LITERATURE REVIEW

1. Hindustan Abdul Ahad et al., [2010], have developed matrix moderated transdermal systems of Indomethacin using various proportions of Ficus *carica* fruit mucilage by the solvent evaporation technique. In these study shows that the release of drug from the patch delayed in controlled manner as the proportion of Ficus *carica* increased.

2. Cordero et al., [1997], carried out a comprehensive study of transdermal penetration of series of Nonsteroidal anti inflammatory drugs (Indomethacin, Ketoprofen, Diclofenac sodium, Piroxicam, Tenoxicam, Ketorolac, and Aceclofenac). They have determined the permeation parameters (permeability rate constant $k_p$, lag time $T_L$ and flux $J$) as a measure of the intrinsic transdermal permeabilities of these drugs to predict their potential for formulation in a transdermal therapeutic system.

3. Pandey et al., [2000], prepared different transdermal nimesulide gels using sodium alginate, HPMC, sodium CMC and methylcellulose. In-vitro release studies of the prepared formulation were performed using dialysis membrane. The release pattern of drug from the marketed gel was found to be better than from other gels, the reason may be that the 66% alcohol content of the gels that might have enhanced the solubility of the drug.

4. S.C.Mandal et al., [1991], have reported Ethyl cellulose, Eudragit, Polyvinyl alcohol and Polyvinyl Pyrrolidine as polymer to formulate matrix type transdermal devices of Diazepam, which were then subjected to in-vitro evaluation.

5. F V Manvi et al., [2003], Formulated transdermal films of ketofen fumarate using combination of eudragit L100: hydroxyl propyl methylcellulose and ethyl cellulose: hydroxyl propyl methyl cellulose as polymers along with permeation enhancers such as dimethyl sulfoxide and propylene glycol. Polyethylene glycol was used as a plasticizer. It was found that there was decrease in drug release rate from EL100:HPMC films.
in comparison to EC:HPMC was found, due to the hydrophobic nature of the polymer.

6. **Ubaidulla U et al., [2007]**, developed a matrix-type transdermal therapeutic system containing carvedilol with different ratio of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique and reported that the developed transdermal patches increased the efficacy of carvedilol for the therapy of hypertension by using different polymer ratio.

7. **Gattani SG et al., [2007]**, investigated transdermal films of chlorpheniramine maleate using different polymer combinations and concluded that hydrophilic polymer showed higher release than the lipophilic and hydrophilic-lipophilic combination.

8. **Sankar V et al., [2003]**, investigated ethyl cellulose films for the permeation of the nifedipine drug through the film by using castor oil and glycerol as the plasticizers. It was found that the drug release from the patches containing the glycerol as the plasticizer was more than that from the one containing castor oil.

9. **Agrawal S S et al., [2007]**, developed matrix type transdermal patches of atenolol and metoprolol using polymers like polyvinyl pyrrolidone, cellulose acetate phthalate, hydroxyl propyl methyl cellulose. The results obtained showed drug release from the formulation containing PVP and HPMC was for 48 hour and it caused no irritation on the skin.

10. **Chinna reddy palem et al., [2010]**, prepared bilayered mucoadhesive patches for buccal delivery of felodipine shows release of felodipine was zero order and controlled by secondary layer of eudragit RLPO.

11. **Madishetti S.K et al, [2010]**, prepared domperidone bilayered transdermal therapeutic systems which shows required flux and suitable mechanical properties.

12. **Calpena A.C et al., [1994]**, studied comparative in vitro study of transdermal absorption of antiemetics that was used in treatment of nauseas and their use.
in patients receiving oncogenic treatment with chemotherapy. They studied permeation parameters of antiemetics in order to predict their potential therapeutic formulation in TDD

13. **Elvira et al., [2003]**, studied on the transdermal permeation of diclofenac sodium using different liquid formulations. In-vitro permeation studies were carried out using human skin as membrane. They have reported that there is no skin irritation with the inclusion of permeation enhancers like oleic acid. They suggested that the topical delivery of diclofenac sodium with an absorption enhancer such as oleic acid and d-limonene may be an effective for both dermal and sub dermal injuries.

