Development and Formulation of Carbomer 934P-containing

Mucoadhesive pellets by Fluid-bed Techniques

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ABBREVIATIONS INDEX

AR	Aspect Ratio
AOR	Angle of repose
Cl-PVP	Cross-linked Polyvinyl pyrrolidone
CP	Carbomer 934P
Fig.	Figure
GI-Tract	Gastro-Intestinal-Tract
GMP	Good manufacturing Practice
HPMC	Hydroxypropylmethylcellulose
MCC	Microcrystalline Cellulose
Mw	Molecular weight
PEG	Polyethylen glycol
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
Tab.	Table
ρ	Density
η	Dynamic viscosity

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].
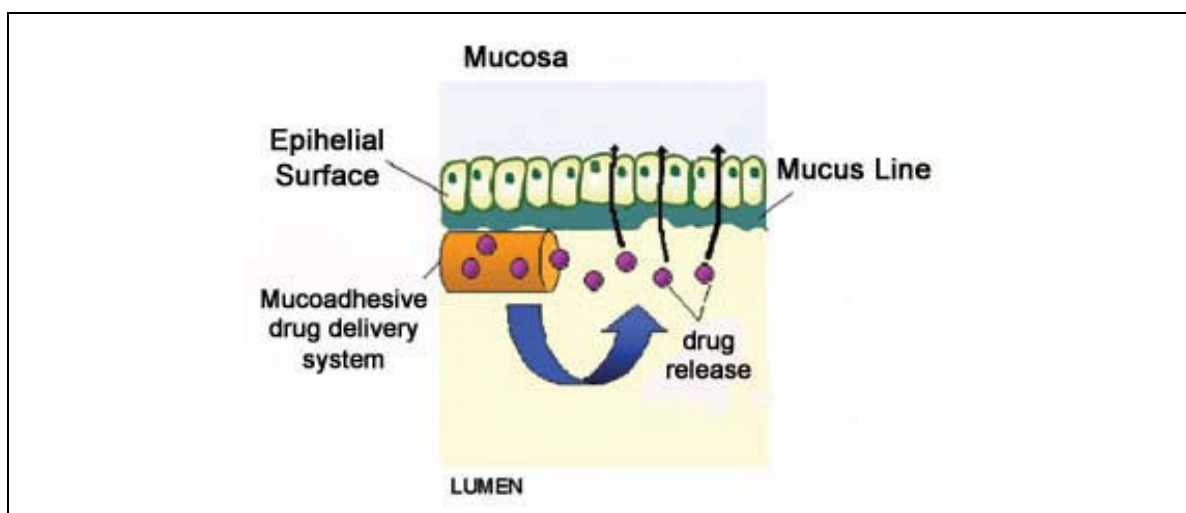
Fig. 1.1: Schematic of Mucoadhesion

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.

2. Theoretical overview

2.1 Basics of bioadhesion

2.1.1 Advantages and applications of bioadhesive dosage forms

Bioadhesive drug delivery has been applied as a desirable system to various administration routes. In particular, the study has been intensively carried out for the development of better oral bioadhesive dosage forms [5, 21-25]. The advantages of the bioadhesives in oral drug delivery can be summarized [1-5]:

> a) can prolong GI transit time and improving oral drug absorption should ideally be nontoxic, non-absorbable from the GI tract,
>
> b) preferably form a strong non-covalent bond with mucin-epithelial cell surfaces
>
> c) adhere quickly to moist tissue
>
> d) allow easy incorporation of drug and offer no hindrance to its release
>
> e) possess specific sites of attachment
>
> f) and be economical

Several dosage forms for oral use have been reported as follows [4]:

a) Tablets
Multilayered tablet allows a variety of geometrical arrangement.
Such systems that consist of acrylic polymers or cellulose provide immediate and high adhesion strength at a certain site for a prolonged period of time.

b) Micro- and/or Nanoparticles
Despite the limited loading capacity of drug, bioadhesive micro- and/or nanoparticles have been widely investigated for three major features:

- immobilization of particles on the mucosal surface by adhesion after modification of surface properties via bioadhesive polymers,
- very large specific surface between the dosage form and the oral mucosa, and
- sustained release of entrapped drug, leading to higher absorption.

c) Capsules
Capsules, usually gelatin capsules containing a suspension or liquid, include bioadhesive polymers such as polycarbophil or carbopol. Gelatin interacts with the bioadhesive polymer during or

following dissolution, and thus bioadhesiveness of the polymer is lost before the bioadhesive polymer has a chance to interact with the mucus layer.

2.1.2 Bioadhesive polymers

Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. For the purpose of bioadhesion they have been also in pharmaceutical industries extensively used and investigated. Bioadhesive polymers can be grouped into synthetic and natural polymers. Most of the current synthetic bioadhesive polymers are [5, 26]:

a) <u>Polyacrylic acid-based polymers</u> :
carbopol, polycarbophil, polyacrylic acid, (PAAc), polyacrylate, poly(methylvinylether-co-methacrylate), poly(methacrylate), poly(acrylcyanoacrylate), poly(isohexylcyanoacrylate), and poly(isobutylcyanocrylate), etc.

b) <u>Cellulose derivatives</u> :
Carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, and methylhydroxyethyl cellulse, etc.

c) <u>Semi-natural polymers</u> :
chitosan,, various gums such as guar, xanthan, gellan, carrageenan, pectin, and alginate

Choice of a particular polymer type will depend on a number of formulation issues as well as patent status. Some properties and characteristics of bioadhesive polymers used commonly are described in table 2.1.

Tab. 2.1: Some Bioadhesive Polymers and their Properties [4]

Bioadhesives	Properties[a]	Characteristics
Carbopol/carbomer	• Mw $1 \times 10^6 \sim 4 \times 10^6$ • pH 2.5~3.0 • ϕ water, alcohol, glycerin • η 29,400~39,400 Pa s at 25°C (0.5% aq.soln.)	• synthesized by cross-linker of allyl sucrose or allyl pentaerythritol • excellent thickening, emulsifying, suspending, gelling agent • common component in bioadhesive dosage forms
Sodium carboxymethyl cellulose	• Mw $9 \times 10^4 \sim 7 \times 10^5$ • η 1200 Pa s (1.0%aq.soln.) • pH 6.5~8.5 • ϕ water	• sodium salt of a polycarboxymethyl ether of cellulose • emulsifying, gelling, binding agent good bioadhesive strength

Hydroxymethylcellulose	• pH 6~8.5 • ρ 0.6 g/ml	• suspending or viscosity increasing agent • binder, film former, thickener
Alginate	• pH 7.2 • η 20-400 Pa s (1% aq.soln.)	• stabilizer in emulsion, suspending agent, tablet disintegrant, tablet binder

(^{a} η: dynamic viscosity; ρ: density; Mw: molecular weight; pH measured at 1.0%-aqueous solution(aq.soln.); φ: soluble solvent)

2.2 Theory of granule formation

2.2.1 Methods of granulation

The principal methods of granulating pharmaceuticals may be classified into three main categories: wet processes, dry processes, and other processes [Tab.2.2].

Tab. 2.2: Processes used for pharmaceutical granulation [6]

General process	Specific methodology
Wet processes	• Wet massing • Fluid bed granulation • Spray drying • Pan granulation • Extrusion and spheronization
Dry processes	• Roller compaction • Slugging
Other processes	• Humidification • Prilling • Melt pelletization

Although some or all these methods are used in the pharmaceutical industry, wet granulation has been, and continues to be the most widely used agglomeration process. Typically, the wet massing of pharmaceutical powders is carried out in high-shear mixers before wet screening, and often, the moist granules are dried in fluidized-bed granulators in which the liquid phase is sprayed onto fluidized powders as the hot airflow simultaneously dries the granules.

2.2.2 Fluid-bed granulation

2.2.2.1 System description

Fig.2.1 and 2.2 show the fluid bed granulator and its components used in this study (GPCG 1, Glatt GmbH, Germany).
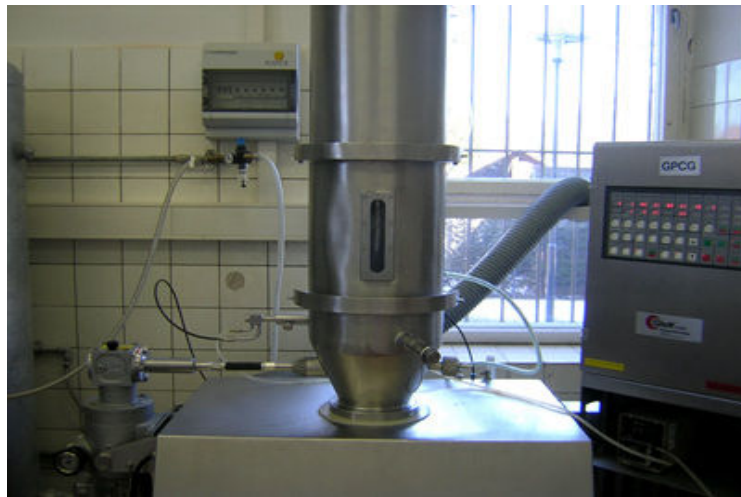
Fig. 2.1: Fluid-bed granulator (GPCG 1, Glatt, Germany)

A fluid bed processor is a system of unit operations involving the heating of process air, directing it through the material to be processed, and then have the same air (usually laden with moisture) exit the unit void of the product.

Fig. 2.2a: Product container

Fig. 2.2b: Control panel of parameters

Two types of disc are used in container [Fig. 2.2a]- hatched and smooth type. The hatched one is employed for granulation process from the powdery starting material, and the smooth type is used

in the coating procedure of core granules. At the downstream end of the fluid bed processor, an exhaust blower or fan is situated to draw the air through the entire unit. This arrangement provides negative pressure in the fluid bed, which is necessary to facilitate material loading, maintain safe operation, prevent material escape, and carry out the process under good manufacturing practices (GMP). Mixing of dry powders, granulating and drying can be successively carried out within a single piece of equipment. Reduction in the manufacturing process steps results in overall shortening of manufacturing time. Fluid bed granulation and drying also reduces handling of raw materials, and hence, reduces operator exposure to irritating and/or toxic compounds. The theory and techniques of fluidization have been known for many years and have been described extensively in the literatures. Fluidized bed technique has been used in pharmaceutical industry for drying, coating, and recently granulating. Wurster (1959) first described granulation in the fluid bed [6, 7].

2.2.2.2 Variables in the fluid-bed granulation process

Granulation is a dynamic process affected by many variables. To produce a desirable product, these variables are understood and properly controlled. Factors affecting the fluid bed granulation process can be divided into three categories [6, 7, 130, 131].

1. Formulation-related variables
2. Equipment-related variables
3. Process-related variables

● **Formulation-related variables**

a) Properties of primary Materials

Ideally, the particle properties desired in the starting material include, a low particle density, a narrow particle size range, a particle shape that approaches spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing. Properties such as cohesiveness, static charge, particle size distribution, crystalline or amorphous nature, and wettability are some of the properties that impact on the properties of the granules formed. The cohesiveness and static charges on particles present fluidization difficult.

b) Binder

Different binders have different binding properties and the concentration of individual binder may have to be changed to obtain similar binding of primary particles. Thus, the type of binder, the binder content in the formulation, and the concentration of the binder have major influence on the granule properties. These properties include friability, flow, bulk, density, porosity, and size distribution.

c) <u>Binder Solvent</u>

The selection of solvent, such as aqueous or organic, depends on the solubility of the binder and the compatibility of product being granulated. Generally, organic solvents, because of their rapid evaporation from process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization. The requirement of solvent for the binder can be eliminated by incorporating binder, or a mixture of binders, of low melting point and incorporating it with the drug substance in the dry form. The temperature of the incoming air is sufficient to melt the binder and form the granules [6, 7, 130, 131].

- **Equipment-related variables**

a) <u>Design</u>

The availability of the fluid bed processors from different suppliers of the equipment is essentially similar. But the differences in design of different suppliers sometime provide difficulty in scaling-up from the laboratory units in a linear scale.

b) <u>Air Distributor Plate</u>

Air distributor plates provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air distributor plates that have 3-40% open area are normally available. A plate that having a small open area to give large enough pressure drop may provide uniform fluidization of such a product without reaching entraining velocity. To overcome this deficiency, an overlap gill plate has recently been introduced.

c) <u>Pressure Drop</u>

The airflow through the fluid bed processor is created by the blower or a fan located downstream from the process chamber. Blower size is determined by calculating the pressure drop (ΔP) created by all the components of the fluid bed-processing system. Proper selection of a blower is essential in fluid bed design. A blower with an appropriate ΔP will fluidize the process material adequately. However, a blower without enough ΔP will not allow proper fluidization of the product, resulting in longer process time and important granulation. A properly sized blower or fan should develop a ΔP sufficient for the exhaust damper to be used in the 30-60% position.

d) <u>Shaker and Blow-Back Cycle Mechanism</u>

To retain entrained particles of a process material, process filters are used. To keep these filters from building up layers of fine process material, causing a high-pressure drop and, thus, improper fluidization, these filters are cleaned during the granulation process. When bag filters are used, mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation of airflow and thus the fluidization during the filter-cleaning process. To avoid process interruptions, a multi-shaking filter bag arrangement is desired, so that the granulation process is

continuous. The continuous process is also achieved by use of bag filters with a blow-back or use of stainless steel filter bags in which air under pressure is pulsed through the filters. Generally, filters should be frequently during the granulation step, to incorporate the fines in the granulation.

e) Other equipment factors

Granulator bowl geometry is considered to be a factor that may impact on the agglomeration process. Generally, a conical shape of the container and expansion chamber is preferred in which the ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multiprocessor concept, for which a single unit can be used for drying, agglomerating, air suspension coating, or rotor processing, by changing the processing container, whereas the rest of the unit is common [6, 7, 136-139].

- **Process-related variables**

Among all variables, the process variables are considered especially interesting because they could be relative easily controlled by a worker during the process.

Those most important to consider are listed as follows:

- Process inlet air temperature
- Nozzle atomization air pressure and volume
- Fluidization air velocity and volume
- Liquid spray rate
- Nozzle: position and number of spray heads
- Product and exhaust air temperature
- Filter porosity and cleaning frequency
- Bowl capacity

Each process variable should be properly selected and well controlled during granulation process. The significant process parameters and their effect on the granule properties are summarized in Tab.2.3.

Tab. 2.3: Effect of Process Parameters on Granule Properties [7]

Process parameter	Effect
Inlet air temperature	Higher: finer granules
	Lower: larger, stronger granules
Humidity	Increase in humidity: larger granule size, longer drying times

Fluidizing airflow	Proper airflow should fluidize the bed without clogging the filters. Higher airflow will cause attrition and rapid evaporation, generating smaller granules and fines.
Nozzle and nozzle height	A binary nozzle produces finest droplets and is preferred. Optimum nozzle height should cover the bed surface. Too close to the bed: will wet the bed faster, producing larger granules. Too high position: creates finer granules, and increase granulation time.
Atomization air volume & pressure	Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size, and granule size. Higher liquid flow rate will produce larger granules and the reverse will produce smaller granules. At a given pressure, an increase in orifice size will increase droplet size and liquid throughput.
Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity, and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.

2.3 Dry-coating technique

2.3.1 Concept and advantages

Pharmaceutical coating technologies are commonly 'wet process' by spraying of a liquid phase solution of coating materials. But recently, in addition to this liquid-based coating, a new dry powder coating has been introduced. This technique directly attaches polymer particles onto the surface of a solid substrate without organic solvents and large volumes of water [Fig.2.3]. Softening, melting and curing are the principal stages in the film formation during dry powder coating [41, 42].

The advantages of powder dry coating include:

a) a reduction in processing time, due to the absence of large amount of solvents or water;
b) environmental friendliness (no organic solvents, lower energy costs), and
c) applicable also when the material used is unstable in water or in other solvents [41-43].
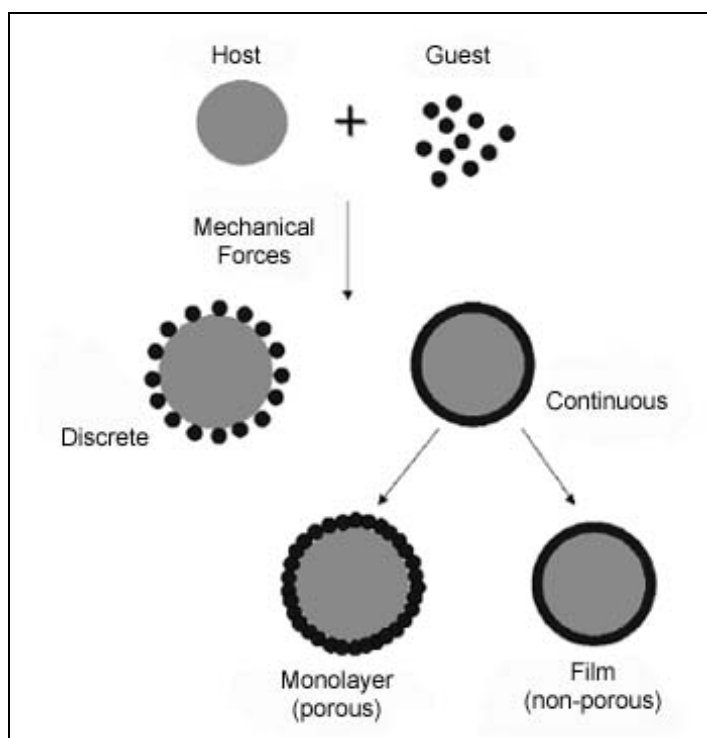
Fig. 2.3: Schematic of dry particle coating [43]

2.3.2 Applications of dry particle coating

In most of the early work reported, the hybridizer was used to produce controlled-release properties. As an example, fines of isoproterenol HCl, 5% by mass, were coated onto potato starch followed by a coating of carnauba wax, 5% by mass, to achieve time-released control of isoproterenol HCl. Furthermore, it has been reported that the hybridizer was useful in preparing composite and encapsulated-coated particles. For instance, if inorganic fine particles were used as coating materials, they were fixed and embedded in the surface of core particles, and if polymer or metallic fine particles were used as coating materials, they partially melted and produced a continuous film coating on the core particle. In pharmaceutical industries dry-coating was introduced as an alternative of conventional liquid-based coating process [41, 42].

2.3.3 Dry-coating by fluid-bed coater

Fluidized bed coater is currently the most widely used equipment for bead coating. Therefore, in this study, the dry coating was examined using a fluidized bed coater. Firstly, the core pellets were prepared and secondly, dry coating technique was employed as a method to layer carbomer powder onto these core pellets. Because this process is carried in dry condition, it was investigated as a way to apply carbomer without the sticking problem commonly occurred in wet processes.

2.3.3.1   System description

The schematic of fluidized bed coater is shown in Fig.2.4.
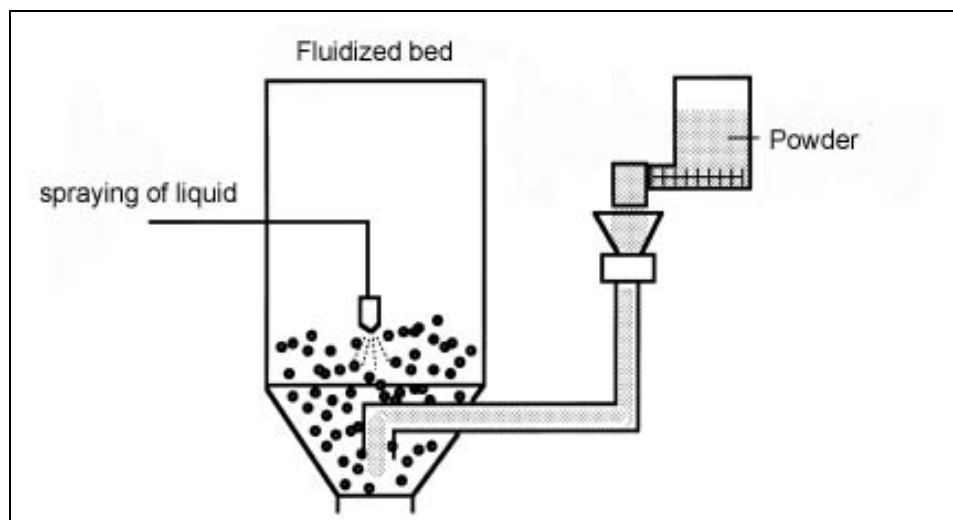
Fig. 2.4: Schematic of dry coating with fluid-bed equipment [42]

The host and guest powder mixture are placed into the rotating bed and is fluidized by the radial flow of gas through the porous wall of the cylindrical distributor, as seen in Fig.2.4, due to the high rotating speeds, very high centrifugal and shear forces are developed within the fluidized gas–powder system leading to the break-up of the agglomerates of the guest particles. Moreover, the very large flow of air needed to fluidize the particles at high rotating speeds and the motion of bubbles when operating the bed above minimum fluidization. That creates strong mixing and hence good coating is achieved [42].

2.3.3.2   Procedures

The powder coating process for solid substrate consisted of three phases: pre-heating, powdering, and curing. In the first phase, the uncoated granules are heated to a selected temperature. During the powdering phase, the polymer powder is transferred into the coating equipment, distributed onto the cores, adhered to the surface of the substrate and a polymeric film coating layer is formed around the granules. Powder adhesion onto the granules is promoted by the partially melted polymer that generated binding forces between particles, and between particles and the granule surfaces. Curing is required as the last step to enhance coalescence of the coating powder particles and the formation of the final film [44, 223].

2.3.3.3 Important process parameters

a) Airflow

A minimum air volume is needed at each gap setting in order to avoid loss of pellets into the plenum below the disk. Excessive air volume may cause loss of active ingredient during powder layering, which occurs when the powder is exhausted from the bed before it adheres to the pellets.

b) Spray rate and powder application rate

Spray rate and powder application rate are considered to be the most critical variables in the process. Adding the powder too slowly leads a wet bed and pellet agglomeration. Adding the powder too quickly results in a dry bed with excessive loss of powder through the exhaust system, powder caking on the walls of the pan, and formation of seedless drug agglomerate of various sizes.

c) Spray atomization

The airless spray system is the most commonly used spray system during drug powder layering in the pan. The main advantage of the airless spray system of the airless spray system over the air-spray system is that it avoids the high air velocity that tends to fluidize the pellets excessively during application.

d) Rotor Speed

Disk rotation speed studies demonstrated that the granules did not tumble and mix at low rotation speed, whereas higher rotation rates resulted in excessive friability of the cores and loss of the coating powder.

e) Inlet and Bed temperature

In powder layering, it is necessary to achieve a state of wetness throughout run. Therefore, for better adhesion and smoother surfaces of pellets, it is ideal to keep the bed temperature at the low range. However, the higher temperatures may also be used when the binder is water [6, 7, 45, 46].

3. Development of Carbomer 934P-containing mucoadhesive pellets through Fluid-bed granulation

3.1 Influence of other excipients on the behavior of carbomer 934P

3.1.1 General

As described in chapter 1, it is hard to granulate carbomer 934P due to its stickiness in water [8, 62]. For this reason, the additives were incorporated into carbomer 934P in order to resolve the tacking problem. Two kinds of substances were proposed as the additives: strong electrolytes and other various excipients. The electrolytes will be investigated in chapter 3.1.2~3.1.3, and other excipients will be focused in chapter 3.1.4 in detail.

Fukumori *et al*. reported that particle agglomeration was reduced by adding sodium chloride to the hydroxypropyl cellulose aqueous coating solution in fine particle coating by the Wurster process, and according to Nakano *et al*., the suppression effect of sodium chloride was due to a reduction in the viscosity of the coating solution caused by salting-out of the polymeric membrane materials [14-17]. Based on that result, in this study also the similar approach was proposed to reduce tack of carbomer 934P. Some strong electrolytes were selected and introduced to prevent the particle agglomeration in the fluidized-bed granulation. Three kinds of salts were investigated (sodium citrate, disodium sulfate, and calcium chloride) as additives for the suppression of particle agglomeration caused by carbomer 934P.

3.1.2 Behavior of carbomer 934P-aqueous dispersion with salts

When strong electrolytes added to polymer aqueous dispersion, the viscosity is decreased and turbidity and precipitation will exist caused by salting-out effect [14, 15]. Thus, in this step, the water for wetting was replaced by an aqueous solution of salts and the viscosity and UV transmittance were measured to elucidate the salting-out effects.

3.1.2.1 Viscosimetrical investigations

2%-aqueous dispersion of carbomer 934P without and/or with sodium citrate, disodium sulfate, and calcium chloride (0.05, 0.08, 0.1, 0.3, 0.5, and 1.0 mol/l) were made and the dynamic viscosity was measured at 20°C using a rotary viscometer at shear rate $100s^{-1}$. The results are shown in figure 3.1.

15
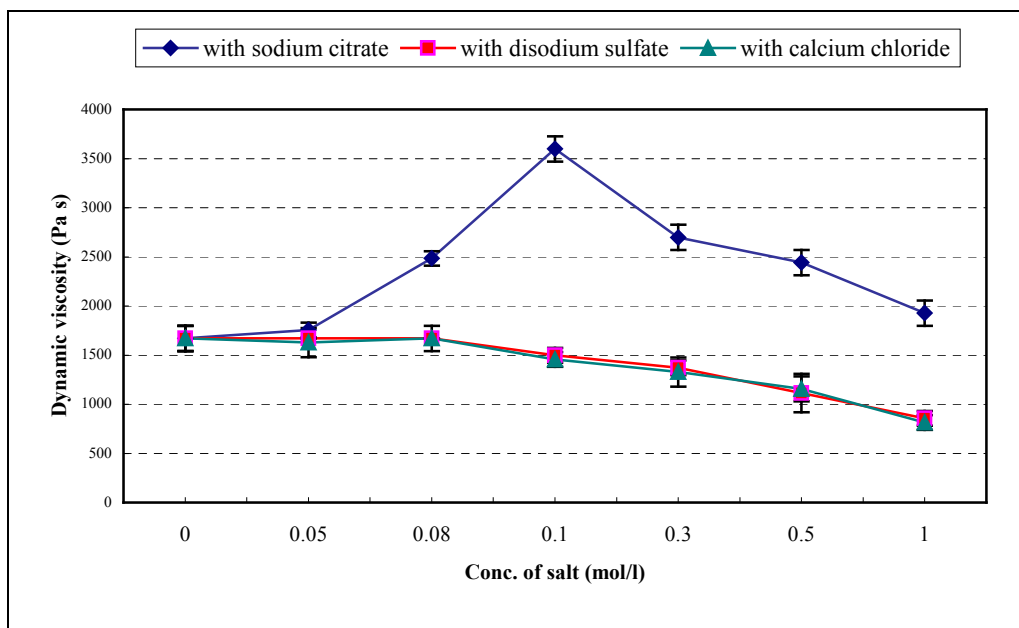
Fig. 3.1: Dynamic viscosity of 2%-carbomer 934P aqueous dispersion with salts

3.1.2.2   Turbidity test

The cloudiness of dispersions was determined by measuring transmittance (800nm) at room temperature against a blank of carbomer 934P dispersion without salts. 2%-aqueous dispersion of carbomer 934P without and/or with sodium citrate, disodium sulfate, and calcium chloride (0.05, 0.08, 0.1, 0.3, 0.5 and 1.0 mol/l) were made and the transmittance was determined at 800nm using a spectrophotometer (Lambda 11, Perkin Elmer).
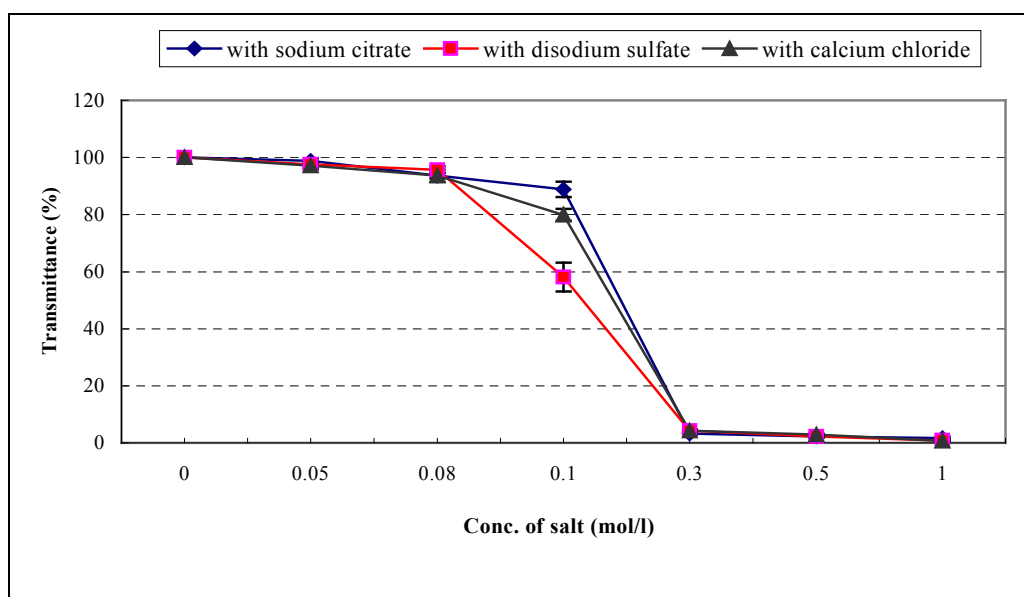
Fig. 3.2: Transmittance of carbomer 934P-aqueous dispersion with salts

As indicated in figure 3.1 and 3.2, in case of disodium sulfate and calcium chloride, when the concentration of salts was lower than 0.1 mol/l, the decrease of dynamic viscosity and cloudiness were hardly observed. However, at higher concentration (above 0.3 mol/l), a remarkable falling of the dynamic viscosity was occurred. The transmittance was also considerably decreased, that is, the turbidity increased. It was considered that the decrease in the transmittance and dynamic viscosity was caused by salting-out effect of increased salts concentration.

