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# A REVIEW ON: TRANSDERMAL PATCH OF ANTIHYPERTENSIVE AGENTS

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***ABSTRACT***

*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. The development of this technology for release of drug at controlled rate into systemic circulation using skin as port of entry has become popular for various reasons because which helped to overcome the side effects associated with conventional system of medication, which require multidose therapy,Hypertension is one of the largest deaths causing disease for the mankind. Since it is a chronic disease it necessitates long term treatment. This article is dedicated to the review of antihypertensive transdermal patches in the perspective of enhancing the bioavailibity as well as in improving the patient compliance. The different drugs includes carvedilol, metoprolol, atenolol, propranolol, indapamide, , timolol maleate, nicardipine hydrochloride, captopril, clonidine, pinacidil, nitrendipine, nicorandil, diltiazem hydrochloride, lisinopril, nifedipine, amlodipine, valsartan, enalapril maleate etc. Clonidine was the first antihypertensive drug developed in the transdermal form. Currently a number of antihypertensive transdermal patches are introduced in to the pharmaceutical market Most of the reported in the literature employed solvent evaporation method or solvent casting method for the preparation of transdermal patches.*

***KEYWORDS :*** *Transdermal Drug Delivery system Transdermal patch , Antihypertensive drugs, Solvent casting method .*

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## INTRODUCTION

With the advent of new era of pharmaceutical dosage form, transdermal drug delivery system (TDDS) established itself as novel drug delivery system **.** Recent trend to drug delivery is to deliver the drug into systemic circulation at a

predetermined rate which is known as controlled release drug delivery system. Such systems helped to overcome the side effects associated with conventional system of medication, which require multidose therapy . The development of technology for release of drug at controlled rate into systemic circulation using skin as port of entry has become popular for various reasons .

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin or is also defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation.[1]

Most of the chronic diseases have genetic, hereditary cause or lifestyle borne like Hypertension. Cardiovascular diseases caused 2.3 million deaths in Indiain the year 1990. According to world health report 2002, it will be the largest cause of death and disability by year 2020 in India . Recent studies using revised WHO guidelines (Systolic BP≥140 and/or Diastolic BP≥90 mmHg) have shown a high prevalence of hypertension as 31.5 million people in rural and 34 million in urban populations . Monotherapy achieves the target BP level of 140/90 mmHg only in50% of patients. More than 2/3 of patients in stage II hypertension will require two or more agents. Combination antihypertensive therapy is an option that is convenient due to single dose regimen, and has lesser side effects .[2]

Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Pooling of Indian epidemiological studies shows that hypertension is present in 25% urban and 10% rural subjects. Therefore cost effective approaches to optimally control blood pressure among Indians are very much needed. Despite the suitability of TDDS in the treatment of chronic disease like hypertension, the high cost of antihypertensive patches than conventional products made the target patients to think twice . In spite of the high cost of transdermal patches for hypertension treatment, antihypertensive patches with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs These advantages prepared the target consumers to accept antihypertensive patches as a costlier alternative to the conventional therapy.

The various antihypertensive drugs considered in the review includes timolol maleate, nicardipine hydrochloride, captopril, atenolol, metoprolol tartrate, clonidine, indapamide, labetolol, pinacidil, verapamil hydrochloride, nitrendipine, nifedipine, nicorandil, propranolol hydrochloride, diltiazem hydrochloride, amlodipine besilate,carvedilol and lisinopril.[3,4]

**SELECTION OF DRUG CANDIDATE FOR TRANSDERMAL PATCH :**[5]

- Dose should be low i.e <20mg/day.
- Half life should be 10 h or less.
- Molecular weight should be <400.
- Partition coffecient should be Log P(octanol-water) between 1-4
- Skin permeability coefficient should be <0.5 X 10-3cm/h.
- Drug should be non irritating and non sensitizing to the skin.
- Oral bioavailability should be low

**ANTIHYPERTENSIVE DRUGS :**

**1. Clonidine :**

Clonidine was the first antihypertensive drug developed in the transdermal form. Currently a number of antihypertensive transdermal patches are introduced in to the pharmaceutical market. Clonidine hydrochloride is the most widely prescribed drug in the long term treatment of hypertension. Following oral administration, Clonidine hydrochloride is rapidly absorbed from the gastrointestinal tract (40 to 60%) but the oral bioavailability remains low (eg 23%) because of significant first-pass hepatic metabolism. Clonidine also has a short plasma half-life of 10 hours. Long term therapy of hypertension by Clonidine oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life,

leading to increased frequency of administration. An alternate route of administration is needed.

