Chapter 2

REVIEW OF LITERATURE
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2. REVIEW OF LITERATURE

2.1. Controlled release Tablets

Oral administration is the most popular route for drug delivery and the concept of regulated drug delivery in the human body has been in existence for many years because of major benefits such as improved patient compliance and decreased side effects. Hydrophillic matrix formulations is one of the least approach for developing extended release dosage forms to allow at least a twofold reduction in dosing frequency or patient compliance when compared to conventional immediate release dosage form. Controlled drug delivery systems are used in the treatment of chronic rather than the acute condition, and they process a good margin of safety\textsuperscript{66,67}.

Mukesh C. Gohel \textit{et al.},\textsuperscript{68} fabricated modified release tablet of metoprolol succinate using hydroxypropyl methylcellulose (HPMC) and xanthan gum as a matrixing agent. A $3^2$ full factorial design was employed for the optimization of formulation. The \textit{in-vitro} drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. The desired drug release pattern can be obtained by using a proper combination of HPMC (high gelling ability) and xanthan gum (quick gelling tendency).

Ramani Gade and TEGK Murthy\textsuperscript{69} designed and evaluate the extended release matrix tablets of metoprolol succinate prepared by direct compression with the combination of hydrophilic and hydrophobic polymers i.e methocel 10000 Cps in combination with
ethyl cellulose 7 Cps, Eudragit® RS100, Eudragit® S100, and Eudragit® L100. Prepared formulations were evaluated for various parameters like weight variation, thickness, hardness, friability, and % drug content. The combination of hydrophilic and hydrophobic polymers can effectively control the drug release for freely water soluble drugs in case of extended release formulations.

Mariyam Akter et al., developed a sustained release matrix tablet Metoprolol Succinate by direct compression method using Kollidon SR as release retardant. The release patterns of different batches were evaluated for Zero order, Higuchi, First order, Krosmeyer-Peppas and Hixson-Crowell kinetics.

J. M Baweja and A. N Misra studied on kinetics of drug release from modified guar gum hydrophilic matrices. In the present investigation guar gum has been methylated using sodium hydroxide and dimethylsulphate. Guar gum and methylated guar gum have been evaluated as hydrophilic matrices for controlled release tablets. Effect of the composition of matrices and the method of preparation of tablets on the drug release kinetics from the guar gum and methylated guar gum matrices have been studied and compared.

MA Roni et al., studied the determination of formulation factors and the in-vitro evaluation of an extended release dosage form of a freely soluble weakly basic drug (alfuzosin hydrochloride). Binary mixer of one hydrophilic polymer (hydroxypropylmethylcellulose) and one directly compressible Eudragit (RSPO) was used in tablets
prepared by direct compression. The amounts of both polymers were taken as independent variables for the $3^2$ Factorial design.

**Pinank Pandya V et al.**\(^7^3\) studied the formulation, evaluation and optimization of captopril matrix tablets. A $3^2$ full factorial design was adopted and all 9 batches were prepared by wet granulation method. Prepared granules and tablets were evaluated for precompression and postcompression characteristics respectively. The results revealed that concentration of matrix forming agent and solution of granulating agent significantly affected *in-vitro* drug release profile.

**Gautam Singhvi et al.**\(^7^4\) designed and evaluate controlled release matrix type tablet of Metoprolol succinate using HPMC K15M and Eudragit (RLPO and RSPO) as a matrix forming agents. Effect of various polymer alone and combinations were studied in pH 1.2 buffer using USP type II paddle at 50 rpm. HPMC was used to form firm gel with Eudragit polymer. The drug release mechanism was predominantly found to be Non-Fickian diffusion controlled.

