Transdermal Drug Delivery System with Antihypertensive Drugs

Ram Ujagar*[1], Dr. Sarika Shrivastava[2]

[1]Ph.D Scholar, Sanjeev Agrawal Global Education (SAGE) University, Bhopal

[2]Professor, Sanjeev Agrawal Global Education (SAGE) University, Bhopal

***Corresponding Authors**

Ram Ujagar

Email: bpart0001@gmail.com

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. Hypertension is one of the common disorders for the mankind. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity. The present article delivers a brief view on the work been done to increase the bioavailability of various antihypertensive drugs by formulated and delivered as transdermal patches. The different drugs includes carvedilol, metoprolol, atenolol, propranolol, labetolol, verapamil, indapamide, losartan, bisoprolol, timolol maleate, nicardipine hydrochloride, captopril, clonidine, pinacidil, nitrendipine, nicorandil, diltiazem hydrochloride, lisinopril, nifedipine, amlodipine, valsartan, enalapril maleate.

KEY WORD: Transdermal, Hypertension, indapamide, losartan, TDDS

INTRODUCTION

First transdermal patch approved in 1979 by FDA was of Scopolamine for motion sickness. Nitroglycerine was the second patch authorized in 1981. A large variety of patches for transdermal application are available on the market[1]. Transdermal delivery not only allows for continuous, predetermined, and consistent drug administration, but also allows for regulated

input of medicines with short biological half-lives and prevents pulsed entrance into systemic circulation, avoiding unwanted side effects. The oral route is the most common method of drug delivery, but it has some drawbacks, such as first pass metabolism (the rapid uptake and metabolism of an agent by the liver into inactive compounds immediately after enteric absorption and before it reaches the systemic circulation), drug degradation in the gastrointestinal tract due to enzymes, pH, and other factors. A new medication delivery method based on transdermal patches was developed to address these issues[2]. A Transdermal Drug Delivery System (TDDS) is a method of delivering drugs via the skin for local or systemic therapeutic effects. It is, together with oral medicine and injectable, one of the primary study topics for third-generation pharmacological preparations[3]. The drug's delivery technique, which is easy, simple to use, non-invasive, and improves patient compliance, is one of the reasons behind this[4]. TDDS also minimizes drug concentration fluctuations in the blood, maintains stable plasma levels, reduces the risk of overdosing, and facilitates drug detection[5,6]. Simultaneously, it avoids issues associated with oral administration, such as the impact of the gastrointestinal environment (pH, enzyme activity, drug-food interaction) on therapeutic effectiveness and the 'first pass effect.' Transdermal drug delivery systems were commonly used to treat various skin disorders. Also, substantive applications have been found in the management of angina pectoris, pains, smoking, cessation & neurological disorders such as Parkinson's disease[7,8]. Transdermal patches, are one of the novel pharmaceutical dosage form for the delivery of drugs upon application to the skin and into the bloodstream. By nature the patches are expected to provide controlled/sustained/modified delivery of drugs for defined period of time with predefined rate. Because the skin is such an efficient barrier, only medicines with a low molecular weight may be administered this way. Transdermal patches are currently accessible in a wide range of medicines. The first commercially available prescription patch was authorized by the US Food and Drug Administration in December 1979. Since then transdermal drugs continued to gain popularity along with further improvements to improve safety and efficacy. Further major step was the production of patches delivering peptide and even protein substances including growth hormone, insulin, and vaccines ect[9]. Transdermal patches can be categorized into three categories - first generation, second generation, and third generation. They are available in different sizes & having more than one ingredients. Once they apply on normal skin they deliver active ingredients into systemic circulation passing through skin barrier. A transdermal patch

containing high dose of drug inside is retained on the skin for prolonged period of time and enters into blood systemic circulation by diffusion process[10].

ANTIHYPERTENSIVE DRUGS DELIVERY THROUGH TDDS

Some of the antihypertensive drugs have already been formulated and evaluated as transdermal patches but most of them still been unexplored. Transdermal formulation of antihypertensive drug is promising aspect in near future. Mortality from heart diseases increases dramatically with age. Hypertension is one of the main causes of heart disease and, in recent years, the age adjusted hypertension and hypertensive disease death rates have been increasing[11]. Consequently, the prevention and treatment of hypertension is of major social significance[12]. Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mmHg, a criterion that characterizes a group of patients whose risk of hypertension-related cardiovascular disease is high enough to merit medical attention. Actually, the risk of both fatal and nonfatal cardiovascular disease in adults is lowest with systolic blood pressures of less than 120 mm Hg and diastolic BP less than 80 mm Hg; these risks increase progressively with higher systolic and diastolic blood pressures[13].

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[14].

CALCIUM CHANNEL BLOCKER

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 hr. Volume of distribution and t1/2 are exceptionally long: diurnal fluctuation in blood level is small1[15].

Tusnova Sharmin, et al (2020) designed to developed Hydroxypropyl Methylcellulose (HPMC) based polymeric films of amlodipine besylate to explore HPMC as a rate retardant polymer in transdermal drug delivery system. Films were formulated by the solvent casting method[16].

Theodore, E. Abraham et al (2016) developed and evaluated transdermal patches containing antihypertensive drug Amlodipine besylate. In-vitro permeation studies of formulations were

performed by using modified Franz Diffusion cell. All prepared formulations were of good physical stability. From all the studies performed it was found that formulation F7 shows optimum release[17].

Lincy John, et al (2014) designed and evaluated Amlodipine transdermal patches & compare these patches using polymers such as hydroxypropylmethylcellulose and chitosan . Amlodipine were prepared by solvent casting method by using polymers like hydroxypropylmethylcellulose and chitosan in different proportions(1%, 1.5%, 2% and 2.5%)[18].

John, Lincy et al (2013) designed and evaluated Amlodipine transdermal patches using polymers such as ethyl cellulose. Matrix type transdermal patches containing Amlodipine were prepared by solvent casting method by using polymers like ethylcellulose 1 %, 1.5 %, 2 % and 2.5 % and a total of eight formulations we re prepared. Out of these eight formulations of EC, 1.5 % Ethylcellulose (E6) was optimized since they produced a sustained and a complete release over a period of 24 hours[19].

Sanju Nanda, et al (2012) developed a matrix-type transdermal therapeutic system containing drug Amlodipine besilate with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (Eudragit RL/RS 100) polymeric systems by the solvent evaporation technique[20].

