



CODEN [USA]: IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1013865>Available online at: <http://www.iajps.com>

Review Article

**TRANSDERMAL DRUG DELIVERY: A WAY FOR BETTER
TOMORROW**

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Abstract

Transdermal drug delivery is defined as self contained, discrete dosage form which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Despite their relatively higher costs, transdermal delivery systems have proved to be advantageous for delivery of selected drugs such as estrogens, testosterone, clonidine, nitroglycerin, scopolamine, fentanyl, and nicotine. The transdermal route has numerous advantages over the more traditional drug delivery routes. These include high bioavailability, absence of first pass hepatic metabolism, steady drug plasma concentrations, and the fact that therapy is non-invasive. Both topical and transdermal drug products are intended for external use. However, topical dermatologic products are intended for localized action on one or more layers of the skin [e.g. Sunscreens, keratolytic agents, local anesthetics, antiseptics and anti-inflammatory agents]. Although some medication from these topical products may unintentionally reach systemic circulation, it is usually in sub-therapeutic concentrations, and does not produce effects of any major concern except possibly in special situations, such as the pregnant or nursing patient. On the other hand, transdermal drug delivery systems use the percutaneous route for systemic drug delivery. To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue.

Keywords: *Transdermal, Patches, Dosage forms, Nitroglycerin, Nicotine***Corresponding Author:****Archana Sharma,**

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Please cite this article in press as Archana Sharma et al, *Transdermal Drug Delivery: A Way for Better Tomorrow*, Indo Am. J. P. Sci, 2017; 4(10).

INTRODUCTION:

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system [TDDS] established itself as an integral part of novel drug delivery systems. From 1979, when the Food and Drug Administration approved the first transdermal drug delivery system [Transderm Scop Patch], to the current transdermal delivery systems, there evolved a successful alternative to systemic drug delivery. Despite their relatively higher costs, transdermal delivery systems have proved advantageous for delivery of selected drugs, such as estrogens, testosterone, clonidine, nitroglycerin, scopolamine, fentanyl, and nicotine. The transdermal route has numerous advantages over the more traditional drug delivery routes. These include high bioavailability, absence of first pass hepatic metabolism, steady drug plasma concentrations, and the fact that therapy is non-invasive. Both topical and transdermal drug products are intended for external use. However, topical dermatologic products are intended for localized action on one or more layers of the skin [e.g. Sunscreens, keratolytic agents, local anesthetics, antiseptics and anti-inflammatory agents]. Although some medication from these topical products may unintentionally reach systemic circulation, it is usually in sub-therapeutic concentrations, and does not produce effects of any major concern except possibly in special situations, such as the pregnant or nursing patient. On the other hand, transdermal drug delivery systems use the percutaneous route for systemic drug delivery, but the skin is not the primary target organ. To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. It is exemplified by the development and marketing of scopolamine-releasing transdermal therapeutic system for 72-hr prophylaxis or treatment of motion-induced nausea, of nitroglycerin and isosorbide dinitrate-releasing trans-dermal therapeutic systems for once-a-day medication of angina pectoris, and of clonidine-releasing transdermal therapeutic system for weekly treatment of hypertension. The intensity of interests in the potential biomedical applications of transdermal controlled drug administration is demonstrated in the increasing research activities in a number of health care institutions in the development of various types of transdermal therapeutic systems for long term continuous infusion of therapeutic agents, including antihypertensive, anti-anginal, anti-histamine, anti-

inflammatory, analgesic, anti-arthritic, steroidal, and contraceptive drugs.

Advantages of Transdermal Drug Delivery Systems

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
2. They can be used for drugs with narrow therapeutic window.
3. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic „first- pass” effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc
4. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.
5. The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.
6. At times the maintenance of the drug concentration within the diphasic is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.
7. Self administration is possible with these systems.
8. The drug input can be terminated at any point of time by removing transdermal patch.

Disadvantages of Transdermal Drug Delivery Systems

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

SKIN AS SITE OF DRUG INFUSION

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis [Fig 1]. Microscopically, the epidermis further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface. Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendage route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules can, thus, be considered as, a process of passive diffusion through the intact stratum corneum in the inter follicular region. So, for the sake of mechanistic analysis of transdermal drug infusion, the various skin tissue layers can be represented by a simplistic multilayer model. In the case that the skin serves as the point of administration for systemically active drugs, the drug applied topically will be absorbed, first into the systemic circulation and then transported to target tissues.