**Vohra D D et al.**\(^7^5\) aimed at studying sustained release behaviour of the Losartan potassium using hydrophilic and hydrophobic polymers and to optimise using a $3^2$ full factorial design. Eudragit and HPMC were used to evaluate the effect of hydrophilic and hydrophobic polymers on the release pattern of the drug. Based on the results, it was found suitable to formulate a dosage form using
optimum concentration of hydrophobic polymer along with hydrophilic polymer to vary the release behaviour for over 12 hours.

Jeon I et al.,\textsuperscript{76} applied roll compaction for the preparation of hydroxypropyl cellulose (HPC)-based sustained-release matrix tablets. Matrix tablets made via roll compaction exhibited higher dosage uniformity and faster drug release than direct-compacted tablets. Roll compaction seems to be an adequate granulation method for the preparation of HPC-based matrix tablets due to the simplicity of the process, less handling difficulty from HPC tackiness as well as easier particle size targeting.

Roy H et al.,\textsuperscript{77} attempted to design a sustained release dosage form using various grades of hydrophilic polymers, Hypromellose (hydroxyl-propyl methylcellulose [HPMC] K15M, HPMC K100M and HPMC K200M) and Polyacrylate polymers, Eudragit RL100 and Eudragit RS100 with or without incorporating ethyl cellulose on a matrix-controlled drug delivery system of Metformin hydrochloride. There was no chemical interaction found between the drug and excipients during Fourier Transform Infrared Spectroscopy (FTIR) and Differential scanning calorimetry study.

Joshi N C et al.,\textsuperscript{78} developed once daily controlled release matrix tablets of Tramadol HCl using different polymers viz. Eudragit RS-100, Ethylcellulose, Carbopol 934P and Polyvinyl Pyrolidone K-90 by wet granulation method. The tablets were evaluated for thickness,
weight variation, hardness, friability, drug content and in-vitro dissolution studies.

Gummudavelly S et al.,79 studied the formulation and characterization of extended release matrix tablets of metoprolol succinate using hydrophilic polymers like Hydroxy Propyl Methyl Cellulose (HPMC K100M), Hydroxy Propyl Cellulose (HPC), Ethyl Cellulose, Carbopol 934 and Megnesium Stearate, and these selected matrices were directly compressed into tablet. Release kinetics evaluated by using USP-22 (Paddle) dissolution apparatus. In-vitro release study showed that ERT10 for 25mg label claimed were well suited to extend release for 20 hours with zero order release.

Raja Sekharan T et al.,80 prepared theophylline controlled release matrix tablets with guar gum in two ratios and with three different hardness of 5, 6 and 7kg/cm and the granules were evaluated for the angle of repose, bulk density, tapped density, compressibility index and hausners ratio. The compressed tablets were evaluated for the hardness, uniformity of weight, friability, drug content and in-vitro dissolution studies. All the formulations showed compliance with pharmacopial standards. There was no interaction between drug, polymer and other excipients by FTIR studies.

Raslan H K and Maswadeh H.,81 prepared theophylline in matrix-type tablets by direct compression method using two kinds of matrices glycerclybehenate (hydrophobic) and hydroxypropylmethyl cellulose (hydrophilic). The in-vitro release kinetics of these
formulations were studied at pH 6.8 using the USP dissolution apparatus with the paddle assemble. The analysis of the dissolution kinetic data for the theophylline preparations in this study shows that it follows the first order kinetics, and the release process involves erosion/diffusion and an alteration in the surface area and diameter of the matrix system as well as in the diffusion path length from the matrix drug load during the dissolution process.

Raja Sekharan T et al.,\textsuperscript{82} studied the formulation of hydroxypropyl methyl cellulose based controlled release matrix tablets for theophylline with varying drug:polymer ratios (1:1 and 1:2) and differing tablet hardness (5, 6 and 7 kg/cm\textsuperscript{2}), and to evaluate the tablet's physicochemical properties such as hardness, uniformity of weight, friability, drug content and \textit{in-vitro} drug release. Initially, granules were made by wet granulation technique and evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and hausner ratio. The results indicate good flow property of the granules and thus, the evaluated tablet physical properties were within the acceptable limits.