Diltiazem hydrochloride: Diltiazem is a non-DHP member of the group of drugs known as benzothiazepines, which are a class of calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some type of arrhythmia. The biological half-life of diltiazem is 3-4.5 hrs. Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect.

Parhi R, et al (2016) focused on the development of Diltiazem HCl (DTH) matrix film and its characterization by *in-vitro*, *ex-vivo* and *in-vivo* methods. Films were prepared by solvent casting method by taking different ratios of hydroxypropyl methylcellulose K4M (HPMC K4M) and Eudragit RS100. he *in-vivo* antihypertensive activity results demonstrated that formulation DF9 was effective in reducing arterial blood pressure in normotensive rabbits[21].

Limpongsa E, et al (2008) investigated the suitable polymeric films for the development of diltiazem hydrochloride (diltiazem HCl) transdermal drug delivery systems. Hydroxypropyl

methylcellulose (HPMC) and ethylcellulose (EC) were used as hydrophilic and hydrophobic film formers, respectively[22].

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 min, and duration of action is between 15-30 min. The half life of the drug varies between 2-4 hr and bioavailability ranges 20-40%.

Aboofazeli Reza et al. (2002), prepared and evaluated flux and elucidate mechanistic effects of formulation components on transdermal permeation of the drug through the skin. Based on the solubility results vehicles are selected and investigated, which include pure solvents alone and their selected blends. Among the systems studied, the ternary mixture of PG/OA/DMI and binary mixture of PG/OA showed excellent flux. The results showed that no individual solvent was capable of promoting NC-HCl penetration[23].

Y S R Krishnaiah et al (2002), developed a membranemoderated 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. The permeability flux of nicardipine hydrochloride through ethylene vinyl acetate (EVA) copolymer membrane was found to increase with an increase in vinyl acetate (VA) content in the copolymer. Nicardipine hydrochloride permeability through EVA 2825 membrane coated with TACKWHITE 4A MED/skin composite was higher than that coated with MA-31or MA-38[24].

Nifedipine: Nifedipine, a calcium channel blocker used in the treatment of angina pectoris and hypertension. Its half life is 2-4 hrs requires frequent dosing of the drug. Even though nifedipine is rapidly and almost completely absorbed from GI tract it undergoes extensive first pass metabolism (around60%) resulting in a poor bioavailability (45%) after oral administration.

Mohammed Gulzar Ahmed et al (2010), prepared Transdermal patches of nifedipine with different composition of PVP and PVA polymers were prepared by moulding technique patches containing 3:2 ratio of PVA: PVP were found to be yellow in color, homogenous and flexible compared to others. Effect of penetration enhancers on the in- vitro permeation of nifedipine across rat abdominal skin was carried out for patches with 3 different types of penetration

enhancers showed all the patches with permeation enhancer increased the permeation of the drug from the membrane[25].

Verapamil: Verapamil is a calcium channel blocker. It has cardio depressant property. It is widely used in the treatment of angina, hypertension and supraventricular tachyarrhythmias. The plasma half-life of verapamil hydrochloride is 2-7 hrs, which necessitates multiple dosing. It is approximately 90% absorbed from the gastrointestinal tract but is subjected to considerable first pass metabolism and its bioavailability is around 20-30%.

Chen, Y.-s et al (2022) developed a sustained-release transdermal delivery system containing losartan potassium (LP) and verapamil hydrochloride (VPH). LP and VPH have low bioavailability and long half-life. The prepared LP-VPH transdermal patch showed good stability and no skin irritation. The developed LP-VPH TDDS showed a sustained-release effect and good characteristics and pharmacokinetics; therefore, it is an ideal formulation[26].

Marapur SC, et al (2018) developed and evaluated a matrix type of transdermal drug delivery system containing Verapamil Hydrochloride. The series of formulations containing Verapamil Hydrochloride were formulated by using different polymers like HPMC (hydrophilic), CAP (hydrophobic) and EC (hydrophobic) in different ratios by solvent evaporation technique[27].

Jatim sood et al (2013) developed matrix-type transdermal patches of verapamil hydrochloride (VPL) with combinations of hydroxypropyl methyl cellulose (HPMC) and hydroxy propyl cellulose (HPC) as matrix polymers and to investigate the influence of oleic acid (OA) on in vitro permeation of VPL through rat skin. In vitro release profiles showed that from optimized combination the release of the drug was sustained and it extended over a period of 24 hr[28].

V. Devi Kusum et al (2003), designed and evaluated diffusion controlled transdermal patches of verapamil hydrochloride using four different polymers (individual and combination): Eudragit RL100 (ERL100), Eudragit RS100 (ERS100), hydroxypropyl methylcellulose 15 cps (HPMC), and ethyl cellulose (EC), of varying degrees of hydrophilicity and hydrophobicity. Different formulations were prepared with ERL100 being the parent polymer. It was concluded that the patch containing ERL100 and HPMC in the ratio 8:2 has achieved the objectives of transdermal drug delivery system, such as avoidance of first pass effect, extended release, and reduced frequency of administration [29].

THIAZIDES DERIVATIVES

Indapamide: Indapamide is a long-acting hypertensive with both diuretic and vasodilative action. first-line drug for the treatment of first-line drug for the treatment of hypertension.

Nagai N, et al (2019) designed the transdermal formulations containing indomethacin (IMC)—1% IMC was crushed with 0.5% methylcellulose and 5% 2-hydroxypropyl-β-cyclodextrin. In an in vitro experiment using a Franz diffusion cell, the skin penetration in N-IMC/MT gel was enhanced than the N-IMC gel, and the percutaneous absorption (AUC) from the N-IMC/MT gel was 2-fold higher than the N-IMC gel. Findings suggest the utility of a transdermal drug delivery system to provide the easy application of solid nanoparticles (SNPs) [30].

G S Sanap et al (2008), employed solvent casting method for preparing transdermal monolithic system using HPMC and EC polymers by incorporating glycerin and dibutyl phthalate as plasticizer, respectively. Eight monolithic systems were prepared. The results indicated which may attributed to high water vapor permeability of HPMC film and hydrophobic nature of EC. HPMC polymer (F3) has shown maximum release than that of systems containing other vegetable oils as permeation enhancers[31].

