

CHAPTER I

INTRODUCTION

The systemic administration of drugs has been approached by various dosage forms and by various routes. The nasal mucosa is considered to be a potential route for systemic administration of drugs. Nasal administration is easy, protects the drug from hepatic first pass metabolism, meets patient compliance, provides a large surface area with a well developed vascular bed for drug absorption and can be used for sustained and controlled drug delivery. The nasal route also eliminates intersubject variation normally associated with the oral route (Hussain, 1980). Moreover, nasally administered drugs such as propranolol, alprenolol and metaprenolol have shown blood levels comparable to those by intravenous administration (Hussain, 1979 and Duchateau, 1986).

Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur and effectively rules out sustained nasal drug administration. However, mucoadhesive preparations have been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities thus enhancing drug absorption (Vidgren, 1991 and Ugwoke, 2000).

Mucoadhesion has been investigated by Nagai et al (Nagai, 1984), reporting an increased intranasal absorption of insulin when mixed with microcrystalline cellulose powder and greater enhancement was achieved when freeze dried insulin was mixed with carbopol 934P powder. In the past mucoadhesive starch microspheres (Bjork, 1990) and dextran microspheres (Edman, 1992) increased their bioavailability after intranasal delivery. Propranolol HCl has been administered by magnetic human serum albumin (Vyas, 1991) and by glutaraldehyde treated erythrocyte microspheres (Vyas, 1993) for delivering into nasal route. These microspheres could prolong the release of drug to 24 h, possess good mucoadhesive properties and maintain constant plasma levels of drug for 10 h. Recently, hydrophilic polymer such

as hydroxypropyl methylcellulose , chitosan , carbopol and polyvinyl alcohol were used as adhesive polymers for producing mucoadhesive microspheres by solvent evaporation technique.

The mucoadhesive polymers provide a relatively adhesion between the drug delivery system and mucus and/or the epithelial cell surface. They have the advantage of not being absorbed and therefore would not be expected to display systemic toxicity. Utilising mucoadhesive polymers in the form of microspheres provides protection to the incorporated drugs from enzymes and due to their sustained drug release, may also result in desirable blood concentration profiles. Furthermore, microspheres have a well controlled particle size distribution which ensures safe deposition in the nasal cavity. It is easy to deliver microspheres in nasal route whereas the nasal formulation in form of viscosity gels is disadvantageous due to the inconvenience of delivering high viscosity gels with ease and consistency.

Spray drying technique has been widely used in the pharmaceutical technological field to dry materials sensible to heat , to improve the drug solubility or the flowability of particular excipients , and several other applications. This technique has received considerable interest as a preparation method of microparticles to obtain a controlled delivery system. The method may offer , in comparison with other techniques , the advantage of realizing for producing microparticles in one step. Moreover, Spray – dryer is considered in the final powder yield of the process and is taken into account a possible industrial application of the method. In comparison between spray – drying technique and traditional techniques (emulsification solvent evaporation , emulsification solvent extraction) , spray drying technique always gives excellent results in the preparation of biodegradable polylactide (PLA) and of poly (DL – lactide – co – glycolide) (PLGA) (Bodmeier, 1988 and Schwach, 2003). The deposition of microparticles in nasal cavity is governed by the individuals nasal resistance to airflow and by particle size diameter. Particles less than 1 μm will escape to the lungs, whereas particles larger than 10 μm will deposit in

the nasal mucus membrane and microparticles larger than 200 μm in diameter will not retain in the nose after nasal administration (Yeo, 1992 and Illum, 1987).

In many previous works for permeation study of drug by nasal delivery, the excised nasal tissues from many animal models such as rabbit, bovine, ovine and canine were used in these studies (Deurloo, 1989; Hermens, 1990; Hagan, 1990 and Christiane, 1997). Disadvantages of such whole animal models are attributed to the differences in anatomy of the nasal cavity compared to the human nose, the large number of animals needed, the large quantities of drugs required and the difficulty in interpreting results influenced by unknown factors within the animal. For this reason the development of an in-vitro cell culture model system for airway epithelial cells is interested for using in permeation study. Airway cells were mainly obtained from hamster trachea , human bronchus or human nose.

The aim of the present study is to design suitable mucoadhesive microspheres formulations that enable adhesion with nasal mucosa and sustain the release of drug from microspheres. Mucoadhesive microspheres are prepared from single polymer and from combined polymer. HPMC , chitosan and carbopol are used as mucoadhesive polymers that represent to non – ionic , cationic and anionic hydrophillic polymers. The microsphere system is prepared by spray – drying technique to obtain a suitable size for nasal delivery and is also investigated the in vitro characterization. The in vitro nasal cell culture model (human nasal cell line, RPMI 2650) is used in permeation study of propranolol HCl.

Objective of this study

On the basis of the rationale mentioned above, the objectives of this research are, therefore,

1. to investigate the optimal conditions of spray drying technique in preparation of mucoadhesive microspheres from anionic, cationic and non-ionic hydrophilic polymers with a suitable size for nasal delivery and to study the factors affecting their preparation process.

2. to examine some physical and physico-chemical properties of these mucoadhesive microspheres.

3. to study the in-vitro mucoadhesive properties of the prepared microspheres.

4. to study the effect of type and amount of different polymers on the release of drug from microspheres and also investigate the model and mechanism of drug release from these microspheres.

5. to study the permeation of drug released from mucoadhesive microspheres formulations by using nasal cell culture model.