Vidyadhara S et al.,\textsuperscript{83} studied the influence of polymer level and type of fillers namely lactose (soluble filler), swellable filler (starch 1500), microcrystalline cellulose and dibasic calcium phosphate (insoluble fillers) on the release rate and mechanism of release for verapamil hydrochloride from matrix tablets prepared by direct compression process. Higher polymeric content in the matrix
decreased the release rate of drug. On the other hand, replacement of lactose with anhydrous dibasic calcium phosphate and microcrystalline cellulose has significantly retarded the release rate of verapamil hydrochloride. *In-vivo* pharmacokinetic study proves that the verapamil hydrochloride from matrix tablets showed prolonged release and were be able to sustain the therapeutic effect up to 24 h.

Sakthikumar T *et al.*,\(^8^4\) developed an extended release tablet of Metoprolol succinate for the treatment of hypertension using HPMC K100M, SCMC, and eudragit L30 D55 by wet granulation and using HPMC K100M, HPMC 5cps by direct compression.

Radhika *et al.*,\(^8^5\) developed a new monolithic matrix tablet to completely deliver glipizide using HPMC K 100 and Eudragit L 100. The results suggested that the formulated tablets of glipizide showed improved efficacy compared with marketed one.

Al-Saidan *et al.*,\(^8^6\) developed guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. Based on the results of *in-vitro* and *in-vivo* studies it was concluded that that guar gum matrix tablets provided oral controlled release of water soluble diltiazem hydrochloride.

Senapati *et al.*,\(^8^7\) prepared matrix tablets of phenylpropanolamine using karaya gum and guar gum, alone or in combination with other excipients. They concluded a combination of karaya gum and guar gum exhibited more sustained release than individual gum.
Deshmukh *et al.*,88 designed oral controlled release theophylline anhydrous bioadhesive tablets and to optimize the drug release profile and *in-vitro* bioadhesion strength. Different types of natural hydrophilic polymers such as xanthan gum, locust bean gum, guar gum, karaya gum, and their combinations were used to formulate matrix tablets. An increase in the gum concentration increases the drug release profile beyond 12 h.

Ghosh and Barik,*89* developed matrix tablets of aceclofenac, using HPMC, EC and Guar gum by wet granulation method. They concluded that the HPMC matrix tablets provided oral controlled release of aceclofenac.

Sahoo *J et al.*,90 prepared verapamil hydrochloride sustained release tablets with Eudragit RLPO and Kollidon SR. The result indicates that the release of verapamil hydrochloride can be effectively controlled from a tablet containing solid dispersions of Eudragit RLPO.

Saurabh Jain *et al.*,91 sustained release tablets of furosemide were fabricated using pectin, guar gum and xanthan gum. The tablet with guar gum exhibited greater swelling index than those with pectin and xanthan gum. A better controlled drug release was obtained with the matrix tablet made-up of the guar gum than with the pectin and xanthan gum. The dissolution profile of furosemide from matrix tablets prepared using different natural polymers were retarded approx 15 h.
Martin et al.,⁹² investigated CMC on the release properties of theophylline from tablet matrices which were prepared by wet granulation method. They concluded that the drug release mechanism was influenced by both the molecular size of CMC and the presence of polymer additive.

Manjunatha et al.,⁹³ sustained release dosage form of diclofenac sodium containing immediate and controlled release components were designed. Solid dispersion of immediate release component was prepared using PVP and mannitol carriers by common solvent method. Controlled release component was prepared in form of spherical beads by ionotropic gelation technique. The formulations were found to be effective in providing controlled release of drug for a longer period of time.

Avachat et al.,⁹⁴ developed and characterized an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate. A hydrophilic matrix-based tablet using different concentrations of HPMC was developed using wet granulation technique. They concluded that the release of chondroitin sulfate and DS can be effectively controlled from a single tablet using HPMC matrix system.