On the contrary, the addition of sodium citrate showed the increase of dynamic viscosity. This result can be explained that sodium citrate provided an alkaline environment. It played as a neutralizing agent to carbomer that causes the gel-forming. The viscosity of carbomer dramatically increases at the pH values above 4 and reaches a maximum near pH 9 [54]. This behavior could be attributed by the molecular structure of the gel. In fact, the polymer chains are initially (i.e. at pH 3) coiled into a spiral form, thus affording a relatively low viscosity. As neutralization progresses, the carboxyl groups of the acrylic acid become ionized, leading to an increasing repulsion of negative charges that causes the molecular structure to unwind, thus inducing a gradual rise in the viscosity [56-60]. A pH value of 0.3 mol of sodium citrate solution was about 5, therefore sodium citrate could actually play as a neutralizing agent. Fig. 3.3 illustrates the change of carbomer-gel structure in different pH values.
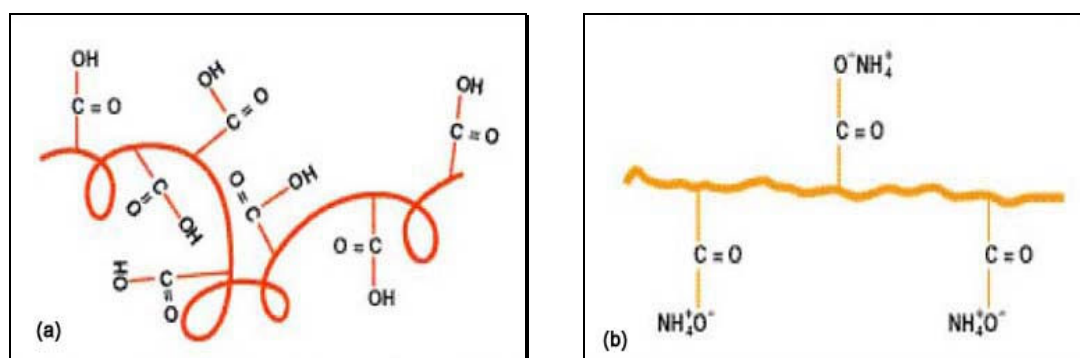
Fig. 3.3: Carbomer resin molecule: unneutrallized (a) and neutralized (b).

3.1.3   Behavior of carbomer 934P / MCC-mixture with salts

3.1.3.1   Investigations of cohesiveness

Rod penetration depth was determined to demonstrate the cohesiveness of the moistened powder mass. The measuring of rod penetration depth can be a useful method for this purpose, since there is a direct relationship between the rod penetration depth and cohesiveness of the wet mass [75, 85, 165]. The cohesive forces during the moist agglomeration processes are mainly due to the liquid bridges between the solid particles. Thus, the addition of liquid to the dry powder provides the cohesive force required for agglomeration, this is reflected by rod penetration depth.

The increased cohesiveness of the powder mass results in a decrease in rod penetration depth.

Cohesiveness = 1 / Penetration depth

30g of powder containing carbomer 934P (20% w/w) and microcrystalline cellulose (80% w/w) was wetted by 30ml of salt-dissolved water in a mortar and kneaded by a pestle. The concentrations of salt-dissolved water were varied as 0.05, 0.08, 0.1, 0.3, 0.5, and 1.0 mol/l. The actual compositions of prepared wet masses after the addition of salt-dissolved water are shown in table 3.1~3.3 in detail. The penetration depth of a conical aluminum rod into the wet mass filled in a glass cup (diameter 70mm, height 50mm) was determined using a penetrometer (Labof, Hungary) [Fig. 3.4].

Fig. 3.4: Measurement of penetration depth by penetrometer

Tab. 3.1: The actual composition of wet mass made with carbomer /MCC/Na citrate-dissolved water

	Conc.of Na citrate (mol/ml)		The actual composition of prepared wet mass (60g)
30g Powder mixture of Carbomer 934P (20%) MCC (80%) + Na citrate-dissolved water (30ml)	0	Kneading in mortar $\rightarrow$	CP (10%) / MCC (40%) / Na citrate (0%) / Water (50%)
	0.05		CP (10%) / MCC (40%) / Na citrate (0.7%) / Water (49.3%)
	0.08		CP (10%) / MCC (40%) / Na citrate (1.2%) / Water (48.8%)
	0.1		CP (10%) / MCC (40%) / Na citrate (1.5%) / Water (48.6%)
	0.3		CP (10%) / MCC (40%) / Na citrate (4.4%) / Water (45.7%)
	0.5		CP (10%) / MCC (40%) / Na citrate (7.3%) / Water (42.8%)
	1.0		CP (10%) / MCC (40%) / Na citrate (14.5%) / Water (35.5%)

Tab. 3.2: The actual composition of wet mass made with carbomer /MCC/ Na_2SO_4 -dissolved water

	Conc.of Na_2SO_4 (mol/ml)	Kneading in mortar $\rightarrow$	Wet mass prepared (60g)
30g Powder mixture of Carbomer 934P (20%) MCC (80%) + Na_2SO_4-dissolved water (30ml)	0		CP (10%) / MCC (40%) / Na_2SO_4 (0%) / Water (50%)
	0.05		CP (10%) / MCC (40%) / Na_2SO_4 (0.4%) / Water (49.6%)
	0.08		CP (10%) / MCC (40%) / Na_2SO_4 (0.6%) / Water (49.4%)
	0.1		CP (10%) / MCC (40%) / Na_2SO_4 (0.7%) / Water (49.3%)
	0.3		CP (10%) / MCC (40%) / Na_2SO_4 (2.1%) / Water (47.9%)
	0.5		CP (10%) / MCC (40%) / Na_2SO_4 (3.6%) / Water (46.4%)
	1.0		CP (10%) / MCC (40%) Na_2SO_4 (7.1%) / Water (42.9%)

Tab. 3.3: The actual composition of wet mass made with Carbomer /MCC/$CaCl_2$-dissolved water

	Conc.of $CaCl_2$ (mol/ml)	Kneading in mortar $\rightarrow$	Wet mass prepared (60g)
30g Powder mixture of Carbomer 934P (20%) MCC (80%) + $CaCl_2$-dissolved water (30ml)	0		CP (10%) / MCC (40%) / $CaCl_2$ (0%) / Water (50%)
	0.05		CP (10%) / MCC (40%) / $CaCl_2$ (0.4%) / Water (49.6%)
	0.08		CP (10%) / MCC (40%) / $CaCl_2$ (0.6%) / Water (49.4%)
	0.1		CP (10%) / MCC (40%) / $CaCl_2$ (0.7%) / Water (49.3%)
	0.3		CP (10%) / MCC (40%) / $CaCl_2$ (2.2%) / Water (47.8%)
	0.5		CP (10%) / MCC (40%) / $CaCl_2$ (3.7%) / Water (46.3%)
	1.0		CP (10%) / MCC (40%) / $CaCl_2$ (7.4%) / Water (42.6%)

(CP: carbomer 934P, MCC: microcrystalline cellulose)

Fig. 3.5: Penetration depth of wet mass made with carbomer 934P/microcrystalline cellulose/salt-dissolved water (the concrete compositions of each wet mass are shown in table 3.1~3.3) (CP: carbomer 934P, MCC: microcrystalline cellulose) (Mean±S.D., n=5)

As indicated in Fig.3.5, when disodium sulfate and calcium chloride were added, the penetration depth of wet mass was increased, that is, the wet mass became less cohesive. It was considered that the salting-out effect by electrolytes led to a decrease in viscosity of carbomer 934P. This resulted in the decrease in cohesiveness of wet mass, reflected by the increase in the penetration depth. This effect was not remarkable at low concentration (below 0.08 mol/l). However, at high concentrations above 0.1 mol/l, the penetration depth was increased considerably. The addition of sodium citrate caused a contradictory result: the stickier, more cohesive wet mass was prepared. The penetration depth was therefore decreased. It was assumed that the viscosity of carbomer 934P was increased due to the action of sodium citrate as a neutralizing agent. Thus the salting-out effect was shielded by this phenomenon.

3.1.3.2 Investigations of adhesion

As well as the cohesiveness, the adhesion of wet mass is also an important characteristic for granulation. Not all wet powder masses can be granulated, in particular, there appears to be an optimal cohesiveness and adhesion for the formation of satisfactory spheres in the spheronization stage. It is suggested that the pastes must neither have too high adhesion nor be too low adhesive [77, 88]. The objective of current step is to investigate these parameters and to find a correlation with the further processing, such as granulation.

The adhesion of wet mass was determined using a texture analyzer (EZ-test, Shimadzu, Japan) [165] [Fig. 3.6]. Wet mass was filled in a metal cup (height 7mm, diameter 20.2mm), and the upper stamp (diameter 10.4mm) was driven in the wet mass at depth 5mm. When this upper stamp was pulled upwards at speed 1mm/min., the software (Win ASG Lite for Windows 95) showed the maximal force required to detach the upper stamp from wet mass (F_{max}) as the adhesive force (N). Because this value is for the contact area 2.37cm^2 between the upper stamp and wet mass, the adhesive force per area (N/cm^2) was calculated and expressed as 'adhesion'.

Fig. 3.6: Measurement of adhesion by texture analyzer

The change pattern of adhesion was similar as the cohesiveness results [Fig. 3.7]. The adhesion was decreased by the incorporating disodium sulfate and calcium chloride. It might be caused by the salting-out effect. On the contrary, sodium citrate made the wet masses tacky due to its pH value. From this result it was supposed that sodium citrate could not be appropriate as an additive to prevent tack during granulation processes.

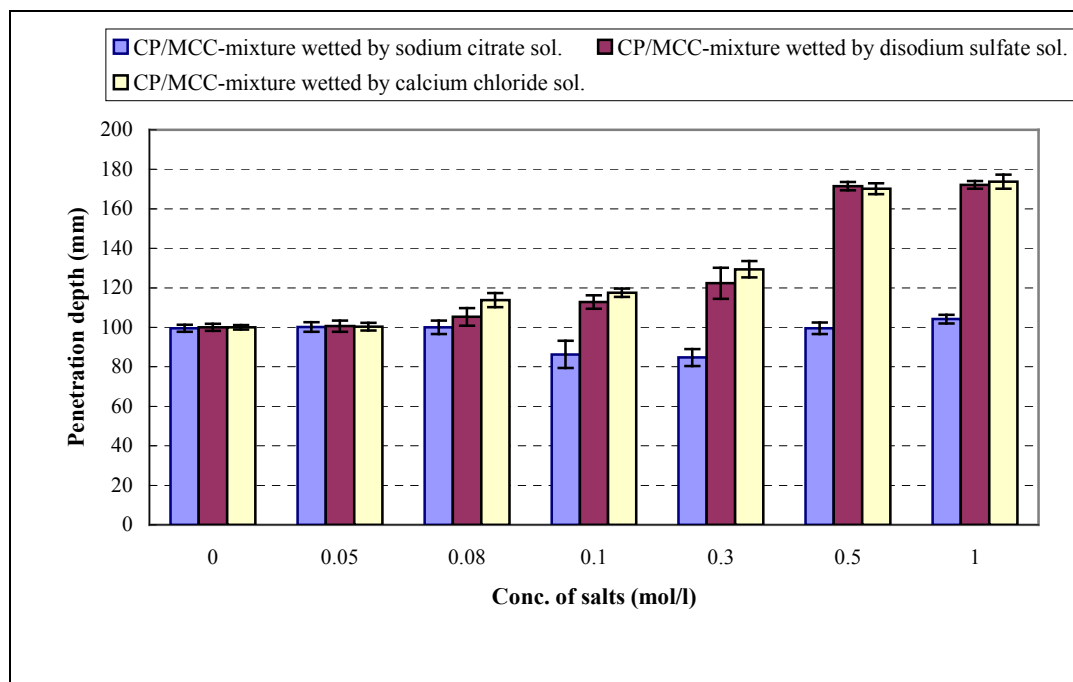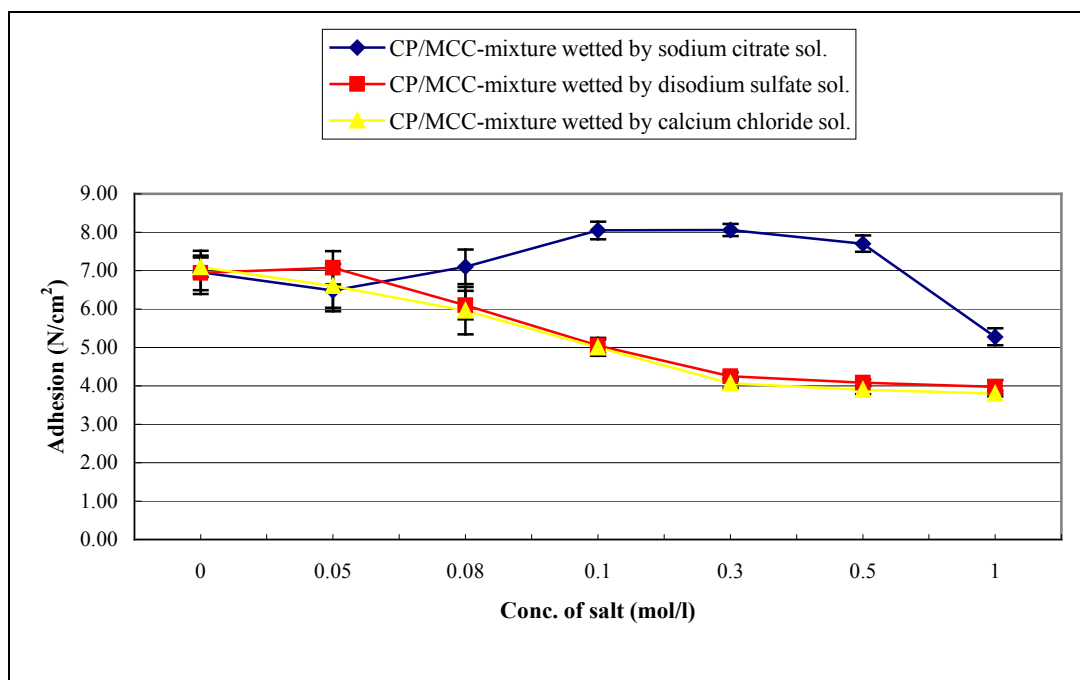**Fig. 3.7:** Adhesion of wet mass made with carbomer 934P/microcrystalline cellulose/salt-dissolved water (the concrete compositions of each wet mass are shown in table 3.1~3.3)

(CP: carbomer 934P, MCC: microcrystalline cellulose) (Mean±S.D., n=5)

3.1.3.3   Granulation process through the fluid-bed granulation

The trial batches were prepared using a fluid-bed granulator (GPCG 1, Glatt, Germany). The composition was made with 400g of powder containing 20% (w/w) of carbomer and 80% (w/w) of microcrystalline cellulose. The salts solutions were used as the binding-liquid with different concentrations (0.05, 0.08, 0.1, 0.3, and 0.5 mol/l). The process parameters were set as described in table 3.4.

It was failed to produce granules when sodium citrate solution was used as a binder. Powder bed agglomerated immediately. In case of disodium sulfate and calcium chloride, it was failed to produce granules when the salt concentration was lower than 0.1mol. However, with higher concentrations above 0.1 mol/l, granules were prepared with the following results [Tab.3.5, 3.6 and Fig.3.8, 3.9].

Tab. 3.4: Process conditions during granulation

Parameter	Setting
Batch size (g)	400
Type of disc	Hatched
Inlet air volume (m^3/h)	60-70
Inlet air temperature (°C)	40

Rotor rotation speed (rpm)	600(during drying: 450)
Process time (min)	45
Spheronization time (min)	10
Spray rate (g/min)	25
Spray pressure (bar)	1.5
Shaking interval (time/sec)	5 / 3

Tab. 3.5: The properties of granules produced by spraying of Na_2SO_4 solution

Conc. (mol/l)	Total yield (%)	Yield of 500-1180μm fraction (%)	Mean diameter (μm)	Sphericity (%)	Hardness (N)
0.1	58.3±1.1	29.9±3.4	1872±240	69.2±1.2	9.7±0.4
0.3	69.7±0.9	44.3±2.6	1451±69	73.1±2.4	8.5±1.4
0.5	76.5±2.1	48.7±4.1	1326±74	74.2±3.2	4.2±2.2

(Mean±S.D., n=3)

(a)   (b)   (c)

Fig. 3.8: CP/MCC-granules produced by spraying of Na_2SO_4 solution: (a) at 0.1 mol/l, (b) at 0.3 mol/l, (c) at 0.5 mol/l (CP: carbomer 934P, MCC: microcrystalline cellulose)

Tab. 3.6: The properties of granules produced by spraying of $CaCl_2$ solution

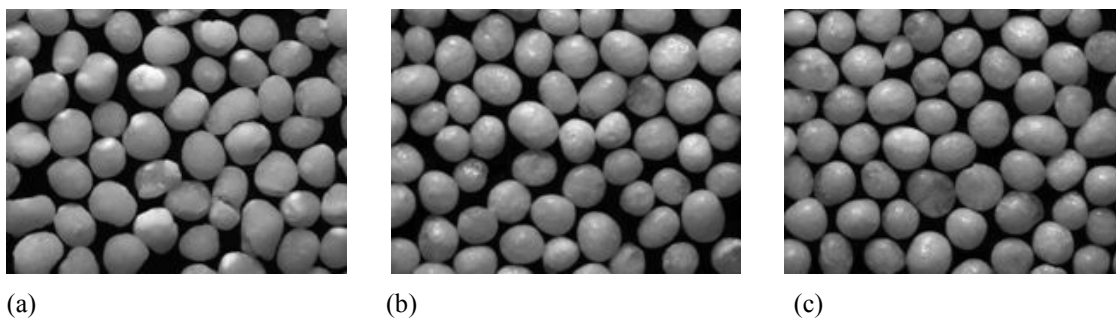| Conc. (mol/l)	Total yield (%)	Yield of 500-1180μm fraction (%)	Mean diameter (μm)	Sphericity (%)	Hardness (N)
0.1	55.8±3.7	30.3±1.9	1808±37	72.5±1.1	8.5±3.1
0.3	70.2±3.2	40.8±2.2	1440±29	77.7±1.4	6.3±1.6
0.5	75.4±2.9	45.2±3.5	1272±11	80.9±1.9	3.8±2.0

(Mean±S.D., n=3)

(a) (b) (c)
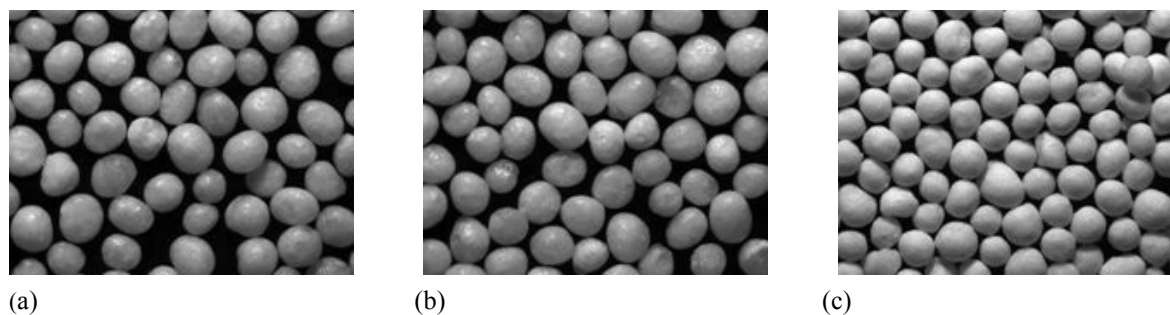
Fig. 3.9: CP/MCC-granules produced by spraying of CaCl$_2$ solution: (a) at 0.1 mol/l, (b) at 0.3 mol/l, (c) at 0.5 mol/l (CP: carbomer 934P, MCC: microcrystalline cellulose)

As shown in table 3.5 and 3.6, the more spherical and uniform pellets were prepared with the better yield at the higher salt concentrations. On the contrary, the hardness of granules was decreased as the salts concentration was increased. This may be attributed by the salting-out effect of disodium sulfate and calcium chloride. The both substances reduced the tack through the salting-out of carbomer 934P. Therefore, the gel-formation of carbomer became weaker, this resulted in the production of more brittle granules.

3.1.4 Behavior of carbomer 934P with various other excipients

In this chapter, the influence of various other excipients was examined on the cohesiveness and adhesion of carbomer 934P. Because these are the important factors to show the characteristics of wet mass, they can be useful not only to compare the influence of excipients on the wet mass, but also for a better prediction of the feasibility for the granulation processes [74, 75, 77, 108, 109, 165]. In addition, enslin number [306] of substances was measured as the indicator of water uptake ability, since the cohesiveness is closely related with a moistening level [75, 85, 165].

3.1.4.1 Investigations of water uptake

Enslin number was determined to compare the water uptake ability. Enslin number is defined as the absorbed water amount (g or ml) by 1g of powder for 15 min [306]. For each substance, 1g of powder were placed in enslin-apparatus (see figure I.4 in appendix I), and the absorbed water amount was written in 15min. In addition, the powder mixtures were prepared with carbomer 934P plus any one of excipients (microcrystalline cellulose, lactose, tri-calcium phosphate, cross-linked PVP and talc). The content of excipient in the mixtures was varied at the range of 0, 10, 20, 40, 50, 60, 80, and 100% (w/w). The change of enslin number was observed as a function of excipient content. The results are shown in Fig. 3.10 and 3.11.
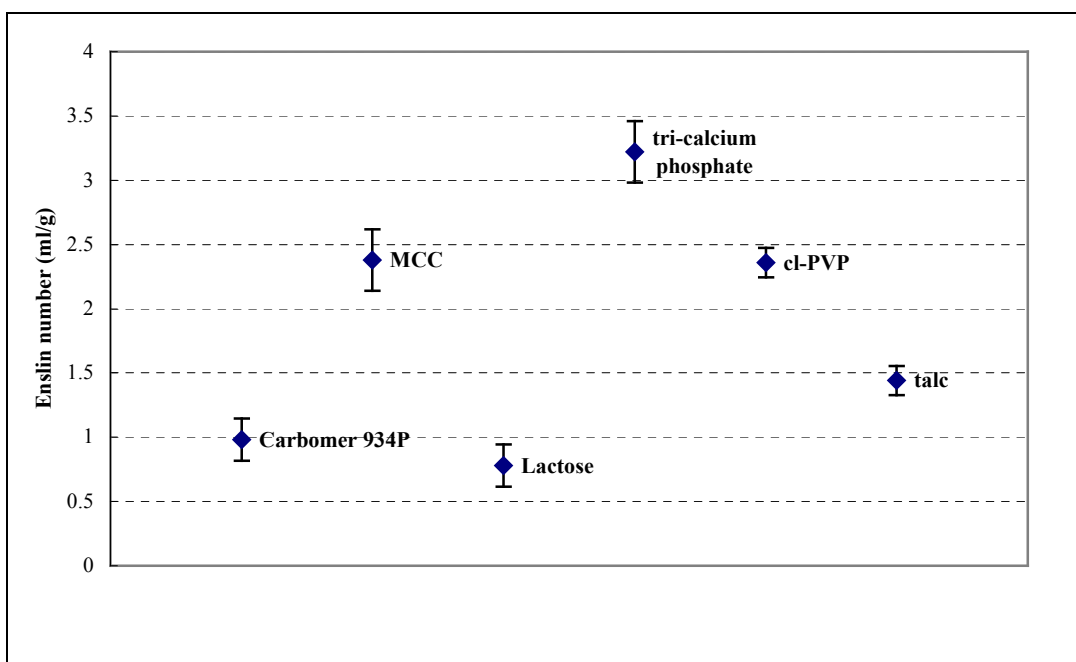
Fig. 3.10: Enslin number of investigated excipients (Mean±S.D., n=5)
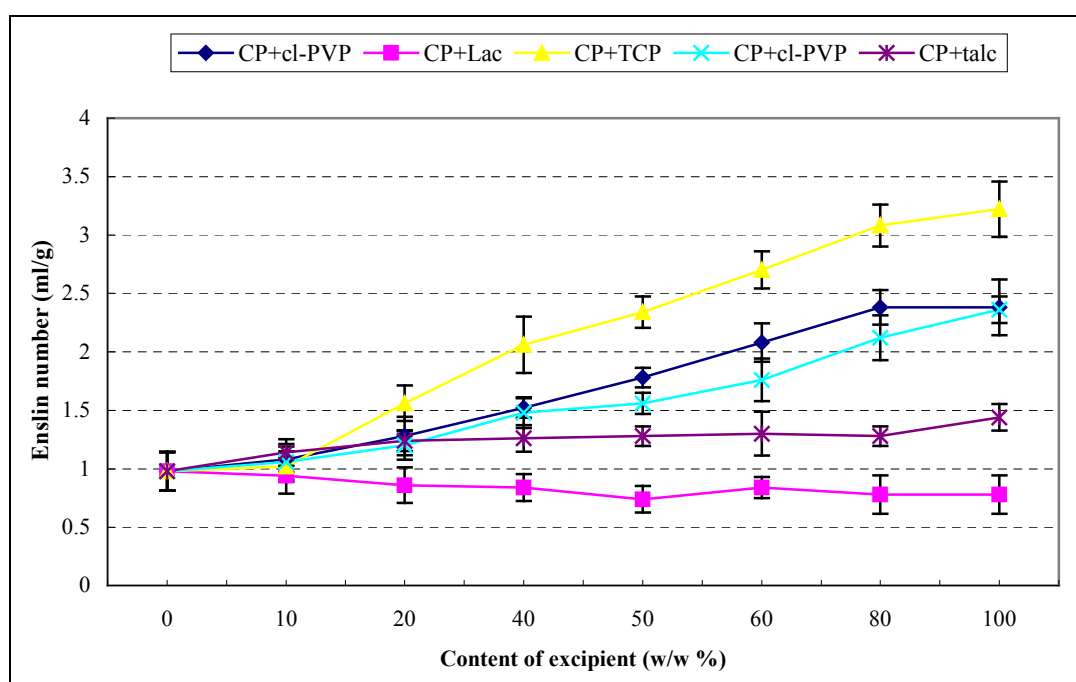
Fig. 3.11: Enslin number of carbomer 934P/excipient-mixtures (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

The measured enslin number of each substance were: lactose < carbomer 934P < talc < cross-linked PVP < microcrystalline cellulose < tri-calcium phosphate [Fig.3.10]. Tri-calcium phosphate showed the greatest number (3.22 g / min), that was about 4 times greater than that of lactose (0.78 g / min). From the result, the substances could be roughly sorted as two groups. First group is consisted with

tri-calcium phosphate, microcrystalline cellulose, and cross-linked PVP, which showed relative great enslin number. The second group included the substances showing the small enslin number- talc, carbomer 934P, and lactose. Enslin number was increased as the content of excipient was increased in powder blend, for exception of lactose [Fig. 3.11]. In particular, the effect of tri-calcium phosphate and microcrystalline cellulose was considerable. It assumed therefore that the water uptake of powder blend could be improved by the incorporation of tri-calcium phosphate and microcrystalline cellulose. In contrast, no remarkable difference was found in the enslin number when talc was added. From the results of figure 3.10 and 3.11, it could be concluded that the enslin number of powder mixtures was mainly dependent on that of individual excipient. This finding supposed that the addition of appropriate excipients could modify the water uptake of powder mixtures containing carbomer.

3.1.4.2 Investigations of cohesiveness

Wet masses were prepared with each additive (microcrystalline cellulose, lactose, tri-calcium phosphate, cross-linked PVP and talc). The moistening level was varied at the range of 5~95%. The penetration depth of a conical aluminum rod into a moistened powder mixture was determined using a penetrometer (Labof, Hungary) [Fig. 3.4]. The results are shown in figure 3.12.
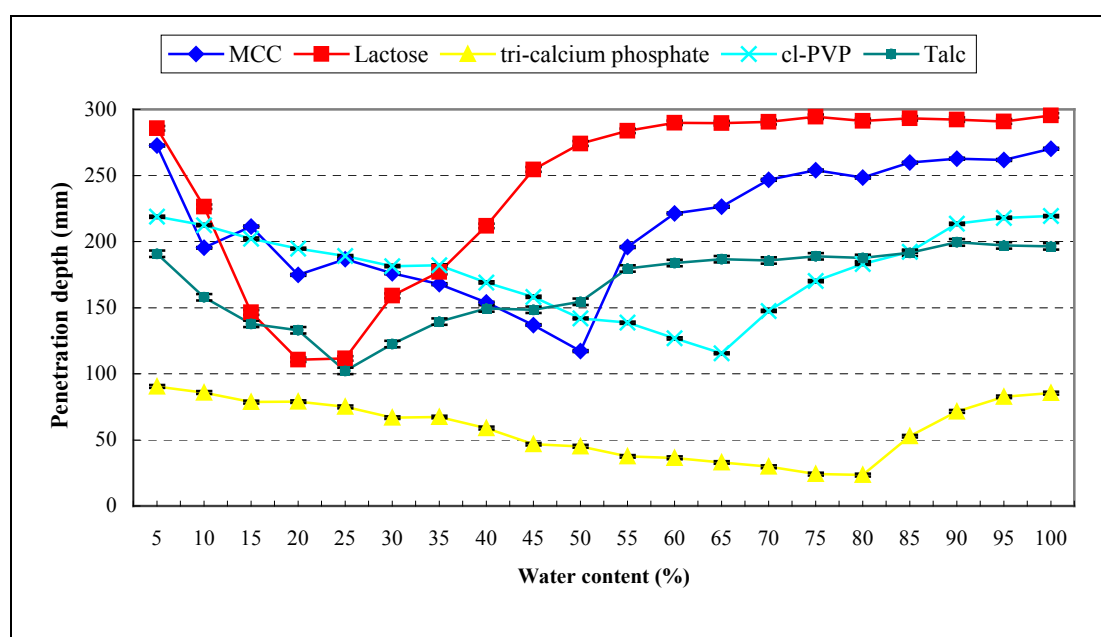
Fig. 3.12: Penetration depth of excipients (cl-PVP: cross-linked PVP, MCC: microcrystalline cellulose)

From the figure 3.12, all substances showed the similar pattern in rod penetration depth. When the water was added, the penetration depth firstly decreased, that is, the cohesiveness was increased and reached the highest value. A further increase in the moistening liquid led to a decrease in the cohesiveness, as reflected by a rise in penetration depth. These results were in good agreement with

the study of Pilpel [74, 75, 88, 165]. When little water was added, most of it was absorbed by powder. As more water was introduced, the surfaces of a powder particles dissolved and asperities present were reduced. This increased the contact area between particles, resulting in an increased cohesiveness of the powder mass, given by the initial progressive decrease in rod penetration depth. On further addition of water, a minimum was reached, corresponding to maximum cohesiveness of the moistened powder, probably with a maximum number of liquid bridges. The addition of more water decreases the cohesive strength due to the lubricating effect [74, 75, 165].

