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A BRIEF VIEW ON ANTIHYPERTENSIVE DRUGS DELIVERY THROUGH TRANSDERMAL PATCHES

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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. Hypertension is one of the common disorder 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.

INTRODUCTION: More recent approach 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 [1, 2]. 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 [3].

Transdermal drug delivery system (TDDS) are adhesive drug containing devices of defined surface area that delivers predetermined amount of drug to the intact skin at the preprogrammed rate [4, 5]. The transdermal delivery has gained importance in the recent years. The TDDS has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation and improved patient compliance [6].

Since the early 1980s, transdermal patch dosage form of transdermal therapeutic system (TTS) has been available commercially. Such a system offers a variety of significant clinical benefits over other conventional systems. Therefore the TTS is of particular clinical significance for the prevention and long-term treatment of chronic diseases like hypertension [7]. 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 [8]. Consequently, the prevention and treatment of hypertension is of major social significance [9]. Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mm Hg, 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.[10]

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.[11] 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 [12].

In spite of the high cost of transdermal patches for hypertension treatment, antihypertensive patch 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. Further, 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 [13].

Carvedilol: Carvedilol is a β_1 + β_2 + α_1 adrenoceptor blocker; produces vasodilation due to α_1 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 [14].

Shashikant D. Barhate *et al.,* formulated 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 a plasticizers. The prepared formulations were evaluated for thickness, drug content uniformity, folding endurance, percent elongation at break, tensile strength, in-vitro permeation studies. It was observed that the system with PVA:PVP in the ratio 8:6 along with used plasticizers was a promising controlled release transdermal drug delivery system for carvedilol. Formulated transdermal patches of carvedilol, exhibits zero-order release kinetics [15].

Sanjay Dey *et al.,* prepared Transdermal Matrix patches of carvedilol by using solvent casting method using hydroxyl propyl methyl cellulose (HPMC) and eudragit RS100 polymers by incorporating dibutyl phthalate and propylene glycol as plasticizer and permeation enhancer, respectively. All the patches were uniform with respect to physicochemical and scanning electron microscopy (SEM) evaluation. The *in-vitro* permeation studies indicated that matrix patches containing hydroxylpropylmethylcellulose and eudragit RS100 in the ratio of 1:4 shown better releases. The formulation containing 30% w/w propylene glycol has exhibited better enhancement for the permeation of carvedilol. Skin irritation study revealed that the free of irritation. The selected patch was found to be stable at 37^{o}C and 45^{o}C with respect to their physical parameters and drug content [16].

Udhumansha Ubaidulla *et al***.**, designed matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy and differential scanning calorimetry. The results suggested no physicochemical incompatibility between the drug and the polymers. In vitro permeation studies were performed by using Franz diffusion cells.

The results followed Higuchi kinetics (r=0.9953–0.9979), and the mechanism of release was diffusion mediated. Based on physicochemical and in vitro skin permeation studies, patches coded as F3 (ethyl cellulose: polyvinylpyrrolidone, 7.5:2.5) and F6 (Eudragit RL: Eudragit RS, 8:2) were chosen for further in vivo studies. The bioavailability studies in rats indicated that the carvedilol transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability of 71% (for F3) and 62% (for F6) in comparison with oral

administration. The antihypertensive activity of the patches in comparison with that of oral carvedilol was studied using methyl prednisolone acetate—induced hypertensive rats. It was observed that both the patches significantly controlled hypertension from the first hour (*P*<.05). The developed transdermal patches increase the efficacy of carvedilol for the therapy of hypertension [17].

Shashikant D. Barhate *et al*., formulate and optimize the transdermal patch of carvedilol by using the combination of HPMC K100M, HPMC E5, PVA, Eudragit RL100, oleic acid and propylene glycol. Formulation optimization of transdermal patch was done by using 32 factorial design and by response surface methodology. The formulations were evaluated for thickness, tensile strength, folding endurance, drug content, moisture vapour transmission in 24 hr, moisture content. The values for these were practically acceptable. The in vitro permeation studies showed higher permeation of carvedilol with permeation rate ranges from 0.964 to 1.616 mg/cm^2/hr. The kinetic treatment of permeation data reveals zero-order drug release. Stability studies of the optimized batch at 25 ±2^{o}C, 4^{o}C and 45 ±2^{o}C showed no significant alteration in drug content.[18]

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 hrs and undergoes extensive first pass metabolism.[14]

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 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 to permeate into dissolution medium and 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.

Also the diffusion coefficient of release profiles (slope) had a value of nearly 0.5, which indicated fickian transport diffusion. The patches were found to be free of any skin irritation. Based on the above observations, itcan be reasonably concluded that Eudragit RL100/PVP polymers are better suited than EC/PVP polymers for the development of transdermal patches of Metoprolol tartrate [19].

Dr. B. Anil Reddy *et al.,* observed *in-vitro* characterization and evaluated the prepared transdermal films of metoprolol tartarate by using polymers such as ethyl cellulose, poly vinyl alcohol, eudragit RL100, eudragit L100. Di-n-butylphlthalate was used as plasticizer. The study was undertaken to report the film forming properties of polymers used and *in vitro* drug release from the prepared monolithic matrices. Effect of drug loading on the drug release rate was also studied.

The transdermal films were prepared using solvent casting method. These films were evaluated for Thickness, Percent moisture loss, Percent moisture absorption, Drug content, Weight variation and folding endurance. *In-vitro* drug release kinetics was studied using Franz-diffusion cell. Drug release followed zero order kinetics. Drug loading at different concentrations found to have less effect on the film forming properties of the constituent polymers. Results have shown enhanced flux per unit time across rat skin. In conclusion combination of ethyl cellulose, poly vinyl alcohol, eudragit RL100, eudragit L100 and Di-n-butylphlthalate can potentially be optimized to develop an effective transdermal drug delivery system for metoprolol tartarate [20].