Kuksal et al.,⁹⁵ prepared and characterized extended release matrix tablets of zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. They concluded that the results suggest that the developed
sustained-release tablets of zidovudine could perform therapeutically better than conventional dosage forms, leading to improve efficacy and better patient compliance.

**Yeole et al.,** developed sustained release matrix tablets of diclofenac sodium by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. And concluded Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium.

**Mathur V et al.,** developed a sustained release matrix tablet of verapamil hydrochloride (VH) using ethyl cellulose, methyl cellulose, Eudragit RS 100, hydroxypropyl methylcellulose and carboxymethyl cellulose and to evaluate the drug release kinetics. The formulated tablets were characterized for pre-compression and post-compression parameters and they were in the acceptable limits. The drug release data obtained after an in-vitro dissolution study was fitted to various release kinetic models in order to evaluate the release mechanism and kinetics. The criterion for selecting the best fit model was linearity (coefficient of correlation). Drug release mechanism was found to follow a complex mixture of diffusion, swelling and erosion.

**Nagendrakumar D et al.,** designed and evaluate once-daily sustained release matrix tablets of metoprolol succinate by direct
compression method. The tablets were prepared using HPMC K4M and K10M, guar gum and xanthan gum, carbopol 934p and Eudragit L-100 lactose as a channeling agent. Prepared matrix tablets were evaluated for various parameters like hardness, thickness, weight variation, friability and percent drug content. All the prepared formulations showed first-order release kinetics with matrix diffusion mechanism of drug release.

Jishnu V et al.,\textsuperscript{99} prepared extended release film coated matrix tablets of cephalixin using binary mixture of two grades of hydrophilic polymer, hydroxypropyl methyl cellulose (HPMC), by direct compression method. The concentration of HPMC K15M and HPMC 15cps were used as independent variables, while percentage drug release was selected as dependent variable. The dissolution data were fitted into zero-order, first-order, Higuchi and Korsemeyer-Peppas models to identify the pharmacokinetics and mechanism of drug release.

Umarunnisha AM et al.,\textsuperscript{100} prepared controlled release matrix tablets of famotidine by wet granulation method using HPMC K100M which forms the gel barrier. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and Hausners ratio. The tablets were subjected to weight variation, hardness, friability and drug content.
2.2. Transdermal patches/films

Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. The stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules. There are three main routes of drug penetration, which include the appendageal, transcellular and intercellular routes\textsuperscript{101}. TDDS are adhesive drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation\textsuperscript{102,103}. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first-pass metabolism, respectively. Transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of a fixed dose at regular intervals, due to which the drug concentration in the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdosing\textsuperscript{104-106}. 
Shinde AJ et al.,\textsuperscript{107} prepared transdermal matrix-type patches of gliclazide by film casting techniques on mercury using polymers like HPMC, Eudragit RL-100, and chitosan. Also an attempt was made to increase the permeation rate of drug by preparing an inclusion complex with hydroxypropyl β-cyclodextrin (HP β-CD). The possibility of a synergistic effect of chemical penetration enhancers (CPE) (propylene glycol and oleic acid) on the transdermal transport of the drug was also studied. Folding endurance was found to be high in patches containing higher amount of the Eudragit. There was increase in tensile strength with an increase in Eudragit in the polymer blend. \textit{In-vitro} drug release profile indicates that the drug release is sustained with increasing the amount of Eudragit in patches.

Chathoth S et al.,\textsuperscript{108} prepared matrix type transdermal films of lisinopril by solvent casting technique using a combination of ammonia methacrylate copolymer, type A. USP/NF (EudragitRL100) and poly vinyl pyrrolidone (PVP) as polymers. Propylene glycol was used as plasticizer. Glycerine, dimethyl sulphoxide (DMSO) and span-60 were used as penetration enhancers. The physicochemical parameters like thickness, folding endurance, drug content, tensile strength and stability were evaluated. \textit{In- vitro} drug release and \textit{in-vitro} skin permeation studies were carried out using modified Keshary-Chien permeation cell. Infra red spectroscopy (IR) and differential scanning colorimetry (DSC) were performed to follow drug carrier interactions. The results indicated that the permeation of lisinopril from films containing span-60 as penetration enhancer was
the best at all polymer ratios as compared to the films containing DMSO and glycerine.

