; and TAC for anesthesia when suturing small lacerations.

Types

There are five main types of transdermal patches listed below.

Single-layer Drug-in-Adhesive

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

Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

Reservoir

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order

Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

REGULATORY ASPECTS[22,23]

A transdermal patch is classified by the U.S. Food and Drug Administration as a combination product, consisting of a medical device combined with a drug or biological product that the device is designed to deliver. Prior to sale in the United States, any transdermal patch product must apply for and receive approval from the Food and Drug Administration, demonstrating safety and efficacy for its intended use.

Application of Transdermal Therapy[25]

Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine

for motion sickness, and estradiol for estrogen deficiency, all through patches. At that time, biotechmedicinals were still being developed. During the past decade biotech products have come into their own, buttransdermals have essentially remained static. The numberand there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used . One reason forthis undoubtedly is the fact that only certain specialized firms can manufacture transdermal patches. Companies prefer to have full control of their projects, and to enjoythe higher profits on products developed and manufactured in house. Another reason is that only a limited numberof drugs fit the molecular weight, lipophilicity, andpotency requirements for transdermal absorption.

MOLECULAR ABSORPTION ENHANCEMENT[24,26,27]

Considerable research has been done on absorption enhancers, compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as wellas certain phenols seem to improve transdermal absorption. For example, linalool, alpha terpineol, and carvacrolwere studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to atherapeutic level . Limonene, menthone, and eugenolwere found to enhance transdermal absorption of tamoxifen. Phloretin, a polyphenol, enhanced the absorption of lignocaine . In general, absorption enhancement research has been done with excised animal skin(pig or rabbit) or human skin obtained from cadavers or plastic surgery procedures. In contrast, an interesting clinical trial was reported from Australia where estradiol was formulated asa metered-dose aerosol, using padimate O [a para-aminobenzoicacid (PABA) derivative used as a sunscreen agent] as the penetration enhancer. The volunteer subjects were four healthy, postmenopausal women. The aerosolwas applied to the ventral forearm in three sprays, each delivering one milligram of estradiol. Each spray covered10 cm2 of skin. After administering the spray, the skinwas not touched for two minutes, but then normal activity, including washing and dressing, was resumed. The drugwas applied in this way for nine successive days. Plasmaestradiol/estrone ratios obtained for the topical aerosol were consistent with those produced by a topical gel and transdermal patch, showing that a clinically relevantdose of estradiol was delivered. Using the Draize skin irritation test, no irritation was

observed. This dosage form appears to be a practical alternative tothe patch, unless inadvertent inhalation of the spray turnout to be a problem.

ABSORPTION ENHANCEMENT BY ENERGY INPUT[28]

The above are potential adjutants to the existing "passive"transdermal systems. Also under study is the possibility of active transfer of drugs through the skin by theaction of electrical or other forms of energy. The mostresearch has been devoted to iontophoresis; sonophoresisand electroporation have been less well studied.Transdermal Drug Delivery:

Iontophoresis is a method of transferring substances acrossthe skin by applying an electrical potential difference. It promotesthe transfer of charged ionic drugs and possibly highmolecular weight substances such as peptides. Electric currentis applied through two electrodes, placed on the patient's skin. The first, or donor, electrode (cathode) delivers the negatively charged therapeutic agent (e.g., an organic acid),whereas the second, or receptor, electrode (anode) serves toclose the circuit. This setup is named cathodal iontophoresis.For positively charged drugs (e.g., amines or peptides), thecell arrangement is reversed (anodal iontophoresis). The silver (anode) and silver chloride (cathode) electrode system—utilized in both types of iontophoresis—is favored largely
because it does not affect the drug solution to the extent that other electrode systems can

