9. Summary, conclusion and recommendation

9.1 Summary and conclusion

The research work highlights the development and evaluation of novel transbuccal drug delivery system selective H2 receptor antagonist of Famotidine. Drugs administered through the buccal route have a rapid onset of action and lead to improved bioavailability of drugs. The buccal route can bypass the first-pass metabolism, contact of the drugs with the gastrointestinal fluids and paves way for easy access to the membrane sites so that the delivery system can be applied, localized and removed easily. Furthermore, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity. The resulting of low bioavailability and short biological half life of Famotidine following oral administration favors development of sustained release formulation. The present investigation of research deals by using of Famotidine and formulated a potential dosage forms for buccal drug delivery system as buccal films and buccoadhesive tablets in order to improve the bioavailability, minimize the dose, localization of drug to oral cavity for prolonged period of time and avoid pre-systemic elimination of the drug. The experimental part consisted of pre-formulation studies, formulation and characterization of buccal film and formulation and evaluation of buccoadhesive tablets.

Pre-formulation is an investigation of physicochemical properties of drug substance, individually and in combination with
excipients. Drug-polymer compatibility studies by physical observation, FTIR and DSC studies revealed that there is no significant interaction between the drug-polymer hence the selected raw materials very much suitable for the formulation of buccal films and buccal tablets of Famotidine. Linearity of the curve was observed in the calibration curve which shows that the selected wavelength 272 nm is ideal for the Famotidine.

The Famotidine buccal mucoadhesive films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers such as HPMC, Carbopol-P934 (CP) and PVP. Ethanol (70 % v/v) is used as the solvents. Propylene glycol serves as the plasticizer as well as penetration enhancer. Triethanolamine was used to neutralize the carbopol polymeric solution. The prepared Famotidine buccal films were characterized based upon their physicochemical characteristics like weight, thickness, folding endurance, surface pH, PMA, PML, swelling percentage, water vapor transmission and drug content. The combination of HPMC and Carbopol shows good adhesion. Upon addition of PVP the bioadhesive strength increases which may be due to hydrogen bond formation and vanderwaals forces. The tensile strength is an important phenomenon to show the flexibility and convenience of the film during administration in the oral cavity. The mechanical strength is the measure of the force applied for the film for elongation until it breaks. The SEM photographs revealed that the
surface topography, morphology, texture and uniform distribution of drug and polymer.

The Novel mucoadhesive buccal tablets of Famotidine were prepared by the method of direct compression by using 9 mm flat punch, 9-station rotary machine. The prepared tablets having two layers, first layer contains pure drug with the mucoadhesive polymers such as Sodium Alginate, HPMC, SCMC, Eudragit RL100 and PVP. Second layer contains Ethyl cellulose; it acts as a backing layer to prevent release of drug into saliva of buccal cavity.

The drug and polymer used for the buccal tablets were characterized for their micromeritic properties. The powder material is characterized for bulk density, tapped density, Hausner’s ratio, Angle of repose and Carr’s index. The formulations were characterized based on their physicochemical parameters such as thickness, weight variation, hardness, friability, drug content and surface pH. The results obtained for the parameters are satisfactory in all the formulations of buccal tablets.

The observed surface pH of the formulations was found to be there is no significant difference of surface pH in all the formulations and the pH range lies within the range of salivary pH i.e. 6.5 to 6.8, hence do not cause irritation and achieve patient compliance. The swelling behavior of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the
degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration. The observed results of content uniformity indicated that the drug was uniformly dispersed in formulations and with minimum intra batch variability. Carbopol and sodium alginate being an anionic polymer gives the highest bioadhesive force. The bioadhesive strength exhibited by Famotidine buccal films and buccal tablets was satisfactory for maintaining them in oral cavity.

Distinguishable difference was observed in the release of Famotidine in all formulations of buccal films and tablets. The in-vitro drug release and Higuchi’s plot have shown that the drug release followed zero order kinetics, which was known from the regression value ($r$). Histomorphological analysis were confirmed that there is no change cell morphology and tissue organization of sheep buccal mucosa. The basic pharmacokinetic parameters such as peak plasma concentration, time to reach maximum plasma concentration and total area under the plasma concentration-time curve ($\text{AUC}_{0-t}$) were measured by using plasma concentration-time profiles. The in-vivo kinetics was shows in the extent of bioavailability and in the rate of absorption. The optimized formulations (F12 and T5) were stable in human saliva and at accelerated conditions with level of significance $P>0.05$. Good correlation was observed between in-vitro and ex-vivo, in-vitro and in-vivo profile revealed the ability of the formulation to
reproduce the *in-vitro* release pattern through the biological membrane.

