Chapter -2

REVIEW OF LITERATURE
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Pao-chu wu et al.,\textsuperscript{21} have performed \textit{in vitro} percutaneous absorption of Captopril through excised rabbit skin. Surfactants were utilized as permeation enhancers to increase the percutaneous absorption of Captopril. Among the surfactants, SLS demonstrated the highest effect on infiltration which amplified the flux roughly 58.8 fold and the improvement enhanced with the raise of surfactant concentration.

Pao-chu wu et al., \textsuperscript{22} performed percutaneous absorption of Captopril from hydrophilic cellulose gel through excised human skin and rabbit skin. They reported that required flux for Captopril was 1488\(\mu\)g/h to retain the therapeutic least efficient concentration. The results specify that the formulations enclosing 3, 5 and 10\% Captopril with 5\% capric acid achieved the beneficial least efficient concentration.

Dubey BK et al., \textsuperscript{23} prepared and evaluated lyophilized aqueous based polymer matrices for transdermal delivery of Captopril. Transdermal system(s) bearing Captopril were set using a low temperature casting process and aqueous method using aqueous based polymers viz; polyvinyl pyrrolidone (PVP) and eudragit RL-100. The study exposed that the system(s) arranged using low temperature casting technique executed superior in evaluation to those organized at room temperature.
Pao-chu Wu et al.,\textsuperscript{24} have performed \textit{in vitro} percutaneous absorption of Captopril. They utilized four accessible skin membranes (rat, mouse, pig, rabbit) and human skin to estimate the \textit{in vitro} permeation penetration of Captopril. The flux of Captopril amplified in the array of human < pig < rabbit < rat < mouse. The rabbit skin was chosen as a model membrane for \textit{in vitro} penetration experiments of Captopril. The enhancing effect of penetration enhancers comprising aliphatic esters (2C-10C), fatty alcohols (2C-14C) and other compounds on Captopril penetration through excised rabbit skin were also estimated. The C6-C~0 of fatty alcohols, N-dodecyl-7-1actame and butyl acetate demonstrated the most enhancing effect on Captopril penetration.

Anroop B et al.,\textsuperscript{25} have synthesized ester prodrug of Atenolol and Propranolol with an objective of enhancing their lipophilicity so that permeability of Atenolol was increased.

Ghosh B and Reddy LH.,\textsuperscript{26} found that there was a correlation between the steady state fluxes of some antihypertensive and their melting points when assessed with the physicochemical parameters.

Okumara et al.,\textsuperscript{27} have investigated the permeability of several water-soluble drugs. It was established that the skin permeability coefficient of water soluble drug were lower than that of lipophilic drugs and permeation rates were higher than that of lipophilic drugs. The result suggests that a few soluble drugs with high solubility in
water and low molecular weight might be good candidates for transdermal drug delivery.

Modamio P et al., have studied a comparative study of percutaneous penetration of β blockers in human skin. It was found that there was an elongated lag time and also a low steady state flow for all drugs analyzed and the skin permeability did not reach therapeutic concentrations.

Shokri et al., studied the effect of surfactants on the skin permeation of Diazepam using rat skin. The effects of a variety of surfactants sodium lauryl sulphate (SLS), cetyltrimethyl ammonium bromide (CTAB), tween 80 and benzalkonium chloride with dissimilar concentration were estimated. The study revealed that the benzalkonium chloride exhibited the maximum enhancement for Diazepam flux (7.98 fold).

Kunta JR et al., have investigated the latent use of terpenoids/terpenes as penetration enhancers in the transdermal drug delivery of Propranolol hydrochloride. The Terpenes studied incorporated (+) limonene, L-menthol, carvacrol (±) and linalool at 1, 5 and 10% w/v concentrations. The result proposed that the menthol as efficient penetration enhancer.

Kalia YN and Guy R et al., have developed an impedance spectroscopy, a non-invasive biophysical technique, to evaluate the communication between electrical and chemical modes of
percutaneous penetration improvement *in vivo*. The consequences demonstrated that Azone and Sodium lauryl sulphate had a intense effect on post iontophoretic skin impedance. Stearic acid and linoleic acid had no comparable effects.

Marro D et al.,32 have typify the permselective properties of porcine and human skin. In this work Mannitol was used as a model compound for *in vitro* studies. The steady isoelectric points and comparable pH dependent permselectivite observed for pig and human skin established that porcine skin is suitable model for iontophoretic studies.

Ruland A and Kreuter J et al.,33 have investigated the influence of different penetration enhancers on the penetration of amino acids through shaved mouse skin. The consequences illustrated that the oleic acid was the most efficient enhancer followed by Azone.

