# CHAPTER-2

## REVIEW OF LITERATURE

**Kim JH *et al.,*** have studied the effects of various pressure sensitive adhesives (PSA) on the percutaneous absorption of physostigmine across hairless mouse skin. They have studied in addition, the influences of various vehicles and polyvinyl pyrrolidone (PVP) on the percutaneous absorption of physostigmine from PSA matrix across hairless mouse skin using a flow through diffusion cell system at 37°C and found the highest permeability of the drug from silicone adhesive matrix.

**Sagar P *et al.,*** have demonstrated the development of membrane controlled transdermal therapeutic systems of ethyl cellulose and polyvinyl alcohol containing an antihypertensive drug, verapamil hydrochloride by the method of casting on mercury surface. They have evaluated the thickness uniformity, content uniformity, skin irritation and *in vitro* drug permeation of the formulations through excised mouse skin and found promising results.

**Chowdary KPR *et al.,*** have studied the permeability of ethyl cellulose films towards salicylic acid and diclofenac sodium with a view to evaluate the films for effective use as rate controlling membrane for transdermal drug delivery systems. Solutions in chloroform, acetone and isopropyl alcohol were found to give good flexible films of ethyl cellulose alone and in combination with PVP and PEG. The films were permeable to water vapor, salicylic acid and diclofenac sodium. Drug diffusion through these films followed zero order kinetics. Incorporation of PVP and PEG has considerably increased the permeability of the ethyl cellulose films.

**Baichwal MR *et al.,*** have investigated films comprising of ethyl cellulose and polyvinyl pyrrolidone for their potential transdermal use. Placebo films were initially evaluated for their mechanical and physical properties. They have evaluated single films and laminates (double layered films) cast on a backing membrane of polyvinyl alcohol containing salicylic acid for *in vitro* and *in vivo* drug release. They concluded that the studied formulation appears with promising result from their experiment.

**Mukherjee B *et al.,*** have studied the matrix type transdermal drug delivery system (TDDS) of dexamethasone using blends of two different polymeric combinations, povidone (PVP) with ethylcellulose (EC) and eudragit with PVP. After studying physicochemical properties and *in vitro* skin permeation rate of the formulated patches, they concluded that the PVP-EC polymer combination was better suited than PVP-eudragit polymer combination for the development of TDDS of dexamethasone.

**Rao PR *et al.,*** have studied the plasticized free films of cellulose acetate (CA) alone and in combination with different concentrations of polyvinyl pyrrolidone (PVP). Adaptation of mercury substrate method and incorporation of dibutyl phthalate (40 % w/w of polymer) yielded thin, uniform and flexible films. Both water vapor transmission and drug diffusion through the free films followed zero order kinetics and decreased with increase in film thickness. Permeability of films increased with increasing PVP concentration and this may be due to leaching out of PVP fraction, which leads to improved porosity and permeability. CA:PVP (2:1) was used as the rate controlling membrane for the development of transdermal drug delivery system (TDDS).

**Suwanpidokkul N *et al.,*** have reported four binary vehicles (ethanol/water, isopropyl alcohol/water, polyethylene glycol 400/water, and ethanol/isopropyl myristate [IPM]) tested for zidovudine solubility and permeability across pig skin. Next, the addition of various concentrations of different enhancers (N-methyl- 2-pyrrolidone [NMP], oleic acid and lauric acid) to different volume ratios of ethanol/IPM was investigated for their effect on zidovudine solubility and permeability across pig skin.

**Satturwar PM *et al.,*** have worked on evaluation of polymerized rosin for the formulation and development of transdermal drug delivery system using matrix type transdermal patches composed of different ratios of polymerized rosin (PR), polyvinyl pyrrolidone (PVP) and diltiazem hydrochloride and showed that PR in combination with PVP and with incorporation of dibutyl phthalate (30 % w/w) produces smooth flexible films with improved tensile strength and percentage elongation. The patches containing PR:PVP (7:3) on pharmacokinetic and pharmacodynamic performance evaluation in a suitable animal model

showed promising result proposing that PR can be used in the design of a matrix type transdermal drug delivery system to prolong the drug release.

**Manitz R *et al.,*** have studied on mathematical modeling of dermal and transdermal drug delivery. This paper deals with two extensions of diffusion models for the drug delivery process into human skin in order to give a more realistic approach. Various penetrating substances formulated within a vehicle are considered for modeling the case of an applied drug and some penetration modifiers (enhancers and reducers). A coupling via concentration dependent diffusivities between the diffusion equations of the involver substances was used to model the dependencies between them. Furthermore, a moving boundary problem for the diffusion equation of the drug delivery process was developed to describe the time dependent maximum penetration depth of each penetrant marked by a moving boundary. On this basis a model was developed that can predict both the concentration profile and the position of the penetration boundary depending on time. Both concepts were described on a two-dimensional multilayered domain representing a cross section through human skin. The model equations were solved by exploiting a suitable numerical discretization method.

**Costa P *et al.,*** have studied the evaluation of mathematical models describing drug release from estradiol transdermal system. The transdermal systems were membrane controlled type or matrix diffusion-controlled type. The estradiol content of test aliquots of the dissolution medium was determined by HPLC. To analyze the release mechanism, several release models were tested such as zero order, first-order, higuchi, weibull, korsmeyer-peppas, and makoid-banakar. The release profiles showed that the drug was released at a constant rate from three patches. The drug-release rate from the other 10 patches was not constant and diminished with the square-root of time (higuchi model).

**Finnin BC *et al.,*** have discussed about the transdermal penetration enhancers, their applications, limitations and potential. They have concluded that limited number of penetration enhancers have been shown to produce useful enhancement *in vivo*. Out of the list only a few have actually been incorporated into products and successfully tested in humans,

and, other than previously used ingredients of topical preparations, none has yet been successful in the market place.

