



A Review on: Antihypertensive Drugs Delivery through Transdermal Patches

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Abstract: It is the category of controlled drug delivery system is sub-categories in which drug is deliver through skin in a predetermined and controlled rate. Now a days hypertension is one of the most common disorder as found in human. It is not a disease in itself, but is an important risk factor cardiovascular mortality and morbidity. The present article delivers a brief view on the work has been done to increase the bioavailability of various antihypertensive drugs by formulated and delivered as transdermal patches. The different drugs include carvedilol, metoprolol, atenolol, propranolol, nicardipine hydrochloride, clonidine, nicorandil, amlodipine. These drugs were penetrating through the various penetration routes in to the skin, like appendageal, epidermal, transcellular, intracellular.

Index Terms - Antihypertension, transdermal, TDDS, NC-HCL, skin, hydrophilic polymer matrix, HPLC.

Introduction

Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mm Hg, a criterion that characterizes a group of patient whose risk of hypertension related cardiovascular disease is high enough to merit medical attention. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India.

Antihypertensive patch with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs. These advantages prepared the target consumer to accept antihypertensive patches as a costlier alternative to the conventional therapy. The possibility of achieving controlled zero order absorption, simple mode of administration and the option of easy withdrawal of dose in case of adverse manifestations make them desirable in antihypertensive therapy. ^[04]

Transdermal Drug Delivery System (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through skin in a predetermined and controlled rate. Hypertension is one of the common disorders for the mankind.

Drawbacks of conventional dosage form:

Oral drug administration is limited by many disadvantages, some of them are mentioned below:

- 1) Some of oral preparations undergo a first - pass effect in the liver, requiring larger doses.
- 2) The rate and extent of absorption can vary greatly depending on the drug, its formulation, presence or absence of food in the stomach, drug interactions and pH of gastrointestinal fluids.
- 3) Drug metabolite formed following first - pass through the liver may not be as active or as potent drug (e.g. butorphanol), thus necessitating the oral doses to be much greater than the parenteral dose required to cause the same clinical effect. ^[27]

DRUGS USED AS ANTIHYPERTENSIVE PATCHES:**CARVEDILOL:**

Carvedilol is a $\beta_1 + \beta_2 + \alpha_1$ adrenoceptor blocker; produces vasodilatation due to α_1 blocked as calcium channel blocked, and has antioxidant property. It has been used in hypertension and is the beta blocker especially employed as cardio protective in congestive heart failure (CHF).

Shashikant D. Barhate *et al.*, formulate transdermal patches of carvedilol by using combination of polyvinyl alcohol (PVP) and polyvinyl pyrrolidone (PVP K30) along with glycerin, polyethylene glycol 400 and propylene glycol as plasticizers.^[05]

METOPROLOL:

It is a prototype of cardio-selective (β_1) blockers; is incompletely absorbed (oral bioavailability 35%), has short elimination half life of 2-3 hours and undergo extensive first pass metabolism.

Meenakshi Bharkatiya *et al.*, prepared transdermal patch of metoprolol tartrate by solvent casting method employing a mercury substrate by using the combinations of EC: PVP and Eudragit RL100:PVP in different proportion.^[06]

ATENOLOL:

Atenolol is relatively a selective β_1 blocker having low lipid solubility. It is completely absorbed orally, but first pass metabolism is not significant. It is one of the most commonly used beta blockers for hypertension and angina.

P Eswaramma *et al.*, developed matrix type transversal films of atenolol by optimizing different ratios of cellulose acetate phthalate (CAP) and polyvinyl pyrrolidone (PVP) incorporating 15% w/w dibutyl phthalate as a plasticizer with different concentration of oleic acid and isopropyl myristate as permeation enhancer by the solvent evaporation technique.^[07]

PROPRANOL:

Propranolol is a β blocker which is used in management of hypertension. Due to short biological half - life of 3.9 hours it necessitates for controlled delivery.

Guru Sharan *et al.*, prepared Propranolol hydrochloride loaded patches using various biocompatible polymers like (EC:PVP) and (Acrycoat L-100: HPMC) by using solvent casting and evaporation and checked the effect of various permeation enhancers on formulated patches.^[10]

NICARDIPINE HYDROCHLORIDE (NC-HCL):

Nicardipine hydrochloride (NC-HCl) a calcium channel blocker for the treatment of chronic stable angina and hypertension. The onset of action is 5-10 minute and duration of action 15-30 minute. The half life of the drug varies between 2-4 hour and bioavailability ranges 20-40%.