Figueroa MJA et al.,34 have performed *in vitro* iontophoretic transdermal delivery of ethotrexate crosswise pig skin. It was instituted that the methotrexate iontophoretic transport declines with NaCl content, and amplified with raised current density.

Meidan VM et al.,35 studied the *in vitro* iontophoretic delivery of Buspirone hydrochloride and also observed the influence of chemical enhancers. Iontophoresis at 0.5 mA/cm² for 24 h did not change skin morphology and reverted to its pre-iontophoretic level. With Azone and Oleic acid the flux was significantly enhanced.
Chesnoy S et al., have evaluated the structural parameters involved in the permeation of Propranolol HCl by permeation enhancers and iontophoresis, showed two fold raise in flux with united effect.

Bhatia HS and Singh J et al., scrutinized the effect of 5% terpenes and iontophoresis on the in vitro permeability of luteinizing hormone releasing hormone (LHRH) through the porcine skin. Terpenes in grouping with ethanol considerably raised the flux of LHRH. Iontophoresis further improved the flux of LHRH through ethanol/ terpenes treated epidermis.

Sebastiani P et al., considered the efficiency of Lactic acid across the skin as permeation enhancer for drug molecules. They also studied the combination of iontophoresis and lactic acid as a means of drug delivery. The consequences attained specify that Lactic acid has promising effects on drug permeation across the skin.

johnson ME et al., investigated the enhancers and therapeutic ultrasound (1MHz, 1.4w/cm², continuous) on transdermal drug transport. In this work Corticosterone was employed as a model drug. The results suggested that Linoleic acid/ ethanol significantly increased the Corticosterone permeability from all the enhancers examined.

Sang et al., investigated percutaneous absorption of Piroxicam from poloxamer gels in rats. They have shown that the percutaneous
absorption of Piroxicam from the gel enclosing polyoxyethylene-2-oleyl ether as an enhancer was 1.8 fold elevated than that from the gel without enhancer. Percutaneous administration of Piroxicam gel having polyoxyethylene-2-oleyl ether to rats illustrated a moderately stable, constant blood concentration with least variation.

Yasuko et al.,\textsuperscript{41} synthesized l-cyclohexanol derivatives for percutaneous absorption enhancers selecting l-menthol as lead compound. An in vivo percutaneous absorption study was carried out using rats with hydrogel enclosing Ketoprofen and the plasma concentration was estimated after the application of hydrogel to the abdominal area of rats. They have recommended that the most advantageous log P value reveals the supporting activity to increase percutaneous absorption.

Iervolivo et al.,\textsuperscript{42} studied on the membrane penetration enhancement of Ibuprofen using super saturation formed using the cosolvent technique across silicone as model membrane. The flux of Ibuprofen was increased with the degree of saturation prepared in a 60:40 water, propylene glycol cosolvent mixture.

Elvira et al.,\textsuperscript{43} studied on the transdermal permeation of Diclofenac sodium using different liquid formulations. In-vitro permeation studies were performed using human skin as membrane. They have reported that there is no skin irritation with the inclusion of permeation enhancers like oleic acid. They suggested that the topical release of Diclofenac sodium with an absorption enhancer such as d-
limonene and oleic acid may be an effective for both dermal and subdermal injuries.

Valenta et al.\textsuperscript{44} studied the effect of permeation enhancers on the permeation of progesterone through porcine skin. In diffusion testing with porcine skin, there was improved stable state flux of Progesterone, it was raised upto 2.4 fold by means of 15 mol \% 6-ketocholestanol and 1.4 fold by means of 30 mol \% Phloretin.

Dave et al.\textsuperscript{45} formulated Diclofenac sodium gels containing permeation enhancers using carbomer as polymer. Formulation containing l-limonene showed better flux through excised rat skin than that of formulation containing same composition without limonene from 5\% to 10\% w/w. It was found that in presence of higher amount of ethanol, flux of Diclofenac sodium through rat skin decreased.

Jonathan et al.\textsuperscript{46} conducted an analysis to illustrate the penetration for the assortment of non steroidal antiinflammatory agents (NSAIDs) through the skin. They suggest that the bioeffectiveness of the NSAIDs will be a role of both its penetration through the skin and its strength. The majority NSAIDs are carboxylic acid, therefore the pKa will be an significant determination in ionization and hence penetration.

Arellano et al.\textsuperscript{47} investigated the influence of propylene glycol on the \textit{in vitro} penetration of Diclofenac sodium through an abdominal rat skin and a synthetic membrane from carbopol gel. The gel
enclosing 40 % PG demonstrated the chief permeation representing that a releasing limit subsists for PG content which offers the entirely solubilized drug in the vehicle. Diclofenac sodium flux declined with raising PG content of the gels due to raise of the drug attraction to the vehicle. Maximum enhancing activity was attained from gels enclosing 40 % PG which gives an development ratio of about 8. Raising IPM content from 3 to 5 % amplified the flux and reduced the lag time taken to achieve a steady-state intensity.

