



REVIEW ARTICLE

**ANTIHYPERTENSIVE DRUGS USED FOR TRANSDERMAL DRUG
DELIVERY: A REVIEW**

***Ranju Pal¹, Ragini Shukla²**

1. Department of Pharmacy, Barkatullah University, Bhopal, India

2. Peoples Institute of Pharmacy and Research Centre, Bhopal (M.P.) India

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***Correspondence for
Author:**

Mrs. Ranju Pal

Department of Pharmacy,
Barkatullah University, Bhopal,
M.P

Email: pal.ranju@gmail.com

Abstract:

Hypertension is one of the largest deaths causing disease for the mankind. Since it is a chronic disease it necessitates long term treatment. But most of antihypertensive drugs available today showed extensive first pass metabolism and variable bioavailability, more frequent of administration make it is an ideal candidate for transdermal drug delivery systems. Transdermal Drug Delivery Systems enhances the drug permeation through the skin which can be achieved by using chemical enhancers and various solvents. Use of chemical enhancers is limited for its chronic application as it causes irritation at the site of application. Microemulsion or nanoemulsion technique proved to be one of the most promising techniques for enhancement of transdermal permeation of drugs. The present article gives the brief view on different antihypertensive drugs formulated as transdermal patch and transdermal nanoemulsion or microemulsion based formulation and their methodology in detailed to enhance the bioavailability as well as to improve the patient compliance.

Keywords: Transdermal drug delivery, hypertensive drugs, transdermal patch, micoemusion, Nanoemusion.

Introduction:

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect. Hypertension, a cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Global Burden of Disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries¹. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension². 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. Clonidine was the first antihypertensive drug developed in the transdermal form. Currently a number of antihypertensive transdermal patches are introduced in to the pharmaceutical market. The first of the two major problems associated with transdermal delivery is the excellent barrier property of the skin. This resides in the outermost layer, the stratum corneum. This unique membrane is only some 20 μm thick but has evolved to provide a layer that prevents us from losing excessive amounts of water and limits the ingress of chemicals with which we come into contact.^{3, 4} The precise mechanisms by which drugs permeate the stratum corneum are still under debate but there is substantial evidence that the route of permeation is a tortuous one following the intercellular channels. The diffusion path length is between 300 and 500 μm rather than the 20 μm suggested by the thickness of the stratum corneum^{5, 6, 7}. The physicochemical properties of the permeant are therefore crucial in dictating the overall rate of delivery. A molecule that is hydrophilic in nature will be held back by the lipophilic acyl chains of the lipids and conversely, a lipophilic permeant will not penetrate well through the hydrophilic head-group regions of the lipids. Furthermore, the lipids appear to pack together very effectively, creating regions in the alkyl chains close to the head groups that have a high micro viscosity. This creates multiple layers in which diffusion is comparatively slow⁸. There has been a continue interest during recent years for modifying drug penetration into and through the skin. It can be possible by use of physical or chmical means of penetration enhancement. Physical means of penetration enhancement

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include use of iontophoresis, Sonophoresis and microneedle. Chemical means of penetration enhancement include use of chemical penetration enhancers⁹. The physical means are relatively complicated to use and will affect patients compliance. Most of the topical vehicles contain chemical enhancers and non-friendly solvents to achieve improved permeability¹⁰. But these vehicles usually results in various degree of irritancy and permanent damage to skin in case of chronic treatments. Therefore it is desirable to develop topical vehicles that do not use chemical enhancers to facilitate drug penetration into and through the skin¹¹. One of the most promising techniques for enhancement of transdermal permeation of drug is to develop microemulsion or nanoemulsion¹². Microemulsions are quaternary systems composed of an oil phase, a water phase, and surfactant in combination with cosurfactant¹³. These spontaneously formed systems pose specific physicochemical properties such as transparency, optical isotropy, low viscosity and thermodynamic stability

WORK DONE ON TRANSDERMAL SYSTEMS OF ANTIHYPERTENSIVE DRUGS

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 level¹⁴.

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. Ethanolchloroform (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

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PVA (10%) system provide higher 1.589 ± 0.20 SD % drug/ cm² of permeation rather than HPMC: EC (2:8), i.e., 0.987 ± 0.20 % drug/cm² in 4 h period¹⁵.

