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A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM – TRANSDERMAL PATCH

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ABSTRACT

Transdermal drug delivery system is an essential part of novel drug distribution system. The topically administered medications in the form of patches which when applied to the skin deliver the drug. For operative TDDS the drug are easily able to penetrate the skin and easily reach the target site. TDDS avoids the first pass metabolism, less frequency of administration, reduction gastrointestinal side effects. Adverse effects are minimized due to steady and optimum blood concentration. It has greater bioavailability and efficacy of drug. A transdermal patch is amedicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of body. An advantage of a transdermal drug delivery route over other types of medication delivery 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. Polymer should be chemically non-reactive, should not decompose on storage, should be non-toxic, cost should not be high. E.g. cellulose derivatives, zein, gelatin etc. Backing films play a vital role in the transdermal patch and the role of the film is to protect the active layer. Transdermal patches can be evaluated by interaction studies thickness, weight uniformity, drug content, in vitro study, moisture content, swelling index basic component of TDDS.

KEYWORDS: Human skin, Trandermal routes and permeation, Physicochemical and biological factors, Advance development.

INTRODUCTION

In recent years, there has been a resurgence of interest in creating innovative drug delivery systems for existing pharmaceutical compounds. Designing a new delivery system for established drugs not only enhances their performance regarding efficacy and safety but also significantly boosts patient compliance and overall therapeutic benefits. Transdermal Drug Delivery Systems (TDDS) are defined as discrete, self-contained dosage forms, commonly referred to as "patches." When applied to unbroken skin, these patches deliver medication through the skin at a controlled rate into the systemic circulation. TDDS are specifically designed to provide a therapeutically effective dose of medication through the skin of the patient. The primary goal of a transdermal drug delivery system is to achieve the controlled release of medications into systemic circulation at a set rate, with minimal variation between individuals. Presently, transdermal delivery stands out as one of the most promising methods for drug administration. It alleviates the burden that traditional oral routes impose on the digestive system and liver, enhances patient adherence, and minimizes the adverse effects associated with temporary overdoses. Moreover, transdermal drugs that can be applied weekly offer added convenience. This method improves bioavailability, maintains more stable plasma levels, extends the duration of action, and leads to a reduction in dosing frequency while decreasing side effects and enhancing therapeutic efficacy, as it sustains plasma levels throughout the dosing interval, unlike conventional oral forms that often experience a decline. Transdermal delivery not only facilitates the controlled and consistent administration of medications but also provides a continuous supply of drugs with short biological half-lives, effectively eliminating fluctuations in systemic circulation which frequently leads to unwanted side effects. Several key benefits of transdermal drug delivery include the reduction of hepatic first-pass metabolism, an increase in therapeutic efficacy, and the maintenance of consistent plasma drug levels. The development of transdermal drug delivery systems (TDDS) is a multidisciplinary effort that involves essential feasibility studies, beginning with drug molecule selection and extending to the demonstration of adequate drug flux in both ex vivo and in vivo models. This process is followed by the creation of a drug delivery system that satisfies all stringent criteria specific to the drug (such as physicochemical and stability factors), the patient (including comfort and cosmetic appeal), the manufacturer (considering scalability and manufacturability), and importantly, economic viability.

The first transdermal system, Transdermal SCOP, received FDA approval in 1979 for preventing nausea and vomiting related to travel. Most transdermal patches are engineered to release the active ingredient at a zero-order rate over several hours to days after application to the skin. This feature is particularly beneficial for prophylactic treatment of chronic conditions. Evidence of percutaneous drug absorption can be determined through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in urine, and the clinical response of the patient to the administered drug therapy.[1][2]

Transdermal route and drug delivery prospects Skin

The Largest Organ

The skin is the most extensive organ in the human body, encompassing a surface area of about 2 square meters and receiving approximately one-third of the body's blood circulation. It acts as a barrier against the transdermal absorption of various chemical and biological substances. With a thickness of just a few millimeters (averaging 2.97 ± 0.28 mm), the skin is one of the most accessible organs and serves several important functions, including.

- Distinguishing the underlying circulation system from the external environment.
- Acting as a defense against physical, chemical, and microbiological threats.
- Functioning as a thermostat to regulate body temperature.
- Contributing to blood pressure regulation.
- Protecting against UV radiation.
- Playing a significant role in the drug delivery process, particularly regarding the permeation and absorption of medications through the dermis.
- The skin's anatomical structure and ultrastructure significantly influence its diffusional resistance.