**Kulkarni RV *et al.,*** have studied the effect of plasticizer on the permeability and mechanical properties of eudragit films for transdermal application as a rate controlling membrane for transdermal use and effect of different concentration of various plasticizers on the permeability and mechanical properties. They also studied the thickness uniformity, tensile strength, percentage of elongation and water vapor transmission. Verapamil hydrochloride has been used as the model drug and films plasticized with polyethylene glycol showed higher permeability. Permeability decreased as the concentration of dibutyl phthalate was increased.

**Fauth C *et al.,*** have studied adhesive backing foil interactions affecting the elasticity, adhesion strength of laminates and how to interpret these properties of branded transdermal patches. Study revealed that there was no correlation between the elasticity and peel adhesion of both the laminates and the branded patches. Likewise, for the branded patches the peel adhesion to stainless steel had no correlation with skin adhesion obtained from clinical trials.

**Cho YA *et al.,*** have studied the effect of vehicles and penetration enhancers on the *in vitro* permeation of ketorolac tromethamine across excised hairless mouse skin. Amongst pure vehicles examined, propylene glycol monolaurate (PGML) showed highest drug permeation fluxes. The skin permeability of the drug was markedly increased by adding diethylene glycol monoethyl ether (DGME). They evidenced that PGML and DGME in combination increased the drug flux to almost two times than those used alone. They found different permeation enhancing property of different fatty acids depending on the concentration and highest effect of permeation enhancer was seen with 10 % caprylic acid.

**Pandey S *et al.,*** have performed a comparative study of transdermal and oral preparation of diclofenac sodium using sodium alginate as carrier to assess the pharmacokinetic profile. Transdermal gel containing 15 % w/v sodium alginate and 1 % w/w diclofenac sodium were prepared and 0.5 % w/v of sodium alginate and 1 % w/w of

diclofenac sodium were used for oral administration where 200 ± 10 gm of albino rats were selected for the study. A dose of 10 mg of drug was administered orally and the gel was applied to 1 $cm^2$ area on the interscapular region of the rats. The pharmacokinetic studies showed a similar AUC and $C_{max}$ for the both formulation. However, $T_{max}$ after oral administration was found to be shorter (4 hours) as compared to that of transdermal application (8 hours).

**Jain GK *et al.*,** have studied the release of verapamil from transdermal patches that prepared using polyvinyl alcohol and polyvinyl pyrrolidone as polymers, glycerol as plasticizer and d-limonene as enhancer. Comparative study of flux across human cadaver skin and guinea pig dorsal skin were performed with varying concentration of d-limonene (5 and 20 %). Lag time for appearance of drug in receptor phase was longer in human cadaver skin as compared to guinea pig skin. Lag time was found to be increased with decreasing concentration of d-limonene.

**Panigrahi L *et al.*,** have studied pseudolatex transdermal patches by incorporating terbutaline sulphate as an effective mode of therapy for nocturnal asthma. The pseudolatex patches were formulated using combinations of eudragit RS 100 and RL 100 with eudraflex as plasticizer. The physicochemical characterization of the films was evaluated for drug release profile from the films as well as for ascertaining skin permeation aspects for therapeutic efficacy. The drug release profile from the patches followed apparent zero order pattern up to a period of 12 hours. The cumulative amount of drag permeated over a period of 24 hours was found to be 4.8 $mg/cm^2$, which was about 50 % of the loaded dose. The suitability of the drug loaded transdermal patches of terbutaline sulphate has been confirmed as it has been noticed that skin permeation took place at a steady rate over a period of 12 hours.

**Kanikkannan N *et al.*,** have studied several matrix type polymeric patches that prepared and evaluated for *in vitro* release of indomethacin in order to select a suitable system for transdermal delivery. The solution casting technique employing both glass and mercury substrate was used for the preparation of the patches. Keshary-Chien type diffusion cell was

used for *in vitro* release studies. The PVA-PVP patches released 100% drug within a period of 24 hours. Eudragit RL 100-PVP with PEG 400 as plasticizer yielded smooth and flexible patches with good drug release profile. The release of drug from the eudragit based patches followed the diffusion controlled higuchi model. They concluded that the PVA-PVP and eudragit RL 100-PVP matrices may potentially be developed as a transdermal therapeutic system.

**Naidu RAS *et al.,*** have studied transdermal diffusion of diclofenac sodium from eight different semisolids across cellulose acetate (CA) films, rat abdominal skin and combination of the two, employing the permeation apparatus. Various semisolids revealed slow diffusion of the drug over extended periods of time. Similarly zero order diffusion was observed with solutions and gels of alginate and carbopol. CA films were reported to control the drug diffusion through rat abdominal skin.

**Kanikkannan N *et al.,*** have studied the monolithic drug-in-adhesive transdermal patches of melatonin containing penetration enhancers like fatty alcohols, fatty acids, and terpenes. The patches were prepared using eudragit E 100 as the adhesive polymer. The release profile of melatonin from control as well as enhancer-containing patches showed an initial burst of melatonin release for up to 4 hours and then a plateau after 8 hours. The release profiles of melatonin from patches containing various enhancers were similar to the control patch. However, the addition of enhancers in the patch increased the permeation of melatonin through hairless rat skin. The flux values of patches containing octanol, nonanoic acid, and myristic acid were higher than the control patch (no enhancer), but the differences were not statistically significant. Decanol, myristyl alcohol, and undecanoic acid at 5 % w/w concentrations showed significantly higher flux values through hairless rat skin. Menthol and limonene at 5 % w/w showed maximum permeation of melatonin among all enhancers studied.

**Rathore RPS *et al.,*** have worked transdermal matrix type patches of terbutaline sulphate using ethyl cellulose and cellulose acetate polymer along with polyvinyl pyrrolidone. They observed the highest drug release rate from CA:PVP (3:2) and EC : PVP (2:3) patches.