Pandey et al.,48 prepared different transdermal Nimesulide gels using sodium alginate, HPMC, sodium CMC and methylcellulose. In-vitro release studies of the prepared formulation were carried out by means of dialysis membrane. The discharge pattern of drug from the promoted gel was found to be better than from other gels, the reason may be that the 66% alcohol content of the gels that might have enhanced the solubility of the drug.

Gohel et al.,49 reported on the application of simplex lattice design for the improvement of transdermal gels Diclofenac sodium. They have prepared and evaluated Diclofenac sodium gels using Acrypol 940 as gelling agent. A simplex lattice design was employed for preparation of the gel possessing optimized characteristics. The amount of ethanol, polyethylene glycol 400 and propylene glycol were chosen as the independent variables to study the combined effect of cosolvents.
Patavardhan et al., have developed and evaluated the formulation of Diclofenac sodium hydroxy ethyl pyrrolidine containing penetration enhancers. They formulated the DHEP gel using carbopol 940 and 941 grade separately incorporating different penetration enhancers, and evaluated for their physicochemical properties. In-vitro drug permeation studies were determined in a keshary-chien glass diffusion cells using freshly isolated guinea pig skin for all the formulation in comparison with gels containing no penetration enhancers.

Sang et al., have developed tretinoin gels using carbopol. The discharge distinctiveness of drug from the carbopol gel were compared in different conditions (drug concentration, receptor medium and temperature). It is observed that the donor concentration had control on the permeation pace.

Jae et al., carried out a study to conclude the viability by means of gel formulation for the transdermal delivery of Triamcinolone acetonide (TA) and to extend the carbopol gels of TA.

Estelle et al., have studied the control of the physicochemical and pharmacokinetic factors of preferred NSAIDs on their transdermal absorption after topical gel administration. They have accomplished that most consistent factor for transdermal absorption was lipophilic nature of a drug (log P value). The solubility constraint, percentage unionized moiety and molecular mass can merely be used in grouping
with other factors in the calculation of potential Transdermal drug delivery.

Babua et al.,\textsuperscript{54} have designed and evaluated different gel reservoir type formulation of Bupranolol (BPL) with penetration enhancers. They have excised rat skin as a blockade for permeation experiments. The discharge rate of BPL from nonionic polymer gel reservoirs (HPMC) was much elevated than anionic polymer gel reservoirs (sodium CMC, sodium alginate). Penetration rates of the devices enclosing 1-methyl –2-pyrrolidone or (5% w/v) pyrrolidine were about 3 and 1.5 fold higher than control.

Wan L.S.C., et al,\textsuperscript{55} studied the action of HPMC on aqueous infiltration into matrices having HPMC of unstable concentration and viscosity. The integration of HPMC into Ibuprofen matrices enhanced wetting and develop water uptake into the matrices. A huge volume of water uptake was acquired with a better quantity of HPMC utilized. They also reported that the action of HPMC on liquid uptake depends on molecular weight and liquid uptake into such matrices and on the resulting balance between the raised inflated volume of the HPMC and viscous drug.

Chi. S.C., Park E.S. and Kim. H., et al.,\textsuperscript{56} studied the consequence of infiltration enhancers on Flurbiprofen penetration through rat skin. Urea and fatty acids were added in propylene glycol vehicle enclosing Flurbiprofen.
Seki. T. and Kawaguchi, T., et al., studied continuous transdermal delivery of Zidovudine via controlled release of infiltration enhancer. The effects of N-methyl pyrrolidone on the permeation of Zidovudine in isopropyl myristate through rat skin were studied in-vitro. Zidovudine permeation was significantly enhanced by N-methylpyrrolidone. When ethylene vinyl acetate copolymer (EVA) membrane was used for controlled release of N-hylpyrrolidone, a considerable plasma Zidovudine level was maintained for 10hrs. It was accomplished that N-methylpyrrolidone enhances the infiltration of Zidovudine through rat skin, with sustained plasma levels achieved with the addition of EVA membrane.

Bernhard P. Winkers and Bernhard C. Lippold et al., studied on Skin infiltration of nonsteroidal anti inflammatory drugs out of Lipophilic Vehicle: They studied Influence of the viable epidermis and distinguished the blockade function of the viable epidermis and the stratum corneum, they predicted their control on the skin permeabilities and the highest fluxes of the NSAIDs by model equations. The permeability of the human skin for NSAIDs applied in a lipophilic vehicle is task of their hydrophilicity, whereas the highest flux is principally dependent on their vehicle solubilities. The viable epidermis was instituted to signify the significant resistant to the drug transport.