The mixtures made with carbomer 934P and other excipients were also investigated. The binary mixtures were prepared with 20%(w/w) of carbomer 934P and 80% (w/w) of other excipient as shown in table 3.7~3.11. The powder mixture was wetted by demineralized water using a pipette in a mortar and kneaded by a pestle. The amount of water added should be varied for each substance and its content. For the meaningful cohesiveness study, the water content must be in the range between 'lower limit' (wet mass is too dry below this limit. Thus the failure is occurred to produce rounded pellets or unable to agglomerate) and 'upper limit' (wet masses become a slurry because of excessive water). In this study therefore, the water amount was selected allows the ball-formation of powder mixtures. However, it was impossible to produce agglomerates at high content of carbomer 934P. In these cases, the water amount was recorded to obtain not 'too dry' wet masses. The results are shown in figure 3.13~3.17.

Tab. 3.7: Preparation of binary mixtures (carbomer/MCC) and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / MCC (80%)	21.9	Kneading in mortar →	CP (11.6%) / MCC (46.2%) / Water (42.2%)	M1
CP (40%) / MCC (60%)	19.5		CP (24.2%) / MCC (36.4%) / Water (39.4%)	M2
CP (60%) / MCC (40%)	18		CP (37.5%) / MCC (25%) / Water (37.5%)	M3
CP (80%) / MCC (20%)	15.9		CP (52.3%) / MCC (13.1%) / Water (34.6%)	M4

(CP: carbomer 934P, MCC: microcrystalline cellulose)

The required water amount became greater by increasing the proportion of microcrystalline cellulose [Fig. 3.13]. This result was as expected, since microcrystalline cellulose has a good water-absorbing ability called as a 'molecular sponge' [85, 100]. The penetration depth was dramatically decreased as the carbomer 934P content increased. That is, the cohesiveness was increased due to the gel-forming of carbomer 934P.
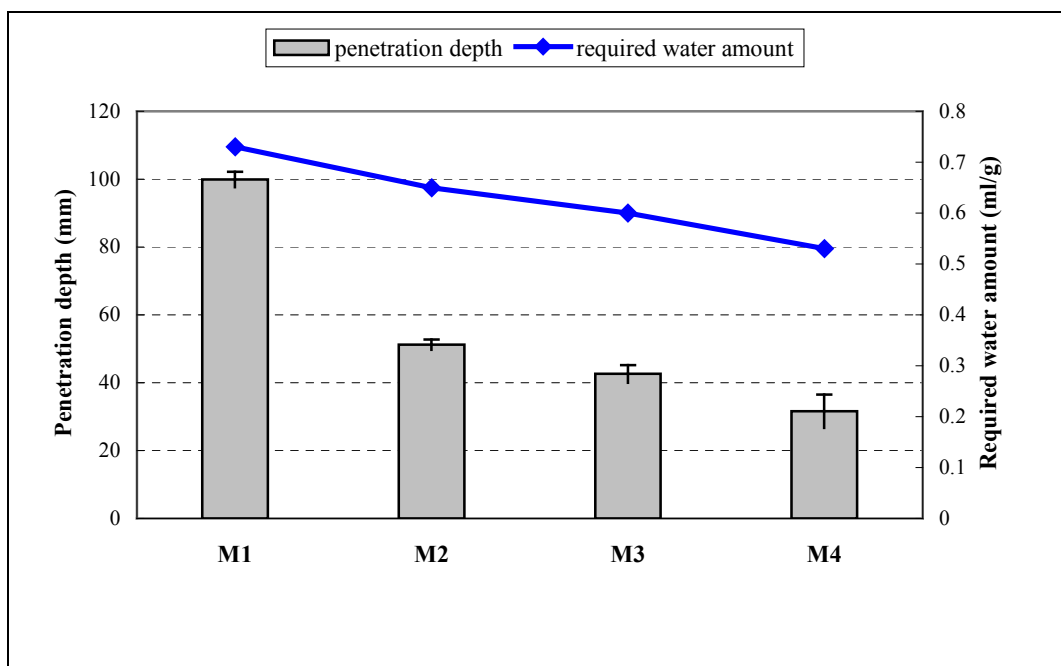
Fig. 3.13: Penetration depth and required water amount of carbomer 934P/microcrystalline cellulose-mixtures (Mean±S.D., n=5)

Lactose needed the smallest amount of water [Tab. 3.8 and Fig. 3.14]. This result was consistent with the published reports [76, 165].

Tab. 3.8: Preparation of binary mixtures (carbomer/lactose) and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / Lac (80%)	6.6	Kneading in mortar $\rightarrow$	CP (16.4%) / Lac (65.6%) / Water (18%)	L1
CP (40%) / Lac (60%)	7.5		CP (32%) / Lac (48%) / Water (20%)	L2
CP (60%) / Lac (40%)	7.8		CP (47.6%) / Lac (31.7%) / Water (20.7%)	L3
CP (80%) / Lac (20%)	8.7		CP (62%) / Lac (15.5%) / Water (22.5%)	L4

(CP: carbomer 934P, Lac: lactose)

It may be attributed by the water-solubility of lactose. Lactose is a representative water-soluble excipient [76]. It dissolved easily in the added water, therefore, the wet mass contains a lower quantity of solid particles plus a rather viscous lactose solution. This led to the stickiness and more agglomeration in the wet mass.
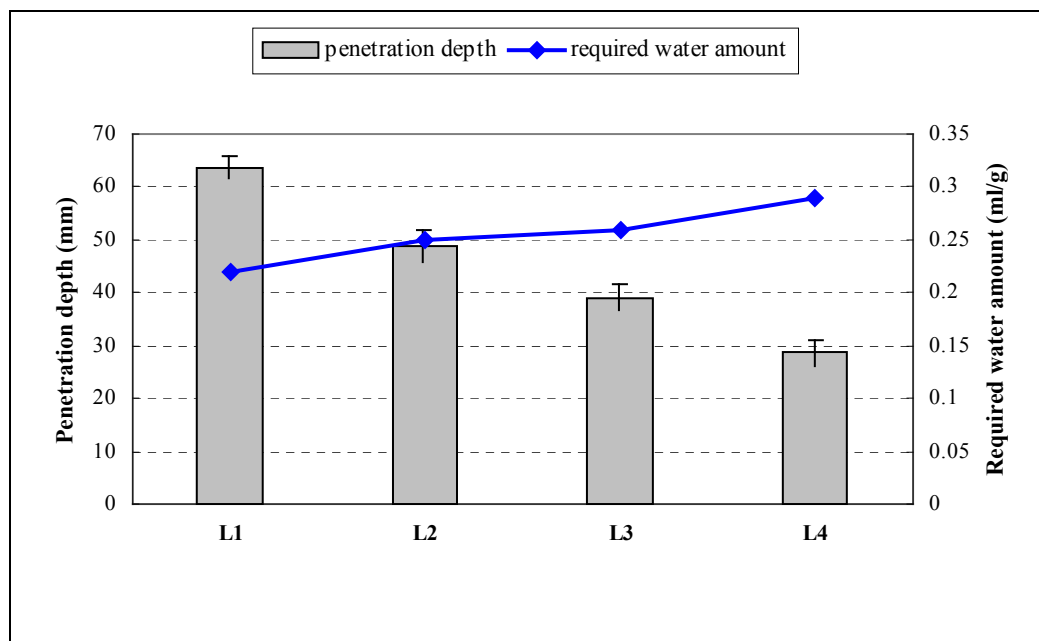
Fig. 3.14: Penetration depth of carbomer 934P/ lactose-mixture (Mean±S.D., n=5)

Tri-calcium phosphate required the greatest amount of water among all excipients. The penetration depth and required water amount by differing tri-calcium phosphate content were illustrated in figure 3.15. The penetration depth was dramatically increased by increasing the content of tri-calcium phosphate. It could be explained by a high water uptake ability of tri-calcium phosphate. When the water was added, the tri-calcium phosphate particles absorb most of water, thus the smaller amount of water became available to penetrate into the carbomer. This could prevent effectively the gel-forming of carbomer 934P. The relative high penetration depth was therefore obtained. Since the mixture containing 20% (w/w) of carbomer 934P + 80% (w/w) of tri-calcium phosphate (in dry state) showed a possibility to produce the pellets from this results, the content of carbomer 934P was kept as 20% (w/w, in dry state) for the further investigations in chapter 3.1.4.3.

Tab. 3.9: Preparation of binary mixtures (carbomer/tri-calcium phosphate) and their actual compositions (CP: carbomer 934P, TCP: tri-calcium phosphate)

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / TCP (80%)	34.2	Kneading in mortar →	CP (9.3%) / TCP (37.4%) / Water (53.3%)	T1
CP (40%) / TCP (60%)	30		CP (20%) / TCP (30%) / Water (50%)	T2
CP (60%) / TCP (40%)	15.9		CP (39.2%) / TCP (26.1%) / Water (34.7%)	T3
CP (80%) / TCP (20%)	12		CP (57.1%) / TCP (14.3%) / Water (28.6%)	T4
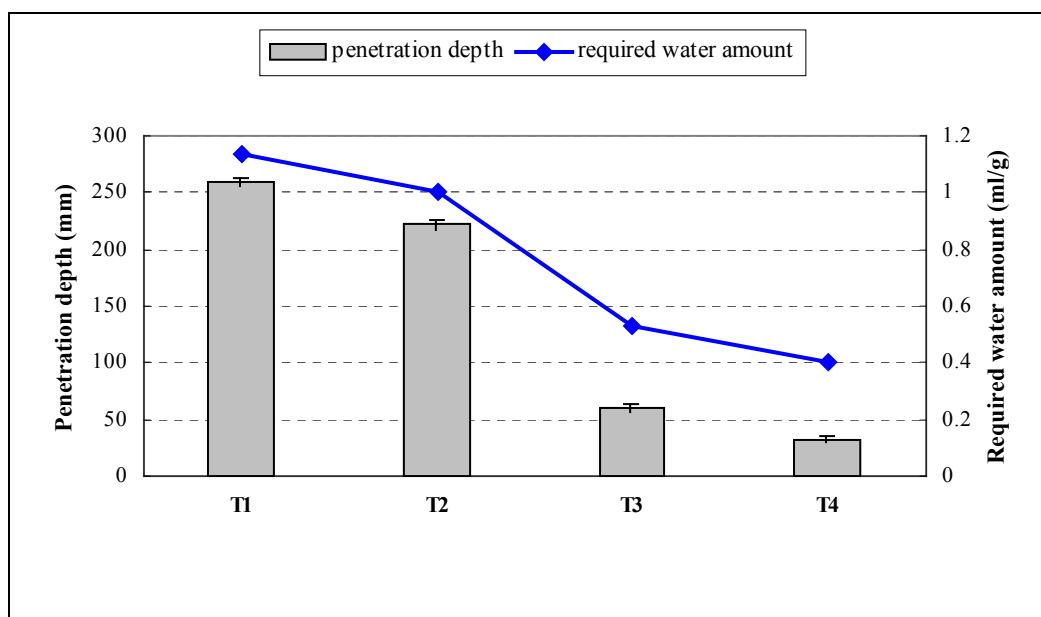
Fig. 3.15: Penetration depth of carbomer 934P/tri-calcium phosphate-mixture (Mean±S.D., n=5)

The higher was the cross-linked PVP content, the more quantity of water was required [Tab.3.10 and Fig.3.16]. However, carbomer 934P/cross-linked PVP-mixture appeared not so appropriate practically. These mixtures showed the handling difficulty even at the lowest carbomer content. According to a published study [50], cross-linked PVP could reduce the tack during a coating process using hydroxypropylmethyl cellulose. The similar effect was expected with carbomer 934P, but it was found that its effect was not considerable. Therefore, it was appeared that cross-linked PVP could not be a first choice as an additive for reducing tack of carbomer.

Tab. 3.10: Preparation of binary mixtures (carbomer/cl-PVP) and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / cl-PVP (80%)	33.9	Kneading in mortar →	CP (9.4%) / cl-PVP (37.6%) / Water (53%)	P1
CP (40%) / cl-PVP (60%)	24		CP (22.2%) / cl-PVP (33.3%) / Water (44.5%)	P2
CP (60%) / cl-PVP (40%)	22.5		CP (34.3%) / cl-PVP (22.9%) / Water (42.8%)	P3
CP (80%) / cl-PVP (20%)	21		CP (47%) / cl-PVP (11.8%) / Water (41.2%)	P4

(CP: carbomer 934P, cl-PVP: cross-linked PVP)
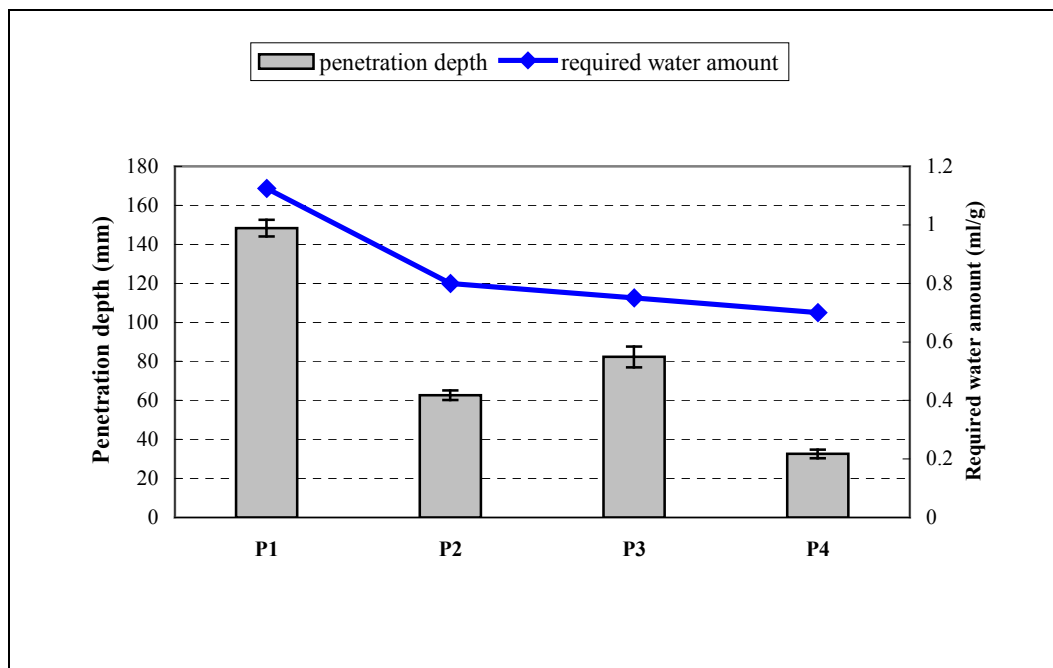
Fig. 3.16: Penetration depth of carbomer 934P/cross-linked PVP-mixture (cl-PVP: cross-linked PVP) (Mean±S.D., n=5)

Tab. 3.11: Preparation of binary mixtures (carbomer/talc) and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / Talc (80%)	28.5	Kneading in mortar →	CP (10.3%) / Talc (41%) / Water (48.7%)	C1
CP (40%) / Talc (60%)	22.8		CP (22.7%) / Talc (34.1%) / Water (43.2%)	C2
CP (60%) / Talc (40%)	16.5		CP (38.7%) / Talc (25.8%) / Water (35.5%)	C3
CP (80%) / Talc (20%)	14.1		CP (54.4%) / Talc (13.6%) / Water (32%)	C4

(CP: carbomer 934P)

As shown in figure 3.17, talc showed a similar pattern as that observed in carbomer 934P/cross-linked PVP-mixture. Carbomer 934P/talc-mixture also caused a tacking problem even at the 20% (w/w, in dry state) of carbomer 934P content. Talc has been used traditionally as an anti-tack agent [50], but in this study it did not show a considerable effect. It could be considered that the content of talc might be insufficient for an anti-tack effect, since a relative high content of carbomer was used in this investigation than a normal tabletting or coating processes.
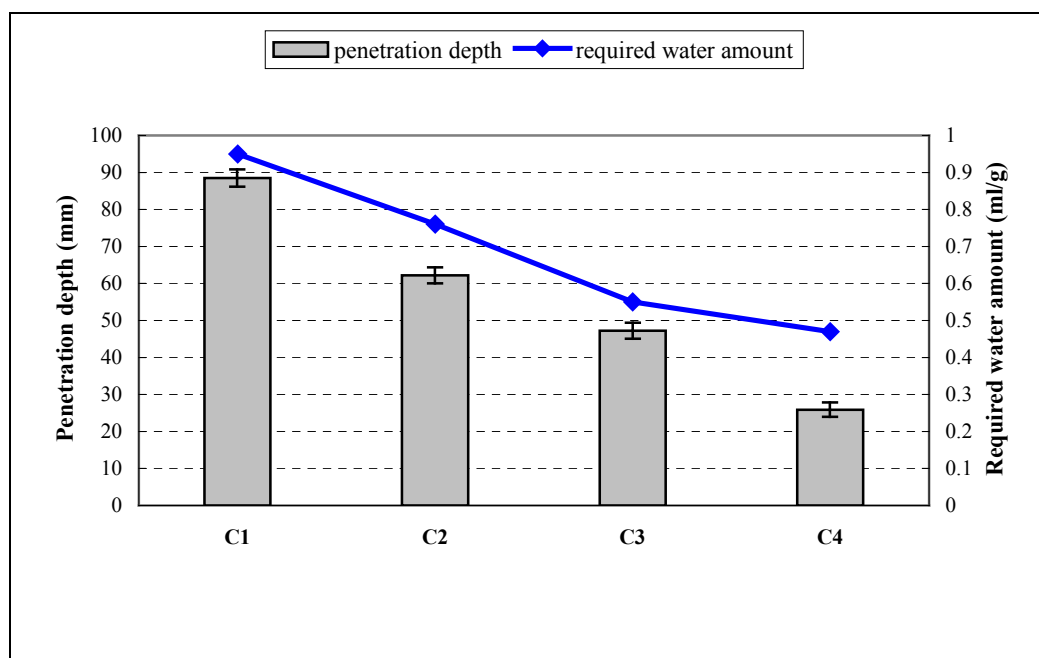
Fig. 3.17: Penetration depth of carbomer 934P/talc-mixture (Mean±S.D., n=5)

3.1.4.3 Behavior of 20%-carbomer 934P with various other excipients

In chapter 3.1.4.2, it was found that the 20% of carbomer 934P/ 80% of tri-calcium phosphate-mixture (in dry state) appeared very hopeful for granulation. Therefore, a further investigation was performed for the 20% of carbomer 934P/80% of excipient-mixtures. Firstly, the binary mixtures were made with 20% of carbomer 934P/ 80% of any one of excipients (microcrystalline cellulose, lactose, tri-calcium phosphate, cross-linked PVP and talc). In addition, the ternary mixtures were also investigated: the content of carbomer 934P was kept as 20%, and two kinds of excipients were incorporated as 80% (w/w). The content of one of excipients was varied as 20, 40, 50, 60, 80, and 100% of total 80% excipients content. The enslin number was investigated in powder mixtures, and the cohesiveness and adhesion of prepared wet masses were determined as a function of excipient content.

3.1.4.3.1 Investigations of water uptake

- Binary mixtures (20% carbomer 934P + 80% other excipient)

Tri-calcium phosphate has very high water uptake ability, thus its influence was also found in the carbomer 934P/tri-calcium phosphate- mixture. Lactose needed a small amount of water due to its solubility, therefore, the overall enslin number of carbomer 934P/lactose-mixture was also small. Since carbomer forms a gel immediately in water, its water uptake can be negligible in the mixture. The overall enslin number was dependent on the water uptake of additive.
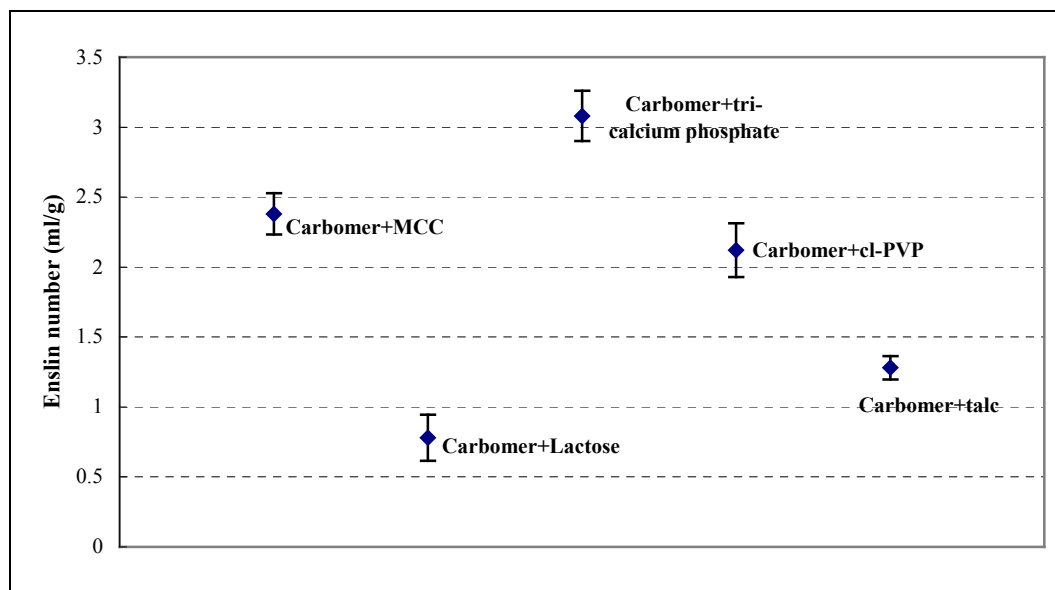
Fig. 3.18: Enslin number of binary mixtures (carbomer 934P/excipient) (Mean±S.D., n=5)

- Ternary mixtures (20% Carbomer 934P + 40% excipient A + 40% excipient B)

a) Influence of microcrystalline cellulose

The addition of microcrystalline cellulose caused an increase in the enslin number in most cases [Fig.3.19]. However, in the combination with tri-calcium phosphate, the overall enslin number decreased by the addition of increased microcrystalline cellulose. This could be due to the higher water uptake ability of tri-calcium phosphate than that of microcrystalline cellulose.
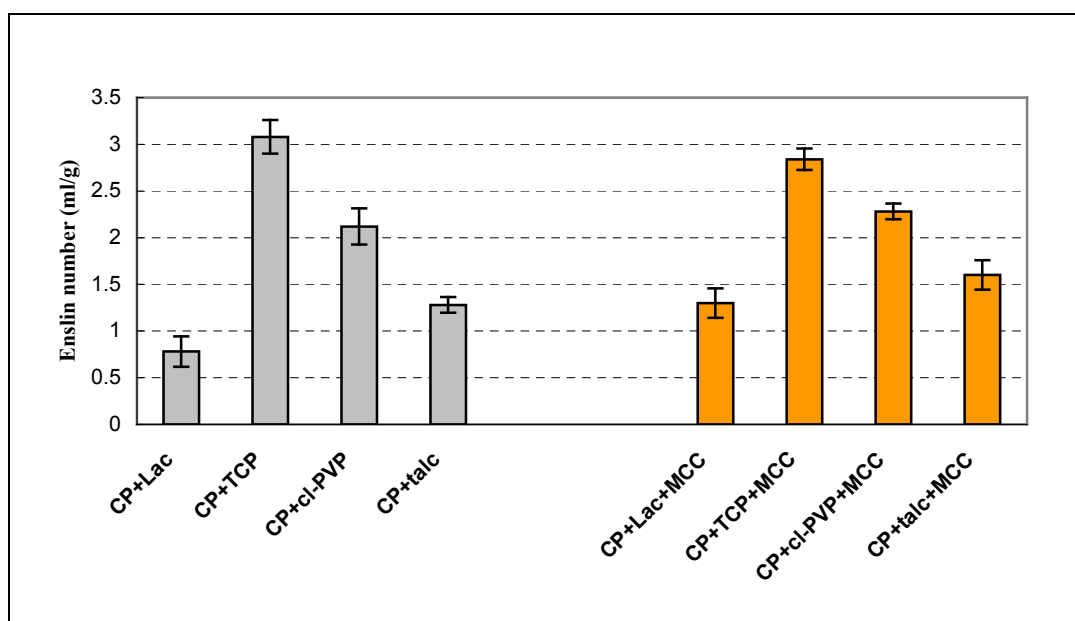
Fig. 3.19: Influence of microcrystalline cellulose on the enslin number (CP: carbomer 934P, cl-PVP: cross linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

b) Influence of lactose

When lactose content was higher, the enslin number was decreased [Fig.3.20]. Lactose has the smallest enslin number among the investigated excipients, thus its influence was found also in all mixtures containing it.
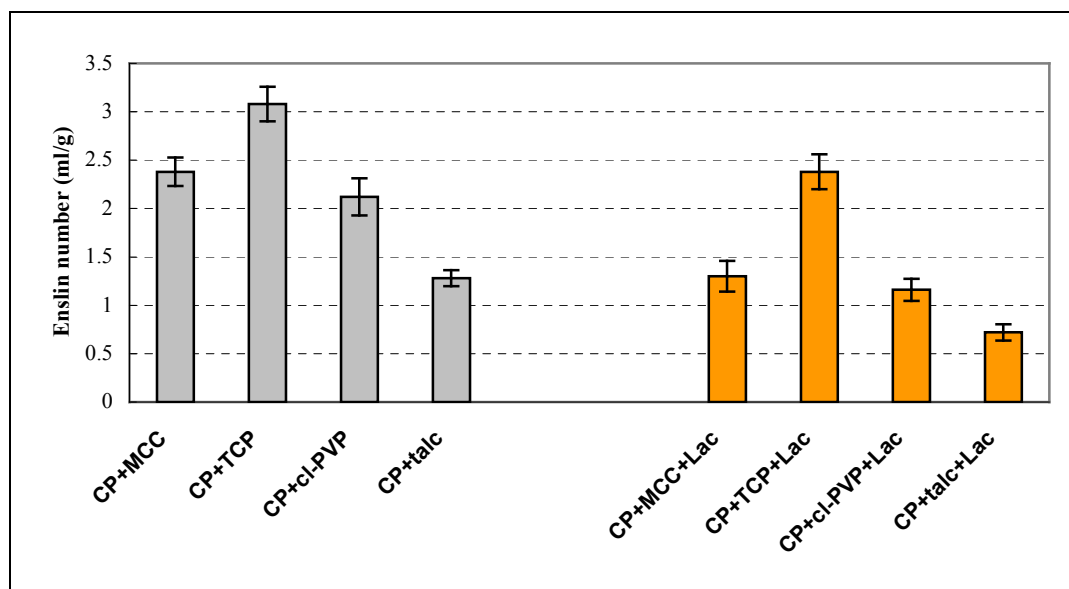
Fig. 3.20: Influence of lactose on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

c) Influence of tri-calcium phosphate

Tri-calcium phosphate caused a considerable increase in enslin number in all cases [Fig.3.21].
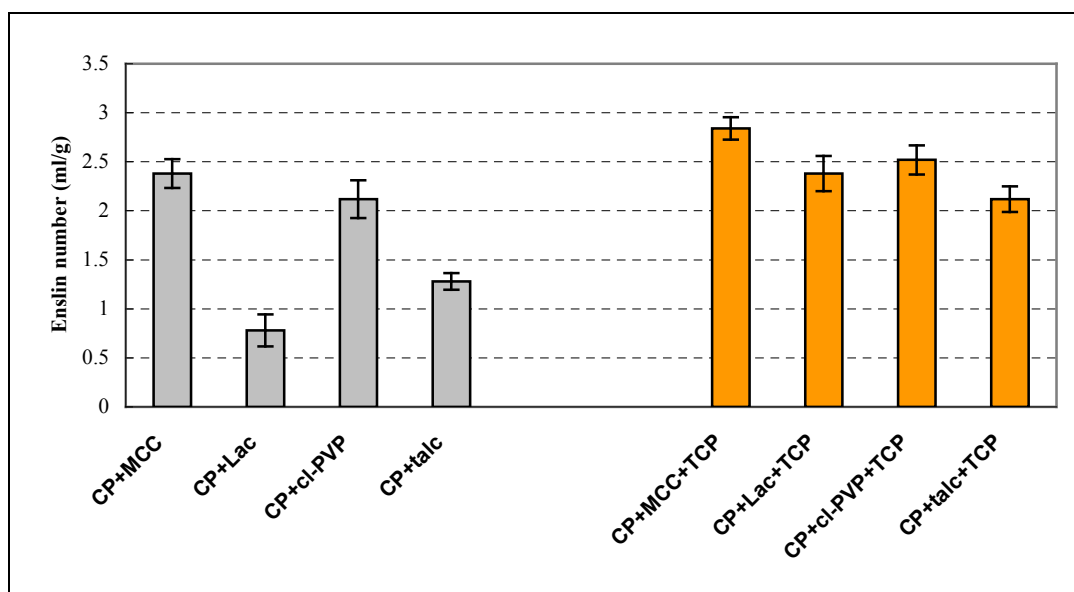
Fig. 3.21: Influence of tri-calcium phosphate on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

d) Influence of cross-linked PVP

Cross-linked PVP resulted in an overall decrease in the enslin number when it was combined with microcrystalline cellulose or tri-calcium phosphate [Fig. 3.22]. It might be attributed by their better water uptake ability than that of cross-linked PVP. However, cross-linked PVP affected positively in the mixtures made with lactose or talc, because they have smaller enslin number than that of cross-linked PVP.
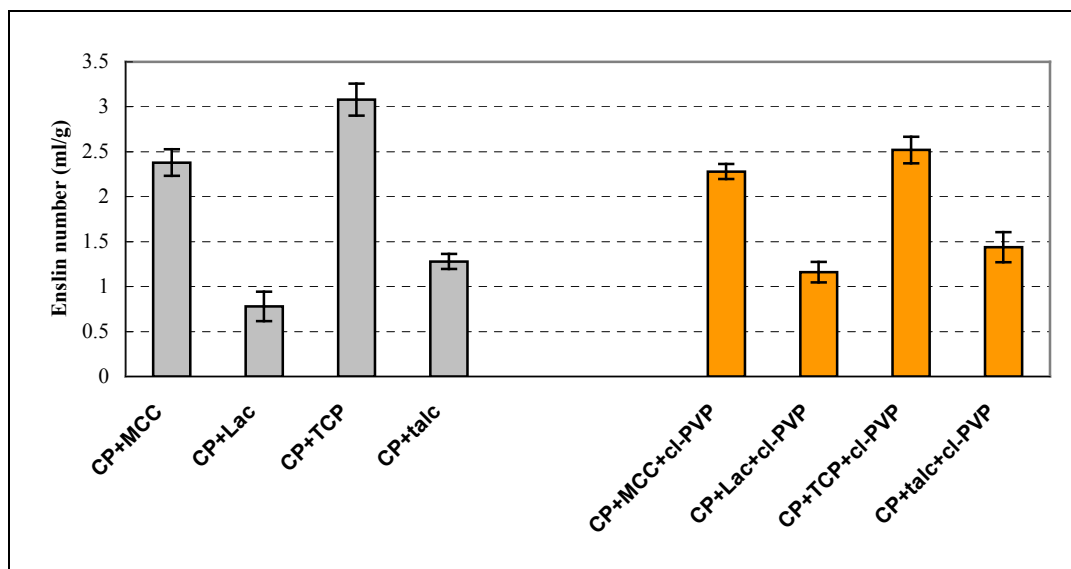
Fig. 3.22: Influence of cross-linked PVP on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

e) Influence of talc

Fig. 3.23: Influence of talc on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

Enslin number was decreased by increasing the content of talc [Fig.3.23]. Talc has also a relative low water uptake potential, it affected therefore negatively in the combinations with other excipients.