**Al-Khalili M *et al.,*** have studied the transdermal delivery of buspirone hydrochloride across hair less mouse skin. The combined effect of iontophoresis and terpene enhancers were evaluated. Iontophoretic delivery was optimized by evaluating the effect of drug concentration , current density from 0.05 – 0.1 $mA/cm^2$ resulted in doubling of the iontophoretic flux of buspirone hydrochloride, while increasing drug concentration from 1 % to 2 % had no effect on flux. Use of phosphate buffer to adjust the pH of the drug solution decreased the buspirone hydrochloride iontophoretic flux whereas incorporation of buspirone hydrochloride water solution into ethanol: water (50:50 v/v) based gel formulations using CMC and HPMC had no effect on iontophoretic delivery of the drug. Incorporation of three terpene enhancers (methanol, ciniol, and terpineol) into the gel resulted in a synergistic effect in iontophoresis. Methanol was found to be the most active enhancer when assessed for iontophoresis and a delivery rate of 10 $mg/cm^2$/day of buspirone hydrochloride was evident.

**Gupta SP *et al.,*** have formulated matrix diffusion controlled transdermal drug delivery system of metoprolol tartarate by using eudragit RL and hydroxypropyl methyl cellulose (HPMC). Then they have studied the formulations for their thickness, tensile strength , drug content , *in vitro* and *in vivo* drug release characteristics. The two polymers at a ratio of 40:60 have showed a better drug skin permeation of 87.5µg/h/$cm^2$.

**Manvi FV *et al.,*** have formulated transdermal films of ketotifen fumerate using the polymeric combination of eudragit L 100:hydroxypropyl methyl cellulose and ethyl cellulose:hydroxypropyl methyl cellulose. The formulated films were evaluated for their physicochemical properties, *in vitro* diffusion study and skin permeation characteristics. They found the feasibility of formulating the rate controlling films of the mentioned polymeric combination containing ketotifen fumerate.

**Sankar V *et al.,*** have demonstrated the preparation of polymeric films of ethyl cellulose for suitable delivery of the drug nifedipine. The drug was incorporated in 4 % w/w hydroxypropyl methyl cellulose gel and formulated ethyl cellulose films were then subjected to various physicochemical characteristics. They have concluded from the study that there was a faster drug release from ethyl cellulose patches containing glycerol as plasticizer.

**Thomas SM *et al.,*** have developed transdermal patches containing crystals of estradiol suspended in pressure sensitive adhesive. A significant quantity of the adhesive matrix layer was to be adhering to the brass and polypropylene moulds which were used for preparation of the patches by solvent evaporation technique. However, *in-situ* preparation of the patches by solvent evaporation from a cavity, showed a mass balance. The release profile of estradiol from adhesive matrix was found to be similar to that of suspension matrix system.

**Arora P *et al.,*** have studied matrix-type transdermal patches containing diclofenac diethylamine prepared using different ratios of polyvinyl pyrrolidone (PVP) and ethylcellulose (EC) by solvent evaporation technique. Based on the physicochemical and *in vitro* skin permeation study, formulation containing PVP and EC in a ratio of 1:2 and formulation containing PVP and EC 1:5 were chosen for further *in vivo* experiment and hence, they concluded that diclofenac diethylamine can be incorporated into the transdermal matrix type patches to sustain its release characteristics and the polymeric composition of PVP and EC (1:2) was found to be the best choice for manufacturing transdermal patches of diclofenac diethylamine among the formulations studied.

**Gupta R *et al.,*** have studied transdermal drug delivery system of diltiazem hydrochloride using different ratios of polymers, ethyl cellulose and povidone and concluded that the films composed of povidone:ethyl cellulose (1:2) can be selected for the development of transdermal drug delivery of diltiazem hydrochloride, using a suitable adhesive layer and backing membrane for potential therapeutic use.

**Aqil M *et al.,*** have worked on *in vivo* characterization of monolithic matrix type transdermal drug delivery system (TDDS) of pinacidil monohydrate using polymers eudragit RL 100 and polyvinyl pyrrolidone K 30 (in 8:2, 4:6, 2:8, and 6:4 ratios), 5 % w/w of plasticizer; polyethylene glycol 400 and 5 % w/w of penetration enhancer dimethyl sulfoxide (based on total polymer weight) and showed that a single patch application of pinacidil TDDS can effectively control hypertension in rats for 2 days. The system holds promise for clinical studies.

**Devi K *et al.,*** have developed transdermal patches of ketorolac tromethamine, where polyvinyl pyrrolidone and polyvinyl alcohol polymeric matrix has been used for preparing free films and acrylic and silicone based pressure sensitive adhesives were used as adhesive matrix for the transdermal patches. Glycerol or propylene glycol was used as the plasticizer. A comparison of various penetration enhancers and enhancement techniques were also made. It was evident from the skin irritation study that the formulated transdermal patches were non irritant to the skin.

**Rana V *et al.,*** have studied the transdermal film formulations containing primary fatty amines and pyrrolidones ion-paired with diclofenac sodium which were evaluated for enhancement of diclofenac permeation through rat abdominal skin. Dodecylamine and methyl-2 pyrrolidone exhibited maximum flux of diclofenac sodium. The maximum flux obtained from dodecylamine-diclofenac sodium ion paired films was 62.4 $\mu g/h/cm^2$, which was approximately 4.5 times greater than that from the ion-paired films. The result showed that dodecylamine can be advantageously used to enhance the percutaneous permeation of diclofenac sodium.

**Tanwar YS** have studied the transdermal drug delivery systems of salbutamol sulphate using eudragit RL 100 and PVP, which were developed by solvent casting technique employing mercury as a substrate. Propylene glycol was used as plasticizer. *In vitro* permeation profiles across the guineapig dorsal skin using Keshary-Chien diffusion cell were found to be promising. Incorporation of PEG 400 and tween 60 enhanced the drug permeation across guineapig skin; the permeation rate was greater with films containing PEG-400 and followed zero order kinetics.

