Transdermal patch: An overview

[1]Asfiya Sultana, [2] Abdul Mannan

[1]Student, [2]Professor
Department of Pharmaceutics
[1]Deccan School of pharmacy, Hyderabad, India.

***Abstract*: A Transdermal patch may be a medicated bioadhesive patch that's placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Which promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other routes of delivery system such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive patch. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into circulation through skin at predetermined rate with minimal inter and intrapatient variations. The main disadvantage to transdermal delivery systems stems from the very fact that the skin could also be a really effective barrier, as a result, only medications whose molecules are small can easily penetrate the skin, so it can be delivered by this method. This review describes the transdermal patches including types of transdermal patches, method of preparation of transdermal patches and factor affecting etc.**

***Keywords*: Transdermal, Delivery, Patches**

1. Introduction:

Oral drug delivery system is the most used route of drug delivery system but it has some disadvantages including first pass metabolism, drug degradation etc in digestive tract because of enzymes, pH etc. to beat these problems, a completely unique drug delivery system was developed by Chien in 1992. it had been Transdermal patches or Transdermal delivery system.This medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin. They are available in several sizes & having more than one ingredient. Once they been applied on unbroken skin they deliver active ingredients into blood stream passing via skin barriers. A skin patch containing high dose of drug inside which is retained on the skin for prolonged period of your time , which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathwaysa) Through hair follicals. b) Through sebaceous glands. c) Through ductule . Transdermal drug delivery systems are utilized in various skin disorders, also within the management of angina , pains, smoking cessation & neurological disorders like Parkinson's disease [1,2].

Transdermal route and drug delivery prospects

Skin:The largest organ:

The skin is the largest organ of the human body which covers a surface area of approximately 2 sq.m. and receives about one third of the blood circulation through the body. [5] It serves as a permeability barrier against the transdermal absorption of various chemical and biological agents. It is one of the most readily available organs of the body with a thickness of few millimeters **(**2.97 0.28 mm**)** which,

- Separates the underlying blood circulation network from the outside environment
- Serves as a barrier against physical, chemical and microbiological attacks.
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.
- Skin is a major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. The diffusional resistance of the skin is greatly hooked on its anatomy and ultrastructure.[1,2]

Advantages of transdermal drug delivery systems [3]: Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are:

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility
- Predictable and extended duration of activity
- Minimizing undesirable side effects
- Provides utilization of drugs with short biological half lives, narrow therapeutic window
- Improving physiological and pharmacological response
- Maintain plasma concentration of potent drugs
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Ability to deliver drug more selectively to a specific site
- Provide suitability for self administration

- Enhance therapeutic efficacy

Limitations of transdermal drug delivery systems [1, 2, 3]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

2.Anatomy of Skin:

The structure of human skin (fig.1) can be categorized into four main layers

- The epidermis
- The viable epidermis
- A non-viable epidermis (*Stratum corneum*
- The overlying dermis

The innermost subcutaneous fat layer **(**Hypodermis) [4]

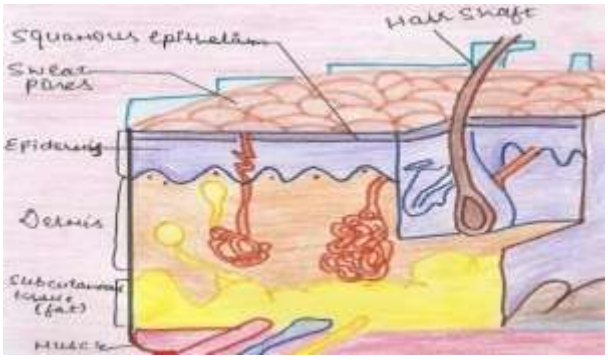

Fig. 1: Schematic representation of skin and its appendages

Structure of skin

The subcutaneous fat layer : It bridges between the overlying dermis and the underlying body constituents. It is relatively thick in order of several millimeters. The layer of adipose tissue serves to insulate the body and to provide mechanical protection against physical shock. It also provide supply of high energy molecules . Principal blood vessels and nerves are carried to the skin in this layer.

The dermis : It contains blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands (eccrine and apocrine). It provides physiological support for the epidermis. It is typically 3-5 mm thick and is the major component of human skin. It is composed of a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility, embedded in a mucopolysaccharide gel (Wilkes et al., 1973). It provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

The epidermis : It is 100 µm thick. It contains various layers. The stratum germinativum is the basal layer. Above the basal layer are the stratum spinosum, the stratum granulosum, the stratum lucidum, and finally, the stratum corneum (SC). SC is the rate limiting barrier that restricts the inward and outward movement of chemical substances consists of flattened keratin-filled cells (e.g., corneocytes). Upon reaching the SC, these cells are cornified and flatten. The corneocytes are then sloughed off the skin at a rate of about one cell layer per day, a process called desquamation. The main source of resistance to penetration and permeation through the skin is the SC.