Advantages of Transdermal Drug Delivery Systems

1) Transdermal systems provide a consistent release of medication over time, minimizing the adverse effects and therapeutic failures commonly seen with intermittent dosing.

2) This method can enhance the therapeutic effectiveness of various drugs by circumventing issues like gastrointestinal irritation, low absorption, degradation from the hepatic "first-pass" effect, formation of side-effect-inducing metabolites, and the need for frequent dosing due to short half-lives.

3) As a result of these advantages, it may be possible to achieve equivalent therapeutic effects with lower daily drug doses compared to oral administration.

4) A simplified medication regimen improves patient compliance and reduces variability in effects among different patients and within the same patient.

5) In some cases, maintaining drug concentration levels throughout treatment isn't desirable; applying and removing a transdermal patch can create an optimal pharmacological response.[5]

Disadvantages of Transdermal Drug Delivery Systems

1) The drug must possess suitable physicochemical properties to penetrate the stratum corneum effectively; doses exceeding 10 mg per day may complicate transdermal delivery.

2) Only relatively potent medications are viable candidates for transdermal delivery systems due to the skin's natural impermeability.

3) Some individuals may experience contact dermatitis at the application site, necessitating the discontinuation of the system.

4) The clinical rationale must be thoroughly evaluated before deciding to develop a transdermal product.

5) The skin's barrier function can vary across different areas of the same individual, among different individuals, and with age.[5]

Applications of Transdermal Patches

1) The most popular transdermal patch in the United States is the nicotine patch, which provides controlled doses of nicotine to assist with quitting tobacco.

2) Fentanyl (branded as Duragesic) and Buprenorphine (branded as BuTrans) are opioid medications available in patch form for round the clock severe pain relief.

3) Estrogen patches are prescribed for menopausal symptoms and post-menopausal osteoporosis, along with contraceptive patches like Ortho Evra or Evra.

4) Nitroglycerin patches are sometimes used for angina treatment as an alternative to sublingual tablets.

5) Clonidine, an antihypertensive drug, is also available in transdermal patch form.

6) The MAOI selegiline became the first transdermal delivery system for an antidepressant.

7) There are also transdermal agents available for Attention Deficit Hyperactivity Disorder (ADHD).[6-8]

Basic Principle of Transdermal Permeation

Transdermal permeation relies on passive diffusion. The skin, being the most extensive and accessible organ, separates just a fraction of a millimeter of tissue from the underlying

capillary network. The process of releasing a therapeutic agent from the skin-applied formulation into systemic circulation involves several steps.

1) The drug diffuses from the formulation to the rate-controlling membrane.

2) It dissolves within the formulation and then is released.

3) The drug is absorbed by the stratum corneum and penetrates through the viable epidermis.

4) It is taken up by the capillary network in the dermal papillary layer.

7) Finally, it exerts its effects on the target organ.[11]

Types of Transdermal Patches

1. Single-layer Drug-in-Adhesive

In this system, the adhesive layer contains the drug itself. The adhesive not only binds the various layers together and secures the entire patch to the skin, but it also controls the release of the drug. This layer is protected by a temporary liner and a backing.

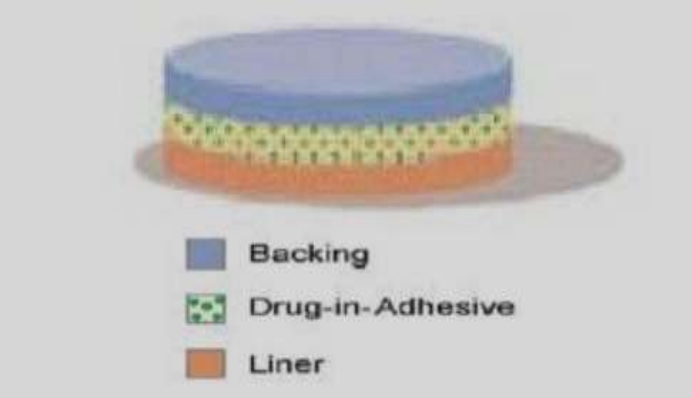

Fig 1: Single-layer Drug-in-Adhesive.

