ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A REVIEW ON NOVEL DRUG DELIVERY SYSTEM – TRANSDERMAL DRUG DELIVERY SYSTEM AND ITS STATISTICS

Ayesha Sultana*, Vidya Birajdar, K. Venu Madhav, M. Kiranmai, Sravanthi

St. Pauls College of Pharmacy,Turkayamjal, Hyderabad, Telangana, India.

***Corresponding Author E-mail: vidyabirajdar0608@gmail.com**

ARTICLE INFO

Key words:
Application, Evaluation, Global market, Transdermal patches, Transdermal drug delivery system.

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

The transdermal route has numerous advantages over the drug delivery routes. TDDS was presented to overcome the difficulties of drug delivery especially oral route. Transdermal drugs are self-contained, discrete dosage form. Advantage of transdermal delivery route over other types of delivery system such as oral, topical, intravenous etc., is that it provides controlled release of the medication into the patches. This review article covers brief outline of advantages, disadvantages, skin pathways for transdermal drug delivery system, types of transdermal patches, components of transdermal patches, preparation and evaluation of transdermal patches and its applications, future of transdermal drug delivery system are also described. The global market size for the Transdermal patch was estimated at $22 billion in 2010 and the market expanded to $32 billion by 2015. From 2017 to 2022 is expected to increase by 4.2%.

1. INTRODUCTION

Oral route is the most popular route of drug delivery system but it has some disadvantages including first pass metabolism, drug degradation etc in gastrointestinal tract due to enzymes, pH etc. To overcome theseproblems, a novel drug delivery system was developed by chien in, 1992, Banker in 1990, Guy in 1996. It was transdermal patches or transdermal delivery system. [1] 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.[2] They are available in different sizes and having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. A transdermal patch Containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathways-

A] Through hair follicles. b] Through sebaceous glands. c] Through sweat duct.

Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation and neurological disorders such as Parkinson's disease. [3, 4]

Advantages:

- Avoids vagaries, associated with gastro-intestinal absorption due to pH, enzymatic activity and rug food interaction.
- Avoid first pass effect.

© Journal of Global Trends in Pharmaceutical Sciences

- It is a substitute of oral route.
- Constant drug levels can be maintained in the systemic circulation.
- Avoid the pain of injection.
- Easy to discontinue in case of toxic effects.
- Multi day therapy with single application.
- Improved patient compliance and acceptability of the drug therapy
- Extends the activity of drug with short life.
- Provides suitability for self administration.
- Great advantage for the patients who are unconscious.
- The drug input can be terminated at any point of time by removing transdermal patch.

Disadvantages:

- Drug must have some desirable physic-chemical properties to penetrate through stratum corneum.
- Daily dose of the drug should be less than 5 mg/ day. If dosage is more than 10-25 mg/ day transdermal drug delivery will be difficult.
- Local irritation can be caused at the site of administration.
- Skin rashes and sensitization.
- It cannot deliver ionic drug.
- Drugs of large molecular size cannot be formulated.
- It cannot deliver the drug in pulsatile fashion.
- The barrier function of the skin changes from one site to another, from person to person with age.
- It cannot achieve high drug levels in Blood/ plasma.
- Has poor skin permeability which limits the passage of drug.

PHYSIOLOGY OF THE SKIN:

Skin of an average adult body covers a surface of approximately $2m^2$ and receives about one-third of the blood circulating through the body. Skin contains (figure 1) an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosam and uppermost stratum corneum, it consists of highly confide (dead) cells embedded in a continuous matrix of lipid membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human's skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimetres of the skin area. It is one of the most readily accessible organs of the human. [5]

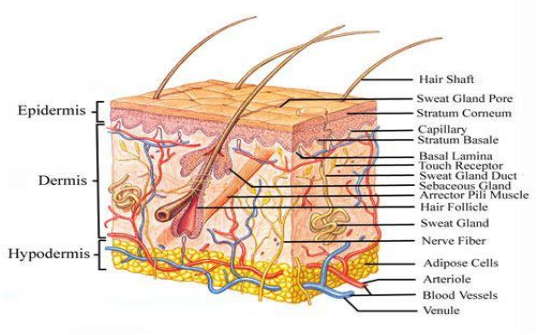


Figure 1: Anatomical physiological structure of skin

Skin pathways for transdermal drug delivery system:

When drugs are applied on the skin surface, penetration into and through the skin can occur via various routes. Drugs penetrate either via the stratum corneum (transepidermal) or via the appendages (transappendageal) (figure 2). During penetration through the stratum corneum, two possible routes can be distinguished, i) penetration alternating through the coenocytes and the lipid lamellae (transcellular route) and ii) penetration along the tortuous pathway along the lipid lamellae (intercellular route).