Hydrochlorothiazide:

Thyagarajan A, et al (2015) developed a transdermal patch containing Atenolol and hydrochlorothiazide in combination using blends of different polymeric combinations such as hydroxypropyl methyl cellulose, sodium alginate, and polyethylene glycol. The patches were subjected to physicochemical tests and in-vitro drug release study. Developed transdermal delivery system containing Atenolol & hydrochlorothiazide might be a milestone in the combinational therapy of hypertension[32].

Agrawal SS, et al (2010) compares the bioavailability of these two study drugs from a TDDS with conventional immediate release oral tablets in healthy volunteers. It was concluded from these observations that the TDDS meets the intended goal of at least 2day management of stage II hypertension with application of a single transdermal patch, hence improving patient compliance over the inconvenience seen with frequent oral administration[33].

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Captopril: Captopril has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered asa drug of choice in anti-hypertensive therapy due to itseffectiveness and low toxicity[34].

Bharati R. Gondane, et al (2023) developed Captopril liposomsal gel in order to accomplish short half life of captopril to eliminated a first-pass metabolism of captopril in GIT. To enhances the bio-availability of drug. To increases a sustained release of drug for prolonged period of time. Firstly, developed liposomes by ether injection method and then formulated a liposomal gel by using dispersion method. Captopril gel formulation used transdermally to treat a hypertension. Also, eliminated a problem of orally administered drug caused. It also protects a drug from hepatic degradation. Increase better patient compliances[35].

Pravin Uttekar, et al (2016) formulated matrix type TDDS which contains the drug captopril using hydroxy propyl methyl cellulose E-15(HPMC E-15), Eudragit RS 100 as a release controlling polymers. The formulated patches were characterized by diffusion studies. The work was aimed to develop the TDDS which controls the release of captopril up to max time period[36].

S, Duraivel et al (2014) formulated a Transdermal drug delivery system of captopril, to investigate the effect of different penetration enhancers, and to study the in vitro permeation characteristics of the drug through the excised rat skin. Transdermal patches of captopril were formulated using EC, PVA, PVP, PEG6000. In-vitro skin permeation studies indicated that PVA: PEG6000 matrix type film may be fabricated in to effective system and DMF showed better result[37].

Mohabe, Vandana et al (2011) Transdermal matrix patches of captopril were prepared by casting method employing different ratios of polyvinyl alcohol, ethyl cellulose, polyvinyl pyrrolidone and hydroxypropyl methylcellulose. The hydrophilic and hydrophobic polymers in combination showed sufficient potential for the development of transdermal drug delivery system of captopril[38].

Rajesh Sreedharan Nair et al (2013) formulated and evaluated the matrix type transdermal drug delivery systems of captopril, with different polymer combinations and penetration enhancers. Eight formulations (F1eF8) were prepared by the solvent casting technique using varying proportions of polymers such as hydroxypropyl methylcellulose (HPMC), poly-ethylene

glycol (PEG) 400, along with the permeation enhancers such as menthol and aloe vera at different concentrations. The formulation coded as F6 was found to be the ideal patch, shown the maximum drug permeation of 90.04% at the end of 24 h followed Higuchi diffusion kinetics[39].

Enalapril : Enalapril is used in the treatment of hypertension, congestive heart failure and to alleviate strain on heart damaged by heart attack. EP has low logPof 0.19 and the effective half-life following multiple doses is 11–14 h. It has low bioavailability (about 40–60%) due to its hepatic first-pass metabolism. The administration of this antihypertensive drug via the transdermal route is needed to achieve controlled release in order to minimize adverse effects associated with oral administration and to improve its therapeutic efficacy and bioavailability[40].

Chandrashekar C. Patil, et al (2016) developed and evaluated matrix type transdermal patch of Ramipril, an ACE inhibitor and anti hypertensive drug using with Eudragit RL 100, Eudragit RS 100 and Ethyl cellulose in different ratios prepared by the Mercury Substrate Technique. It is shown that drug release follows zero order and the mechanism of release is diffusion from the polymer. All the systems were found to be stable with respect to drug content as well as physical changes at 40 ºC and 75 % RH[41].

Natrajan, R. et al (2011) developed the Transdermal matrix patches of Enalapril maleate, an angiotensin converting enzyme inhibitor. The Matrix patches were prepared by solvent casting technique with propylene glycol (3%) as plasticizer and Water as solvent. The patches were formulated by using hydroxyl propyl methyl cellulose alone having drug and polymer ratio 1:5, 1:7, 1:9 and one more patch was formulated using hydroxyl propyl methyl cellulose with permeation enhancer, Span 80 (1%) in ratio of 1:9. Enalapril maleate could be administered transdermally through the matrix type TDDS for effective control of hypertension; congestive heart failure and angina pectoris[42].

Lisinopril: Lisinopril is used against chronic conditions like hypertension, diabetes nephropathy and cardiac heart failure. It does not undergo metabolism and excreted unchanged in urine. The logP and half-life of LP is1.2 and 12 h, respectively, thus effective as single daily dose medication, but severely suffers from average inter-subject bioavailability of 25%[43].

Jain A, et al (2012) focused to assess iontophoretic permeation of Lisinopril at different current densities and concentrations for development of patient-controlled active transdermal system.

The obtained results indicate that permeation rate of Lisinopril across the pigskin can be considerably enhanced, controlled or optimized by the use of Iontophoresis technique[44].

Banweer et al. (2010) overcome the poor oral bioavailability of the LP, transdermal patches were prepared using HPMC and polyvinyl alcohol in 1:1 ratio as polymeric matrix using glycerol (6%) as plasticizer. Isopropyl alcohol and oleic acid alone and in combination were added as the penetration enhancers in different concentrations and ratios. It was described that blend of oleic acid and isopropyl alcohol produced more pronounced release via goat skin, which clearly dictates the synergistic effect of the enhancers if used in combination and the effect found to be dependent on the concentration of the enhancers[45].

Ramipril: Ramipril is an antihypertensive drug, has logP of 0.92. Following oral administration it undergoes extensive firstpass metabolism and presented a bioavailability of 55–65%. Moreover, it has a half-life of 13 to 17 h. RP seems to be a potential candidate for transdermal delivery system[46].

K. P. Sampath Kumar, et al (2018) formulated Transdermal patch containing by solvent casting technique using as film former and propylene glycol as plasticizer such Transdermal patches are advantages in providing effective treatment for Hypertension with enhanced patient compliance. the formulation R10 is emerged as ideal formulation for Ramipril because it showed better release with sustained effect as compared to other formulations[47].