MECHANISM OF TRANSDERMAL PERMEATION [3]

For a systemically-active drug to reach a target tissue, it has to possess some physico-chemical properties which facilitate the absorption of the drug through the skin [Fig 1], and also the uptake of the drug by the capillary network in the dermal papillary layer. The rate of permeation, dQ/dt , across various layers of skin tissues can be expressed as.

$$dQ/dt = P_s [C_d - C_r] \text{ ----- [1]}$$

Where, C_d and C_r are, respectively, the concentrations of skin penetrate in the donor phase [stratum corneum] and the receptor phase [systemic circulation]; and P_s is the overall permeability coefficient of the skin and is defined by

$$P_s = K_s D_{ss} / H_s \text{ -----[2]}$$

Where,

K_s = Partition coefficient of the penetrant

D_{ss} = Apparent diffusivity of penetrant

h_s = Thickness of skin

Thus, permeability coefficient [PS] may be a constant since K_s ; D_{ss} and h_s terms in equation [2] are constant under the given set of conditions.

A constant rate of drug permeation achieved, if $C_d > C_r$, then the equation [1] may be reduced to

$$dQ/dt = P_s . C_d \text{ -----[3]}$$

And the rate of skin permeation [dQ/dt] becomes a constant, if the C_d value remains fairly constant throughout the course of skin permeation. To maintain the C_d at a constant value, it is critical to make the drug to be released at a rate [R_r] which is always greater than the rate of skin uptake [R_a], i. e., $R_r >> R_a$

- Relationship between the rate of drug release [R_r] from a transdermal drug delivery system [TDDS] and the rate of drug uptake [R_a] by the skin.

By doing so, the drug concentration on the skin surface [C_d] is maintained at a level which is always greater than the equilibrium [or saturation] solubility of the drug in the stratum corneum [C_{es}], i.e., $C_d >> C_{es}$; and a maximum rate of skin permeation [dQ/dt]_m, as expressed by equation [4], is thus reached:

$$[dQ/dt]_m = P_s . C_{es}$$

Apparently, the magnitude of [dQ/dt]_m is determined by the skin permeability coefficient [PS] of the drug and its equilibrium solubility in the stratum corneum [C_{es}].

TYPES OF TRANSDERMAL PATCHES [1-5]

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

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The intrinsic rate of drug release from this type of drug delivery system is defined by

$$dQ/dT = C_r / 1/P_m + 1/P_a$$

Where C_r is the drug concentration in the reservoir compartment and P_a and P_m are the permeability coefficients of the adhesive layer and

the rate controlling membrane, P_m is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. P_m and P_a , respectively, are defined as follows.

$$P_m = K_m/r \cdot D_m / h_m$$

$$P_a = K_a/m \cdot D_a / h_a$$

where K_m/r and K_a/m are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; D_m and D_a are the diffusivity coefficients in the rate controlling membrane and adhesive layer, respectively; and h_m and h_a are the thicknesses of the rate controlling membrane and adhesive layer, respectively.

• Multi-layer Drug-in-Adhesive

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film. The rate of drug release in this system is defined by,

$$dQ/dt = K_a/r \cdot D_a / h_a * C_r$$

Where K_a/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

• Drug Reservoir-in-Adhesive

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane. The rate of drug release from this drug reservoir gradient controlled system is given by,

$$DQ/dt = K_a/r \cdot D_a / h_a [t] * A [h_a]$$

In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time $h_a [t]$. To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path $A [h_a]$.

• Drug Matrix-in-Adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug

solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix. The rate of drug release from this type of system is defined as,

$$DQ/dt = AC_p D_p^{1/2} / 2t$$

Where A is the initial drug loading dose dispersed in the polymer matrix and C_p and D_p are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, C_p is essentially equal to C_r , where C_r is the drug concentration in the reservoir compartment. [8, 9]

BASIC COMPONENT OF TDDS [1,2,8,11,12]

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive [PSA]
- Backing laminates
- Release liner and other excipients like plasticizers and solvents

1. Polymer matrix / Drug reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the products intended shelf life and should be of safe status. Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate [EVA] copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber. Similarly Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethyl cellulose for isosorbide dinitrate matrix. The polymers utilized for TDDS can be classified as,

Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc.*

Synthetic Elastomers: e.g. polybutadiene, hydri rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl rubber *etc.*

Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc.*

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

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 which causes non-compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight [less than 500 Daltons], have adequate solubility in oil and water [log P in the range of 1-3], a low melting point [less than 200°C] and are potent [dose in mg per day]. Table 1 enlists the currently available drugs for transdermal delivery. In addition drugs like rivastigmine for Alzheimers and Parkinson dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS. Drug must have

Physicochemical properties [36]

- The drug should have a molecular weight less than approximately 1000 daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have a low melting point.

