CHAPTER-10

SUMMARY AND CONCLUSION

10.1 Summary of chapter 1:

The strategies used by the pharmaceutical industry for discovery of a potential new drug delivery system have been changed dramatically in recent years. These changes in strategy present new challenges and opportunities for the application of new methodologies in the drug delivery processes. The study of the controlled release of drugs for their extended and safe use has become an important field of research and drug delivery to the systemic circulation through the intact skin is one of the most potential areas of controlled release of drugs. Skin is one of the most readily accessible organs of the human body and large numbers of drugs are successfully administered through the skin from different types of transdermal formulations. Formulations applied on skin can be classified into two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous microvascular network and the other exhibits local effects in the skin. Theoretically, the two most important advantages of transdermal delivery of drugs are (1) reduction of side effects due to optimization of the blood concentration-time profile; and (2) extended duration of activity, which allows greater patient compliance owing to elimination of multiple dosing schedules. The simply designed transdermal patch has undergone a dramatic transformation over the past decade. In its strictest sense, all transdermal systems attempt to create a balance between a number of key factors including size of patch or coverage area, concentration of the drug, duration of therapeutic drug level, and use of an enhancer. The first transdermal systems were simply pieces of plastic dipped into a drug that was dissolved in alcohol. The plastic had an adhesive around the edges. Later on drug in the adhesive type of transdermal patches has been designed which was associated with the advantages of minimum or no skin irritation. Recently patches have come up with an acrylic reservoir that holds the drug. Silicon adhesive is added to create the semisolid suspension of microscopic, concentrated drug cells. Three main factors like physicochemical properties of the penetrant molecule, drug delivery system and physiological and pathological conditions of the skin govern the permeation of any drug through skin. Transdermal permeation of a drug involves mainly three steps like sorption by stratum corneum, penetration of drug through viable epidermis and uptake of the drug by the capillary network in the dermal papillary layer. Different formulation approaches have been made so far like matrix type, reservoir type,

micro-sealed drug delivery device, macromolecular type and poroplastic type to serve a wide range of benefits to the user. Requirements of materials in the preparation of matrix type transdermal patches include polymer matrix or matrices, the drug, permeation enhancers and other excipients like plasticizer, solvent etc. The compact and stressful schedule of today's life is inevitable and often results in high blood pressure level, which is the common disorder covering almost all age group and if not treated effectively, results in a greatly increased probability of coronary thrombosis, strokes and renal failure. Until about 1950, there was no effective treatment, and the development of antihypertensive drugs, which greatly increase life expectancy, has been a major, but largely unsung, therapeutic success story. Wide ranges of antihypertensive drugs are available now for the effective control of hypertension but still many of them are yet to be formulated in to the dosage form of transdermal patch.

10.2 Summary of chapter 2:

Researchers have demonstrated effective formulations of transdermal delivery system of variety of drugs ranged from analgesics to steroidal drugs and hormones to antihypertensive drugs. Several investigations were carried out to assess the reproducibility of the formulated devices and to ensure superior safety profile and desired drug release. Many drugs like dexamethasone, diclofenac sodium, verapamil hydrochloride etc has been enthralled to formulate as transdermal patches. Effect of various polymers on the drug release was also investigated and many polymers like ethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol etc were found to have great potential to control the release of contained drug when incorporated in the formulation in optimum concentration and combination. Extensive studies also has been carried out on the permeation enhancing activity of many compounds like ethanol, polyethylene glycol 400, isopropyl myristate, propylene glycol monolaurate, diethylene glycol monoethyl ether etc and they were found to increase the permeation through the skin for the drugs showing poor permeability.

10.3 Summary of chapter 3:

Hypertension results from increased peripheral vascular smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed

early and is treated properly. β-blockers are proved to be effective in controlling hypertension and are currently recommended as first line drug therapy for hypertension when indicated. Propranolol hydrochloride is a synthetic β-adrenergic receptor blocking agent and plays its role sequentially by decreasing cardiac out put, by inhibiting rennin release by the kidneys and by reducing the tonic sympathetic nerve outflow vasomotor centers in the brain. Propranolol hydrochloride is a white to off-white odorless crystalline powder soluble in water and in alcohol, slightly soluble in chloroform and practically insoluble in ether. The drug has a poor oral bioavailability of 10 to 50 % with a low plasma half life of 3 to 6 hours which suggest controlled release formulation of the drug.