3.1.4.3.2 Investigations of cohesiveness and adhesion

- Binary mixtures (20% carbomer 934P + 80% other excipient, w/w in dry state)

Tab. 3.12: Preparation of binary mixtures (carbomer/other excipient) and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / MCC (80%)	21.9		CP (11.6%) / MCC (46.2%) / Water (42.2%)	B1
CP (20%) / Lac (80%)	6.6	Kneading in mortar →	CP (16.4%) / Lac (65.6%) / Water (18%)	B2
CP (20%) / TCP (80%)	34.2		CP (9.3%) / TCP (37.4%) / Water (53.3%)	B3
CP (20%) / cl-PVP (80%)	33.8		CP (9.4%) / cl-PVP (37.6%) / Water (53%)	B4
CP (20%) / Talc (80%)	14.1		CP (13.6%) / Talc (54.4%) / Water (32%)	B5
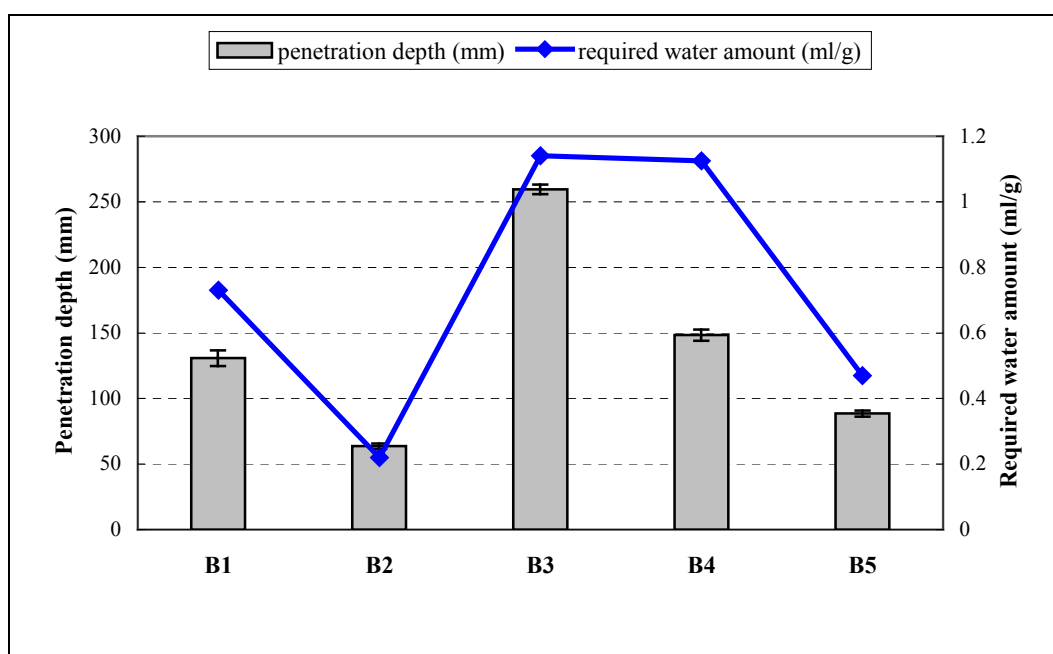
Fig. 3.24: Penetration depth of carbomer 934P/ other excipient-mixtures (CP: carbomer 934P, cl-PVP: cross-linked PVP, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

Fig. 3.25: Adhesion of carbomer 934P/ other excipient-mixtures (CP: carbomer 934P, cl-PVP: cross-linked PVP, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

According to figure 3.24, carbomer 934P/lactose-mixture showed the smallest value in the penetration depth, that is, the highest cohesiveness among the investigated mixtures. It was also revealed that carbomer 934P/lactose-mixture had the greatest adhesion [Fig.3.25]. When tri-calcium phosphate was added into carbomer 934P, a very low cohesiveness and adhesion were observed. Cross-linked PVP and talc showed the similar pattern each other, but their effects in the adhesion were not remarkable.

- Ternary mixtures (20% carbomer 934P+ 40% excipient A + 40% excipient B, w/w in dry state)

a)   Influence of microcrystalline cellulose

Tab. 3.13: Preparation of ternary mixtures with carbomer 934P/MCC/other excipient and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass
CP (20%) / Lac (40%) / **MCC** (40%)	17.9	Kneading in mortar →	CP (12.5%) / Lac (25.1%) / MCC (25.1%) / Water (37.3%)
CP (20%) / TCP (40%) / **MCC** (40%)	24.6		CP (11%) / TCP (22%) / MCC (22%) / Water (45%)
CP (20%) / cl-PVP (40%) / **MCC** (40%)	30.3		CP (10%) / cl-PVP (19.9%) / MCC (19.9%) / Water (50.2%)
CP (20%) / Talc (40%) / **MCC** (40%)	18.0		CP (12.5%) / Talc (25%) / MCC (25%) / Water (37.5%)

Figure 3.26 and 3.27 illustrate the influence of microcrystalline cellulose. The addition of microcrystalline cellulose into tri-calcium phosphate and cross-linked PVP caused the increase in cohesiveness and adhesion. No remarkable effect was found when microcrystalline cellulose was added in lactose and talc.
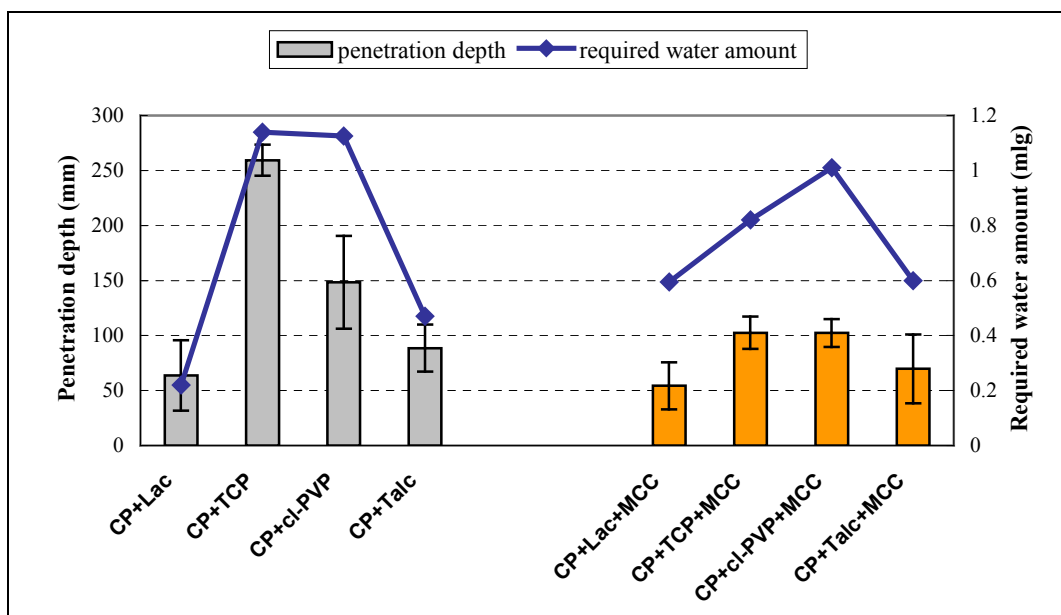
Fig. 3.26: Influence of microcrystalline cellulose on penetration depth (CP: carbomer 934P, cl PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean± S.D., n=5)
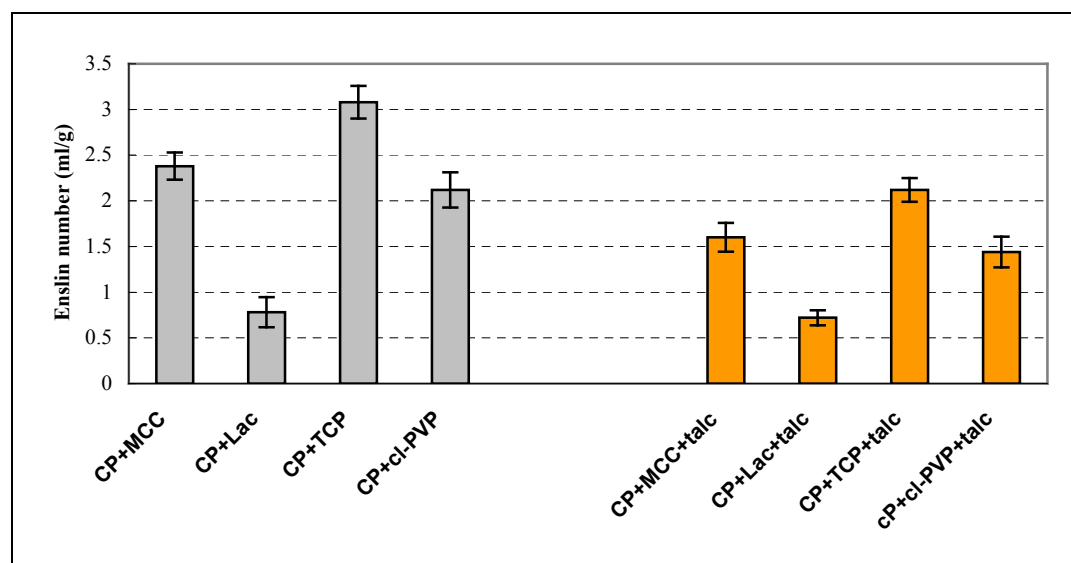

Fig. 3.27: Influence of microcrystalline cellulose on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

This result was attributed by a good water absorbing ability of microcrystalline cellulose [85, 100]. It is able to hold large amounts of freely mobile water in the wet stage. Therefore, the addition of microcrystalline cellulose into tri-calcium phosphate and cross-linked PVP improved their too low cohesiveness and adhesion. When microcrystalline cellulose was incorporated into lactose and talc, no considerable differences were observed in cohesiveness. It might be caused by the better water absorbability of PVP and its higher cohesiveness than microcrystalline cellulose. However, the tackiness was decreased, that resulted in a decrease in adhesion.

b) Influence of lactose

Tab. 3.14: Preparation of ternary mixtures with carbomer 934P/lactose/other excipient and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass
CP (20%) / MCC (40%) / Lac (40%)	17.9	Kneading in mortar →	CP (12.5%) / MCC (25.1%) / Lac (25.1%) / Water (37.3%)
CP (20%) / TCP (40%) / Lac (40%)	27.9		CP (10.4%) / TCP (20.7%) / Lac (20.7%) / Water (45%)
CP (20%) / cl-PVP (40%) / Lac (40%)	19.2		CP (12.2%) / cl-PVP (24.4%) / Lac (24.4%) / Water (39%)
CP (20%) / Talc (40%) / Lac (40%)	15.3		CP (13.2%) / Talc (26.5%) / Lac (26.5%) / Water (33.8%)

Lactose caused a decrease in the penetration depth in all cases and the adhesion was increased. The required water amount was decreased by increasing lactose content [Fig.3.28 and 3.29].
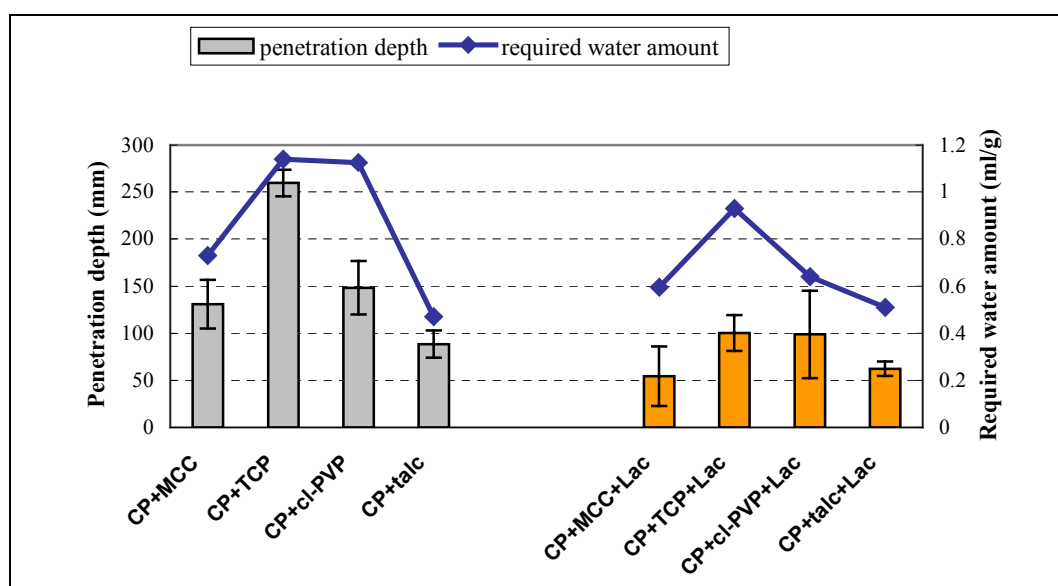
Fig. 3.28: Influence of lactose on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)
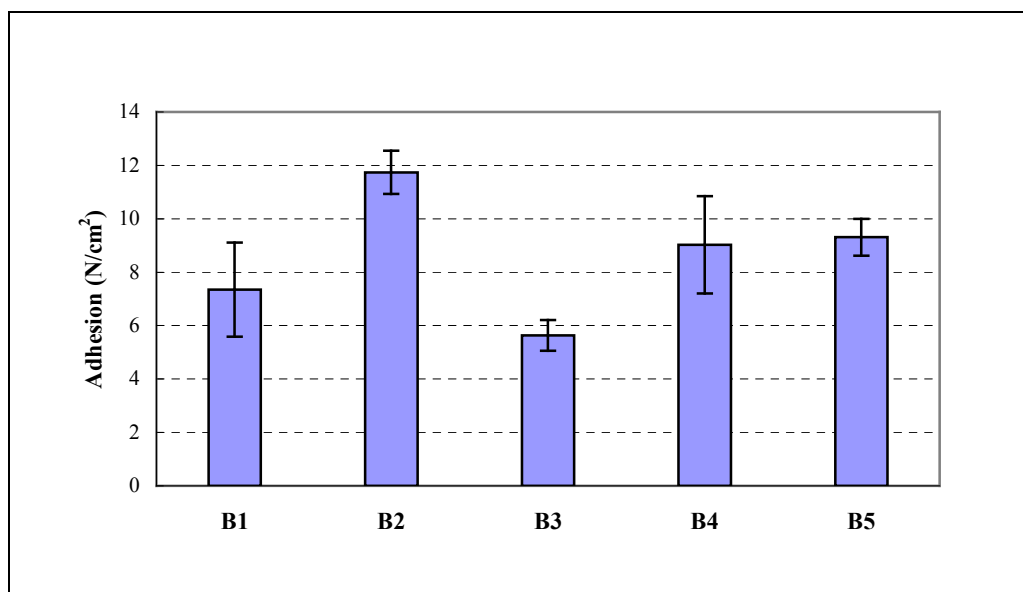
Fig. 3.29: Influence of lactose on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

This result could be a consequence of the property of lactose. It is a highly water-soluble excipient, which dissolves easily even in small amount of water. That is, the more free water could be available for the carbomer particles. From this reason, the wet mass became sticky, hence caused an increase in cohesiveness and adhesion.

c)   Influence of tri-calcium phosphate

Tri-calcium phosphate resulted in an increase in the required water amount and a decrease in cohesiveness. Adhesion was also decreased as the content of tri-calcium phosphate was increased [Fig.3.30 and 3.31].

Tab. 3.15: Preparation of ternary mixtures with carbomer 934P/TCP/other excipient and their actual compositions

| Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass
CP (20%) / MCC (40%) / TCP (40%)	24.6	Kneading in mortar →	CP (11%) / MCC (22%) / TCP (22%) / Water (45.1%)
CP (20%) / Lac (40%) / TCP (40%)	27.9		CP (10.4%) / Lac (20.7%) / TCP (20.7%) / Water (45%)
CP (20%) / cl-PVP (40%) / TCP (40%)	31.8		CP (9.7%) / cl-PVP (19.4%) / TCP (19.4%) / Water (51.5%)
CP (20%) / Talc (40%) / TCP (40%)	20.4		CP (11.9%) / Talc (23.8%) / TCP (23.8%) / Water (40.5%)

Fig. 3.30: Influence of tri-calcium phosphate on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean ±S.D., n=5)
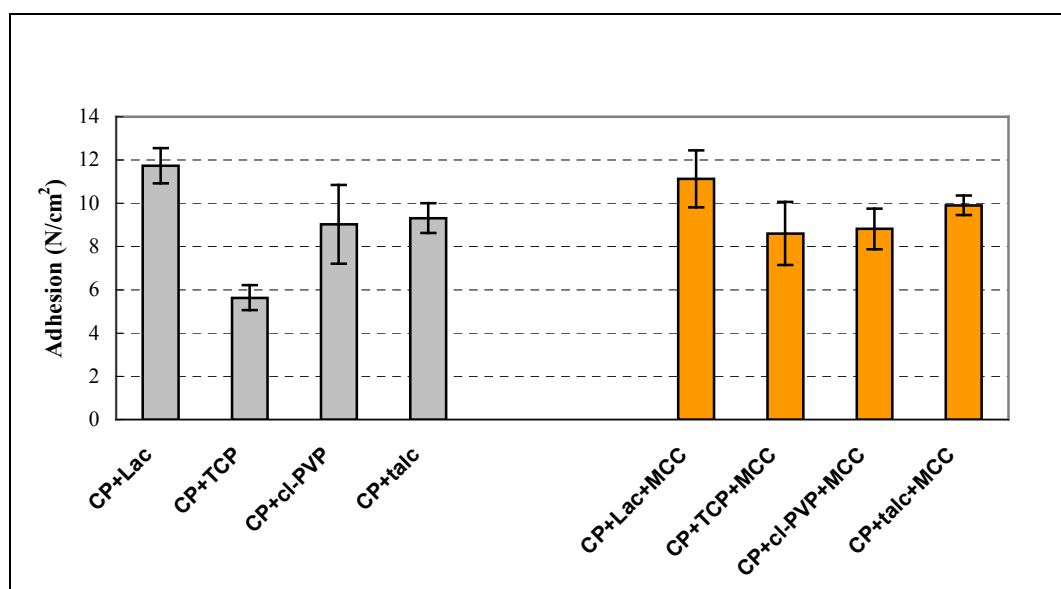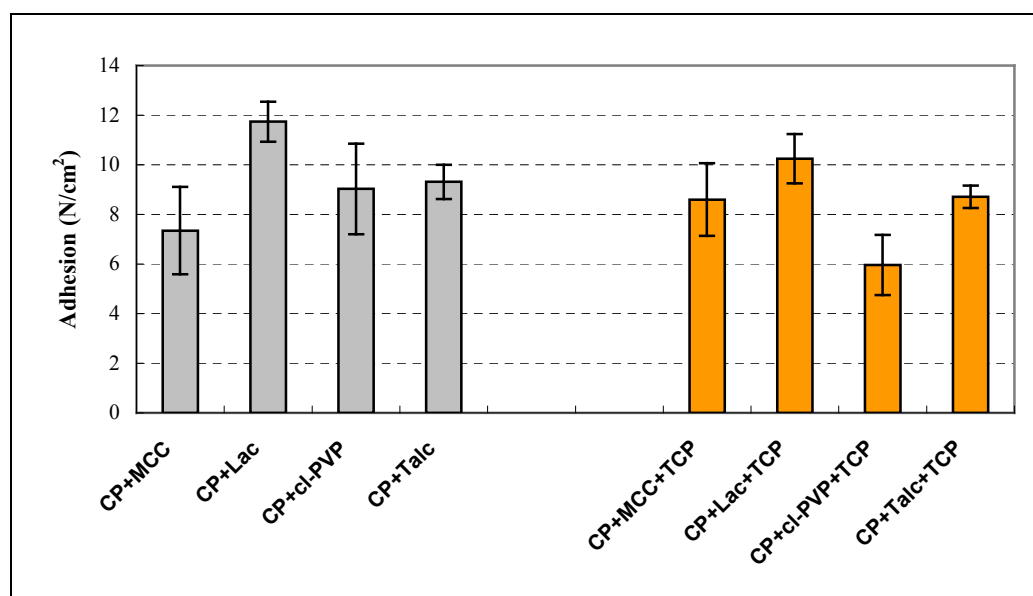

Fig. 3.31: Influence of tri-calcium phosphate on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

It might be due to a very good wettability of tri-calcium phosphate in water: its contact angle is known as almost 0° [165]. It assumed that when tri-calcium phosphate was incorporated to carbomer, it surrounded carbomer particles and absorbed most of water, therefore less free water became available for the penetration into carbomer powder. That prevented the gel-forming of carbomer and this suppression effect was shown as the decrease in cohesiveness and adhesion.

d)   Influence of cross-linked PVP and Talc

The addition of cross-linked PVP and talc caused an increase in cohesiveness and adhesion, particularly to tri-calcium phosphate [Fig. 3.32~3.35]. However, the anti-tack effects of cross-linked PVP and talc were not clearly found, although they were used traditionally as an anti-tack agent in coating operation to polymers [50].

Tab. 3.16: Preparation of ternary mixtures with carbomer934P/cl-PVP/other excipient and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass
CP (20%) / MCC (40%) / **cl-PVP** (40%)	30.3	Kneading in mortar →	CP (10%) / MCC (19.9%) / cl-PVP (19.9%) / Water (50.2%)
CP (20%) / Lac (40%) / **cl-PVP** (40%)	19.2		CP (12.2%) / Lac (24.4%) / cl-PVP (24.4%) / Water (45%)
CP (20%) / TCP (40%) / **cl-PVP** (40%)	31.8		CP (9.7%) / TCP (19.4%) / cl-PVP (19.4%) / Water (51.5%)
CP (20%) / Talc (40%) / **cl-PVP** (40%)	26.5		CP (10.6%) / Talc (21.3%) / cl-PVP (21.3%) / Water (46.9%)

Tab. 3.17: Preparation of ternary mixtures with carbomer/talc/other excipient and their actual compositions

| Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass
CP (20%) / MCC (40%) / **Talc** (40%)	18.0	Kneading in mortar →	CP (12.5%) / MCC (25%) / Talc (25%) / Water (37.5%)
CP (20%) / Lac (40%) / **Talc** (40%)	15.3		CP (13.2%) / Lac (26.5%) / Talc (26.5%) / Water (45%)
CP (20%) / TCP (40%) / **Talc** (40%)	20.4		CP (11.9%) / TCP (23.8%) / Talc (23.8%) / Water (40.5%)
CP (20%) / cl-PVP (40%) / **Talc** (40%)	26.5		CP (10.6%) / cl-PVP (21.3%) / Talc (21.3%) / Water (46.9%)
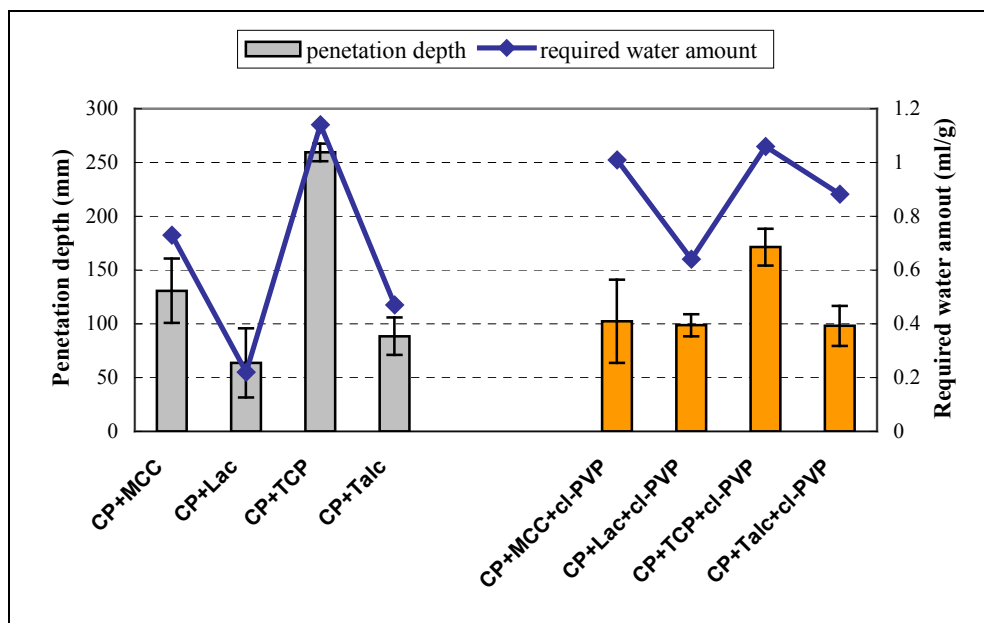
Fig. 3.32: Influence of cross-linked PVP on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean± S.D., n=5)
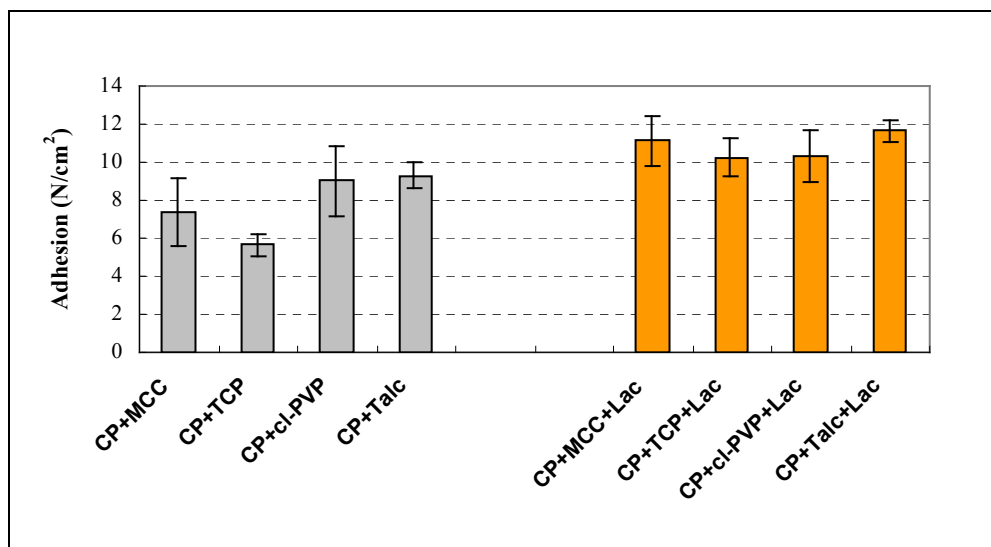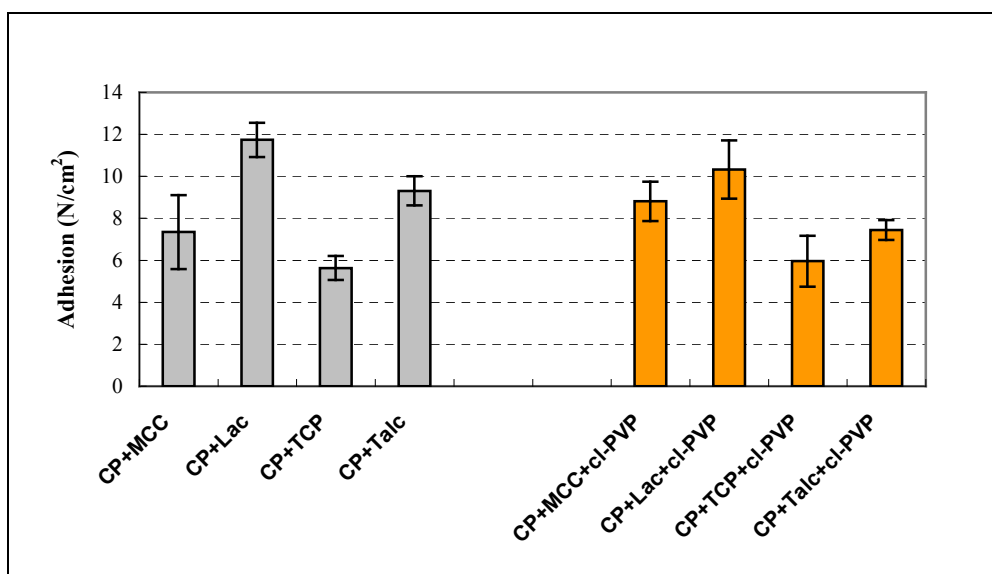