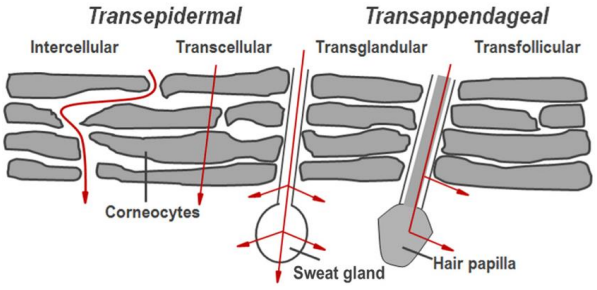


Figure 2: Possible pathways for permeation of drug across the skin barrier.

© Journal of Global Trends in Pharmaceutical Sciences

Generally, it is accepted that the predominant route of penetration through the stratum corneum is the intercellular route. This is mainly caused by the densely cross-linked cornified envelope coating the keratinocytes. However transcellular transport for small hydrophilic molecules such as water cannot completely be excluded. The appendage route or shunt route includes either the duct of the eccrine sweat glands or the follicular duct. The content of the eccrine sweat glands is mainly hydrophilic, while the content of the follicular duct is lipophilic. This is mainly due to sebum excreted into the opening of the follicular duct. It is generally accepted that due to its large surface area, passive skin permeation mainly occurs through intact stratum corneum. [6-9].

2. LITERATURE REVIEW:

AGRAHARI SAURABH et al., (2019): Developed of transdermal patches of Piroxicam. Piroxicam is basically a steroidal anti-inflammatory drug. Various batches were prepared using hydroxyl propyl methylcellulose, PVP and ethyl cellulose. Eight batches of transdermal patches were prepared evaluation of each formulation was performed and formulation F6 was optimized best. It shows that less dosage results in the longer duration of action which makes these patches remarkable in curing the infection. In vitro release study provides information that transdermal patches are able to release 99.9% of drug. [10]

SYED ATA UR RAHMAN et al., (2018): Transdermal patches were prepared using polymers like Chitosan, Hydroxy propyl methylcellulose and ethyl cellulose of various concentrations by using solvent casting technique. Dibutyl phthalate used as plasticizers and isopropylmyristate as permeation enhancer. An in vitro drug release study was determined using Franz diffusion cell. The formulation studies showed that at the end of 12th hour, the min and max drug release was observed for the formulations F12 and F4 i.e., 80.012% ± 2.012% and 98.365% ± 3.0125%. It was concluded that Glibenclamide can be delivered by transdermal route in a controlled manner. [11]

ASHADASetal.,(2017): Developed a transdermal patch of Indomethacin containing Patchouli oil as permeation enhancer. The transdermal patches were evaluated for various physicochemical properties. In-vitro transdermal study was carried out using Kehary-chein diffusion cell on rat skin. Fourier transforms infrared spectroscopy studies on rat were done to understand the mechanism of permeation enhancing effect of oil. It showed that Patchouli oil can remarkably enhance the permeation of Indomethacin across rat skin, it can be concluded that patchouli oil can effectively enhance the transdermal permeation and can be used as natural permeation enhancer for transdermal drug delivery system. [12]

SAJIDALIetal.,(2014): Studied the effect of permeation enhancers on Bisoprolol fumarate across animal membrane using Franz diffusion cell. Transdermal patch containing eudragit RS100 and hydroxyl propyl methylcellulose are used as polymers. Permeation enhancer's tween 80, propylene glycol and dimethyl sulfoxide are evaluated. For in-vitro skin permeation study rabbit skin was taken and was performed on Franz diffusion cell using phosphate buffer pH 7.4 as receptor fluid. As a result, permeation rate had a greater flux in presence of propylene glycol at 30% compared to tween 80 and dimethyl sulfoxide at same concentrations. Increase in flux was observed with increase in tween 80 concentrations and decreases when a dimethyl sulfoxide and propylene glycol concentration was increased more than 30% TO 40%. [13]

FEDERICABIGUCCI etal., (2014): Formulated the capacity of cellulose film to enhance the transdermal permeation of Propranolol hydrochloride. Oleic acid and polysorbate 80 are used as enhancers. Polymeric films were prepared using hydroxyl propyl methylcellulose and carboxymethyl cellulose. In-vitro experiment was performed to evaluate the permeation enhancing ability of oleic acid and polysorbate 80. As a result, oleic acid and polysorbate 80 had a great permeation enhancer compared to hydroxyl propyl methylcellulose and carboxymethyl

© Journal of Global Trends in Pharmaceutical Sciences

cellulose. Hence Oleic acid and polysorbate 80 increase transdermal permeation of propranolol hydrochloride. [14]