**Arabi H *et al.,*** have studied the controlled reservoir system for scopolamine hydrochloride (SH) under *in vitro* condition by determination of the role of membrane on SH release rate. In the method SH was incorporated into two polymers (polyisobutylene and polybutyl acrylate) and SH release rate across ethylene-vinyl acetate copolymer (EVA) and ethyl cellulose (EC) membranes was measured. The obtained result showed that in the EVA membrane, the permeability of SH across membrane increased with the increase of vinyl

acetate percentage in copolymer. Microscopic studies of EVA membrane surface showed that the size of surface porosity increases with the increase of vinyl acetate percentage in the copolymer and according to the result obtained, it showed an increase in drug's release rate. In case of EC membrane, the result showed that the rate of drug release increases with the increase of pore size of EC surface despite of having high molecular weight.

**Das MK *et al.,*** have investigated the effect of polymeric composition, drug content, and plasticizer on the permeation of trazodone hydrochloride across the mouse epidermis for the development of transdermal therapeutic system, using eudragit RL 100 and RS 100 and triethyl citrate as plasticizer. They studied the *in vitro* release and skin permeation through mouse epidermis using Keshary-Chien diffusion cell and found an increased *in vitro* drug release with increasing amount of eudragit RL100 in the film. They also observed that the maximum skin permeability was attained at a loading dose of 10 % w/w in the film, and the *in vitro* flux decreased gradually at higher concentration up to 13 % w/w and concentration of triethyl citrate in the film markedly affected the skin permeation properties of trazodone hydrochloride.

**Agrawal SS *et al.***, have experimented matrix type transdermal patches for carvedilol using different concentrations (1:7 to 1:10) of carvedilol and chitosan by solvent casting method (4 % v/v lactic acid solution) and found the feasibility of formulating carvedilol transdermal patches with chitosan.

**Udupa N *et al.,*** have reported membrane moderated transdermal systems using ethyl cellulose, eudragit RS 100, eudragit RL 100 and ethylene vinyl acetate (2 %, 9 % and 19 % vinyl acetate content) for glibenclamide and found better control of hyperglycemia than oral glibenclamide administration in mice.

**Saraf S *et al.,*** have studied transdermal delivery of norfloxacin using various combination of ethyl cellulose (EC):hydroxypropyl methyl cellulose (HPMC) and various concentration of polyvinyl alcohol (PVA) with different skin permeation enhancers like benzyl alcohol, lauric acid, oleic acid, lauryl alcohol, sodium lauryl sulphate (SLS) and

dimethyl sulfoxide (DMSO) and observed that HPMC:EC (20:80) and PVA 10 % was most suitable for drug loading and DMSO showing highest permeability with no lag time.

**Mehdizadeh A *et al.,*** have designed to evaluate different matrix, drug-in-adhesive and reservoir formulations of fentanyl transdermal patches. They targeted to design drug-in-adhesive patches (DIAPs), using full factorial design. Different types and amounts of liquid, pressure-sensitive adhesives (PSAs) were used and evaluated with respect to drug release and adhesive properties. A simple but precise method, the simplified peel 180° test, was developed to measure and compare adhesive properties of transdermal patches and results showed that release kinetics obeyed the square root of time or higuchi model, indicating the diffusion controlled release mechanism. They found that the amount of fentanyl needed for each 10 $cm^2$ three-days DIAP should be 3.3 mg. The respective amounts for reservoir and matrix patches were 2.5 and 5 mg. It was concluded that acrylic PSAs showed the best adhesion and release properties.

**Mutalik S *et al.,*** have worked on membrane-moderated transdermal systems of glipizide, prepared using drug containing carbopol gel (drug reservoir) and ethyl cellulose, as well as eudragit RS 100, eudragit RL 100 and ethylene vinyl acetate (EVA; 2, 9 and 19 % vinyl acetate content) rate-controlling membranes, and were subsequently evaluated *in vitro* (drug content and drug permeation studies) and *in vivo* (acute and long-term hypoglycemic activity, effect on glucose tolerance, biochemical and histopathological studies, skin irritation test and pharmacokinetic studies in mice) and concluded that the transdermal system successfully prevented severe hypoglycemia in the initial hours and it was also effective for chronic conditions.

**Khatun M *et al.,*** have worked on polymeric films of eudragit RS 100 prepared by solvent casting method to explore the possibilities of using this polymer in transdermal therapeutic system (TTS). Naproxen was used as a model drug and incorporated in two different percent loading (8.3 % w/w and 20.8 % w/w of films). Effects of two plasticizers namely polyethylene glycol 1500 and 4000 (PEG 1500 and PEG 4000) and two release modifiers polyvinyl alcohol (PVA) and hydroxypropyl methyl cellulose (HPMC) 15 cps on *in*

*vitro* drug release from naproxen loaded eudragit RS 100 films were assessed. Drug release was found to be a function of drug load, PEG molecular weight and physico-chemical property of the release modifiers incorporated. At low drug load, highest amount of drug was released from films containing PEG 1500 (more than 95 %). However, a burst release was evident in case of all the experimental batches except that loaded with HPMC 15 cps. With this formulation, more than 75 % of active principle was released after 8 hours while only 12% of naproxen was liberated in the first hour of dissolution. Increasing drug load increased the rate and extent of drug release from eudragit RS 100 films; however this effect was minimized when PEG 4000 was used as release modifier. For PEG 1500 loaded films, drug release was decreased with increasing drug concentration. They found inclusion of PEG in eudragit RS 100 films caused the drug to be released by diffusion (Fickian) kinetics whereas PVA and HPMC containing formulations released drug by diffusion mechanism coupled with erosion.

**Sridevi S *et al.,*** have developed a acrylate based transdermal drug delivery system (TDDS) with polymethyl methacrylate and ethyl cellulose for glibenclamide and evaluate for its pharmacodynamic performance in male wistar rats and showed that TDDS significantly sustained the hypoglycemic activity for 24 hours in normal rats when compared to oral administration where the effect declined after 8 hours and the transdermal system is effective in preventing the frequent hypoglycemic episodes encountered after oral glibenclamide administration.

**Murthy N *et al.,*** have studied transdermal formulations containing theophylline and salbutamol sulfate using hydroxypropyl methyl cellulose and formulations were subjected to *in vitro* release studies and pharmacodynamic studies in guinea pigs and showed that the drug release was effective and above the minimum effective concentration from the formulation.