Chandrashekar et al (2016) developed and evaluated matrix type transdermal patch of Ramipril, an ACE inhibitor and anti hypertensive drug using with Eudragit RL 100, Eudragit RS 100 and Ethyl cellulose in different ratios prepared by the Mercury Substrate Technique. Drug permeation through rat skin was carried out using Keshary-chein diffusion cells by in-vitro study. All the systems were found to be stable with respect to drug content as well as physical changes at 40 ºC and 75 % RH[48].

ANGIOTENSIN –II RECEPTOR BLOCKERS (ARBs)

Losartan: Losartan was the first ARB and it is widely used for the management of hypertension (Velasquez, 1996). LS is the drug of choice for sustained release formulation since it has a short half-life of about 1.5 to 2 h, which requires frequent dosing necessary to maintain the therapeutic

blood level for long-term treatment. LS shows considerable first-pass metabolism in the liver and thereby has poor bioavailability (25–35%) when administered orally[49].

Almazan E A, et al (2020) developed of a losartan potassium patch for the treatment of hypertension showed that a combination of hydrophobic and hydrophilic polymers, using as a plasticizer citroflex and succinic acid as a cohesion promoter result in homogeneous films. In the in-vitro penetration studies by passive diffusion, a flow (J) of 42.2 μg/cm2h, a permeability constant (kp) of 2.1793E-03 cm/h and a latency time (tL) of 17.20 h and with the use of microneedles a flow (J) of 61.7 μg/cm2h, a permeability constant (kp) of 3.1869E-03 cm/h and a latency time (tL) of 17.74 h were obtained[50].

Kumar, et al (2019) prepared patches by solvent evaporation method. The patches were subjected for following evaluation parameters such as physical appearance, weight variation, thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss, water vapour transmission rate, tensile strength, diffusion studies and skin irritation studies. he patches F4 to F6 were prepared by incorporating permeation enhancers, which showed promising result. The patches containing oleic acid shows near complete release followed by DMSO and DMF[51].

Adamude,et al (2017) designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of Losartan potassium. Study concluded that Losartan potassium can be formulated into the transdermal matrix type patches to sustain its release characteristics. Polymeric composition of batch TP1 (PVP K30: Chitosan: 70:30) was found to be the best choice for manufacturing transdermal patches of Losartan potassium among the formulations studied[52].

Valsartan: Valsartan is a highly selective angiotensin II type 1 receptor blocker that has been widely used for the treatment of hypertension. When administrated orally in humans, VS is rapidly absorbed. It has a favorable logP(4.5) and mean halflife (7.5 h). Its Cmaxoccurs at 2 to 4 h, and it is then excreted into bile. The oral bioavailability of VS is 10–35%, which is mainly due to poor absorption in the gastrointestinal tract. Additionally, food intake is known to reduce the Cmax and AUC of VS by 50 and 40%, respectively. The transdermal administration of VS is a possible solution to overcome these problems[53].

Ahad et al. (2014b), developed transdermal carbopol gel formulation bearing VS and 1,8-cineole. The optimized formulation demonstrated highest transdermal flux, with an enhancement ratio of 4.53 when compared to control gel formulation. Incorporation of 1,8-cineole and ethanol in gel formulation enhance the permeation of VS significantly. Skin irritation study revealed that the developed formulation was safe, less irritant and well tolerable formulation for transdermal delivery and was successful in reverting the rat BP to normal values in experimental hypertensive rats. Optimized a transdermal gel formulation of VS using the Box–Behnken design containing iso-eucalyptol as permeation enhancer and evaluated for pharmacokinetic study. The independent variables were carbopol 940, polyethylene glycol 400 and ethanol, while transdermal flux, Tlag, and gel viscosity were the reported dependent variables. Overall, it was accounted that iso-eucalyptol can be successfully used as a potential permeation enhancer for the enhancement of skin permeation and bioavailability of lipophilic drug[54].

Rizwan et al., investigated the feasibility of VS for transdermal delivery and examined the effect of various terpenes, namely forskolin, 1,8-cineole, d-limonene, l-menthol and linalool on skin permeation of VS. Authors exhibited that, no apparent skin irritation (erythema, edema) was observed on treatment of skin with aforementioned terpenes. Authors concluded that 1,8-cineole was found to be the most effective enhancer for diffusion of VS through rat skin[55].

Olmesartan: Olmesartan is a selective AT1subtype angiotensin II receptor antagonist. It exhibits more than 12 500-fold greater affinity for the angiotensin II receptor type 1 than for the angiotensin II receptor type 2, making it theoretically the second most potent agent [56]. Oral OS 10–40 mg once daily is recommended for the treatment of adult patients with hypertension. It is an effective and well-tolerated agent, with a long duration of action, and single daily dose may be used to treat hypertension[57].

El-Dahmy et al (2023) aimed to develop oleogel formulations to decrease OLM side effects and boost its therapeutic efficacy and bioavailability. OLM oleogel formulations were composed of Tween 20, Aerosil 200, and lavender oil. The pharmacokinetic study showed that the optimized oleogel increased OLM's bioavailability by more than 4.5- and 2.5-folds compared to the standard gel and the oral market tablet, respectively. These results confirmed the success of oleogel formulations in the transdermal delivery of OLM[58].

Naga et al (2022) created matrix-type Olmesartan medoxomil transdermal patches utilizing the solvent evaporation method and various polymer ratios, including HPMC 15 cps, HPMC 5 cps, and Eudragit S 100. Plasticizers like glycerin, propylene glycol, and PEG 200 are used, along with solvents like methanol and chloroform. According to FT-IR studies, pure drugs and excipients are compatible with each other. The generated patches are assessed for their thickness, weight variation, folding endurance, moisture content, drug content, surface pH, and in vitro diffusion studies. Among all the formulations, F6 showed the best characteristic properties and in vitro drug diffusion[59].

Telmisartan: Telmisartan is used in the management of hypertension. TS bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial BP. It is used alone or in combination with other classes of anti-hypertensives for the treatment of hypertension[60].