Bharkatiya M et al.,\textsuperscript{109} prepared transdermal patches containing Metoprolol tartrate by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The patches were evaluated for their physicochemical properties, \textit{in-vitro} permeation and skin irritation studies. There is no interaction between drug and polymers evinced by FTIR, DSC and UV. Eudragit RL100-PVP polymers are better suited than the EC-PVP polymers.

Dinesh Chandra B et al.,\textsuperscript{110} prepared transdermal matrix films of metoprolol tartrate (MT) by casting on mercury substrate employing different ratios of polymers, ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP), using dibutyl phthalate (DBT) as a plasticizer. The formulations were subjected to various physical characterization studies namely, thickness, weight variation, drug content, moisture uptake, \textit{in-vitro} drug release and \textit{in-vitro} skin permeation. The \textit{in-vitro} permeation studies were carried out across excised porcine ear skin using Franz diffusion cell.

Jayaprakash S et al.,\textsuperscript{111} prepared Celecoxib transdermal patches by using different polymers such as HPMC, methylcellulose (MC), PVP. The \textit{in-vitro} release of the drug from the formulations was studied using commercial semi permeable membrane. The prepared
formulation were subjected to various physicochemical evaluation test, *in-vitro* dissolution studies, kinetics studies shows diffusion might be one of the prominent mechanism influencing the drug release. To confirm the fact Peppa’s plot was drawn, which confirmed that the diffusion mechanism involved in the drug release was of non fickian diffusion type. *ex-vivo* diffusion studies by using rat skin, guinea pig skin & pig ear skin and finally *in-vivo* evaluation studies were carried out by using rabbits.

**Deepak and Pundarikakshudu,**\textsuperscript{112} designed and evaluated unilaminate transdermal adhesive matrix systems using Eudragit E as the adhesive and rate-controlling polymer. Triethylcitrate (TEC) and dibutylphthalate (DBP) 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.

**Agarwal and Priya,**\textsuperscript{113} different matrix type transdermal patches of atenolol and metoprolol tartrate were formulated with PVP, CAP, HPMC phthalate and EC. The patches were formulated using combination of polymers and propylene glycol and 1,8-cineole as plasticizer and penetration enhancer, respectively. The results indicated that maximum release was obtained at 48 h.
Parikh and Ghosh,\textsuperscript{114} developed a transdermal drug delivery of fluoxetine and permeation studies across human cadaver skin were carried out using Franz diffusion cells. Permeation enhancement was achieved by azone, SR-38 and ethanol. Ethanol at 65\% vol/vol was able to increase the permeation of fluoxetine.

Ubaidulla et al.,\textsuperscript{115} developed a matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The bioavailability studies in rats indicated that the carvedilol transdermal patches provided steady-state plasma concentrations and improved bioavailability in comparison with oral administration.

Ting Li et al.,\textsuperscript{116} formulated transdermal drug delivery system of indomethacin, MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers (i.e. azone, L-menthol, 2-isopropyl-5-methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween- 80 and oleic acid) and concluded, the present data confirm the feasibility of developing indomethacin transdermal patches.

Yuvaraj and Chetan,\textsuperscript{117} transdermal patches of carvedilol with a HPMC-drug reservoir were prepared by the solvent evaporation technique. In this investigation, the membranes of Eudragit RL100 and Eudragit RS100 were cast to achieve control led release of the
drug. The non-ionic surfactants in the patches increased the permeation rate, Span 80 exhibiting better enhancement relative to Tween 80.