**Tipre DN *et al.,*** have investigated the acrylate-based transdermal therapeutic system of nitrendipine using d-limonene as permeation enhancer and reported that the drug can be delivered at high input rate through transdermal route.

**Sumanta MK *et al.,*** have studied the matrix diffusion type transdermal drug delivery system of haloperidol prepared with eudragit NE 30D copolymer to overcome haloperidol induced extrapyramidal syndrome and pointed out that the system might be a better alternative over conventional dosage form in case of long term psychiatric treatment.

**Venkateswarlu V *et al.,*** have studied the film forming abilities of the natural polymer from *Salacia macrosperma*. Both the reservoir type as well as the matrix type transdermal drug delivery systems was prepared for diltiazem. After evaluating the formulations, they have experienced an encouraging result and suggested the promising role of the natural polymer from *Salacia macrosperma* in release rate control of the loaded drug in transdermal drug delivery systems.

**Nath BS *et al.,*** have reported that the different grades eudragit polymers exhibit varying permeability of diltiazem hydrochloride in transdermal system. Eudragit RL100 grade was found to increase the permeation significantly whereas eudragit RS100 and NE 30 D was found to decrease the permeability. But the combination of the polymers (eudragit RL100 and Eudragit RS100:eudragit RL100 and Eudragit NE 30 D) enhanced the drug release, followed the diffusion equations and showed no swelling of the film.

**Schurad B *et al.,*** have studied the transdermal *in vitro* permeation behavior of the highly potent dopamine agonist proterguride in matrix formulation based on different types of pressure-sensetive adhesives eudragit E 100 and gelva 7883 as acrylates, oppanol B 15 SFN as polyisobutylene and BioPSA 7-4202 as silicons using hairless mouse model membrane and showed suitability of gelva based patches having good physical stability, good skin adhesion and moderate flux values for formulation of transdermal administration of proterguride.

**Funke AP *et al.,*** have developed matrix type transdermal system containing a highly lipophilic drug antiestrogen along with the permeation enhancers propylene glycol and lauric acid and found that pretreatment of skin with permeation enhancer raised the transdermal flux of subsequently applied antiestrogen.

**Budhathoki U *et al.,*** have studied the effect of combination of propylene glycol (PG) with dimethyl sulphoxide (DMSO), benzalkonium chloride (BKC), isopropyl myristate (IPM), tween 80 and sodium lauryl sulphate (SLS) on *in vitro* drug release rate of a transdermal system of salbutamol sulphate, prepared with eudragit RL 100 and showed that concentration of DMSO and tween 80 have directly proportional whereas concentration of BKC and SLS have inversely proportional relationship with drug release rate. The increase followed by decrease in drug release rate was reported with increase in IPM concentration.

**Panigrahi L *et al.,*** have studied polymeric dispersion type transdermal drug delivery system of diclofenac sodium for prolonged and controlled release of drug using different combinations of hydrophilic and hydrophobic polymers pseudolatex systems. They have evaluated permeation kinetics of diclofenac sodium from transdermal system alone and in presence of an enhancer isopropyl myristate at different concentrations and observed the permeation flux, permeation coefficient and found an increase in presence of enhancer isopropyl myristate maximum at a concentration of 10 %.

**Parikh DK *et al.,*** have developed a transdermal drug delivery of fluoxetine with permeation enhancement of fluoxetine, either in the salt or base form using various enhancers like azone and ethanol and studied permeation enhancement of fluoxetine across human cadaver skin using Franz diffusion cell with receptor phase consisted of pH 7.4 phosphate buffer maintained at 37°C and found the permeation of fluoxetine obtained using a 65 % v/v ethanolic solution to be sufficient to deliver the required dose (20-80 mg) from a patch of feasible size.

**Rejendran D *et al.,*** have studied the feasibility of development of a transdermal delivery system for terbutaline sulphate using eight non-ionic surfactants as permeation enhancers and determined the flux of terbutaline sulphate from transdermal patches containing any of the selected non-ionic surfactants or without surfactants using Keshary-Chien cell and reported that among the spans used, span 80 produced the highest permeation of the drug and of the tweens used, tween 80 produced the highest permeation of the drug.

**Gondaliya D *et al.*,** have worked on designing and evaluating unilaminate transdermal adhesive matrix systems capable of diffusing bupropion base at a constant rate over an extended period of time as an alternative route of administration with different concentrations of eudragit E as the adhesive and rate controlling polymer and showed that the release of drug from the matrices obeyed zero order release kinetics ($r^2$ = 0.9810 to 0.9960), the delivery rate of bupropion ranged from 10.5 mg to 31.4 mg per day from a 3.14 $cm^2$ area of matrix, the relation between concentration of bupropion base in matrix and epidermal flux, concentration of drug in matrix, and epidermal adsorption of bupropion during diffusion follow hyperbolic fashion, triethyl citrate and dibutyl phthalate have no influence on the diffusion of bupropion through human cadaver skin when used as plasticizers, incorporation of succinic acid in the adhesive matrix retarded diffusion due to the formation of rigid cross linking of the polymer, while propylene glycol and myristic acid, alone or in combination, significantly enhanced the flux of bupropion through human cadaver skin.

**Benes L *et al.*,** have studied transmucosal, oral controlled-release (CR) and transdermal administration in human subjects. A crossover study with melatonin (MT) and its principal metabolite in human subjects using a crossover, single dose design was evaluated. Twelve adult male volunteers participated in the study and received all three dosage forms on three separate occasions. All patch dosage forms were removed after 10 hours of wear. Plasma concentration of the parent drug and its metabolite, 6-sulfatoxymelatonin ($MT6_S$) were measured by radioimmunoassay. Between subject plasma concentrations of MT were very variable following both oral CR and TDD. Use of the oral CR system gave plasma MT profiles in some subjects that were initially similar to physiological levels, but then differed substantially from physiological level in the rate of MT offset; in a few subjects, plasma MT levels remained consistently much below normal nocturnal physiological levels. Also, the ratio of metabolite to parent drug by the oral CR route was many times greater than physiological level.