Kandalkar A, et al (2021) developed Transdermal patches of Telmisartan and Telmisartan plus various extract of Cinnamon bark to find out the bioenhancing effect of various extract of Cinnamon bark. The transdermal patches were formulated using solvent casting technique with the help of various polymers. Formulation no. F37 shows maximum bioenhancing action compared to all other patches which contains Telmisartan along with the Ethanolic extract of the Cinnamon bark[61].

Yadav, et al (2017) developed a polymer matrix diffusion controlled transdermal drug delivery system containing drug Telmisartan with different ratio of hydrophilic (HPMC) and lipophilic (EC, Eudragit RS 100) polymeric system by solvent casting technique. The invitro permeation study performed by diffusion cells. The maximum invitro % drug release was observed up to 48 hrs with formulation F8 containing HPMC: EC: Eudragit RS 100 in (5:0:1) ratio[62].

Candesartan: Candesartan may be used alone or with other agents to treat hypertension. It is administered orally as the prodrug, CS-cilexetil, which is rapidly converted to its active metabolite during absorption in the gastrointestinal tract[63].

Hira et al (2019) formulated and characterized the transdermal patch of Candesartan celexitil. The objective is study was to increase the bioavailability of drug. In the present study, transdermal patch of Candesartan celexitil were prepared by solvent casting technique employing

HPMC cps 50 polymer and glycerin as plasticizer using mercury as substrate. Total thirteen formulation (F1-F13) were prepared. It was concluded that the prepared formulation F13 (4% w/v of oleic acid) showed highest cumulative percent drug release and increase the bioavailability of the drug[64].

Reddy, et al (2013) developed a suitable matrix type transdermal patch of Candesartan Cilexetil, using blends of two different types of polymeric combinations viz. HPMC K100 and Eudragit RL100 prepared formulations. Based on the observation, it was revealed that HPMCK100-eudragit RL100 polymers are better suited for the development of Candesartan cilexetil transdermal patches[65].

POTASSIUM-CHANNEL OPENERS

Pinacidil: Pinacidil is a lipophilic drug used for the management of mild-to-moderate essential hypertension and has fewer side effects. It is belonging to the class of potassium channel openers. It acts by opening the potassium channels leading to hyperpolarization and peripheral vasodilation. It possesses low oral bioavailability (57%) due to hepatic first-pass metabolism after oral administration. It has a logP of 0.107 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, PD is an ideal drug candidate for transdermal drug delivery[66].

Krosuri, et al (2021) formulated and evaluated matrix type transdermal patches of pinacidil monohydrate in order to improve patient compliance by sustaining its action and by avoiding its gastrointestinal side effects. he developed transdermal films prolonged release for 24 hrs and thus found useful to improve the patient compliance of Pinacidil monohydrate[67].

BETA - BLOCKERS

Carvedilol: Carvedilol is a β1 + β2 + α 1 adrenoceptor blocker; produces vasodilation due to α1 blockade as as calcium channel blockade, and has antioxidant property. It has been used in hypertension and is the β blocker especially employed as cardioprotective in congestive heart failure (CHF). Oral bioavailability of carvedilol is 30%. It is primarily metabolized and has a half-life of 6-8 hrs.

Mo L et al (2022) optimized and evaluated transdermal patch of Carvedilol by the use of different polymer and different permeation enhancers which help to release drug in controlled action and thereby increase the bioavailability of the drug. The conclusion was, transdermal patch of Carvedilol which contains Eudragit RS-100 polymer and Span 80 as penetration enhancer produced sustained and continued drug release[68].

Mo, et al (2021) optimize and evaluate transdermal patch of Carvedilol by the use of different polymer and different permeation enhancers which help to release drug in controlled action and thereby increase the bioavailability of the drug. The conclusion was, transdermal patch of Carvedilol which contains Eudragit RS-100 polymer and Span 80 as penetration enhancer produced sustained and continued drug release[69].

Niharika Lal, et al (2018) prepared Transdermal patches containing Carvedilol by spreading method by using a fixed concentration of various grades of acrylic polymer; drug and penetration enhancers. The patches were evaluated for different physical parameters with Ex-vivo permeation studies. Skin irritation studies are conducted by using Albino Rats. Ex-vivo permeation across excised rat skin from these formulated carvedilol patches were found to be sustained over 12 h and followed the zero-order model with Fickian diffusion mechanism. The effect of permeation enhancers was in order: Span 80> farnesol >oleic acid. The skin irritation test demonstrated absence of any sign of skin irritation[70].

Pisipati Aparna, et al (2013) developed and optimized carvedilol transdermal delivery system. F19 yielded release profile nearer to the theoretical predictions with R 2 of 0.9888 and followed Higuchi ki netics. Thus a diffusion-mediated carvedilol matrix patch was successfully developed[71] .

Metoprolol: It is a prototype of cardio-selective (β1) blockers; is incompletely absorbed (oral bioavailability 35%), has short elimination half life of 2-3 hrs and undergoes extensive first pass metabolism.

Chauhan, et al (2019) formulated, developed and evaluated metoprolol tartrate transdermal patches using various synthetic and natural penetration enhancers. . It can be concluded that naturally occurring volatile oils i.e., terpenes appear acceptable permeation enhancer and shows the best permeation across skin as indicated by high percutaneous enhancement ability[72].

Malipeddi et al (2017) developed matrix-type transdermal drug delivery system (TDDS) of metoprolol tartrate using polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA). The transdermal films were evaluated. The transdermal films showed good stability in the 180-day stability study. It can be concluded that the TDDS of MPT can help in bypassing the first-pass effect and will provide patient improved compliance, without sacrificing the therapeutic advantages of the drugs[73].

Anisree, et al (2012) formulated different matrix-type transdermal films containing Metoprolol tartrate with an objective to study the effect of polymers on the release characters. The fabricated films were evaluated for various parameters. Invitro permeation studies were carried out to identify the ideal film. The formulation having the polymeric combination of Ethyl cellulose and Hydroxy propyl methyl cellulose (1.5: 3.5) met all the evaluation parameters and selected as ideal formulation[74].

Atenolol: Atenolol is relatively a selective β1blocker having low lipid solubility. It is completely absorbed orally, but first pass metabolism is not significant. It is one of the most commonly used β blockers for hypertension and angina.

P Eswaramma et al (2010) developed matrix type transdermal films of atenolol Formulated films were evaluated physically. In-vitro permeation studies of formulations were performed by using Franz diffusion cells. The results followed the release profile of Atenolol followed mixed zero-order and first-order kinetics in different formulation. These results indicate that the formulation containing the F4 [CAP : PVP (6:1)] has shown optimum release in concentration independent manner[75].