Y. S. R. Krishnaiah *et al.* developed a membrane - moderated transdermal therapeutic system (TTS) of nicardipine hydrochloride using 2% w/w hydroxypropyl cellulose (HPC) gel as a reservoir system containing 4% w/w of limonene as a penetration enhancer.^[09]

CLONIDINE:

Clonidine is a centrally acting antihypertensive drug having plasma half life of 8-12 hours and peak concentration occurs in 2-4 hours effectively reduces blood pressure in patients with mild-to-moderate hypertension.

Mao Zhenmin *et al.*, prepared, a new type of polyacrylates polymer synthesized in lab by UV curing method and studied in membrane controlled drug release systems.^[11]

NICORANDIL:

Nicorandil to the class of potassium channel activators, which exert their action by arteriole - dilating and vasodilating properties and represents a novel type of compound for use in the treatment of angina pectoris.

V G Jamakandi *et al.*, employed solvent casting technique to formulate HPMC patches containing different grades of HPMC polymer (6cps, 15cps and K4M) as matrix base, polyethylene glycol as plasticizer.^[09]

AMLODIPINE:

Pharmacokinetically it is the most distinct dihydropyrimidines belonging to the class of calcium channel blockers. It has complete but slow oral absorption: peak after 6-9 hours. Volume of distribution and $t^{1/2}$ are exceptionally long: diurnal fluctuation in blood level is small.

Jiang Yu-xuan *et al.*, prepared drug - in adhesive patches for amlodipine besylate and evaluate its in vitro transversal permeability. Drug in adhesive patches of amlodipine besylate were prepared by dissolving amlodipine besylate and different enhancers into the home made pressure sensitive adhesive. [14]

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS):

Transdermal drug delivery system (TDDS) are defined as self - contained, discrete dosage form which, when applied to the intact skin, deliver the drug's, through skin at controlled rate to the systemic circulation. To provide continuous drug infusion through an intact skin several transversal therapeutic systems have been developed for topical application into the intact skin surface through the skin tissue. FDA approved the first transversal patch products in 1981. Nitroglycerine for the prevention of angina pectoris associated with conventional to systemic circulation in a more convenient and effective way than is possible with conventional dosage form. The potential of skin as a path of a drug administration has been amply demonstrated by the acceptability of marketed therapeutics system. Administration of systemic drugs using a transversal patch represents a noninvasive route, with improved patient compliance.

Transdermal drug delivery can provide a number over conventional methods of drug administration, including enhanced efficiency, increased safety, greater convince and improved patient compliance. By delivery a steady flow of drugs in to bloodstream over an extended period of time, transversal system can avoid "peak and valley" effect of oral or inject able therapy and can enable more controlled, effective treatment. By avoiding first pass metabolism through the gastrointestinal tract and liver, the therapeutically equivalent dosage for the transversal delivery of certain compound can be side effect. [16][13]

ADVANTAGES

The avoidance of first pass metabolism and other variables associated with the GI tract, suches pH, and gastric emptying time. Sustained and controlled delivery for a prolonged period of time. Reduction in side effects associated with systemic toxicity, i.e. minimizing of peaks and troughs in blood-drug concentration. Improved patient acceptances and compliances. Self-administration is possible with this system. Ease of dose termination in the event of any adverse reaction, either systemic or local. Convenient and painless administration. Ease of use may reduces overall healthcare treatment costs. Provides an alternative in circumstances where oral dosing is not possible (in unconscious or nauseated patients). [16]

DISADVANTAGES

The drug must have some desirable physicochemical properties for penetration through stratum corneum. If the drug dosage required for therapeutic value is more than 10mg/day, the transversal delivery will be very difficult. Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation. The barrier function of the skin changes from one site to another on the same person, from person and with age. [16]

THE SKIN:

The skin covers the external surface of the body. It is the largest organ of the body in surface area and weight. In adult, the skin covers an area of about 1.5-2.0 square meters and weights 4-5 kg, about 16% of total body weight. However, over most of the body it is 1-2 mm thick. The average square inch of skin holds 650 sweat glands, 20 blood vessels, 60,000 melanocytes and more than a thousand nerve endings. Structurally, the skin consists of two main parts. The superficial, thinner portion, which is composed of epithelial tissue, is the epidermis. The deeper, thicker connective tissue part is the dermis. The subcutaneous tissue just deep to known as the hypodermis. [04]

Function of skin:

1. Thermoregulation: The skin contributes to thermoregulation, the homeostatic regulation of body temperature, in two ways: by

liberating sweat at its surface and by adjusting the flow of blood in the dermis.