10.4 Summary of chapter 4:

Various polymers like ethyl cellulose, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose and acrycoat S100 has been used to formulate the transdermal patches of propranolol hydrochloride. Ethyl cellulose (EC) has got solubility in a variety of organic solvents and is miscible with various water soluble materials. Acrycoat S100 is a methacrylic acid copolymer type-B and is insoluble in acids and in pure water; soluble in neutral to weakly alkaline medium. Both the polymers (EC and acrycoat S100) were chosen to render hydrophobicity to the transdermal patch formulations. Polyvinyl pyrrolidone (PVP) is a white to slightly creamy-white, hygroscopic powder and is freely soluble in water, in alcohol and in methyl alcohol, slightly soluble in acetone, practically insoluble in ether. Hydroxypropyl methyl cellulose (HPMC) is an odorless, tasteless, white or creamy white fibrous or granular powder and is soluble in cold water, insoluble in ether and chloroform, but soluble in mixture of methylene chloride and methanol. These two polymers (PVP and HPMC) were intended to provide hydrophilicity to the formulated patches. All the polymers were investigated in respect to their ability of controlling the release of containing drug from the formulations.

Other excipient like polyvinyl alcohol is a yellowish white powder or transparent granules and is soluble in water, slightly soluble in dehydrated alcohol; practically insoluble in acetone. Polyvinyl alcohol (PVA) is used in the present study to prepare the impermeable backing membrane on to which the drug-polymer film has been prepared by casting. Dibutyl phthalate used to give plasticity to the patches is a clear, oily, colorless or very slightly yellow

liquid, practically insoluble in water, miscible with alcohol and ether. Casting solution composed of the polymers, drug and plasticizer was prepared by using ethanol as the solvent.

10.5 Summary of chapter 5:

The drug under study propranolol hydrochloride has been confirmed for any possible impurities and interaction with the excipients. Assay of propranolol hydrochloride was carried out potentiometrically and the percent purity was found to be 99.15 (w/v). Standard curves of the drug were prepared by using spectrophotometric method and HPLC method. Drug-polymer interaction study was carried out using FT-IR spectrophotometer and the analysis of peaks confirmed the compatibility of the drug with polymers.

Initial patch formulations were prepared by employing both glass moulds wrapped with aluminium foil and mercury within petridishes as the backing support. Polyvinyl alcohol has been used to form the impermeable backing film on to which the drug-polymer film was formed. Transdermal patches were formulated by framing four combinations of the polymers (EC, PVP, HPMC and acrycoat S100), each of which were contained dibutyl phthalate and the drug.

All the transdermal patch formulations were then subjected to various physical evaluations like physical appearance, thickness, weight variation, folding endurance, percent flatness etc. Transdermal patches of propranolol hydrochloride prepared by using glass moulds wrapped with aluminium foil were found to have better smoothness, flexibility and were easily removed from the moulds in comparison to the patches prepared by using mercury as the substrate. Low standard deviations were found when the results of thickness data, weight variation data and folding endurance data were compared for the patches prepared by using aluminium foil with the patches prepared by using mercury backing. Patches were found to show 100 % flatness where aluminium foil was used, whereas there was few amount of constriction observed for the patches where mercury was used. From the results of various physical evaluations conducted on the formulated transdermal patches it was evidenced that ethyl cellulose containing patches are better than the patches containing acrycoat S 100. So, for designing of final formulation and their *in vitro* and *in vivo* study ethyl

cellulose, polyvinyl pyrrolidone and hydroxypropyl methyl cellulose were selected as polymers to prepare matrix diffusion controlled transdermal patches. Moreover the method in which aluminium foil was used to prepare backing membrane has been found to be more convenient and reproducible than the method where mercury was used as substrate.