M. Aqil *et al*., formulated monolithic matrix type transdermal drug delivery system of metoprolol tartrate. The patches were prepared by the film casting on a mercury substrate and characterized in vitro by drug release studies, skin permeation studies and

drug-excipients interaction analysis. Four formulations were developed, which differed in the ratio of matrix-forming polymers. Formulations MT-1, MT-2, MT-3 and MT-4 were composed of Eudragit RL-100 and polyvinyl pyrrolidone K-30 with the following ratios: 2:8, 4:6, 6:4 and 8:2, respectively. All the four formulations carried 10%(m/m) of metoprolol tartrate, 5% (m/m) of PEG-400 and 5% (m/m) of dimethyl sulfoxide in isopropyl alcohol: dichloromethane (40:60).

Cumulative amounts of the drug released in 48 hours from the four formulations were 61.5, 75.4, 84.3 and 94.5%, respectively. The corresponding values for cumulative amounts of the permeated drug for the said formulations were 53.5, 62.5, 69.8 and 78.2%. On the basis of in vitro drug release and skin permeation performance, formulation MT-4 was found to be better than the other three formulations and it was selected as the optimized formulation.[21]

S. Ramkanth *et al.*, designed and characterized transdermal drug delivery system of Metoprolol tartrate using various polymers such as HPMC, PVP by solvent casting technique. Propylene glycol (30% v/v) used as a plasticizer. The prepared formulation were evaluated for different physicochemical characteristics like thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss and weight uniformity. The drug release characteristics of the formulation were studied in *In-vitro* conditions by using artificial semi-permeable membrane.

In-vitro dissolution studies were performed in phosphate buffer (pH 7.4) for 12 hrs by using Keshery Chein apparatus. The *in-vitro* drug release plot has shown that the drug release followed zero order kinetics, which was evidenced from the regression value. Based on the drug release and physicochemical values obtained the formulation M VI is considered as an optimized formulation which shows higher percentage of drug release (98.92 % at 12 hour) with non-fickian type diffusion mediated mechanism.[22]

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 β blockers for hypertension and angina [14].

P Eswaramma *et al*., developed matrix type transdermal 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. Formulated films were evaluated physically with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate.

All prepared formulations indicated good physical stability. In-vitro permeation studies of formulations were performed by using Franz diffusion 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 F4 (r^2 = 0.9935 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. These results indicate that the formulation containing the F4 [CAP: PVP (6:1)] has shown optimum release in concentration independent manner.[23]

S S Agrawal *et al.,* prepared different matrix type transdermal patches incorporating atenolol and metoprolol tartrate with an objective to study the effect of polymers on transdermal release of the drugs. The polymers selected were polyvinylpyrrolidone (PVP), cellulose acetate phthalate, hydroxyl propyl methylcellulose phthalate and EC. Propylene glycol (40%w/w of dry weight of polymers, used as a plasticizer) and 1,8-cineole (penetration enhancer). Backing membrane was prepared by wrapping aluminum foil over the Teflon mold. The physical appearance of the patches and the effect on ageing indicated that the patches need to be stored in properly sealed air tight packing to keep them protected from extremes of moisture that may alter their appearance, thus, the properties were found to be within limits and satisfactory.

In vitro permeation studies were performed using rat abdominal skin as the permeating membrane in Keshary-Chien cell. The results indicated that maximum release was obtained at 48 h (85% and 44% of atenolol and metoprolol tartrate, respectively). The drug permeation studies across cadaver skin showed about 27% of reduction in the amount of drug release as that compared to rat abdominal skin was used [24].

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 [11].

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 technique and checked the effect of various permeation enhancers on formulated patches. Patches obtained were almost flat and smooth having very less weight variation and optimum flexibility suggesting the reproducibility of the formulation technique and were evaluated under various parameters such as *in vitro* skin permeation studies which were carried out by using excised skin of hairless albino rats.

The formulation containing oleic acid as permeation enhancer showed the better permeation in comparison to the other enhancers. Further study was conducted on healthy adult male rabbits for 24 hours, no any trace of edema, erythema or any skin irritation on site of application of the patch was observed. They concluded that, formulations are non irritable to the skin tissue and it can be safer for therapeutic use.[24]

R. Krishna *et al*., formulated and evaluated carboxy methylcellulose-sodium (CMC-Na) based transdermal system for propranolol. *In-vitro* permeation studies using the excised hair-free rat skin model resulted in 66.54% permeation at the end of 24 h in a modified Franz diffusion cell. This zero-order permeation profile was characterized by a drug permeation rate of 52.87 +/- 11.63 micrograms cm^{-2} h^{-1}. Skin irritation studies in rats (n = 5), evaluated for flare-and-wheal with respect to a formalin control, indicated that the drug-containing patch evoked only a mild response over a 7-day period. Preliminary *in-vivo* studies in male albino rabbits (n = 3), indicated that plasma drug levels averaged 11.75 +/- 3.40 ng mL^{-1} in a 24-h study period before patch removal [25].

Tegk Murthy *et al.,* prepared rate controlling membrane for TDDS using cellulose acetate and ethyl cellulose using various solvents to evaluate the influence of the solvent on the mechanical and permeability properties of the films. Acetone: methanol (8:2), dichloromethane: methanol (8:2), chloroform: methanol (8:2) and ethyl acetate: methanol (8:2) were used as solvents in the preparation of cellulose acetate and ethyl cellulose films. Plasticizer such as dibutyl phthalate or propylene glycol is used at the concentration of 40%w/w of the polymer weight.

The rate of water vapour transmission was decreased in the order of films in various solvents is as follows in both cases .Ethyl acetate: methanol> Acetone: methanol (8:2)> dichloro methane: methanol (8:2), chloroform: methanol (8:2). Cellulose acetate films employed with ethyl acetate: methanol (8:2) ratio as casting solvent yielded low area (1.29 sq cm) of patch with desired release rate.[11]

Tegk Murthy *et al.,* prepared and evaluated rate controlling membranes for transdermal drug delivery using cellulose acetate, ethyl cellulose and eudragit RS-100. The solvent used to prepare the films were acetone: methanol (8:2), chloroform: methanol (8:2), dichloromethane: methanol (8:2) and ethyl acetate: methanol (8:2). Dibutyl phthalate or propylene glycol 40% of polymer weight is used as plasticizer in preparation of cellulose acetate and ethyl cellulose film. Dibutyl phthalate 15% of the polymer weight was used as plasticizer in eudragit RS-100. The drug release was governed by Peppas model. The results obtained in the study indicated that the polymer and solvents used for the preparation of films have significant influence on the water vapour transmission, drug diffusion and permeability of film.[11]

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**.**

A. Mittal *et al.,* 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 patches were characterized for physical, in vitro release studies & ex-vivo permeation studies (human cadaver skin). In vitro drug release and skin permeation performance of formulation A1 was found to be better than the other formulations and it was selected as the optimized formulation.