14. **H.S. Gwak et al., [2003]**, found feasibility of developing an Ondansetron transdermal system using Duro-Tak 87-2100 and Duro-Tak 87-2196 as pressure sensitive adhesives (PSA). Effect of vehicles, propylene glycol monocaprylate (PGMC)-diethylene glycol mono ethyl ether (DGME)-propylene glycol (PG) co solvents with 3% oleic acid, was studied & found that DGME in PGMC-DGME co solvent system decreased release rate as its concentration was increased. Also as amount of PSAs increased, the permeation flux was decreased.

15. **H.S. Gwak et al., [2004]**, studied effect of vehicles and penetration enhancers on transdermal delivery of Ondansetron across dorsal hairless mouse skin. Among vehicles used, water and ethanol showed high permeation fluxes. The highest flux was achieved at 40% of DGME combinations with PGMC & ethanol (80:20) and PGMC & PG (60:40) increased permeation by six- & two-fold respectively, compared to PGMC alone.

16. **Kale et al., [1996]**, have studied the Preformulation stability and Permeation of Transdermal patches of salbutamol. The study involves screening a suitable enhancer for the drug. The influence of Lauryl alcohol and Tween 80 was reported to be less but the oleic acid and Sodium lauryl sulphate to be greater extent could enhance the permeation of salbutamol sulphate.

17. **Gattani SG et al. [2006]**, formulated transdermal films of anti-emetic drug
by using different hydrophilic and lipophilic polymers. In vitro results obtained showed that hydrophilic polymers had higher release than the lipophilic and hydrophilic-lipophilic combinations. Permeation enhancers like oleic acid, limonene were found to give favourable permeation enhancement.

18. **P.K. Suryadevara et al., [2010]**, in his dissertation work prepared matrix type transdermal patches of ondansetron HCl by combination of polymer (PVP:PVA, 5:5) and oleic acid 10% was used as a permeation enhancer shows 76.69% drug release in 10 hr.

19. **Yellela S.R. et al., [2009]**, formulated patches containing EVA1802 membranes as rate controlling membrane which contain selected concentrations (0, 5, 10 and 15% w/w) of PEG6000 were prepared, and subjected to in vitro permeation studies from a nerodilol-based drug reservoir shows flux of 194.9 ± 4.6 μg/cm²·h. 10%w/w of PEG6000 (EVA1802-PEG6000-10).

20. **Ramesh Panchagnula et al., [2001]**, The effect of the solvent systems water, ethanol (EtOH), propylene glycol (PG) and their binary combinations was studied on the ex vivo permeation profile of the opioid receptor antagonist, naloxone, through rat skin. The flux of naloxone was found to increase with increasing concentrations of EtOH, upto 66% in water, and PG upto 50% in water.

21. **Amit Kumar Jain et al., [2002]**, this investigation was to study the effect of different terpenes on IMH permeation in EtOH:W (2:1)system. Permeation studies of IMH were carried out with unjacketed Franz diffusion cells through rat skin. The flux of IMH with terpenes was found to be significantly higher than that in control (EtOH:W, 2:1) (P<0.05). It was found that the contribution of diffusivity in enhanced permeation of IMH was much higher in comparison to partitioning of IMH in skin with terpene treatment.

22. **Panigrahi. L et al., [2002]**, studied the pseudo latex transdermal patches incorporation terbutaline sulphate was prepared as an effective mode of therapy for nocturnal asthma using Eudragit RS 100 and RL 100andeudraflex
as a plasticizers.

23. **Jain S. et al., [2003]**, studied the protransfersomes for effective transdermal delivery of Norgestrel preparation and Invivo characterization. They concluded that the protransfersomes formulation for transdermal drug delivery of Norgestrel provides effective contraception. Better stability, higher entrapment efficiency, easy to scale up and better for transdermal delivery as compared to prolipoprotines.