**Saxena M *et al.*,** have studied transdermal patches of metoclopramide hydrochloride for its physicochemical parameters with drug release and found that the formulation exhibit

uniform thickness and weight, good drug content, and little moisture content and uptake. The drug release from the patches was found to be diffusion dominated.

**Udhumansha U *et al.,*** have studied transdermal therapeutic system of carvedilol and effect of hydrophilic and hydrophobic matrix on *in vitro* and *in vivo* characteristics and concluded that transdermal patches of carvedilol can effectively release the drug for the therapy of hypertension.

**Bharkatiya M *et al.,*** have prepared nimesulide transdermal films using four different polymers by solvent casting technique and dibutyl phthalate as plasticizer and evaluated physicochemical parameters of the films like weight variation, thickness, folding endurance, drug content, tensile strength and stability. An *in vitro* study was also carried out using Keshary-Chien permeation cell and concluded that formulation containing drug reservoir with HPMC:PVP showed highest permeation, the release of drug from all the formulations followed the diffusion controlled higuchi model and zero order release kinetics.

**Ilango R *et al.,*** have studied on the formulation of transdermal preparation of nimesulide gel and observed the effect of polymer concentration on *in vitro* drug release from carbopol 940, hydroxypropyl methyl cellulose (HPMC) gel. The effect of permeation enhancers like tween 80 and sodium lauryl sulphate (SLS) at different concentration on drug release pattern were also been observed. Pharmacodynamic studies of selected formulations for anti-inflammatory activity by carrageenin-induced paw edema in rats and comparison with marketed ibuprofen gel preparation were also carried out where HPMC and carbopol based nimesulide dosage forms showed promising result.

**Felton LA *et al.,*** have studied the influence of hydroxypropyl-β-cyclodextrin (HPCD) on the transdermal permeation and skin accumulation of oxybenzone. They have calculated the flux from the permeation data of drug. The aqueous solubility of oxybenzone increased linearly with increasing HPCD concentration. They observed the maximum flux of the drug at 10 % concentration of HPCD.

**Nalluri BN *et al.,*** have studied the *in vitro* release characteristics of naltrexone (NTX) from matrix type transdermal drug delivery system. Amongst the four DURO-TAK adhesive polymers tested 87-2516 proved to be the most suitable and compatible polymer for transdermal delivery of NTX. The release of NTX from the patches showed a good correlation ($R^2 > 0.99$) profile, indicating a higuchi type matrix diffusion mechanism of drug release. They found an overall significant higher drug release from the NTX prodrug patches than from NTX patches at all three drug loading levels.

**Krishnaiah YSR *et al.,*** have studied the nerodilol-based transdermal therapeutic system for its ability to reach desired steady state plasma concentration of nicorandil in human volunteers. The flux of nicorandil from the nerodilol-based hydroxypropyl methyl cellulose (HPMC) drug reservoir across excised rat skin was found to be more when compared to EVA 2825 membrane, indicating that the latter was more effective as rate controlling membrane. They have concluded that the nerodilol-based TTS of nicorandil provided the desired plasma concentration of the drug for the predetermined period of time with minimal fluctuation.

**Nicolazzo AJ *et al.,*** have studied the effect of occlusion, octisalate (OS) and propylene glycol (PG) on the *in vitro* skin permeability of testosterone. Testosterone (either alone or with OS 5 % w/v) was applied as a finite dose to full thickness neonatal porcine skin mounted in flow-through diffusion cell and the amount of drug appearing in the receptor solution (20% v/v ethanol) was determined up to 24 hours. In addition, the effect of solugel (a proprietary hydrogel containing PG 25 % w/w) and tegaderm (a semi permeable film dressing) on the permeation of testosterone was assessed. They have concluded that by combining OS, PG and occlusion, testosterone permeation was increased 8.7 fold, which was a synergistic enhancement. They found same enhancement efficacy of solugel and tegaderm when applied to the skin in relation to enhancement produced by PG 25 % w/w and occlusion.

## REFERENCE


1. Kim JH, Lee CH. and Choi HK. Transdermal delivery of physostigmine: Effects of enhancers and pressure-sensitive adhesives. *Drug Dev. Ind. Pharm.* 2002; **28(7)**: 833 – 839.

2. Sagar P, Kulkarni RV. and Doddayya H. Development and evaluation of membrane controlled transdermal therapeutic system. *The Pharma Review.* 2006; April: 90-92.

3. Chowdary KPR. and Naidu RAS. Studies on permeability of ethyl cellulose films for transdermal use. *The Eastern Pharmacist.* 1991; September: 119-121.

4. Baichwal MR, Deshpande SG, Singh PK. and Venkitachalam P. Studies on polymeric films for transdermal use. *Indian J. Pharm. Sci.* 1988; **50(3)**: 153-156.

5. Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A. and Arora P. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on *in vitro* skin permeation. *European J. Pharmaceutics and Biopharmaceutics.* 2005; **59**: 475-483.

6. Rao PR. and Diwan PV. Drug diffusion from cellulose acetate-polyvinyl pyrrolidone free films for transdermal administration. *Indian J. Pharm. Sci.* 1996; **58(6)**: 246-250.

7. Suwanpidokkul N, Thongnopnua P. and Umprayn K. Transdermal delivery of zidovudine (AZT): The effects of vehicles enhancers and polymer membranes on permeation across cadaver pig skin. *AAPS Pharm. Sci. Tech. 2004*; **5(3)**: 48. ([illegible]).

8. Satturwar PM, Fulzele SV. and Dorle AK. Evaluation of polymerized rosin for the formulation and development of transdermal drug delivery system: A technical note. *AAPS Pharm. Sci. Tech.* 2005; **6(4)**: E649-E654.