2. Multi-layer Drug-in-Adhesive

The multi-layer drug-in-adhesive patch resembles the single-layer version, as both types utilize the adhesive layers for drug release. However, the multi-layer patch incorporates an additional layer of drug-in-adhesive, which is typically separated by a membrane, although this is not always the case. Like the single-layer patch, it also includes a temporary liner and a permanent backing.

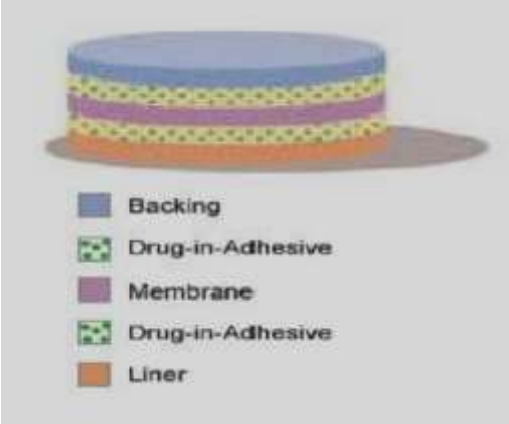

Fig 2: Multi-layer Drug-in-Adhesive.

3. Reservoir

The reservoir transdermal system differs from both the Single-layer and Multi-layer Drug-in-Adhesive systems by utilizing a distinct drug layer. This layer consists of a liquid compartment that holds a drug solution or suspension, separated from the adhesive layer. The patch is reinforced with a backing layer, and in this design, the drug release follows a zero-order kinetics.

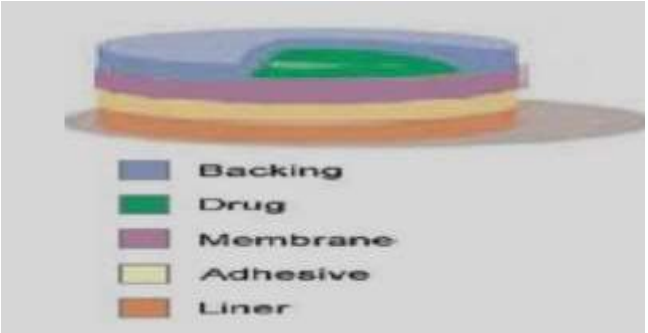

Fig 3: Reservoir.

4. Matrix

The Matrix system features a drug layer made of a semi-solid matrix that contains a drug solution or suspension. The adhesive layer envelops the drug layer, partially covering it.

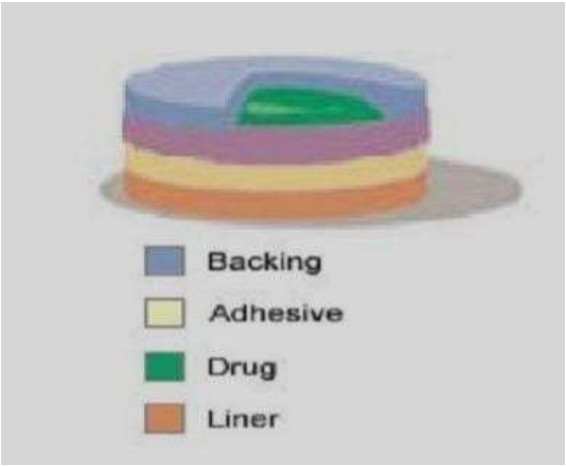

Fig 4: Matrix.

5. Vapor Patch

In vapor patches, the adhesive layer serves a dual purpose: it secures the various layers and facilitates the release of vapors. These patches are relatively new to the market and can emit essential oils for up to six hours. They are primarily used for decongestion, while other varieties, such as controlled vapor patches, aim to enhance sleep quality. Additionally, vapor patches designed to help reduce monthly cigarette consumption are also available.[11]

Factors affecting transdermal permeation

A) Biological factor

1) Skin conditions

The intact skin itself acts as barrier but many agents like acids, alkali cross the barrier cells and penetrates through the skin, many solvents open the complex dense structure of horny layer Solvents like methanol, chloroform remove lipid fraction, forming artificial shunts through which drug molecules can pass easily.

2) Skin age

It is seen that the skin of adults and young ones are more permeable than the older ones but there is no dramatic difference .Children shows toxic effects because of the greater surface area per unit body weight .thus potent steroids, boric acid, hexachlorophene have produced severe side effects.