Current commercial applications of iontophoresis includeintradermal administration of lidocaine as a local anesthetic and dexamethasone for local inflammation. The devices
used are typically bench-top systems with patches connected to a power supply through cables; however, innovations in electronic circuit and battery technology may make small,
integrated patch-like systems practicable A small number of human trials have been conducted as proof of concept. Thus, fentanyl was tested in twelve healthy volunteers who were protected from its opioid effects by naltrexoneadministration. Analysis of plasma levels of fentanylrevealed transdermal absorption. Luteinizing hormone-releasing
hormone (LHRH), a decapeptide having a molecular weight of about 1200 Da, was tested in eight healthy male volunteers, demonstrating that pulsatile delivery of this hormone
is feasible Electroporation is a technique that delivers high voltage pulses of micro-to-millisecond duration to the skin, causing transient changes in cell membranes or lipid bilayers It is hypothesized that pretreatment of the skin in this waywould enable the passage of large, polar molecules such asheparin and peptides. Low frequency ultrasound treatment, or sonopheresis, was reported to enhance absorption of mannitol, which was usedas a model for highly hydrophilic drugs

PATCH TECHNOLOGY FOR PROTEIN DELIVERY[24,25]

Transdermal delivery of large proteins is a novel and exciting delivery method. There is
no commercial technology currently available that incorporates proteins into transdermal
patches. TransPharma uses its unique printed patch technologyfor transdermal delivery of
proteins thereby complementing its ViaDermdelivery technology . Such printed
patches contain accurate doses of proteins in adry state. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through theRF-MicroChannels, forming a highly concentrated protein solution in situ.The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels,
into the viable tissues of the skin, diffusing across a steep concentration gradient. This
brings about a high delivery rate, as well as apeak blood profile of the drug resembling thatof a subcutaneous injection. The protein patches do not contain any enhancers to
facilitate the delivery process, thereby insuring an easier development process and regulatorypathway.TransPharma has adapted a manufacturing dispensing technology, widely used in the diagnostics industry, to successfully manufacture the printed patches. This manufacturing method enables complete and flexible control of drug load on the patch, control of patch size and shape, as well as high manufacturing yield with minimal protein losses. In addition, it was found that this manufacturing method fully retains the biological activity of the protein drug. Printed patches were used in studies inwhich human growth hormone (hGH), insulin, and Teriparatide (PTH1-34) were delivered in animals (guinea-pigs and pigs) and humans.

MAXIMIZING TRANSDERMAL DRUG DELIVERY[15,16]

This drug delivery system is available since many years. Previously, the most frequently systems for applications were topical ointments and creams for various dermatological disorders. Here, various drugs are applied to your skin for providing systemic treatment. This system comprises of various topically monitored drug formulations that have the ability for delivering active components into general circulation. This system is formulated for providing controlled uninterrupted drug delivery through skin for systemic circulation and distribution in the body. Due to the relative and impermeability property of skin, transdermal drug delivery system doubles the protection barricade to avert intrusion by microbes and prevents loss of physiological substances including water. Drug delivery technologies are now receiving considerable attention from pharmaceutical companies.

The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety of drug delivery and provide more convenience for the patient. Substantial research conducted during the past several years has lead to the development of technologies that meet the requisite criteria for delivering the drug through a non-invasive route. One of such technologies is transdermal drug delivery.Transdermal drug delivery is the non-invasive delivery of medications from the surface of the skin - the largest and most accessible organ of the human body - through its layers, to the circulatory system. Medication delivery is carried out by a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. A skin patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream. The first transdermal patch was approved by the FDA in 1979. It was a patch for the treatment of motion sickness. In the mid-1980s, the pharmaceutical companies started the development of a nicotine patch to help smokers quit smoking, and within a few months at the end of 1991 and beginning of 1992 the FDA approved four nicotine patches.Today drugs administered through skin patches include scopolamine (for motion sickness), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), lidocaine to relieve the pain of shingles (herpes zoster). Non-medicated patches include thermal and cold patches, weight loss patches, nutrient patches, skin care patches (therapeutic and cosmetic), aroma patches, and patches that measure sunlight exposure.