Nicardipine hydrochloride

Nicardipine hydrochloride, a calcium channel blocker is used for the treatment of chronic stable angina and hypertension. The onset of action of the drug is 5-10 min and duration of action is between 15-30 min¹⁶. The half life of the drug varies between 2-4 h and bioavailability ranges 20- 40%¹⁷.

Krishnaiah YSR *et al.*,¹⁸ developed a membrane moderated transdermal therapeutic system of nicardipine hydrochloride using 2% w/w hydroxyl propyl cellulose (HPC) gel as a reservoir system containing 4% w/w of limonene as a penetration enhancer. The permeability flux of nicardipine hydrochloride through ethylene vinyl acetate copolymer membrane was found to increase with an increase in vinyl acetate content in the copolymer. The effect of various pressure-sensitive adhesives MA-31 (moderate acrylic pressure sensitive adhesive), MA-38 (mild acrylic pressure sensitive adhesive) or TACKWHITE A 4MED (water based pressure sensitive acrylic emulsion) on the permeability of nicardipine hydrochloride through ethylene vinyl acetate membrane 2825 (28% w/w vinyl acetate) or membrane/skin composite was also studied. The results showed that nicardipine hydrochloride permeability through ethylene vinyl acetate 2825 membrane coated with TACKWHITE 4A MED/skin composite was higher than that coated with MA-31 or MA-38.

Captopril

Captopril, an orally active inhibitor of an angiotensin converting enzyme 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 toxicity¹⁹. It has a mean half life of 2 to 3 h²⁰ but action lasts for 6-12 h²¹. 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 intestine²².

Sunita Jain *et al.*,²³ developed matrix diffusion type of TDDS of captopril employing different ratios of polymers, EC and HPMC as (3:1) and (2:2). The *in vitro* skin permeation

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and *in vitro* dissolution studies showed that captopril release was more in matrices containing ratio EC: HPMC as 2:2 compared to 3:1. Captopril from matrix containing EC: HPMC ratio 2:2 was able to penetrate through rabbit abdominal skin. The *in vivo* study shows that the prepared matrices were free from any irritating effect and stable for 3 months.

Dubey B.K., et al²⁴ had developed transdermal system bearing captopril were developed using a low temperature casting method and aqueous based polymers viz., **Eudragit RL-100** and **polyvinyl pyrrolidone (PVP)**. The results were compared with the transdermal systems of the same composition prepared at room temperature. The study revealed that the system prepared using the low temperature casting method performed better in composition to those prepared at room temperature.

Atenolol and metoprolol tartrate Atenolol and metoprolol tartrate are β_1 blockers that are incompletely absorbed from gastrointestinal tract having halflives of about 6-7 h.

Agrawal SS *et al.*,²⁵ 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, cellulose acetate phthalate, HPMC and EC. PG was used as a plasticizer and 1,8-cineole as 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 and 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.

Gupta S.P., et al²⁶ had developed transdermal Atenolol patch for its prolonged and controlled release systemic availability. To achieve the desired and controlled release rate, different combinations of **Eudragit RL** with **polyvinyl pyrrolidone** and **polyethylene** matrix system. These preparations were evaluated for *in vitro* release and permeation of the drug across pig skin. The drug plasma profile was compared with the plasma profile obtained following the administration of a conventional oral dose of Atenolol. The study revealed that

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the designed polymeric matrix transdermal drug delivery system of Atenolol could be successful with improved performance.

Aqil M *et al.*,²⁷ formulated a matrix type TDDS of metoprolol were by film casting technique using a fabricated stainless steel film casting apparatus. The different films are prepared by varying the concentration of matrix forming polymers ie., Eudragits and PVA. Formulations M1, M2, M3, and M4 were composed of Eudragit RL100 and PVA with the following ratios: 2:8, 4:6, 6:4, and 8:2, respectively. All the four formulations carried 10% w/w of metoprolol tartrate, 5% w/w of dibutylphthalate, and 5% w/w of (\pm) menthol in dichloromethane: isopropyl alcohol (80:20 v/v). Cumulative amount of drug released in 48 h from the four formulations was 79.16%, 81.17%, 85.98% and 95.04%. The corresponding values for cumulative amount of drug permeated for the said formulations were 59.72%, 66.52%, 77.36% and 90.38%. On the basis of *in vitro* drug release and skin permeation performance, formulation containing Eudragit: PVA (8:2) was found to be better than the other three formulations and it was selected as the optimized formulation.