Clonidine hydrochloride possesses ideal characteristics—such as a low molecular weight (266.6),smaller dose range (100µg), and poor oral bioavailability—for formulation as a transdermal patch. There are reports describing the use of Eudragit L (EL),HPC and PVP transdermal delivery systems as well as other dosage forms for controlled release of drugs . EL and PVP is freely permeable to water These transdermal delivery systems are neither extremely hydrophobic nor extremely hydrophilic. Therefore, varying the ratio of these polymers in the composition of the films provides control of drug release characteristics

**Alka Verma** et.al Develop different matrix patches with various ratios of hydrophilic and hydrophobic polymer combinations such as hydroxypropyl cellulose (HPC) and EL100-55 and (b) EL100 -55 and polyvinylpyrrolidone (PVP), containing Clonidine hydrochloride using polyethyleneglycol as a plasticizer by solvent casting method. They also Perform physicochemical characterization and in vitro permeation studies through rat skin.show the report for controlled release over a period of 48 hours. The system was free of any hazardous skin irritation.[6]

**2. Olmesartan medoxomil** :

Olmesartan medoxomil (OLM) is a non peptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. OLM is poorly soluble and aqueous solubility is reported to be less than 1 mg/ml. The drug is rapidly absorbed following oral administration, with a bioavailability approximately 26%. Peak plasma concentrations of OLM occur 1 to 2 h after an oral dose and are highly bound to plasma proteins (99%) . Rapid onset of action is desirable to provide fast relief in the treatment of heart failure. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of OLM to obtain faster on set of action,minimize the variability in absorption, and improve its overall oral bioavailability. The various formulation strategies reported like transdermal patch.[7]

**3. Indapamide :**

is a long-acting hypertensive with both diuretic and vasodilative actions and is defined by the 1999 WHO/ISH Hypertension Guidelines and JNC VII as a first-line drug for the treatment of hypertension. Anti-hypertensive action is maximal at a dose of 2.5 mg/day and the diuretic effect is slight,usuallywithout any clinical manifestation although at higher doses the diuretic effect becomes more prominent. The extra-renal antihypertensive action of 2.5 mg/day is demonstrated as a reduction in vascular hyperactivity and a reduction in total peripheral and arteriolar resistance. The extra-renal mechanism of action has also been demonstrated by the maintenance of the anti-hypertensive effect in functionally anephric patients. [8]

Shashikant D. Barhate *et al.,* fabricated and evaluated a transdermal bioadhesive film containing indapamide using Eudragit RS100, lauric acid, adipic acid, polyvinyl alcohol, sorbitol. The in-vitro permeation experiments were performed in Franz-diffusion cell using freshly excised rat skin for 12 h. The permeation results of indapamide form 2 mg/ml and 5mg/ml solutions in phosphate buffer (pH7.4) showed significant permeation behavior. The *in-vitro* permeation results of transdermal films showed good permeation characteristics across the skin, with linear release from film .

The Eudragit RS 100 and polyvinyl acetate in 1:2 proportions proved to be better composition for preparation of transdermal film which can be a prosmising and innovative therapeutic system for indapamide . [9]

**4. Pinacidil** :

Pinacidil monohydrate (PM) is a lipophillic drug used for the management of mild to moderate essential hypertension and has very few side effects. It acts by opening the potassium channels leading to hyperpolarisation and peripheral vasodilation . After oral administration, peak plasma concentrations reached within 0.5–1.0 h . The antihypertensive action requires plasma concentrations in the range of 100–300 ng/ml. There is highly significant correlation between the change in mean blood pressure and the serum

concentration of pinacidil of patients with essential hypertension. Oral treatment is usually begun with a dose of 12.5 mg twice daily. If oedema develops, a diuretic may be added. The usual maintenance dose is 12.5– 25 mg b.i.d. and can be increased up to 150 mg daily in two divided doses . It possesses low oral bioavailability due to hepatic first pass metabolism after oral administration and has a short biological half life of 1.6–2.9 h . which makes frequent dosing necessary to maintain the drug within the therapeutic blood levels for long periods. Hence,PM is an ideal drug candidate for transdermal drug delivery.

The monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate (PM) were prepared by film casting technique on mercury substrate and characterised in vitro by drug release studies using paddle over disc assembly, skin permeation studies using Keshary and Chein diffusion cell on albino rat skin and drug-excipient interaction analysis Four formulations were developed which differed in the ratio of matrix forming polymers, Eudragit RL-100 and PVP K-30 & 20% w/w of PM,with 5% w/w of plasticiser, PEG-400 and 5% w/w of DMSO (based on total polymer weight) in isopropyl alcohol: dichloromethane (40:60) solvent system.[10]

**5. Carvedilol** :

Carvedilol is an novel multiple-action cardiovascular which is currently approved in many countries for the treatment of hypertension. The carvedilol shows reduction in blood pressure by beta-adrenoceptor blockade and vasodilation and latter resulting from alpha 1-adrenoceptor blockade . Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; its absolute bioavailability is about 25%. It has a half-life of 2.2 ± 0.3 h; longer half-lives of about 6 h have been measured at lower concentrations .

Transdermal patches of carvedilol with a HPMC-drug reservoir were prepared by the solvent evaporation technique. In this investigation drug reserviour was prepared by dissolving hydroxyl propyl methyl cellulose in distilled water. Eudragit RL100 and Eudragit RS100 were used to achieve controlled release of the drug and Propylene glycol 30% as a plasticizer The fabricated patches possessed satisfactory physicochemical characteristics. Thickness, mass and drug content were uniform in prepared batches. Moisture vapour transmission through the patches followed zero-order kinetics. *In vitro* permeation studies were carried out using a K-C diffusion cell across hairless guinea pig skin . The non--ionic surfactants in the patches increased the permeation rate, Span 80 exhibiting better enhancement relative to Tween 80. The patches were seemingly non irritation to skin.[11]

**6. Nicardipine** :

Nicardipine a calcium-channel blocker, is used alone or with an angiotensin converting enzyme inhibitor to treat hypertension and angina pectoris . Nicardipine hydrochloride [NC-HCL] is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first pass hepatic metabolism. Following oral administration of NCHCL was shown to be rapidly and extensively metabolised in the liver and to be rapidly eliminated from plasma through urine and faeces,mainly as inactive metabolites. Oral bioavailability of about 30- 35% has been reported after a 30 mg dose.

Y.S.R. Krishnaiah *et al*., [16] developed a membrane moderated transdermal therapeutic system of nicardipine hydrochloride using 2% w/w hydroxyl propyl cellulose (HPC) gel as a reservoir system containing 4% w/w of limonene as a penetration enhancer. The permeability flux of nicardipine hydrochloride through ethylene vinyl acetate copolymer membrane was found to increase with an increase in vinyl acetate content in the copolymer.

The effect of various pressure-sensitive adhesives MA-31 (moderate acrylic pressure sensitive adhesive), MA-38 (mild acrylicpressure sensitive adhesive) or TACKWHITE A 4MED(water based pressure sensitive acrylic emulsion) on the permeability of nicardipine hydrochloride through ethylene vinyl acetate membrane 2825 (28% w/w vinyl acetate) or membrane/skin composite was also studied. The results showed that nicardipine

hydrochloride permeability through ethylene vinyl acetate 2825 membrane coated with TACKWHITE 4A MED/skin composite was higher than that coated with MA-31or MA-38.[12]

**7. Valsartan** :

Valsartan is rapidly metabolized by first pass metabolism so transdermal patch is preferred to reduce first pass metabolism. Valsartan is a poorly soluble drug with poor bioavailability & is a AT1 receptor antagonist . Its oral bioavailabilty averages 23% . Elimination occurs mainly by the liver in unchanged form with a half life of 6-9 hours; action Slasts 24 hours .

Transdermal patch containing valsartan were casted on glass slide by solvent casting Method. The drug matrix was prepared by dissolving hydroxyl propyl methyl cellulose in distilled water. polyethylene glycol as a plasticizer. drug was dissolved in 5 ml ethanol and homogeneous dispersion stired with magnetic stirrer. Eudragit RS 100 and ethyl cellulose was incorporated into drug reservoir and tween 80 as a penetration enhancer.after complete drying stored between sheet of wax paper in descicator and patch evaluated for drug content thickness ,weight variation,moisture uptake studies,moisture vapour transmission studies and in-vitro permeation studies.[13]

**8. Amlodipine** :

Amlodipine is a calcium ion antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodi[ine has half life of about 30-50 h and a bioavailability of 60-65% . It undergoes extensive first pass metabolism.

