2 LITERATURE REVIEW

Tiwary A K, et al (2007) had explained developments in the transdermal drug delivery system. The strategies considered while developing transdermal products were explained. The authors found the major obstacle in drug delivery through skin is the excellent barrier of skin. Different techniques were used to overcome the obstacles for successful drug delivery to systemic circulation across skin.

Kandavilli S, et al (2002) explained the polymers utilized in the drug delivery through skin. They had summarized the formulation concepts of transdermal drug delivery system. Physicochemical properties of polymers used in transdermal drug delivery system were explained.

Jain N K; (2010) revealed that transdermal drug administration is intended through skin for the localized treatment of tissues beneath the skin or for systemic therapy. Goal of dosage form design of transdermal products is to increase the diffusion across the skin into systemic circulation.

B Anilreddy; (2010) showed that transdermal drug delivery system bypass the hepatic first pass metabolism. The plasma level fluctuations are also minimized and the drug degradation in gastrointestinal tract by pH and enzymes is avoided. As a result, patient compliance is improved.

Robbins, et al (2005) explained the inflammation as complex response to injurious agents. The inflammation response has two main components a cellular reaction and vascular reaction. It also focuses the patterns of Inflammation which are acute and chronic. Pathophysiology and cellular mechanisms of inflammation are discussed in detail.
Eseldin K, et al (2002) reviewed that the skin is the most readily accessible organs of the human body. For several decades, intact skin is utilized as route of drug administration. However, being skin acts a barrier to cross and only few drugs and drugs in limited quantities can penetrate the barrier. They focused on the ideal characteristics of drug candidates for formulation of transdermal delivery.

D P Patel; (2011) defined the transdermal drug delivery system as the dosage form formulated to deliver the drug through the skin. Basic components of transdermal drug delivery system include polymer, drug penetration enhancer, adhesive, release liner, backing membrane, and other excipients like plasticizer and solvent explained and method of preparation and evaluation are explained.

A E Benson, (2005) revealed that transdermal drug delivery system is one of the excellent penetration techniques and can be applied for local and systemic effects. Delivery of drug takes place across the human skin, penetration enhancement through optimization of drug and vehicle properties, penetration enhancement across stratum corneum by any of the factor like hydration, fluidization, lipid disruption, by chemical penetration enhancers, interaction with keratin, etc.

Kim H, et al (2007) mentioned that Meloxicam as a weak lipophilic drug (Log P=1.9), but is sparingly water soluble. (0.009 mg/mL at 25°C).

Fahmy M; (2006) explained that common oral dose of Meloxicam is 7.5–15.0 mg/day. The author further described that the aqueous solubility of Meloxicam is poor and the rate of dissolution is low (15% in 5 min).

Chiou W L; (1977) observed variations in bioavailability due to poor dissolution, and gastric irritation on oral administration of Meloxicam.


Gambero A, et al (2005) described that Meloxicam is comparatively safer drug as compared to other non steroidal anti-inflammatory drugs. Meloxicam may show adverse effects in gastro-intestinal tract. To overcome the possible adverse effects in the gastrointestinal tract an alternative drug delivery method may be useful. The authors further described that the drug delivery through skin has proved to be an excellent method for administration of the drug to overcome the possible adverse effects from oral administration.

Szejtli J, (1998) had reviewed that cyclodextrins has been used since approximately 100 years. Cyclodextrins have been used as stabilizers, solubilizers for biologically active substances, in chromatography as separating agents or as additives for their detergent, viscosity modifying actions.

Loftsson T, et al (1996) revealed that cyclodextrins have been used to improve the solubility of drugs which are poorly soluble.
Loftsson, T et al, (2001) reviewed that the cyclodextrins form solid inclusion complexes with lipophilic water-insoluble drugs. The complexes are soluble in water. The drug molecule gets trapped in the central cavity of cyclodextrins. When the drug is placed with cyclodextrins in the aqueous complexation media, the lipophilic molecules compete with each other in the cavity for a space. Only a small amount of cyclodextrins and drug-cyclodextrin complexes can penetrate into lipophilic barrier of intact skin because of their size and hydrophilicity.

Redenti E, et al (2001) reviewed that as cyclodextrins can form complexes with different types of drug molecules, cyclodextrins and their derivatives are commonly employed in pharmaceuticals. The complex shows a number of effects like enhancement in solubility, bioavailability and improvement in stability and formation of drug release systems.