2. Protection: Keratin in the tissue protects underlying tissue from microbes, abrasion, heat, and chemicals. It also protects from physical agents like dehydration, UV light.
3. Cutaneous sensation: These include tactile sensation – touch, pressure, vibration, and tickling as well as thermal sensation and pain.
4. Excretion: It has small role in the excretion; about 400ml of water evaporates through it daily. It also eliminates nitrogen containing wastes like ammonia, urea and uric acid.
5. Absorption: Absorption of lipid soluble material like ammonia fat soluble vitamins A, D, E and K certain drugs, steroids, heavy metals, organic solvents, O₂ and CO₂.
6. Synthesis of Vitamins D: Synthesis of Vitamins D is done by activation of precursor molecules in the skin in presence of UV rays in sunlight.
7. Blood Reservoir : The dermal vascular supply is extensive and can hold large volumes of blood.^{[04][20]}

DRUG PERMEATION PATHWAY:

There are following critical ways in which a drug molecule can cross the stratum corneum:

- Via skin appendages (shunt route)
- Epidermal route^[21]
 - 1) Through intracellular lipid domains.
 - 2) By a transcellular route.

The appendageal route:

The permeation of drug through the skin includes the diffusion through the intact epidermis and through the skin appendages, i.e. hair follicles and sweat glands, which form shunt pathways through the intact epidermis. However, these skin appendages occupy only 0.1% of the total human skin surface and the concentration of these pathways is usually considered to be small.^[21]

Epidermal route:

For drugs, which mainly cross the intact horny layer, two potential micro routes of entry exist, the transcellular (intracellular) and intracellular pathway.^[21]

Transcellular route:

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrated keratin, provide an aqueous environment for which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partition and diffusion steps.^[21]

Intracellular route:

The intracellular pathway involves drug diffusion through the continuous lipid matrix. This route is a significant obstacle for two reasons:

1. Recalling the 'bricks and mortar' model of the stratum corneum, the integrating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route.
2. The intracellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small unchanged molecules penetrating the skin.^[21]

FACTORS AFFECTING TRANSDERMAL PERMEABILITY:

Biological condition:

SKIN CONDITION: The intact skin is a tough barrier but many agents like acids and alkalis; many solvents such as chloroform and methanol injure barrier cells thereby promote penetration. Diseased state alters the skin conditions of patient.

SKIN AGE: The skin of young and elderly is more permeable than adult tissue. Children are also more susceptible to toxic of drugs and chemicals; partly because of their greater surface area thus skin age also affects the penetration of drug through TDDS.

BLOOD FLOW: The changes in the peripheral circulation cloud affect transdermal absorption. In clinically hyoeraemic skin, any increase in absortion almost always arises because the disease damages the skin barrier.

REGIONAL SKIN SITES: Variations in cutaneous permeability around the body depend on the thickness and nature of the stratum corneum and the density of skin appendeges. These factors affect significantly to the penetration.

SKIN METABOLISM: The skin metabolises steroid hormones, chemical carcinogens and some drugs. Metabolism of skin determines efficacy of drug permeated through the skin.

SPECIES DIFFERENCES: Skins thickness, sweat gland and hair follicle densities and pelt condition affect the routes of penetration and the resistances to permeation.^[27]

Physicochemical factors:

SKIN HYDRATION: In contact with water saturates skin the tissues swells, softness and wrinkles results increase permeability. Hydration of the stratum corneum is one of the most important factors in increasing the penetration rate, so use of humectants is done in the transdermal therapeutics system.

TEMPERATURE AND PH: The penetration rate of material through human skin can changes tenfold for a large temperature variation, as the diffusion coefficient decreses as the temperatue falls. Weak acid and bases dissociate to different degrees, depending on the Ph and their pKa or pKb values. Thus, the proportion of unionized drug in the applied phase determines the effective the effective concentration gradients, and this fraction depends on pH. Thus, temperature and pH are factors which affect the penetration of drug.