9. Manitz R, Lucht W, Strehmel K, Weiner R. and Neubert R. On mathematical modeling of dermal and transdermal drug delivery. *J. Pharm. Sci.* 1998; **87(7)**: 873-879.

10. Costa P. and Sousa LMJ. Evaluation of mathematical models describing drug release from estradiol transdermal system. *Drug Dev. Ind. Pharm.* 2003; **29(1)**: 89-97.

11. Finnin BC. and Morgan TM. Transdermal penetration enhancers: applications, limitations, and potential. *J. Pharm. Sci.* 1999; **88(10)**: 955-958.

12. Kulkarni RV, Mutalik S. and Hiremath D. Effect of plasticizers on the permeability and mechanical properties of eudragit films for transdermal application. *Indian J. Pharm. Sci.* 2002; **64(1)**: 28-31.

13. Fauth C, Wiedersberg S, Neubert RHH. and Dittgen M. Adhesive backing foil interactions affecting the elasticity, adhesion strength of laminates, and how to interpret these properties of branded transdermal patches. *Drug Dev. Ind. Pharm.* 2002; **28(10)**: 1251-1259.

14. Cho YA. and Gwak HS. Transdermal delivery of ketorolac tromethamine: effects of vehicles and penetration enhancers. *Drug Dev. Ind. Pharm.* 2004; **30(6)**: 557-564.

15. Pandey S, Singh UV, Naresh R. and Udupa N. Comparative pharmacokinetic evaluation of oral Vs. transdermal diclofenac sodium. *The Eastern Pharmacist.* 1994; October: 21-23.

16. Jain GK. and Agarwal SS. Transdermal permeation of verapamil across human cadaver skin. *Scientific abstract, 45th I.P.C. New Delhi.* 1993; December: no-A24.

17. Panigrahi L. and Ghosal SK. Formulation and evaluation of pseudolatex transdermal drug delivery system of terbutaline sulphate. *Indian J. Pharm. Sci.* 2002; **64(1)**: 79-82.

18. Kanikkannan N, Jayaswal SB. and Singh J. Transdermal delivery of indomethacin: I. Release profile of drug from polymeric patches. *Indian Drugs.* 1992; **30(9)**: 441-445.

19. Naidu RAC. and Chowdary KPR. Transdermal diffusion of sodium diclofenac through cellulose acetate films and rat abdominal skin. *Scientific abstract, 44th I.P.C. Bangalore.* 1992; December: no-A34.

20. Kanikkannan N, Andega S, Burton S, Babu RJ. and Singh M. Formulation and *in vitro* evaluation of transdermal patches of melatonin. *Drug Dev. Ind. Pharm.,* 2004; **30(2)**: 205-212.

21. Rathore RPS, Chauhan CS, Naruka PS, Tanwar YS. and Chauhan LS. Transdermal formulation of terbutaline sulphate..
(http:/ /www.priory.com / pharmol/transdermal.pdf: 1st April, 2006)

22. Al-Khalili M, Meidan VM. and Michniak BB. Iontophoretic transdermal delivery of buspirone hydrochloride in hairless mouse skin. *AAPS Pharm Sci. Tech. 2003*; **5(2)**: 1-11.

23. Gupta SP. and Jain SK. Effective and controlled transdermal delivery of metoprolol tartarate. *Indian J. Pharm. Sci.* 2005; **67(3)**: 346-350.

24. Manvi FV, Dandagi PM, Gadad AP, Mastiholimath VS. and Jagadeesh T. Formulation of a transdermal drug delivery system of ketotifen fumarate. *Indian J. Pharm. Sci.* 2003; **65(3)**: 239-243.

25. Sankar V *et al.* Design and evaluation of nifedipine transdermal patches. *Indian J. Pharm. Sci.* 2003; **65(5)**: 510-515.

26. Thomas SM, Gandhi K. and Shrivastava R. Adhesive matrix type transdermal systems of estradiol. *Scientific abstract, 43th I.P.C. Goa.* 1991; December: no-C3.

27. Arora P. and Mukherjee B. Design, development, physicochemical, and *in vitro* and *in vivo* evaluation of transdermal patches containing diclofenac diethylammonium salt. *J. Pharm. Sci.* 2002; **91(9)**: 2076-2089.

28. Gupta R. and Mukherjee B. Development and *in vitro* evaluation of diltiazem hydrochloride transdermal patches based on povidone-ethylcellulose matrices. *Drug Dev. Ind. Pharm.* 2003; **29(1)**: 1-7.

29. Aqil M, Ali A, Sultana Y, Dubey K, Najmi AK. and Pillai KK. *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.

30. Devi K. and Paranjothy KLK. Development and evaluation of free films and transdermal patches of ketorolac tromethamine using polymer and pressure sensitive adhesives. *The Eastern Pharmacist.* 1998; May: 97-100.

31. Rana V, Rai P, Tiwary AK. and Gupta S. Enhanced *in vitro* percutaneous permeation of diclofenac sodium with primary amine and pyrrolidone ion-pairs. *Indian Drugs.* 1999; **36(1)**: 21-28.

32. Tanwar YS. Formulation and evaluation of transdermal films of salbutamol sulphate. *Dhaka University J. Pharm. Sci.* 2005; **4(2)**: ISSN-1816-1820.

33. Arabi H, Hashemi SA. and Ajdari N. Preparation of a transdermal delivery system and effect of membrane type for scopolamine drug. *Iranian Polymer Journal.* 2002; **11(4)**: 245-250.

34. Das MK, Bhattacharya A. and Ghosal SK. Transdermal delivery of trazodone hydrochloride from acrylic films prepared from aqueous latex. *Indian J. Pharm. Sci.* 2006; **68(1)**: 41-46.

35. Agrawal SS. *In vitro, in vivo* transdermal permeation of carvedilol from chitosan based matrix-type transdermal patches. AAPS National Biotechnology Conference: Delhi Institute of Science and Research.
( ).