Basic principles of Transdermal permeation :[5]

Transdermal permeation is based on passive diffusion. Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum .The skin permeation barrier. In the initial transient diffusion stage drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium through the intact stratum corneum becomes the primary pathway for transdermal permeation. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves [5]

- Dissolution with in and release from the formulation.
- Partitioning into the skin's outermost layer, the stratum corneum.
- Diffusion through the SC, principally via a lipidic intercellular pathway .
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake into the papillary dermis and into the microcirculation.

3. Factors affecting transdermal permeation: [6]

Physicochemical properties of the penetrant molecules

Partition coefficient:A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability. It may be altered by chemical modification without affecting the pharmacological activity of the drug.

pH conditions :Applications of solutions whose pH values are very high or very low can be destructive to the skin. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

Penetrant concentration Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

Physicochemical properties of the drug delivery system

Release characteristics: Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors: Whether the drug molecules are dissolved or suspended in the delivery systems. The interfacial partition coefficient of the drug from the delivery system to the skin tissue. pH of the vehicle

Composition of the drug delivery systems: The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight.

Enhancement of transdermal permeation: Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems.

Types of Transdermal Drug Delivery System:

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

Reservoir System: In this System the drug reservoir is kept in between backing layer and a rate controlling membrane. And drug releases through microporous rate controlled membrane. Drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix in the reservoir compartment.

4.Matrix System: This system is of Two type

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

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

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

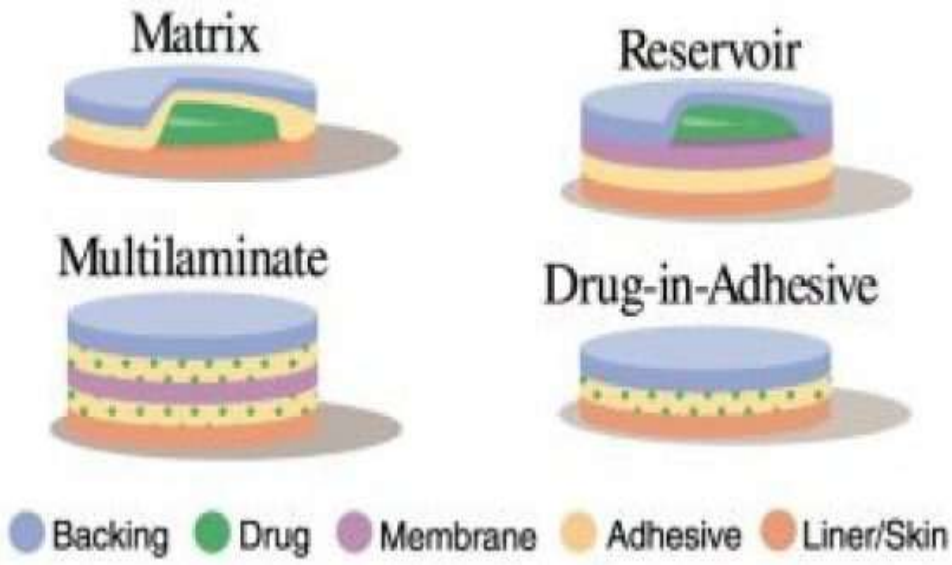

Figure 2. **Types of Transdermal Drug Delivery System:**

Components of Transdermal Drug Delivery System

a) Polymer matrix/ Drug reservoir
b) Drug c) Permeation enhancers.
d) Pressure sensitive adhesive (PSA).

e) Backing laminate.
f) Release liner.
g) Other excipients like plasticizers and solvents. [10]