Hemangi J. Patel *et al.,* developed and evaluated matrix type transdermal drug delivery for sustained release of Amlodipine besilate using different polymers like Carbopol 934, 940, HydroxyPropyl Methyl Cellulose and Eudragit L100 in varied ratios. The permeability studies indicate that the drug is suitable for transdermal drug delivery. The patches were evaluated for various parameters like thickness, water-vapor permeability, tensile strength, drug content, diffusion and dissolution studies. The patches were further evaluated by DSC and SEM, to ensure uniform distribution of the drug and compatibility of drug with polymer.[14]

**9. Enalpril Maleate :**

Enalapril maleate is a prodrug act a the second ACE inhibitor approved in the United States. it is hydrolyzed by esterases in the liver to produce the active dicarboxylic acid, enalaprilat. Enalaprilat is a highly potent inhibitor of ACE. Although it also contains a "proline surrogate" . Enalapril is absorbed rapidly when given orally and has an oral bioavailability 60% . Enalapril has a half-life of only 1.3 hours, but enalaprilat, because of tight binding to ACE, has a plasma half-life of about 11 hours.

Pravin Gavali, prepared a transdermal patch of Enalapril Maleate by using different concentrations and polymeric grades of hydroxypropyl methylcellulose (K4M, K15M and K100M) for the development of transdermal drug delivery system .It is an antihypertensive drug. Matrix films were evaluated for their physicochemical characterization followed by *in vitro* evaluation. The Thickness and weight of patch increase with the increase in. Fourier transforms infrared spectroscopy and differential scanning calorimetry results confirmed that there is no interaction between drug and polymer used.[15]

**10. Timlol Maleate:**

Timolol maleate (TM) is a beta adrenoceptor-blocking agent used in treatment of cardiovascular diseases like myocardial infarction, angina pectoris and hypertension. [16]It is 8-10 times potent than propranolol. It is rapidly absorbed from gastrointestinal tract with peak plasma and metabolized up to 80% in liver with a mean half-life of 2.0-2.5 hr. [17]

Swarnlata Saraf *et al*., formulated two types of polymer patches; combination of hydroxy propyl methylcellulose (HPMC) and ethyl cellulose (EC) and with polyvinyl alcohol (PVA) alone. Methanol- chloroform (1:1) mixture is used to prepare polymer PVA matrix patches preparation having polymer concentration of 5, 10 and 15% in water with 0.5% glycerin as plasticizer.

The studies suggest that both reservoir as well as matrix system of transdermal delivery of TM is possible. The reservoir system followed zero order while the matrix system followed first order release profile. Among both matrix systems PVA (10%) patch have more permeability than HPMC: EC (2:8). When we compare both patches, the PVA (10%) system provide higher permeation rather than HPMC:EC (2:8) .[18]

**11.Diltiazem Hydrochloride :**

Subash S. Pilla has formulated a transdermal patch of Diltiazem Hydrochloride (DH), a calcium channel blocker, mainly use for the treatment of hypertension by using hydroxy ethyl cellulose, ethyl *cellulose* and Eudragit RLPO. deltiazem having half life 3-4.5 and low molecular weight. The prepared patches were spherical, uniform in shape and white in color and evaluated for physico-chemical characteristics, in vitro release profile and in vivo evaluation in albino mice. Higuchis plot studies revealed that the predominant mechanism of drug release was diffusion. [19]

**12.Captopril :**

Captopril is used as as antihypertensive agent act by inhibiting an angiotensin converting enzyme and due to its effectiveness and low toxicity is considered as a drug of choice in antihypertensive therapy[20] . It. Captopril shows 75% bioavailability.According to a previous research, the oxidation rate of captopril in dermal homogenateis significantly lower than the intestinal homogenate because the oxidative product of captopril, a captopril disulfide shows poor absorption from the intestine .[ 21]

Sunita Jain *et al*.,developed matrix diffusion type of TDDS of captopril employing different ratios of polymers, EC and HPMC as (3:1) and (2:2). The *in vitro* skin permeation and *in vitro* dissolution studies showed that captopril release was more in matrices containing ratio EC: HPMC as 2:2 compared to 3:1. Captopril from matrix containing EC: HPMC ratio 2:2 was able to penetrate through rabbit abdominal skin. The *in vivo* study shows that the prepared matrices were free from any irritating effect and stable for 3 months.[22]

**13. Nitrendipine:**

Nitrendipine is a potent antihypertensive which block calcium entry is reported to be well absorbed following oral administration, but undergoes extensive first pass metabolism and oral bioavailability in the range from 10% to 20% .