Clonidine Clonidine is a centrally acting antihypertensive drug having plasma half life of 8-12 h and peak concentration occurs in 2-4 h. Clonidine effectively reduces blood pressure in patients with mild-to-moderate hypertension²⁸. 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 clonidine²⁹.

Mao Zhenmin *et al.*,³⁰ 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-phenoxypropylacrylate, 4-hydroxybutyl 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 TDDS.

Ming KEG *et al.*,³¹ characterized a newly developed clonidine transdermal patch, KBD-transdermal therapeutic system, for the treatment of attention deficit hyperactivity disorder in children. *In vitro* release, penetration, and *in vivo* pharmacokinetics in rabbits were

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investigated. The smaller size of KBD-transdermal therapeutic system (2.5 mg/2.5 cm²) showed a similar *in vitro* penetration to those of Cataprestransdermal therapeutic system (2.5 mg/3.5 cm², a clonidine transdermal patch used for the treatment of hypertension, Alza Corporation, USA). 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-transdermal therapeutic system) or Catapres-transdermal therapeutic system was transdermally administered to rabbits (n=6 each) and removed after 168 h. The average half-life, T_{max}, C_{max} and C_{ss} values of clonidine in rabbits following administration of KBD-transdermal therapeutic system 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-transdermal therapeutic system, respectively. The clonidine plasma concentration of KBD-transdermal therapeutic system reached a steady state at 24 h through 168 h. The *in vitro* release rate of the clonidine from KBD transdermal therapeutic system significantly correlated with the *in vivo* absorption rate (p<0.001).

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 firstline drug for the treatment of hypertension. This antihypertensive action is maximal at a dose of 2.5 mg/day, and the diuretic effect is slight, usually without clinical manifestation. The oral delivery of this drug has certain disadvantages such as frequent administration and adverse drug reactions. Additionally, since indapamide is usually intended to be taken for a long period, patient compliance is also very important.

Sanap GS *et al.*,³² employed solvent casting method for preparing transdermal monolithic system using HPMC and EC polymers by incorporating glycerine 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.

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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.

Aqil M *et al.*,³³ adopted solvent evaporation technique for preparation of TDDS. Different formulations were prepared using different combination ratios of Eudragit RL100, Eudragit RS 100 and PVP K30. Dimethyl sulfoxide (10-12% w/w) was employed as an enhancer and PEG 400 (2.5-7.5% w/w) as plasticizer. 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 h for the formulation having Eudragit RL100: Eudragit RS100 (7.5:4.5) and it was 83.24% for the formulation having Eudragit RL100: PVP K30 (9.0:2.0).

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 h, 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 300 $\mu\text{g/L}$.

Aqil Mohd *et al.*,³⁴ employed film casting technique to prepare TDDS of pinacidil monohydrate for effective management of hypertension for up to 48 h. The transdermal film consists of Eudragit RL100 and PVP K30 with different polymer ratios along with 20% w/w of drug, 5% w/w of plasticizer (PEG 400), 5% of DMSO as penetration enhancer. The TDDS were evaluated *in vitro* for drug release (using paddle over disc assembly) and skin permeation (using a diffusion cell) on rat skin model. The formulation of polymer ratio 6 parts of Eudragit RL100 and 4 parts of PVP K30 were found to be most effective when compared to other polymer ratio.

Verapamil hydrochloride

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Verapamil hydrochloride is a calcium ion influx inhibitor. It is widely used in the treatment of angina, hypertension, and supraventricular tachyarrhythmia. The plasma half-life of verapamil hydrochloride is 2-7 h, which necessitates multiple dosing. It is approximately 90% absorbed from the gastrointestinal tract but is subject to considerable first pass metabolism and its bioavailability is around 20-30%.

Kusum Devi V *et al.*,³⁵ prepared transdermal patches of verapamil hydrochloride using four different (single & combination) polymers like HPMC 15 cps, Eudragit RL100, Eudragit RS100 and EC into which the drug was incorporated. The formulations were optimized employing 23 factorial designs, with Eudragit RL100 being the parent polymer. The patch prepared from Eudragit RL 100 showed maximum water vapour transmission rate, % moisture absorption and % moisture loss, which is due to hydrophilicity. Substitution with Eudragit RS100, HPMC and EC decreased all the above values with their decreasing degree of hydrophilicity. The patch containing 8 parts of Eudragit RL 100 and 2 parts of HPMC with plasticizer i.e., dibutyl phthalate (30% of the polymer weight) emerged as the most satisfactory formulation by considering technological properties.