Ehab and Tadros,\textsuperscript{118} prepared transdermal patches of salbutamol sulfate as ethosomes and classic liposomes containing different cholesterol and dicetylphosphate concentrations. The entrapment efficiency percentage was significantly increased by increasing cholesterol, dicetylphosphate and ethanol concentrations. \textit{In-vitro} permeation studies of the prepared gels containing the selected vesicles showed that ethosomal systems were much more efficient at delivering SS into mice skin than were liposomes or aqueous or hydroalcoholic solutions.

Aqil et al.,\textsuperscript{119} characterized transdermal drug delivery systems of pinacidil monohydrate \textit{in-vivo} by monitoring the effect of the TDDS on blood pressure of methyl prednisolone acetate induced hypertensive rats and concluded that a single patch application of pinacidil TDDS (B-4) can effectively control hypertension in rats for 2 days.

Malay and Saroj,\textsuperscript{120} investigated and evaluated the biopharmaceutical behaviors of the matrix patch containing trazodone hydrochloride (TZN) following transdermal administration in rabbits. The \textit{ex-vivo} skin permeation study was performed using Keshary-Chien glass diffusion cell and mouse epidermis with intact stratum
corneum as membrane. The plasma level of TZN following transdermal application could be maintained for 24 h.

_Srinivas and Udupa,_121 developed the membrane controlled transdermal systems of glibenclamide using drug containing carbopol gel as reservoir and EC, Eudragit RS-100, Eudragit RL-100 and EVA as rate controlling membranes. They revealed that the glibenclamide patches exhibited better control of hyperglycemia than oral glibenclamide administration in mice.

_Ekapol and Kraisri,_122 developed diltiazem hydrochloride patches with HPMC and EC. The influence of enhancers dibutyl phthalate, isopropyl myristate, isopropyl palmitate, N-methyl-2-pyrrolidone, oleic acid, polyethylene glycol 400, propylene glycol and Tween80 on permeation was evaluated. And concluded that the film composed of 8:2 HPMC/EC, 30% DBP and 10% IPM, IPP or Tween80 loaded with 25% diltiazem should be selected for manufacturing transdermal patch.

_Malay and Saroj,_123 investigated and evaluated the biopharmaceutical behaviors of the matrix patch containing trazodone hydrochloride (TZN) following transdermal administration in rabbits. The _ex-vivo_ skin permeation study was performed using Keshary-Chien glass diffusion cell and mouse epidermis with intact stratum corneum as membrane. The plasma level of TZN following transdermal application could be maintained for 24 h.
**Satturwar PM et al.,**\(^{124}\) study concludes that polymerized rosin 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 release rate of drug from films and permeation across skin increases with increase in drug and PVP loading but is independent of film thickness. Patches containing PR:PVP (7:3) show promise for pharmacokinetic and pharmacodynamic performance evaluation in a suitable animal model.

**Bagyalakshmi et al.,**\(^{125}\) developed membrane-moderated transdermal systems of ampicillin sodium using HPMC, MC, CAP, chitosan, sodium alginate and sodium CMC in an ethanol: pH 4.7 buffer volatile systems by the solvent evaporation technique with HPMC as the rate-controlling membrane for all the systems. They concluded that hydrophilic ampicillin sodium can be developed as a transdermal delivery system with sodium alginate that is an alternative to intravenous administration and has minimal adverse effects.

### 2.3. Polymers used for Controlled drug delivery system

**Shah SS et al.,**\(^{126}\) prepared transdermal patches of papaverine hydrochloride by the solvent casting method using EC: PVP, PVA: PVP and Eudragit RL-100: Eudragit RS-100 using different ratios. The *in-vitro* diffusion studies were carried out using modified Keshery Chein cell using cellophane as the diffusion membrane. The formulation containing PVA: PVP as polymers showed faster release rate
(hydrophilic polymers) compared to Eudragit RL-100: Eudragit RS-100 (hydrophobic polymers) or combination of hydrophilic and hydrophobic polymers (ethyl cellulose and PVP). Compatibility studies indicated that there was no interaction between the drug and polymers. *In-vivo* studies showed that papaverine hydrochloride helps in decreasing the effect of isoproterenol induced myocardial necrosis.