Biological properties [36]

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half life [t_{1/2}] of the drug should be short.
- The drug must not induce a cutaneous irritant or allergic response.
- Drugs which degrade in the GI tract or are inactivated by hepatic first pass effect are suitable candidates for trans-dermal delivery.
- Tolerance to the drug must not develop under the near zero-order release profile of trans-dermal delivery.
- Drugs which have to be administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for trans-dermal delivery.

Permeation Enhancers [36]

Three pathways are suggested for drug penetration through the skin: polar, non-polar, and polar/non-polar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway [this substantially increases diffusion]. The fatty acid enhancers increase the fluidity of the lipid portion of the Stratum Corneum. Some enhancers [binary vehicles] act on both polar and nonpolar pathways by altering the multilaminar pathway for penetrants. Enhancers can increase the drug diffusivity in the Stratum Corneum [SC] by dissolving the skin lipids or by denaturing skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. The success of dermatological drug products that are intended for systemic drug delivery, such as the transdermal, depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve its desired therapeutic effect. The methods employed for modifying the barrier properties of the SC to enhance the drug penetration [and absorption] through the skin can be categorized as

[1] Chemical and

[2] Physical methods of enhancement.[15]

Chemical Enhancers

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers. Chemical enhancers act by

- Increasing the drug permeability through the skin by causing reversible damage to the SC.
- Increasing [and optimizing] thermodynamic activity of the drug when functioning as co solvent.
- Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin.
- Conditioning the SC to promote drug diffusion.
- Promoting penetration and establish drug reservoir in the SC.

Physical enhancers

The iontophoresis and ultra sound [also known as phonophoresis or sonophoresis] techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration [and absorption] of various therapeutic agents.

Pressure sensitive adhesives

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physicochemically and biologically compatible and should not alter drug release.

Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner 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 up of silicon or

Teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates.

Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

APPROACHES TO DEVELOP TD SYSTEMS [2,8,11,12]

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into four approaches as follows:

1. Membrane permeation – controlled systems
2. Adhesive dispersion – type systems.
3. Matrix diffusion – controlled systems.
4. Micro reservoir type or micro sealed dissolution controlled systems.

1. Membrane Permeation – Controlled Systems

In this type of system, drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate – controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogeneously in a solid polymer matrix [e.g. Polyisobutylene adhesive] or suspended in an unbleachable, viscous liquid medium [e.g. Silicon fluids] to form a paste like suspension. The rate of drug release from this type of system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or rapid release of entire drug content. Examples of this system are

Transderm – Nitro

Nitroglycerin – releasing transdermal system for once a day medication in angina pectoris.

Transderm – Scop

Scopolamine – releasing transdermal system for 72 hrs. Prophylaxis of motion sickness.

Catapres

Clonidine-releasing transdermal system for 7 day therapy of hypertension.

Estraderm

Estradiol –releasing transdermal system for menopausal syndrome for 3 – 4 days.

2. Adhesive Dispersion – Type Systems

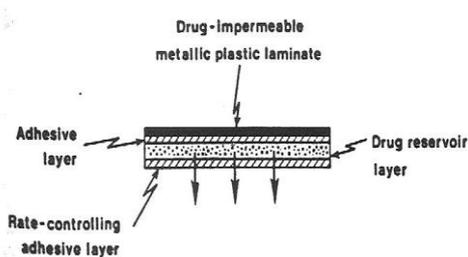
This is a simplified form of the membrane-permeation controlled system. As represented in Fig 6, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly [isobutylene] or poly [acrylate] adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion – controlled delivery system. Examples are:

Frاندol tape

Releases Isosorbide dinitrate for once-a-day medication of angina pectoris.

Deponit

Delivers nitroglycerine for the treatment of angina pectoris.

**3. Matrix Diffusion- Controlled Systems**

In this approach, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross-linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can also be formed by dissolving the drug and the polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic

backing membrane. Instead of applying the adhesive polymer directly on the surface of the medicated disc as discussed earlier in the first two types of transdermal delivery systems, the polymer is spread along the circumference of the patch to form an adhesive rim around the medicated disc. e.g. Nitro-Dur: Delivers nitroglycerin for the treatment of angina pectoris.

4. Micro reservoir type or Micro sealed Dissolution

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer [e.g. Polyethylene glycol] and then dispersing the drug suspension homogeneously in lipophilic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unreachable micro spheres of drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim. E.g. Nitroglycerin: Releasing transdermal therapeutic system for once – a day treatment of angina pectoris.

