CHAPTER 4

SUMMARY AND CONCLUSION

To present succinctly, it can be stated that the present investigation was carried out to develop a more effective non-invasive dosage form with maximum bioavailability that bypasses the hepatic first pass metabolism by delivering the drug unidirectionally towards buccal mucosa. An additional investigation is the exploration of some mucoadhesive polymers from natural edible sources. The dosage form developed is expected to have better patient acceptability due to its unique ability of masking bitter taste. Biodegradability and biocompatibility are the additional meritorious advantages of these dosage forms.

Diltiazem, the drug in the present investigation is widely used in the chronic treatment of angina pectoris, to control the blood pressure and cardiac arrhythmias. Since unstable angina occurs mostly at a time when a person is at rest or nocturnally, the pain accompanying it is severe and the situation is very dangerous at that time because the patient cannot get any ready assistance. Diltiazem is completely absorbed in gastrointestinal tract but exhibits very low oral bioavailability due to extensive first pass metabolism in the liver by the enzyme CYP3A of cytochrome P450 enzyme group. Though parenteral administration can overcome this limitation, its small biological half-life necessitates its repeated administration making it the least accepted by the patients for chronic usage.

The various approaches through transepithelial routes for bypassing the extensive hepatic first pass metabolism suffers from some serious drawbacks such as slow onset of action, non unidirectional release, histological damage of buccal mucosa, non-masking of bitterness or lack of retentivity at the applied site. The main objective of present work is to develop retentive sustained release buccal Diltiazem tablets that avoid hepatic first pass metabolism and mask the bitterness using mucoadhesive agents from natural edible sources.

Natural mucoadhesive agents were isolated from the natural edible sources by cold/hot aqueous extraction followed by organic solvent precipitation. The methods used were found to give satisfactory yield and are reproducible. The physical properties of the substances such as pH, swelling, moisture sorption capacity, loss on drying etc

mucoadhesiveness of aqueous solutions of natural polymers were evaluated by shear stress method and Park and Robinson method and compared with the commercially used GRAS (Generally Regarded As Safe) category polymers HPMC, CP, sodium alginate and guar gum. From these findings, it was evident that the natural mucoadhesive agents possess good handling properties and comparable bioadhesive strengths.

The Novel Buccal Adhesive Tablets were formulated and compressed by three-stage process using specially fabricated punches and dies. Sucrose as sweetener and vanillin as flavor were used to improve the palatability of the dosage form. Adhesive cups were formulated by wet granulation method and the flow properties of the granules such as bulk and tap densities, angle of repose, Hauser indices, compressibility indices etc were determined and found to be satisfactory. The mucoadhesive strengths susch as tensile, shear and peel strengths were measured by using specially fabricated apparatus using bovine and porcine buccal mucosa as model substrates to assess the actual bioadhesive strengths at variable textural states. *In vitro* residence time was measured by using modified disintegration apparatus. From all the results, the best possible combination possessing better characteristics were selected for the preparation of NBATs. Core tablets were prepared at varying proportions of drug to the polymer by direct compression technique. Finally NBATs were compressed after inserting suitable cores into cups manually.

The NBATs were evaluated for their physical properties like hardness, weight variation, content uniformity, friability and thickness and the results were found to be within the pharmacopoeial standards. Acceptability studies on human volunteers using placebo tablets suggest these dosage forms are small, palatable and convenient for usage and were retained at the site of application during the period of study. Infrared analysis and Differential Scanning Colorimetry showed that the Diltiazem has not undergone any unacceptable interactions with the mucoadhesive agents in tablet formulations.

In- vitro release studies showed that the tablet formulations containing natural mucoadhesive agent exhibited sustained release kinetics. Further, the amount of drug that leached through the backing layer was also found to be very minimal. *Ex-vivo* permeation studies

through the porcine buccal mucosa also exhibited similar release profile. It was found that the release is delayed as the amount of polymer is increased in the core tablets. *In vivo* studies on the anaesthetized New Zealand rabbits showed good absorption profiles with reduced excretion rates.

In the light of the above consideration, it can be concluded that

1. All the materials isolated from natural sources were found to possess good physical characteristics that are essential for utilization as a mucoadhesive agent for drug delivery.
2. The pH of the mucoadhesive substances was nearer to buccal pH suggesting non-irritability to mucosa.
3. The moderate swellability of these substances suggests their suitability as mucoadhesive agent without damaging the structural integrity of the dosage form.
4. The prepared granules for compression of adhesive cups possess good flow properties.
5. The adhesive cups exhibited comparable tensile, shear and peel strengths with the synthetic polymers.
6. *In vitro* residence times of the optimized cups were comparable with those of the commercially used polymers.
7. Human volunteers have expressed their acceptability and suitability without noticeable discomfort.
8. No remarkable amount of drug was leached through the backing layer suggesting the unidirectional release and taste masking ability of the mucoadhesive agent used.
9. FTIR and DSC studies indicated no remarkable interaction between the drug and the mucoadhesive substances isolated from natural edible sources.
10. *In-vitro* dissolution and *ex-vivo* permeation studies suggests the sustained release characteristics of the dosage forms.
11. *In-vi*vo studies on rabbits exhibited excellent pharmacokinetic patterns with two-fold increase in bioavailability compared to the oral route.
12. The Novel Buccal Adhesive Tablets developed in this investigation using biodegradable mucoadhesive substances isolated from natural edible sources will certainly be a promising option for noninvasive delivery of drugs.

In spite of the above-mentioned superior qualities of the prepared dosage forms, preparation of tablets in a three-stage process is time consuming and may not be industrially acceptable at this point. However, this problem may be solved in future by the automation of the process.