**Iman I S et al.**\(^{127}\) aimed to formulate an anti-histaminic drug-Chlorpheniramine maleate (CPM) as transdermal patch using different bioadhesive polymers such as ethyl cellulose, cellulose acetate, and polyvinyl pyrrolidone with different plasticizers such as propylene glycol (PG) and polyethylene glycol 400 (PEG400). Patches were prepared though solvent evaporation method, evaluated for their physical and mechanical properties and then subjected to stability study to select the best formulae to be evaluated *in-vitro* and *in-vivo*.

**Jamakandi V G et al.**\(^{128}\) aimed to evaluating the possibility of using different polymeric grades of hydroxy propyl methyl cellulose (6cps, 15cps, and K4M) for the development of transdermal drug delivery systems of nicorandil, an antianginal drug. Prepared matrix-type patches were evaluated for their physicochemical characterization followed by *in-vitro* evaluation. Selected formulations were subjected for their *ex-vivo* studies on porcine ear skin.

**Shinde AJ et al.**\(^{129}\) designed to develop suitable transdermal matrix patches of tramadol hydrochloride using HPMC, Eudragit RL-100 and Eudragit RS-100 with triethyl citrate as a plasticizer and
dimethyl sulfoxide (DMSO) as a penetration enhancer. Drug excipients interaction study was further carried out using Fourier transform infrared (FTIR) spectroscopic technique. Physical evaluation was performed such as moisture content, moisture uptake, tensile strength, flatness, and folding endurance. In-vitro diffusion studies were performed using cellulose acetate membrane (pore size 0.45 µ) in a Franz’s diffusion cell.

Nayak BS et al., aimed to develop and evaluate transdermal patches of nebivolol prepared by solvent evaporation technique. The prepared transdermal patches were evaluated for thickness, mass variation, drug content, moisture content, moisture vapor transmission, folding endurance, tensile strength, ex-vivo drug permeation study, drug release kinetics, scanning electron microscopy, primary skin irritancy study, and stability study. The mechanical properties and tensile strength revealed that the formulations were found to be strong enough but not brittle. FTIR studies did not show any evidence of interaction between the drug and the polymers.

Adhyapak A et al., developed matrix-type transdermal drug delivery system of tamoxifen citrate using a different ratio of eudragit-RL100, HPMC-K15, and ethyl cellulose (EC), by the solvent evaporation technique. The effect of the binary mixture of polymers with a penetration enhancer on the physical chemical parameters and in-vitro drug permeation were evaluated. The in-vitro drug permeation
studies were conducted by using modified Keshary-Chein diffusion cells through female Sprague Dawley rat skin using pH 7.4 PBS. The stability studies were conducted as per the International Conference on Harmonization (ICH) guidelines, and did not show any degradation of the drug.

Modi C,\textsuperscript{132} studied on the basis to evaluate the amount to be needed for fabrication of diclofenac transdermal patch. It shows that HPMC has great influence on transdermal patch, if it is used alone in combination with glycerin or PEG-4000 plasticizer.

Chandrashekar NS and Shobha Rani RH,\textsuperscript{133} evaluated skin of an average adult body covers a surface of approximately 2 m\textsuperscript{2} and receives about one-third of the blood circulating through the body. The transdermal route of administration cannot be employed for a large number of drugs. The rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug are the important factors to be considered for deciding its suitability of drug for delivery by transdermal route.

