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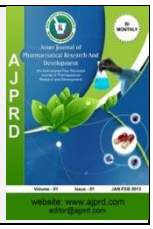

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Review Article

Role of Transdermal Drug Delivery System

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A B S T R A C T

For several decades, many drug types, including tablets, capsules, pills, creams, ointments, liquids, injectables, have been used for the treatment of disease. These dosage forms must be taken multiple times a day to maintain the concentration of the medication. Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms Built to deliver a therapeutically efficient quantity of medicine through the skin of a patient. By increasing patient compliance and preventing first pass metabolism, transdermal delivery offers a leading edge over injectables and oral routes. Transdermal drug delivery provides the patient with controlled release of the drug, allowing for a stable blood level profile, leading to decreased systemic side effects and often increased effectiveness over other types of dosage. The primary objective of the transdermal drug delivery system is to deliver drugs with minimal inter-and intrapatient variations into systemic circulation via the skin at a fixed rate.To address the difficulties of drug distribution, primarily oral routes, the transdermal drug delivery system was implemented. Modifications of the materials used were mainly limited to refinements. The present review paper discusses the overall research on the transdermal drug delivery system (TDDS) leading to the current drug delivery system (NDDS). We used convectional dosage method earlier, but we are now using a novel system of drug delivery. The transdermal patch is one of the biggest advances in the delivery of new medicines. The value of the transdermal drug delivery system is that it is a painless drug administration procedure. There are variables that influence the bioavailability of transdermal products. Such as physiochemical and biological factors. Iontophoresis, phonophoresis, electroporation and micro needles, etc, are many new techniques that have drawn interest due to technological development.

Keywords: Types of Transdermal Patch, Drug release, Mechanism of Transdermal Patch

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INTRODUCTION

Transdermal patches uses as a special membrane to control the rate at which liquid drugs membrane to control the rate at which the liquid drug contained in the reservoir within the patches can pass through the skin and into the blood stream. Nowadays when drug administered in the conventional dosage form usually produce high range in the fluctuation in the plasma drug concentration which leads to undesirable toxicity and poor therapeutic. Currently transdermal delivery is one of the most useful method for drug application. It reduce the load that oral route of administration place on the digestive system and liver.

Over the past three decades developing controlled drug delivery has become increasing in the pharmaceutical industry. From the skin is readily accessible from surface for transdermal drug delivery system. The pharmacological response both the desire therapeutics effects and the undesired adverse effects of a drug on the concentration of the transdermal drug delivery of the drug at the site of

action. On highly successful alternative delivery method is transdermal drug delivery system, the transdermal drug delivery of a drug into the body through the transdermal layer of skin, it is necessary to understand about the skin.

Transdermal drug delivery is the novel drug delivery from new ideas on controlling the pharmacokinetic, pharmacodynamics non specific toxicity immunogenicity and efficacy of drug generated after drug delivery are the adhesive drug containing deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation delivery of the drug. Transdermal drug delivery within full benefits has an optimal concentration range and concentrations above or below the range may be harmful or do not show any drug therapeutic effects.

Transdermal drug delivery refers to the approaches formulation and system for transporting a pharmaceutical compound in the body as need safely to achieve its desire therapeutics effects. [1,2,3,4,5]

Advantage

- Avoids first pass metabolism and enzymatic degradation by GIT.
- Self -administration is possible in transdermal drug delivery system.
- Topical patches have sustained release of drug in the blood stream.
- Patches are painless as compared other routes of administration.
- Transdermal patches have less side effects over oral routes.
- Incompatibilities of GIT is avoided.
- Dose and therapeutic effects are predictable.
- Prolonged therapeutic.