Nitrendipine

Nitrendipine a potent antihypertensive molecule which is a calcium entry blocker and potent peripheral vasodilator, reported to be well absorbed following oral administration, but undergoes extensive first pass metabolism³⁶ and oral bioavailability in the range from 10% to 20%³⁷.

Tipre D *et al.*,³⁸ fabricated monolithic transdermal therapeutic system 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 transdermal therapeutic system was evaluated for in-vitro flux through human skin (volar arm) to determine patch size needed to deliver drug through the transdermal route. Patches were evaluated for different parameters.

Optimized transdermal therapeutic system was found relatively stable at refrigeration only. The stability study encourages conducting a clinical study to determine if an Eudragit E100

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based nitrendipine transdermal patch could become a new product in treatment of hypertension.

Nifedipine

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

Sankar V *et al.*, ³⁹ designed and evaluated nifedipine transdermal patches. In the investigation drug free polymeric films of EC was prepared to know their suitability for transdermal application as controlling membrane and plasticizer such as castor oil (30% w/w) and glycerol (40% w/w) were incorporated. In the study EC was used for the fabrication which had a good film forming property. The physicochemical evaluation study reveals that there were no physical changes like appearance, colour and flexibility when the films stored at room temperature. The folding endurance was better in castor oil containing films when compared with glycerol containing films. The *in vivo* drug release studies in rabbits revealed that *in vivo* controlled delivery of nifedipine is possible with patches. Even though the drug release was slow during the initial hours (up to 4 h) from the EC patches containing 40% glycerol as plasticizer, the maximum percentage release was attained within 24 h. The delivery was found to be 82.6% of loaded drug at the end of 24 h.

Propranolol hydrochloride

Propranolol hydrochloride is a beta blocker which is used in management of hypertension. Due to its short biological half life (3.9 h) it necessitates for controlled delivery⁴⁰

Murthy TEGK *et al.*, ⁴¹ prepared rate controlling membrane for TDDS using cellulose acetate and EC using various solvents to evaluate the influence of the solvent on the mechanical and permeability properties of the films. Acetone: methanol (8:2), dichloro methane: 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

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employed with ethyl acetate: methanol (8:2) ratio as casting solvent yielded low area (1.29 cm²) of patch with desired release rate.

Raffee-Teharin M. et al⁴² had prepared transdermal multilaminar device of propranolol using various acrylic polymers. The release of the drug containing combination of **Eudragit RL and RS** obeyed a zero-order pattern across rat skin. The use of plastoid E35M effectively enhanced the penetration of the drug through rat skin.

Diltiazem hydrochloride

Diltiazem hydrochloride is a calcium channel blocker used in the treatment of arrhythmia, angina pectoris and hypertension. The literature survey reveals that it undergoes variable and extensive first pass metabolism before entering into systemic circulation and varies with species.

Rama rao P *et al.*,⁴³ prepared the polymeric films containing EC: PVP: drug (8:2:2 and 8:2:3). The *in vitro* skin permeation studies revealed that the skin permeation of diltiazem increases with increase of initial drug concentration and PVP content in the film and is optimum at the ratio of above said. The polymeric films composed of EC: PVP: drug (8:2:2 and 8:2:3) were prepared by mercury substrate method. Dibutyl phthalate was incorporated, at a concentration of 30% w/w of dry weight of polymers, as plasticizer. Briefly, the method involved the pouring of a chloroform solution containing drug, polymers and plasticizer on a mercury surface contained in a petri dish.

Amlodipine besilate

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Elimination from the plasma is biphasic with a terminal elimination half life of about 30-50 h and a bioavailability of 60-65%⁴⁴. It undergoes extensive first pass metabolism.

Patel JH *et al.*,⁴⁵ prepared matrix type transdermal drug delivery system of Amlodipine besilate, using different polymers like Carbopol 934, 940, HPMC and Eudragit L100 in varied ratios. The permeability studies indicate that the drug is suitable for TDDS. The optimized formulation containing Carbopol 934: Eudragit L100 (3:7), with hyaluronidase as

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enhancer showed 84% drug release after 24 h. Higuchi and Peppas's models were used for optimizing the formulation.