Evaluation of transdermal films [15-30]

Evaluation parameters include:

1. Interaction studies
2. Thickness of the patch
3. Weight uniformity
4. Folding endurance
5. Percentage Moisture content
6. Percentage Moisture uptake
7. Water vapour permeability [WVP]

evaluation

8. Drug content
9. Uniformity of dosage unit test
10. Polari scope examination
11. Shear Adhesion test
12. Peel Adhesion test
13. Thumb tack test
14. Flatness test
15. Percentage Elongation break test
16. Rolling ball tack test
17. Quick Stick [peel-tack] test
18. Probe Tack test
19. In vitro drug release studies
20. In vitro skin permeation studies
21. Skin Irritation study

In-Vitro Skin Permeation and Release Kinetics Studies:-

The design and development of transdermal drug delivery systems is greatly aided by in vitro studies.

In vitro studies can help in investigating the mechanism of skin permeation of drug before it can be developed into a transdermal therapeutic system. The methodology used in the in vitro study is relatively easy to follow and generally affords the investigator better control over the experimental conditions than is possible in-vivo,

The factors that require consideration when selecting an in vitro system include:

1. The rate limiting process: Drug solubilization or diffusion in the vehicle, partitioning from the vehicle, diffusion through the test membrane or partitioning and removal by the receptor phase.
2. The intrinsic diffusivity of the permeate and apparent diffusivity.
3. The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery and receptor phases.
4. The predominating route of diffusion during the experimentation and the relative extents of drug binding.
5. The intrinsic barrier potential of the membrane and the effects that vehicle components may have on retardative properties.

Hydration of the membrane and the presence of penetration enhancers may be important here. The kinetics of skin permeation can be more precisely analyzed by studying the time course for the permeation of drug across a freshly excised skin mounted on a diffusion cell, such as the Franz diffusion cell [Fig 9]. Keshary and Chien have pointed out certain deficiencies in the Franz cell and modified to obtain closer approximation to in vivo conditions [17]. Some diffusion cells are designed to hold the skin at a vertical position between donor and receptor chambers. A more recent example is the valia, Chien cell, which is superior to similar earlier models in that it does not expose both, the donor and the receptor phases to the same temperature, and does not allow solvent loss from either phase. Moreover, the design overcomes another inadequacy of the Franz cell, namely the susceptibility of its donor phase to the changes in ambient temperature. Finally the donor compartment contents may be stirred which makes the cell suitable for transdermal drug delivery from solutions and suspensions. Various types of in vitro apparatus for measuring drug permeation profiles across the skin have been reported in the literature. They can be broadly classified into two categories as shown below.

A. Physical design of diffusion cell

- Horizontal type
- Vertical type

- Flow-through type
-
- B. Method of sampling and measurement
- Continuing system
- Fluid circulation system
- Non circulation system

- Intermittent system:
- rotating agitation systems

1. Donor Compartment

- Easy access to deliver the penetrant to the skin.
- Stirred were possible.
- Temperature controlled [32 OC + 1 OC]
- Control of evaporation for vehicles and penetrant

2. Membrane

- For the study of penetration kinetics, only human skin should be used.
- For vehicle/device release studies other barrier may be used.
- The skin sample should contain both stratum corneum and viable epidermis.
- A molecule of known penetration kinetics should used prior to the test molecule, to assess barrier function.

3. Receptor Compartment

- Either, flow – through or static.
- Temperature controller [32 OC + 10C]
- Sufficient volume to maintain infinite sink conditions
- Stirred without obvious formations of boundary layers.

4. Receptor Fluid

- Should not compromise barrier function.
- Should be of favorable partitioning.
- Capable of maintaining epidermal viability where ever necessary.
- Must be contained once collected.

Majority of In vitro experiments are conducted in animal skin i.e. hairless mouse, guinea, rabbit etc. Although these exist a number of similarities there is as yet no animal skin that complete mimics the penetration characterization of human skin.

In-vivo Evaluation of Transdermal Drug Delivery:-

Systems: In-vivo evaluation of TDDS can be carried out using,

- A. Animal models
- B. Human volunteers
- C. Biophysical models

A. Animal models

In vivo animal models are preferred because considerable time and resources are required to

carry out studies in humans. Some of the species that have been used for in vivo testing include; mouse, rat, guinea pig, rabbit, hairless mouse, hairless rat, hair less dog, cat, dog, miniature pig, pig, horse, goat, squirrel, monkey, rhesus monkey, chimpanzee, etc. Various experiments have been carried out to determine which of the animal models provide the best prediction of the behavior of the device, being tested, in humans.