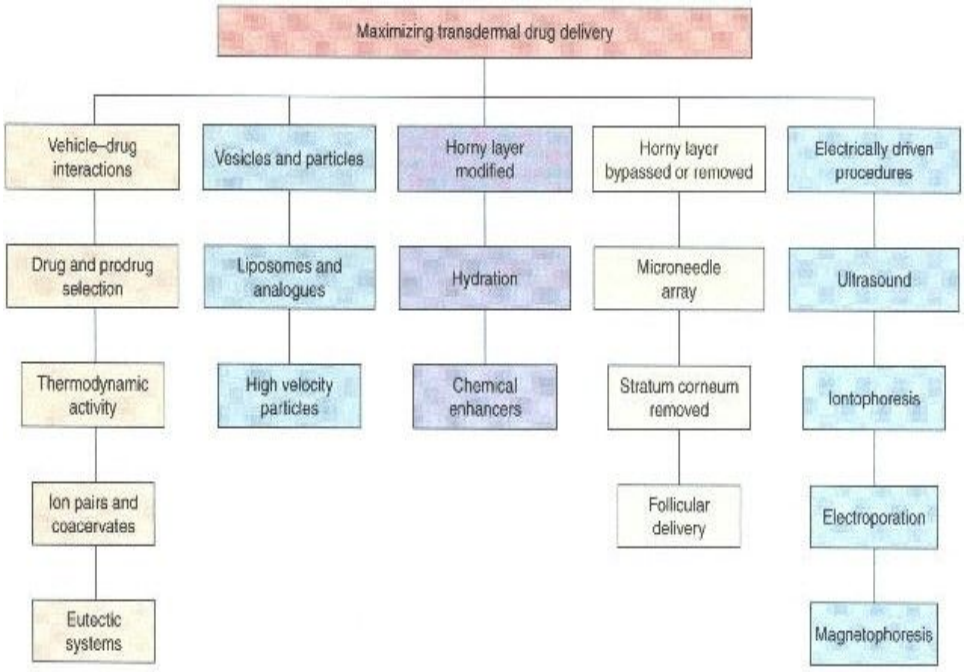

Figure-Maximizing transdermal drug delivery system

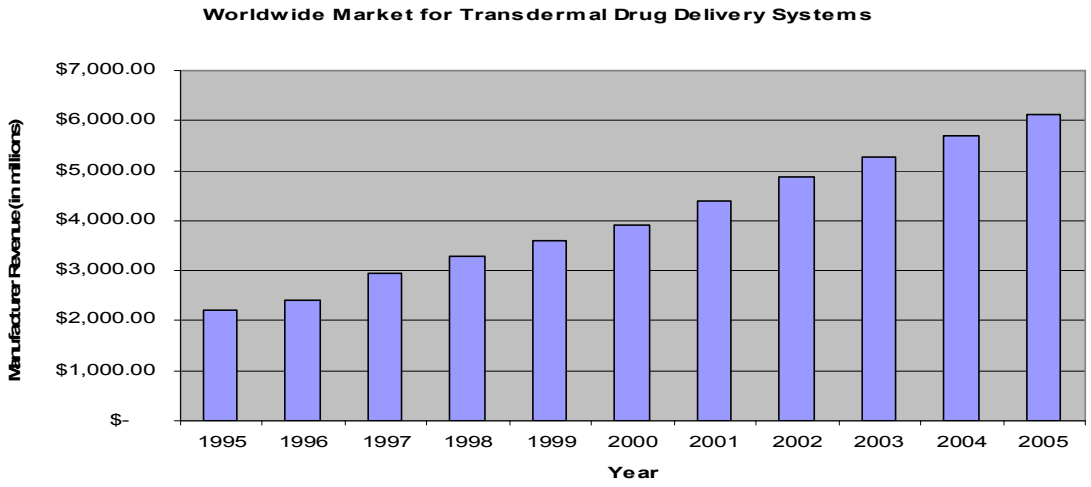

Figure-Worldwide Market for Transdermal Drug Delivery Systems

Physicochemical Evaluation[4,7,9]

Thickness and Weight Variation

The thickness of the patches was assessed at 6 different points using screw gauze. For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

Flatness

Longitudinal strips were cut from each film, one from the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining percent constriction, considering 0 % constriction equivalent to 100% flatness (20).

% Constriction = l_1-l_2/ l_2 X 100

Where l_1 is initial length of each strip, l_2 is final length of each strip.