MOHAMEDAEINABARAWIetal.,(2013): Designed to evaluate the short life of Lornoxicam (LX) transdermal patches through in-vitro studies, Lornoxicam patches were prepared using polymers and plasticizers. Span 80 and transcutol are used as enhancers. Ethyl cellulose and eudragit E100 was mixed in different ratios, ethyl cellulose and PVP in different ratios and eudragit RS100 and PVP in different ratios. To these 5 plasticizers namely PEG400, propylene glycol, dibutyl phthalate, isopropyl myristate and oleic acid were added. Firstly, there was good correlation between LX, isopropyl myristate, oleic acid and propylene glycol compared to others oils. Secondly, span 80 improved LX permeation.While combining transcutol showed no increase in drug flux. The primary irritancy index proved the non-irritancy and showed that the films are safe to be applied to the skin. [15]

VIJAYSINGHJATAVet al.,(2012): Studied was carried out to investigate the effect of permeation enhancers on the in-vitro permeation of Nebivolol hydrochloride across rat skin. Film was prepared using eudragit RS100, hydroxyl propyl methylcellulose as polymers and PEG 400 as plasticizers by using solvent evaporating method. Eight different formulations were prepared by using same drug, different polymers and some with dimethyl sulfoxide (DMSO) as permeation enhancers. The in-vitro release studies showed that DMSO showed high penetration rate than without DMSO. The properties of the drug did not change during the studies. [16]

RADHIKAGADEKARetal.,(2012): Studied Curcumin patches formulation (CPF) as a transdermal therapeutic system for wound healing potential. Materials like PVP and ethyl cellulose are used as permeation enhancer for Curcumin patch. An albino rat was selected to carryout in-vivo studies. Transdermal patch of Curcumin follows first order kinetics with diffusion-controlled mechanism. Results showed that the animals treated with vicco turmeric cream and CPF showed faster wound healing when compared with other groups because of the antioxidants effect present in the Curcumin. Curcumin patches showed well organized collagen fibres, increased fibroblast cells and new blood vessels. [17]

GAJANANDARWHEKARet al., (2011): The purpose of this research work was to formulate and evaluate transdermal drug delivery system of Clopidrogelbisulfate using various polymers such as hydroxyl propyl methylcellulose (HPMC), PVP, ethyl cellulose (EC) by solvent evaporation technique to improve bioavailability of drug and reduce toxic effects. The diffusion test was performed by using Franz diffusion cell. As a result, the formulation, F2 (HPMC and PVP) showed maximum release of 90.06% whereas, F5(HPMC and EC) showed minimum release of 78.24% in 24hrs. Therefore, F2 was concluded as an optimized formulation, which shows its higher percentage of drug release. [18]

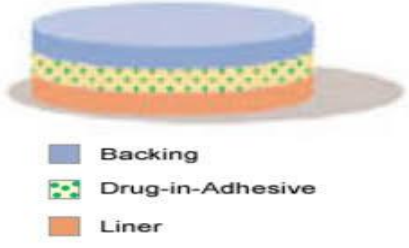
SUCHIKA SHARMA et al.,(2010): Designed transdermal patches of Olanzapine containing vegetable oil as permeation enhancers. PVP and ethyl cellulose polymeric combinations are used. In-vitro permeation studies is carried out using Franz diffusion cell, using rat skin, in-vitro release studies indicated that by increasing the concentrations of the olive oil upto 10% showed better results than other concentrations (1% and 5%). This study confirmed that the permeation of drug through skin is better by using natural oil as permeation enhancers. It was found that the transdermal patch containing polymers like 20% Olanzapine; 30% dibutylthalate and 10% olive oil showed best release and permeation. [19]

3. THEORY:

Types of Transdermal Patches

Four Major Transdermal Systems

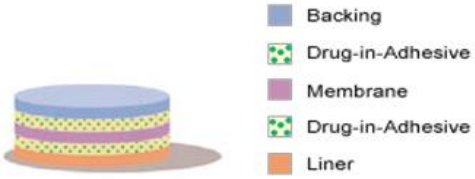
1. Single-layer Drug-in-Adhesive



© Journal of Global Trends in Pharmaceutical Sciences

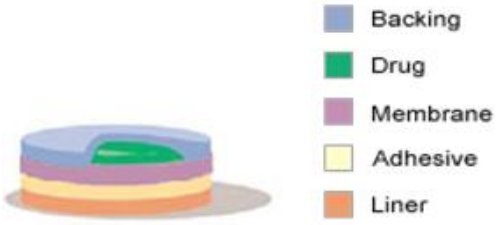
The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and 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.