B. Human volunteers

The final stage in the development of transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the device to human volunteers. An in vivo evaluation using human subjects should give pertinent information with minimum risk to the subjects within a reasonable period of time. In vivo evaluation using human models involve determination of percutaneous absorption by an indirect method of measuring radio activity in excreta following topical application of the labeled drug. C-14 is generally used for radio-labelling Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body, or excreted by routes not monitored. This necessitates measurement of dose absorbed. However this method has certain limitations, to overcome the limitations inherent in this method, various refinements have been made. These are described below

1. Reservoir Technique

This method involves a simple, short exposure of the skin to the [radio-labeled] compound under study followed by removal of the stratum corneum by tape stripping and analysis of the content of the compound in the stratum corneum. From this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

2. Mass balance Technique

This method involves the application site is covered with an occlusive chamber, the chamber being replaced by a new one after a particular time interval. The site is also subjected to washing at these times. Radio-labeling techniques are used and the chambers, washings and the faces and urine of the patients are subjected to analysis. Advantage of this technique include achievement of mass balance between the applied dose and excretion levels and the use of surface wash measurements for predicting percutaneous absorption.

C. Biophysical Models

Models based on steady-state mass balance equation, solution of Fick's second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been

described in the literature. It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward there is scope for further refinement. Some of the unresolved issues include the barrier function of the skin with age, skin metabolism, in-vivo functioning of penetration enhancers etc.

METHODS TO ENHANCE TRANSDERMAL DELIVERY [31, 32,33]

1. Chemical enhancers- Because the skin provides such a formidable barrier to the delivery of most drugs, a broad range of different chemical additives have been tested to enhance transdermal penetration. chemical penetration enhancers provide certain advantages, including design flexibility with formulation chemistry and an easier possibility of patch application over a large area [$>10\text{ cm}^2$]. Chemical penetration enhancers can increase skin permeability by various mechanisms, including enhancing solubility, increasing partitioning into the stratum corneum, fluidizing the crystalline structure of stratum corneum and causing dissolution of stratum corneum lipids.

Example - Surfactants [Tween], fatty acids/esters [oleic acid], terpenes [limonene], and solvents [dimethyl sulphoxide and ethanol].

limitation - potent chemical enhancers are usually potent irritants to the skin at concentrations necessary for achieving useful levels of penetration enhancement and are therefore physiologically incompatible

2. Iontophoresis: - Rates of transdermal transport can also be increased through Iontophoresis, which uses an electric field to move both charged and uncharged species across the skin. Transdermal iontophoresis has been most extensively applied to the delivery of anti-inflammatory agents and other compounds for local effects in the context

of physical therapy. Other FDA-approved uses include pilocarpine delivery to induce sweating as part of a cystic fibrosis diagnostic test, tap-water delivery to treat hyperhidrosis, lidocaine delivery for local anesthesia, especially before venipuncture, and extraction

of interstitial fluid for monitoring glucose levels in diabetics. Typically, a few milli amperes of current are applied to a few square centimeters of skin, which generally causes no pain or irritation beyond mild erythema. Iontophoresis can enhance transport across skin by a number of possible mechanisms, including an electrophoretic driving force, an electro osmotic driving force, and transiently increased skin permeability. The electrophoretic mechanism can drive charged compounds across the skin by a direct interaction with the electric field. Species with greater charge and smaller molecular mass are generally delivered more

rapidly. Enhancement by electro-osmosis involves the delivery of molecules that are dragged by electrically induced solvent flow.

3. Electroporation: - Another approach to increase transdermal transport using electric fields involves the application of short, high voltage pulses to the skin to transiently increase skin permeability by a mechanism related to electroporation. Transdermal transport has been shown to increase by orders of magnitude using electroporation, with partial Reversibility within seconds and full reversibility, in some cases, within minutes to hours. The largest fluxes have been observed for synthetic molecules and small macromolecules [<10 kDa], including a clinical study of lidocaine delivery in humans. Larger macromolecules have also been delivered, including heparin, insulin, vaccines, oligonucleotides, DNA and microparticles, in which electroporation combined with chemical-enhancement methods have been most effective