Fig. 3.33: Influence of cross-linked PVP on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)
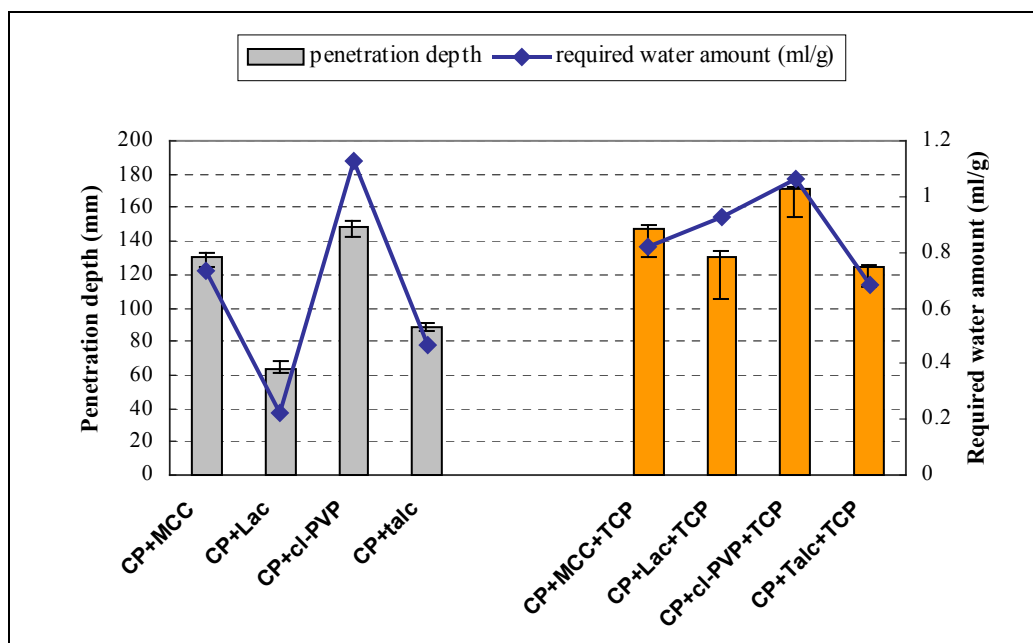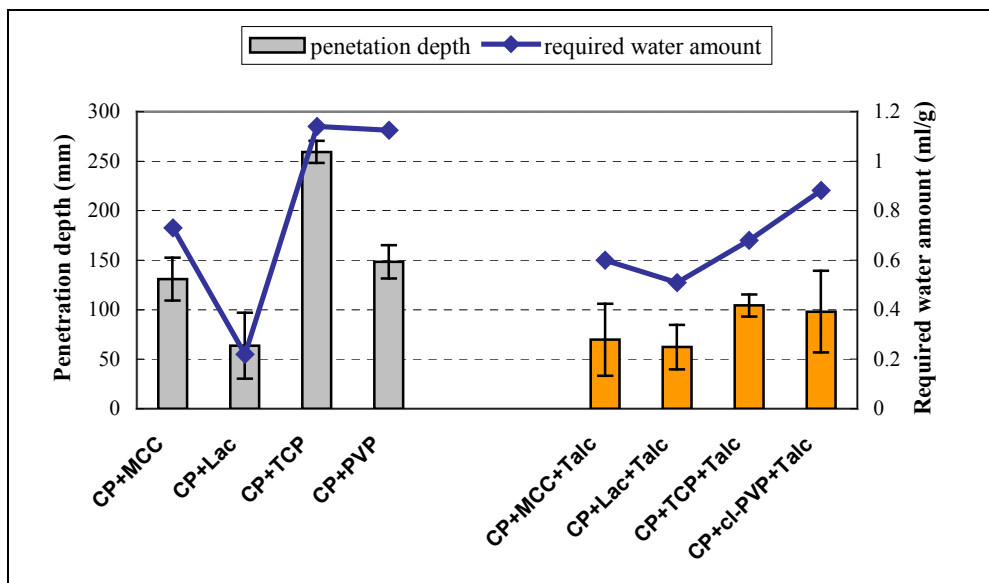
Fig. 3.34: Influence of talc on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)
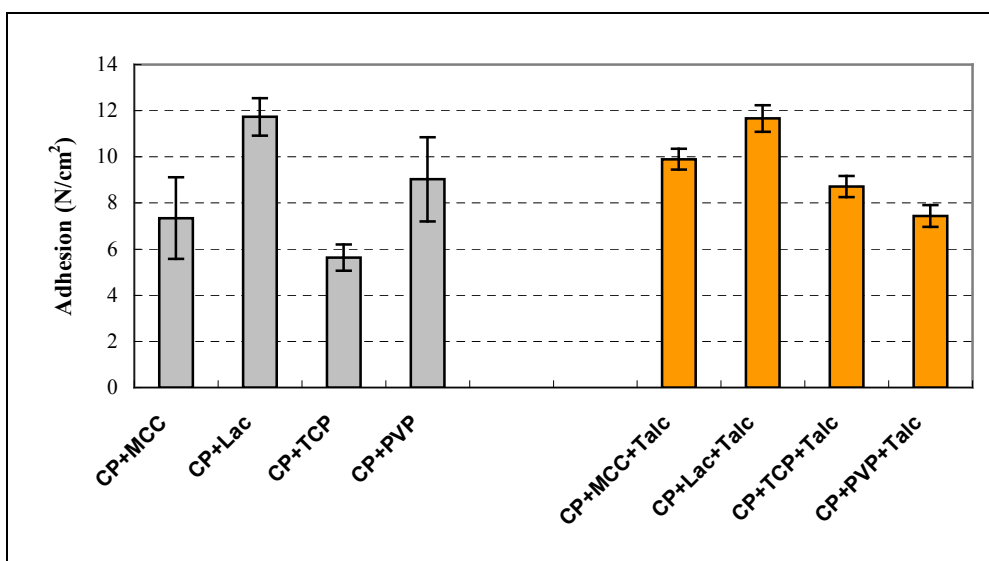
Fig. 3.35: Influence of talc on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, ac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

3.1.4.3.3　Investigations through the fluid-bed granulation

Trial batches were prepared with various combinations [Tab.3.18] using a fluid-bed granulator (GPCG 1, Glatt, Germany) to find a proper composition for granulation. The process parameters were arranged as described in table 3.4.

Tab. 3.18: Compositions of trials (% w/w in dry state)

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15
CP	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
MCC	80					40	40	40	40						
Lac		80				40				40	40	40			
TCP			80				40			40			40	40	
cl-PVP				80				40			40		40		40
Talc					80				40			40		40	40

(CP: carbomer 934P, MCC: microcrystalline cellulose, Lac: lactose, TCP: tri-calcium phosphate)

Only C3 and C7 showed a possibility to produce pellets [Fig.3.36b, c]. With the other compositions it was failed to prepare the granules, because the powder beds tended to be too sticky and became severely agglomerated [Fig.3.36a].

  (a) Failed   (b) 20%-CP + 80%-TCP   (c) 20%-CP+40% MCC+40% TCP
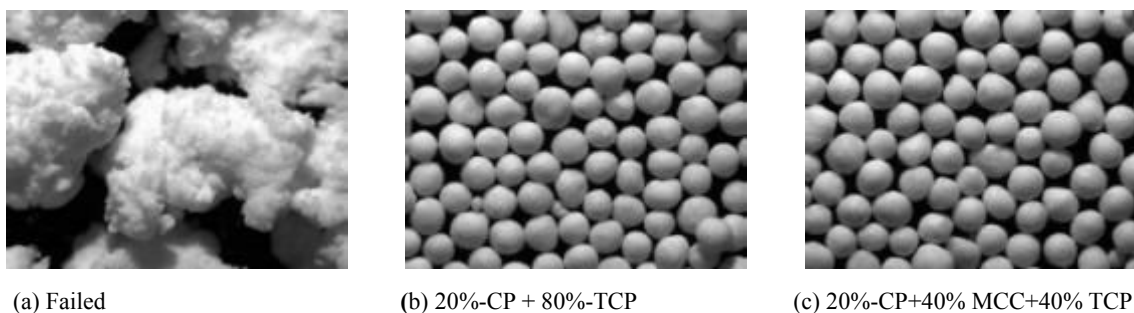
Fig. 3.36: Products of trials (CP: carbomer 934P, TCP: tri-calcium phosphate)

It was indicated that in chapter 3.1.4.2, microcrystalline cellulose and tri-calcium phosphate could be the useful excipients for the granulation of carbomer 934P. Tri-calcium phosphate reduced remarkably the tackiness of carbomer-containing wet mass. Microcrystalline cellulose had also a positive effect to achieve a suitable wet mass (neither too friable nor too cohesive) for granulation. According to this result of trials, the granulation processes were carried out through fluidized-bed granulation. It was also found that the both substance (microcrystalline cellulose and tri-calcium phosphate) could be the additives of choice for the granulation processes. Therefore, it could be concluded that there is a relationship between the results of wet mass investigations and the practical granulation process.

3.1.4.3.3.1 Establishment of the final composition for pellets production

An investigation was carried out to establish the final composition for pellets. Based on the results of chapter 3.1.4.2, tri-calcium phosphate and microcrystalline cellulose were selected as the additives for granulation process. It appeared that approximately 30% (w/w, in dry state) of tri-

calcium phosphate was necessary in a powder blend to avoid the tacking problem when the content of carbomer 934P was 20% (w/w, in dry state). Therefore, the carbomer content was kept always as 20%. The content of microcrystalline cellulose was varied and its influence on the produced pellets was examined [Tab. 3.19]. Theophylline was incorporated as a model drug. The composition was targeted to obtain a maximal yield of 500-1180 fraction and a maximal sphericity of the pellets.

Tab. 3.19: Yield and sphericity of produced pellets at different content of MCC

Compositions in dry state	Yield of 500-1180μm (%)	Sphericity (%)
CP 20% + Theophylline 20% + TCP 60% + MCC 0%	20.5 ± 2.03	59.3 ± 0.97
CP 20% + Theophylline 20% + TCP 50% + MCC 10%	29.8 ± 1.66	62.6 ± 1.02
CP 20% + Theophylline 20% + TCP 40% + MCC 20%	33.6 ± 1.21	68.8 ± 1.13
CP 20% + Theophylline 20% + TCP 30% + MCC 30%	41.2 ± 0.89	71.5 ± 0.99

(CP: carbomer 934P, MCC: microcrystalline cellulose, TCP: tri-calcium chloride) (Mean±S.D., n =3)

As observed in table 3.19, the more spherical pellets were obtained when microcrystalline cellulose content was increased in a powder blend. And the yield of 500-1180 μm fraction was also increased with increasing microcrystalline cellulose content. When the amount of microcrystalline cellulose was increased from 0% to 30%, the sphericity was increased for 12.2%, the yield of 500-1180μm fraction was increased for 20.7%, respectively. Therefore, it could be concluded that the higher microcrystalline cellulose content in a powder blend, the better quality of pellets were produced. From this result, the final composition was established: Carbomer 934P 20% + theophylline 20% + tri-calcium phosphate 30%+ microcrystalline cellulose 30% (w/w, in dry state).

3.1.4.3.3.2 Preparation of pellets

Pellets were produced with 400g of powder blend containing 20% of carbomer 934P, 30% of microcrystalline cellulose, 30% of tri-calcium phosphate and 20% of theophylline as a model drug. 1%-PVP K90 solution was used as a binding-liquid. The process conditions were set as listed in table 3.4.

3.1.4.3.3.3 Results

Pellets could be successfully produced and the results of evaluations are shown in table 3.20.
It was concluded that not all produced pellets were acceptable for a general use. An optimization step was therefore necessary through the controlling of process parameters in order to obtain the pellets of better quality.

Tab. 3.20: Results of evaluation of produced pellets

Total yield (%)	79.77 ± 4.17
Yield of 500~1180 μm fraction (%)	42.18 ± 5.67
Mean diameter (μm)	972 ± 14.3
Oversize fraction (% of > 2000 μm)	4.02 ± 4.50
Proportion of fines (% of < 250 μm)	0.60 ± 1.57
Friability (%)	1.51 ± 0.18
Hardness (N)	6.87 ± 0.98
Hausner Index	1.02 ± 0.01
Sphericity (%)	72.6 ± 0.66
Roughness	1.04 ± 0.01
Aspect ratio	1.13 ± 0.01

(Mean ± S.D., n =3)

3.1.4.4 Investigations of the anti-tack mechanism of some excipients

Tri-calcium phosphate is insoluble in water. It was assumed therefore that, its anti-tack action to carbomer 934P is not because the effect of its Ca ions. In order to elucidate this hypothesis, the amount of Ca ions in the composition was detected by chelate titration method (see chapter I.2.1) [306]. Wet mass was prepared with a wetting liquid containing the same amount of Ca ions (0.006 mg Ca/ml = 0.88g $CaCl_2$/l) instead of the adding tri-calcium phosphate. The adhesion of the wet mass were [Tab. 3.21]:

Tab. 3.21: Adhesion of wet mass containing tri-calcium phosphate and/or calcium chloride

	Carbomer 934P + theophylline + microcrystalline cellulose + tri-calcium phosphate	Carbomer 934P + theophylline + microcrystalline cellulose + $CaCl_2$
Adhesion (N/cm^2)	5.77 ± 1.0	8.91 ± 1.32

(Mean±S.D., n =3)

As proved by the chelate titration method, tri-calcium phosphate incorporated in the final composition of pellets contains a very small amount of Ca ions. From the result of table 3.21, it could be concluded that this amount of Ca ions had no anti-tack effect to carbomer. The anti-tack action of tri-calcium phosphate was not caused by any chemical interactions [54-57, 59, 60, 64, 66, 68] or complex formation between carbomer and Ca ions [231], but attributed by some physical action of tri-calcium phosphate. Based on this assume, some other substances having similar properties with tri-calcium phosphate were investigated. Crospovidone (Polyplasdone XL®), di-

calcium phosphate, and bentonite were selected. They are practically insoluble or very slightly soluble in water, and have a relative great enslin number [Tab.3.22] like tri-calcium phosphate.

Tab. 3.22: Enslin number of selected excipients

	Lactose	Tri-calcium phosphate	Crospovidone	Di-Ca phosphate	Bentonite
Enslin number	0.8	3.2	3.7	2.3	2.0

These substances were introduced into the composition instead of tri-calcium phosphate, and the adhesion was measured. The compositions used were therefore, carbomer 934P 20% + theophylline 20% + microcrystalline cellulose 30% + A 30% (w/w, in dry state). For A, crospovidone, di-calcium phosphate, and bentonite were incorporated, respectively. The results are shown in figure 3.37.
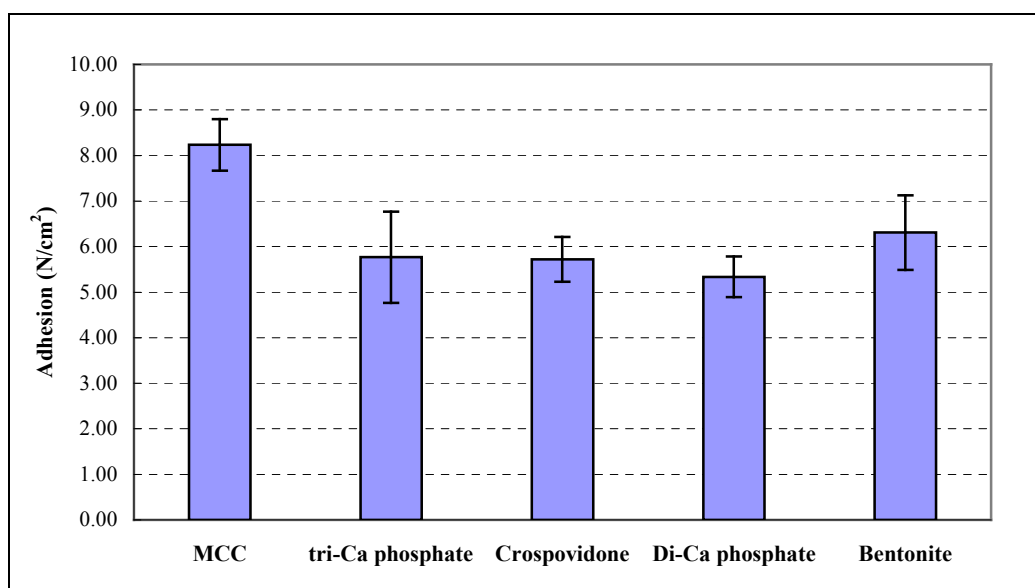
Fig. 3.37: Adhesion of wet mass containing tri-calcium phosphate and other excipients instead of tri-calcium phosphate (Mean $\pm$ S.D., n =5)

Crospovidone, di-calcium phosphate, and bentonite could also reduce considerably the tack of wet mass, like tri-calcium phosphate. In case of di-calcium phosphate, the effect of Ca ions was excluded, because it was proved that the amount of Ca ions was negligible in di-calcium phosphate dispersion. In addition, it was indicated that these substances made it possible to produce carbomer 934P-containing granules. [Fig.3.38~3.40].
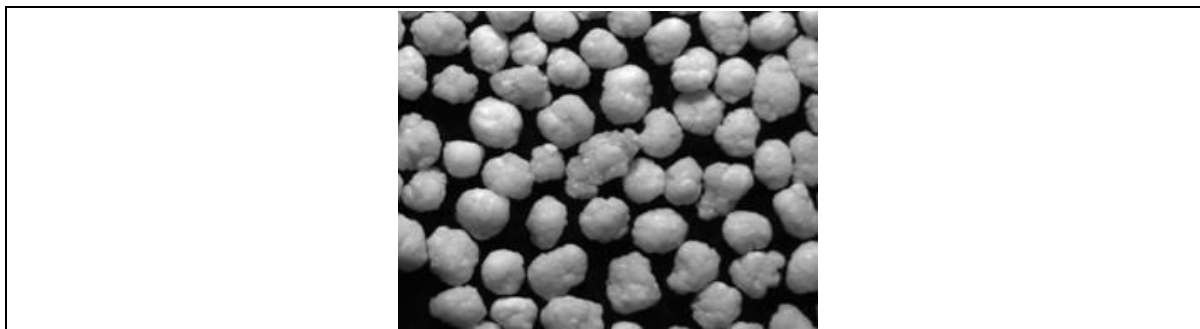
Fig. 3.38: Product made with carbomer 934P 20% + theophylline 20% + MCC + **Crospovidone** 30%-mixtures
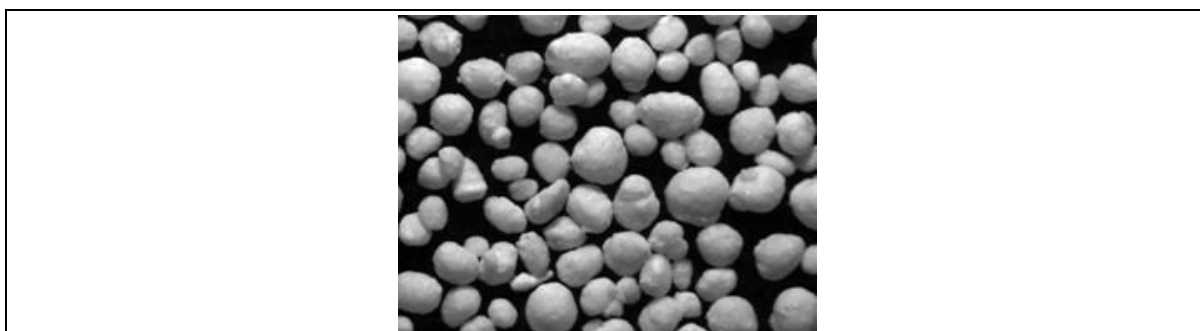
Fig. 3.39: Product made with carbomer 934P 20%+ theophylline 20%+ MCC 30% + **di-calcium phosphate** 30%-mixtures
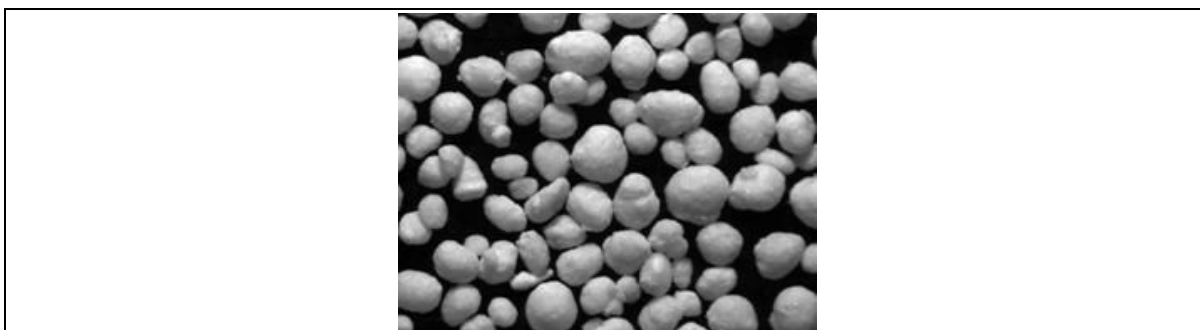
Fig. 3.40: Product made with carbomer 934P 20%+ theophylline 20%+ MCC 30% + **Bentonite** 30%-mixtures

3.2 Influence of process parameters on the produced pellets

3.2.1 Investigations through factorial design

The influences of process parameters on the produced pellets were investigated through a 2^3 factorial design [124, 148, 149, 189]. Three process variables (rotor speed, spray rate of the binder solution, and the spheronization time) were studied at two levels. The factors and their levels were shown in table 3.23~3.25.

Tab. 3.23: The fixed parameters

Inlet air temperature (°C)	40
Drying air temperature (°C)	60
Spray pressure (bar)	1.5
Inlet air volume (m^3/h)	60
Shaking interval (time/sec)	5/3
Batch size (g)	400

Tab. 3.24: Factors and their settings in the factorial design

Factors	Level	
	Low (-1)	High (+1)
A: rotor speed (rpm)	250	750
B: spray rate (g/min)	20	40
C: spheronization time (min)	0	10

Tab. 3.25: Combination of factors (-, low level; +, high level)

	A	B	C
-1	-	-	-
a	+	-	-
b	-	+	-
ab	+	+	-
c	-	-	+
ac	+	-	+
bc	-	+	+
abc	+	+	+

3.2.2   Results

Tab. 3.26: Results of the evaluation of pellets (a)

Batch	Total yield [%]	Yield of 500~1180 µm [%]	Mean diameter [µm]	Oversize fraction (> 2000 µm) [%]	Proportion of fines (< 250 µm) [%]
-1	80.94±3.82	59.33±5.61	476±46.50	1.72±0.65	3.10±0.47
a	80.68±9.87	75.94±13.66	812±93.50	1.06±2.02	0.21±0.28
b	82.37±7.43	59.50±5.51	863±71	2.40±0.60	1.13±0.90
ab	82.25±2.72	79.87±4.33	907±126.50	2.21±0.63	0.14±0.32
c	80.37±12.10	54.80±4.52	923±26.50	1.56±0.58	2.45±0.25
ac	81.19±4.30	70.32±3.43	1002±43	1.31±1.40	1.49±1.71
bc	81.19±5.19	57.64±4.80	987±78.50	2.97±0.63	1.41±0.10
abc	81.62±3.58	76.28±2.05	1014±38	2.52±1.43	0.17±0.19

(Mean ± S.D., n =3)

Tab. 3.27: Results of the evaluation of pellets (b)

Batch	Sphericity (%)	Roughness	Aspect ratio	Friability (%)	Hardness (N)
-1	64.6±1.99	1.13±0.01	1.26±0.05	1.48±0.10	4.90±0.68
a	78.1±1.13	1.06±0.02	1.20±0.05	1.02±0.10	10.38±1.56
b	67.4±2.18	1.11±0.01	1.25±0.01	1.44±0.20	9.03±1.08
ab	77.4±1.08	1.07±0.01	1.14±0.05	1.04±0.05	11.92±1.45
c	72.5±2.74	1.10±0.01	1.16±0.07	1.52±0.37	9.44±1.74
ac	84.8±0.70	1.04±1.50	1.11±0.06	0.98±0.19	10.86±1.05
bc	69.1±2.32	1.10±0.02	1.26±0.02	1.18±0.12	11.04±1.12
abc	82.3±0.85	1.05±0.01	1.10±0.01	1±0.19	12.42±1.49

(Mean ± S.D., n =3)

Tab. 3.28: Effect and Significance of process parameters (a)

	500~1180µm (%)		Mean diameter (µm)		Oversized (%)		Fines (%)	
	E	*S*	*E*	*S*	*E*	*S*	*E*	*S*
A	17.79	+	121.5	+	-0.39	-	-1.52	+
B	3.23	-	139.5	+	1.11	-	-1.10	+
C	-3.90	-	217.0	+	0.24	-	0.24	-
AB	1.72	-	-86.0	+	0.07	-	0.40	-
AC	-0.71	-	-68.5	-	0.04	-	0.42	-
BC	1.18	-	-101.5	+	0.20	-	-0.08	-
ABC	0.32	-	60	-	-0.17	-	-0.55	-

(**A**: rotor speed, **B**: spray rate, **C**: spheronization time, +, statistically significant ($P < 0.05$) *E*: Effect, *S*: Significance)

Tab. 3.29: Effect and Significance of process parameters (b)

	Sphericity (%)		Roughness		Aspect ratio	
	E	*S*	*E*	*S*	*E*	*S*
A	12.25	+	-0.055	+	-0.091	+
B	-0.95	-	0.002	-	0.004	-
C	5.32	+	-0.02	+	-0.054	+
AB	-0.65	-	0.01	-	-0.04	+
AC	0.49	-	0.003	-	-0.01	-
BC	-1.99	+	0.006	-	0.04	+
ABC	1.08	-	-0.001	-	-0.016	-

(**A**: rotor speed, **B**: spray rate, **C**: spheronization time, +, statistically significant ($P < 0.05$) *E*: Effect, *S*: Significance)

Tab. 3.30: Effect and Significance of process parameters (c)

	Hardness (N)		Friability (%)	
	E	*S*	*E*	*S*
A	2.79	+	-0.395	+
B	2.21	+	-0.085	-
C	1.88	+	-0.078	-
AB	-0.66	+	0.105	-
AC	-1.39	+	0.034	-
BC	-0.63	+	-0.076	-
ABC	0.63	+	0.078	-

(**A**: rotor speed, **B**: spray rate, **C**: spheronization time, +, statistically significant ($P < 0.05$) *E*: Effect,

S: Significance)

3.2.2.1 Influence on the yield of 500–1180 μm fraction

It is ideal when the yield of 500~1180μm fraction is maximized, since this size range of pellets are appropriate for the pharmaceutical use. The effect of rotor speed was found to be the most potent on the yield of 500-1180μm [Fig. 3.41].
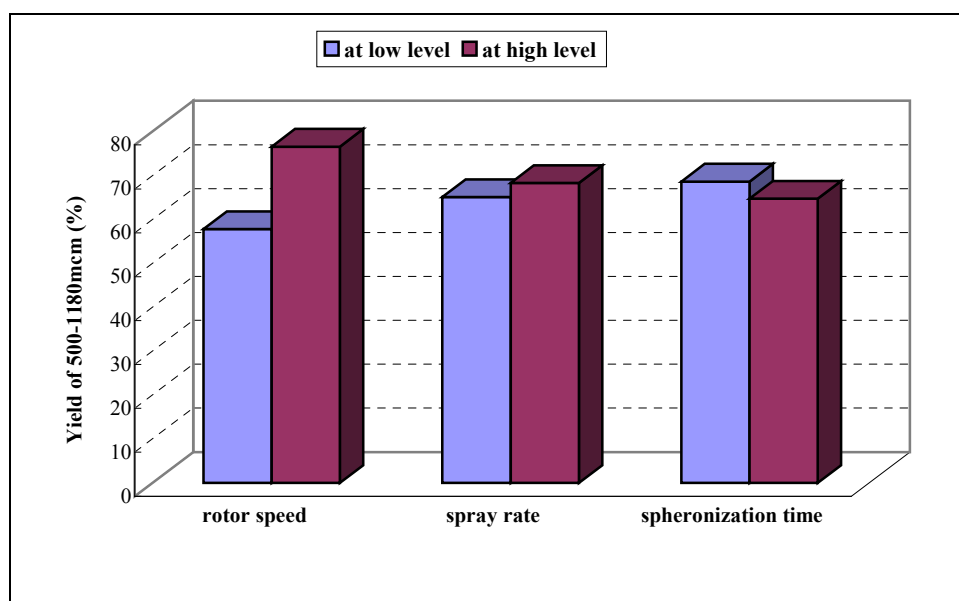
Fig. 3.41: Influence of parameters on the yield of 500~1180 μm of fraction
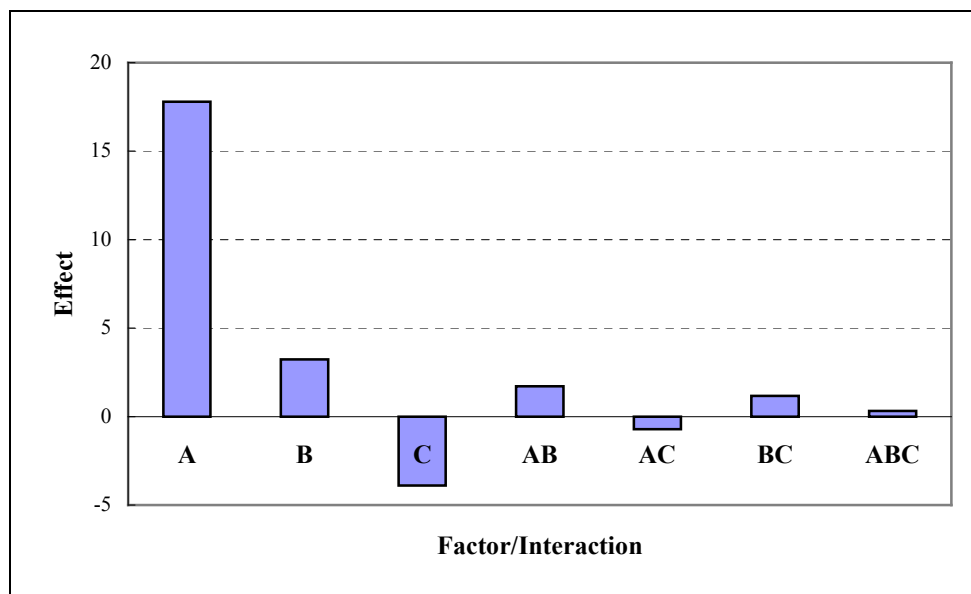
Fig. 3.42: Effect and interactions of parameters on the yield of 500~1180 µm of fraction

Factor A, the rotor rotation speed, showed a remarkable positive effect. When the rotor speed was increased up to the high level, the yield of 500~1180µm increased to 75.6%. It was significantly ($P < 0.05$) higher than that (57.8%) of at the low level of rotor speed. This result may be attributed that a higher rotor speed allowed a more intensive contact between the particles [124, 131, 152, 139, 142, 151, 165]. It might also help an even distribution of the sprayed binding-liquid in the powder bed. This could result in the formation of more uniform pellets. The spray rate of binder also affected positively, but it was statistically not significant. In addition, no considerable interactions were found among the factors [Fig.3.42].