Hitoshi Sasaki, et al., studied on cause of skin temperature on transdermal absorption of Flurbiprofen from a cataplasm.
Transdermal absorption of Flurbiprofen (FP) from a cataplasm (CFP) and its anti inflammatory effect were investigated in the rat under various skin temperature conditions. As the skin temperature was raised, the plasma concentration of FP after application of the cataplasm increased significantly. It was demonstrated by the discharge and \textit{in-vitro} infiltration experiment that skin penetration is the rate determining step for absorption, and both release and penetration increased with rise of temperature.

Sheikh A. Akhter and Brain W. Barry, et al.,\textsuperscript{60} studied on absorption of Flurbiprofen and Ibuprofen through human skin. Result of dose difference, occlusion, deposited drug films and the effect penetration enhancer, N-methyl – 2 – pyrrolidone were investigated. The study from drug films deposited by acetone evaporation on cadaver skin was performed in an open cell \textit{in vivo} mimic design. Improved dosage did not create a comparative raise in the penetration and maximizing the skin drug contact did not raise diffusion; both features specify that absorption from deposited drug films was dissolution rate-limited. Occlusion of the skin did not raise the dissolution rate of the deposited drug film, but did lift up the diffusion of drug already present at the time of occlusion within the skin. N-Methyl – 2 – pyrrolidone improved the diffusion flux of Ibuprofen sixteen fold and Flurbiprofen, over three fold.

Li, C. Nguyen et. al.,\textsuperscript{61} investigated in the work of transdermal administration of ACE inhibitor and enhanced the absorption of their
prodrug. They evaluated that the possibility of constant controlled release of therapeutically efficient amount of ACE inhibitor in matrix kind of transdermal drug delivery system to develop the transdermal absorption by production of prodrug with enhanced matrix solubility and lipophilicity. They reported that permeation rate of Eenalapril can be improved by using prodrug strategy by improving the lipophilicity of drug.

Liang. B.W., Chang, Y.P., and Lu.Y., et al.,62 studied restricted discharge of Scopolamine through EVA membrane was investigated in transdermal Scopolamine patch formulations with drug discharge rates matched up to uninhibited reservoirs. An EVA membrane patch released Scopolamine at a steady rate for more than 72 hrs.

Rajesh Krishna., and Pandit .J.K.63 organized three transdermal formulations enclosing Propranolol hydrochloride in a hydrophilic polymer matrix, one without rate controlling membrane[H1], one with 20ìm thick ethylene vinyl acetate (EVA) rate controlling membrane H2 and one with 65ì thick EVA membrane[H3]. These were estimated for their in-vitro performance through excised hair free rate skin. Cumulative percentage drug permeated from H1 patch 79.2%, from H2 patch 65.53% & from H3 53.44%, increased thickness of EVA lead to better retention of the drug in device. A zero order profile was seen with patches H2 and H3 and matrix diffusion profile with H1 patch.

J. Hadgraft et.al.,64 studied Skin permeability data and the records has revealed that a few compounds emerge to comprise
abnormal skin permeability coefficients. These consist of penetrants such as atropine, nicotine and naproxen. The permeabilities of these resources were re-determined collectively with benzoic acid, aspirin, methyl nicotinate, Diclofenac and Ibuprofen.

P. Minghetti, et al.65 investigated permeability of dermal therapeutic systems to water vapour from self adhesive patches that consist of an adhesive controlled release matrix layer and a flexible backing layer containing the drug. They are created to acquire a controlled release of drugs in order to care for topical skin pathologies. As permeability to water vapour is an essential feature for DTS, the plan of this work was to widen systems with dissimilar conventional water vapour permeabilities (WVP), to be preferred according to the therapeutic needs of the treated disease, and with excellent adhesive properties.

M. Guyot and F. Fawaz., et al.66 studied on design and in-vitro evaluation of adhesive matrix for transdermal delivery of Propranolol and found the influence of dissimilar features (drug content, polymeric material, presence of a dissolution enhancer, thickness of the adhesive layer and matrix thickness) was examined. In vitro dissolution study was performed according to European Pharmacopoeia. Discharge from HPMC matrices without adhesive coating was rapid. Discharge from these matrices became more normal (reduction of the burst effect) and slow when they are coated
with a 12im thick Ucecryl layer. The most excellent release odulation was attained from Ucecryl matrices.

M.S. Nagarsenker and D.D. Hegde.,\textsuperscript{67} studied on optimization of the mechanical characteristics and water vapour transmission characteristics of free films of hydroxypropylmethylcellulose and instituted their moisture permeability characteristics and mechanical properties. A 22 factorial design was employed to quantitate the effect of each polymer on the tensile strength and permeability constant of the films.

