Chapter- 7

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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 nasal 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.

Carvedilol, the drug in the present investigation is widely used in the chronic treatment of congestive heart failure and to control the blood pressure. Carvedilol's $\beta_1$, $\beta_2$ and $\alpha_1$ receptor blocking character minimize the heart rate, myocardial contractility and myocardial oxygen demand. The antihypertensive property of carvedilol is influenced by a reduce in peripheral vascular resistance. Carvedilol is completely absorbed in gastrointestinal tract but exhibits very low oral bioavailability due to extensive first pass metabolism in the liver. As parenteral administration is not suitable for carvedilol, nasal route is the only alternative route to achieve rapid onset of action.

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-biodegradable, histological damage of 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 nasal gel that avoid hepatic first pass metabolism and better permeation 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 were evaluated. The 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, SCMC, sodium alginate and guar gum. From these findings, it was evident that the natural mucoadhesive agents possess good handling properties and comparable bioadhesive strengths.

Nasal gels were prepared by dissolving mucoadhesive material and pluronic F127 in nasal solution pH 6.4, finally Carvedilol was incorporated and kept at 4°C over night in a refrigerator to ensure complete swelling. The gelation temperature was determined by visual inspection method and by viscometric method and found it was near to the nasal temperature. The peel strengths of formulations were
measured by using Ultra teat using goat nasal mucosa as model substrates to assess the actual bioadhesive strength.

Acceptability studies on human volunteers using placebo nasal gels suggest these dosage forms are easy and convenient for administration and were retained at the site of application during the period of study. Infrared analysis and Differential Scanning Colorimetry showed that the Carvedilol has not undergone any unacceptable interactions with the mucoadhesive agents in gel formulations.

*Ex vivo* release studies through the goat nasal mucosa showed that the gel formulations containing natural as well as synthetic mucoadhesive agents exhibited sustained release kinetics. *In vivo* studies on the anaesthetized New Zealand albino rabbits showed good absorption profiles with reduced excretion rates.

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

1. All the mucoadhesive materials isolated from natural sources such as whole leaves of *aloe vera*, yellow mustard seeds, fresh leaves of China rose, kenaf, Madras thorn and Okra 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 nasal 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 isolated mucoadhesive materials possess good handling properties.

5. The isolated mucoadhesive materials possess comparable tensile, shear and peel strengths with the synthetic polymers.

6. Human volunteers have expressed their acceptability and suitability without noticeable discomfort.

7. FTIR and DSC studies indicated no remarkable interaction between the drug and the mucoadhesive substances isolated from natural edible sources.

8. From the histological studies, it was evident that the gels formulated have not cause any damage to the applied mucosa.

9. Ex vivo permeation studies suggest the sustained release characteristics of the dosage forms.

10. In vivo studies on albino rabbits exhibited excellent pharmacokinetic patterns with three-fold increase in bioavailability compared to the oral route.

11. The thermoreversible nasal gels formulated in this investigation using biodegradable mucoadhesive substances isolated from natural edible sources will certainly be a promising option for noninvasive delivery of drugs.

Since all mucoadhesive agents, used in formulations, were isolated from natural edible materials that are biodegradable and bio-
compatible. All natural substances exhibited comparable handling and mucoadhesive properties in comparison with Sodium CMC and HPMCK4M. The formulated natural mucoadhesive nasal gels investigated were easy to formulate, economical and abundantly available all over the world. These formulations may certainly an alternative way of administration for maintenance of chronic hypertension with wide patient acceptance.

With the present investigation, it is possible to extend the same technology for the drugs that are instable in the gastric environment, high hepatic first pass effect, low bioavailability and/or with short biological half lives can safely be administered in the form of thermorevesible mucoadhesive nasal gel formulations as these are patient friendly, economical, self administerable and possess rapid onset of action and prolonged duration of stay. Many more natural substances can also be evaluated for such properties to develop formulations for all transmucosal routes of administration.