The optimized patch was assessed for its pharmacokinetic, pharmacodynamic, skin irritation potential, and stability studies. The maximum percentage drug release & Permeation in 48 hrs were 92.43 % and 76.24 % respectively for optimized patch. The Korsmeyer Peppas release exponent value of 0.604 suggested release mechanism towards first order release in the optimized formulation. The results obtained from the *in-vivo* characterization of the optimized patch showed sustained action of the developed formulation. The interaction studies analysis indicated no chemical interaction between the drug and polymers. The optimized patch was seemingly free of potentially hazardous skin irritation as suggested by skin irritation score of 0.915<2.00 (under Draize score test). 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 [26].

M Aqil *et al.,* adopted solvent evaporation technique for preparation of TDDS. Different formulations were prepared using different combination ratios of Eudragit RL 100, Eudragit RS 100 (7.5:4.5, 5.0:5.0, 3.5:8.5 in formulations X-1, X-2, X-3) and Eudragit RL 100, PVP K-30 (9.0:2.0, 5.0:5.0, 4.0:7.0 in formulations Y-1, Y-2, Y-3). 36%w/w Labetalol HCl, 10-12%w/w of dimethyl sulfoxide (DMSO) (enhancer) and 2.5-7.5%w/w of PEG 400 (plasticizer) were incorporated in all the formulations. The prepared TDDS were evaluated by *in-vitro* drug release, *ex-vivo* skin permeation, stability and *in-vivo* pharmacodynamics study. The maximum drug release was 90.26% in 48 hrs for the formulation having ERL 100:ERS 100 (7.5:4.5), and it was 83.24% for the formulation having ERL100: PVP K-30 (9.0:2.0) [27].

Verapamil: Verapamil is a calcium channel blocker. It has cardio depressant property. It is widely used in the treatment of angina, hypertension and supra-ventricular 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%.

V. Devi Kusum *et al.,* 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. The patch containing ERL100 alone showed maximum water vapor transmission rate, percentage moisture absorption and percentage moisture loss (ML), which could be attributed to its hydrophilic nature.

From *in-vitro* release studies which zero-order release of the drug from all the patches the mechanism of release was diffusion mediated. A12 emerged as the most satisfactory formulation. Further, release and permeation of the drug from the most satisfactory formulation (A12) was evaluated through different biological barriers (shed snake skin, rabbit skin, and rat skin) to get an idea of the drug permeation through human skin. Shed snake's skin was found to be most permeable (82.56% drug release at 24 hr) and rat skin was least permeable (52.38%).

Percutaneous absorption studies in rabbits maintain adequate plasma levels for 24 hr. [AUC: 3.09 mg/mL hr, C_{max}: 203.95 microg/mL, T_{max}: 8 hr]. It can therefore, be 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 [28].

Indapamide: Indapamide is a long-acting hypertensive with both diuretic and vasodilative action and is defined by the 1999 WHO/ISH Hypertension Guidelines and JNC VII as a first-line drug for the treatment of

hypertension. This anti-hypertensive action is maximal at a dose of 2.5 mg/day, and the diuretic effect is slight, usually without clinical manifestation.

G S Sanap *et al.,* 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 by using a drug polymer ratio of 1:4 with different vegetable oils as permeation enhancers in appropriate concentrations. The *in-vitro* release of drug across rat skin from HPMC and EC films showed only 53.63% and 36.50% at the end of 24 h, respectively.

The results indicated that HPMC film has shown better release than that of EC film, which may attributed to high water vapour permeability of HPMC film and hydrophobic nature of EC. Among the systems, film containing 30% w/w olive oil in HPMC polymer (F3) has shown maximum release than that of systems containing other vegetable oils as permeation enhancers.[11]

C Ren *et al.,* developed and evaluated a novel drug-in-adhesive transdermal patch system for indapamide. The effects of the type of adhesive and the content of permeation enhancers on indapamide transport across excised rat skin were evaluated. The results indicated that DURO-TAK adhesive 87-2852 is a suitable and compatible polymer for the development of transdermal drug delivery systems for indapamide. The final formulation contained 4% N-dodecylazepan-2-one, 6% l-menthol and 3% isopropyl myristate. For *in-vivo* studies patch systems were administered transdermally to rats while orally administered indapamide in suspension was used as a control [11].

In contrast to oral delivery, a sustained activity was observed over a period of 48h after transdermal administration. This sustained activity was due to the controlled release of drug into the systemic circulation following transdermal administration. C Ren *et al*., investigated the transdermal properties of indapamide and to explore the efficacy of various permeation enhancers and organic acids with regard to the percutaneous absorption of indapamide. Permeation experiments were performed *in-vitro*, using rat abdominal skin as a barrier.

The results obtained indicated that N-dodecylazepan-2-one, N-methyl-2-pyrrolidone, menthol and oleic acid had a strong enhancing effect on the permeation of indapamide and N-dodecylazepan-2-one exhibited the most potent enhancing effect. The study reveals that all eight of the organic acids chosen had a potent enhancing effect on the permeation of indapamide across rat abdominal skin. Among the organic acids examined, lactic acid had the greatest enhancing effect. The formation of an ion-pair between indapamide and organic acids may be responsible for the enhanced skin permeation of indapamide [11].

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 F3. 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 promising and innovative therapeutic system for indapamide [29].

Losartan: Losartan is a competitive antagonist and inverse agonist of A-II, 10,000 times more selective for AT_1 and AT_2 receptor. Losartan causes fall in BP in hypertensive patients which lasts for 24 hrs. Oral absorption is not affected by food, but bioavailability is only 33% due to first pass metabolism. The plasma half-life is 2hr [14].