Masson, et al (1999) had studied and revealed that the solubility of poorly water soluble drug was improved in presence of cyclodextrins. The cyclodextrins acted as penetration enhancers by carrying the drug across the skin barrier.

E M Martin, et al (2004) reviewed the properties and applications of cyclodextrins. Many derivatives of parent cyclodextrins like hydroxypropyl-β-cyclodextrin have been synthesized by several reactions like amination, esterification and etherification of cyclodextrins. The most important property of cyclodextrins is their ability to form the solid inclusion complex with wide range compounds.

David C Bibby, et al (2000) had reviewed that the drug form complex with cyclodextrin and release of drug of several drug candidates was modified. The efficacy was improved alongwith sustaining effect or minimizing toxicity. Several attempts were made to modify drug release like polymeric delivery systems including microspheres, nanospheres and polymeric films.

Sheth S K, et al (2010) had prepared and evaluated taste masked oral disintegrating tablet of Lornoxicam using β-cyclodextrin. They had masked the bitter taste of poorly soluble Lornoxicam and developed a taste masked oral disintegrating tablet for Lornoxicam. Solid inclusion complexes containing Lornoxicam and β-cyclodextrin were prepared at different molar ratios of 1:1, 1:2 and 1:3. On the basis of characterization of solid complex molar ratio 1:2 was selected for formulation of tablets and tablets were evaluated.

Hamza Y S, et al (2009) designed and evaluated the sustained release bilayer tablets of Lornoxicam using β-cyclodextrin and xanthan gum. They developed double layered tablets for highly potent NSAID. Drug and β-cyclodextrin complexes were made at different molar ratios (1:1 and 1:2) by freeze drying and kneading method. On the basis of dissolution properties the molar ratio 1:2 prepared by freeze drying method was optimized for further formulations of fast release layer of double layered tablet. β-cyclodextrin was used to enhance the dissolution of Lornoxicam and assure the rapid onset of action. Xanthan gum was used as hydrophilic matrix forming agent that regulate appropriate sustained release of drug. Double layered tablet has shown sustained release for nearly about 8 hrs.

Reddy M N, et al (2004) investigated that the solubility and rate of dissolution of nonsteroidal anti-inflammatory drug Celecoxib was enhanced when it was complexed with β-cyclodextrin. Celecoxib is a drug from BCS-II class. Phase-solubility studies showed that the solubility of Celecoxib was enhanced when the complex was prepared with β-cyclodextrin. The complexes were prepared and evaluated for scanning electron microscopy, powder x-ray diffractometry and differential scanning calorimetry. Complexes formed by freeze-drying method showed a higher dissolution rate than other complexes.
Deepthi Mathew; (2009) had prepared Nimesulide–β-cyclodextrin complex by the method of co-precipitation. The complexation was confirmed for solubility and DTA analytical methods. It was observed that dissolution profile of Nimesulide was improved by complexation with β-cyclodextrin.

Rajendrakumar K, et al (2004) compared the inclusion behavior of Rofecoxib with β-cyclodextrin and its sulfobutyl ether-7 derivative in solution and solid state with that of natural β-cyclodextrin in terms of toward a poorly water-soluble anti-inflammatory agent. A phase solubility method was used to evaluate the stoichiometries and stability constants of ROFXβCD and ROFX-SBE7βCD complexes. It was observed that solubility enhancement was much greater for the Rofecoxib-SBE7βCD complex compared to Rofecoxib-β-cyclodextrin complex. The stability constant obtained for the SBE7βCD inclusion complex of Rofecoxib was higher. Dissolution profiles obtained showed that SBE-β-cyclodextrin was more significant than β-cyclodextrin to improve the pharmaceutical properties of Rofecoxib.

Shukla Vikesh, et al (2009) studied and reported that the solubility of Ketoprofen was enhanced when it was complexed with β-cyclodextrin. Faster dissolution rates were observed with the formulations containing Ketoprofen-β-cyclodextrin inclusion complexes.

Malay K Das, et al (2006) had investigated the effects of drug content, plasticizers and polymeric composition on the permeation of Trazodone hydrochloride across the skin. It was observed that the plasticizers had markedly enhanced the skin permeation properties of Trazodone hydrochloride.


Chien Yie W; (1988) had described the use of polymers in the development of TDDS and has recommended suitable diffusion cells for the evaluation of transdermal patches.