2. Multi-layer Drug-in-Adhesive



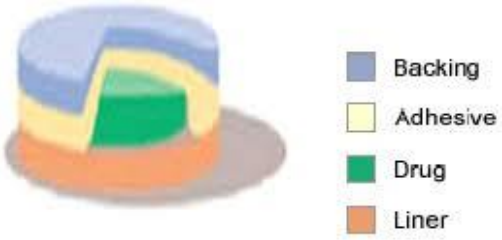
The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive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

3. 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.

4. 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. [20-24]

4. COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM:

- Polymeric matrix / Drug reservoir
  - Drug
  - Permeation enhancers
  - Pressure sensitive adhesive (PSA)
  - Backing laminate
  - Release liner
  - Other excipients like plasticizers and solvents.

i. Polymer Matrix/ Drug Reservoir: Polymers used in the preparation of various components of transdermal drug delivery system should have following requirements:

- ✓ Molecular weight, physical characteristics and chemical functionality of the polymer must allow the diffusion of the drug substances at desirable rate.
- ✓ The polymer must not decompose o storage or during the life of the device.
- ✓ The polymer and its decomposed product should not be toxic.
- ✓ The polymer must be easy to manufacture and fabricate into the desired product.
- ✓ The polymer should be chemically non-reactive or it should be inert drug carrier.
- ✓ The cost of the polymer should not be high.

Polymers used in Transdermal drug delivery systems are classified as-

© Journal of Global Trends in Pharmaceutical Sciences

a) Natural Polymers: E.g. Cellulose derivatives, Zein, Gelatin, Waxes, Natural rubber, Starch, Proteins etc.
b) Synthetic Elastomers: E.g. Polybutadiene, Hydrin rubber, Polysiloxane, Silicon rubber, Nitrile, Acrylonitrile, Butyl rubber etc.
c) Synthetic Polymers: E.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone etc. [25- 27]

ii. Drugs- : Some of ideal properties of drug & some factors to be consider during preparation of Transdermal patches are as follows:

iii. **Permeation Enhancers:**

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 non-polar 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 non-polar pathways by altering three pathways are suggested for drug penetration through the skin: polar, non-polar, and polar/non-polarmulti-laminate pathway for penetrants. Enhancers can increase the drug diffusivity in the Stratum Corneum (SC) bydissolving 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 enhancer and
(2) Physical enhancer.[28]

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 stratum corneum.
- 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 stratum corneum to promote drug diffusion.
- Promoting penetration and establish drug reservoir in the stratum corneum.

Physical enhancers

The iontophoresis and ultrasound (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.

iv. **Pressure sensitive adhesives**

A Pressure-sensitive adhesive 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 transdermal drug delivery system. 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

© Journal of Global Trends in Pharmaceutical Sciences

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, pressure sensitive adhesive should be physic chemically and biologically compatible and should not alter drug release.

v. **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.

vi. **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 releasecoating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminates.

vii. **Other excipients**

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

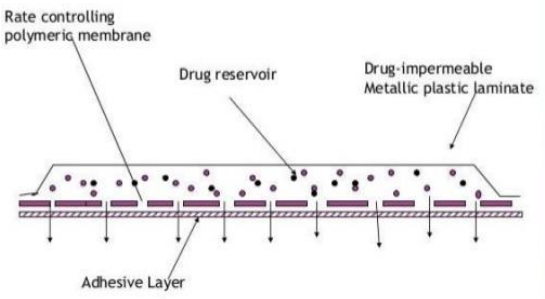
5. APPROACHES TO DEVELOP TRANSDERMAL THERAPEUTIC SYSTEMS

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 system.
2. Adhesive dispersion- type system.
3. Matrix diffusion- controlled system.
4. Micro reservoir type or micro sealed dissolution.

1. Membrane Permeation – Controlled Systems

In this type of system, drug reservoir is encapsulated in a shallow compartment molded 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 homogenously 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

© Journal of Global Trends in Pharmaceutical Sciences

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-

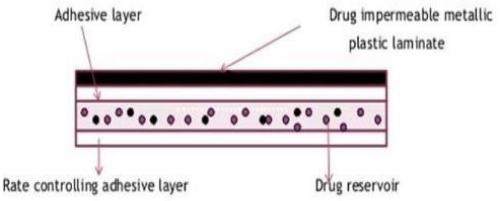
Nitroglycerin – releasing transdermal system (Transderm-Nitro/ Ciba, USA) for once a day medication in angina pectoris.

Scopolamine – releasing transdermal system (Transderm-Scop/ Ciba, USA) FOR 72 hr prophylaxis of motion sickness. Clonidine – releasing transdermal system (Catapres/ BoehringerIngelheim, USA) for 7 days therapy of hypertension. Estradiol – releasing transdermal system (Estraderm/Ciba, USA) for the treatment of menopausal syndrome for 3-4 days.