Arnab Bagchi *et al*., prepared 18 different medicated transdermal films by using blends of hydrophobic and hydrophilic polymers like ethyl cellulose with polyvinyl pyrrolidone and ethyl cellulose with hydroxypropyl methyl cellulose and dibutyl phthalate was used as plasticizer by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane. Several physicochemical parameters like moisture content, moisture uptake, thickness, film folding endurance, tensile strength, skin irritation and surface morphology of the films were studied.

For all the formulations, skin permeation of the loaded drug through albino mice skin was studied using Keshary-Chien diffusion cell. Formulations containing higher proportion of hydrophilic polymers blended with lower proportions of hydrophobic polymer were found less consistent in comparison to the patches comprised of higher proportion of hydrophobic polymer [30].

Bisoprolol: Bisoprolol is a cardioselective β blocker lacking intrinsic sympathomimetic activity. It has a plasma half-life of 9-10 hrs and oral bioavailability is 80% but it has a considerable first pass metabolism [14].

Panati Dinakar *et al.,* developed the bisoprolol transdermal patches by using Poly vinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) using glycerin as plasticizer. After optimizing the polymer ratio the best patches were selected based on the physical evaluation. Then physical evaluation and in vitro studies were performed by using Franz diffusion cell employing porcine ear skin as the membrane. From the above results F2 formulation was found to have good controlled release over the formulation F1. Further in order to find the effect of plasticizer in the drug release for the F2 formulation, glycerin was replaced with Tri ethyl citrate (TEC). Thus the prepared film shows good release of about 98.3% with TEC as plasticizer.[31]

Timolol maleate: Timolol maleate (TM) is a beta adrenoceptor-blocking agent used in treatment of cardiovascular diseases like myocardial infarction, angina pectoris, hypertension, respiratory complications and migraine. It is 8-10 times potent than propranolol. It is rapidly absorbed from gastrointestinal tract with peak plasma concentration of 5-10 ng/ml after 1 hr and metabolized up to 80% in liver with a mean half-life of 2.0-2.5 hr, thus necessitating frequent administration of larger doses to maintain therapeutic drug level.

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 solutions of HPMC 10% and EC 10 %. Both solutions were mixed together in various combinations.

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 1.589+0.20 SD % drug/cm^2 of permeation rather than HPMC:EC (2:8), i.e., 0.987+0.20 % drug/ cm^2 in 4h of period [11].

***M Hanan** et al.,* investigated the feasibility of matrix controlled transdermal patch based on sugar fatty acid ester (SE) as penetration and absorption enhancer containing Timolol maleate (TM). The influence of fatty acid type, chain length and hydrophilic–lipophile balance (HLB) on the in vitro drug release as well as its permeation across hairless rat skin were studied and compared aiming to select a patch formula for clinical performance.

The results indicated that among different SEs tried, laurate SE with shorter fatty acid chain length and higher HLB value significantly increased the amount of TM liberated from the patch (99 ± 2.1%) and its permeation across rat skin (86 ± 4.3%). The total drug permeation and flux values were approximately 5-fold greater compared to SE free patch. The developed patch was well tolerated by all the subjects with only moderate skin irritation, which was recovered in 24 h after patch removal. The results are very encouraging and offer an alternative approach to maintain higher, prolonged and controlled blood level profile of the drug over 18–24 h.[32]

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.,* 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. The solubility of drug in various solvent systems was found to be in decreasing order as propylene glycol (PG)/oleic acid (OA)/dimethyl isosorbide (DMI) (80:10:10 v/v) > PG > PG/OA (90:10 v/v) > polyethylene glycol 300 > ethanol/PG (70:30 w/w) > transcutol > dimethyl isosorbide (DMI) > ethanol > water and buffer 4.7 > 2-propanol. Propylene glycol was then selected as the main vehicle in the development of a transdermal product.

As a preliminary step to develop a transdermal delivery system, vehicle effect on the percutaneous absorption of NC-HCl was determined using the excised skin of a hairless guinea pig. 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.[33]

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. 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.

The effect of various pressure-sensitive adhesives MA-31(moderate acrylic pressure sensitive adhesive), MA-38(mild acrylic pressure sensitive adhesive) or TACKWHITE A 4MED (water based pressure sensitive acrylic emulsion) on the permeability of nicardipine hydrochloride through EVA membrane 2825 (28%w/w VA) or membrane/skin composite was also studied. The results showed that nicardipine hydrochloride permeability through EVA 2825 membrane coated with TACKWHITE 4A MED/skin composite was higher than that coated with MA-31or MA-38 [34].

Captopril: Captopril, an orally active inhibitor of an angiotensin-converting enzyme (ACE) has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity.

It has a mean half life of 2 to 3 hr but action lasts for 6-12 hr. Captopril shows 75% bioavailability but presence of food reduces the oral absorption by 30-50%. According to a previous research, the oxidation rate of captopril in dermal homogenate is significantly lower than the intestinal homogenate because the oxidative product of captopril, a captopril disulfide shows poor absorption from the intestine [35].

Sunita Jain et al., Developed matrix diffusion type of transdermal delivery system 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 prepared matrices were free from any irritating effect and stable for 3 months [36].

Clonidine: Clonidine is a centrally acting antihypertensive drug having plasma half life of 8-12 hrs and peak concentration occurs in 2-4 hrs Clonidine effectively reduces blood pressure in patients with mild-to-moderate hypertension. When transdermal therapy was compared with oral delivery of clonidine, efficacy was similar for the two delivery modalities. However, side effects such as drowsiness and dry mouth occurred less frequently in patients treated with transdermal clonidine [37].

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.

In this method, membranes were photosynthesized by UV radiation of mixtures of three acrylate monomers: 2-hydroxy-3-phenoxypropyl acrylate, 4-hyroxybutyl acrylate and sec-butyl tiglate in different ratios with photo initiator, benzoyl peroxide.

The effects of monomers ratios, membranes thickness and clonidine concentration on the membrane permeation rates were investigated. The membranes were characterized by FTIR, DSC, and SEM. It was found that the new type of membranes could control clonidine linear release in the transdermal drug delivery systems [38].