DIFFUSION COEFFICIENT: Penetration of drug depends upon the diffusion coefficient. For a constant temperature, the diffusion coefficient of a drug in a topical vehicle or in skin depends on the properties of the drug and the diffusion medium and on the interaction between them.

DRUG CONCENTRATION: The flux of solute is proertional to the concentration gradient across the entire barrier phase and concentration gradient will be more if drug concentration saturated across donor site.

PARTITION COEFFICIENT: The optimal K, partition coefficient is required for good skin penetration required a K close to unity. However, drug with low values they are too water soluble to partition well into the horny layer. At higher values the compounds are so soluble that they do not readily pass from the stratum corneum into the water-rich viable tissue.

Molecular Size and Shape: Absorption is apparently inversely related to molecular weight; small molecules penetrate faster than large ones. However, the specific effect of the size of the penetrating molecules on the flux could be determined if the effect of size could be separated from the resultant change in solubility characteristics. This is difficult to do, as the role of the partition coefficient is so dominant. Because it is determine the effect to determine the effect of molecular shape, separated from partition coefficient domination and so nothing is known about this factor in skin permeation.^[27]

COMPONENTS OF A TRANSDERMAL PATCH:

Transdermal patch may include the following components:

Liner - Protects the patch during storage. The liner is removed prior to use.

Drug – Drug solution in direct contact with release liner.

Adhesive – Serves to adhere the components of the patch together along with the skin.

Membrane – Controls the release of the drug from the reservoir and multi-layer patches.

Backing – Protects the patch from the outer environment.^[25]

Polymer Matrix:

The polymer controls the release of the drug from the device. Criteria for polymer to be used in a transdermal system as Molecular weight, glass transition temperature and chemical functionally of the polymer should be such that the specific drug diffuses properly and get released through it. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive. The polymer and its degradation product must be non-toxic or non- antagonistic to the host. The mechanical properties of the polymers should not deteriorate excessively when large amounts of agent are incorporated into it.^[25]

Useful polymers for transdermal delivery system are:

Natural: Cellulose derivative, Gelatines, Gums, and their derivatives, etc.

Synthetic polymers: Polyvinyl alcohol, Polyvinyl chloride, Polymethacrylates.

Synthetic Elastomers: Polybutadiene, Polysiloxane, Silicon rubber, etc.

DRUG:

For successfully developing transdermal drug delivery system selection of drug is most important.

Ideal properties for selection of drug:

Following are some of the desirable properties of drug for transdermal delivery:

1) Physicochemical properties:

- The molecular weight is less than 500Da.
- Aqueous solubility >1mg/ml.
- An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ml).
- Optimum partition coefficient is required for good therapeutic action.
- Low melting point of drug is desired. (<200°C).
- The pH of the saturated solution should be in between 5 to 9.
- The potent drug with dose deliverable 10-15 mg/day. [24]

2) Biological Properties:

- The drug should be potent with daily dose <10-15mg/day.
- The half ($t_{1/2}$) life of drug should short.
- The drug must nonirritant to skin and not produce allergy. [24]

Technologies for developing transdermal drug delivery systems:

1) Polymer Membrane Penetration – Controlled TDD System:

In this type of system the drug reservoir is sandwich between a drug – impermeable backing laminate and a rate controlling polymeric membrane allowed to release only through the rate controlling polymeric membrane. The drug solids are dispersed homogeneously in solid membrane of polymer matrix, e.g., polyisobutylene, suspended in an unextractable, viscous liquid medium to form a paste like suspension e.g. silicon fluid, or dissolved in a release solvent to form a clear drug solution e.g. alkyl alcohol. The rate controlling membrane can be either a microscopic or a non-porous polymeric membrane, e.g. ethylene vinyl acetate copolymer with specific drug permeability. On the external surface of the polymeric membrane a thin layer of the drug-compatible, hypo allergic pressure-sensitive adhesive polymer, e.g., silicon adhesive, may be applied to provide intimate contact of the TDD system with the skin surface. [14]

The rate of drug release through TDDS can be controlled by varying the composition of drug reservoir formulation and the permeability coefficient and thickness of the rate-controlling membrane. [26]

e.g., Several FDA approved system-

- a. Transdermal- Nitro system for once-a-day medication of angina pectoris,
- b. Transdermal- SCOP system for 3-day protection of motion sickness,
- c. Catapres- TTS system for weekly therapy of hypertension.