Jamakandi V G et al.,\textsuperscript{134} reviewed recent trends in transdermal cardiovascular therapy. Transdermal dosage forms, though a costly alternative to the conventional formulations, are becoming popular because of some unique advantages. Controlled zero-order absorption, simple administration mode and the option of easy removal in case of adverse manifestations make them particularly desirable in
cardiovascular therapy. Currently a number of antihypertensive drugs are being developed for transdermal administration.

**Agrawal S S et al.,**\(^{135}\) formulated 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 PVP, cellulose acetate phthalate, HPMC phthalate and ethyl cellulose. The patches were formulated using combination of polymers and propylene glycol and 1,8-cineole as plasticizer and penetration enhancer, 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.

**Sanap G S et al.,**\(^{136}\) formulated indapamide transdermal drug delivery systems by using solvent casting method. Monolithic systems were prepared by using HPMC and ethyl cellulose (EC) polymers by incorporating glycerine and dibutyl phthalate as plasticizers, respectively. All the patches were uniform with respect to physicochemical and scanning electron microscopy (SEM) evaluation. The *in-vitro* drug release studies indicated that HPMC containing films have shown better release than that of EC containing films without any permeation enhancer. A significant improvement of flux was observed in the following order: olive oil > linseed oil > sunflower oil > cottonseed oil > coconut oil > castor oil. Further improvement of flux
was observed, when 30% w/w olive oil was applied directly onto the skin prior to the studies.

**Prabhu P et al.,**\(^{137}\) prepared the domperidone patches using EC: PVP, PVA:PVP and HPMC:SCMC as polymers in combination. The physicochemical parameters like thickness, drug content, weight variation, moisture absorption and drug permeation studies were evaluated for the prepared patches. No significant difference in thickness, average weight and in the drug content among the patches.

**Sadashivaiah R et al.,**\(^{138}\) prepared matrix type transdermal drug delivery systems of haloperidol lactate using different ratios of EC:PVP by solvent evaporation technique. Physicochemical parameters were characterized, and dissolution studies of the formulated films were performed. *In-vitro* permeation studies were done using modified Franz diffusion cells through human cadaver skin utilizing 20% PEG 400 in normal saline. Permeation studies illustrated that 4% hyaluronidase enzyme was a good enhancer.

**Sarfaraz Md et al.,**\(^{139}\) prepared the transdermal patches of selegiline hydrochloride (SH) by solvent casting method using HPMC, PVA and methyl cellulose (MC) as reservoir polymers in different ratios (1:1, 1:2 and 1:3). Rate controlling membrane was caste by using 2% EC membrane. The prepared patches possessed satisfactory physicochemical characteristics. The patches were seemingly free of potential hazardous skin irritation. FTIR and DSC studies revealed no interaction between the drug and polymers used.
Vandana M et al.,\textsuperscript{140} prepared transdermal matrix patches of captopril by casting method employing different ratios of polyvinyl alcohol, ethyl cellulose, PVP and HPMC. The prepared matrix patches were evaluated for physicochemical characteristics such as thickness, weight variation, folding endurance, drug content, percent moisture content, water vapour transmission and \textit{in-vitro} drug permeation studies. The hydrophilic and hydrophobic polymers in combination showed sufficient potential for the development of transdermal drug delivery system of captopril.

Jatav VS et al.,\textsuperscript{141} prepared matrix type transdermal patches containing Nebivolol hydrochloride using two polymers by solvent evaporation technique using EudragitRS100, HPMC K100M. Aluminium foil was used as a backing membrane. PEG 400 was used as plasticizer and DMSO was used as penetration enhancer. Drug polymer interactions determine by FTIR and standard calibration curve of ketoprofen were determine by using UV estimation. All prepared formulations indicated good physical stability. \textit{In-vitro} drug permeation studies of formulations were performed by using Franz diffusion cells using abdomen skin of Wistar albino rat. Result, showed best \textit{in-vitro} skin permeation through rat skin as compared to all other formulations prepared with hydrophilic polymer containing permeation enhancer.