Chapter 12

Summary and conclusions

12.1 SUMMARY

Sublingual delivery has received considerable attention during last few years for quick onset of action. The sublingual mucosa is relatively permeable due to the thin membrane and large veins, allows rapid absorption and acceptable bioavailabilites of many drugs, and is a convenient and easily accessible location. Drugs absorbed sublingually enter the bloodstream directly and can start working within moments. The present work has developed two immediate release formulations for sublingual administration for the fast drug action.

This thesis describes the development, characterization and evaluation of fast dissolving film and fast dissolving tablets for sublingual delivery for the rapid onset of drug action. Salbutamol sulphate, ondansetron hydrochloride and lamotrigine were selected as model drugs for the study. Salbutamol sulphate is an antiasthmatic agent. In, asthmatic attack, quick onset of drug action is required. Ondansetron hydrochloride an antiemetic agent. In emesis, quick drug action is required and intake of water is also not acceptable. Lamotrigine is used in epilepsy the conditions which require the rapid drug action.

Chapter 1 gives introduction, objectives and plan of the work done. Chapter 2 reviews the corresponding literatures and chapter 3 describes the profiles for drugs used in the study.

Chapter 4 describes the development of analytical techniques of salbutamol sulphate, ondansetron hydrochloride and lamotrigine for the evaluation of drug content in film and tablets and assessment of drug release characteristics from the films and tablets. The analytical methods developed were subjected to statistical analysis and the relevant parameters were established. The methods were evaluated for the accuracy and precision. The results revealed that the analytical methods were selective, and accurate with high precision. The methods could also estimate the respective drugs in presence of other constituents of film and tables with negligible interference. The simple and sensitive HPLC methods were developed for the estimation of salbutamol sulphate, ondansetron hydrochloride and lamotrigine in rabbit plasma. The analytical parameters calculated from the calibration curve were found to be satisfactory. The proposed HPLC assay for

the determination of salbutamol sulphate is suitable for pharmacokinetic study of it in rabbits. This assay is convenient, simple, precise and accurate and there is no need of utilizing the fluorescence detector. The HPLC method of ondanstron hydrochloride is simple and rapid for the analysis of drug from biological samples as simple extraction procedure is required and can be recommended for routine patient monitoring and for pharmacokinetic studies. The HPLC method of lamotrigine is simple, accurate, precise and rapid for the analysis of drug from biological samples as simple extraction procedure is required. There is no need of utilizing the fluorescence detector and can be recommended for routine patient monitoring and for pharmacokinetic studies.

Chapter 5 reviews the artificial neural network (ANNs) modeling in pharmaceutical research: theory and applications. The ANNs modeling are newly developed strategies and an alternative to conventional modeling techniques. The utility of ANNs in the pharmaceutical field and drug discovery has recently grained enormous popularity due to their ability to model process that can not be modeled by classical methods. The ANNs need no special computer as neural nets are described using mathematical models and implemented using ordinary computer software. Training time for networks is long but the advantages are overwhelming. The ANNs is better than response surface methodology because they allow incorporation of literature and experimental data to solve common problems in pharmaceutical industry. It is capable of solving problems involving complex pattern recognition which is advantageous in pharmaceutical product development. The use of artificial neural network in pharmaceutical research drug discovery is growing at a fast rate.

Chapter 6 describes the in vitro buccal permeation study of all three drugs at different pH conditions (pH 4.0, pH 6.0, pH 6.8, pH 7.4, pH 8.0 and pH9.0) through guinea pig buccal mucosa. The results of the studies revealed that salbutamol sulphate permeated through the buccal mucosa by passive diffusion over the range of concentrations examined. Permeability coefficient and steady state flux of salbutamol sulphate across porcine buccal mucosa increased with increasing pH values. The 1-octanol/buffer partition coefficient of the drug also increased with increasing pH. The permeability coefficient of unionized species was greater than that of ionized species which indicated that the