Carvedilol

Carvedilol, a non-selective β -adrenergic blocker used in hypertension, it is rapidly and extensively absorbed from the gastrointestinal tract. Following oral administration, the apparent mean terminal elimination half life of carvedilol generally ranges from 6 to 10 hr, the absolute bioavailability is approximately 25% to 35% due to a significant degree of first pass metabolism.

Barhate SD *et al.*, ⁴⁶ prepared carvedilol patches by solvent casting method by using combination of PVA and PVP K30 along with glycerine, PEG 400 and PG as plasticizers. It was observed that the patch with PVA: PVP in the ratio 8:6 along with used plasticizers was a promising controlled release transdermal drug delivery system for carvedilol. The *in vitro* drug skin permeation studies of the formulated transdermal patches revealed that the drug permeation from formulation containing 20% w/w and 40% w/w of PEG 400 were 91.50% and 94.21%, respectively. The results indicate that PEG 400, basically included as plasticizer also improves the *in vitro* permeation of carvedilol. Formulated transdermal patches of carvedilol, exhibits zero order release kinetics.

Ubaidulla U., *et al.*⁴⁷ had developed a 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

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was observed that both the patches significantly controlled hypertension from the first hour (P G .05). The developed transdermal patches increase the efficacy of carvedilol for the therapy of hypertension.

Lisinopril dihydrate

The Lisinopril dihydrate (angiotensin converting enzyme inhibitor) is a lysine derivative of enalapril and does not require hydrolysis to exert pharmacological activity. It undergoes extreme hepatic first pass metabolism resulting in bioavailability of 6-60%.

Banweer J *et al.*,⁴⁸ prepared transdermal patches by solvent casting technique employing HPMC and PVA in the ratio of 1:1 as polymeric matrix and plasticized with glycerol (6%). Binary solvent system (water: methanol) in the ratio of 70:30 was taken for the study. Oleic acid and IPA were added as the penetration enhancers separately and blend in different concentrations and ratios. The best results in terms of cumulative percentage release obtained through oleic acid and IPA patches were 54% and 70.65%, respectively at the highest concentration (15%) of enhancer employed individually. But when the mixture of enhancers was used in lowest concentration of 5%, they produced the cumulative percentage release of 84.33%, which clearly shows that synergistic effect of the enhancers if used in combination. 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 physico-chemical properties at normal and accelerated temperature conditions.

Nanoemulsion Assisted Transdermal Permeation of Antihypertensive Drugs

As demonstrated by recent publication, these systems themselves act as penetration enhancers and there is no need of incorporation of the conventional chemical enhancers.

Nifedipine

Though nifedipine is a potent antihypertensive drug, it has extensive first pass metabolism and low bioavailability.

K. Panduranga Rao *et al.*⁴⁹ prepared oil/water microemulsion of nifedipine by incorporating six lipophilic skin penetration enhancers such as ylang ylang oil, lavender oil, cinnamon oil, cineole, menathone and menthol. Ethanol was used as emulsifying agents. Three vehicle systems were used for developing microemulsion TDDS of nifedipine; first containing 25%

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ethanol, second system containing 50% ethanol and third system consisting of solutions of penetration enhancers in 100% ethanol saturated with nifedipine. The concentration of the penetration enhancers were kept same in all preparation. It was observed that maximum percutaneous nifedipine flux obtained with microemulsions containing 50% aqueous ethanol as compared to formulations consisting of 100% ethanol. It was also found that the formulation which contain cinnamon oil was the most efficient. Thus the result indicates that penetration enhancers when used as microemulsions are more efficient than their solution form.

Ramipril

Ramipril a potent antihypertensive drug is almost completely converted to its active metabolite ramiprilat (a dicarboxylic acid) by hydrolytic cleavage of the ester group in the liver. It has about 6 times the angiotensin-converting enzyme inhibitor activity of ramipril. It is a lipophilic, poorly water soluble drug with variable oral absorption.

Shaikh Shafiq-Un-Nabi et al⁵⁰ explain the basis for calculation and construction of pseudoternary phase diagram and also explain the selection of the formulation from the phase diagrams to avoid metastable formulations having minimum surfactant concentration in the least possible time. They had prepared nanoemulsion by spontaneous emulsification method by using Safsol 218 as oil, Cremophor EL as surfactant and Carbitol as cosurfactant. Pseudoternary phase diagrams were developed to select best formulation which contains 20% oil, 27% Smix and 53% aqueous phase. Best nanoemulsion region were selected for incorporation of Ramipril. 5mg of ramipril was selected as a dose for incorporation into the oil phase. The selected formulation was subjected to different stress test such as centrifugation, heating- cooling cycle and freeze-thaw cycle test. The stable nanoemulsion formulation was evaluated for droplet size and for viscosity. The result showed the uniformity of droplet size i.e. 34.5 nm and the lowest viscosity because of its lower oil content.