36. Udupa N. and Mutalik S. Formulation development, *in vitro* and *in vivo* evaluation of membrane controlled transdermal system of glibenclamide. *J. Pharm. Pharmaceut. Sci.* 2005; **8(1)**: 26-38.

37. Saraf S. and Dixit VK. Transdermal delivery of norfloxacin. *The Eastern Pharmacist.* 2006; May: 74-76.

38. Mehdizadeh A. Design and *in vitro* evaluation of new drug-in-adhesive formulations of fentanyl transdermal patches. *Acta. Pharm.* 2004; **54**: 301-317.

39. Mutalik S. and Udupa N. Pharmacological evaluation of membrane-moderated transdermal system of glipizide. *Clin. Exp. Pharmacol. Physiology.* 2006; **33**: 17-26.

40. Khatun M, Islam SMA, Akter P, Quadir MA. and Selim MR. Controlled release of naproxen sodium from eudragit RS 100 transdermal film. *Dhaka University J. Pharm. Sci.* 2004; June-December; **3**: 1-2.

41. Sridevi S, Chary MG, Krishna DR. and Diwan PV. Pharmacodynamic evaluation of transdermal drug delivery system of glibenclamide in rats. *Indian J. Pharmacol.* 2000; **32**: 309-312.

42. Murthy N, Rani S. and Hiremath R. Formulation and evaluation of controlled-release transdermal patches of theophylline salbutamol sulfate. *Drug Dev. Ind. Pharm.* 2001; **27(10)**: 1057-1062.

43. Tipre DN. and Vavia PR. Acrylate-based transdermal therapeutic system of nitrendipine. *Drug Dev. Ind. Pharm.* 2003; **29(1)**: 71-78.

44. Sumanta MK, Dube R. and Suresh B. Transdermal drug delivery system of a haloperidol to overcome self-induced extrapyramidal syndrome. *Drug Dev. Ind. Pharm.* 2003; **29(4)**: 405-415.

45. Venkateswarlu V *et al.* Development of transdermal drug delivery system with natural polymer from salacia macrosperma. *Indian Drugs* 2000; **37(9)**: 407-411.

46. Nath BS. and Patil AY. Development studies on ethyl cellulose films in presence of three added eudragit polymers as rate limiting membranes for transdermal use for diltiazem hydrochloride. *Scientific abstract, 46th I.P.C. Chennai (Madras).* 1996; December: no-A19.

47. Schurad B, Tack J. and Lipp R. Evaluation of the transdermal permeation behavior of proterguride from drug in adhesive matrix patches through hairless mouse skin. *Drug Dev. Ind. Pharm.* 2005; **31(6)**: 505-513.

48. Funke AP, Gunther C, Muller RH. and Lipp R. Development of matrix patches for transdermal delivery of a highly lipophilic antiestrogen. *Drug Dev. Ind. Pharm.* 2003; **29(7)**: 785-793.

49. Budhathoki U. and Thapa P. Effect of chemical enhancers on *in vitro* release of salbutamol sulphate from transdermal patches. *Kathmandu University J. Sci. Eng. Tech.* 2005; September: 1-6.

50. Panigrahi L, Pattnaik S. and Ghosal SK. Permeation kinetics of diclofenac sodium from pseudolatex transdermal formulations through lipidized and delipidized mouse skin. *Indian J. Pharm. Sci.* 2005; **67(1)**: 124-127.

51. Parikh DK. and Ghosh TK. Feasibility of transdermal delivery of fluoxetine. *AAPS Pharm. Sci. Tech.* 2005; **6(2)**: E144-E149.

52. Rejendran D, Prabushankar GL, Dhanraj SA, Dube R. and Suresh B. Enhanced transdermal delivery of terbutaline sulphate *in vitro* using non-ionic surfactants. *Indian J. Pharm. Sci.* 1996; **58(6)**: 251-253.

53. Gondaliya D. and Pundarikakshudu K. Studies in formulation and pharmacotechnical evaluation of controlled release transdermal delivery system of bupropion. *AAPS Pharm. Sci. Tech.* 2003; **4(1)**: article 3.
(http://www.aapspharmscitech.org).

54. Benes L *et al.* Transmucosal, oral controlled-release, and transdermal drug administration in human subjects: A crossover study with melatonin. *J. Pharm. Sci.* 1997; **86(10)**: 1115-1119.

55. Saxena M, Mutalik S. and Reddy MS. Formulation and evaluation of transdermal patches of metoclopramide hydrochloride. *Indian Drugs* 2006; **43(9)**: 740-745.

56. Udhumansha U, Reddy MVS, Ruckmani K, Farhan JA. and Khar RK. 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)**: article 2.
(http://www.aapspharmscitech.org).

57. Bharkatiya M. and Nema RK. Designing and evaluation of nimesulide transdermal patches.
(http://www.scientificpharmacy.com).

58. Ilango R, Kavimani S, Kumar KS, Deepa KR. and Jaykar B. Formulation and evaluation of transdermal preparations of nimesulide gel. *The Eastern Pharmacist.* 1998; November: 123-125.

59. Felton LA, Wiley CJ. and Godwin DA. Influence of hydroxypropyl-β-cyclodextrin on the transdermal permeation and skin accumulation of oxybenzone. *Drug Dev. Ind. Pharm.* 2002; **28(9)**: 1117-1124.

60. Nalluri BN, Milligan C, Chen J, Crooks PA. and Stinchcomb AL. *In vitro* release studies on matrix type transdermal drug delivery systems of naltrexone and it's acetyl prodrug. *Drug Dev. Ind. Pharm.* 2005; **31(6)**: 871-877.

61. Krishnaiah YSR, Al-Saidan SM, Chandrasekhar DV. and Satyanarayana V. Bioavailability of nerodilol-based transdermal therapeutic system of nicorandil in human volunteers. *J. Controlled Release.* 2005; **106**: 111-122.

62. Nicolazzo JA, Morgan TM, Reed BL. and Finnin BC. Synergistic enhancement of testosterone transdermal delivery. *J. Controlled Release.* 2005; **103**: 577-585.