Disadvantage

- TDDS is not suitable for high drug dosages.
- Large molecular size of drugs having difficulty in absorption.
- Skin irritation and hyper sensitivity of reaction may occurs.
- Drug with long half- life cannot be formulated.
- High drug levels in blood cannot be achieved by transdermal drug delivery system.
- Transdermal drug delivery system cannot deliver ionic drugs.
- Barrier of the physiological different in the function.[6,7]

Physiology:

Layer of Skin and drug penetration:

It is important to understand the structural and biochemical characteristics of human skin and those characteristics that contribute to the barrier function and the rate of drug access through the skin into the body to understand the definition of the transdermal drug delivery system.

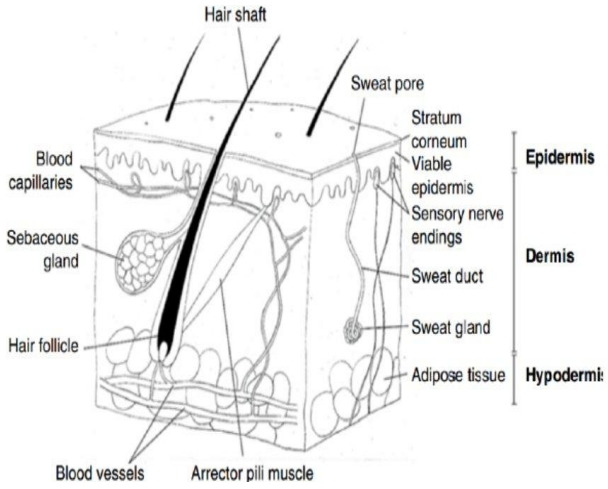

Figure 1: Structure of skin

Epidermis:

Most superficial layer and is composed of stratified keratinized squamous epithelial cell. There are no blood vessels or nerve ending in the epidermis. In this germinative layer and under incremental changes, epidermal cells originate as they migrate towards the surface of the skin. The surface cells are smooth, small, non-nucleated, dead or squamous cells in which the fibrous protein keratin has replaced the cytoplasm. The barrier function of the skin is responsible for the stratum corneum. It also serves as the main obstacle to percutaneous absorption.

Dermis:

The dermis is an efficient envelope stretch that helps to keep the body together. The dermis is a 3 to 5 mm thick layer that is made up of a connective tissue matrix that includes lymph vessels, nerves, and blood vessels. It supplies nutrients and oxygen to the skin to eliminate contaminants and waste materials. While capillaries exceed 0.2 mm of the skin surface, for most molecules entering the skin barrier, they provide skin condition.

Hypodermis:

The hypodermis layer is composed of loose connective tissue and its thickness varies according to the body surface. The region which is attached to the underlying organ such as bone and muscles by subcutaneous layer called hypodermis. The hypodermis and subcutaneous fat tissue supports the dermis and epidermis. The hypodermis serves as a fat storage area. This layer provides the nutritional supports and mechanical protection by regulating the temperature.

Drug penetration

a. The appendgeal route:

Skin appendges provides a continuous channel directly across the stratum corneum barrier. A variety of factors inhibit their effect on drug penetration.. The surface area occupied by a number of factors. The surface area occupied by hair follicles and sweat glands are small therefore limiting the area available for direct contract of the applied drug formulation.

b. Transcellular route:

Drug entering via the transcellular routes pass through corneocytes. Corneocytes, containing highly hydrates keratin, provides an aqueous environment for which hydrophilic drug can pass.

c. Intracellular route:

The intracellular pathways involves drug diffusing through the continuous lipid matrix. This route is significant obstacle for two reason,

(i) Recalling the bricks and mortar model of stratum corneum

(ii) The intracellular domain is a region of alternating structural bilayers. [8,9]

Basic Components

a. Drug:

The drug should be chosen with great care, some of the desirable properties of a drug and factors to be considered for transdermal delivery

Physicochemical Properties:

- The molecular weight of the drug should be less than approximately 1000 Daltons.
- For both- lipophilic and hydrophilic stages, the drug should have affinity.
- Extreme partitioning features are not conducive to the efficient distribution through the skin of medicines.
- A low melting point should be given for the drug.