nonionized species of salbutamol sulphate penetrated well through porcine buccal mucosa and the permeation was a function of pH. The results of this study indicate that the salbutamol sulphate penetrated well through porcine buccal mucosa. This might be due to the paracellular route of permeation. Ondansetron hydrochloride permeated through the buccal mucosa by passive diffusion. Permeability coefficient and steady state flux of ondansetron hydrochloride across porcine buccal mucosa increased with increasing pH values. The 1-octanol/buffer partition coefficient of the drug also increased with increasing pH. The permeability coefficient of uionized species was greater than that of ionized species which indicated that the nonionized species of ondansetron hydrochloride penetrated well through porcine buccal mucosa and the permeation was a function of pH indicating the trancellular route of permeation. Permeability coefficient and steady state flux of lamotrigine across porcine buccal mucosa increased with increasing the pH values. The 1-octanol/buffer partition coefficient of the drug also increased with increasing the pH. The permeability coefficient of unionized species was greater than that of ionized species which indicated that the unionized species of lamotrigine penetrated well through porcine buccal mucosa and the permeation was a function of pH. This indicated that main transport route of buccal permeation of lamotrigine is through transcellular route.

Permeations of all three drugs were highest at pH 9.0 than that of the other pH studied. The permeated amount of each drug increased linearly after 1 hr at each pH value. The flux rate of the each drug increased as the pH value of the donor solution increased, and the total flux at pH 9.0 was approximately 3.5 times higher for salbutamol sulphate, 2.5 times for ondansetron hydrochloride and 2.8 times for lamotrigine than that of it at pH 4.0. The permeability coefficient of each drug increased with increasing the pH value.

Chapter 7 describes the parallel artificial membrane permeability assay (PAMPA) to study the effect of pH on in vitro permeation study of salbutamol sulphate. Propanolol, carbamezapine and timolol were used for validation of the method used for the PAMPA study. The value of the permeability coefficients of salbutamol sulphate at pH 4.0, 7.0 and 9.0 were 1.08×10^{-6}, 1.54×10^{-6} and 2.25×10^{-6} respectively. The values of the permeability coefficients of salbutamol sulphate calculated using the PAMA assay

increased with increasing the pH from 4.0 to 9.0. The results of increase in the permeability values of salbutamol sulphate with increase in pH by the PAMPA assay was further confirmed by the in vitro buccal permeation study using guinea pig buccal mucosa. The permeability coefficient (Pe) of ondansetron hydrochloride in at pH 4.0 was 1.04×10^{-4}. The permeability of ondansetron hydrochloride was less than that of salbutamol sulphate at pH 4.0. This may be due to less solubility of the ondansetron hydrochloride at pH 4.0 than that of salbutamol sulphate.

Chapter 8 describes the development and evaluation of fast dissolving film of all the three drugs. Solvent evaporation method was used for the preparation of the film. The results of the mechanical properties of the film of each drug showed acceptable mechanical characteristics and high % drug release. The scanning electron photomicrographs of the films of each drug at 2000× magnifications showed smooth surface with some little pores and with out any scratches or transverse striations. The prepared films of each drug were clear and colorless. The intact DSC peak of drug in the each physical mixture and each film indicated that the drug did not interact with the excipients used in the preparation of the each film. Dissolution studies of films were carried out using distilled water, simulated saliva (pH 6.8) and simulated gastric fluid (pH 1.2) as absorption of drug from the film is through sublingual mucosa, esophagus and stomach. The dissolution data of films in distilled water were compared with the dissolution data in simulated saliva and simulated gastric fluid using S_d statistics. An S_d values for simulated saliva and for simulated gastric fluid were near to zero for film of each drug which indicated that the release profile of film in distilled water and simulated saliva and simulated gastric fluid are comparable. In simulated gastric fluid, % drug release at 2 minute were 92.11% for salbutamol sulphate film, 89.11% for ondansetron hydrochloride and 92.15% for lamotrigine film which revealed high efficacy of the film for rapid drug release. The results of the stability study showed that there is no any unacceptable change in mechanical properties and % drug release of the film at intermediate and accelerated stability study.

Chapter 9 describes the dissolution enhancement of lamotrigine using solid dispersion technique using beta-cyclodextrin and transcutanol. The DSC, XRD, SEM and in vitro dissolution studies were used to characterize the solid dispersions. DSC study indicated no interaction between lamotrigine and β-cyclodextrin. The solid dispersions produced by coprecipitated method and cogrinding method showed a broad, diffuse pattern indicating that the process of coprecipitation and cogrinding led to a grater amount of amorphous nature. Analysis of SEM revealed that the elongated crystalline forms of lamotrigine and relatively larger elongated crystals of β-CD, clearly visible in the physical mixture were transferred to less crystalline structures in the solid dispersions. These observations provided further evidence of solid solution formation, and are in accordance to the results obtained from DSC and x-ray diffraction studied. The % lamotrigine dissolved from the physical mixture, coprecipitation method and cogrinding method was about 72 %, 91 % and 97 %, respectively. The coprecipitation treated lamotrigine and cogrinding-treated lamotrigine was slightly more soluble in comparison with intact lamotrigine, because the crystallinity of lamotrigine was decreased by coprecipitation and cogrinding treatment. Samples stored at room temperature and at 45 °C showed no changes in dissolution patterns at the end of 6 months.