Bharkatiya M, et al (2006) had fabricated transdermal films of Nimesulide employing four different polymers by solvent casting technique. Dibutylphthalate was used as plasticizer. Satisfactory permeation was observed when the in-vitro permeation profile of different formulations was studied. However, the formulation containing drug reservoir with HPMC: PVP showed better permeation.

Manvi F V, et al (2003) studied the physicochemical properties of transdermal film formulated using different polymeric combination plasticized with polyethylene glycol 400. They studied the influence of permeation enhancers on kinetics of skin permeation by franz diffusion cell. They observed that prophylaxis of allergic asthma can be achieved by formulating rate controlled transdermal therapeutic system.

Xiaoping Zhan, et al (2007) investigated the influence of ratio of monomers used, thickness of membrane and concentration of drug on rate of permeation. Formulated membranes were evaluated for FTIR, DSC and SEM studies. It was observed that the copolymer membranes have controlled drug release from transdermal drug delivery system.

Parthasarathy G et al (2011) concluded that transdermal patches released Naproxen in prolonged release manner. They further described that high proportion of hydrophobic polymer ethyl cellulose was responsible for sustaining the drug release.

K V Vilegave, et al (2012) studied the antihypertensive activities of the patches on methyl prednisolone acetate induced hypertensive rats. The authors found that HPMC: EC combinations patches had shown the reduction of systolic BP.

Mohd. Amjad, et al (2011) developed transdermal patches of matrix type containing Atenolol in different ratios of HPMC and ethyl cellulose by solvent casting method. Prepared patches were characterized for various physicochemical parameters, in-vitro permeation studies. The formulations were exposed to stability studies, good physical stability was observed with all the formulations.

A A Attama, et al (2008) had formulated buccoadhesive patches of hydrochlorothiazide with Ethyl cellulose and Hydroxypropyl methylcellulose. The patches were evaluated for various parameters like swelling index, thickness, buccoadhesive strength, drug content studies and in-vitro release studies. The study revealed that the combination of polymers gave the highest buccoadhesive strength.

Nirav S Sheth, et al (2011) had prepared matrix- type transdermal patches incorporating Propranolol Hydrochloride. Patches were prepared employing PVP, HPMC and EC to sustain drug release. Combination of polymers in various ratios was used and the plasticizer used was propylene glycol. The formulations were characterized for different parameters. In-vitro diffusion studies were performed across abdominal skin of rat in franz diffusion cell. Maximum release was observed when 2% solution of EC was used.

Rajan Rajabalaya, et al (2012) studied the release and permeation studies of Ondansetron Hydrochloride by developing transdermal therapeutic systems. The patches were prepared with Eudragit RS/RL as polymer and plasticizer like dibutylsebacate and
triethyl citrate was used in different ratios. The prepared formulations were evaluated for different parameters like tensile strength, thickness, drug content analysis and water vapor absorption studies. *In-vitro* permeation studies were performed using a Franz diffusion cell. Chemical enhancers like eugenol and Virgin linseed oil were used in the formulation. All the formulations are developed and passed the mechanical as well as physiochemical properties, while in the case of release profile, the patch containing dibutylsebacate had better percentage cumulative release compared to those with triethyl citrate containing patches. Eugenol acted as a good chemical enhancer as it increased percentage of permeation compared to linseed oil significantly.

**Kooriyattil Naseera, et al (2012)** had developed transdermal drug delivery system of Simvastatin using DMSO and eugenol as penetration enhancers. Hydrophobic and hydrophilic polymers and their combinations were used in different concentration. The patches were formulated by solvent evaporation technique. The prepared patches were characterized for various physicochemical parameters including weight variation, thickness, folding endurance, tensile strength, swelling index, water vapor transmission studies, etc. Dialysis membrane and goat skin were used for drug permeation studies by franz diffusion cell.

**Subhash P G, et al (2011)** studied and revealed that several methods can be employed to increase the permeation of drugs. The most convenient method is application of penetration enhancers in the preparation of patches. Patches were prepared using Lercanidipine hydrochloride. Penetration enhancers used were eugenol and DMSO. *In-vitro* drug diffusion studies were conducted using franz diffusion cell. It was observed that the terpene has enhanced the permeation of drug across the skin.

**V R Sinha, et al (2000)** reviewed that DMSO has enhanced the transdermal permeation of different types of drugs including β-blockers, ephedrine hydrochloride and papaverine hydrochloride. It was observed that the release of Azapropazone from its ointments was also enhanced.
Yogesh M. Amgaokar, et al (2011) had employed DMSO and urea as penetration enhancers in formulation of transdermal delivery of Budesonide. The polymers like ethyl cellulose, eudragit RS, eudragit RL 100 and PVP were used in different concentrations. PEG-400 was used as plasticizer. The formulations were evaluated for different parameters. The formulated patches had shown uniformity in thickness, drug content, swelling behaviour, better in-vitro drug permeation and water vapor transmission rate.