24. **Yasunori Morimoto et al., [2003]**, the preparation of mefenamic acid (MH)-alkanolamine [monoethanolamine, diethanolamine, triethanolamine and propanolamine] complexes was attempted to increase the transdermal flux of MH. The stratum corneum immersed in IPM forms a continuous phase of vehicle and stratum corneum and, from the phase, ethanol transport the MH–alkanolamine complexes to the epidermis and dermis, and the complexes, which are more water soluble than MH, exhibit increased partition into the epidermis and dermis, as the flux increases.

25. **Marc B. Brown et al., [2004]**, The effect of heat on the transdermal delivery of model penetrants of differing lipophilicity through artificial membranes (non-rate limiting) and human epidermis was investigated in vitro. Saturated suspensions of the model penetrants; methyl paraben (MP), butyl paraben (BP) and caffeine (CF) in deionised water (vehicle) were used to attain maximal thermodynamic activity. The amount of penetrant retained in the epidermis was found to be in the order BP > CF > MP whilst the transdermal fluxes increased in the order MP > BP > CF with increasing receptor temperature.

26. **S. Narasimha Murthy et al., [2004]**, Carboxymethyl guar (CMGS), an anionic semi synthetic guar gum derivative was evaluated for its suitability of use in transdermal drug-delivery systems. Terbutaline sulfate (TS) was used as a model drug. The diffusion of terbutaline sulfate from CMGS solution was relatively slower at pH 5 than at pH 10. It is most likely that the interaction between CMGS and terbutaline sulphate at pH 5 is physical, involving static interaction. The ability of such interactions in modifying the
release kinetics of drug from the CMGS transdermal films was studied.

27. **Darshan K. Parikh et al., [2005]**, Feasibility of developing a transdermal drug delivery of fluoxetine has been investigated. Permeation studies of fluoxetine across human cadaver skin were carried out using Franz diffusion cells. The permeation of fluoxetine obtained using a 65% vol/vol ethanolic solution was found to be sufficient to deliver the required dose (20—80 mg) from a patch of feasible size. The results seem promising for developing a transdermal drug delivery system of fluoxetine.

28. **Mounir S. Mesiha et al., [1995]**, the diffusion characteristics of CPM were determined using Franz diffusion cells, from gelled ethanol-water solutions of CPM (5, 10, and 20%). The 0.6 volume fraction of ethanol gave the highest diffusion rate of CPM \( J_{\text{cm}} = 1.591 \text{ mg/cm*h} \). The diffusion and partition coefficient data revealed that changes in ethanol volume fraction of the vehicle and ethylene vinyl acetate (EVA) membrane characteristics directly affect CPM partitioning and diffusion across EVA membranes and EVA-pressure sensitive adhesive (PSA) laminates.

29. **Yasuko Obata et al., [2010]**, In this study, ondansetron hydrogels were prepared, and their skin permeation and pharmacological effects were evaluated in mice. To prepare the hydrogels, a Box–Behnken design was introduced. They performed an in vitro skin permeation study and an in vivo skin irritation study with the test hydrogels. The flux and the total irritation score were selected as response variables. The optimal formulation also delivered the desired pharmacological activity. These results indicated the feasibility of delivering ondansetron transdermally.

30. **H.O. Ammar et al., [2006]**, This study comprised formulation of aspirin in different topical bases. Release studies revealed that hydrocarbon gel allowed highest drug release. In vitro permeation studies revealed high drug permeation from hydrocarbon gel. Combination of propylene glycol and alcohol showed maximum enhancing effect and, hence, was selected for biological investigation. The results demonstrated the feasibility of successfully influencing platelet function and revealed that the drug
therapeutic efficacy in transdermal delivery system is dose independent. Biological performance was re-assessed after storage and the results revealed stability and persistent therapeutic efficacy.

31. J.C. Olivier et al., [2003], the aim of this work was to compare in vitro the performances at delivering nicotine of two transdermal delivery system (TDS). Nicorette (8.3 mg/10 cm2 nicotine content) and Nicopatch (17.5 mg/10 cm2). Release profiles were obtained using the FDA paddle method, and skin permeation profiles using Franz-type diffusion cells. Reducing the trimmed TDS surface area led not only to a reduction of the cumulative permeated amounts, but also to a reduction of the permeation rates.