3.2.2.2 Influence on the pellet size

The mean diameter of pellets was significantly increased by three investigated variables. It was increased for 12% by the level-up of rotor speed, and for 18% at the high level of spray rate, respectively. Spheronization time also affected significantly positively. The mean diameter of pellets increased about 18% at the high level of spheronization time [Fig.3.43].
The similar results have been previously reported by other researchers [153, 161, 162, 165, 173]. According to published studies, the larger spheroids were produced with increasing the spray rate with a fixed volume of moistening liquid sufficient for spheronization.
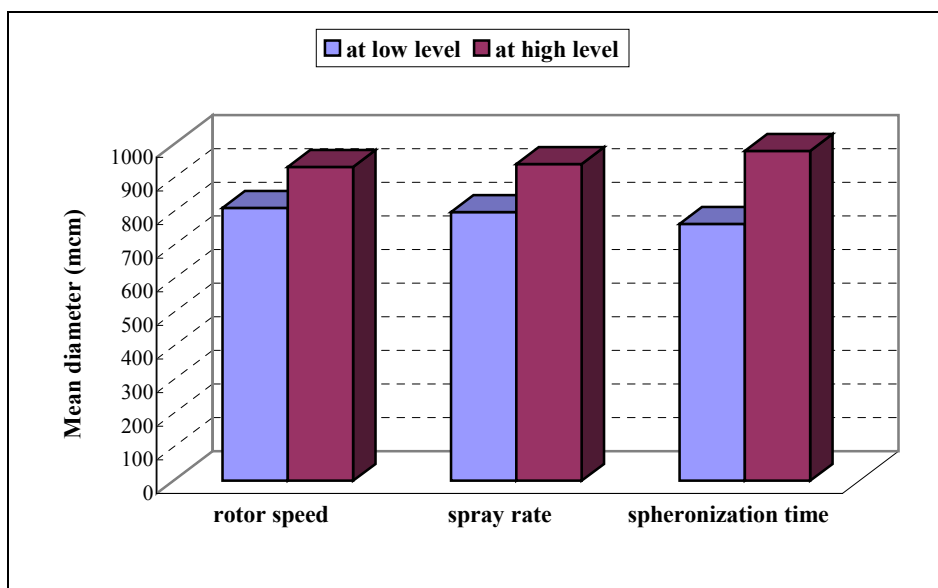
Fig. 3.43: Influence of parameters on mean diameter of pellets
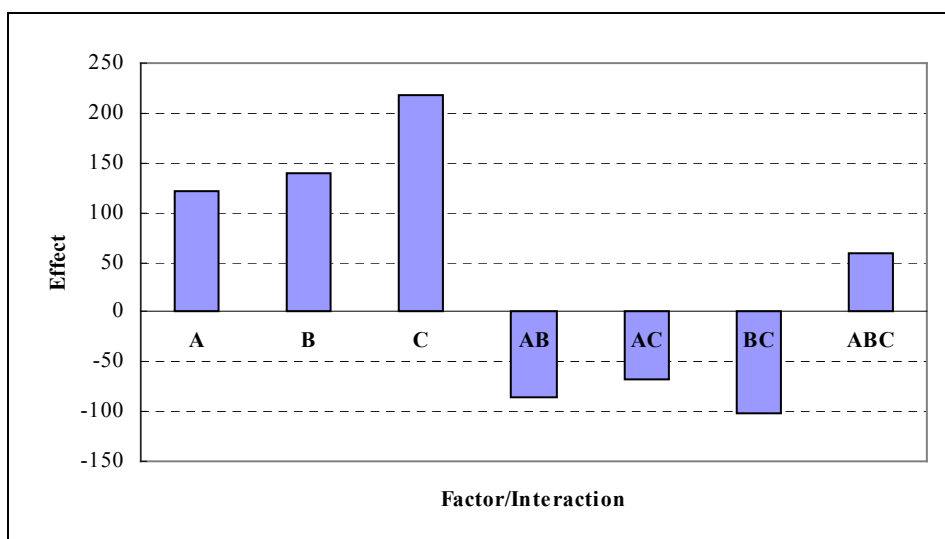
Fig. 3.44: Effect and interactions of parameters on mean diameter of pellets

It was considered that the increased wetting per unit time resulted in the formation of larger nuclei and enhanced the growth rate of spheroids [153, 161, 162, 173]. The spheronization step could lead to the even distribution of sprayed binder solution in powder bed. This caused finally an increase in the granule size and the oversized fraction. Moreover, it was indicated that there was a positive interaction between A, B, and C [Fig.3.44]. When the rotor speed, spray rate, and spheronization time were all at high level, the mean diameter of pellets was increased. The higher rotor speed could provide an intensive contact between the particles, and this acted synergistically with the high spray rate of binder and spheronization step. Therefore, the increase of mean diameter occurred. As the spray rate of the binder increased, the ability of the solution to wet and penetration into the powder was enhanced. This also affected positively the mean diameter of pellets.

3.2.2.3 Influence on the oversized (> 2000 µm)

The oversized fraction must be minimized because this size is not appropriate for a pharmaceutical use. As indicated in figure 3.45, the spray rate of binder and spheronization time had a positive effect on the % of oversized pellets. The oversized pellets were increased for 79% at the high level of spray rate.
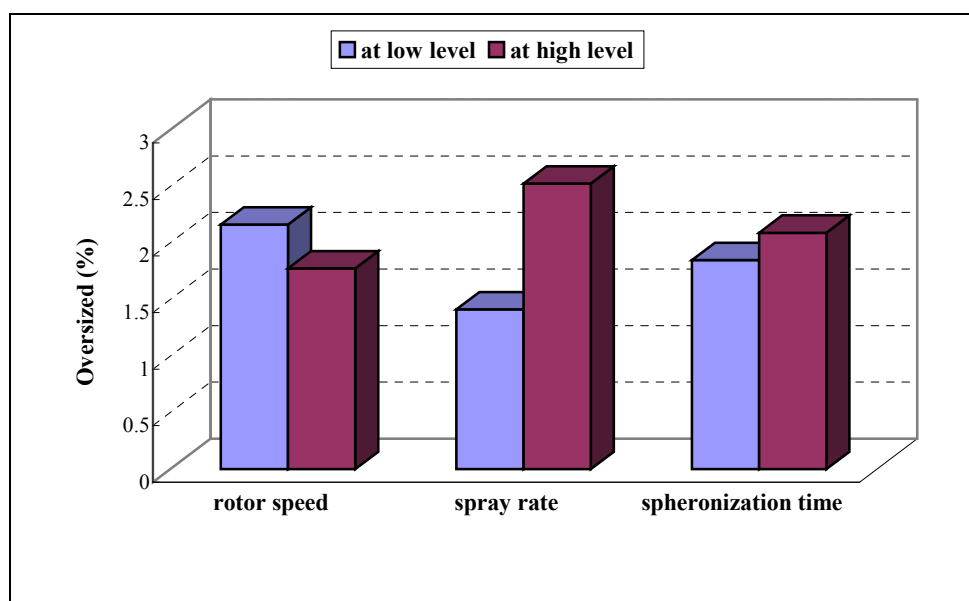
Fig. 3.45: Influence of parameters on % oversized
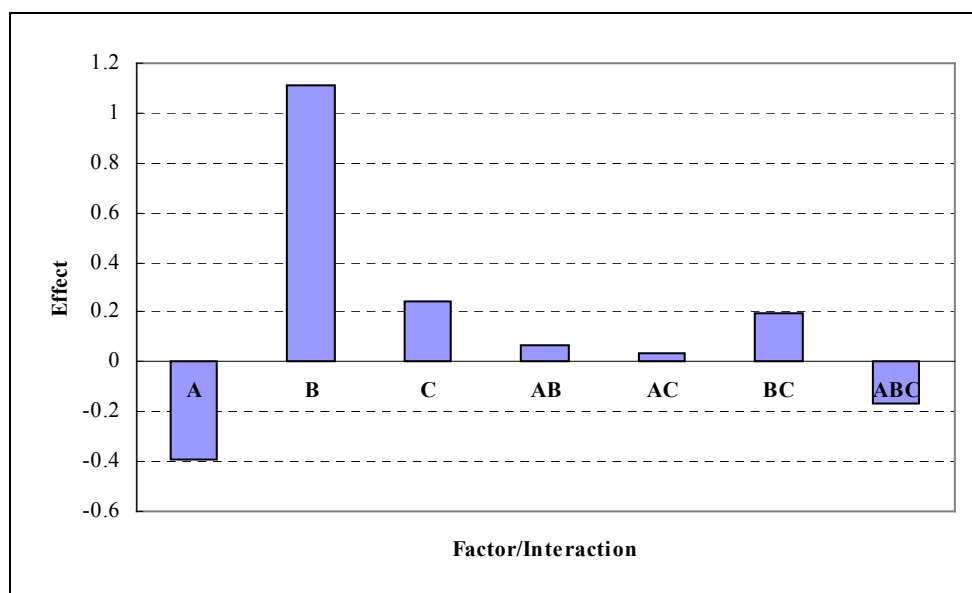
Fig. 3.46: Effect and interactions of parameters on % oversized

According to Vertommen and Kinget [139, 140], the high spray rate of binder leads to an uncontrollable growth of the particles. When an equal spreading of the liquid was not ensured, that

causes a local over-wetting and the pellets were produced with a less equal size. Overall, an increase in the spray rate of the binder led to a corresponding increase in the granule size (both percentage coarse and geometric mean diameter). As also summarized by Seo *et al.* [125, 127, 135, 137, 138, 141, 142], the higher spray rate allows a greater number of droplets to be sprayed onto the starting material per unit time. However, there were also other studies [151-153, 161, 162, 173], which reported the contradictory results. For example, it was reported that the mean diameter of pellets did not considerably increased with increasing the spray rate of binder and the atomizing pressure of spray gun. It was also found that the size of granule was not only dependent on spray rate of binder, but also on the spray pressure. Since the droplet size of binder liquid becomes finer, when the spray pressure is higher, this leads the uniform wetting of powder bed despite of high spray rate of binder. In current study a relative high spray pressure (1.5 bar) was employed, and the mean diameter of pellets was considerably positively affected by the increase of the spray rate. In addition, no considerable interactions were found among the factors.

3.2.2.4   Influence on the fines (< 250 µm)

Rotor speed and the spray rate of binder showed a remarkable negative effect on the proportion of the fines. At the high level of rotor speed and spray rate, the fines decreased approximately 60% and 40%, respectively. On the contrary, the spheronization time did not show any significant effect [Fig.3.47].
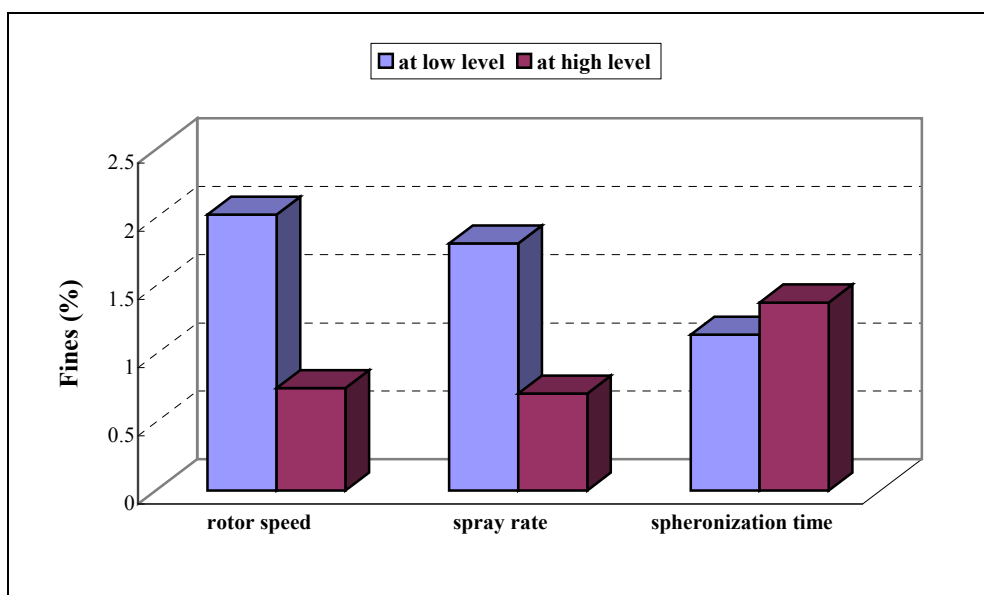
Fig. 3.47: Influence of parameters on % fines
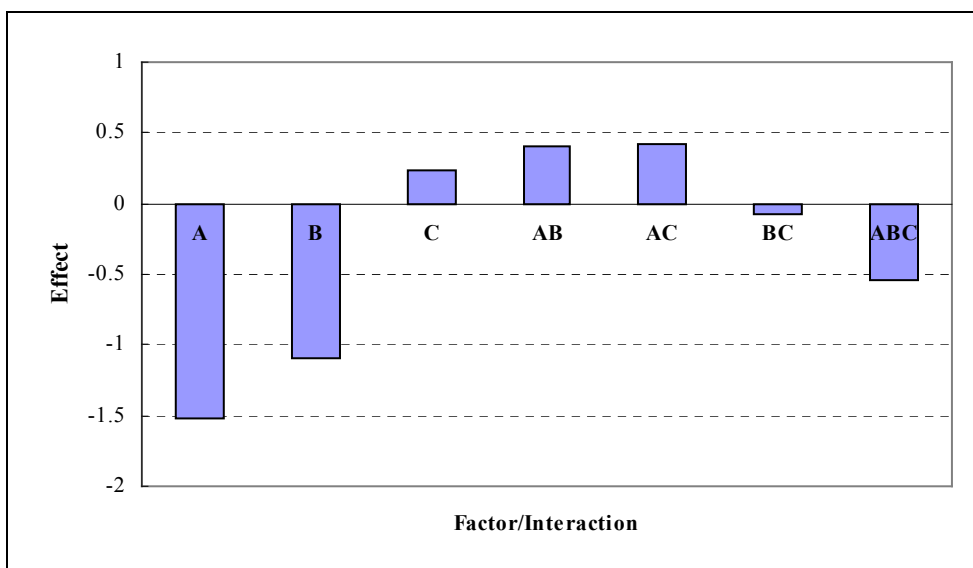
Fig. 3.48: Effect and interactions of parameters on % fines

The proportion of fine particles is one of responses, which should be minimized as possible. It was possible to reduce the fine particles by increasing the rotor rotation speed and the spray rate of binder. According to previous studies [124, 131, 132, 139, 142, 151], the agglomeration rate could be activated through the higher spray rate of binder. Furthermore, the higher rotor rotation speed can provide more intensive contacts between the powder particles. Therefore, the proportion of fines could be also decreased.

3.2.2.5   Influence on the sphericity, aspect ratio and roughness
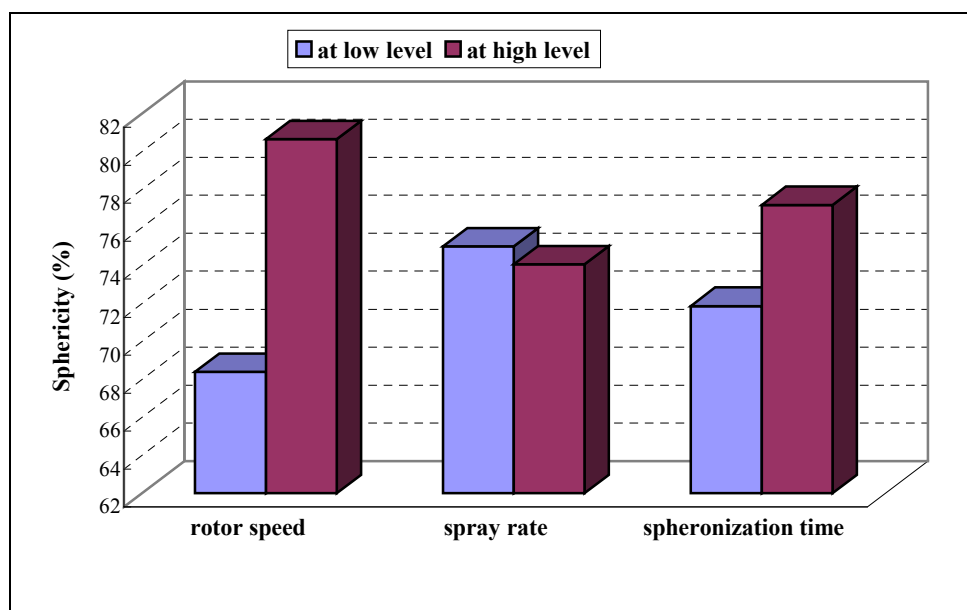
Fig. 3.49: Influence of parameters on sphericity of pellets

The sphericity, roughness and aspect ratio are the parameters showing directly the surface properties of pellets. For a pharmaceutical use, the more spherical pellets of smoother surface are better, since they are more appropriate for a further process, such as coating. The sphericity, roughness and the aspect ratio can be all determined by the microscopic image analysis [165, 195, 196, 202]. Figure 3.49 and 3.50 describe the effects of process variables on the sphericity of pellets.
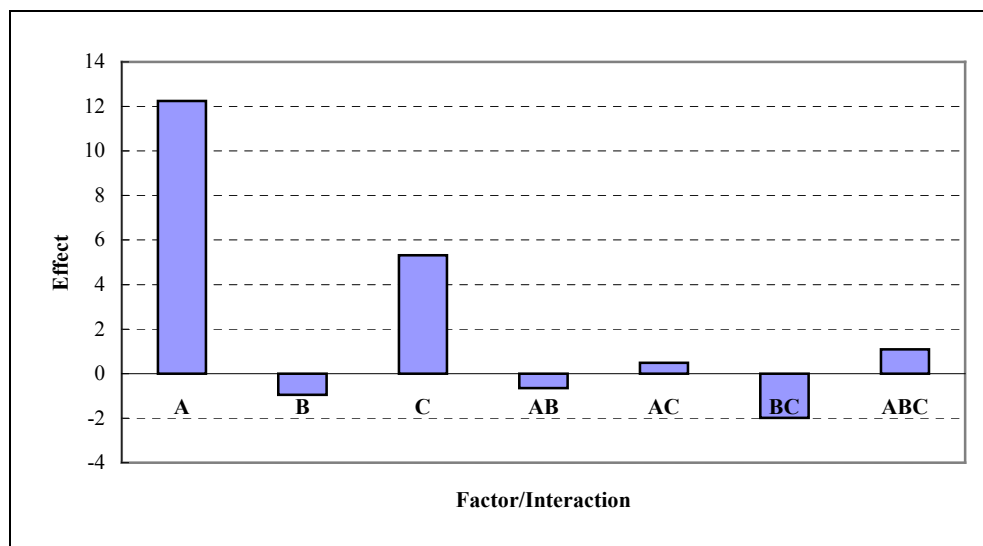
Fig. 3.50: Effect and interactions of parameters on sphericity of pellets

The sphericity of pellets was dramatically increased at the high rotor speed. The average sphericity of pellets produced at high rotor speed was 80.7%, it was significantly higher ($P < 0.05$) than that (68.4%) of pellets formed at low level of rotor speed [Fig.3.51].

a) At low rotor speed   **(b) At high rotor speed**
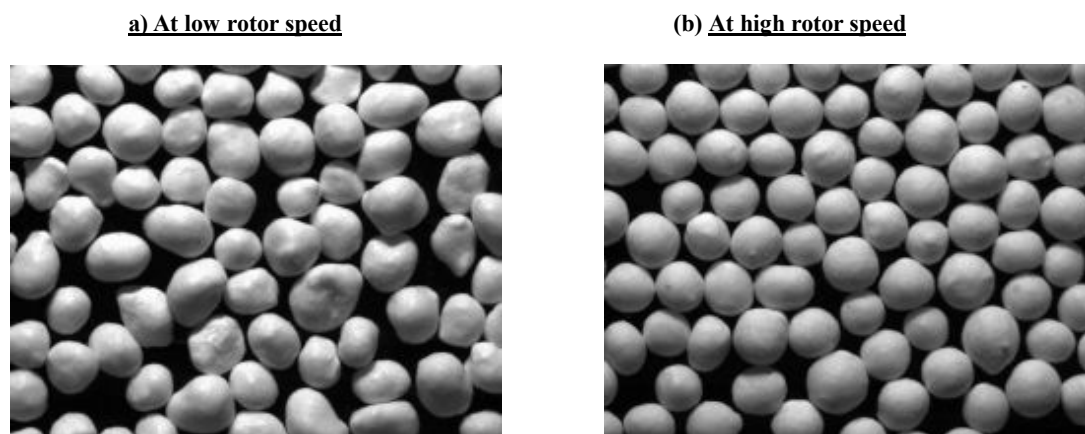
Fig. 3.51: Granules produced at different rotor speed

It was also found that the spheronization step was significantly positively affected the sphericity. The spheronization time in this study is defined as the time of rotation after the completion of pelletization. A rolling action after the pelletization can affect the surface morphology of the pellets

[165]. It was indicated that 10 minutes of spheronization step led to a remarkable improvement in sphericity [Fig.3.52].

(a) Without spheronization   **(b) With 10 min. spheronization**
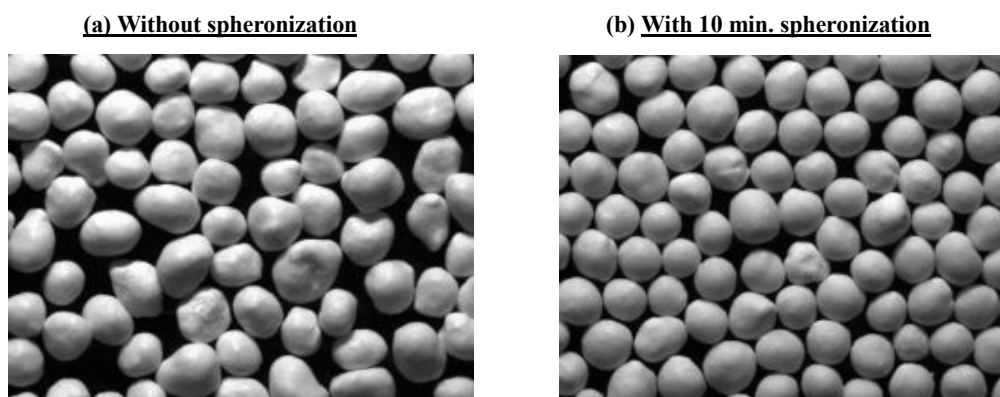
Fig. 3.52: Granules produced with at different spheronization time

It was clear that spherical pellets could not be obtained without spheronization step. At the low level of spheronization, 0 minute, the pellets showed a poor sphericity [Fig.3.52a]. However, it increased considerably [Fig.3.52b] after 10 minutes of spheronization time.

Furthermore, it was found that there was a significant negative interaction between spray rate of binder and spheronization time. Fig.3.53 shows the difference of pellets produced at two level of spray rate. From this result it could be concluded that the spray rate of binder is particularly critical factor in the sphericity of pellets. Although spheronization time can affect positively the sphericity, this positive effect could not be found when the pellets were produced with high level of spray rate.
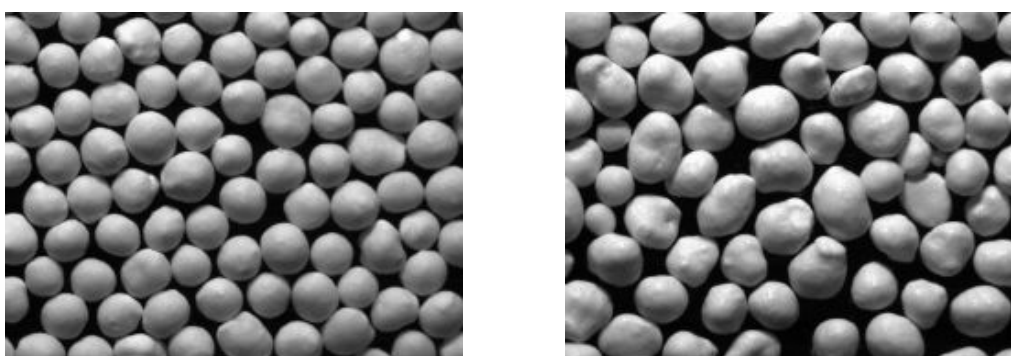
Fig. 3.53: Granules produced at different level of spray rate and spheronization time: at low spray rate + spheronization time (left), at high spray rate + spheronization time (right)

Influence on the aspect ratio

The aspect ratio of a perfect sphere is 1. This value becomes higher or lower than 1 as the spheroids become less spherical [165, 195, 196, 202]. According to figure 3.54 and 3.55, the aspect ratio was mainly affected by the rotor rotation speed and the spheronization time. This observation was in good agreement with expectations. Since aspect ratio is closely related with sphericity, it is

decreased as the sphericity increased. Rotor speed and spheronization time affected positively the sphericity of pellets, aspect ratio was decreased as a consequence near to 1.
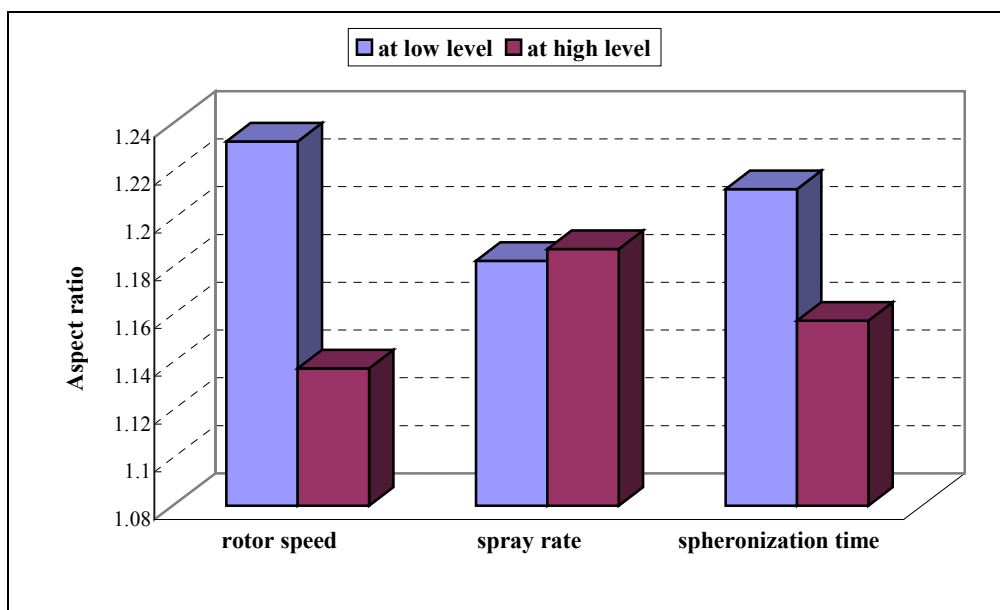
Fig. 3.54: Influence of parameters on aspect ratio of pellets
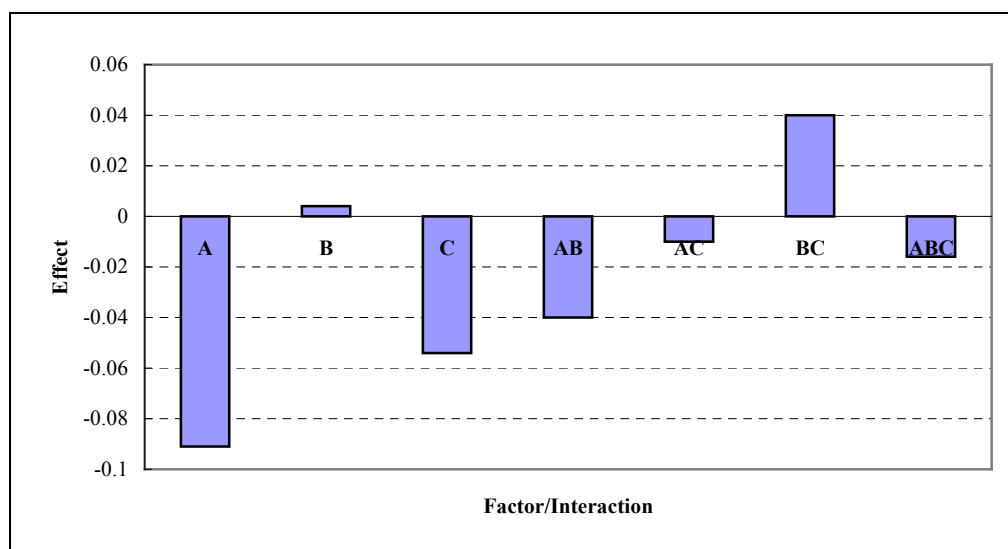
Fig. 3.55: Effect and interactions of parameters on aspect ratio of pellets

Influence on roughness

The smoother pellets were produced at the higher rotor speed and at the high spheronization time level. The similar results were previously reported [154, 155, 163, 167, 178, 182, 191, 192]. The roughness of pellets decreased significantly at high rotor speed and spheronization time [Fig. 3.56 and 3.57]. As mentioned above, the higher rotor speed provided more intensive contact between particles [124, 131, 152, 139, 142, 151, 165] and helpful for the equal distribution of binder liquid.

