1. Introduction and Objectives

1.1 Introduction

The term ‘bioadhesion’ is defined as the attachment of a synthetic or natural macromolecule to a biological tissue for an extended period of time. The biological tissue can be epithelial tissue, or it can be the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as ‘mucoadhesion’ [Fig. 1.1] [1-3].

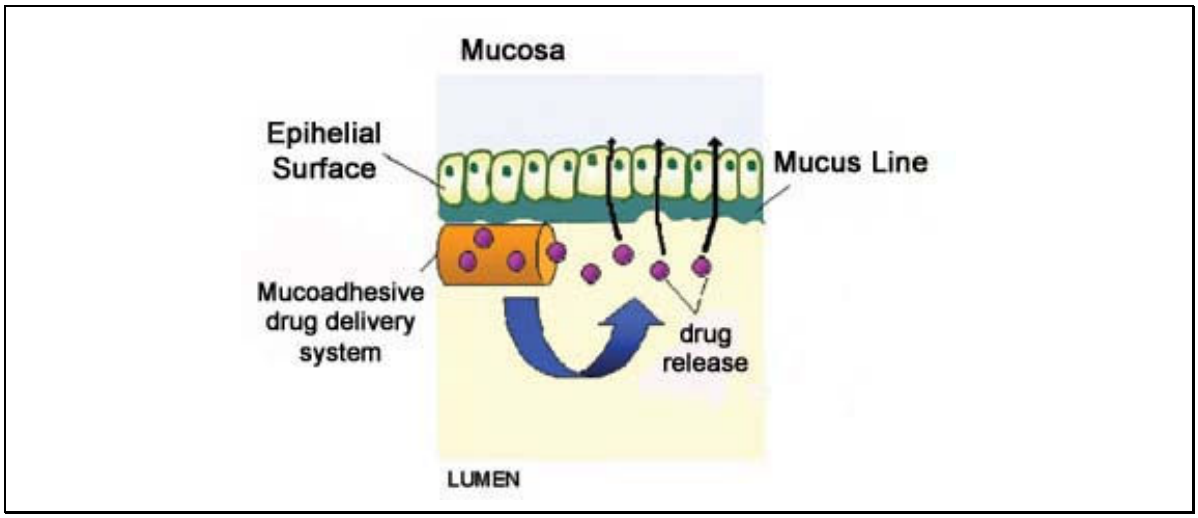

Fig. 1.1: Schematic of Mucoadhesion

Because the bioadhesive dosage forms are very useful for drug delivery, they have been widely applied to various administration routes: not only per oral, for example, nasal, transdermal, rectal, vaginal, ocular routes [1-5, 18-20, 245-248, 252, 259]. In rececent years, many bioactive peptides have been produced due to developments in biotechnology. In most cases such peptide drugs are administered only by an injectable route, since most of them are poorly absorbable across the mucosa and are highly proteolytically degradable. Considering the quality of life of the patients, however, the oral route is more convenient and desirable for peptide drugs. Therefore, the oral bioadhesive dosage forms have been especially intensively studied [5, 21-25].

Among the oral bioadhesive dosage forms, multiparticulates such as pellets are favored due to their advantages. Multiparticulates have small size, which is responsible for their easy dispersibility within the intestine with highly inter- and intra-reproducible gastrointestinal transit rate. They also cover a larger surface of the mucosa and develop stronger mucoadhesive bindings than single unit dosage forms instead of tablets because of the greater predictability and reproducibility of their therapeutic effect [4, 5].

There are several different methods to produce pellets, such as extrusion-spheronization, using a high-shear mixer, etc. Among those methods, the fluid-bed granulation offers particularly more

advantages than other multi-step granulations. Mixing of dry powders, granulating and drying can be successively carried out within a single piece of equipment. Therefore, it can shorten the manufacturing time effectively [6, 7].

Many synthetic or natural polymers are used for the purpose of bioadhesion. Carbomer 934P is a polyacrylic acid polymer which has a wide variety of applications in controlled drug delivery systems. It has been also extensively employed in the formulation development of oral mucoadhesive controlled drug delivery systems [8-10, 238, 239]. However, the use of polyacrylic acid for pelletization has a number of technological problems due to their tendency to gel.

1.2 Objectives

The aim of this study was to produce mucoadhesive pellets containing carbomer 934P by the fluid-bed granulation.
There are several studies for the production of granules containing carbomer by the extrusion-spheronization method [11-13]. However, there was no publication yet by the fluid-bed rotor granulation. This study could be useful to elucidate the feasibility of the fluid-bed granulation for the production of carbomer 934P-containing pellets.
Because carbomer 934P shows serious problems regarding formulation processes owing to its swelling and gelling properties in water, the reduction of tack is necessary for a successful formulation. According to previous reports [14-17], electrolytes were added to the wet masses, such as sodium chloride or calcium chloride as an anti-tack agent. This procedure proved successful at eliminating tack for the preparation of the beads containing up to 40% carbopol® 974 by extrusion-spheronization. The authors proved that the addition of electrolytes led to a decrease in the bioadhesion properties and the consistency of the used polymers. The efficiency of calcium chloride for reducing the tackiness of wetted Carbopol® 974P results from its ability to decrease the interactions between carboxylate groups on adjacent polymer molecules, which leads to a loss of viscosity. As a positive consequence, the manufacture of pellets is facilitated and the yield of production is increased. As a negative consequence, the bioadhesive properties are considerably decreased. From the results above, it could be an interesting issue to produce mucoadhesive pellets containing carbomer without a tacking problem during in the granulation process.

In this study, two methods were investigated as a way to produce carbomer 934P-containing granules:

1. Direct granulation using a fluid-bed granulator;
2. Powder-layering technique in fluid-bed equipment.

Firstly, for the direct fluid-bed granulation, two types of additives- electrolytes and excipients- were incorporated to overcome the tacking problem. As another additive, various excipients were examined. Secondly, dry-coating technique was employed as a method to load carbomer onto the core pellets. The core pellets were prepared firstly, and carbomer 934P was layered onto this core pellets by dry-coating process. It was expected that the dry-coating technique could be a method to produce carbomer 934P-containing granules, since this process is carried out without any liquid-binder.

Through this study, the feasibility of fluid-bed techniques could be intensively investigated. Furthermore, the behavior of carbomer 934P will be elucidated with various additives. The results of this study could provide the useful information for a successful formulation using carbomer 934P.