Daas et.al.,\textsuperscript{68} investigated the physical/ rheological characteristics of a series of commercial galactomannans. Both rheological properties of the galactomannans and solubility of galactomannan solutions and galactomannan/xanthan mixtures were examined. By means of a statistical study approach an effort was undertaken to distinguish correlations between rheological and structural data. The most excellent association found was between the large quantity of galactose substituents at a standard distance (type of galactomannan) and the storage modulus (G') of varied galactomannan/xanthan gels, underscoring the proposition that branching obstructs the configuration of a network with xanthan gum. Moreover, the G' for the group of locust bean gums linked with the degree of blockiness, that is, the size and occurrence of nonsubstituted regions on the mannose backbone. In addition, galactomannans exhibited an evident reduce in gelling capacity with
raising standard molecular weight. That G’ also communicate to the kind of galactomannan can consequently to a certain extent be recognized to variation in standard molecular weight for the assorted galactomannan types. However, within the sequence of locust bean gums tested, also an raise of G’ with molecular weight was recorded. This can be elucidated by the declining number of loose ends of the polymers and the concomitant raising effectiveness in network contribution with raising molecular weight.

Cardero, JA, et.al.,69 studied a Comparative study of the transdermal penetration of a sequence of non-steroidal anti-inflammatory drugs. The transdermal absorption of a series of non-steroidal anti-inflammatory drugs (NSAID’S): Diclofenac, Indomethacin, Piroxicam, Ketoprofen, Ketorolac, Aceclofenac and Tenoxicam, were calculated in vitro with human skin. The principle of the study was to conclude the permeation factors (permeability), rates constant, TL, Flux and Kp; lag time, as measures of the essential transdermal permeability’s of these drugs to calculate their latent for formulation in a transdermal therapeutic system (TTS).

In another study Hinz B et.al.,70 liquid-liquid extraction-based reversed-phase HPLC method with UV detection was authorized and applied for the examination of Aceclofenac and three of its metabolites (4’-hydroxy-Diclofenac, 4’-hydroxy-Aceclofenac, Diclofenac) in human plasma. The analytes were alienated by means of an acetonitrilephosphate buffer gradient at a flow velocity of 1 mL/min,
and UV detection at 282 nm. The retention times for ketoprofen, Aceclofenac, 4’-hydroxy-Aceclofenac, Diclofenac, 4’-hydroxy-Diclofenac and (internal standard) were 69.1, 60.9, 46.9, 28.4 and 21.2 min, correspondingly. The authenticated quantitation array of the technique was 10-10000 ng/mL for Diclofenac, 4’-hydroxy-Aceclofenac and Aceclofenac and 25-10000 ng/mL for 4’-hydroxy-Diclofenac. The developed method was applied to evaluate the pharmacokinetics of Aceclofenac and its metabolites following administration of a single 100 mg oral dose of Aceclofenac to three healthy male volunteers. To generate novel transdermal formulation for Aceclofenac.

Yang JH et al.,71 prepared microemulsion for raising its skin permeability. Based on phase studies and solubility, surfactant and oil was preferred and composition was determined. Microemulsion was instinctively prepared by incorporating constituents and the physicochemical parameters was examined. The mean thickness of microemulsion were about 90 nm and the system was actually constant at room temperature at least for 3 months. In addition, the in vitro and in vivo performance of microemulsion formulation was assessed. Skin permeation of Aceclofenac from microemulsion formulation was elevated than that of cream.

Bort R, Ponsoda X. and Carrasco et al.,72 studied metabolism of the new NSAID’s drug Aceclofenac both in the in vitro and in vivo hepatic human models. It was established that Aceclofenac is
metabolized in human microsomes and human hepatocytes to form major and minor metabolite. After oral administration to human volunteers (100 mg single dose), Aceclofenac attained a Cmax value of 7.6 g/ml & a tmax of 2.6.

Bort R, Ponsoda X. and Carrasco E .et al.,\textsuperscript{73} studied metabolism of the new NSAID’s drug Aceclofenac both in the in vitro hepatic human models and in vivo. It was found that Aceclofenac is metabolized in human hepatocytes and human microsomes to form major and minor metabolite. After oral administration to human volunteers (100 mg single dose), Aceclofenac reached a Cmax value of 7.6±1.3 µg/ml & a tmax of 2.6±1.8.

H.K. Vaddi et.al.,\textsuperscript{74} investigated the influence of carvacrol, linalool, and á-terpineol on the permeation of haloperidol. Carvacrol followed by linalool and terpineol improved permeability coefficient and flux but only carvacrol offered the permeated daily doses and the necessary plasma concentration. All terpenes raised the activity coefficient of HP in the skin. Carvacrol raised the lag time, which could be due to slow rearrangement within SC.