Biological Properties:

- The medication should be potent at a daily dosage of a few mg/day.
- The drug's half -life (t1/2) should be short.
- Cutaneous discomfort or allergic reaction must not be caused by the medication.
- Reasonable candidates for transdermal delivery are drugs that degrade in the GI tract or are inactivated by hepatic first-pass effects.
- Under the near zero-order release profile of Transdermal delivery, tolerance of the drug must not develop.
- For transdermal delivery, medications that have to be given for a long period of time or that cause adverse effects on non-target tissues may also be formulated.

A. Polymer matrix:

Polymer controls the drug's release from the system. It is necessary to satisfy the following requirements for a polymer to it can be used in the transdermal process.

- Molecular weight, temperature of glass transition and polymer chemical functionality should be such that special drug diffuses and get released from it properly.
- The polymer should be stable, drug-neutral, simple to produce and properly and cheaply produced to the desired level.
- The polymer and its components for degradation must be non-toxic.
- When large amounts of active agents are added, the mechanical properties of the polymer do not deteriorate excessively.

Table no 1: Polymers matrix

Natural Polymers	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives, zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch.	Polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, Nitrile, Acrylonitrile, Butylrubber, Styrenebutadiene, Neoprene etc.	Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyvinylpyrroli done, Polymethyl methacrylate, Epoxy, Polyurea, etc.

B. Permeation enhancer

Permeation improvements are also known as promoters of accelerants (or) sorption, compounds that promote permeability. The flux (J) of drug molecules from the stratum corneum in order to achieve higher therapeutic levels. The flux of drugs through the skin can be defined as:

$$J = D \, Xdc/dx$$

Where,

D = diffusion coefficient
C = concentration of diffusing special
X = special coordinate

Mechanism of permeation enhancer:

- By interrupting the arrangement of the lipids of the stratum corneum
- By dealing with intercellular proteins
- Co-enhancer (or) solvent in the stratum corneum by optimizing drug partitioning.
- Dissolution of medication in the vehicle
- Drug diffusion from vehicle to skin surface

Other excipients

i. **Adhesives:** Pressure-sensitive adhesive is a substance that allows transdermal devices to bind to the skin over long periods of time. These adhesives may be mounted peripherally at the back of the device Known as the Adhesive Peripheral Device and on the face of a device known as the face adhesive system e.g. polyisobutylenes, acrylics and silicones.

ii. Backing membranes:

These are versatile and have a strong bond with the drug reservoir and accept impermeable printing as well. Is substance that, during use on the skin, protects the product e.g. Metallic plastic laminate, flexable adhesive foam pad with occlusive base plate, plastic backing with absorbent pad and aluminium foil.[10,11]

Mechanism of action of Transdermal Patches

Different approaches include the application of the transdermal patch and the movement of the active drug constituent through the skin from the patch to the circulatory system.

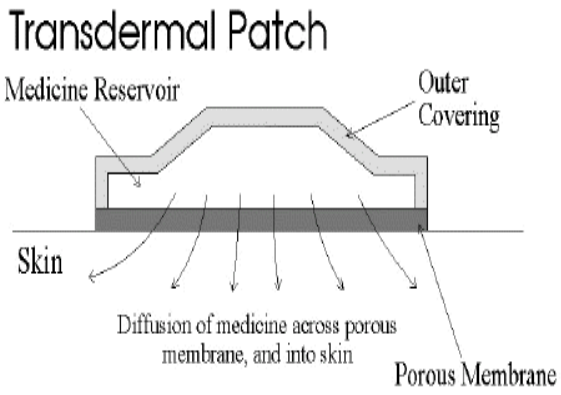

Figure 2: Transdermal patch

a. The Lontophoresis:

Iontophoresis, passes through the electrode put in contact with the formulation, transfers a few milliamperes of current to a few square centimeters of tissue, allowing drug delivery through the barrier. Pilocarpine delivery is mainly used as part of the cystic fibrosis diagnostic test to cause sweating. Iontophoretic lidocaine delivery tends to be a promising approach to quick anesthesia onset.

b. Electroporations:

A method of applying small, high-voltage electrical pulses to the skin is electroporation. The permeability of the skin to drug diffusion after electroporation is increased by orders of magnitude. The electrical pulses in the stratum corneum, through which drug transmission occurs, are thought to form transient aqueous pores. It is healthy and the electrical pulses can be painlessly administered to limit the electrical field inside the nerve-free stratum corneum.

c. Ultrasound Application

It has been shown that the use of ultrasound, especially low-frequency ultrasound, improves the transdermal transport of different drugs, including macromolecules. It's recognized as sonophoresis as well. For topical delivery of EMLA cream, reported on the use of low frequency sonophoresis.

d. Use of microscopic

To allow transdermal drug delivery, transdermal patches with microscopic projections called microneedles were used. Needles that vary in length from around 10-100 μm are arranged in arrays. The arrays make microscopic punctures when pressed into the skin, which

They are large enough to deliver macromolecules, but small enough that the penetration or discomfort is not felt by the patient. To help in rapid absorption, the medication is surface-coated on the microneedles. They are used in the manufacture of tetanus and influenza dermal vaccines.[12]

Types of transdermal patches

Single layer drug in adhesive:

In this type the drug contains by the adhesive layer. The adhesive layer is surrounded by a temporary liner and a backing membrane. The property of adhesive layer is not only adhere the various layer together although this type of layer is responsible for the releasing the drug to the skin.

Multi-layer drug in adhesive:

The multi-layer drug in adhesive is similar to the single layer but it contains an immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. In this the drug release by the adhesive layer. A temporary liner-layer and a permanent backing are also required for this patch.

Vapour patch:

The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Differents other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

Reservoir system:

In this system the two layers; an impervious backing layer and a rate controlling membrane are responsible for embedded drug reservoir in between them. The drug is only released by the rate-control membrane, which can be micro-

porous or non-porous. The drug may be in the form of a solution, suspension, gel or distributed in a solid polymer matrix in the drug reservoir compartment. The hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

Microreservior system:

Microreservior system is the combination of the reservoir and matrix dispersion system. By suspending the drug in an aqueous solution of water soluble polymer the drug reservoir is formed and then dispersing the solution homogeneously in a lipophilic polymer to form thousand of unreachable, microscopic spheres of drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.

Matrix system:

Drug-in-adhesive system

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs.

a.Matrix dispersion system

This polymer disk-containing drug is bound to an occlusive base plate in a compartment made of an impermeable drug backing sheet. It is stretched alongside the circumference to shape a strip of adhesive film, applying the adhesive on the face of the drug reservoir.[8,13]

EVALUATION PARAMETERS:

1. **Interaction studies:** The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.,
2. **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.
3. **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.
4. **Folding endurance:** A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.
5. **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.
6. **Percentage Moisture content:** The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula. Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.
7. **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.
8. **Moisture Loss:** The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40oC. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss from the below formula.
9. **Water vapour permeability (WVP) evaluation:** Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula WVP=W/A Where, WVP is expressed in gm/m2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m2 .
10. **Swellability:** 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 45 . The degree of swelling (S) was calculated using the formula, S (%) = Wt – Wo /Wo × 100 Where S is percent swelling Wt is

the weight of patch at time t and Wo is the weight of patch at time zero.

11. **Uniformity of dosage unit test:** An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

12. **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.

13. **Rolling ball tack test:** This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

14. **Quick Stick (peel-tack) test:** In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

15. **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 × 1 cm2) is fixed between these cell grips and force is gradually applied till the film broke31 . 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.

16. **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 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.

17. **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.