3) Blood Supply: Changes in peripheral circulation can affect transdermal absorption.

4) Regional skin site: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

5) Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

6) Species differences: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

B] Physicochemical factors

1) Skin hydration: In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

2) Temperature and pH: The permeation of drug increases ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

3) Diffusion coefficient: Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

4) Drug concentration: The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

5) Partition coefficient: The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the ipid portion of skin. Also, drugs with low K will not be permeated.

6) Molecular size and shape: Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

C] Environmental factors

1) Sunlight: Due to Sunlight the walls of blood vessels become thinner leading to bruising with only minor trauma in sun-exposed areas. Also pigmentation: The most noticeable sun-induced pigment change is a freckle or solar lentigo.

2) Cold Season: Often result in itchy, dry skin. Skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

3) Air Pollution: Dust can clog pores and increase bacteria on the face and surface of skin, both of which lead to acne or spots. This affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with skin's natural protection system, breaking downthenaturalskin'soilsthatnormally trap moisture in skin and keep it supple.[14][20]

MATERIAL AND METHOD

1. Polymer: The polymer backbone in transdermal drug delivery systems (TDDS) regulates drug release. It should be chemically inert, stable during storage, non-toxic, and cost-effective. Examples include cellulose derivatives, zein, gelatin, shellac, waxes, gums, polybutadiene, hydrin rubber, polyisobutylene, silicone rubber, nitrile, acrylonitrile, neoprene, polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, and polymethylmethacrylate.

2. Backing Films: Backing films are crucial in transdermal patches and their usage. They protect the active layer, maintain system stability, and influence skin permeation and tolerance based on their occlusion or breathability. To prevent incompatibility, the release liner needs to be fully inert to its components. It should also be flexible, comfortable, compatible with the adhesive, and have excellent printability. Common materials for release liners include polypropylene, polyesters, PVC, and nylon**.**

3. Release Liners: Release liners are coated with an anti-adherent layer. Their purpose is to protect the system while packaged and to be removed right before applying the TDDS to the skin. Release liners are essential for the patch's stability, safety, and efficacy. Choosing the right release liner is crucial; an unsuitable one can hinder the patch's release and interact negatively with its active or other ingredients, potentially reducing shelf life. Typical release liner materials include paper-based, plastic film-based, and composite films, with silicones and fluoropolymers being the two primary types of coatings.

4. Pressure Sensitive Adhesives: Pressure-sensitive adhesives (PSAs) are vital for both types of TDDS, acting as the medium that carries active ingredients, additives, and permeation enhancers, while also ensuring the patch adheres to the skin. PSAs are categorized into three groups: rubber-based, acrylic (available as solutions, emulsion polymers, or hot melts), and silicone PSAs. Each category has several sub-categories that provide necessary flexibility to the patch.

5. Penetration Enhancers: Penetration enhancers are distinct chemical compounds that share common characteristics. They significantly boost the permeation rate of active ingredients through the skin, improving the system's effectiveness, as many active substances cannot penetrate the skin adequately through a relatively small area. Often, a combination of these agents is required to achieve the desired enhancement effect. These agents work by modifying the skin barrier, facilitating the penetration of the target substance.[14]

Evaluation of transdermal patches

The transdermal patches can be characterized in terms of following parameters.

A] Physicochemical evaluation B] In vitro evaluation C] In vivo evaluation

A] Physicochemical evaluation: Transdermal patches can be physicochemically evaluated in terms of these parameters.

1) Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.[15]

2) 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]

3) 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.[17]

4) 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.[18]

5) 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.***

B] 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 the receptor compartment. The drug content is analyzed using suitable method, maintenance of sink condition is essential.[19]

C] 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.[20]