K E Ming, characterized a newly developed clonidine transdermal patch, KBD-transdermal therapeutic system (TTS), for the treatment of attention deficit hyperactivity disorder in children. In vitro release, penetration, and in vivo pharmacokinetics in rabbits were investigated. The smaller size of KBD-TTS (2.5 mg/2.5 cm^2) showed a similar in vitro penetration to those of Catapres-TTS (2.5 mg/3.5 cm^2, a clonidine transdermal patch used for the treatment of hypertension, Alza Corporation, U.S.A.).

The Transdermal penetration rate of clonidine was mainly controlled by the ethylene vinylacetate membrane used in the patch.. A single dose of clonidine transdermal patch (KBD-TTS) or Catapres-TTS was transdermally administered to rabbits (n=6 each) and removed after 168h. The average half-life, T_{max}, C_{max} and C_{ss} values of clonidine in rabbits following administration of KBD-TTS were 19.27′4.68 h, 52.56′25.77 h, 27.39′9.03 ng/ml, and 25.82′9.34 ng/ml, similar to those of Catapres-TTS, respectively. The clonidine plasma concentration of KBD-TTS reached a steady state at 24 h through 168 h. The in vitro release rate of the clonidine from KBD-TTS significantly correlated with the in vivo absorption rate ($p<0.001$).[39]

Pinacidil: Pinacidil, an antihypertensive drug belonging to the class of potassium channel openers, has been found to be a good candidate for transdermal drug delivery. The bioavailability of pinacidil from oral formulations is only 57% due to hepatic first-pass metabolism. The drug has a short biological half-life of 1.6 to 2.9 hours, which makes frequent dosing necessary to maintain the drug within the therapeutic blood levels for long periods. The antihypertensive action requires plasma concentration in the range of 100 to 300µg/L [40].

Aqil Mohd *et al*., fabricate Eudragit RL 100-polyvinyl acetate films and evaluate their potential for transdermal drug delivery in a quest to develop a suitable transdermal therapeutic system for pinacidil. The polymeric films (composed of Eudragit RL100 and polyvinyl acetate in 2:8, 4:6, 6:4, 8:2 ratios in films P-1, P-2, P-3, P-4 respectively, together with 5% w/w of pinacidil and 5% w/w of dibutylphthalate in all the films) were cast on a glass substrate and evaluated for physicochemical parameters viz. thickness, weight, folding endurance (a measure of fragility), percent elongation at break (a measure of flexibility), drug content uniformity, water absorption capacity, moisture vapor transmission, drug-polymer interaction, *in vitro* drug release and skin permeation profiles. The films were also evaluated for appearance, smoothness and transparency. The film finally selected was assessed for its skin irritation potential, and its stability on storage under accelerated temperature and humidity conditions.

The values of thickness, weight, folding endurance, percent elongation at break, percentage water absorbed, moisture vapor transmission, cumulative amount of drug released and permeated for different films were in the following order: P-1 < P-2 < P-3 < P-4. The results suggest that Eudragit RL 100, a freely permeable polymer, has a major influence on the physicochemical profile of the films. The higher the quantity of Eudragit RL100 in the film, the better its strength and flexibility as well as higher drug release and skin permeation potential. The final optimized film (with a composition of Eudragit RL 100: polyvinyl acetate: pinacidil monohydrate: dibutylphthalate in 8.0:2.0:0.5:0.5 ratio) was found to be the best in terms of drug release (cumulative amount of drug released in 48 h was 96.09%) and skin permeation (permeability coefficient, 0.0164 cm/h).

There was no apparent drug-polymer interaction in the films. The optimized film was seemingly free of potentially hazardous skin irritation. The film was found to be stable and intact at ambient temperature and humidity conditions. The films hold promise for the development of a matrix type transdermal therapeutic system for pinacidil [41].

Nitrendipine: Nitrendipine a potent antihypertensive molecule which is an calcium entry blocker and potent peripheral vasodilator, reported to be well absorbed following oral administration, but undergoes extensive first-pass metabolism and oral bioavailability in the range from 10% to 20% [42].

D Tipre *et al.,* fabricated monolithic TTS of 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. Optimized TTS was evaluated for in-vitro flux though human skin (volar arm) to determine patch size needed to deliver drug through the transdermal route. Patches were evaluated for different parameters. Optimized TTS was found relatively stable at refrigeration only. The stability study encourages conducting a clinical study to determine if an Eudragit E100-based nitrendipine transdermal patch could become a new product in treatment of hypertension.[43]

M Y Rao et al., prepared matrix type TDDS of nitrendipine by solvent evaporation technique. The film forming polymers used in the formulation, ten formulations (composed of Eudragit RL 100 and Hydroxypropyl methyl cellulose in the ratios of 5:0, 4:1, 3:2, 2:3, 1:4 in formulations A set and Eudragit RS 100 and Hydroxypropyl methyl cellulose in the same ratios in formulation B set respectively) were prepared. All formulations carried 6 % v/w of carvone as penetration enhancer and 15% v/w of propylene glycol as plasticizer in dichloromethane and methanol as solvent system.. The maximum drug release in 24 hrs for A series formulations was 89.29% (2:3) and 86.17% for B series (1:4). Nifedipine, a potent drug is widely used for the treatment of hypertension. Due to extensive first pass metabolism its bioavailability is low [11].

Ramesh Gannu *et al*., developed and evaluated ten formulations (composed of Eudragit RL 100 and Hydroxypropyl methyl cellulose in the ratios of 5:0, 4:1, 3:2, 2:3, 1:4 in formulations A1, A2, A3, A4, A5 and Eudragit RS 100 and Hydroxypropyl methyl cellulose in the same ratios in formulation B1, B2, B3, B4, B5 respectively)matrix type transdermal drug delivery systems (TDDS) of nitrendipine by using solvent evaporation technique All formulations carried 6 % v/w of carvone as penetration enhancer and 15% v/w of propylene glycol as plasticizer in dichloromethane and methanol as solvent system.

The maximum drug release in 24 hrs for A series formulations was 89.29% (A4) and 86.17% for B series (B5), which are significantly ($p < 0.01$) different to the lowest values (57.58 for A1 and 50.64 for B1). Again formulations A4 (flux 23.51 µg/hr/cm^2) and B5 (flux 22.98 µg/hr/cm^2) showed maximum skin permeation in the respective series.