The membrane permeation – controlled technology has also been used for controlled percutaneous absorption of prostaglandin-derivatives.

2. **Adhesive Dispersion – Type System**

This is a simplified form of the membrane permeation controlled system. As represented in below figure, 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.

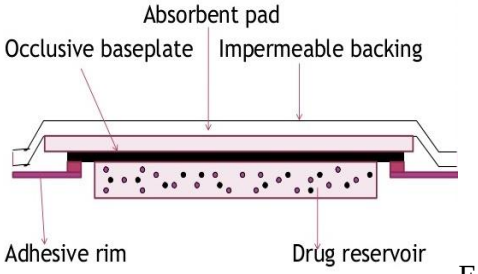


An example of this type of system are- Frandol tape releases Isosorbidedinitrate for once-a-day medication of angina pectoris.

Deponit delivers nitroglycerine for the treatment of angina pectoris.

3. **Matrix Diffusion – Controlled Systems**

In this approach, the drug reservoir is formed by homogenously 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.



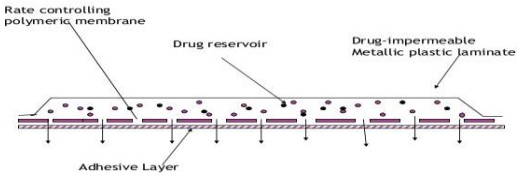
E.g. Nitro-Dur: Delivers nitroglycerin for the treatment of angina pectoris.

4. **Micro Reservoir Type or Micro Sealed Reservoir**

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug

© Journal of Global Trends in Pharmaceutical Sciences

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 homogenously in lipophillic 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 tratment og angina pectoris.[20,21,46,47]

6. PREPARATION OF TRANSDERMAL PATCHES:

Transdermal drug delivery patches can be prepared by various methods

- **Mercury Substrate Method:**

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is kept aside until air bobbles removed completely and then poured in to a glass ring which is placed over the mercury surface in a glass Petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The dried films are to be stored in a desiccator. [29-33]

- **Circular Teflon Mould Method:**

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular Teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on Teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccator. [34, 35]

- **Glass Substrate Method:**

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and driedan umbra petriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After over night, the dried films are taken out and stored in a desiccator.

- **By Using IPM Membranes Method:**

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

- **By Using EVAC Membranes Method:**

In order to prepare the target transdermal therapeutic system, 1% Carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; Carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

- **Aluminum Backed Adhesive Film Method:**

© Journal of Global Trends in Pharmaceutical Sciences

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminum backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesivematerial will be added to the drug solution and dissolved. A custom-made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks. [36-40]

- **Asymmetric TPX Membrane Method:**

A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. [41]

7. EVALUATION TEST OF TRANSDERMAL PATCHES:

- **Drug Excipients Interaction Studies:** The drug and excipients should be compatible to produce a stable product, and it is mandatory to detect any possiblephysical and chemical interaction. Interaction studies are commonly carried out using thermal analysis, FT-IR studies, UV and chromatographic techniques by comparing their physiochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima etc.
- **Drug Content:** A specified area of the patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug content with the suitable method (UV or HPLC technique). Each value represents average of three samples.
- **Weight Uniformity:** The prepared patches are to be dried at 60°C for 4 hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights
- **Thickness of the Patch:** The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.
- **Flatness Test:** Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.
- **Percentage Moisture Uptake:** The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture uptake = [Final Weight-Initial weight/ initial weight] × 100.

- **Moisture Loss:**The prepared films are to be weighed individually and to be kept in a desiccators containing calcium chloride at 40°C. After 24 hrs the films are to be weighed and determine the percentage of moisture loss from the below formula.

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

- **Water Vapor Transmission Rate (WVTR) Studies:** Glass vials of

© Journal of Global Trends in Pharmaceutical Sciences

equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100°C for some time. About 1g anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after storage. The amount of water vapor transmitted was found using following formula.

Water Vapor Transmission Rate = Final Weight –Initial Weight/ Time X Area

It is expressed as the number of grams of moisture gained/hr/cm.sq.

- **Swell ability:** The patches of 3.14 cm^2 was weighed and put in a petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed

The degree of swelling (S) was calculated using the formula,

$S\ (\%) = W_t - W_o/W_o \times 100$

Where, S is percent swelling.

W_t is the weight of patch at time t.

W_o is the weight of patch at time zero.

- **Folding Endurance:** A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be fold at the same place without breaking gave the value of the folding endurance.
- **Polari scope Examination:** This test is performed to examine the drug crystals from patch by Polari scope. A specific surface area of the piece is to be kept on the on object slide and observe the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.
- **Percentage Elongation Break Test:**

The percentage elongation break is to be determined by noting the length justbefore the break point, the percentageelongation can be determined from the below mentioned formula.