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

Guru Sharan et al 2010) prepared Propranolol hydrochloride loaded patches using solvent casting and evaporation technique and checked the effect of various permeation enhancers on formulated patches. They concluded that, formulations are non irritable to the skin tissue and it can be safer for therapeutic use[76].

Labetolol: Labetolol is α and β non-selective blocker of adrenergic receptors. It binds competitively with these receptors and inhibits proliferation of cardiovascular symptoms e.g. hypertension. It also undergoes extensive hepatic first pass metabolism (60-75%) leading to poor bioavailability on oral administration.

Mittal A. et al (2009) developed and evaluated matrix type transdermal films containing new polymeric combinations (Eudragit E PO/Eudragit RL 100 & Plasdone S 630) as polymers and Labetalol Hydrochloride (LBHCl) as a model drug by film casting technique. The optimized formulation was found to be stable at ambient storage conditions and holds promise for improved bioavailability and better management of hypertension on long term basis[77].

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 amount 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 healthcare treatment 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 drug delivery 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.

Amongst the approaches used, chemical penetration enhancers have been intensively investigated over the years. Extensive research during the past two decades has revealed considerable information on several classes of chemical penetration enhancers. Efforts have been directed at identifying safe and effective enhancers from both natural products and synthetic chemicals. There have been noteworthy research attempts made globally to examine the percutaneous permeation and to develop TTS of various antihypertenstion drugs.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Dipen Patel, Sunita A. Chaudhary, Bhavesh Parmar, Nikunj Bhura, Transdermal Drug Delivery System: A Review, The Pharma Innovation. 2012; 1(4):66-75.
2. Nidhi S. A Brief Review on Transdermal Patches. Organic & Medicinal Chem IJ. 2018; 7(2):55570.
3. Hao, Y.; Li, W.; Zhou, X. L.; Yang, F.; Qian, Z. Y. Microneedles-based transdermal drug delivery systems: A review. J. Biomed. Nanotechnol.2017; 13:1581-1597.
4. Barry BW. Mode of action of penetration enhancers in human skin. J Control Release 1987; 6: 85-97.
5. Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. Drug Deliv. 2016; 23(2):564-578.
6. Meng S, Zhang C, Shi W, Zhang XW, Liu DH, Wang P, Li JX, Jin Y. Preparation of osthole-loaded nano-vesicles for skin delivery: Characterization, in vitro skin permeation and preliminary in-vivo pharmacokinetic studies. Eur J Pharm Sci. 2016 Sep 20; 92:49-54.
7. Arti Kesarwani, Ajit Kumar Yadav, Sunil Singh, Hemendra Gautam, Haribansh N Singh. A review-Theoretical aspects of Transdermal Drug Delivery System. Bulletin of Pharmaceutical Research. 2013; 3(2):78-89.
8. Venkatraman S, Gale R. Skin adhesives and skin adhesion 1. Transdermal drug delivery systems. Biomaterials 1998; 19(13):1119-36. https://doi.org/10.1016/S0142-9612(98)00020-9
9. Wu J, Nyborg W, editors. Emerging Therapeutic Ultrasound. London: Imperial College Press; 2006.
10. Z. A. M. Yasin, F. Ibrahim, N. N. Rashid, M. F. M. Razif, and R. Yusof. The importance of some plant extracts as skin anti-aging resources: a review. Current Pharmaceutical Biotechnology. 2017; 18 (11):864-876.
11. Hoyert DL, Kung HC and Smith BL: Deaths: preliminary data for 2003. National Vital Statistics Reports 2005; 53:1–48.

12. Kim J and Kitakaze M: Prevention and treatment of the hypersensitive organopathy—the necessity of cardiovascular protection. Nippon Rinsho 2004; 62:120–127.
13. Brunton Laurence L, Lazo John S, Parker Kieth L: Goodman &Gilman's The pharmacological basis of therapeutics. McGrawHill, New York, Eleventh edition 2006.
14. Sivakumar T, Selvam Panner R and Singh Anoop Kumar: Transdermal drug delivery systems for antihypertensive drugs -A review. International Journal of Pharmaceutical and Biomedical Research 2010; 1(1):1-8.
15. Tripathi KD: Essentials of Medical Pharmacology. Jaypee Brothers Medical publisher(P) Ltd, Sixth edition 2008
16. Tusnova Sharmin, Mamun OR Rashid, Giash Uddin, Mohammad Salim Hossain, Sayema Arefin, Monir Hossain. Formulation Design and Characterizationof Transdermal Films of Amlodipine Besylate for Enhancing Therapeutic Efficacy. Jordan Journal of Pharmaceutical Sciences, 2020;13(4): 379-87
17. Theodore, E. Abraham et al. "Formulation and evaluation of transdermal patches of amlodipine besylate. International research journal of pharmacy, 2016; corpus ID: 56126034.
18. Lincy John, Arun Kumar. Comparison of amlodipine transdermal patches using hydroxypropylmethylcellulose and chitosan. Asian J Pharm Clin Res, 2014;7(1): 86-90
19. John, Lincy & Kumar, Arun & Samuel, Sandra. (2013). Formulation and Evaluation of Amlodipine Transdermal Patches using Ethyl Cellulose. International Research Journal of Pharmacy. 2013;4: 84-88.
20. Sanju Nanda, Kamal Saroha, Bhavna Yadav and Benika Sharma. Formulation and Characterization of Transdermal Patch of Amlodipine Besylate. International Journal Of Pharmaceutical And Chemical Sciences, 2012;1(3): 2012.
21. Parhi R, Suresh P. Transdermal delivery of Diltiazem HCl from matrix film: Effect of penetration enhancers and study of antihypertensive activity in rabbit model. J Adv Res. 2016 ;7(3):539-50.
22. Limpongsa E, Umprayn K. Preparation and evaluation of diltiazem hydrochloride diffusion-controlled transdermal delivery system. AAPS PharmSciTech. 2008;9(2):464-70.
23. Aboofazeli Reza, Zia Hossein and Needham E Thomas: Transdermal Delivery of Nicardipine: An Approach to In Vitro Permeation Enhancement. Drug Delivery 2002; 9(4):239 – 247.