4. Sonophoresis :- Ultrasonic waves, as well as short-duration shock waves, have been used to facilitate transdermal drug delivery. ultrasound at various frequencies in the range of 20 kHz–16 MHz has been used to enhance skin permeability by a method called SONOPHORESIS. Traditionally, ultrasound at high frequencies [$f > 1$ MHz, therapeutic ultrasound] was a popular choice for sonophoresis. Since Fellingner and Schmidt reported the treatment of polyarthritis of the digital joints of the hand using hydrocortisone ointment with therapeutic ultrasound in the 1950s, sonophoresis has been used to facilitate topical drug delivery, especially in the context of physical therapy. Low-frequency sonophoresis has been shown to enhance *in vitro* transdermal transport of a variety of high-molecular mass drugs, including insulin, erythropoietin, interferon and low-molecular weight heparin. The efficacy of low-frequency sonophoresis to deliver macromolecules has also been demonstrated *in vivo* for insulin, for low-molecular weight heparin in animals and recently in human volunteers for topical delivery of local anaesthetics. In one of its modes, low-frequency ultrasound has been shown to quickly permeabilize human skin and maintain it in a state of high permeabilization for a number of hours, thereby opening a window for drug delivery using a simple patch. Enhanced skin permeability during low-frequency sonophoresis has also been used to extract glucose and other constituents of interstitial fluid across permeabilized skin. Several possible mechanisms of sonophoresis have been investigated.

- First, thermal effects due to absorption of ultrasound by the skin;

- acoustic streaming caused by development of time-independent fluid velocities in the skin due to ultrasound;
- cavitation effects due to the formation, oscillation and possible collapse of bubbles in or next to the skin. Among these, cavitation was found to be primarily responsible.

5. Microneedles [34]:- Recently, arrays of microscopic needles have been used for transdermal drug delivery. Needles of micron dimensions can pierce into the skin surface to create holes large enough for molecules to enter, but small enough to avoid pain or significant damage. *In vitro* experiments have shown that inserting microneedle into skin can increase permeability by orders of magnitude for small drugs, large macromolecules and nanoparticles. Animal experiments have similarly shown large increases in transdermal delivery of compounds, including oligonucleotides, insulin, desmopressin and human growth hormone. Microneedle-based delivery of vaccines, including proteins and DNA, is of special interest, in part to target langerhans cells in the skin's epidermis. Human studies have shown that microneedles are reported as painless when inserted into the skin of human subjects. A number of Fortune 500 corporations, as well as startup companies, are actively developing microneedles for transdermal drug delivery. This can be carried out as a pretreatment to increase skin permeability before the subsequent application of a drug-loaded patch. Alternatively, microneedles can be coated with drug that is released from the needles while they are embedded in the skin. Hollow microneedles have also been fabricated and used to flow drug solutions into the skin.

GENERAL CLINICAL CONSIDERATION IN USE OF TDDS

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating location is important to allow the skin to regain its normal permeability and to prevent skin irritation.

1. TDDS should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken. Wet or moist skin can accelerate drug permeation time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.
2. Use of skin lotion should be avoided at the application site, because lotions affect the

hydration of skin and can alter partition coefficient of drug.

3. Patient should not physically alter TDDS, since this destroys integrity of the system.
4. The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds.
5. A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing or swimming.
6. A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system.
7. The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system.
8. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.
9. Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets.

EFFECT OF HEAT ON TRANSDERMAL PATCH [35]

Heat is known to increase skin permeation of drugs by several mechanisms. Higher temperatures increase microcirculation and blood vessel permeability, which facilitates drug transfer into the systemic circulation. A rise in temperature may also increase drug solubility both in the patch formulation and within the skin, thus increasing the release rate of the drug from local skin tissue into the systemic circulation. In fact, a new technology utilizing heat's ability to increase transdermal permeation called the controlled, heat-aided drug delivery [CHADD] system is currently under review by the FDA. Since heat increases skin permeation, there are concerns that excessive exposure to heat will increase absorption of transdermally delivered drugs and lead to overdosage. In fact, the U.S. prescribing information for *Duragesic* warns patients to avoid exposing the application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the patch. In addition, the Canadian *Duragesic* drug monograph also warns patients to avoid hot water bottles, hot whirlpool spa baths, and intensive sun-bathing. A pharmacokinetic model showed that serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C [104°F]. Therefore, the

manufacturer also recommends close monitoring for opioid side effects in patients who have developed fevers while wearing a *Duragesic* patch. Heat-induced increased absorption of transdermally delivered drugs is well documented. However, many patients are not aware of the possibility of overdosing on transdermally delivered drugs when the application site is exposed to heat. It is important to educate patients about this possibility to prevent drug overdose and/or compromise efficacy. Patients should be advised to avoid exposing the patch application site to external heat sources including, but not limited to, heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, hot water bottles, hot whirlpool spa baths, and intensive sun-bathing. They should also be advised that fever and an increase in body temperature from intense physical activity may also increase the absorption of transdermally delivered drugs. In the event of drug overdose, the drug patch should be removed immediately and appropriate treatment measures should be employed. Patients should also be reminded to store transdermal drug patches in their original packaging and keep in a cool, dry place until they are ready to be used.

