6. Summary

The aim of this study was to produce mucoadhesive pellets containing carbomer 934P by the fluid-bed granulation.
Carbomer 934P is a polyacrylic acid polymer which has a wide variety of applications in controlled drug delivery systems. However, its use for pelletization has a number of technological problems due to its tendency to gel. Therefore, the reduction of tack is necessary for the successful formulation. According to previous reports [14-17], the additives were used such as electrolytes, to suppress the tack in the granulation process. As a positive consequence of those additives, the manufacture of pellets was facilitated and the yield of production was increased. However, there was also a negative consequence, such as a considerable decrease of bioadhesive properties. Therefore, it was an interesting issue if the pellets containing carbomer 934P could be produced without tacking. Furthermore, it was investigated if the produced pellets could still have the mucoadhesive availability.

Two methods were examined as a way to produce carbomer 934P-containing mucoadhesive pellets:

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

Two types of additives were investigated to overcome the tacking problem. Firstly, based on ‘salting-out effect’, some electrolytes were examined as an anti-tack agent. As another additive, various excipients were investigated because they could prevent the tack as a different mechanism with electrolytes.

Three kinds of salts (sodium citrate, disodium sulfate, and calcium chloride) were investigated.
Sodium citrate facilitated the gel-forming of carbomer, thus it could not prevent the tack. On the contrary, it was possible to produce carbomer 934P-containing pellets with the help of disodium sulfate and calcium chloride. It was considered that their salting-out effects reduced the gel-formation of carbomer 934P. The yield and the pellet properties were affected by the salt concentration. When high concentration of electrolytes was incorporated, more spherical and uniform pellets were produced. However, an excessive addition of electrolytes could result in the production of the brittle pellets. Therefore, the type and concentration of electrolyte should be optimized to obtain an acceptable quality of pellets.

As well as electrolytes, several excipients were also investigated. Carbomer 934P-containing wet masses were prepared with various other excipients (microcrystalline cellulose, lactose, tri-calcium phosphate, cross-linked PVP, and talc) and their cohesiveness and adhesion were measured.

The result revealed that the cohesiveness and adhesion were remarkably affected by the kind and proportion of these excipients. Microcrystalline cellulose improved the plasticity of wet mass. Tri-calcium phosphate was particularly effective for reducing tack. On the other hand, lactose caused a very sticky surface because of its high water-solubility. Cross-linked PVP and talc made wet mass less adhesive, but their effects were not considerable. Therefore, microcrystalline cellulose and tri-calcium phosphate were used as the additives in the fluid-bed granulation.

As proved by chelate titration method, it was considered that this anti-tack action of tri-calcium phosphate is not because of a chemical interaction between carbomer 934P and Ca ions, but because of some physical action of tri-calcium phosphate. This hypothesis was supported by the results of investigations using other excipients. Other substances having similar properties with tri-calcium phosphate, such as a high water uptake ability and water insolubility, also made the granulation processes possible.

Three important process variables- the rotor rotation speed, the spray rate of binder, and the spheronization time- were selected and their influences were investigated. It was shown that the se parameters are the key variables determining the properties of produced pellets. The rotor rotation speed affected significantly positively the yield of 500-1180μm fraction, the sphericity, the mean diameter, and the hardness of pellets. When the spray rate of binder was increased, the mean diameter of pellets and % oversized were considerably increased. The spheronization time showed a significant positive effect on the sphericity. From these results, it could be indicated that it is very important to clarify and optimize the process variables for a successful granulation.

The dry-coating technique was employed as another way to produce carbomer 934P-containing pellets. Carbomer 934P powder was layered onto the core pellets by the dry-coating process.
The following problems were indicated making difficult the powder layering using carbomer 934P. Firstly, carbomer 934P is a very cohesive powder showing poor flow properties. This effect caused very ununiform feeding of powder in the process with fluctuations. Furthermore, carbomer powder could not be evenly spread out onto the core pellets. Secondly, although a very small amount of binding-liquid was introduced, carbomer powder formed a gel easily on the pellet surface. Therefore, the investigation was essential to modify the characteristics of powder before the dry-coating process.

Two characteristics of the powder were investigated: the flow property and water uptake potential.
The effects of several excipients (talc, tri-calcium phosphate, starch and magnesium stearate) were investigated on the flow rate and the angle of repose. And the enslin number was determined as an indicator to evaluate the water uptake ability. The excipients showing a good flow property and the high water uptake ability could be the excipients of choice. The results revealed that talc and tri-calcium phosphate were highly effective.

The decreased yield, rough surface of pellets were obtained by the dry-coating technique. In addition, the process parameters affected significantly on the yield, powder layering efficiency, and the surface properties of produced pellets. Therefore, it is extremely important to optimize and evaluate these variables.

As the last step, the mucoadhesion and the drug release profile were investigated using the produced pellets. The results of mucoadhesion test using a rat intestine showed a parallel pattern with the adhesion measured without mucus membrane. Therefore, the preliminary test using the texture analyzer (EZ-test, Shimadzu, Japan) could be a useful tool for the prediction of mucoadhesion.
The pellets containing carbomer 934P showed the slower release of theophylline than the pellets produced without carbomer 934P. The incorporation of strong electrolytes, for example disodium sulfate and calcium chloride, caused an excessive inhibition of the gel-formation of carbomer 934P. That led to no remarkable delay of theophylline release. This result supposed that the reducing tack of carbomer should be optimized in order to maintain the essential mucoadhesive ability. Carbomer 934P-layered pellets showed the different drug release profiles according to their coating levels. The uncoated pellets and the pellets with the low coating level (below 3 mg/cm^2) showed no considerable sustained-release. However, the slight delay was shown at higher coating level (above 3 mg/cm^2).

In summary, from this study it could be concluded:

- Carbomer 934P-containing pellets were successfully prepared by the fluid-bed granulation with the help of anti-tack action of electrolytes and excipients.

- The anti-tack action of these additives were elucidated that: electrolytes reduced the viscosity of carbomer gel through the ‘salting-out effect’. Certain excipients, such as tri-calcium phosphate, suppressed the tack by the physical action caused by its high water uptake ability.

- Carbomer 934P-layered pellets could be produced by the dry-coating technique.

- The influence of critical process variables were investigated affecting the properties of produced pellets.

- The investigation using a texture analyzer could be very useful for the prediction of mucoadhesion.