24. Krishnaiah YSR, Satyanarayana V and Bhaskar P: Influence of limonene on the bioavailability of nicardipine hydrochloride from membrane-moderated transdermal therapeutic systems in human volunteers. International Journal of Pharmaceutics 2002; 247:91-102
25. Mohammed Gulzar Ahmed, GB Kumar Kiran and BP Kumar Satish. Formulation and Evaluation of Nifedipine Transdermal Patches. Journal of Pharmacy Research 2010; 3(8):1785-1787
26. Chen, Y.-s.; Sun, Y.-y.; Qin, Z.-c.; Zhang, S.-y.; Chen, W.-b.; Liu, Y.-q. Losartan Potassium and Verapamil Hydrochloride Compound Transdermal Drug Delivery System: Formulation and Characterization. *Int. J. Mol. Sci.* 2022, *23*, 13051.
27. Marapur SC, Wali DS, Hunasagi BS, Chetankumar M, Patil RG, Formulation and evaluation of transdermal drug delivery system of verapamil hydrochloride, Journal of Drug Delivery and Therapeutics. 2018; 8(6-s):70-77
28. Jatim sood varinder kaur, pravin pawar., Transdermal Delivery of Verapamil HCl: Effect of Penetration Agent on In Vitro Penetration through Rat Skin. J App Pharm Sci. 2013; 3 (03): 044- 051.
29. Kusum Devi V, Saisivam S, Maria GR and Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Development and Industrial Pharmacy 2003; 29(5):495-503
30. Nagai N, Ogata F, Yamaguchi M, Fukuoka Y, Otake H, Nakazawa Y, Kawasaki N. Combination with l-Menthol Enhances Transdermal Penetration of Indomethacin Solid Nanoparticles. Int J Mol Sci. 2019 Jul 25;20(15):3644.
31. Sanap, Dr Gajanan & Dama, GY & Hande, AS & Karpe, SP & Nalawade, SV & Kakade, RS & Jadhav, UY. (2008). Preparation of transdermal monolithic systems of indapamide by solvent casting method and the use of vegetable oils as permeation enhancer. International Journal of Green Pharmacy. 2. 10.4103/0973-8258.41189.
32. Thyagarajan A, Udaya Chander JSJ, Senthil Kumar C, Sreenivasan V, Venkata Narayanan R. Preparation, In-Vitro Characterization of Transdermal Patch Containing Atenolol and Hydrochlorothiazide: A Combinational Approach. J App Pharm Sci, 2015; 5 (Suppl 3): 033-039.

33. Agrawal SS, Aggarwal A. Randomised, cross-over, comparative bioavailability trial of matrix type transdermal drug delivery system (TDDS) of carvedilol and hydrochlorothiazide combination in healthy human volunteers: a pilot study. Contemp Clin Trials. 2010 Jul;31(4):272-8.
34. Nur AO, Zhang JS. (2000). Recent progress in sustained/controlled oral delivery of captopril: an overview. Int J Pharm 194:139–46
35. Bharati R. Gondane, Dinesh M. Biyani, Milind Umekar. Formulation and evaluation of captopril transdermal liposomsal gel. Formulation and evaluation of captopril transdermal liposomsal gel; 2023;9(8):219-36.
36. Pravin Uttekar, Akshata Kulkarni, Pravin Chaudhari, Manoj Dhage and Vishal Dhangarmali. Formulation and Evaluation of Captopril Transdermal patches for the treatment of hypertension. Der Pharmacia Lettre, 2016, 8 (5):12-16
37. S, Duraivel & Bhowmik, Debjit. Formulation and evaluation of captopril Transdermal Patches. Elixir Pharmacy, 76 (2014) 28209-28213.
38. Mohabe, Vandana & Akhand Giri, Rachana & Pathak, Anupam. (2011). Preparation and evaluation of captopril transdermal patches. Bulletin of Pharmaceutical Research 2011;1(2):47-52
39. Rajesh Sreedharan Nair Tai Nyet LingMohamed Saleem Abdul ShukkoorBalamurugan Manickam. Matrix type transdermal patches of captopril: Ex vivopermeation studies through excised rat skin. Journal of pharmacy research, 2013;6: 774-779.
40. Ferguson RK, Vlasses PH, Swanson BN, et al. (1982). Effects of enalapril, a new converting enzyme inhibitor, in hypertension. Clin Pharmacol Ther 32:48–53.
41. Chandrashekar C. Patil, Bhavin Patel, Vitthal. K.Vijapure. Formulation and Evaluation of Transdermal Drug Delivery System of Ramipril. Research J. Pharm. and Tech 2016; 9(12):2127-2134.
42. Natrajan, R. & Rajendran, N.N. & Sabareesh, M. & Selvaraj, Surya. (2011). Formulation and evaluation of transdermal delivery of enalapril maleate. International Journal of Pharmaceutical Research. 3. 73-78.
43. Gomez HJ, Cirillo VJ, Moncloa F. (1987). The clinical pharmacology of lisinopril. J Cardiovasc Pharmacol 9:S27–34.

44. Jain A, Nayak S, Soni V. Iontophoretic permeation of lisinopril at different current densities and drug concentrations. Adv Pharm Bull. 2012;2(2):239-44.
45. Banweer J, Pandey S, Pathak AK. (2010). Formulation, optimization and evaluation of matrix type transdermal system of lisinopril dehydrate using permeation enhancers. Drug Invent Today 2:134–7.
46. Shafiq S, Shakeel F, Talegaonkar S, et al. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm ,2007;66:227–43
47. K.P.Sampath Kumar, Debjit Bhowmik , Rishab Bhanot. Design and Development of Ramipril Transdermal Patch For Treating Hypertension. Indian Journal of Research in Pharmacy and Biotechnology, 2018, 6(2):47- 53
48. Chandrashekar C. Patil, Bhavin Patel, Vitthal. K.Vijapure. Formulation and Evaluation of Transdermal Drug Delivery System of Ramipril. Research J. Pharm. and Tech 2016; 9(12):2127-2134
49. Carr AA, Prisant LM. (1996). Losartan: first of a new class of angiotensin antagonists for the management of hypertension. J Clin Pharmacol 36:3–12
50. Almazan E A, Castañeda P S, Torres R D, Escobar-Chavez J J. Design and Evaluation of Losartan Transdermal Patch by Using Solid Microneedles as A Physical Permeation Enhancer. Innov J Pharm Res. 2020;19(1):e124558.
51. Kumar, P & K, Balamurugan. (2019). Design and evaluation of transdermal drug delivery of an losartan drug. IJIPSR, 2014;2 (7): 1473-1484
52. Adamude, F. A. ., and U. K. Chukwuka. “Development and in-vitro evaluation of matrix-type transdermal patches of losartan potassium”. *Universal Journal of Pharmaceutical Research*, vol. 2, no. 2, Mar. 2017,
53. Israili ZH. (2000). Clinical pharmacokinetics of angiotensin II(AT1) receptor blockers in hypertension. J Hum Hypertens 14:S73–86.
54. Ahad A, Aqil M, Kohli K, et al. (2014). Design, formulation and optimization of valsartan transdermal gel containing iso-eucalyptol as novel permeation enhancer: preclinical assessment of pharmacokinetic in wistar albino rats. Expert Opin Drug Deliv (Published online 15 May 2014; DOI:10.1517/17425247.2014.914027)
55. Rizwan M, Aqil M, Ahad A, et al. (2008). Transdermal delivery of valsartan: I. Effect of various terpenes. Drug Dev Ind Pharm 34:618–26.