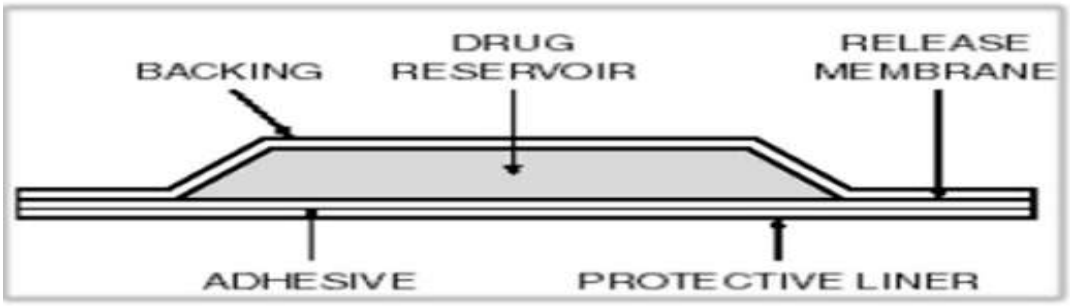

Figure.3:Components of Transdermal Drug Delivery System

Polymer Matrix/ Drug Reservoir: It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. It should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status. Polymers used in Transdermal drug delivery systems are classified as
a) Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
b) Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.
Drugs: Some of ideal properties of drug & some factors to be consider during preparation of Transdermal patches are as follows:

a. Ideal Properties of Drugs: Table no.1

S,No	Parameter	Properties
1	**Dose**	**Should be low in weight(less than 20mg)**
2	**Half life**	**10/less (hrs).**
3	**Molecular weight**	**<400da.**
4	**Skin permeability coefficient**	**>0.5*10-3cm/h.**
5	**Skin reaction**	**Non irritating, Non sensitizing**
6	**Oral bioavailablity**	**Low.**

Permeation Enhancers: The chemical compounds that enhance the permeability of stratum corneum so as to attain therapeutic levels of the drug candidate. They improve the permeability by interacting with Stratum corneum.
a) Ideal Properties of Permeation Enhancers
i. They should be non-irritating, non-toxic & non- allergic.
ii. They should not bind to receptor site i.e. not showing any pharmacological activity.
iii. They should be cosmetically acceptable with an appropriate skin feel. [11]
Backing Laminate: It is a supportive material which is impermeable to drugs and also to permeation enhancers. They should chemically compatible with the drug, enhancer, adhesive and other excipients. Ex: Vinyl, Polyethylene and Polyester films [12].
Release Liner: This is the primary packaging material that can protect the patch during application. It is made up of base layer which may be a) Non-occlusive (e.g. paper fabric) OR b) Occlusive (e.g. polyethylene, polyvinylchloride) It is made up of silicon or Teflon. Release liner should be chemically inert & it should be permeable to drug, penetration enhancers & water.
Other Excipients Like Plasticizers and Solvents
a) Solvents: Chloroform, methanol, acetone, isopropanol and dichloromethane.
b) Plasticizers: Dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol [13]

5. Evaluation of Transdermal patches:

The Transdermal patches can be characterized in terms of following parameters

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

Physicochemical evaluation:
Transdermal patches can be physicochemically evaluated in terms of these parameters:
Thickness:

The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.4

Uniformity of weight:
Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight .[16, 36]

Drug content determination:
An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.[8, 39]

Content uniformity test:
10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test. [29]

Moisture content:
The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content = Initial weight – Final weight X 100 [4]

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.[35]

% moisture uptake = Final weight – Initial weight X 100

Flatness:
A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent

% constriction = I1 – I2 X 100

I2 = Final length of each strip
I1 = Initial length of each strip [29]

Folding Endurance:
Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value. [31, 21]

Tensile Strength:
To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. [26]

Tack properties:
It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer. [30]

Thumb tack test:
The force required to remove thumb from adhesive is a measure of tack. [31]

Rolling ball test:
This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel. [30]

Quick stick (Peel tack) test:

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inch/min. [17]

Probe tack test:
Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.[26]

***In vitro* release studies:**
Transdermal patches can be *in vitro* evaluated in terms of Franz diffusion cell the cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds th**e** receptor compartment. The drug content is analyzed using suitable method, maintenance of sink condition is essential.[31]

***In vivo* Studies:**
Transdermal patches can be *in vivo* evaluated in terms of *In vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using animal models human volunteers.[26]

Animal models:
Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted leads to a conclusion that hairless animals are preferred over hairy animals in both *in vitro* and *in vivo* experiments. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man. [26]

Human model
The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers.39 Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources best to assess the performance of the drug. [.26]

REFERENCES:

[1] Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm Res. J. 2010; 3:139-149.
[2] Bhowmik D, Chiranjib, Chandira M, Jayakar B, Sampath KP. Recent advances in transdermal drug delivery system. Int. J Pharm Tech Res. 2010; 2(1):68-77.
[3] Kumar A, Pullankandam N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. Int. J Pharm Sci. Review Res. 2010;3(2):49-54.
[4] Divya A, Rao MK, Gnanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. A review on current scenario of transdermal drug delivery system. Int. J Res. Pharm Sci. 2012;3(4):494-502.
[5] Jain NK, Controlled and novel drug delivery. 1st Ed., CBS Publisher and Distributors, New Delhi. 2001:100-129.
[6] **Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. Plegia** Res. Lib. 2011;2(5):17-29.
[7] Dhawan S, Aggarwal G. Development, fabrication and evaluation of transdermal drug delivery system- a review. Pharm info.net. 2009:1-25.
[8] Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovation. 2012;1(4):66-75.
[9] Mehta R. Topical and transdermal drug delivery: what a pharmacist needs to know. InetCE. 1st Ed., Arizona;2004:1-10.
[10] Loyd V, Allen Jr, Nicholas G, Popovich, Howard C, Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers, New Delhi;2005:298-299.
[11] Jain NK. Pharmaceutical product development. 1st Ed. CBS Publisher and Distributors. New Delhi. 2002:221-228.
[12] Robinson JR, Lee VH. Controlled drug delivery fundamentals and applications. 2nd Ed. New York. 2005:523-536.
[13] Wilson R, Waugh A, Grant A. Anatomy and physiology in health and illness. 9th Ed. 2001 pg. 363-366.
[14] Kumar D, Sharma N, Rana AC, Agarwal G, Bhat ZA. A review: transdermal drug delivery system: a tools for novel drug delivery sestem. Int. J Drug Dev. Res. 2011;3(3):70-84.
[15] Ramteke KH, Dhole SN, Patil SV. Transdermal drug delivery system: a review. J Advanced Sci. Res. 2012;3(1):22-35.
[16] Yadav V. Transdermal drug delivery system: review. Int. J Pharm Sci. Res. 2012;3(2):376-382.
[17] Dhiman S, Thakur GS, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int. J Pharmacy Pharm Sci. 2011;3(5):26-34.
[18] Sharma RK, Keleb E, Mosa EB, Aljahwi AAZ. Transdermal drug delivery system- design and evaluation. Int. J Advances Pharm Sci. 2010;1:201-211.

[19] Sandhu P, Bilandi A, Kataria S, Middha A. Transdermal drug delivery system (patches), applications in present scenario. Int. J Res. Pharm Chem. 2011;1(4):1139-1151.
[20] Singh MC, Naik AS, Sawant SD. Transdermal drug delivery system with major emphasis on transdermal patches: a review. J Pharm Res. 2010;3(10):2537-2543.
[21] Yadav B, Sharma B, Saroha K. Transdermal patches: a discrete dosage form. Int. J Current Pharm Res. 2011;3(3):98-108.
[22] Tom WC. Effects of heat on transdermal drug patches. 1st Ed.:1-2.
[23] Kumar KPS, Bhowmik D, Chiranji BB, Chandira RM. Transdermal drug delivery system- a novel drug delivery system and its market scope and opportunities. Int. J Pharm Bio Sci. 2010.1(2):1-21.
[24] Sharma RK, Keleb E, Mosa EB, Aljahwi AAZ. Transdermal drug delivery system- design and evaluation. Int. J Advances Pharm Sci. 2010;1:201-211.
[25] Yadav B, Sharma B, Saroha K. Transdermal patches: a discrete dosage form. Int. J Current Pharm Res. 2011;3(3):98-108.
[26] Gupta IK, Chokshi MM. Transdermal drug delivery system: an overview. Asian J Pharm Sci. Clinical Res. 2011;1(1):25-43.
[27] Jatav VS, Saggu JS, Jat RK, Sharma AK, Singh RP. Recent advances in development of transdermal patches. Pharmacophore Int. Res. J. 2011;2(6):287-297.
[28] Joshi K, Selvaduary G. Transdermal drug delivery system and their use of polymers. MatE 175- Biomaterials. 1st Ed. 2008:1-28
[29] Patel DS, Patel MV, Patel KN, Patel BA, Patel PA. Transdermal patches: a complete review on transdermal drug delivery system. Int. J Pharm Res. Scholars. 2012;1(1):55-71.
[30] Lende LK, Grampurohit ND, Gaikwad DD, Gadhave MV, Jadhav SL. Transdermal patches: a review. Int. J Pharm Res. Dev. 2011;4(3):96-103.
[31] Sakalle P, Dwivedi S, Dwivedi A. Design, evaluation, parameters and marketed products of transdermal patches: a review. J Pharm Res. 2010;3(2):235-240.