Elongation percentage = [L1-L2 / L2] × 100

Where,

L1 is the final length of each strip

L2 is the initial length of each strip

- **Tensile Strength:** Tensile strength of the film determined with universal strength testing machine. The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one is fixed and upper one is movable. The test film of size ($4 \times 1\ c^{m2)}$ is fixed between these cell grips and force is gradually applied till the film broken. The tensile strength of the film is taken directly from the dial reading in kg. Tensile strength is expressed as follows.

Tensile strength =Tensile load at break / Cross section area

- **Probe Tack test:** In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.
- **Skin Irritation Study:** Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50 cm^2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the

© Journal of Global Trends in Pharmaceutical Sciences

representative formulations can be applied over the skin. The patch is to be removed after 24 hrs and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

- ***In-vitro* drug release studies:** The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-ml of the dissolution medium or phosphate buffer (pH 7.4) and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or high-performance liquid chromatography (HPLC). The experiment is to be performed in triplicate and the mean value can be calculated.
- ***In-vitro* skin permeation studies:** An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wister rats weighing 200 to 250 g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before starting the experiment. Diffusion cell filled with diffusion medium and placed on a magnetic stirrer with a small magnetic bead for uniform distribution of the diffusion. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or high-performance liquid chromatography (HPLC).

Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^{-2}) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^{-2}).

- ***In-vivo* studies:** In-vivo evaluations are the depiction of the drug performance. The variables which cannot be considered during in-vitro studies can be fully explored during in-vivo studies. In-vivo evaluation of transdermal drug delivery system can be carried out using. Animal models and Human models.

Table a. Ideal Properties of Drugs

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

© Journal of Global Trends in Pharmaceutical Sciences

6	Oral bioavailability	Low

Table b. **Factors Affecting Transdermal Drug Delivery System**

Physicochemical	Pharmacokinetics	Biological
Solubility	Half-life	Skin toxicity
Crystalinity	Volume of distribution	Site of application
Molecular weight	Total body clearance	Allergic reaction
Polarity	Therapeutic plasma conc.	Skin metabolism
Melting point	Bioavailable factor	—

i. **Animal models:** 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.

ii. **Human models:** The final stage of the development of a transdermal drug delivery system involves collection of pharmacokinetic and pharmcodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

- **Stability Studies:** Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.[41-44]

8. APPLICATIONS OF TRANSDERMAL PATCHES:

- 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 from 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 systems as well as postmenopausal 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).
- Scopolamine patch used to prevent nausea and vomiting caused my motion sickness.

Transdermal Diclofenac patch is used to treat short term pain due to minor strains, sprains and bruises.

- Alpha-hydroxy acids such as glycolic acid and lactic acid are used in cosmetic patch.[20-21]

9. FUTURE OF TRANSDERMAL DRUG DELIVERY SYSTEM:

Future aspects in drug delivery system include liposomes, noisome and micro emulsion. Aim of this development is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal patches has been estimated to increase in

© Journal of Global Trends in Pharmaceutical Sciences

future and has recently experienced annual growth of at rate of 25%. This figure will increase in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are future improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology the utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules.[45]

10. STATASTICS OF TRANSDERMAL PATCHES:

The global market size for the transdermal patches industry has expanded rapidly. The global transdermal skin patches market was worth $22 Billion in 2010, the market expanded to $32 Billion by 2015 at Compound Annual Growth Rate (CARG) of 80%. From 2017 to 2022, the global market size is increased by 4.2%.

- The global market is divided into five segments: North America, Europe, Asia-Pacific, Latin America and Middle East/ Africa.
- North America market was the largest of all having 50% of total market share, followed by European region than Asian-Pacific region is the third largest segment.
- India is classified as a member of the Asia-Pacific sector. It holds the third largest share of the global market; it is the fastest growing segment.
- India is expected to increase annual growth rate of global transdermal drug market from 2017 to 2025 at 12.0%.
- The global transdermal drug patches market is anticipated torise at a considerable rate during the forecast period, between 2012 to 2026.