10.6 Summary of chapter 6:

Transdermal patches of propranolol hydrochloride were finally prepared by using three polymers (EC, PVP and acrycoat S100) in different combination and different proportion along with the dibutyl phthalate as the plasticizer. Polyvinyl alcohol was homogeneously mixed with warm distilled water and the resulting solution was poured in the moulds wrapped with aluminium foil and the moulds were then dried. Matrix type transdermal patches containing propranolol hydrochloride were prepared using different ratios of ethyl cellulose (EC) with polyvinyl pyrrolidone (PVP) and ethyl cellulose with hydroxypropyl methyl cellulose (HPMC) combination by solvent evaporation technique in the cylindrical glass moulds containing PVA backing membrane. The two polymers in each combination were weighed in requisite ratio and were then dissolved in ethanol. The ratios of the polymers were varied for all the formulations keeping the total weight fixed. Dibutyl phthalate and propranolol hydrochloride were added to the casting solution containing the polymers and a homogeneous dispersion was made. The dispersion was then cast on the prepared PVA backing membrane in each mould. The rate of evaporation was controlled by inverting a funnel over the mould.

10.7 Summary of chapter 7:

All the formulated transdermal patches were then subjected to various physicochemical evaluations like moisture content, moisture uptake, tensile strength, water vapor transmission rate etc. Patches with higher concentrations of hydrophilic polymers (PVP and HPMC) blended with ethyl cellulose were found to show higher amount of moisture content and moisture uptake. Whereas patches with higher concentrations of hydrophobic polymer (EC) blended with PVP and HPMC were found to show lesser amount of moisture content and moisture uptake. Increase in the concentration of PVP and HPMC in the formulations were found to results in decrease of tensile strength. Transdermal patches

composed of higher proportion of ethyl cellulose have showed a lesser affinity towards water, whereas higher proportions of PVP and HPMC in the patches rendered increased affinity towards water. Drug content of the formulated patches of propranolol hydrochloride were found to be more than 99 %. Selective electron microscopy (SEM) examination of the patches at different conditions like blank (without drug), before permeation study, and after permeation study revealed the fact that transdermal patches were smooth, uniform and were having pores indicating the released portions of loaded drug.

10.8 Summary of chapter 8:

Propranolol hydrochloride transdermal patches were studied for their *in vitro* drug release through dialysis membrane. Other than confirming the polymer dissolution criteria, this study was conducted to verify the ability of the drug to be released from the formulation and to check the permeability of the drug through a semi permeable membrane without agglomeration. *In vitro* permeation studies were carried out using modified Keshary-Chien diffusion cell. The dialysis sac was previously soaked for 24 hours in distilled water. The patches were adhered to the barrier membrane (dialysis membrane) and the sac is tied firmly to the donor compartment of the Keshary-Chien diffusion cell, the receptor compartment of which is filled with 100 ml phosphate buffer of pH 7.4. The donor compartment is lowered to the receptor compartment in such a way that the dialysis sac just touches the media of the receptor compartment. The total setup was placed on a thermostatically controlled magnetic stirrer set at 37 ± 1°C and the content of the diffusion cell was stirred using a teflon coated bead at a constant speed (100 rpm). Up to 48 hours samples were withdrawn (1 ml) at predetermined time intervals and replaced with same amount of phosphate buffer of pH 7.4 to maintain the sink condition. After suitable dilution, the samples were analyzed for drug content using UV spectrophotometer at λ_{max} 290 nm against a blank. It was observed that the patches prepared with hydrophilic polymer (PVP and/or HPMC) in a higher concentration, the release of drug was very quick and the patches released more than 98 % of the loaded drug within 15 to 20 hours in case of EC-PVP formulations and 14 to 20 hours in case of EC-HPMC formulations respectively. But the patches containing ethyl cellulose in a gradual increasing order of concentration with minimum concentration of PVP and HPMC have showed a sustained release of the loaded drug over an extended period of 48 hours.

The data obtained from the *in vitro* permeation study of all the transdermal patches were fitted to various kinetic models (Zero order, Higuchi, First order, Korsmeyer-peppas) to determine the kinetics of drug release from the drug-polymer matrix. Higher proportions of hydrophobic polymer blended with minimum concentration of hydrophilic polymer in two combinations (EC:PVP and EC:HPMC) have showed good regression (R^2) values obeying Zero order, which suggests controlled release of the loaded drug. Almost all the formulations exhibited R^2 values close to 1 when data was fitted to Higuchi and Korsmeyer-peppas kinetic model, which suggest diffusion dominated release of the drug. Korsmeyer's exponent (n) values were close to 5, which further confirmed the diffusional drug release from the formulations. It was found that formulations containing maximum concentration of hydrophobic polymer along with minimum concentration of hydrophilic polymer in both the combinations have shown the most extended % cumulative drug release/cm^2 amongst all the formulations.