2) Polymer Matrix Diffusion-Controlled TTD System:

In this type the drug reservoir is formed by homogeneously dispersing the drug solid in a hydrophilic polymer matrix disks with a defined surface area and controlled thickness. This drug reservoir containing polymer disks is then mounted on occlusive base plate in a compartment fabricated from drug-impermeable plastic backing. In this type of CrDDS, the drug reservoir is produced from the homogeneous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix. The drug dispersion in the polymer matrix is accomplished by either 1) blending a dose of finely ground drug particles with a viscous liquid (or a semisolid) polymer, followed by a crosslinking of polymer chains or 2) mixing drug solids with a melted polymer at an elevated temperature. The resultant

drug-polymer dispersion is then molded or extruded to form drug delivery devices of various shapes and sizes designed for a specific application. [14, 26]

E.g., Minitran system, Nitro Dur II System for Angina Pectoris. [21]

3) Drug Reservoir Gradient-Controlled TDD System:

Polymer matrix drug dispersion – type TDD system can be modified to have a drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusion path across the m-laminate adhesive layer. [14]

In this system, the thickness of diffusional path through which drug molecules diffuse increases with time i.e. $h_a(t)$. The drug loading level in the multilaminate adhesive layer is designed to increase proportionally i.e. $L_d(h_a)$ so as to compensate time dependent increase in diffusional path as a result of drug depletion due to release. Thus, theoretically this should increase a more constant drug release profile. eg. Deponit system containing nitroglycerine for angina pectoris. [21]

4) Microreservoir Dissolution-Controlled TDD System:

This type of a drug delivery system can be considered a hybrid of the reservoir and matrix dispersion type drug delivery system. In this approach the drug reservoir is formed by the first suspending drug solids in an aqueous solution of water – miscible drug a solubilizers, e.g., polyethylene glycol and then homogeneously dispersing drug suspension, with controlled aqueous solubility in a lipophilic polymer, using higher shear mechanical force to form thousands of unclenables microscopic drug reservoirs.

Thermodynamically unstable dispersion is quickly stabilizers by immediately in situ cross linking of the polymer chains to form a medicated polymer disk with constant surface area and fixed thickness. [14]

E.g., Nitro disc system once a day treatment of angina pectoris. [21]

CONCLUSION

TDDS are topically administration of medicaments through the skin for systemic effects at a predetermined and controlled rate in the form of transdermal patches. Transdermal drug delivery of antihypertensive drugs is able to provide optimum of drug to control the disease condition along with minimum side effects. This review on different antihypertensive drugs showed that, by delivering drug through this route improves bioavailability a well as patient compliance. This can also lead to cost effectiveness of a healthcare for the long term management of hypertension. But the main limitation is that, the drug should possess certain specific physicochemical properties which should be suited to permeate through the skin, therefore all antihypertensive drugs cannot be given by this route.

Transdermal drugs market is growing and there is a prospect of higher growth in this market over the next several years. Transdermal delivery of antihypertensive drugs is expected to have a profound impact on patient care.

REFERENCES

- [1] Brunton LL, Lazo Js, Parker KL, Goodman & Gilman's. The pharmacological basis of therapeutics. McGraw – Hill, New York 2006; 11.
- [2] Jamarkandi V, Ghosh B, Khanan J. Recent Trends in Transdermal Cardiovascular Therapy. Ind J Pharma Sci 2006; 6(8):556-61.
- [3] Sivkumar T, Selvan P, Singh A. transdermal drug delivery system for antihypertensive drugs. Int J Pharma Sci Biomed Res 2010; 1(1); 1-8.
- [4] Tripathi K.D. Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers (P) Ltd, 6th edition 2008.
- [5] Barhate D, Dr. Patel M., Sharma S, Nerkar P, Shankhapal G. Formulation and evaluation of transdermal drug delivery system of carvedilol. J Pharm Res 2009; 2(4): 663-665.
- [6] Bharktiya M, Kumar N, Bhatnagar M. Development and characterization of transdermal patches of metrolol tartarate. Asian J of Pharm and Clinical Research 2010; 3(2):130-134.
- [7] Eswaramma P, Karthikeyan M, Arunachalam, Vinaykumar N, Krishnareddy Y, Anjaaneyaula V. Formulation and evaluation of transdermal patch of atenolol. Int J Compre Pharm, 2010; 1(10):1-5.
- [8] Jayaraj K, Suneetha K, Uma K, Prasanthi N, Pravalika C, Prasnaaa D, Kalayan P. A Brief view on drug delivery system through transdermal patches. Int J Pharm Sci 2010; 1(2):305-319.