CONCLUSION:

The transdermal drug delivery review article provides valuable information regarding the transdermal drug delivery system and its evaluation process details. Transdermal drug delivery system is a painless, convenient and potentially effective way to deliver regular dose of many medications. Dermal patches are the most common form of transdermal delivery of drug. If a drug has right mix of physical, chemical and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the transdermal drug delivery system, many new researches are going on in the present day to incorporate newer drugs via the system. All though patches used by over a million patients per year.[48-49]

REFERENCES:

1. Nidhi Sharma. A brief review on transdermal patches. Organic and medicinal chemistry international journal. 2018; 7(2): 1-5.
2. A.Arunchalam, M.Karthikeyan, D.Vinay Kumar, Pratap, M.S.Sethurama, S.Ashutosh Kumar, S.Manidipa. Transdermal drug delivery system: A review. Current pharma research. 2010; 1(1): 70-81.
3. ArtiKesarwari, Ajit Kumar Yadav, Sunil Singh, HemendraGautham, Haribansh N Singh. A review-theoretical aspects of transdermal drug delivery system. Bulletin of pharmaceutical research. 2013; 3(2): 78-89.
4. Sampath Kumar KP, DebjitBhowmik, Chiranjib B, RM Chandira. A Review-Transdermal drug delivery system-A Novel drug delivery system and its

© Journal of Global Trends in Pharmaceutical Sciences

market scope and opportunities. International journal of pharma and bio sciences. 2010; 1(2).
5. Arunchalam, M.Karthikeyan, D.Vinay Kumar, Pratap, M.S.Sethuraman, S.Asuthosh Kumar, S.Manidipa. Transdermal drug delivery system: A Review. Current pharma research. 2010; 1(1): 70-81.
6. Ankush I, Shembale. Useful permeation enhancers for transdermal drug delivery-A Review. IJPRD. 2010; 5: 1-6.
7. Brain w, Barry. Dermatological Formulations Percutaneous absorption. 18: 95-126.
8. Hadgraft J.W, Somers G.F. Review article percutaneous absorption. International journal f pharmaceutics. 2005; 305: 2-12.
9. Gilbert S, Banker, Christopher T, Rhoder. Modern pharmaceutics. Revised and expanded. 40: 236-298.
10. AgrahariSaurabh, Sharma Atul, Kumar Sachin, Sharma Amit, SagarManoj Kumar. Formulation and development of transdermal patches of Piroxicam. Asian journal of pharmaceutical research and development. 2019; 7(3): 119-128.
11. Syed Ata Ur Rahman, Neeraj Sharma. Formulation and evaluation of matrix transdermal patches of Glibenclamide. Journal of drug delivery and therapeutic. 2018; 8(5): 366-371.
12. Asha das, Abdul Baquee Ahmed. Transdermal patch of Indomethacin containing patchouli as natural penetration enhancers. Asian journal of pharmaceutical and clinical research. 2017; 10: 320-325.
13. Sajid Ali, Maryam Shabbir, Muhammad Farooq, Sherjeel Adnan, NabeelShahid. Enhancement effect of permeation enhancers on Bisoprolol fumarate. Research J.pharm and tech. 2014; 7(12): 1391-1395.
14. Federica Bigucci, Angela Abruzzi, Teresa Cerchiara, Maria Caterina Gallucci and Barbara Luppi. Drug dev ind pharma. 2015; 41(60): 1017-1025.
15. Mohamed A EiNabarawi, Dalia S Shaker, Dalia A Attia, Shereen A Hamed. Invitro skin permeation of Lornoxicam monolithic transdermal patches. International journal of pharm sci. 2013; 5(2): 242-248.
16. Vijay Singh Jatav, Jitendra Singh Saggu, Ashish Kumar Sharma, Ravindra Pal Singh. Effect of Dimethyl Sulfoxides as permeation enhancer on transdermal patch of Nebivolol hydrochloride. Pharmacophore journal research. 2012; 3(6): 307-313.
17. Radhika Gadekar, Manoj Kumar Saurabh, Gulab S, AvinashSaurabh.Study of formulation and would healing potential of transdermal patches of Curcumin. Asia journal of pharmaceutical and clinical research. 2012; 3(4): 225-230.
18. Gajanan Darwhekar, Dinesh Kumar Jain, Vinod Kumar Patidar. Formulation and evaluation of transdermal drug delivery system of Clopidrogelbisulphate. Asian journal of pharmacy and life sciences. 2011; 1(3): 269-278.
19. Suchika Sharma, Geeta Aggarwal, SanjuDhawan. Design and evaluation of Olanzapine transdermal patches containing vegetable oils as permeation enhancers. Der pharmaciaLettre. 2009; 2(6): 84-98.
20. Jain NK. Controlled and novel drug delivery. CBS Publishers and distributors. 2002; 107.
21. Chein YW. Novel drug delivery system. Drugs and the pharmaceutical sciences. 1992; 50.
22. Roberts MS. Targeted drug delivery to skin and deeper tissues:

© Journal of Global Trends in Pharmaceutical Sciences

role of physiology, solute structure and diseases. ClinExppharmacol physiol. 1997; 24(11): 874-879.
23. Aulton.M.E. Pharmaceutics- The science of dosage form design. Harcourt publishers. 2002.
24. Ansel.H.C, Loyd.A.V, Popovich.N.G. Pharmaceutical dosage forms and drug delivery system. Lippincott Williams and Willkins publications.
25. Vandana Yadav, SipiaAltafbhai.M, Mamatha, Prashanth V V. Transdermal drug delivery system: A technical write-up. Journal of pharmaceutical and scientific innovation. 2012; 1(1).
26. Nikhil Sharma, Bharat parushar, Shalini Sharma, Uday Mahajan. Blooming pharma industry with transdermal drug delivery system. Indo global journal of pharmaceutical sciences. 2012; 2(3): 262-278.
27. Saurabh Pandey, AshutoshBadola, Ganesh Kumar Bhatt, PreethiKothiya. An Overview of transdermal drug delivery system. International journal of pharmaceutical and chemical sciences.
28. Kusum Devi and Dr.K.L.K.Paranjothi. Development and evaluation of free films and transdermal patches of Ketorolac Trimethamine using polymers and pressure sensitive adhesives the eastern pharmacist. 1998; 485: 97-100.
29. Mohamed Aqil, Yasmin Sultana and Asgar Ali. Matrix type transdermal drug delivery system of Metoprolol tartrate. Acta pharma. 2003; 53: 119-125.
30. Basubramanian V, Iyer and Ravindra C, Vasaveda. Evaluation of lanolin alcohol films and kinetics of Triamcinolone acetonide release. Journal of pharmaceutical sciences. 1979; 68(6): 119-125.
31. Chowdary K.PR and Naidu R.A.S. Preparation and evaluation of cellulose acetate films as rate controlling membranes for transdermal use. Indian drugs. 1991; 29(7): 312-315.
32. Mamatha T, Venkateshwara Rao J, Mukkanti.K. Development of matrix type transdermal patches of Lercanidipine hydrochloride, physicochemical and in-vitro characterization. DARU. 2010; 18(1): 9-16.
33. Sridevi.S,. Pharmacodynamic evaluation of transdermal drug delivery system of Glibenclamide in rats. Indian journal of pharmacology. 2000; 32: 309-312.
34. Sharma teja, Rawal Gaurav. Transdermal therapeutic system-An Overview. International journal of pharmaceutical and biological archives. 2011; 2(6): 1581-1587.
35. Wiechers J. Use of chemical penetration enhancers in transdermal drug delivery possibilities and difficulties. Acta pharm. 1992; 4: 123.
36. Manvi F.V, Dandagi P.M, Godad A.P, Mastiholimat V.S and Jagadesh T. Formulation of transdermal drug delivery system of Ketotifen fumarate. IJPS. 2003; 65(3): 239-243.
37. Kanikkannan N, Jayaswal S.B and Singh J. Transdermal delivery of Indomethacin: Release profile of drug from polymeric patches. Indian drugs. 30(9): 441-445.
38. Sankar V, Velrajan G, Palaniappan R and Rajashekar S. Design and evaluation of Nifedipine transdermal patches. IJPS. 2003; 65(5): 510-515.
39. Ryan F, Donnelly, Paul A, Mc Carron. Design and physicochemical characterization of a bio-adhesive patch for dose-controlled topical delivery of Imiquimod. International journal of pharmaceutics. 2006; 307: 318-325.

© Journal of Global Trends in Pharmaceutical Sciences

40. Kavitha K and MangeshRajendra. Design and evaluation of transdermal films of Lornoxicam. IJPBS. 2011; 2(2): 54-62.
41. Shalu Rani, Kamal Saroha, NavneetSyan, Pooja Mathur. Transdermal patches-A successful tool in transdermal drug delivery system: An Overview. Der PharmaciaSinisa. 2011; 2(5): 17-29.
42. Koteshwar K.B, Udupa N, Vasantha Kumar. Design and evaluation of Captopril transdermal preparations. Indian drugs. 15(29): 680-685.
43. Diveyesh Patel, Nirav Patel, MeghalParmar. Transdermal drug delivery system-Review. International journal of Biopharmaceutical and toxicological research. 2011; 1(1): 61-80.
44. P.Mayorga, F.Puisieux, Covarraze G. Formulation study of transdermal delivery system Primaquine. International journal of pharmaceutics. 2005; 291: 11-19.
45. Dhiman Sonia. Transdermal patches- A Recent approach to new drug delivery. International journal of pharmacy and pharm. 3(5).
46. Jain.N.K, Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi. 1997.
47. Suresh P.Vyas, RoopK.Khar, Controlled drug delivery system, second edition, VallabhPrakashan, 2012.
48. http://askwonder.com/research/what-s-market-transdermal-patches-india-lh3po2fqp.
49. http://reports.valuates.com/sreport/QYRE-Auto-18M196/Global_Transdermal_Drug_Patches_market

© Journal of Global Trends in Pharmaceutical Sciences