32. M.M. Feldstein et al., [1996], For many drugs with various chemical structures, delivery rates from the hydrophilic polyvinyl pyrrolidone (PVP)-polyethylene oxide (PEO) based pressure sensitive adhesive (PSA) matrices of transdermal therapeutic, systems (TTS) are higher compared to the hydrophobic TTS matrices. Delivery of propranolol, glyceryl trinitrate (GTN) and isosorbide dinitrate (ISDN) from the hydrophilic water soluble TTS matrix across human cadaver skin epidermis or skin-imitating poly dimethyl siloxane-polycarbonate block copolymer Carbosil membrane in vitro is characterized by high rate values and zero-order drug delivery kinetics up to the point of 75-85% drug release from their initial contents in matrix.

33. Senshang Lin, et al., [1993], Nicotine transdermal delivery systems (nicotine-TDSs) have provided effective assistance to smokers in smoking cessation with minimal occurrence of withdrawal symptoms. However, substantial skin reactions have been reported with the four nicotine-TDSs marketed recently. To reduce the skin reactions, a new type of nicotine-TDS has been recently developed. In vitro skin permeation studies demonstrated that this nicotine-TDS yields a constant skin permeation profile with a permeation rate of 0.068 (± 0.003) mg/cm2/h across human cadaver skin and 0.059 (± 0.014) mg/cm2/h across hairless rat skin, which are comparable to the steady-state permeation rates attained by HabitrolTM and Nicoderm@ systems.
34. **D. Thacharodi et al., [1996]**, Membrane permeation-controlled transdermal delivery devices for the controlled delivery of nifedipine were developed using collagen (which was extracted from calf fetus skin) and chitosan membranes as rate-controlling membrane. To increase the stability of nifedipine in the systems, alginate gel was used as drug reservoir. Drug release was found to depend on the type of membrane used to control the drug delivery, suggesting that drug delivery is efficiently controlled by the rate-controlling membranes.

35. **Philip J. Lee et al., [2006]**, the effect of various classes of chemical enhancers was investigated for the transdermal delivery of the anesthetic lidocaine across pig and human skin in vitro. The binary system of IPM/n-methyl pyrrolidone (IPM/NMP) improved drug transport. At 2% lidocaine dose, this synergistic enhancement peaked at 25:75 (v/v) IPM:NMP with a steady state flux of 57.6±8.4 g cm⁻² h⁻¹ through human skin. This observed flux corresponds to a four-fold enhancement over a 100% NMP solution and over 25-fold increase over 100% IPM at the same drug concentration (p < 0.001). NMP was also found to co-transport through human skin with lidocaine free base and improve enhancement due to LDA.

36. **Ralph Lipp et al., [2002]**, Transdermal systems (TDS) are a well-known application form for small, moderately lipophilic molecules. The aim of this study was to investigate the possibility of applying a highly lipophilic drug, the antiestrogen AE (log $P_{55.82}$) transdermally by polyacrylate-based matrix TDS. For this purpose, two effects of both drug and enhancer concentration in TDS were investigated: in-vitro release and transdermal permeation of drug and enhancers. Increase in enhancer content resulted in a higher permeation of enhancers, whereas skin pretreatment did not. It was shown that the highly lipophilic antiestrogen can be administered transdermally by pretreating the skin with the fluid permeation enhancer combination propylene glycol–lauric acid (9:1) and then applying a matrix TDS.

37. **Ascensao Farinha et al., [1997]**, In vitro release rates of nicotine from three transdermal systems available in the Portuguese and Spanish markets have
been compared in vitro by methods based on recently proposed USP release tests and assay, and using Franz diffusion cells with membranes of 'full thickness' porcine ear or human breast skin. No significant differences were found between the release profiles obtained by the different release test methods for each device and it may be possible and desirable to further standardize testing recommendations.