Application:

To avoid problems associated with first pass metabolism or Presystemic metabolism and to provide local and systemic action, the transdermal drug delivery system is essential. Transdermal gel is an effective application for preventing skin irritation.

Ethosome is a new approach used in the transdermal drug d elivery system to increase the rate of drug absorption and sk in penetration to give maximum bioavailability. It is necessary for the transdermal drug delivery system to Nanoemulsion, Liposomal Approach, Micro Emulsion For skin infection prevention. Transdermal delivery systems for drugs are a significant application for the innovative solution of transdermal patches and transferosomes to avoid skin injury and preserve the protection of the skin.[14]

CONCLUSION:

A painless, easy, and potentially efficient way to administer daily doses of several medications is the delivery of transdermal drugs. The above suggests that TDDS has tremendous potential to be able to use promising deliverable drugs for both hydrophobic and hydrophilic active substances. Greater knowledge of the various mechanisms of biological interactions and polymers is needed to optimize this drug delivery system. 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. One day, the transdermal drug delivery system may be one of the strongest modern delivery mechanisms for drugs. The delivery mechanism of transdermal drugs is useful for the drug's topical and local action. The appropriate candidate for TDDS is the drugs exhibiting hepatic first pass effect and dysfunctional in GI conditions. Transdermal drug delivery system may be ideal for many injected as well as orally given drugs, but many drugs cannot penetrate the skin membrane effectively because of low permeability of skin barrier.

REFERENCE:

1. Mali D A, Bathe R, Patil M. An updated review on transdermal drug delivery system. Int. J Adv. Sci. Res. 2015; 1(6):244-54.

2. Prabhakar D, Sreekanth J, Jayaveera K N. Transdermal drug delivery patches: A review. J Drug Deliv. Thera. 2013; 3(4): 213-21.
3. Tanwar H, Sachdeva R. Transdermal drug delivery system: A review. Int. J Pharm Sci. Res. 2016; 7(6):2274-90.
4. Sharma N, Agrawal G, Rana A C, Bhat Z A, Kumar D. A review: Transdermal drug delivery system: A tool for novel drug delivery system. Int. J Drug Dev. Res. 2011; 3(3):70-84.
5. Jadhav M A, Vidhate M S, More M A, Bhujbal M N, Kshirsagar D S. Review on transdermal drug delivery system: Novel approaches. Sch Acad J pharm. 2018; 7(9): 407-13.
6. Karbhari V N, Tanuja W. Transdermal drug delivery system: A review. World J Pharm Res. 2016; 5(9): 1733-42.
7. Sharma N. A brief review on transdermal patches. Org. Medi Chem Int. J. 2018; 7(2):01-5.
8. Rana R, Saroha K, Handa U, Kumar A, Nanda S. Transdermal patches as a tool for permeation of drug through skin. J. Chem. Pharm. Res. 2016; 8(5): 471-81.
9. Gandhi K, Dahiya A, Monika, Kalra T, Singh K. Transdermal drug delivery: A review. Int. J Res Pharm. Sci. 2012; 3(3): 379-88.
10. Prabhakar D, Sreekanth J, Jayaveera K N. Transdermal drug delivery patches: A review. J Drug. Deliv. Thera. 2013; 3(4): 213-21.
11. Sirisha V, Sailaja A k. Review on recent approaches in transdermal drug delivery system. J. Nursing Patient Health Care. 2019; 1(1):01-12.
12. Rajini, Rohit K, Nitan B, Neeraj B. Review on transdermal patches. World J. Pharm. Pharma Sci.2016; 5(5): 492-10.
13. Alam I, Alam N, Singh V, Alam S, Ali S, Anwer T *et al*. Type, prepration and evaluation of transdermal patches: A review. World J. Pharm. Pharma Sci.2013; 2(4): 2199-33.
14. Sagar K. Savale. A review: Transdermal drug delivery system. Asian J. Res. Bio. Pharm Sci. 2015; 3(4): 150 - 61.