56. Destro M, Preti P, D'Ospina A, et al. (2009). Olmesartan medoxomil:recent clinical and experimental acquisitions. Expert Opin Drug Metab Toxicol 5:1149–57.
57. Manoria P. (2006). Olmesartan medoxomil: a clinical review. Indian Heart J 58:282–6.
58. El-Dahmy RM, Elsayed I, Hussein J, Althubiti M, Almaimani RA, El-Readi MZ, Elbaset MA, Ibrahim BMM. Development of Transdermal Oleogel Containing Olmesartan Medoxomil: Statistical Optimization and Pharmacological Evaluation. *Pharmaceutics*. 2023; 15(4):1083.
59. Naga Anusha Nadimpalli & Sunitha Reddy, M (2022). Formulation and Evaluation of Olmesartan Medoxomil Transdermal Drug Delivery System. Saudi J Med Pharm Sci,2022; 8(10): 518-526
60. Sharpe M, Jarvis B, Goa KL. (2001). Telmisartan: a review of its use in hypertension. Drugs 61:1501–29.
61. Kandalkar A, Singh N. Formulation and evaluation of a unique transdermal patch comprising of telmisartan for hypertension therapy, IJBPAS, 2021;10(7): 2472-2485.
62. Yadav, Pavan. (2017). Transdermal patch of an antihypertensive drug: its development and evaluation. World Journal of Pharmaceutical Research. 2017;6(4):1355-1374.
63. Easthope SE, Jarvis B. (2002). Candesartan cilexetil: an update of its usein essential hypertension. Drugs 62:1253–87.
64. Hira S, Dua JS, Prasad D, Puri A, Kaushal S. THE Formulation and Characterization of Transdermal Patch of Candesartan Celexitil. JDDT [Internet]. 15Jun.2019 [cited 26Apr.2023];9(3-s):255-62.
65. Reddy, Rajareddy & Valluru, Rajashekar & Jayanthi, Bangaru & Shaik, Saleem & Sridhar, Katta. (2013). Formulation and in-vitro evaluation of transdermal films of an anti hypertensive drug. international research journal of pharmacy. 2013;4: 66-71.
66. McBurney A, Farrow PR, Ainsworth S, Ward JW. (1985). Serum concentrations and urinary excretion of pinacidil and its major metabolite, pinacidil pyridine-N-oxide following i.v. and oral administration in healthy volunteers. Br J Clin Pharmacol 19:91–4.
67. Krosuri, Pavankumar & Maheswara Reddy, Dagada & Gurrappagari, Geethavani & Dakka, Geetha & Burrareddy, Pavani & Bonala, Babu & Chetty, Madhusudana. (2021). Formulation and evaluation of pinacidil monohydrate transdermal patches. J Compr Phar 2018; 5(2):36-41.

68. Mo L, Lu G, Ou X, Ouyang D. Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure. Saudi J Biol Sci. 2022;29(1):266-272.
69. Mo, Long & Lu, Guijing & Ou, Xiping & Ouyang, Dongsheng. Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure. Saudi Journal of Biological Sciences. 2021;29. 10.1016/j.sjbs.2021.08.088.
70. Niharika Lal, Navneet Verma. Development and Evaluation of Transdermal Patches containing Carvedilol and Effect of Penetration Enhancer on Drug Release. Research J. Pharm. and Tech 2018; 11(2):745-752
71. Pisipati Aparna, Lyadella Divya, Kalva Bhadrayya, Chavali VS Subrahmanyam. Formulation and In vitroEvaluation of Carvedilol Transdermal Delivery System. Trop J Pharm Res,August 2013;12 (4):461-67.
72. Chauhan, Shikha & Saini, Sushila. Formulation and evaluation of transdermal patches of metoprolol tartrate using permeation enhancers of natural and synthetic origin. International Journal of Applied Pharmaceutics, 2019; 11(5): 317-323.
73. Malipeddi VR, Awasthi R, Ghisleni DD, de Souza Braga M, Kikuchi IS, de Jesus Andreoli Pinto T, Dua K. Preparation and characterization of metoprolol tartrate containing matrix type transdermal drug delivery system. Drug Deliv Transl Res. 2017 ;7(1):66-76.
74. Anisree, G.S. & Ramasamy, C. & Wesley, I. & Koshy, B.M.. (2012). Formulation of transdermal drug delivery system of metoprolol tartrate and its evaluation. Journal of Pharmaceutical Sciences and Research. 4. 1939-1942.
75. Eswaramma P, Karthikeyan M, Arunachalam, Vinaykumar N, Krishnareddy Y and Anjaneyulua V. Formulation and evaluation of transdermal patch of atenolol. International Journal of Comprehensive Pharmacy 2010; 1(10):1-5
76. Sharan Guru, Dey Kumar Biplab, Nagarajan K, Das Sujit, Kumar Vijaya S and Dinesh V: Effect of various permeation enhancers on propranolol hydrochloride formulated patches. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(2):21-31
77. Mittal A, Parmar S and Singh B: In vitro and in vivo assessment of matrix type transdermal therapeutic system of labetalol hydrochloride. Current Drug Delivery 2009; 6(5):511-5192