Carvedilol

Carvedilol is used in the long term treatment of hypertension and angina pectoris. It has α_1 and β -receptor blocking activity. It is well absorbed from the gastrointestinal tract, but it is

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subjected to considerable first pass metabolism in the liver which lead to low oral bioavailability (25-30%). It is highly lipophilic and practically insoluble in water.

Mohammed Aquil⁵¹ designed nanoemulsion as a possible vehicle for transdermal therapeutic system of carvedilol. For fabrication of nanoemulsion, solubility of carvedilol in oil, surfactant and co-surfactants was employed. They had selected Miglyol 810 as an oily phase as it showed the highest solubility. Whereas Acconon CC6 and Co-20 were selected as a surfactant and co-surfactant respectively. The pseudo-ternary phase diagrams were developed for various nanoemulsion formulations composed of surfactant/cosurfactant ratio 1:1. The optimized nanoemulsion system was evaluated for *in-vitro* flux through an excised wistar rat skin using Franz diffusion cell. The result of their study showed that the formulation which contain 0.25% w/w carvedilol, 12.5% w/w Miglyol 810, 50% w/w Acconon CC6/Co-20 (1:1) and water has the maximum skin permeation rate (161.53 ug/cm²/h). The nanoemulsions were also evaluated for their physiochemical characterization. The result of which revealed that nanorange size of oil globules provide intimate contact with skin layer which would help in achieving effective drug concentration.

Sanjula Baboota et al also developed and evaluated nanoemulsion for increasing the solubility and determine the *in-vitro* drug release of carvedilol. By using oleic acid and isopropyl myristate (IPM) (1:1) as the oil, Tween 80 as surfactant and Transcutol P as cosurfactants, various nanoemulsion formulations were prepared. For optimization of nanoemulsion formulation, pseudoternary phase diagrams were developed. The optimized formulation consists of 0.5% w/w of carvedilol, 6% w/w of oleic acid: IPM (1:1), 22.5% w/w of Tween 80, 22.5% w/w of Transcutol P and 49% w/w of distilled water in which the solubility of drug is higher. The optimized nanoemulsion formulation was evaluated for *in-vitro* flux through rat abdominal skin by using Keshany-Chein diffusion cell. It shows the highest value for different permeability parameters. Prepared nanoemulsion were subjected to determine physical parameters such as PH, conductivity, viscosity, droplet size, droplet shape and refractive index. The stability and irritation studies encourages conducting a clinical study to determine nanoemulsion based carvedilol could become a new product in treatment of hypertension.

Nicardipine Hydrochloride

Nicardipine hydrochloride a dihydropyridine calcium channel antagonist is used in the treatment of angina pectoris and hypertension. The oral bioavailability ranges from 20 to 30% because of extensive hepatic first pass metabolism. The elimination half-life is also very short i.e about 1 hour. Nanoemulsion vehicles for enhanced and sustained transdermal delivery of Nicardipine were developed by using isopropyl myristate (IPM) as oil, surfactant mixture of tween 80 / span 80 and / or Tween 80 / Span 20, co-surfactant (ethanol) and aqueous phase respectively. The components for nanoemulsion were selected on the basis of high solubilization capacity of drug, nanoemulsifying ability of surfactants and area of NE from pseudo-ternary phase diagrams. The area of nanoemulsion isotrop region was larger in presence of ethanol as compared to in absence of ethanol. The mean droplet size was ranged from 70-123 nm and the droplet size became smaller with addition of ethanol. The selected NE from pseudo- ternary phase diagrams was finally optimized for high flux by *in-vitro* skin permeation studies. On the basis of the highest *ex-vivo* skin permeation profile, lowest droplet size and lowest viscosity, the nanoemulsion formulation was said to be optimized. It contains 52% IPM, 35% surfactant mixture and 13% water and had higher permeation rate through rat skin above $122.53 \pm 1.87 \mu\text{g}/\text{cm}^2/\text{h}$. Thus the developed nanoemulsion has been successfully prepared and was expected to develop a teansdermal delivery system.