- [9] Aboofazeli R, Hossein Z, Thomas E. Transdermal Delivery of Nicardipine. An approach to In Vitro Permeation Enhancement. Drug Delivery 2002; 9(4): 239-247.
- [10] Sharan G, Biplab D, Nagarajan K, Sujit D, Vijaya S, Dinesh V. Effect Of various permeation enhancers on Propranolol HCL formulated patches. Int J Pharm Sci, 2010; 2(2): 21-31.
- [11] Ishii R, Tagawa T, Ishida t, Narsue T. Antihypertensive effects of a new TDS of Clonidine in genetic and experiment rats. Aezneimittel-forschung 1996; 46: 261-268.
- [12] Zhan X, Guchun T, Chen S, Zhenmin M. A new copolymer membrane controlling clonidine linear release in a transdermal drug delivery system. Int J Pharm 2006; 322(12): 1-5.
- [13] Rastogi V, Pragma, P. Upadhyay, A brief view on antihypertensive drugs delivery through transdermal patches, IJPSR, 2012; Vol. 3(7): 1955-1970.
- [14] Jamakandi V.G, Mulla J.s, Vinay B.L, Shivshankar H.N. Formulation, characterization and evaluation of matrix type transdermal patches of a model antihypertensive drug. Asian J Pharm 2009; 3: 59-65.
- [15] Vyas S P, Khar R K. Controlled drug delivery: Concept and Advances, Vallabh Prakashan, 1st edition. 2002:411-447.
- [16] Jai K: Transdermal drug delivery system. Skin Perturbation devices in Drug delivery system, Human Press, 118-130.
- [17] Jain NK: Controlled and novel drug delivery. CBS publishers and distributors. 1st edition. 1997: 100-129.
- [18] Toratora G, Derrickson B, The Intergumentary system, In Priciples of anatomy and physiology. 12th edition. John Wiley and Sons, Inc. 148-61.
- [19] Marib E. The Integumentary system, In: Human anatomy and physiology in Health and Illness, 6th edition. Pearson Education, 152-66.
- [20] Waugh A, Grant A, Ross and Wilson: Anatomy and Physiology in Health and Illness, 10th edition. Churchill Livingstone (Elsevier). 200; 358-67.
- [21] Sharma N, Agrawal G, Rana Ac, Bhat ZA, Kumar D. A review: Transdermal drug delivery system: a tool for novel drug delivery system Int J Drug Develop Res July-sep 2011; 0975-9344.
- [22] Moster K, Kriwat K, Naik A, Khalia YN, Guy RH. Passive skin permeation enhancement and its quantification in vitro. Eur J Pharm Biopharm. 2001; 52:103-112.
- [23] Barry B. Transdermal drug delivery system. In Ed: Aulton M E, Pharmaceutics: The sciences of dosage form design, Churchill Livingston. 2002; (2)1: 68-77.
- [24] Naik A, Kalia YN, and Guy R. H, Transdermal Drug delivery: overcoming the skin's barrier function. PSTT 2000; 499-533.
- [25] Bhowmilk D, Chirnajib, Chandira M, Jaykar, Sampanath K. P, Recent Advances in Transdermal Delivery System. Int J. Pharm tech Res 2010; (2)1: 68-77.
- [26] Chein Yei W. Novel Drug Delivery System 2nd Edition, Drug and Pharmaceutical Sciences. Volume-50, Marcel Dekker, Inc.
- [27] Allen LV, Popovich NG, Ansel's Pharmaceutical Dosage Forms and Drug Delivery System. 8th Edition, Lippincott Williams & Wilkins, 2005: 298-315.