This could improve the surface plasticity of wet mass, therefore the smoother surface was found. Roughness can be also explained by the correlation with sphericity. The more spherical and smoother pellets show the smaller aspect ratio and roughness.
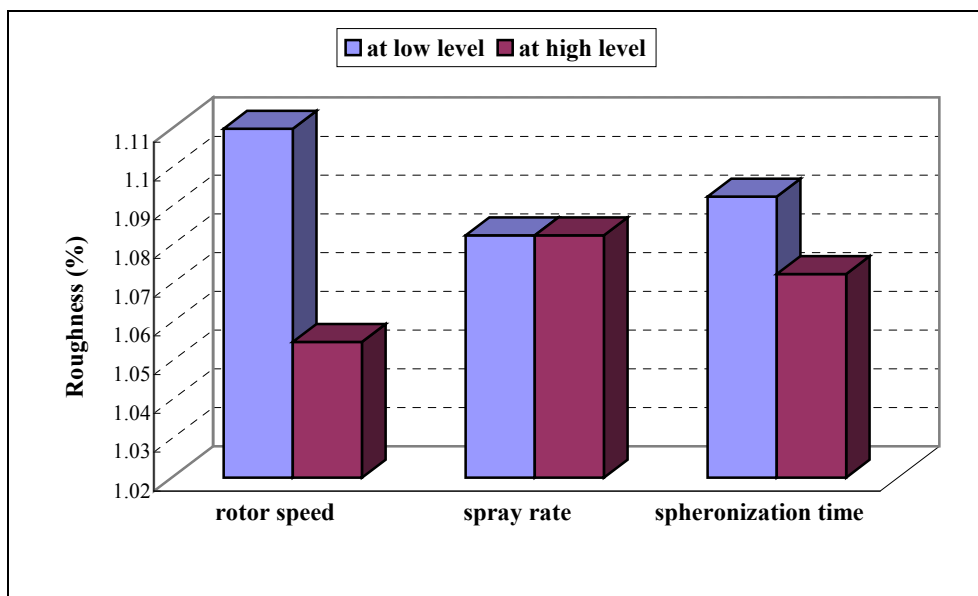
Fig. 3.56: Influence of parameters on roughness of pellets
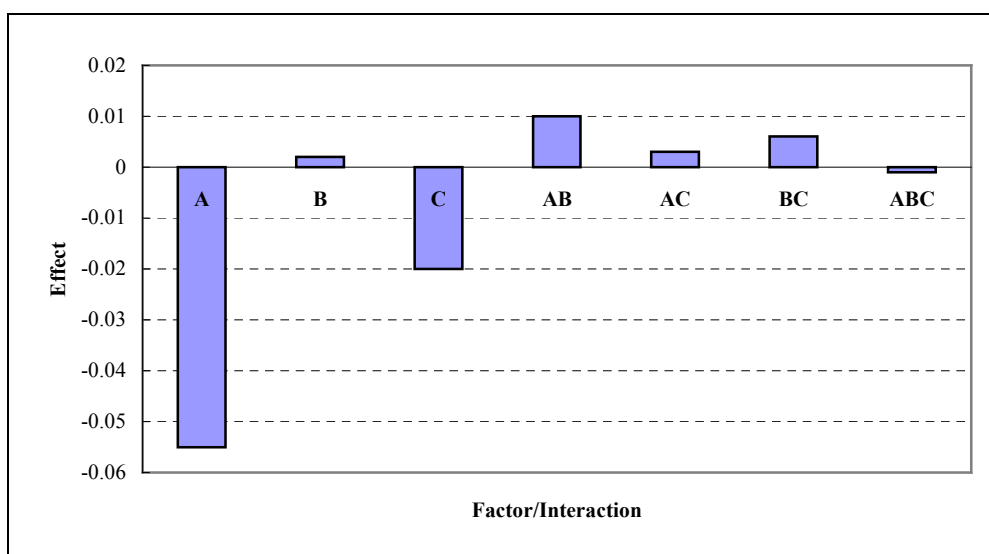
Fig. 3.57: Effect and interactions of parameters on the roughness of pellets

3.2.2.6   Influence on the friability and hardness

The hardness of pellets increased in all cases with an increased rotor rotation speed, spray rate of binder, and spheronization time [Fig.3.58 and 3.59]. Their effects were found all statistically significant ($P < 0.05$). The pellets produced at high level of parameters needed a greater crushing force at hardness test, whereas the friability was decreased [Fig.3.60 and 3.61]. This result could be

considered that a high spray rate enhanced the wetting per unit time [153, 161, 165, 173]. And the higher rotor speed and spheronization step might help the mixing and the growth of powder particles. The growth procedure of particles was enhanced by this sufficient and even wetting. Therefore, the denser and harder pellets could be prepared.
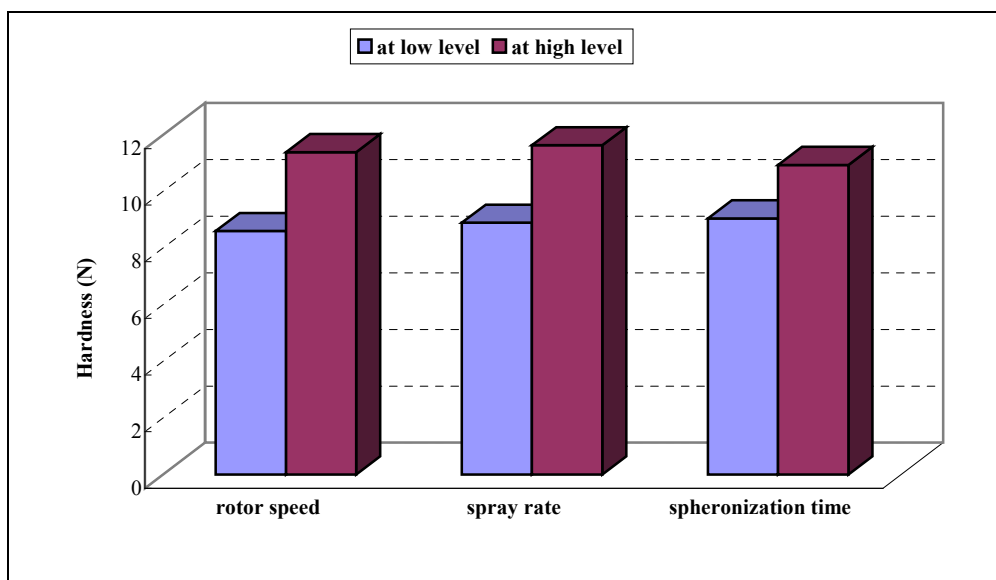
Fig. 3.58: Influence of parameters on the hardness of pellets
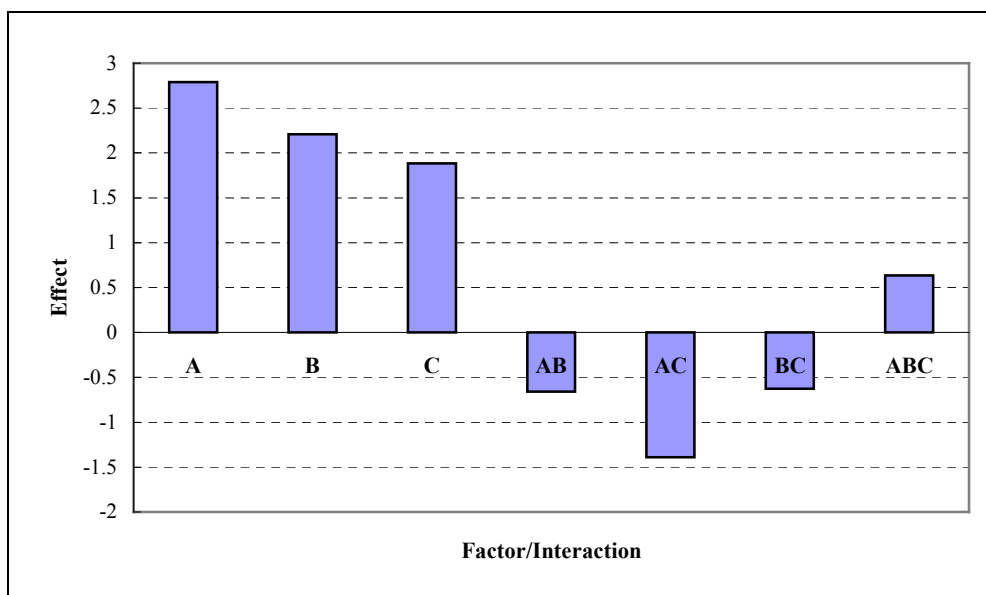
Fig. 3.59: Effect and interactions of parameters on the hardness of pellets
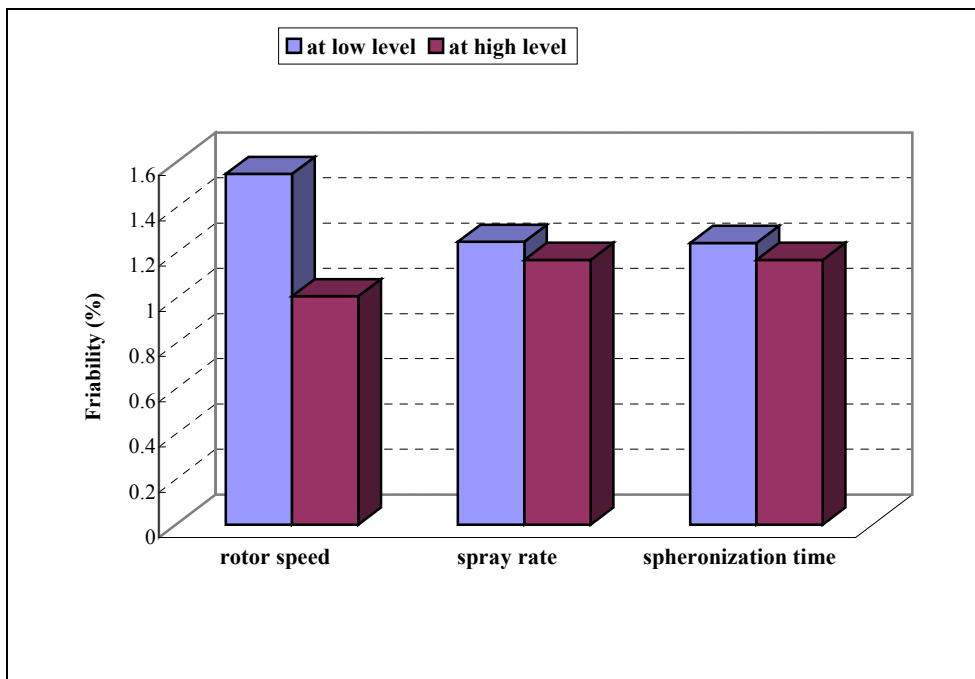
Fig. 3.60: Influence of parameters on the friability of pellets
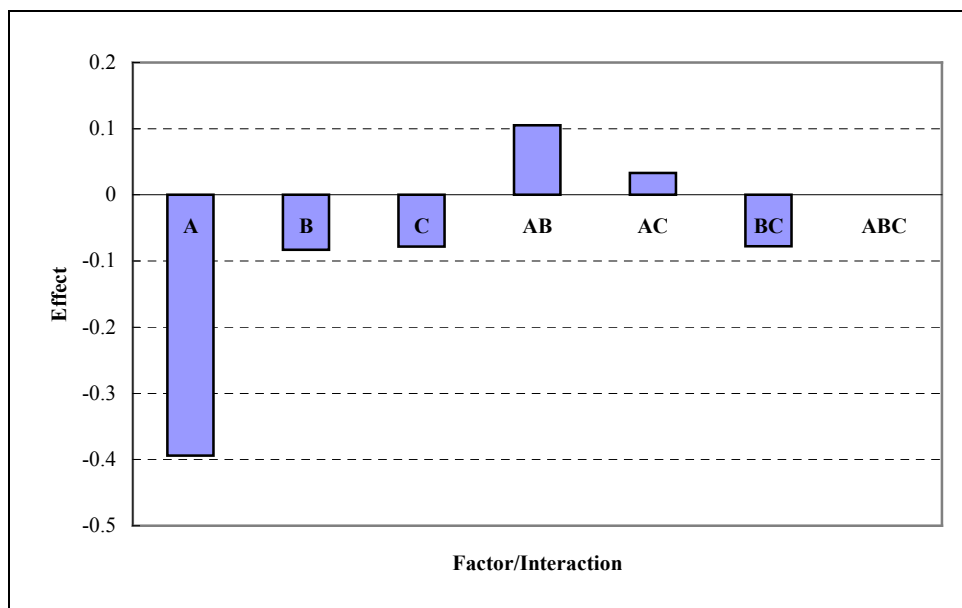
Fig. 3.61: Effect and interactions of parameters on the friability of pellets

4. Development of Carbomer 934P-containing mucoadhesive pellets through Dry-coating technique

4.1 General

Presently, most commercial coatings are done using a wet process. However, these coating techniques suffer from the problems such as the use of organic solvents, high-energy consumption and aging phenomena during storage. And this approach is not always applicable due to several limitations, such as the problems of solution viscosity and spray nozzle clogging, the sensitivity of certain active compounds to water. For these reasons, a new dry-coating has been introduced [41, 225]. This technique directly attaches polymer particles onto the surface of a solid substrate without organic solvents and large volumes of water. Softening, melting and curing are the principal stages in the film formation during dry powder coating. Because of the absence of large amounts of solvents or water, the processing times are much shorter [41-45, 224].

Carbomer 934P is a polyacrylic polymer, which can be used as a coating material for extended release of oral dosage forms [8-10]. However, it has the limitations due to its sticking problems in water. Therefore, the dry-coating method was investigated in current study as a way to produce carbomer 934P-layered pellets.

4.2 Preliminary investigations in a fluid-bed equipment

A preliminary study was carried out to investigate the behavior of carbomer 934P powder in fluidized-bed equipment. The process conditions were: batch size 500g, inlet air volume 60 m^3/h, inlet air temperature 40°C, the spray rate of binder 3-5 g/min, atomizing pressure 1.5 bar, powder feed rate 5-8 g/min, and drying temperature 60-70°C. Sugarpellets (600-800 µm of fraction) and demineralized water were used as the core pellets and the binder, respectively.

It was failed to produce carbomer 934P-coated pellets, because carbomer 934P powder was agglomerated immediately with the core pellets [Fig. 4.1].

The following problems were indicated in the powder-layering process using carbomer 934P. Firstly, carbomer 934P is very cohesive powder showing poor flow property. That caused very ununiform feeding of powder with fluctuations. Therefore, the powder could not be evenly spread out onto the core pellets. Secondly, carbomer powder formed a gel easily on the pellet surface, although a very small amount of binding-liquid was introduced.

For these reasons, it was necessary to modify the powder properties by the addition of appropriate excipients.
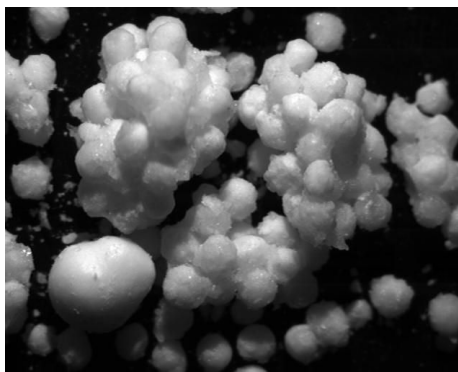
Such an excipient could be a choice, which can improve the flow property of carbomer powder. In addition, a good water uptake potential is also necessary, because the undesirable agglomeration should be suppressed. According to several previous studies [207, 208, 213, 215, 220], it is possible to improve the flow properties of powder by employing a glidant.

Fig. 4.1: Product of dry-coating trial using carbomer 934P

When the glidants are incorporated, they improve the flow properties of cohesive powders and granules [220]. In current step therefore, the effects of some additives (talc, tri-calcium phosphate, cornstarch and magnesium stearate) were studied on the flow property of carbomer 934P powder. The flow rate and angle of repose were investigated, and the water uptake was also determined.

4.3   Characterization of powder

4.3.1   Influence of other excipients on the flow property of carbomer 934P

Carbomer 934P is very cohesive powder showing poor flow property. That causes in the powder coating process serious problems, such as uniform feeding onto the core pellets. Several commonly used substances- talc, starch, magnesium stearate, and tri-calcium phosphate- were investigated as the additives to solve this problem.

4.3.1.1   Determination of flow rate and angle of repose
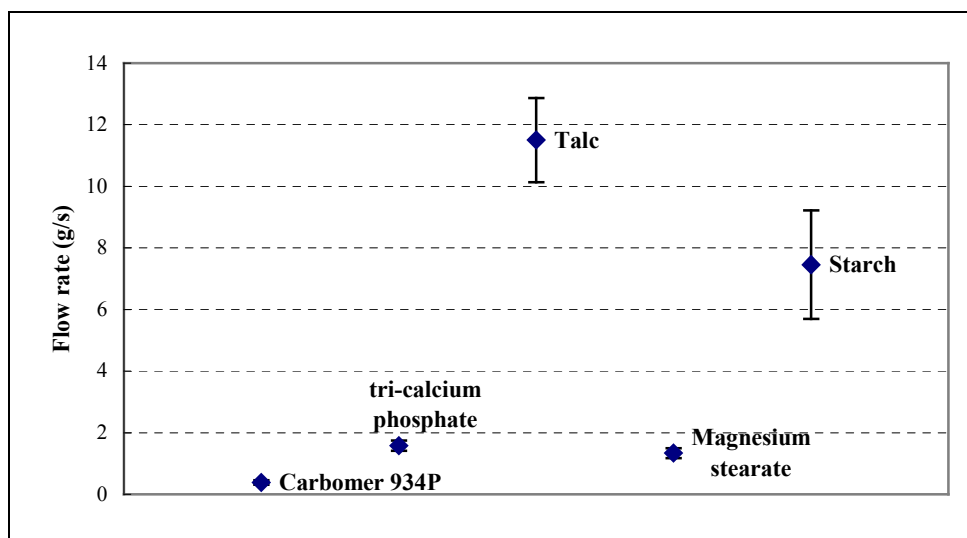
Fig. 4.2: Flow rate of carbomer 934P and other excipients (Mean±S.D., n=5)

66
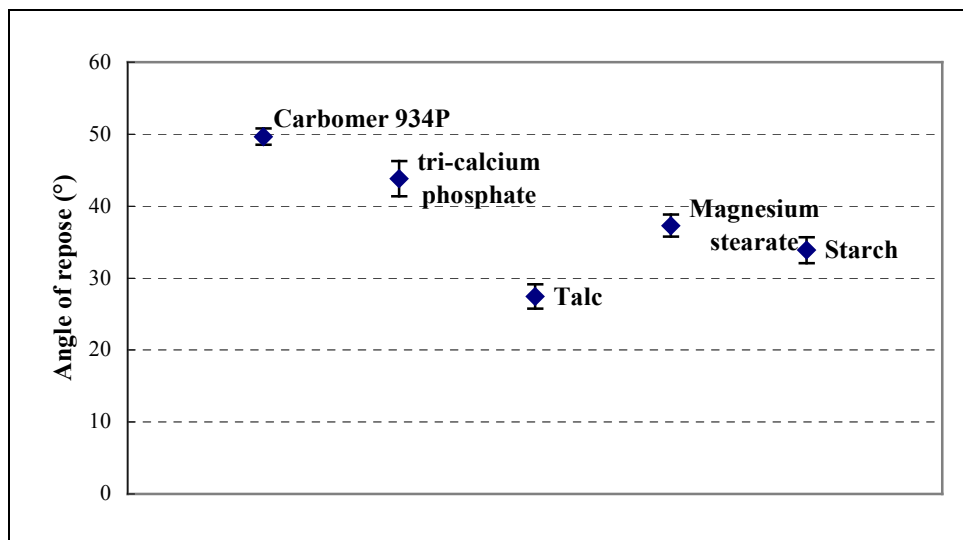
Fig. 4.3: Angle of repose of carbomer 934P and other excipients (Mean±S.D., n=5)

The flow rate and the angle of repose [221, 306] of substances were illustrated in Fig.4.2 and 4.3. As higher is the flow rate, and as smaller is the angle of repose, the better flow property is expected. Carbomer 934P showed the lowest flow rate and the greatest value of angle of repose. That is, it has the poorest flow property, as expected. It was very likely to adhere on the wall of funnel, and was flown poorly with a fluctuation.

Fig 4.4 and 4.5 illustrate the flow rate and angle of repose as a function of additives.
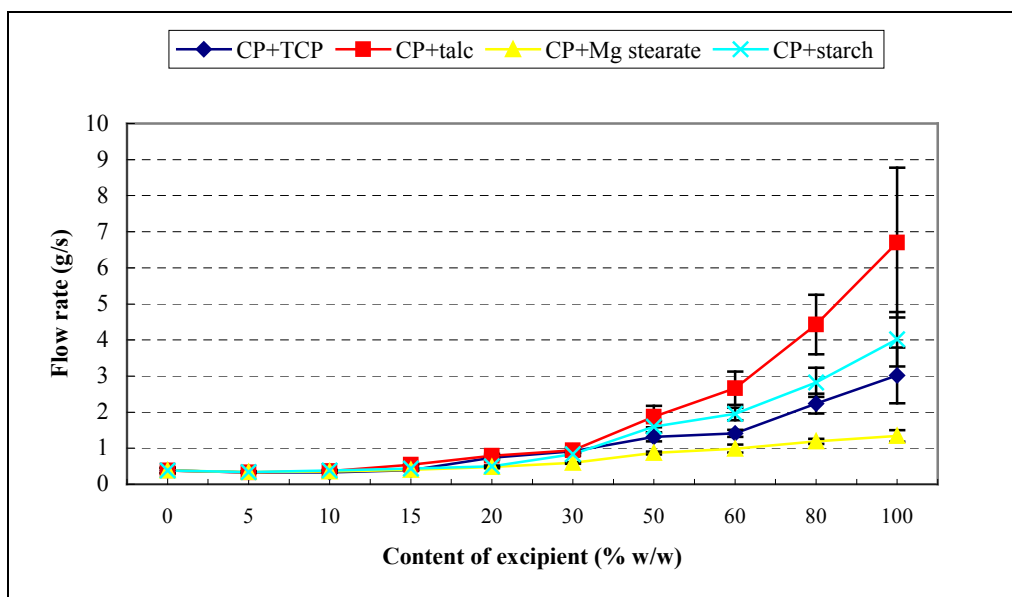
Fig. 4.4: Flow rate of carbomer 934P/excipient-mixtures (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)
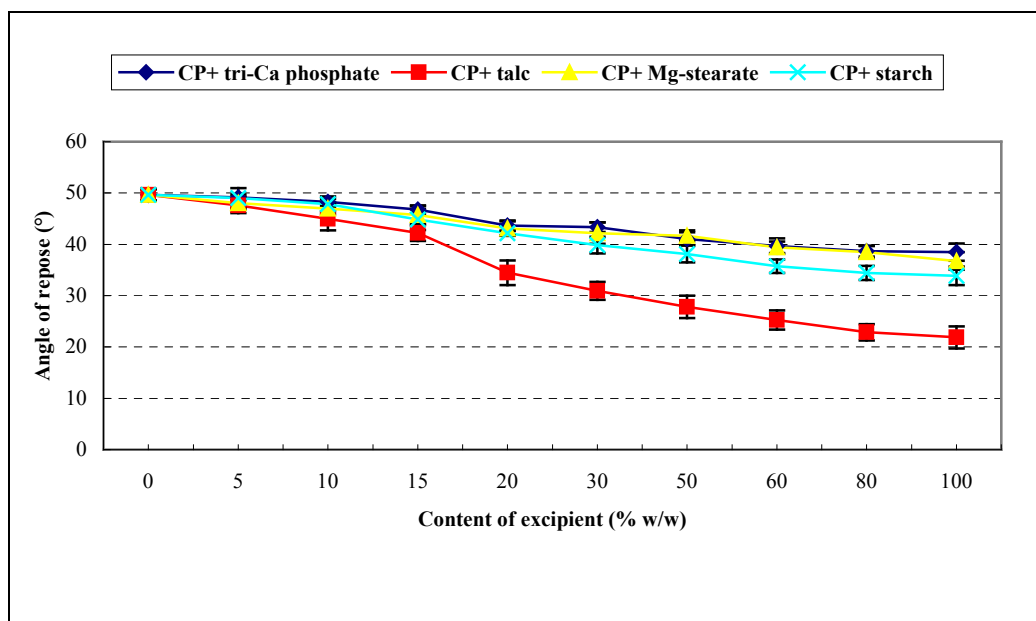
Fig. 4.5: Angle of repose of carbomer 934P/excipient-mixtures (CP: carbomer 934P)
(Mean±S.D., n=5)

It was indicated that the added excipients enhanced the flow rate of carbomer. The angle of repose became smaller, that is, the flow property was improved. This result caused by the action of added excipients as the glidants [207, 208, 213, 215, 220]. As shown in figure 4.4, there were no remarkable differences in the flow rate, when the content of excipient was lower than 30% (w/w). However, at higher content above 30%, the flow rate was considerably increased except for the addition of magnesium stearate. The effects could be ordered as: talc > starch > tri-calcium phosphate. However, the effect of magnesium stearate was almost ignorable.

There was a decrease in angle of repose with increasing the content of excipients [Fig.4.5]. It was found that there was a good correlation between the flow rate and the angle of repose results. The higher was the flow rate, the smaller was angle of repose. Talc was found highly effective amongst the additives investigated.

Ternary mixtures were also investigated [Fig.4.6~4.13]. The content of carbomer 934P was kept as 20% (w/w), and two kinds of additives were introduced. The content of one of these additives was varied as 0~100% (w/w).

a) Influence of talc

The powder blends containing talc showed the higher flow rate than that of without talc [Fig. 4.6]. For example, magnesium stearate/talc-mixture had the higher flow rate about 20% than that of magnesium stearate alone. Starch showed also an improved flow rate for 18% by the addition of talc. It appeared that the overall flow rate of powder was mainly dependent on the flowability of added excipients.
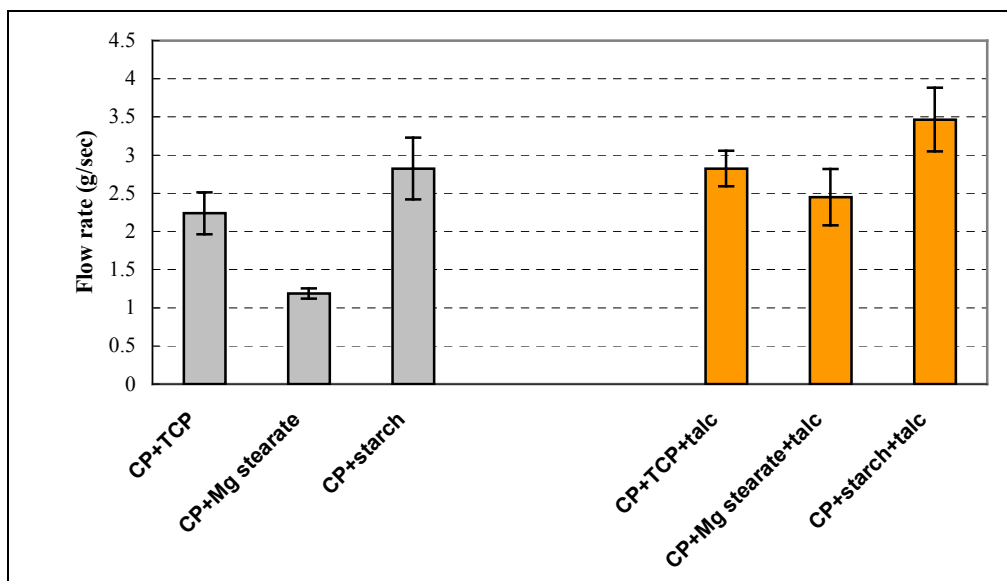
Fig. 4.6: Influence of talc on the flow rate of powder in carbomer 934P:talc:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

In the angle of repose, the addition of talc resulted in a slight decrease [Fig.4.7]. As the content of talc was increased, the angle of repose was decreased.
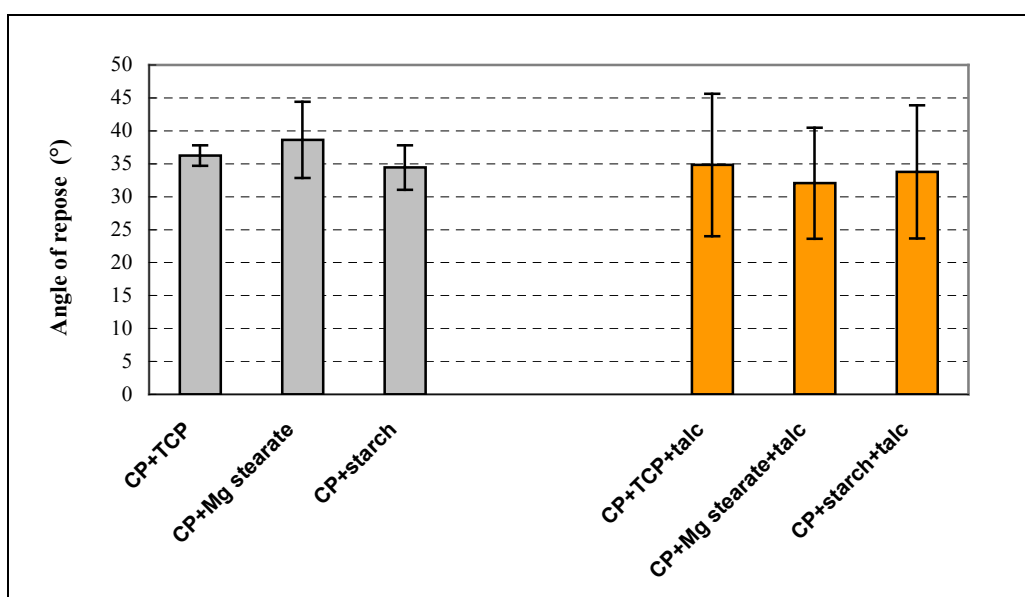
Fig. 4.7: Influence of talc on the angle of repose of powder in carbomer 934P:talc:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

b) Influence of tri-calcium phosphate

When tri-calcium phosphate was incorporated into carbomer 934P/magnesium stearate blend, the flow rate was increased with increasing of tri-calcium phosphate content. In case of carbomer 934P/magnesium stearate-mixture, the flow rate increased about 29% by the addition

of 50% (w/w) of tri-calcium phosphate. On the contrary, a negative effect was found in carbomer 934P/talc-mixture. The addition of tri-calcium phosphate led to a decrease in the flow rate [Fig.4.8].
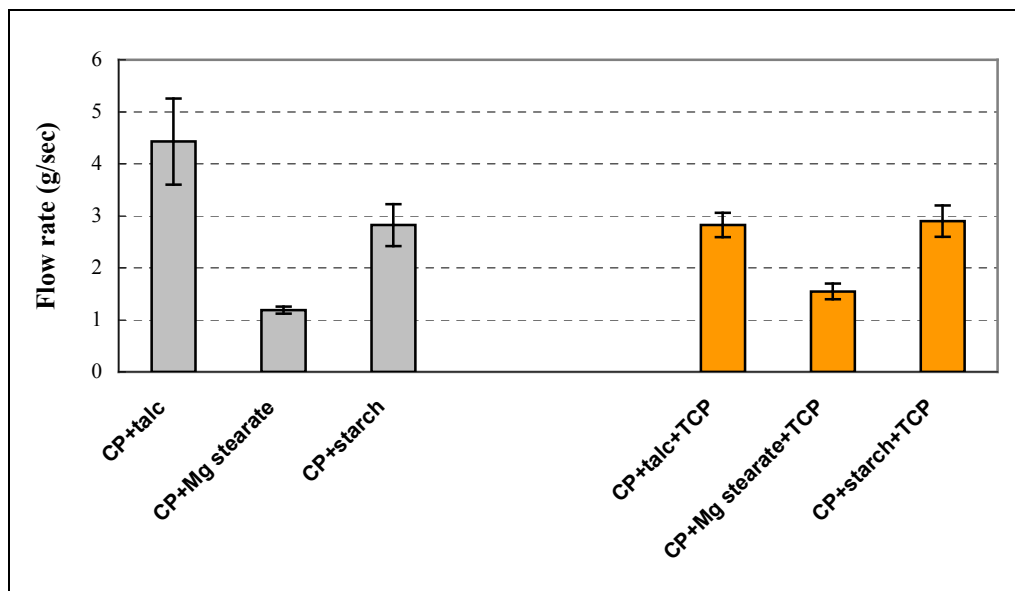
Fig. 4.8: Influence of tri-calcium phosphate on the flow rate of powder in carbomer 934P:tri-calcium phosphate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