Folding Endurance

The folding endurance was measured manually as per the reported method . Briefly, a strip of the film (4 x 3 cm) was cut evenly and repeatedly folded at the same place till it broke. The thinner the film more flexible it is.

Drug Content Determination

The patch (1 cm^2) was cut and added to a beaker containing 100 ml of phosphate buffered saline pH 7.4 (PBS). The medium was stirred (500 rpm) with teflon coated magnetic bead for 5 hours. The contents were filtered using whatman filter paper and the filtrate was analysed by U.V.spectrophotometer (Elico, SL-164, Hyderabad, India) at 269 nm for the drug content against the reference solution consisting of placebo films.

In vitro drug release studies

The in vitro release was carried out with the dialysis membrane using Franz diffusion cell. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5^o C and receptor compartment was provided with sampling port. The diffusion medium used was PBS pH 7.4 solution. The drug containing film with a support of backing membrane was kept in the donor compartment and it was separated from the receptor compartment by dialysis membrane with molecular weight cut off between 12000 to 14000 . The dialysis membrane was previously soaked for 24 hours in PBS pH 7.4. The donor and receptor compartment hold together using clamp. The receptor compartment with 15 ml of PBS pH 7.4 was maintained at 37 ± 0.5 ^{o}C and stirred with magnetic capsule operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane. Samples of 3 ml, were collected at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by UV. spectrophotometrically . Cumulative percentage drug released were calculated and plotted against time . The data was fitted to different kinetic models to explain the release mechanism and pattern using the following equations.

Zero order equation $Q = Q_o - kt$

First order equation $Q = Q_o e^{-kt}$

Higuchi equation $Q = kt^{1/2}$

Where, Q is the cumulative amount of drug released, Q is the initial amount of drug, k is release constant and t is time.

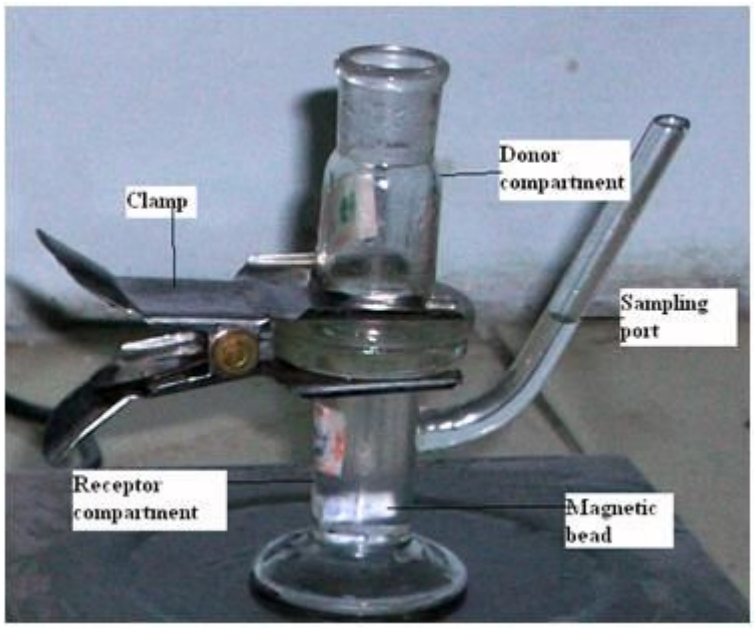

Fig. 3 Schematic diagram of Franz diffusion cell

Preparation of Skin

. Albino rats weighing 170-190 gm were sacrificed using anesthetic ether. The hair of test animals was carefully removed with the help of depilatory and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique (22), which involved soaking the entire abdominal skin in water at 60 °C for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water and used for *ex vivo* permeability studies.