S Amin, et al (2012) had designed transdermal patches containing Metoclopramide using eudragit RL-100 and eudragit RS-100 as rate controlling polymers and DMSO was used as penetration enhancer. Transdermal films were prepared using polymers in different ratios by solvent evaporation method. The prepared formulations were characterized for various physicochemical parameters like drug content, thickness, in-vitro release and skin permeation profile. Better strength, flexibility, drug release and skin permeation potential were observed with the films of eudragit RL-100 used in higher proportion.

Suchika Sharma, et al (2010) had prepared transdermal patches of Olanzapine using blends of polyvinylpyrrolidone and ethyl cellulose. A total of fourteen matrix patches were prepared by using these polymers, dibutylphthalate as plasticizer and vegetable oils (soyabean oil, olive oil, eucalyptus oil) as permeation enhancers in dichloromethane and chloroform solvent system. The formulations were characterized for different parameters including weight uniformity, drug content, moisture content, moisture uptake, thickness, folding endurance, thickness and in-vitro permeation studies. It was observed that maximum drug release was observed in 24 hrs with formulation containing olive oil.

V N L Sirisha, et al (2012) developed matrix type transdermal films of Propranolol hydrochloride by solvent evaporation method using various ratios of Eudragit and dibutylphthalate as plasticizer. The formulations were characterized for various parameters like weight variation, drug content, folding endurance and in-vitro permeation studies by using franz diffusion cell. Hence it has proved that dibutylphthalate can be used as plasticizer.
Eskandar Moghimipour, et al (2012) prepared skin care gels containing 15% glycolic acid using Hydroxypropyl methylcellulose, Hydroxyethylcellulose, carbomer as gel forming agent and Glycerin and propylene glycol as co-solvents. Tween 80 in concentration 0.25 to 1% as surfactant was added to the formulation made of HPMC base and its release behaviour was investigated. pH was adjusted where carbopol was used as gelling agent. Data obtained from drug release study showed that the release pattern from formulations containing 10% propylene glycol in both gel forming agents (HPMC and HEC) improved significantly more than the other formulations.

Azmail Khan, et al (2010) formulated and evaluated Aceclofenac solid dispersion gels of various compositions. Aceclofenac solid dispersion incorporated gel of HPMC and Aceclofenac solid dispersion incorporated gel of Carbopol 940 were subjected for transdermal in-vivo efficacy study on rats through abdominal skin. The results suggested that solid dispersion incorporated gels of HPMC had improved transdermal delivery for Aceclofenac.

Danester Quiñones, et al (2008) had developed and characterized topical delivery of Nystatin incorporating carbopol 934, HPMC and combination of carbopol-HPMC as a gel base and propylene glycol as co-solvent and penetration enhancer. pH of gel was adjusted by triethanolamine. Rheological study revealed that the formulation containing carbopol-HPMC showed the highest viscosity and exhibited an apparent pseudoplastic thixotropic behavior and better diffusion.

M Najmuddin, et al (2010) designed and evaluated gels for topical delivery of water insoluble antifungal agent Ketoconazole to increase its penetration through skin and thereby its flux. It was observed that the after complexation with β-cyclodextrin, solubility of Ketoconazole was enhanced. The complexes were then incorporated into gel formulations. The complexes were characterized by infrared spectroscopy. No interaction was observed between drug and carrier. Ketoconazole gel formulations were made using different polymers carbopol 940, HPMC, MC and sodium CMC, containing
various permeation enhancers like sodium lauryl sulphate (0.5-1.0%) and dimethyl sulfoxide (5-20%) in different proportions. The formulated gels were characterized for different physicochemical parameters including drug content, pH, viscosity, spreadability, extrudability, in-vitro drug release using pH 7.4 phosphate buffer. All the formulated topical preparations showed pH between 6.5 to 7.4. Better spreadability and extrudability was observed. The carbopol 940 with 15% of dimethyl sulfoxide showed best in-vitro drug release 98.07% at the end of 6 hrs.