Chapter 10 describes with the preparation and evaluation of fast dissolving tablets using direct compression method. Microcrystalline cellulose and lactose anhydrous were successfully used as direct compressible diluents. Mannitol was used to enhance palatability of the tablet. Different croscarmellose concentrations showed no significant influence on the tensile strength of tablet. A formulation containing 8.0 % croscarmellose shows an acceptable mechanical strength of 3-5 kg/cm^2 at a compression load of 3.2 kN with an satisfactory disintegration time. The disintegrating time, wetting time and friability of the tablets were satisfactory. The dissolution data of the tablets of all three drugs in distilled water were compared with the dissolution data in simulated saliva using f_2 statistics. An f_2 of above 50 and S_d value near to zero of the tablets of all three drugs indicates that the release profile of tablets in distilled water and simulated saliva are comparable and in a good agreement with each other. The results of the stability study showed that there is no any unacceptable change tensile strength, disintegration time and % drug release of the tablets at intermediate and accelerated study after 6 months.

Chapter 11 describes the pharmacokinetic studies of the fast dissolving film, fast dissolving tablets and conventional tablets of all the three drugs in rabbits. From the different pharmacokinetic parameters of different formulations of all three drugs, it was observed that the time to achieve the peak plasma concentration (T_{max}) was lower (30 min) in case of fast dissolving film and fast dissolving tablet in comparison to the control (2 hr) for all three drugs. Therefore, we can say that there was quicker onset of action in the case of fast dissolving film and fast dissolving tablet. Also, the data show that the peak plasma concentration was almost same for all three formulations of all drugs. The half lives of the fast dissolving film and fast dissolving tablets were less as compared to the control of all three drugs. The area under the Concentratoin v/s Time curve (AUC) for the fast dissolving film and fast dissolving tablets were less as compared to that of control for all drugs. The fast dissolving films and fast dissolving tablets provide a quick onset of action which was confirmed from the dissolution studies and in vivo studies and hence may be beneficial in asthmatic attack (for salbutamol sulphate), emesis (for ondansetron hydrochloride) and epileptic attack (for lamotrigine).

12.2 CONCLUSIONS

Permeability coefficient and steady state flux of all the drugs across porcine buccal mucosa increased with increasing pH values. The PAMPA study showed higher permeability coefficient of salbutamol sulphate at higher pH. The fast dissolving film of each drug obtained by solvent casting method showed acceptable mechanical characteristics and fast percentage drug release. The prepared film of each drug was transparent with smooth surface without any interactions between drug and polymer. Solid dispersions with β-cyclodextrin and transcutanol improved solubility of lamotrigine by cogrinding method. The microcrystalline cellulose, lactose anhydrous, crosscarmellose, mannitol and sodium bicarbonate were used as excipients to prepare fast dissolving tablets in mouth with good taste and sufficient tensile strength. The prepared fast dissolving tablets predicted disintegration time less than 25 seconds and 3-5 kg/cm^2 tensile strength. Sodium bicarbonate was successfully applied to increase the pH of the tablets. The T_{max} values of fast dissolving film and fast dissolving tablets of all three drugs were higher than that of conventional tablets which showed higher bioavailability

and quick onset of action. The proposed fast dissolving film and tablets of salbutamol sulphate can be useful for patient suffering from asthmatic attack while the proposed fast dissolving tablets and films of ondansetron hydrochloride can be useful for patient suffering from post operative or chemotherapy induced sever nausea and vomiting. The proposed both fast dissolving tablets and fast dissolving film of lamotrigine can be useful for patient suffering from epileptic attack. Considering their added advantage of being administered without water, these developed fast dissolving formulations do have promise as New Drug Delivery Systems for improved patient compliance and disease control.