Biswajit Mukherjee et al.,\textsuperscript{75} have conducted relative studies between Povidone-Eudragit and Povidone-Ethyl cellulose. Transdermal Dexamethasone matrix patches based on invitro skin permeation. Physical studies together with flatness, moisture uptake, moisture content, to revise the steadiness of the formulation.
Francesco Cilurzo and Luisa et al., have developed Polymethacrylate as crystallization inhibitors in monolayer. Transdermal patches enclosing Ibuprofen. The possibility of a monolayer patch based on polydimethylsiloxane force sensitive adhesive enclosing Ibuprofen in supersaturated state was considered.

Babwale and Shrivastava., have developed Adhesive matrix type Transdermal drug delivery system for Nitroglycerin. At a elevated drug to adhesive ratio the patch comprised of Nitroglycerin in part suspended as droplets in the adhesive and in part suspended in the adhesive. This patch illustrated instantaneous discharge of a main portion of nitroglycerin in the patch. Narasimha Murthy have developed and evaluated Transdermal matrix devices of Terbutaline Sulphate using HPMC, Sodium CMC, Cellulose acetate and Ethyl cellulose as the polymer base.

Bhalla and Deshpande have studies the Permeation of Fluriprone in a Polyvinyl alcohol– Polyvinyl pyrrolidine matrix for Transdermal use through guinea pig skin.

Bhalla and Deshpande., Have carried out feasibility studies of Transdermal delivery of Terbutaline sulphate. Matrices containing various proportion of polyvinyl alcohol and polyvinyl pyrrolidine, glycerin and drug were prepared and characterized by Physico-chemical assessment and in-vitro drug penetration through guinea pig skin, rabbit skin, human cadaver skin and stripped guinea pig skin.
Giannakou et al.,79 have developed experimental design techniques for in-vitro evaluation of Nitrendipine Transdermal formulation.14 A preliminary study was performed in order to calculate the effect of the enhancer, the concentration of gelling agent and the concentration of enhancer on the flux of Nitrendipine, by means of a 23 factorial design.

Subhas Mandal et al.80 have developed in-vitro release and penetration kinetics of Pentazocine from matrix-dispersion type Transdermal drug delivery systems.15 This system was fabricated using combination of rate controlling polymers, namely Eudragit RS100, RL100, Ethyl cellulose and polyvinyl pyrrolidine with the objective of examining the effects of formulation variables on drug-permeation profiles.

Kale et al.,81 have studied the Preformulation stability and Permeation of Transdermal patches of salbutamol.16 The study involves screening a suitable enhancer for the drug. The influence of Lauryl alcohol and Tween 80 was reported to be less but the oleic acid and Sodium lauryl sulphate to be greater extent could enhance the permeation of salbutamol sulphate.

Bhalla and Jathar et al.,82 have prepared monolithic matrices of Transdermal films of Diclofenac sodium containing varying proportions of the polymers (polyvinyl alcohol–polyvinyl pyrrolidine) and evaluated through Guinea pig skin.
Bhattacharya and Ghosal et al.,\textsuperscript{83} have studied the effect of hydrophobic penetration enhancers on the discharge and skin penetration kinetics from matrix type Transdermal drug delivery system of Ketotifen Fumarate.

Sant and co worker et al.,\textsuperscript{84} have approached Iontophoretically facilitated Transdermal delivery of salbutamol sulphate and reported that the drug penetration could be improved by current application and it was directly proportional to the current intensity and initial drug concentration.\textsuperscript{19} The enhancement showed inverse relationship with nonionic strength of drug in the donor solution. An optimum frequency, on/off ratio and pH were required for maximum permeability. A large number of polymers were evaluated for their matrix and membrane release kinetics with the drug Ephedrine hydrochloride.

Chien et al.,\textsuperscript{85} have described the use of polymers in the development of TDDS and has recommended suitable diffusion cells for the Evaluation of Transdermal patches.

Amaranth et al.,\textsuperscript{86} have described various Penetration enhancers—Dimethyl sulphoxide, n-decyl methyl sulfoxide, Surface active agents like Sodium lauryl sulphate, Fatty acids and alcohols, Azones, Glycols, ethers in semisolid preparations.

Bhalla et al.,\textsuperscript{87} have formulated polymer matrix type Transdermal fibers using PVA And PVP as the polymers and Isosorbide dinitrate as drug and \textit{in-vitro} studies done.
S.C. Mandal et al., have reported Ethyl cellulose, Eudragit, Polyvinyl alcohol and Polyvinyl Pyrrolidin as polymer to formulate matrix type transdermal devices of Diazepam, which were then subjected to in-vitro evaluations.