***Ex vivo* Skin Permeation Studies**

The *ex vivo* skin permeation studies were carried out using Franz diffusion cell with a diffusional area of 3.73 cm^2. Rat abdominal skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The receiver phase is 15 ml of PBS pH 7.4, stirred at 300 rpm on a magnetic stirrer. The stratum corneum side of the skin was kept in intimate contact with the film and over that placed a backing membrane. The whole assembly was kept in a water bath at 37 ± 0.5 ^oC. Samples (3 ml) were collected at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by U.V. spectrophotometrically . Cumulative percentage drug permeated was calculated and plotted against time . Flux was determined directly as the slope of the curve between the steady state values of the amount of drug permeated (mg cm^{-2}) v/s time (hours) (23) and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^{-2})

Stability Studies:

The ability of vesicles to retain the drug (Drug Retention Behaviour) was assessed by keeping the proniosomal gel at three different temperature conditions, i.e., Refrigeration Temperature (4-80C), Room Temperature (25±20C) and oven (45±20C).Throughout the study, proniosomal formulations were stored in aluminum foil-sealed glass vials. The samples were withdrawn at different time intervals over a period of one month and drug leakage from the formulations was analyzed for drug content spectrophotometrically

CONCLUSION

Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Unfortunately, from the perspective of transdermal technology, the skin is impermeable to all but the smallest of molecules. In particular, the upper layer of skin, known as the stratum corneum, presents the most formidable barrier. If the stratum corneum could be pierced or temporarily made more permeable, this would allow more rapid transmission of larger molecules such as the insulin molecule Wide range of drugs can be delivered improved drug uptake Minimal complications and side effects Low cost and Easy to use Flexibility and consistency in dosing. One of the major advantages of transdermal drug delivery is the steady delivery of drug, resulting in consistent drug levels. Another advantage is the convenience of weekly or bi-weekly application resulting in improved patient compliance.Transdermal delivery of a drug product which is currently approved as oral dosage form, allows for the avoidance offirst pass metabolism by the

liver and the delivery of a more even level of the therapeutic agent over the course of 24hours. Dermal patches are the most common form of transdermal delivery of drugs. To obtain FDA approval of a transdermally delivered drug, it is critical to involve the Food and Drug Administration (FDA) early in the development process. During recent years, transdermal drug delivery systems have shown a tremendous potential for their ever-increasing rolein health care. This has been mainly attributed to thefavourable properties of lack of first pass metabolism effects of liver, better patient compliance, steady release profile and lowered pill burden in transdermal system1.

However, thetransdermal technology have limitations due to the inability therapeutic rates because of the presence of a relatively impermeable thick outer stratum corneum layer2. This barrier posed by human skin limits transdermal delivery only tolipophilic, low molecular weight potent drugs. Researchers are trying to overcome this hurdle of poor permeability by physical and chemical means. Chemical means include the prodrug approach and/or use of chemical penetration enhancers that can improve the lipophilicity, and the consequent bioavailability