APPLICATION OF TRANSDERMAL PATCHES [1,2,8]

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl [marketed as *Duragesic*] and Buprenorphine [marketed as *BuTrans*].
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch [marketed as *Ortho Evra* or *Evra*].
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- The anti-hypertensive drug Clonidine is available in transdermal patch form.
- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder [ADHD].

TRANSDERMAL MARKET PRODUCT [13,14]

The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic

benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier [primarily the stratum corneum] or increasing the energy of the drug molecules. These so-called “active” transdermal technologies include iontophoresis [which uses low voltage electrical current to drive charged drugs through the skin], electroporation [which uses short electrical pulses of high voltage to create transient aqueous pores in the skin], sonophoresis [which uses low frequency ultrasonic energy to disrupt the stratum corneum], and thermal energy [which uses heat to make the skin more permeable and to increase the energy of drug molecules]. Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

Examples of marketed transdermal drug delivery system:-

S. No	Therapeutic agent	TDDS	Design
1.	Clonidine	Catapres-TTS [Boehringer Ingelheim]	Four-layer patch
2.	Estradiol	Estraderm [Novartis]	Four layer patch
3.	Estradiol	Vivelle [Novartis]	Three-layer system
4	Estradiol	Climara [Novartis]	Three-layer system
5	Fentanyl	Duragesic [Janssen]	Four-layer patch
6	Nicotine	Prosstep [Lederie]	Multilayer round patch
7	Testosterone	Testoderm [Alza]	Three-layer system

Advancement in tdds [13, 14]

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two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier [primarily the stratum corneum] or increasing the energy of the drug molecules. These so-called “active” transdermal technologies include iontophoresis [which uses low voltage electrical current to drive charged drugs through the skin], electroporation [which uses short electrical pulses of high voltage to create transient aqueous pores in the skin], sonophoresis [which uses low frequency ultrasonic energy to disrupt the stratum corneum], and thermal energy [which uses heat to make the skin more permeable and to increase the energy of drug molecules]. Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

CONCLUSION:

Successful transdermal drug application requires numerous considerations. Bearing in mind that the basic functions of the skin are protection and containment, it would seem exceptionally difficult to target the skin for drug delivery. However, with our greater understanding of the structure and function of the skin, and how to alter these properties, more and more new drug products are being developed for transdermal delivery. The properties of the drug, the characteristics of the transdermal device, selection of in-vivo model and the status of patient’s skin are all important for safe and effective drug delivery. Taking into account the advantages of TDDS, it can be considered a perfect alternative for drugs whose enteral and parenteral dosages forms having drawbacks in performance and also in patient compliance. After rectifying the presently existing short-comings TDDS can surely introduce new dimensions in the field of drug delivery.

REFERENCES:

- 1.Jain, N. K., Controlled and Novel Drug Delivery, CBS Publishers, and Distributors, 2002, 107.
- 2.Chien, YW, Novel drug delivery systems, Drugs and the Pharmaceutical Sciences, Vol.50, Marcel Dekker, New York, NY;1992;797
- 3.Roberts MS, Targeted drug delivery to the skin and deeper tissues: role of physiology, solute structure and