Tipre D *et al*., formulated a transdermal patch of f nitrendipine in Eudragit E100 pressure sensitive adhesive. To enhance flux, d-limonene, was investigated as a permeation enhancer, and effect of concentration of d-limonene on permeation kinetics of nitrendipine through guinea pig skin was examined. Film was evaluated for in-vitro flux though human skin to determine patch size needed to deliver drug through the transdermal route. Patches were evaluated for different parameters. Optimized transdermal therapeutic system was found relatively stable at refrigeration only. [24]

**14.Nifedipine:**

Nifedipine is a potent drug which is widely used for the treatment of hypertension. Due to extensive first pass metabolism its bioavailability is low.

Sankar V *et al*., fabricated and evaluated nifedipine transdermal patches. In which drug free polymeric films of EC was prepared to know their suitability for transdermal application as controlling membrane and plasticizer such as castor oil (30% w/w) and glycerol (40% w/w) were incorporated. In the study EC was used for the fabrication which had a good film forming property. The physicochemical evaluation study reveals that there were no physical changes like appearance, colour and flexibility when the films stored at room temperature. The *in vivo* drug release studies in rabbits shows that *in vivo* controlled delivery of nifedipine is possible with patches. Even though the drug release was slow during the initial hours (up to 4 h) from the EC patches containing 40% glycerol as plasticizer, the maximum percentage release was attained within 24 h. [25]

**15. Nicorandil :**

Nicorandil is a potassium channel activators, which exert their action by arteriodilating and venodilating properties, and

represents a novel type of compound for use in the treatment of angina pectoris and antihypertensive. It has a short half life and the usual oral dosage regimen is 5 to 40 mg taken two to four times a day. Hence, to reduce the frequency of administration and improve patient compliance, once a day TDDS of nicorandil is desirable.

Jamakandi VG *et al*., used a solvent casting technique to fabricate HPMC patches containing different grades of HPMC polymer (6 cps, 15 cps and K4M) as matrix base, polyethylene glycol as plasticizer and DMSO as penetration enhancer. Prepared matrix type patches were evaluated for their physicochemical characterization followed by *in vitro* and *ex vivo* studies on porcine ear skin. The result shows transdermal patches with 6 cps 2% w/v HPMC, 30% w/v PEG 400 and 6%w/v DMSO as a penetration enhancer showed a maximum release (44.7%) and it offers least resistance for the drug diffusion into the skin due to its high hydrophilic nature and high water permeability value to water.[26]

**16. Metoprolol :**

Metoprolol is a prototype of cardio-selective (β1) blockers having oral bioavailability 35% . It has short elimination half life of 2-3 hrs and undergoes extensive first pass metabolism.[27]

Meenakshi Bharkatiya *et al.,* prepared transdermal patch of metoprolol tartrate by solvent casting method by employing a the combinations of EC:PVP and Eudragit RL100:PVP in different proportions. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, flatness, tensile strength, hardness, folding endurance, drug content, swellability, surface pH, water vapor transmission, in vitro permeation and skin irritation studies.

FTIR, DSC and UV studies indicated no interaction between drug and polymers. The permeability of metoprolol tartrate was increased with increase in PVP content. The burst effect due to the incorporation of PVP was because of the rapid dissolution of the surface hydrophilic drug which results in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules and shows higher permeation rates. The in vitro drug permeation followed Higuchi kinetics as its coefficient of correlation values predominates over zero order and first order kinetics.

The patches were found to be free of any skin irritation. Based on the above observations, it can be reasonably concluded that Eudragit RL100/PVP polymers are better suited than EC/PVP polymers for the development of transdermal patches of Metoprolol tartrate

cells. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best in-vitro skin permeation through rat skin (Wistar albino rat) as compared to all other formulations. The results followed the release profile of Atenolol followed mixed zero-order and first-order kinetics in different formulation. However, the release profile of the optimized formulation indicated that the permeation of the drug from the patches was governed by a diffusion mechanism.

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