All the formulations were subjected to *in vitro* skin permeation study using albino rat skin in modified Keshary-Chein diffusion cell taking 100 ml phosphate buffer of pH 7.4 as diffusion media. The data obtained from the *in vitro* permeation study of all the transdermal patches were fitted to the kinetic models (Zero order, Higuchi, First order, Korsmeyer-peppas) as performed in case of *in vitro* diffusion through dialysis membrane to determine the pattern of drug release from the drug-polymer matrix. When data was fitted to different kinetic models, formulations containing EC with PVP and EC with HPMC have showed good R^2 values supporting the findings of permeation study using dialysis membrane. All the formulations have showed the R^2 values in between 0.9532 to 0.9955, when their *in vitro* skin permeation data was fitted to Higuchi kinetic model indicating the diffusion type drug release. When data was fitted to Zero order model, the R^2 values were found to be in between 0.8864 to 0.9037. Which implies drug release pattern was less controlled in comparison to the results observed after *in vitro* permeation study through dialysis membrane. R^2 values obtained after fitting the data to the Korsmeyer-peppas kinetic model for the patches were found to be in between 0.948 to 0.9957, which dictates that the drug release was diffusion controlled. Again Korsmeyer's exponent (n) values were found to be close to 5, which suggest diffusion controlled drug release. It was evident from the % cumulative drug release data after skin

permeation study that the drug release was faster from the patches containing gradually less proportion of EC and higher proportion of PVP and or HPMC. Formulations containing maximum concentrations of hydrophobic polymers along with minimum concentration of hydrophilic polymer in the combinations like EC:PVP and EC:HPMC have shown the most extended % cumulative drug release/cm^2 of 101.47 and 100.28 up to 54 hours and 53 hours respectively, amongst all the formulations.

In vivo drug absorption study was carried out for both the best result showing formulations containing EC:PVP (10:1) and EC:HPMC of the entire lot. When the data was plotted against plasma concentration (ng/ml) versus time after analyzing the samples by HPLC, it was found that up to 24 - 25 hours there was increase in the release of the drug after which it maintained a constant. The concentration of the drug was found to be 14.2793 ng/ml at 24 hours and was extended up to 48 hours giving a concentration of 14.5651 ng/ml of the formulation containing EC and PVP. For formulation containing EC and HPMC, the drug concentration was found to be 13.2982 ng/ml after 24 hours after which there was slight increase in the drug concentration which was found to be 13.4757 ng/ml at 48 hours. Drug concentrations in plasma were increased during the initial hours for both the formulations, after which a steady concentration in plasma has been observed. A distinct trough and peak has been observed when the data was plotted against plasma concentration (ng/ml) versus time for orally administered propranolol hydrochloride and declination in the drug plasma concentration has been observed after every 6 – 7 hours.

10.9 Conclusion:

Propranolol hydrochloride is a β-adrenergic receptor blocking agent and well indicated in hypertension, angina pectoris and in arrhythmia. Poor oral bioavailability and short plasma half-life of propranolol hydrochloride call for alternative route of administration and alternative dosage form of the drug. Formulation of transdermal patches is an attempt made to achieve the release of the drug for extended period of time to reduce the frequency of doses. Different concentrations of polymers in two combinations i.e. ethyl cellulose with polyvinyl pyrrolidone and ethyl cellulose with hydroxypropyl methyl cellulose in the transdermal patches of propranolol hydrochloride were found to impart variable

physicochemical properties to the patches. Higher concentrations of hydrophobic polymer ethyl cellulose blended with minimum concentrations of hydrophilic polymers i.e. polyvinyl pyrrolidone and hydroxypropyl methyl cellulose were found to show better results when evaluated for various physicochemical properties. *In vitro* permeation phenomena of the drug through rat skin were found to support the findings of permeation studies through dialysis membrane and revealed that minimum content of hydrophilic polymer along with higher content of hydrophobic polymer results in extended release of the drug from the formulations. *In vivo* absorption studies of the patches confirmed the steady concentration of the drug in plasma with minimal fluctuation, whereas a distinct trough and peak has been observed in the plasma concentration of the drug after oral administration. Thus propranolol hydrochloride can be delivered effectively through skin from the transdermal patches to maintain a steady concentration in plasma for extended period of time.