ABSTRACT

Pharmaceutical dosage form development is the combination of an art as well as a science with the sole objective to produce a dosage form that is efficacious, patient friendly, stable, economical and delivers the drug as close as possible to the intended target with minimal adverse effects. Conventional forms of drug administration, in many cases, have been supplanted by the advent of novel drug delivery systems. The pharmaceutical companies are presently seeking innovative dosage forms by way of novel drug delivery systems as they represent strategic tool for expanding markets and indications, extending product life cycles and generating newer opportunities. NDDS is a reality and is illustrated by the fact that around 13% of the current global pharmaceutical market is accounted for NDDS. Among the NDDS, transmucosal drug delivery market recorded second highest growth in the last five years with 171% where as overall market growth stands at 106%.

Transmucosal delivery systems exhibit a faster delivery than do transdermal delivery systems. Also, delivery occurs in a tissue that is more permeable than skin and is less variable between patients, resulting in minimal inter subject variability. In addition, these systems could potentially be used to deliver drugs that exhibit poor and variable bioavailability due to significant hepatic first-pass metabolism. The absorptive mucosae include nasal, sublingual, palatal, gingival, nasal, pulmonary, rectal, vaginal and ocular routes.
Nasal region offers added advantages in being highly vascular that has the ability to deliver even to the blood brain barrier. It also promotes rapid bioavailability, with subsequent almost immediate onset of pharmacological effect, whereby the drug enters the systemic circulation directly, bypassing the gastrointestinal tract and the first pass effect in the liver. In order to achieve optimal noninvasive delivery through nasal route the properties of the active compound and other properties of the formulation have to be considered. Moreover the dosage form must be able to be retained in the nasal cavity during the duration of therapy. The presence of mucus layer provides a unique opportunity for prolonged drug delivery via the development of mucoadhesive dosage forms. Mucoadhesive nasal gels have been a debatable subject for development of drug delivery technology to achieve desired dosage form.

Previous works concentrated on synthetic mucoadhesive materials may not be biocompatible and biodegradable. Efforts have been made by recent researches to establish the application of natural mucoadhesive materials from edible vegetables, fruits and seeds to increase contact period with the nasal mucosa for proper release of the drug from the formulation. These materials possess a challenge to synthetic materials because of the extended contact time, edibility and biocompatibility. This investigative work was intended to establish the application of natural mucoadhesive agents from edible sources to overcome allergic and physiological interactions in the long term drug
delivery. The present research envisages development and evaluation of mucoadhesive nasal drug delivery using CARVEDILOL as model drug.

Carvedilol (C_{24}H_{26}N_{2}O_{4}), the β-adrenergic blocking agent with α1-blocking activity is indicated in the treatment of mild to moderate congestive heart failure (CHF) and is used for treating high blood pressure. Carvedilol can reduce the risk of a second heart attack by 40% and increase survival among patients with congestive heart failure. For high blood pressure and congestive heart failure, the dose may range from 3.25mg twice daily to a maximum of 25mg twice daily. Poor oral bioavailability (25-35%), low molecular weight (406.5 g/mol), low dose (3.25 mg), lipophilic log PC value (3.967) with the elimination half-life of 7 to 10 hours makes it suitable for nasal delivery.

The main objective of the present work was focused to develop a thermoreversible mucoadhesive nasal gel of carvedilol using extracts of various natural sources as mucoadhesive agents. All the natural mucoadhesive agents were isolated, physical characteristics and mucoadhesive properties were evaluated. Infrared analysis and DSC Thermographs showed that the nasal gel formulation has no serious interactions between the carvedilol and mucoadhesive agents.

The formulations were evaluated for exact bioadhesive strengths on excised goat nasal mucosa. Human acceptability studies and
histopathological studies revealed the suitability and wide acceptance. *Ex vivo* permeation studies showed that nasal formulations containing carvedilol and various mucoadhesive agents released >90% of drug within 4 hours. *In vivo* studies were performed for the best formulations and compared with the formulation containing Sodium CMC and HPMCK$_4$M polymers as mucoadhesive agents.

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 HPMCK$_4$M. 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 for wide patient acceptance.

Finally the *in-vivo* release profiles of prepared nasal formulations of gels were compared with that of same dose of oral solution. The increased pharmacokinetic datas of $C_{max}$, $T_{max}$, $AUC_{0-t}$ etc as compared to oral solution indicates prolonged drug release over a time and improved bioavailability. Good correlations was observed between *in-vivo* and *ex-vivo* drug release.