The flux obtained with formulation A4 and B5 meets the required flux (19.10 µg/hr/cm^2). The mechanical properties, tensile strength, elastic modulus (3.42 kg/mm^2 for A4 and 4.25 kg/mm^2 for B5) reveal that the formulations were found to be strong but not brittle. FTIR studies did not show any evidence of interaction between the drug and the polymers [44].

Nicorandil: Nicorandil belongs to the class of potassium channel activators, which exert their action by arterio-dilating and vasodilating properties and represents a novel type of compound for use in the treatment of angina pectoris. It has a short half life and the usual oral dosage regimen is 5-40mg taken two to four times a day.

V G Jamakandi et al., employed solvent casting technique to formulate 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 patch 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 movement due to its high hydrophilic nature and high water permeability value to water [45].

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.

A K Dorle *et al.,* prepared matrix type transdermal patches composed of different ratios of PR (polymerized rosin), PVP (polyvinyl pyrrolidone), and DTH (diltiazem hydrochloride) were prepared by solvent evaporation technique in a glass ring. The uniform dispersion obtained was cast on PVA backing membrane and dried at 60°C for 8 hours. Results from the present study conclude that release rate of drug from films and permeation across skin increases with

increase in drug and PVP loading but is independent of film thickness. Patches containing PR: PVP (7:3) show promise for pharmacokinetic and pharmaco-dynamic performance evaluation in a suitable animal model [46].

Lisinopril: It is the lysine derivative of enalaprilat: does not require hydrolysis to become active ACE inhibitor. Its oral absorption is slow and incomplete, but unaffected by food. The drug is used against chronic condition like hypertension, diabetes nephropathy, and cardiac heart failure. The half-life of drug is 12hrs, thus is being used as single dose/day and has bioavailability of 25% [14, 47].

Jitendra Banweer *et al.,* fabricated transdermal patches on glass substrate using solvent casting technique by employing HPMC (hydroxyl propyl methyl cellulose) & PVA (Polyvinyl acetate) in the ratio of 1:1 as polymeric matrix using glycerol as plasticizer in 6% concentration. Binary solvent system (Water: Methanol) in the ratio of 70: 30 was taken for the study Oleic acid and Isopropyl alcohol were added as the penetration enhancers separately and blend in different concentrations and ratios. In-vitro diffusion rate studies using Keshary-Chein diffusion cell on Goat skin done. The patch containing Oleic acid and Isopropyl alcohol in the ratio of 50:50, at 15% shows best promising in-vitro drug flux and possess excellent physicochemical properties at normal and accelerated temperature conditions [47].

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*., 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. The thickness and weight of all patches were in the range of 0.12 to 0.28 mm and 17.26 to 38.60 mg/cm^2 respectively.

Moisture absorption was increased as the concentration of PVP was increased. All the patches exhibited adequate folding endurance and good drug content uniformity. *In vitro* release profiles of the drug from different patches were studied using abdominal skin of albino rats and modified Keshary Chein diffusion cell. In vitro drug release studies were extended up to 24 hrs and it was found that, as the concentration of PVP increased the drug release was also increased.

Polymers and their combination influenced the film properties as well as the release characteristics. 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 [48].

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 small [14].

Jiang Yu-xuan *et al.*, prepared drug-in adhesive patches for amlodipine besylate and evaluate its in vitro transdermal permeability. Drug-in adhesive patches of amlodipine besylate were prepared by dissolving amlodipine besylate and different enhancers into the home-made pressure sensitive adhesive. Permeation characteristics of amlodipine besylate from patches were evaluated using 2-compartment horizontal diffusion cells. They concluded that the drug-in adhesive patches of amlodipine besylate have the potential to become a long-acting transdermal drug delivery system for the treatment of hypertension and are worthy of further investigation.[49]

Yinghua Sun *et al.,* developed and evaluated a drug-in-adhesive transdermal patch for S-amlodipine (S-AM) free base. Initial *in vitro* experiments were conducted to optimize the formulation parameters before transdermal delivery in rats. The effects of the type of adhesive and the content of permeation enhancers on S-AM free base transport across excised rat skin were evaluated.

For *in-vivo* studies, patches were administered transdermally to rats while orally administered S-AM in suspension and intravenously administered S-AM solution were used as controls. This suggests that the transdermal application of S-AM in a drug-in-adhesive transdermal patch may be used for the treatment for hypertension.[50]

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.[51]

Valsartan: Valsartan is a AT_1 receptor antagonist and its AT_1 receptor affinity is similar to that of valsartan. Its oral bioavailabilty averages 23% and food interferes with its absorption. Elimination occurs mainly by the liver in unchanged form with a $t_{1/2}$ of 6-9 hours; action lasts 24 hours [14].

Nishida N *et al.,* investigated the feasibility of a monolithic drug-in-adhesive (DIA) patch as a transdermal therapeutic system for the administration of valsartan (VAL). To improve the penetration of VAL in the patch, several chemical penetration enhancers were investigated by in vitro hairless mouse and Yucatan micro pig (YMP) skin permeation studies. A combination of isopropyl myristate (IPM)/diisooctyl sodium sulfosuccinate (AOT) most strongly enhanced the permeation of VAL.

The plasma concentration-time profile of VAL after the patch was applied in humans was estimated by a convolution technique from the results of the *in vitro* YMP study, which indicated that the concentration of VAL could be sufficient to produce a pharmacological effect.

These results demonstrate that the combination of IPM/AOT may be useful for the development of a practical DIA patch for VAL [52].

Gulam Irfani *et al*., formulated transdermal drug delivery of valsartan in different concentration (10%, 20% and 30%) of glycerin as plasticizer and a blend of two different concentrations of polymers (PVPK30, HPMC and Eudragit RS 100) were formulated by solvent casting method. Drug polymer interaction study was carried out using FTIR. Other characteristics were confirmed by XRD and SEM studies.