REFERENCES

1. Robinson, J. R and Lee, H.L. (1987) Controlled Drug Delivery Fundamentals and Applications 2nd edi, Marcel Dekker, New York. pp. 524-552.
2. Aquil, M., Sultana, Y. and Ali, A. (2003). Matrix type transdermal drug delivery systems of metoprolol tartrate: In vitro characterization. Acta Pharm, 53: 119-125.
3. Ramesh, G., Vamshi Vishnu, Y., Kishan, V and Madhusudan Rao, Y. (2007). Development of nitrendipine transdermal patches: *in vitro* and *ex vivo* characterization. Current Drug Del, 4: 69-76.
4. Singh, J., Tripathi, K.P. and Sakia, T.R. (1993). Effect of penetration enhancers on the in vitro transport of ephedrine through rat skin and human epidermis from matrix based transdermal formulations. Drug Dev. Ind. Pharm, 19: 1623-1628.
5. Valenta, C. and Almasi-Szabo, I. (1995). In vitro diffusion studies of ketoprofen transdermal therapeutic system. Drug Dev.Ind. Pharm, 21:1799-1805.
6. Krishna, R. and Pandit, J.K. (1994). Transdermal delivery of propranolol. Drug Dev.Ind. Pharm, 20: 2459-2465.
7. Aqil, M., Zafar, S., Ali, A. and Ahmad, S. (2005). Transdermal drug delivery of labetolol hydrochloride: system development, in vitro; ex vivo and in vivo characterization. Curr Drug Deliv, 2(2): 125-31.
8. Shin, S. and Lee, H. (2002). Enhanced transdermal delivery of triprolidine from the ethylene-vinyl acetate matrix. Eur. J. Pharm. Biopharm, 54: 161-164.
9. Sweetman S.C. (2005). Martindale – The Complete Drug Reference, 34th edi, Pharmaceutical Press, London (U.K), pp. 1055.
10. August, B.J., Blake, J.A. and Hussain, M.A. (1990). Contributions of drug solubilization, partitioning, barrier disruption and solvent permeation to the enhancement of skin permeation of various compounds with fatty acids and amines. Pharm. Res, 7: 712-718.
11. Cho,Y.J. and Choi, H.K. (1998). Enhancement of percutaneous absorption of ketoprofen: effect of vehicles and adhesive matrix. Int. J. Pharm.169: 95-104.
12. Kim, J., Cho, Y.J. and Choi, H. (2000). Effect of vehicles and pressure sensitive adhesives on the permeation of tacrine across hairless mouse skin. Int. J. Pharm. 196: 105-113.
13. Panchangula, R., Salve, P.S., Thomas, N.S., Jain, A.K. and Ramarao, P. (2001). Transdermal delivery of naloxone: effect of water, propylene glycol, ethanol and their binary combinations on permeation through rat skin. Int. J. Pharm, 219: 95-105.
14. Manvi, F.V., Dandagi, P.M., Gada, A. P., Mastiholimath, V.S. and Jagadeesh, T. (2003). Formulation of a transdermal drug delivery system of ketotifen fumarate. Indian J. Pharm. Sci, 65(3): 239-243.
15. Mollgaard, B. and Hoelgaard, A. (1983). Permeation of estradiol through the skin-effect of vehicles. Acta Pharm. Suec, 20: 443-450.
16. Barry, B.W. (1987). Mode of action of penetration enhancers in human skin J. Control. Release, 6: 85-97.
17. Rowe, E.S. (1985). Lipid chain length and temperature dependence of ethanolphosphatidylcholines. Biochem. Biophys. Acta, 813: 321-330.
18. Kurihara-Bergstrom, T., Knutson, K., Denoble, L.J. and Goates, C.Y. (1990). Percutaneous absorption enhancement of an ionic molecule by ethanol-water systems in human skin. Pharm. Res. 7:762-766.
19. Kim, Y.H., Ghanem. A.H., Mahmoud, H.and Higuchi, W.I. (1992). Short chain alkanols as transport enhancers for lipophilic and

polar/ionic permeants in hairless mouse skin: Mechanism(s) of action. Int. J. Pharm, 80: 17-31.

20. Arora, P. and Mukherjee, B. (2002). Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci, 9: 2076-2089.
21. Devi, K., Saisivum, S., Maria, G.R. and Deepti, P.U.(2003). Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm, 5: 495-503.
22. Kaidi, Z and Jagdish, S (1999). In vitro percutaneous absorption enhancement of propranolol hydrochloride through porcine epidermis by terpenes/ethanol. 62: 359-366.
23. Bonina, F.P., Carellii, V., Cols, G.D., Montenegro, L. and Nannipieri, E. (1993). Vehicle effects on in vitro skin permeation of and stratum corneum affinity for model drugs caffeine and testosterone. Int. J. Pharm, 100: 41-47.
24. Fan, L.T. and Singh, S.K. (1989). Controlled release: A quantitative treatment. Springer-Verlag, New York. 13-56, 85-129.
25. 25. Vamshi Vishnu, Y., Ramesh, G., Chandrasekhar, K., Bhanoji rao, M.E. and Madhusudan Rao, Y. (2007). Development and *in vitro* evaluation of buccoadhesive carvedilol tablets Acta Pharm, 57:185–197.
26. Rama Rao, P. and Diwan, P.V. (1998). Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. Drug Dev. Ind. Pharm, 24: 327-336.
27. Rigg, P.C. and Barry, B.W. (1990). Shed snake skin and hairless mouse skin as model membranes for human skin during permeation studies. J. Invest. Dermatol, 94: 234-240.
28. Valenta, C. and Wedding, C. (1997). Effects of penetration enhancers on the in vitro percutaneous absorption of progesterone. J. Pharm. Phamacol, 49: 955-959.

*****