Advance Development in TDDS

Drug delivery through adhesive technology has emerged as the preferred method for passive transdermal systems, with research concentrated on two main areas: adhesives and excipients. The focus of adhesive research is on tailoring the adhesive properties to enhance skin adhesion during use, boost the stability and solubility of the drug, minimize lag time, and accelerate delivery rates. Since there is no universal adhesive that suits all drugs and formulations, customizing adhesive chemistry enables transdermal formulators to optimize the effectiveness of transdermal patches. Over the past 10 to 15 years, researchers have extensively explored transdermal technologies that leverage mechanical energy to enhance drug flux through the skin. This is achieved by either modifying the skin barrier, particularly the stratum corneum, or by increasing the energy of drug molecules. These "active" transdermal technologies encompass techniques such as iontophoresis, which employs low-voltage electrical currents to facilitate the passage of charged drugs through the skin; electroporation, which generates short high-voltage electrical pulses to create temporary aqueous pores in the skin; sonophoresis, which utilizes low-frequency ultrasonic energy to disrupt the stratum corneum; and thermal energy, which applies heat to enhance skin permeability and elevate drug molecule energy. Additionally, the use of magnetic energy, known as magnetophoresis, has also been studied as a potential method for improving drug absorption through the skin.[21][22]

Regulatory Strategy for Investigational New Drug (Ind) Application and New Drug Application Submissions for TDDS

Standard irritation and sensitization studies should be performed with the patch itself in animals/humans. Negotiate the timing and implementation of the toxicology requirements. The dermatology division at FDA should review dermal aspects of the IND and new drug Application (NDA).Primary review should occur at the division that handles the indication under study. Dose ranging studies are required in Phase 2. Single Phase 3 study could be negotiated.

CONCLUSION

This review article concluded that, an older drug by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. Additionally the TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.[23]

REFRANCES

1. Jain NK, Controlled and novel drug delivery. 1st Ed., CBS Publisher and Distributors, New Delhi, 2001; 100-129.
2. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovation, 2012; 1(4): 66-75.
3. Jain NK, Controlled and novel drug delivery. 1st Ed., CBS Publisher and Distributors, New Delhi, 2001; 100-129.
4. Robinson JR, Lee VH. Controlled drug delivery fundamentals and applications. 2nd Ed. New York, 2005; 523-536.
5. Transdermal Drug Delivery System: A Review 1.Arunachalam Current Pharma Research, October-December 2010; 1(1).
6. Jain NK. Controlled and Novel Drug Delivery. CBS Publishers and Distributors, New Delhi, 2002; 107.

7. Chien YW. Novel drug delivery systems: Drugs and the Pharmaceutical Sciences. Vol.50, Marcel Dekker, New York, 1992; 797.
8. Jain NK. Controlled and novel drug delivery, Ist edition, CBS publishers and distributors, New Delhi, 1997. 35. Singhal P et al., Transdermal Drug Delivery System as a Tool for Novel Drug Delivery System. American Journal of PharmTech Research, 2012; 2(1): 106-125.
9. Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm Res. J., 2010; 3: 139- 149.
10. Dhawan S, Aggarwal G. Development, fabrication and evaluation of transdermal drug delivery system- a review. Pharm info.net, 2009; 1-25.
11. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal Drug Delivery System: A Review, 2012; 1: 78-87.
12. 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.
13. 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.
14. A REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEMBy Ankush Rana Manav Bharti University, Solan (H.P.).WJPR, 2018; 7(11).
15. 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.
16. Gupta IK, Chokshi MM. Transdermal drug delivery system: an overview. Asian J Pharm Sci. Clinical Res, 2011; 1(1): 25-43.
17. Sharma A, Saini S, Rana AC. Transdermal drug delivery system: A review. Int. J Res Pharm Biomedical Sci, 2013; 4(1): 286-292.
18. 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.
19. Thejaswi C, Rao KM, Gobinath M, Radharani J, Hemafaith V, Venugopalaiah P. A review on design and characterization of proniosomes as a drug carrier. Int. J Advances Pharm Nanotechnology, 2011; 1(1): 16-19.
20. Gupta IK, Chokshi MM. Transdermal drug delivery system: an overview. Asian J Pharm Sci. Clinical Res, 2011; 1(1): 25-43.

21. Mitragotri S, Blankschtein D, Langer R. Transdermal drug delivery using lowfrequency sonophoresis. Pharm Res, 1996; 13(3): 411-420.
22. Mitragotri S. Effect of therapeutic ultrasound on partition and diffusion coefficients in human stratum corneum. J Controlled Rel, 2001; 71: 23-29.
23. Singhal P et al., Transdermal Drug Delivery System as a Tool for Novel Drug Delivery System. American Journal of PharmTech Research, 2012; 2(1): 106-125.