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 h and a bioavailability of 60-65%. It undergoes extensive first pass metabolism.

M. Aquil et al⁵² prepared oil-in-water nanoemulsion system for transdermal delivery of amlodipine. The solubility of amlodipine in oil and surfactant was evaluated to identify potential excipient. Various microemulsions were prepared using oleic acid as oil phase, Tween 20 as surfactant and Transcutol P as co- surfactant. The microemulsion existence ranges were defined through the construction of the pseudo-ternary phase diagram. The optimized nanoemulsion was characterized for its morphology, viscosity, pH, globule size and skin permeation of amlodipine through excised rat skin using a Franze diffusion cell. It

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was observed that increasing the concentration of oil and S (mix) decreases the flux; it was believed that due to increased globule size and decreased thermodynamic activity of drug at higher surfactant mixture concentration. Thus it was found that at low oil and S (mix) concentration the highest permeation rate and permeability coefficient obtained. The optimized nanoemulsion formulation shows maximum skin permeation rate of 49.681 ± 1.98 mg/cm²/h and permeability coefficient of 0.497 ± 0.056 cm²/h which contains 2% oil, 20% surfactant, 10% co-surfactants [S (mix) 2:1] and water. The result suggest that with poorly water soluble drugs such as amlodipine, topical delivery using nanoemulsion system may hold a great deal of promise for transdermal drug delivery system.

Felodipine

Felodipine is a calcium channel blocker (calcium antagonist), a drug used to control hypertenaion. Felodipine is well absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism, resulting in an absolute bioavaolability of 13 to 16% in fasted individual.

Dasco R. et al⁵³ designed and evaluated felodipine oil / water microemulsion which containing benzyl alcohol and isopropyl myristate as oil phase. Two suspension systems were developed as an aqueous drug suspension and a drug suspension in an apparent external phase of a microemulsion. Microemulsion was compared with this system for its skin permeation activity by using Franz diffusion cell. The *in vitro* skin permeation study revealed that the skin permeability of the microemulsion with the highest solubility of felodipine has the maximum flux. Whereas it was observed that the permeation rate decreases over time from the suspension in the apparent external phase. It was also found that the flux obtained from aqueous suspension was 10-15 times less than its microemulsion. The result obtained in this study suggest that microemulaion with benzyl alcohol would be a suitable vehicle for transdermal drug delivery in the management of hypertension.

Lacidipine

Lacidipine is a calcium channel blocker used in the treatment of hypertension and atherosclerosis. Lacidipine is completely metabolized in the liver by cytochrome P450 3A4 to pharmacologically inactive metabolite. It undergoes extensive first-pass hepatic metabolism and has a mean absolute bioavailability of about 10%.

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Madhusudan Rao Yamsani et al⁵⁴ Prepared and evaluate elucidate mechanistic effects of microemulsion formulation components on transdermal permeation of the drug through the skin. Based on the solubility results pseudo-ternary phase diagram were constructed for various microemulsion formulation, which includes isopropyl myristate, Tween 80 and Labrasol as oil, surfactant and co-surfactant respectively. In his study for optimization of microemulsion formulation, the Box-Behnken statistical design was used to investigate permeation across the rat skin in 24hr (Q24), flux and lag time. The optimum selected microemulsion was based on the maximum value of Q24, maximum flux and low value of lag time. The optimized formulation was formulated as microemulsion gel using hydroxyl propyl methyl cellulose at 4%w/v in the microemulsion. The flux of microemulsion gel was found to meet the target flux (12.16 $\mu\text{g}/\text{cm}^2/\text{h}$). The bioavailability study of microemulsion gel was compared to the oral suspension. The bioavailability result revealed that Lacidipine is released and permeated well from microemulsion gel by transdermal route as compared to the oral suspension. A good *ex vivo- in vivo* correlation was obtained. The irritation studies suggested that the optimized microemulsion gel was a non-irritant transdermal delivery system.

Conclusion

The brief overview of the different antihypertensive drugs revealed that, by delivering through the transdermal route improves bioavailability as well improve the patient compliance by many fold. But the demerit is that, all the hypertensive drugs cannot be given as transdermal delivery because the drug should have specific physicochemical property which should be suited to permeate through skin. The development of success TDDS depends on proper election of drug, polymer as well as other additives. Further work is needed to allow the antihypertensive drugs for trans-dermal systems and refine it in order to attain suitable clinical levels in patients.

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