The mucoadhesive hydrogels of Famotidine were prepared by physical cross linking orifice ionic gelation process with varying proportions of polymers like HPMC-K100, SCMC and carbopol in combination with sodium alginate. The 2% Cacl\(_2\) solution served for the purpose of cross linking. The all prepared formulation of mucoadhesive hydrogels of Famotidine were dried at room temperature and the dried beads were evaluated for its micromeritic properties which includes angle of repose, bulk density, tapped density, Carr’s Index and Hausner’s ratio. The swelling behavior of the polymer was reported to be crucial for its mucoadhesive character. Hence the polymers were shown enough mucoadhesive character to provide the controlled release of Famotidine towards the mucosal membrane. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration. The formulation H13 shows the maximum swelling at the end of 6 h than the other formulation which is due to more concentration of HPMC with addition of carbopol and excess hydration of polymer. The water uptake of polymers is playing very significant role for swelling and drug release. The drug release followed by diffusion mechanism by the creation of pore in the hydrogel beads only after absorbing the body fluids. The water uptake of polymer mainly depends on the
hydrophilic nature. The formulation H13 shows maximum uptake due to high proportions of HPMC. Distinguishable difference was observed in the release of Famotidine in all formulations. The \textit{in-vitro} drug release and Higuchi’s plot have shown that the drug release followed zero order kinetics, which was known from the regression value (r).

Sodium alginate is present in an ionized state, and as a result, the polymeric network gets loosened comparatively, attributing for the higher drug release. The drug release mainly depends upon the degree of swelling, water uptake based on hydrophilic nature of the polymer, percentage of mucoadhesion. Data of \textit{in-vitro} release were fit into different equations and kinetic models. The formulation H13 was selected and the stability studies were carried out at accelerated condition of 40±2 °C, 75±5% RH conditions, stored in desiccators, the hydrogels were packed in muslin cloth which is covered by aluminium foil and kept for period of three months. The hydrogel beads were analyzed periodically for their morphology, swelling ratio, water uptake, drug content, \textit{in-vitro} mucoadhesion and \textit{in-vitro} drug release. Results were analyzed by One-way ANOVA followed by Tukey’s test. Differences were considered statistically significant at p<0.05. Hence Famotidine oral mucoadhesive buccal films, buccal tablets and mucoadhesive hydrogels could be suitable for oral controlled drug delivery.
**Highlights of the thesis**

- The investigation describes the formulations of buccal film, buccoadhesive tablets and mucoadhesive hydrogels of Famotidine by solvent casting technique, direct compression method and orifice ionic gelation process respectively. Famotidine, a novel drug of choice for the above formulations.
- Formulation of mucoadhesive hydrogels of Famotidine by orifice ionotropic gelation process is the novel approach.
- All the prepared formulations were showing good and satisfactory results in all the evaluation parameters.
- Good correlation has been achieved between *in-vitro* and *in-vivo*, *ex-vivo* and *in-vivo* from the best formulations.
- Stability studies reveal that the formulations were stable over the period.
- Amongst all the prepared formulations buccal film F12, buccoadhesive tablets T5 and mucoadhesive hydrogels H13 were considered as best formulations from the obtained results.
- Famotidine buccal films, buccoadhesive tablets and mucoadhesive hydrogels could be promising one as they, increase bioavailability, minimize the dose, reduce the side effects and improve patient compliance.
- Famotidine might be a right and suitable candidate for oral controlled drug delivery via buccal film, buccal tablets and hydrogels.
9.2 Recommendation

The oral cavity and its highly permeable mucosal tissues have been taken advantage for decades as a site of absorption for delivery of drugs to the systemic circulation. So the formulations which targeting the oral cavity through buccal mucosa is an considerable interest to improve the bioavailability and reduce the frequency of administration of APIs so it is very important phenomenon to develop the cost effective formulation to fulfill the needs of patients. However we made an attempt by the novel selection of drug Famotidine for development of buccoadhesive formulations like buccal films and buccal tablets, mucoadhesive hydrogels gave a very good result in all the aspects. Amongst all the formulation F12, T5 and H13 was the best one. Hence the same composition of polymers might be used for the bulk development after the clinical trials.