The formulated valsartan patches exhibited good physicochemical characteristics. In-vitro diffusion studies were also performed by using cellophane membrane (0.45µ) in an artificial Keshary chein diffusion cell. The results indicated that as the concentration of glycerine increases, the diffusion rate of valsartan patches also increases. Among polymers, the combination of Eudragit RS 100 with HPMC had increased diffusion rate. The diffusion data were fitted in various models to aces the kinetics and mechanism of diffusion [53].

Enalapril Maleate: Enalapril maleate, the second ACE inhibitor approved in the United States, is a prodrug that 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," enalaprilat differs from captopril in that it is an analogue of a tripeptide rather than of a dipeptide. Enalapril is absorbed rapidly when given orally and has an oral bioavailability of about 60% (not reduced by food). 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. Nearly all the drug is eliminated by the kidneys as either intact enalapril or enalaprilat.

Pravin Gavali *et al.*, investigated the possibility of using different concentrations and polymeric grades of hydroxypropyl methylcellulose (K4M, K15M and K100M) for the development of transdermal delivery of enalapril maleate, 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 polymeric grade and content. The in vitro drug release followed Higuchi kinetics as its coefficient of correlation values predominates over first order kinetics. The *in vitro* dissolution profiles by using rat skin and human skin showed significant difference.

Comparison of skin permeation rate between hairless rat and human cadaver skin was done by using Valia-Chien glass diffusion cells [54].

M Aqil *et al*., formulated transdermal therapeutic system (TTS) of an antihypertensive drug enalapril maleate (EM) using a new penetration enhancer, piperidine hydrochloride (PH), belonging to the class of Dihydropyridines. The TTS of EM was prepared by solvent evaporation technique using polymers Eudragit E100 and polyvinyl pyrrolidone K-30 in varying ratios, 5% w/w dibutylphthalate as plasticizer and 10% w/w PH as penetration enhancer. The TTS was evaluated for in-vitro drug release using paddle over disc method and ex-vivo skin permeation using modified Keshary and Chein diffusion cell.

The interaction studies were carried out by comparing the results of assay, UV and TLC analysis for pure drug and medicated and TTS formulation. Skin irritation potential of TTS was assessed by visual examination of treated rat skin.Stability studies were conducted according to ICH guidelines at a temperature of 40+/-0.5^{o}C and 75+/-5% RH. The optimized formulation was evaluated for preclinical bioavailability and antihypertensive efficacy using albino rat model [55].

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.

REFERENCES

1. Sankar V *et al.:* Design and evaluation of nifedipine transdermal patches. Indian Journal of Pharmaceutical Sciences 2003; 65(5):510-515.
2. Pandey S, Praveen SH and Udupa N: Formulation and evaluation of nimesulide transdermal drug delivery systems. Indian Journal of Pharmaceutical Sciences 2000; 62(5):376-379.
3. Chien Y W. In: Transdermal controlled systemic medication. Marcel Dekker, New York, First edition 1976.
4. Mandal Sonjoy, Thimmasetty J, Ratan GN and Kilarimath BH: Formulation and evaluation of carvedilol transdermal patches. International Research Journal of Pharmacy 2011; 2(1):237-248.
5. Kshirsagar NA: Drug delivery systems. Indian Journal of Pharmacology 2000; 32:S54- S61.
6. Mohd A, Asgar A, Yasmin S, Kiran D, Abul KN and Kollapa KP: In vivo characterization of monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate: A technical note. AAPS Pharm. Sci. Tech. 2006; 7(1):E1-E5.
7. Liang Fang et al.: Design and in vivo evaluation of an indapamide transdermal patch. International Journal of Pharmaceutics 2009; 370:129–135
8. Hoyert DL, Kung HC and Smith BL: Deaths: preliminary data for 2003. National Vital Statistics Reports 2005; 53:1–48.
9. Kim J and Kitakaze M: Prevention and treatment of the hypersensitive organopathy—the necessity of cardiovascular protection. Nippon Rinsho 2004; 62:120–127.
10. Brunton Laurence L, Lazo John S, Parker Kieth L: Goodman &Gilman's The pharmacological basis of therapeutics. McGraw-Hill, New York, Eleventh edition 2006.
11. Jayaraj Kumar K, Suneetha KC, Uma Devi SK, Sai Prasanthi N, Pravalika Ch, Lakshmi Prasanna. D, Kalayan Babu P and Venkateswarlu A: Brief view on delivery of antihypertensive drugs through transdermal patches. Journal of Innovative trends in Pharmaceutical Sciences 2010; 1 (7):305-319.
12. Jamakandi VG, Ghosh B, Desai BG and Khanam J: Recent trends in transdermal cardiovascular therapy. Indian Journal of Pharmaceutical Sciences 2006; 68:556-61.
13. 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.
14. Tripathi KD: Essentials of Medical Pharmacology. Jaypee Brothers Medical publisher(P) Ltd, Sixth edition 2008.
15. Barhate D Shashikant, Dr. Patel MM, Sharma S Ankit, Nerkar Prashant and Shankhpal Gaurav: Formulation and evaluation of transdermal drug delivery system of carvedilol. Journal of Pharmacy Research 2009; 2(4):663-665.
16. Dey Sanjay and Malgope Ananya: Preparation of carvedilol transdermal patch and the effect of propylene glycol on permeation. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(1):137-143.
17. Ubaidulla Udhumansha, Molugu VS Reddy, Ruckmani Kumaresan, Ahmad J Farhan and Khar K Roop: Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics. AAPS Pharm Sci Tech 2007; 8(1):E1-E8.
18. Barhate D Shashikant and Potdar B Mrugendra: Formulation of transdermal patch of Carvedilol by using novel polymers. Pelagia Research Library 2011; 2 (2):185-189.
19. Bharkatiya Meenakshi, Nema Kumar Rajesh and Bhatnagar Mahip: Development and characterization of transdermal patches of metoprolol tartrate. Asian Journal of Pharmaceutical and Clinical Research 2010; 3(2):130-134.