Vidya and Naik et al., have formulated Monolithic matrix type of transdermal devices using Eudragit RS-100 and Eudragit NE-30 as the polymers and salbutamol as the drug In Vitro and in vivo studies were performed to evaluate the patches.

Gupta and Jain et al., have developed Transdermal Delivery of Metoprolol Tartrate using Eudragit RL and HydroxyPropyl Methyl Cellulose were used for fabrication of the matrix diffusion restricted Transdermal drug delivery system.

Sang-Chul Shin and Jun-Shik et al., chose determined the possibility of enhancer on Transdermal delivery of Atenolol from the Ethylene-vinyl acetate matrix system having Polyoxyethylene-2-oleyl ether as an enhancer.

Reddy et al., have developed a Spectrophotometric technique of determination of Terbutaline. The process is based on the reaction of Terbutaline with diazotised sulphanilic acid under mild alkaline conditions to produce colored species, which has a λ max at 440nm. The optical feature such as Sandell’s sensitivity, Beer’s range, % relative standard deviation, molar extinction coefficient.

Ibrahim alsarra et al., have developed Preoiosomes as a drug carrier for Transdermal delivery of Ketorolac. Permeation of a potent
nonsteroidal anti-inflammatory, Ketorolac across Preoiosomes gel formulation was examined by means of Franz diffusion cells.

Ogiso and Shintani et al.,\textsuperscript{94} have examined the transdermal penetration of propanolol using a series of fatty acids through rabbit skin using a gel base. The results showed that a 1:1 ratio of a fatty acid:drug, enhanced the permeation of propanolol.

Kunta et al.,\textsuperscript{95} have studied menthol as permeation enhancer, in an effort to raise the penetration rate of propanolol, the results were found to be promising.

Ghosh and Reddy.,\textsuperscript{96} A correlation was established between the steady state fluxes of some antihypertensives and their melting points, when assessed with the physicochemical parameters.

P.Modamioet.al.,\textsuperscript{97} investigated two blockers Celiprolol and Bisoprolol, for transdermal permeation. Celiprolol having short elimination half-life 4-5 hrs and Bisoprolol is one of mainly effective blockers, which is effective at very low dose (5-20 mg Daily). For each drug the chief penetration factors, lag time (TL), permeability coefficient (Kp), and flux (J) were calculated as a measure of essential permeability crosswise human skin. They reported that celiprolol is better than bisoprolol.

N.Udupa et.al.,\textsuperscript{98} investigated the effect of penetration enhancers, vehicles and bases on the percutaneous absorption of Captopril by means of sigma dialysis sacs. Physicochemical characteristics of film, \textit{invitro} diffusion, and pharmacodynamics and
stability studies were conducted. They reported Captopril release to be slowest from sodium alginate gels and to be highest from H.P.M.C. gels. Also the drug release was found to be better from CA films. The stability of Captopril was better in case of film as matched up to to gels.

Mutsuo Okumara., et. al., studied the skin permeability of various water soluble drugs and reported that, when Diclofenac sodium, disodium cromoglycate, diltiazem hydrochloride, dopamine hydrochloride, papaverine hydrochloride and isoproterinol hydrochloride, were preferred as water soluble drugs, lipophilic drug, deuterium oxide and indomethacin were employed for comparison. The water-soluble drug with lesser molecular weight and elevated solubility in water illustrated higher skin permeation rates. Their results suggests that some water soluble drug with high solubility in water low molecular weight might be good candidate for transdermal drug delivery.

Mc Daid et.al., investigated that, the improvement of a transdermal delivery system for the chemically unchanged drug in humans is not likely to be successful. They reported that in case of nifedipine the measured physicochemical parameters influencing percutaneous absorption such as partition coefficient and solubility established the drugs potentiality for such a formulation approach.

Li, C. Nguyen et. al., investigated in the work of transdermal administration of ACE inhibititor and enhanced the absorption of their
prodrug. They evaluated that the possibility of constant controlled delivery of therapeutically efficient quantity of ACE inhibitor in matrix kind of transdermal drug delivery system to increase the transdermal absorption by production of prodrug with enhanced matrix solubility and lipophilicity. They reported that permeation rate of Eenalapril can be improved by using prodrug strategy by improving the lipophilicity of drug.

E. S. Park et. al.,\textsuperscript{102} considered the effect of adhesive and permeation enhancer on the skin penetration of Captopril. They formulated a huge adhesive matrix type patch comprising 20\% Captopril, dissimilar pressure-sensitive adhesive and a range of permeation enhancers were prepared by means of a laboratory-size coater. The effect of permeation enhancer and adhesive on skin penetration of Captopril from the prepared patch were estimated by means of franz diffusion cells fitted with excised rat skin. The penetration rate of drug through excised rat skin was reliant on the kind of polyacrylate copolymer employed in the work. Based on these consequences a Captopril patch may be created with additional optimization.