38. Michael H. Qvist et al., [2002], In this study, the release of eight commonly known enhancers from eight types of polymer adhesives was evaluated using Franz diffusion cells. It was shown that all the enhancers released completely from the adhesives and followed a square root of time kinetic (Higuchi law). Using a statistical analysis it was shown that the release rate was more dependent on the type of enhancer than on the type of polymers. It was found that the observed release rates were probably due to a high diffusion coefficient of the enhancers rather than due to an inhomogeneous embedment of the enhancers in the adhesives.

39. Samir Mitragotri et al., [2009], Here they reviewed systems employing synergistic mixtures of chemicals that offer superior skin permeation enhancement. These synergistic systems include solvent mixtures, microemulsions, eutectic mixtures, complex self-assembled vesicles and inclusion complexes. Methods for design and discovery of such synergistic systems are also discussed.

40. Zan Jia et al., [2005], the transdermal delivery of piroxicam during the electroporation was buffered due to the higher partition in skin lipids than in aqueous environments, which is called entrapment. Entrapment is the main resistance to transdermal delivery of lipophilic drugs. Two types of surfactants were used to enhance the skin electroporation. Tween 80 (0.2 g/L) and sodium dodecyl sulphate (SDS, 3 mg/mL) improve the solubility and diffusion rate of the drug in the hydrophobic local transport regions and reduce the entrapment of piroxicam in the skin. The transdermal delivery rate of piroxicam is increased 30- to 50-fold. However, the entrapment of
piroxicam in the skin still occurred when Tween 80 was added. The SDS provides higher and more stable transdermal delivery rates of piroxicam than Tween 80, and also reduces the entrapment of piroxicam in the skin.

41. **R.J. Babu, et al., [2005]**, A reservoir-type transdermal delivery system (TDS) of bupranolol (BPL) was designed and evaluated for different formulation variables like gel reservoirs (made with anionic and nonionic polymers), rate controlling membranes and penetration enhancers on the drug release and in vitro skin permeation kinetics of the devices. Keshary–Chien type diffusion cells and pH 7.4 phosphate buffered saline (PBS) were used for drug release studies and excised rat skin was used as a barrier for permeation experiments. Reservoir-type TDS of BPL was developed and penetration enhancers increased the skin permeation of BPL at 4–5 times higher levels than the desired target delivery rate.

42. **Yogeshvar N. Kalia et al., [2001]**, Drugs can be administered either as suspensions or as solutions and the formulation can range in complexity from a gel or an ointment to a multilayer transdermal patch. In this review they described the theoretical principles used to describe transdermal release and we show that relatively simple membrane transport models based on the appropriate solution to Fick’s second law of diffusion can be used to explain drug release kinetics into this complex biological membrane.

43. **Shan Yang Lin et al., [1995]**, Piroxicam did not serve as a simple drug, but acted as an additives by molecularly dispersing in the Eudragit E film. The effect of Piroxicam on the mechanical properties the results demonstrated that the release rate of piroxicam from film Cleary increase with the amount of drug loaded but only slightly enhanced by the increasing the plasticizer concentration.

44. **Adrian C. Williams et al., [1995]**, in this review numerous compounds have been evaluated for penetration enhancing activity, including sulphoxides (such as dimethylsulphoxide, DMSO), Azones (e.g.laurocapram), pyrrolidones (for example 2-pyrrolidone, 2P), alcohols and alkanols (ethanol, or decanol), glycols (for example propylene glycol, PG, a common excipient
in topically applied dosage forms), surfactants (also common in dosage forms) and terpenes. Further potential mechanisms of action, for example with the enhancers acting on desmosomal connections between corneocytes or altering metabolic activity within the skin, or exerting an influence on the thermodynamic activity/solubility of the drug in its vehicle are also feasible, and are also considered.

45. Biswajit Mukherjee et al., [2005], The present study was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of dexamethasone using blends of two different polymeric combinations, povidone (PVP) and ethyl cellulose (EC) and Eudragit with PVP. The formulations of PVP:EC provided slower and more sustained release of drug than the PVP:Eudragit formulations during skin permeation studies and the formulation PVP:EC (1:5) was found to provide the slowest release of drug. Based on the above observations, it can be reasonably concluded that PVP–EC polymers are better suited than PVP–Eudragit polymers for the development of TDDS of dexamethasone