20. Dr. Reddy Anil B: In vitro characterzatioan and evaluation of transdermal drug delivery system for metoprolol tartarate. Journal of Pharmaceutical Research and Health Care 2010; 2(4):325-329.
21. M Aqil, Sultana Y and Ali A: Matrix type transdermal drug delivery systems of metoprolol tartrate: in vitro characterization. Acta Pharmaceutica 2003; 53(2):119-25.
22. Ramkanth S et al.: Design and characterization of matrix type transdermal drug delivery system using metoprolol tartarate. International Journal of Advances in Pharmaceutical Research 2010; 1(1):1-5.
23. 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.
24. 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.
25. Krishna R and Pandit JK: Carboxymethylcellulose-sodium based transdermal drug delivery system for propranolol. Journal of Pharmacy and Pharmacology 1996; 48(4):367-70.
26. 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.
27. Aqil M, Zafar S, Ali A and Ahmad S: Transdermal drug delivery of labetolol hydrochloride: system development, in vitro; ex vivo and in vivo characterization. Current Drug Delivery 2005; 2(2):125-131.
28. 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.
29. Barhate D Shashikant and Gholap N Tejaswita: In vitro permeation studies of Indapamide from transdermal films. Scholars Research Library 2010; 2(4):447-451.
30. Bagchi Arnab and Dey Kumar Biplab: Formulation, In-vitro Evaluations and Skin Irritation Study of Losartan Potassium Transdermal Patches. Iranian Journal of Pharmaceutical Sciences 2010; 6(3):163-170.
31. Dinakar Panati, Varalakshmi C, Reddy Prakash PK and Mohanlakshmi S: Formulation and evaluation of Bisoprolol fumarate transdermal patches. Journal of Pharmacy Research 2010; 3(8):1955-1957.
32. Hanan M and Laithy El: Novel transdermal delivery of Timolol maleate using sugar esters: preclinical and clinical studies. European Journal of Pharmaceutics and Biopharmaceutics 2009; 72(1):239-245.
33. 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.
34. 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.
35. Popli S, Daugirdas Jt, Neubauer Ja, Hockenberry B, Hano Je and Ing TS: Transdermal clonidine in mild hypertension. Archives of Internal Medicine 1986; 146:2140-2144.
36. Jain Sunita, Joshi C Suresh, Pharmacology online 2007; 1: 379-390.
37. Ishii R, Tagawa T, Ishida T and Naruse T: Antihypertensive effects of a new TDS of clonidine in genetic and experimental rats. Arzneimittel-Forschung 1996; 46: 261–268.
38. Xiaoping Zhan, Guochun Tang, Sijing Chen and Zhenmin Mao: A new copolymer membrane controlling clonidine linear release in a transdermal drug delivery system. International Journal of Pharmaceutics 2006; 322(1-2):1-5.
39. Ming KEG, Wang LI, Yong XH, Liang LUW, Zhang X, Zhang Q, You GH. Biological and Pharmaceutical bulletin 2005; (28):305-310.
40. Howland Richard D, Mycek Mary J, Harvey Richard A and Champe Pamela C: Pharmacology. Lippincott Williams & Wilkins, Third edition 2005, 225.
41. Aqil M, Ali A, Sultana Y and Najmi AK: Fabrication and evaluation of polymeric films for transdermal delivery of pinacidil. Die Pharmazie 2004; 59(8):631-5.
42. Sclar David Alexander, Skaer Tracy L, Chin Alfred, Okamoto Mark P and Gill Mark A: Utility of a transdermal delivery system for antihypertensive therapy: part 2. American Journal of Medicine 1991; 91(1):S57-S60.
43. Dnyanesh NT and Vavia PR: Acrylate-based transdermal therapeutic system of nitrendipine. Drug Development and Industrial Pharmacy 2003; 29(1):71-78.
44. Gannu Ramesh, Vishnu Vamshi Y, Kishan V and Rao Madhusudan Y: Development of Nitrendipine transdermal patches: In-vitro and Ex-vivo characterization. Current Drug Delivery, 2005; 2:123-131.
45. Jamakandi VG, Mulla JS, Vinay BL and Shivakumar HN: Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian Journal of Pharmaceutics 2009; 3:59-65.
46. Satturwar Prashant M, Fulzele Suniket V, Dorle Avinash K: Evaluation of polymerized rosin for the formulation and development of transdermal drug delivery system: A technical note. AAPS Pharm SciTech 2005; 6(4):E649-E654.
47. Banweer Jitendra, Pandey Subhash and Pathak AK: Formulation, Optimization and Evaluation of Matrix type Transdermal system of Lisinopril dihydrate using permeation enhancers. Journal Of Pharmacy Research 2008; 1(1)
48. 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.
49. Yu-Xuan JIANG, Rui MA, Xi-Cao NIU and Liang FANG: Preparation of drug-in adhesive patches of amlodipine besylate and its in vitro permeability through excised rat skin. Journal of Shenyang Pharmaceutical University 2008; 25 (6):444-447.
50. Yinghua Sun, Liang Fang, Meng Zhu, Wei Li, Ping Meng, Li Li and Zhonggui He: A drug-in-adhesive transdermal patch for S-amlodipine free base: In vitro and in vivo characterization. International Journal of Pharmaceutics 2009; 382(1-2):165-171.
51. Patel Hemangi J, Patel Jitendra S, Desai BGD and Patel Keyur D: Design and evaluation of amlodipine besilate transdermal patches containing film former. International Journal of Pharma Research and Development 2007; 7: 12-21.
52. Nishida N, Taniyama K, Sawabe T and Manome Y: Development and evaluation of a monolithic drug-in-adhesive patch for valsartan. International Journal of Pharmaceutics 2010; 402(1-2):103-9.
53. Irfani Gulam, Raga Sunil Raj, Tondare Amit Tondare and Noola Shivanand: Design and evaluation of transdermal drug delivery system of valsartan using glycerine as plasticizer. International Journal of Pharma Research and Development – Online 2011; 3(2):185-192.
54. Gavali Pravin, Gaikwad Atul, Radhika PR and Sivakumar T: Design and development of hydroxypropyl methylcellulose

(HPMC) based polymeric film of enalapril maleate. International Journal of PharmTech Research 2010; 2(1):274-282.

55. Aqil M, Bhavna, Chowdhary I, Sultana Y, Talegaonkar S, Ahmad FJ and Ali MM: Transdermal therapeutic system of enalapril maleate using piperidine as penetration enhancer. Current Drug Delivery 2008; 5(2):148-52.

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