Hye. Sum. Gwak et. al.,\textsuperscript{103} examined the effect of enhancer and vehicles on the \textit{in vitro} penetration of melatonin through shaved mouse skin. They reported that, propylene glycol laurate (PGL), isopropylene myristate (IPM), propylene glycol monocaprylate (PGMC) and propylene glycol monolaurate (PGML) illustrated high penetration
flux and also PGL, PGMC and PGML reduced lag time considerably. They suggested that for efficient solution formulation in terms of lag time and permeation flux, capric acid comprising PGL-DGME (20: 80v/v) could be employed to improve the skin permeation of melatonin.

Ahmed S. et. al.,\textsuperscript{104} have attempted a novel approach. The drug Propranolol was combined with a number of long chain fatty acid to develop a series of prodrug esters. These prodrugs showed better permeability towards stratum corneum where they are stereoselectively cleaved to yield the drug. However, the lipophilic esters had difficulty in partitioning into deeper layers of skin.

In 1993 Kobayashi, et. al.,\textsuperscript{105} has also studied skin permeation profile of several cardiovascular drugs Nicardipine, Atenolol, Captopril, Nifedipine and vinpchetin etc., from menthol – ethanol system.

Jeck, T. et. al.,\textsuperscript{106} studied transdermal therapy of an antihypertensive drug Bupranolol where transdermal Bupranolol was contrasted with oral metoprolol. Control of blood pressure in patch bearing patients was comparable to that of oral metoprolol.

Tuncer Degim, et. al.,\textsuperscript{107} reported that the examination of available skin penetration records has revealed that some compounds emerge to have irregular skin permeability coefficients. These contain penetrants such as nicotine, atropine and naproxen. The permeabilities of these resources were re-determined collectively with benzoic acid, aspirin, Diclofenac, methyl nicotinate and Ibuprofen.
The consequences are conferred in coincidence with available regression study and matched up with values calculated by estimating the octenol-water partition coefficients by means of profitable software packages.

H.K. Vaddi et.al.,\textsuperscript{108} investigated the influence of carvacrol, linalool, and áterpineol on the permeation of haloperidol. Carvacrol followed by linalool and terpineol improved permeability coefficient and flux but only carvacrol offered the permeated daily doses and the necessary plasma concentration. All terpenes raised the activity coefficient of HP in the skin. Carvacrol raised the lag time, which could be due to slow rearrangement within SC.

Dnyanesh N, Tipre et.al.,\textsuperscript{109} investigated an acrylate-based transdermal therapeutic system (TTS) of Nitrendipine, which could distribute drug at highest input rate so as to distribute drug in least patch size. Transdermal patches were fabricated by means of synthesized acrylate pressure- Sensitive adhesives (PSAs): PSA1, PSA2, and commercially existing PSA3 and PSA4 by means of d-limonene as permeation enhancer. Effect of concentration of dlimonene on permeation kinetics of Nitrendipine in PSAs was considered, out of these PSAs the synthesized acrylate PSA2 copolymer was found to have rate controlling and excellent adhesion properties. The synthesized PSA2 was found skin-compatibility with advantageous wear performance. high peel strength (100g/2x2 cm2 on human skin) and Low Tg (-41oC)of PSA2 released Nitrendipine at
highest input rate and could be helpful in production of drug-inadhesive transdermal system of d-limonene, Nitrendipine was found to be an efficient penetration enhancer at 0.50% in PSA2. It could be possible to distribute Nitrendipine PSA2 through transdermal route in management of hypertension.

Giannakou, S.A, et.al.,\textsuperscript{110} they incorporated Nitrendipine into gels and its efficiency to infuse human skin was scrutinized \textit{in vitro}. A preliminary work was performed in order to calculate the effect of the kind of enhancer, the concentration of gelling agent and the concentration of enhancer on the flux of Nitrendipine, by means of a 23 factorial design, it was demonstrated that the type and concentration of gelling agent influence the flux of Nitrendipine, whereas their communication were found to be not important.

Kerc J, et.al.,\textsuperscript{111} they prepared surface solid dispersions via physical mixture and were either heated in a vacuum dryer or in a microwave oven for different periods of time. The physical state of felodipine in solid dispersion was considered by means of x-ray powder diffractometry and differential scanning colorimetry. USP paddle method was employed for felodipine dissolution studies, the consequences of dissolution illustrated that the dissolution rate of felodipine form solvent deposit as well as vacuum prepared surface solid dispersions raised distinctly as compared to the dissolution rate of felodipine alone, and also raised in comparison to the dissolution fate of ambient-temperature prepared mixture.