Swamy N G N, et al (2010) formulated gels of Diclofenac sodium employing sodium carboxymethyl hydroxypropyl guar and HPMC as gelling agents. Formulated gels were characterized for various evaluation parameters including pH measurement, assay, stability study, rheological properties and in-vitro release studies across albino rat skin. It was observed that the gels containing sodium carboxymethyl hydroxypropyl guar was an excellent gelling agent in the formulation of Diclofenac sodium gels.

Vivek Kumar R, et al (2011) prepared and characterized the gel formulation containing various polymers in various concentrations as gelling agents. The formulated gels were characterized for their anti-inflammatory activity on wistar rat model. The gel formulations containing carbopol 940 (0.2-0.6 % w/v) were observed as better formulation compared to others.

Vinod L Gaikwad, et al (2012) investigated that Fluconazole topical gel formulation can be successfully formulated by using combination of carbopol 934 and carbopol 940. They found that both grades of carbopol (934 and 940) can be used for extending drug release where reduced dose of drug/s is favored.

Manivannan Rangasamy, et al (2008) had prepared tablets containing Meloxicam-β-cyclodextrin complex. They have studied to enhance the solubility of Meloxicam by complexing and the complexes were compressed into tablets by direct compression. Formulated tablets were characterized for different physicochemical parameters like
hardness, uniformity of weight, thickness, content uniformity, friability, disintegration and in-vitro dissolution time. Better results were obtained with the tablets containing complex.

Obaidat A A, et al (2011) prepared Meloxicam-β-cyclodextrin complex and was compressed into fast-dissolving tablets. The tablets were evaluated for the influence of various superdisintegrants on disintegration time and drug release. Superdisintegrants used were crospovidone, croscarmellose sodium and sodium starch glycolate. All the formulated tablets had shown acceptable mechanical properties. It was concluded that solubility of the drug was enhanced on preparation of complex Meloxicam and β-cyclodextrin.

Lenuța Maria Miclea, et al (2010) had prepared the complexes of Meloxicam with β-cyclodextrin by the co-precipitation, kneading and ethanol-water solution methods of complexation. The obtained complexes were evaluated by scanning electron microscopy for morphology of crystals and their approximate size and through thermal analysis using the thermogravimetric method and differential scanning calorimetry. It was confirmed that inclusion complexes of Meloxicam with cyclodextrin were obtained. The DSC analysis showed that the complex obtained by the kneading method is much better formed that those obtained by co-precipitation and crystallization from solution.

Sanjala Baboota, et al (2002) revealed that in-vitro dissolution rate of Meloxicam–β-cyclodextrin complex was faster than the drug alone. Further they investigated that the inclusion complex has shown better release at molar ratio 1:2::Meloxicam-β-cyclodextrin.

Nikhil Kasliwal, et al (2010) prepared Meloxicam gel using different penetration enhancers like linoleic acid, oleic acid, isopropyl myristate and dimethyl sulfoxide. Influence of polymers on the drug diffusion across skin was evaluated. On in-vitro and in-vivo studies, better permeation was observed by using the penetration enhancers.
M V Nagabhushanam; (2010) prepared tablets containing Meloxicam and its solid inclusion complexes with β-cyclodextrin and HP-β-cyclodextrin by kneading method. Solid inclusion complexes of Meloxicam were compressed into tablets. Better dissolution rates were observed with the inclusion complexes of Meloxicam. All the tablets formulated employing β-cyclodextrin and HP-β-cyclodextrin complexes of Meloxicam showed rapid and higher dissolution rates of when compared to that of Meloxicam tablets.

S Rawat; (2011) prepared and studied the release of Meloxicam from its formulated containing drug and its complex with β-cyclodextrin prepared by kneading method. Solid inclusion complexes obtained were then characterized by XRD, IR, DSC and SEM. Gels containing drug, its physical mixture and solid inclusion complex were prepared. Formulated gels were characterized for various physical parameters like pH drug content, viscosity in-vitro drug release studies across cellophane using Franz diffusion cell. It was observed that the gels containing inclusion complex showed better drug release.

Somasundaram Jayaprakash, et al (2010) developed and evaluated transdermal therapeutic system for Meloxicam using various polymers like HPMC, ethyl cellulose and polyvinyl pyrrolidone and plasticizers by solvent casting method. Formulations were characterized for various parameters. In-vitro drug release was studied using various biological membranes like snake shed skin and porcine ear skin. The patches exhibited no skin irritation and better drug release. They concluded that transdermal patches incorporating Meloxicam could be promising controlled drug delivery, as a patient friendly and once a day dosing therapeutic system.