- disease. Clin Exp Pharmacol Physiol 1997 Nov; 24[11]:874-9.
4. Aulton.M.E, Pharmaceutics; The science of dosage form design, second edition, Churchill Livingstone, Harcourt publishers-2002.
5. Ansel.H.C, Loyd.A.V, Popovich.N.G, Pharmaceutical dosage forms and drug delivery systems, Seventh edition, Lippincott Williams and Wilkins publication.
6. Brahmkar.D.M, Jaiswal.S.B, Biopharmaceutics and pharmacokinetics A Teatise. Vallabh Prakashan, Delhi 1995, 335-371.
7. Banker, G. S and Rhodes, C. T Modern pharmaceutics, third edition, New York, Marcel Dekker, Inc, 1990.
8. Jain.N.K, Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi. 1997.
9. Mathiowitz.Z.E, Chickering.D.E, Lehr.C.M, Bioadhesive drug delivery systems; fundamentals, novel approaches and development, Marcel Dekker, inc New York . Basel
10. www.Controlled release drug delivery systems.com
11. 3M World Wide, 3M Drug delivery system, Transdermal patches, www.3Mworldwide.com
12. Ryan D. Gordon, and Tim A. Peterson, transdermal drug delivery , drug delivery technology,
13. Mitragotri S, Blankschtein D, Langer R. Transdermal drug delivery using low-frequency sonophoresis. Pharm Res. 1996;13[3]:411-420.
14. Mitragotri S. Effect of therapeutic ultrasound on partition and diffusion coefficients in human stratum corneum. J Controlled Rel. 2001;71:23-29.
15. Kusum Devi and Dr.K.L.K. paranjothi, Development and Evaluation of free films and Transdermal patches of Ketorolac Tromethamine using polymers and pressure sensitive Adhesives the Eastern pharmacist, XLI, No. 485, 1998, 97-100.
16. R. Ilango, S. S. kavimani, E. Senthilkumar, K.R. Deepa and B. Jaykar, Formulation and evaluation of transdermal preparations of Alimesulide Gel, the Eastern pharmacist, 1998, 123-125.
17. Rajagopal K., Asraf Alim., Arumugam V. and Jayaprakash., Formulation and Evaluation of nimesulide transdermal Patches, the Indian pharmacist, Iv, No.31, 2005, 77-80
18. A. Femenia- Font, C. Padula, F. marra, C. Baloguer-Fernandez, V. Merino, Bioadhesive monolayer film for the *in vitro* transdermal Delivery of sumatriptan, Indian Journal of pharmaceutical sciences, 95 No.7, 2006, 1561-1568.
18. Gattani S.G., Gaud R.S. and Chaturvedi S.C., Formulation and Evaluation of transdermal films of ondansetron Hydrochloride, Indian Drugs, 43 [3], 2006, 245-250.
19. Swarnalata saraf, S. Saraf and V.K. Dixit, transdermal Delivery of Norfloxacin, the Indian pharmacist, 2006, 74-76.
20. S. Narasimha Murthy, YA-Li Zhao, Khin marlan, sek wen hui, A. Latif Kazim, Arindam sen, Lipid and Electroosmosis Enhanced transdermal Delivery of Insulin by Electroporation, Journal of pharmaceutical sciences, 95, No.9, 2006, 2041-2049.
21. J. Bagyalakshmi, A.S. William, A.W. Mithun, T.K. Ravi R. Manavalan and P.K. Manna, pharmacodynamics of Ampicillin sodium transdermal patches in an *in vitro* Infection model, Indian Journal of pharmaceutical sciences, 2006, 68[4]: 540-541.
22. Saxena., Mutalik S. and Reddy M.S., Formulation and evaluation of transdermal patches of metoclopramide Hydrochloride, Indian drugs 43 [9], 2006, 740- 745.
23. Gannu, Ramesh, Vamshi Vishnu, Y.; Krishnan. V., Madhosudan Rao. Y., Development of Mitrendipine transdermal patches science, current Drug Delivery, 4, 2007, 69-76 [8].
24. Gattani S.G., Gaud R.S. and Chaturvedi S.C., Formulation and evaluation of transdermal films of chlorpheniramine maleate, Indian drug 44 [1], 2007, 27-33.
25. Jawahar N. Anoop K.R., Ajish Prasad, Sarfaraz M.D., Gopal Rao M. and Jayaprakash, Evaluation of different formulation variables on transdermal films of verapamil Hydrochloride, the Indian pharmacist, 2007, 67-69.
26. Yuveraj singh Tanwar, Chetan singh chauhan, Anshu Sharma, Development and evaluation of carvedolol transdermal patches, Actapharm. 57, 2007, 151-159.
27. Udhumasha ubaidulla, molugu V.S. Reddy, transdermal therapeutic system of carvediol; effect of Hydrophilic and Hydrophobic metrics on *In Vitro* and *In vivo* characteristics, AAPS pharmscitech, 2007; 8[1].
28. Dey B.K, Nath L.K, mohanti B, Bhowmik B.B., Development and evaluation of propranolol Hydrochloride transdermal patches by using Hydrophilic and Hydrophobic polymer, Indian Journal of pharmaceutical education & Research, 41 [4], 2007, 388-393.
29. Kusum Devi V., Saisivam S., Maria G.R., Depti P.U., Design and evaluation of matrix diffusion controlled Transdermal patches of Verapamil Hydrochloride, Drug development and Industrial Pharmacy, 2003, 29 [5] : 495-503.
30. Rein, H. Experimental electroendosmotic studies on living human skin. Z. Biol. 81, 124- [1924].
31. Blank, I. H. Penetration of low-molecular-weight alcohols into skin. I. Effect of concentration of alcohol and type of vehicle. J. Invest. Dermatol. 43, 415-420 [1964].
32. Scheuplein, R. J. Mechanism of percutaneous adsorption I. Routes of penetration and the influence of solubility. J. Invest. Dermatol. 45, 334-345 [1965].
33. www.nature.com/reviews/drugdisc.
34. http://www.uspharmacist.com/index.aps?show=article&page=8_1061.htm
35. www.mypharmaguide.com/article/100547881.html