In the angle of repose, tri-calcium phosphate caused a slight increase. This result was not fully in agreement with the results of flow rate [Fig.4.9].
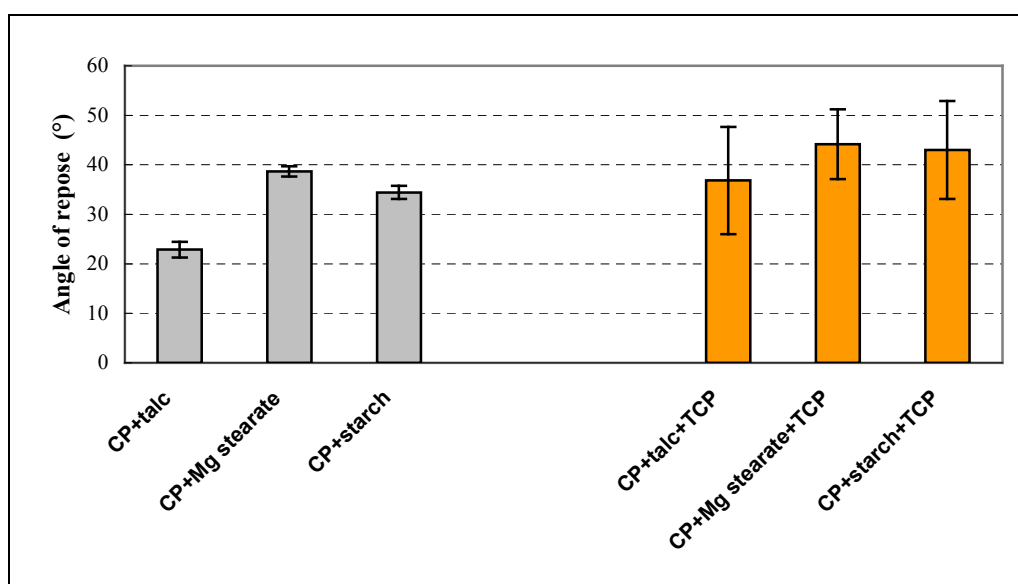
Fig. 4.9: Influence of tri-calcium phosphate on the angle of repose of powder in carbomer 934P:tri-calcium phosphate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

c) Influence of magnesium stearate

Flow rate was decreased magnesium stearate in all cases [Fig.4.10].
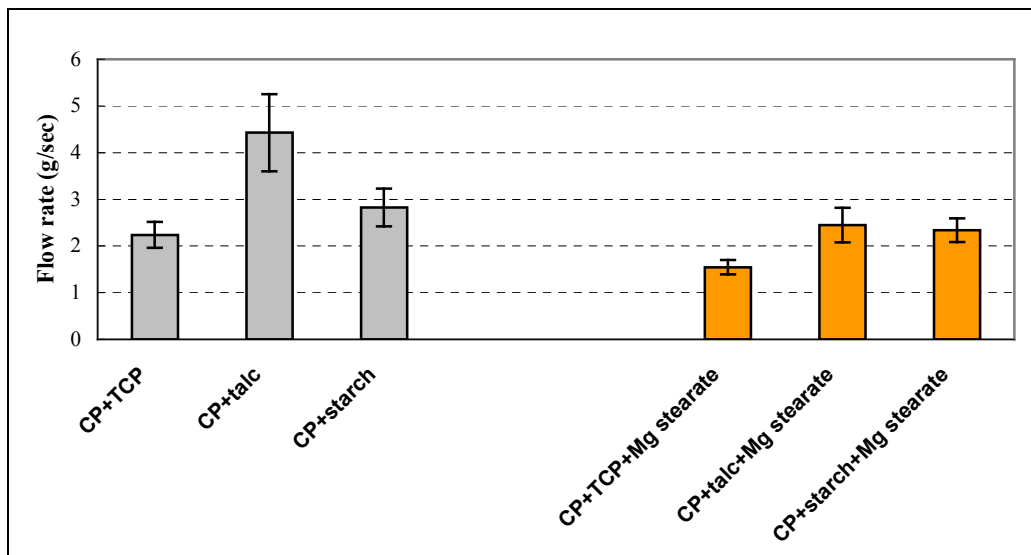
Fig. 4.10: Influence of magnesium stearate on the flow rate in carbomer 934P:magnesium stearate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

In angle of repose measurement, the increases were observed by the addition of magnesium stearate [Fig.4.11]. This result was in good agreement with the result of flow rate. Magnesium stearate showed the lowest flow rate and the greatest angle of repose. These characteristics of individual substances rule the overall water uptake potential of powder blends.
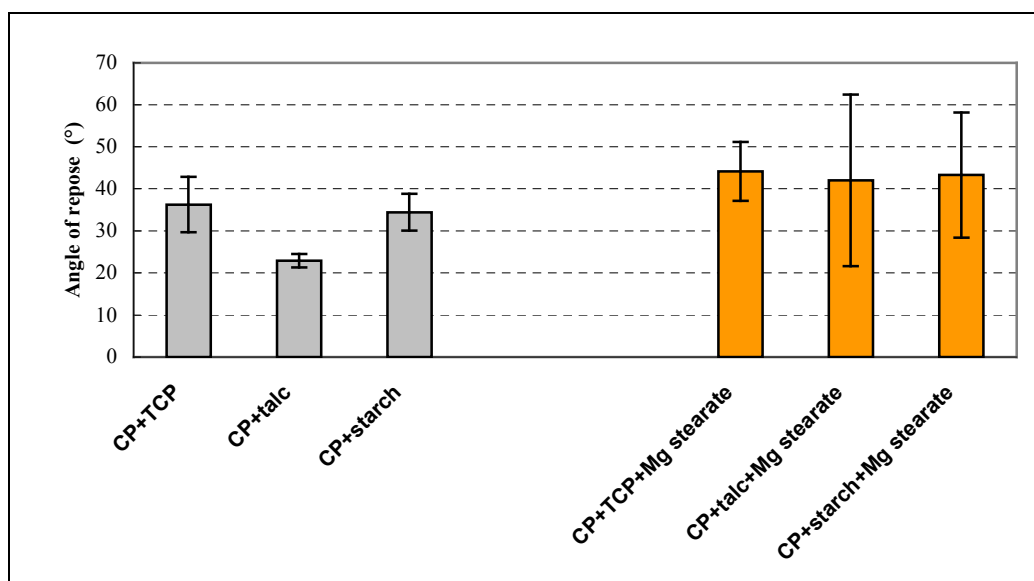
Fig. 4.11: Influence of magnesium stearate on the angle of repose in carbomer 934P:magnesium stearate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

71

d) Influence of starch
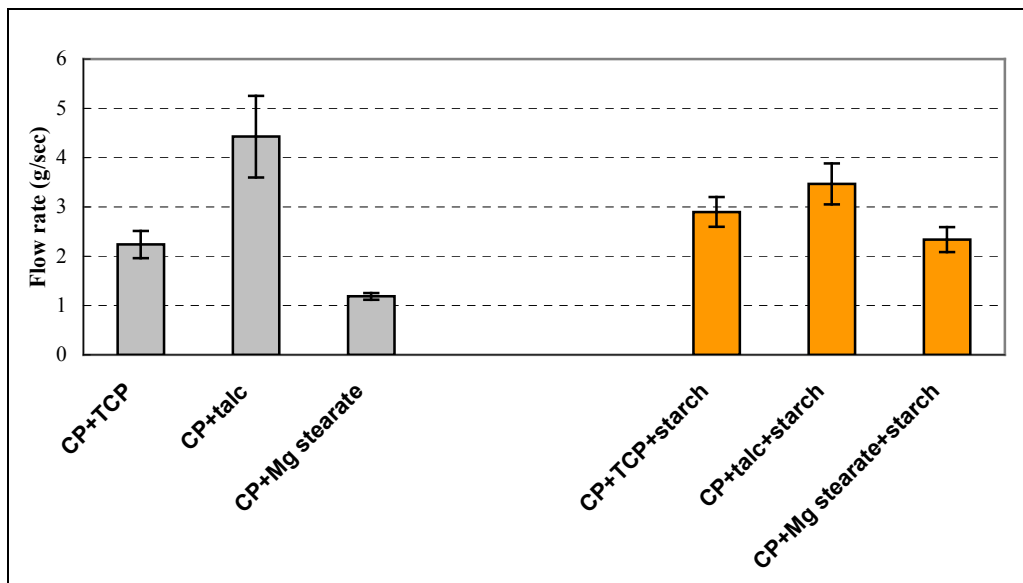
Fig. 4.12: Influence starch on the flow rate in carbomer 934P:starch:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)
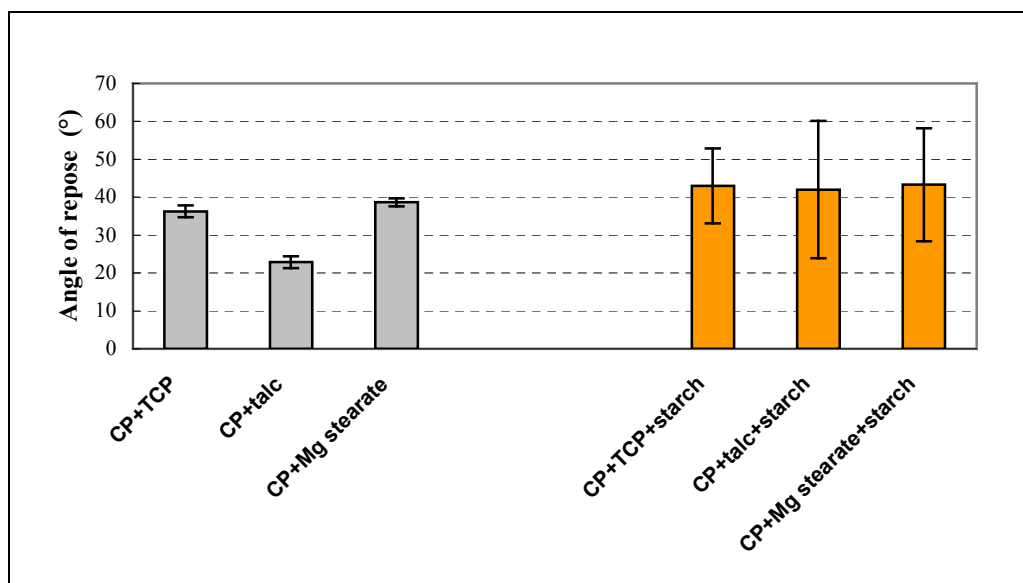
Fig. 4.13: Influence of starch on the angle of repose in carbomer 934P:starch:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

As shown in Fig.4.12, the flow rate of talc was decreased, as the content of starch increased. On the contrary, starch led to an increase in flow rate in carbomer 934P/tri-calcium phosphate and carbomer 934P/magnesium stearate-mixtures. In angle of repose measurement, the increase of observed by the addition of magnesium stearate [Fig.4.13]. This result was not fully agreement with the flow rate due to the experimental variations.

4.3.2 Influence of other excipients on the water uptake of carbomer 934P

4.3.2.1 Determination of enslin number

Theoretically, dry-coating process is performed without any binder-liquid. However, according to the study by Bodmeier [224], it could not be fully realized, since a small amount of binding-liquid is still required in the process for the final curing step to achieve film formation. Carbomer forms the gel very easily in water, thus the behavior of carbomer powder with water should be considered for a successful dry-coating process. Even though only the small amount water is introduced, the undesirable agglomeration in initial phase could be occurred. The water uptake property of powder can be therefore a critical factor for further processing.

In this chapter, enslin number was determined as an indicator to evaluate the water-uptake potential. The results are shown in Fig.4.14.
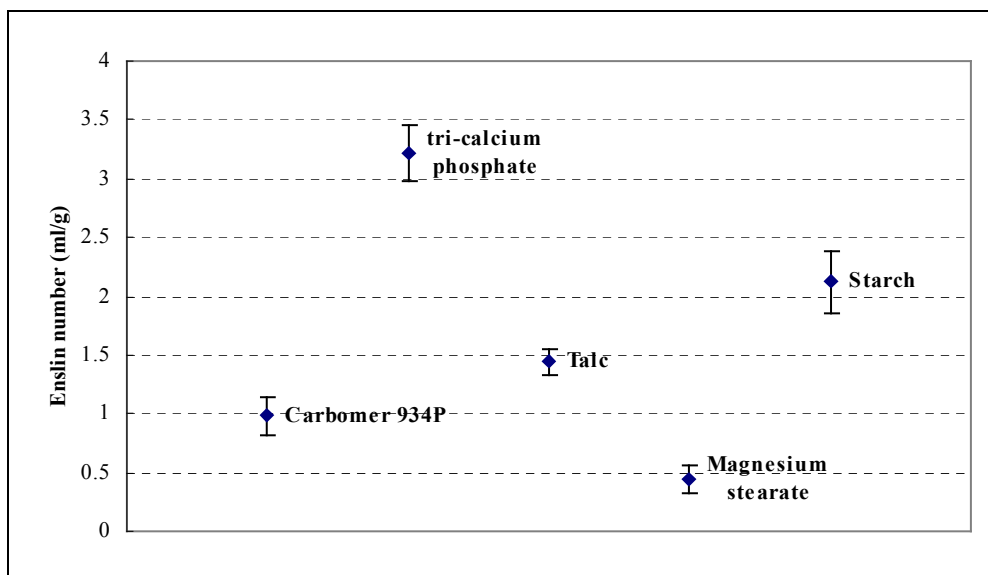
Fig. 4.14: Enslin number of carbomer 934P and other excipients (Mean±S.D., n=5)

All excipients showed the greater enslin number than carbomer 934P, except for magnesium stearate. It was therefore assumed that the wettability of carbomer in water could be improved by the incorporation of talc, starch, and tri-calcium phosphate.

- Binary mixtures (carbomer 934P + other excipient)

The increasing effect was in proportion of the excipient content in all cases [Fig. 4.15]. On the contrary, magnesium stearate led to a decrease in enslin number. This result could be explained by the wettability of individual substance. In case of tri-calcium phosphate, it has a very good wettability in water due to its structural reason [165]. The overall enslin number was increased by

the addition of talc and starch, since the adding these substances shield partially the poor wettability of carbomer. Magnesium stearate showed no considerable effect because of its hydrophobic characteristics.
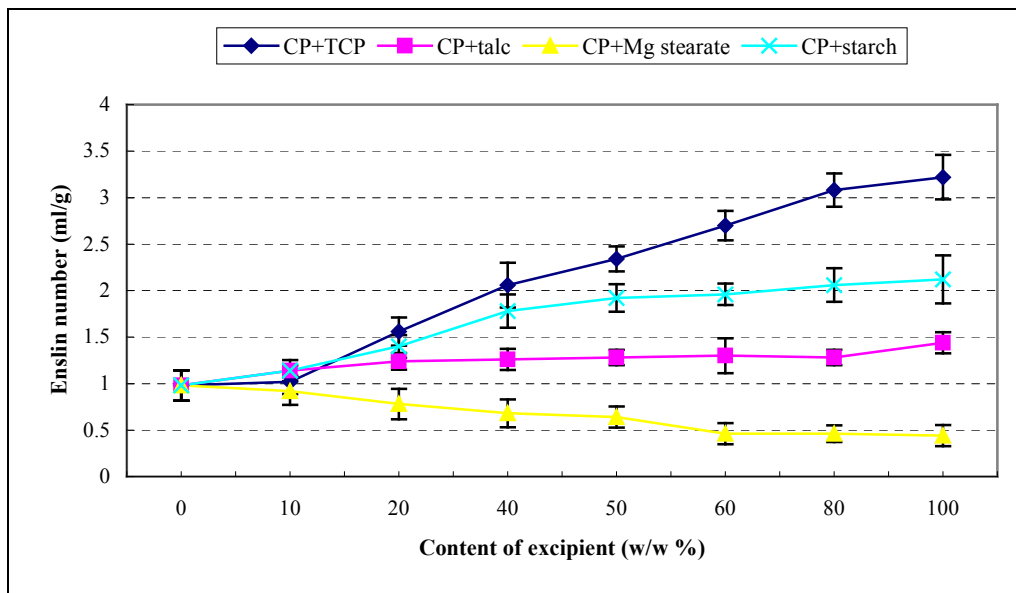
Fig. 4.15: Enslin number of binary mixtures (carbomer 934P/other excipient-mixtures) (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

- Ternary mixtures (20% carbomer 934P + 40% excipient A+ 40% excipient B)

a) Influence of talc
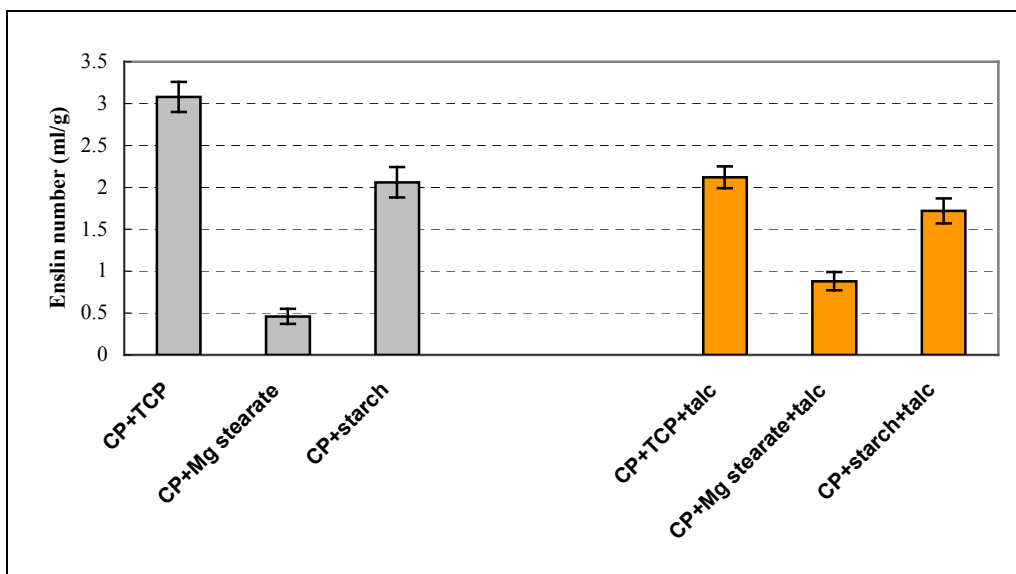
Fig. 4.16: Influence of talc on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

As indicated in figure 4.16, talc affected positively magnesium stearate. The enslin number was increased from 0.46 (g/min) to 0.88 (g/min) by the addition of talc. However, talc showed a negative effect on tri-calcium phosphate and starch. The addition of talc into tri-calcium phosphate and starch led to a decrease in enslin number, for 32% and 17%, respectively. This result was as expected, because the enslin number of talc (1.44 g/min) was smaller than that of tri-calcium phosphate (3.22 g/min) and starch (2.12 g/min). The overall wettability of ternary powder blends was mainly determined by that of added excipient.

b)   Influence of tri-calcium phosphate

The incorporation of tri-calcium phosphate caused a dramatic increase in enslin number [Fig.4.17]. In case of carbomer 934P/talc-mixture, the enslin number was increased from 1.28 (g/min) to 2.12 (g/min). In carbomer 934P/magnesium stearate-mixture and carbomer 934P/starch-mixture, tri-calcium phosphate led to the increase for 82% and 1.1%, respectively. It could be concluded that tri-calcium phosphate could be the most effective additive to suppress undesirable agglomeration in the dry-coating process.
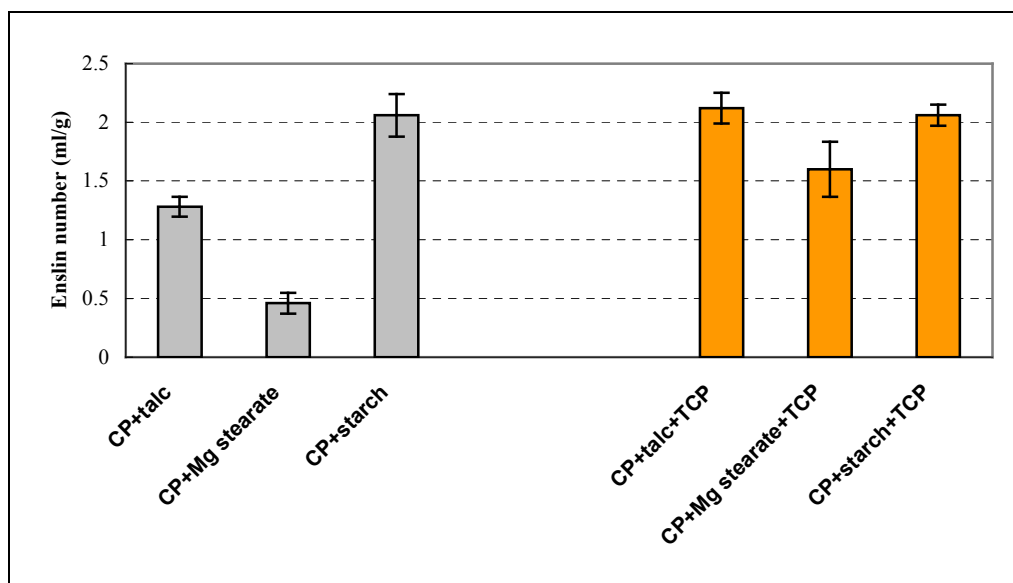
Fig. 4.17: Influence of tri-calcium phosphate on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

c)   Influence of magnesium stearate

As shown in figure 4.18, the enslin number of carbomer 934P/tri-calcium phosphate-mixture was decreased from 3.08 (g/min) to 1.6 (g/min) by the incorporation of magnesium stearate. In carbomer 934P/talc-mixture and carbomer 934P/starch-mixture, it also led to the considerable decrease for 32% and 44%, respectively.
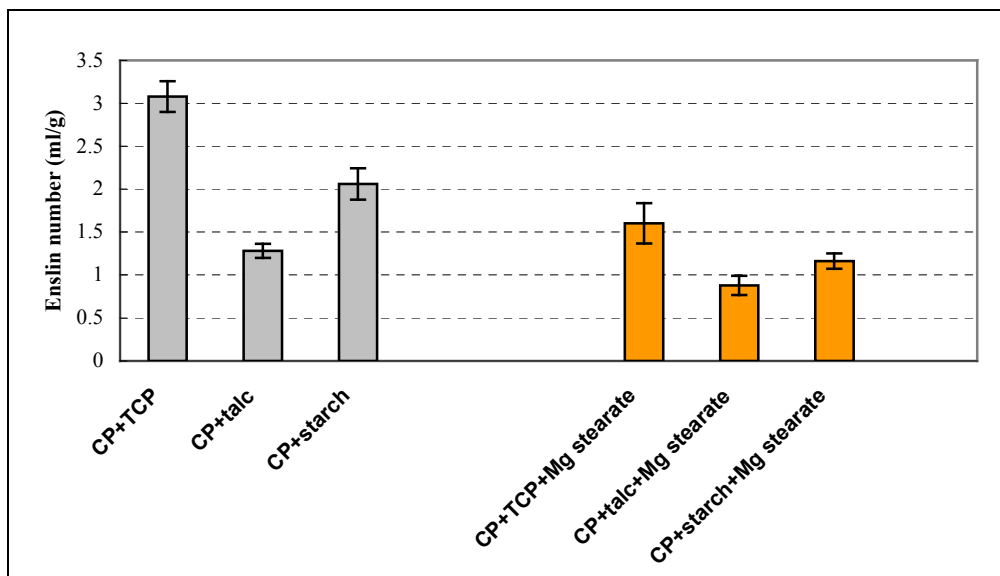
Fig. 4.18: Influence of magnesium stearate on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

e) Influence of starch
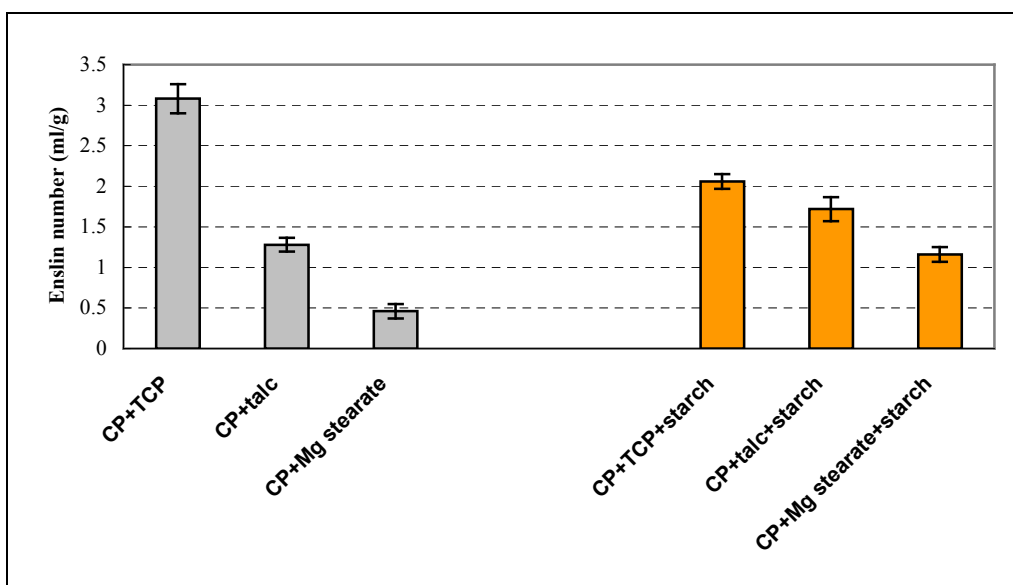
Fig. 4.19: Influence of starch on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

In case of carbomer 934P/tri-calcium phosphate-mixture and carbomer 934P/magnesium stearate-mixture, the enslin number was decreased as the increase of starch content. On the contrary, the increase was observed in carbomer 934P/talc-mixture by the addition of starch [Fig.4.19].

4.4 Investigations in a fluid-bed equipment

4.4.1 Preparation of core pellets

Theophylline-containing pellets were prepared as the core pellets for dry-coating process. The ingredients of pellets were: theophylline (20% w/w), lactose (35% w/w), microcrystalline cellulose (45% w/w), and a 1%- PVP K90 solution was used as a binder liquid. The process conditions were as shown in table 3.4. The evaluation results of produced pellets were shown in table 4.1. 600~800μm fraction of pellets were used for the dry-coating process.

Tab. 4.1: Physical properties of core pellets (Mean±S.D., n=3)

Mean diameter (μm)	732 ± 12.3
Sphericity (%)	90.6 ± 0.78
Roughness	1.03 ± 0.01
Aspect ratio	1.01 ± 0.01
Friability (%)	0.56 ± 0.28
Hardness (N)	11.4 ± 1.22

4.4.2 Dry-coating of core pellets with carbomer 934P powder

500g of theophylline pellets were coated with carbomer 934P powder in a fluidized-bed coater. Carbomer 934P powder and small amount of binding-liquid (demineralized water) were fed separately onto the core pellets. The processing parameters were set as listed in table 4.2.

Tab. 4.2: Process conditions during dry-coating

Parameter	Setting
Batch size (g)	500
Type of disc	Smooth
Inlet air volume (m^3/h)	30-40
Inlet air temperature (°C)	45
Rotor rotation speed (rpm)	600(during drying: 450)
Process time (min)	45
Spheronization time (min)	10
Spray rate (g/min)	3-5
Spray pressure (bar)	1.5
Shaking interval (time/sec)	5 / 3
Powder feed rate (g / min)	10-14

4.4.2.1 Establishment of appropriate process parameters

Preliminary experiments were carried out to establish the appropriate range of process parameters for the powder layering process using carbomer powder.

Inlet air volume

The excessive air volume caused severe loss of powder before it adheres to the core pellets, and resulted in the over-drying of the bed. Therefore, the process carried out under a relative smaller inlet air volume (20-30 m^3/h) in this study.

Inlet air temperature

A lower inlet air temperature (aproximately 20°C) is recommended [46] in a powder layering process compared to a pelletization, because a high temperature can cause the over-drying. However, since the water was used in current study as a binder, a higher temperature was also acceptable. The inlet air temperature was kept as 45°C during the process.

Rotor rotation speed

The lower/upper limit of the rotor rotation speed was set at 200 and 650 rpm, respectively. When the rotor speed was lower than 200 rpm, the core pellets were agglomerated immediately with carbomer powder. And the too high speed (above 650rpm) caused the core pellets to slide on the rotating disk.

Spray rate of binder

It must be adjusted to provide neither too dry nor too wet bed. In this study, it was adjusted for the low level at 2 (g/min), and the high level at 10ml/min, respectively.

Powder feed rate

Powder application rate is also an important variable. Adding the powder too slowly leads to a wet bed and pellet agglomeration. When it is too quick, results in a dry bed and a powder caking on the walls. In current study, the powder feed rate was set at 5 and 15 (g/min) as the low/ high level, respectively.

4.4.2.2 Production of trial batches

Trial batches were prepared with following process conditions and compositions [Tab.4.2 and 4.3]. C1, C2 and C5 showed the possibility to produce carbomer 934P-coated pellets [Fig.4.20]. With the other compositions it was failed to prepare the pellets, since they were agglomerated immediately.

Tab. 4.3: Compositions of coating powder (% w/w)

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Carbomer 934P	50	50	50	50	50	50	50	50	50	50
Talc	50				25	25	25			
Tri-calcium phosphate		50			25			25	25	
Magnesium stearate			50			25		25		25
Starch				50			25		25	25
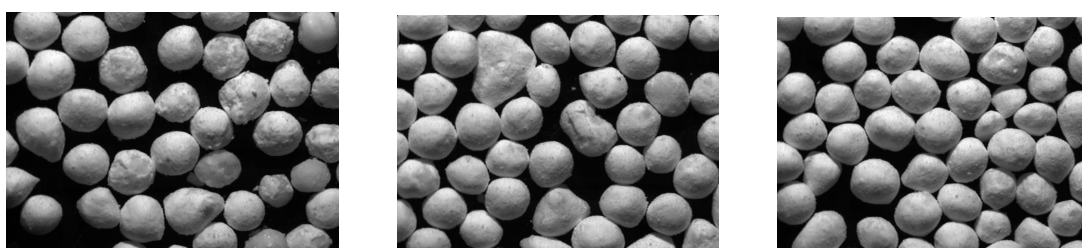
Fig. 4.20: Products of trials; C1 (left), C2 (center) and C5 (right)

C5 produced the better yield and the powder layering efficiency than C1 and C2. The powder property of carbomer could be effectively modified when tri-calcium phosphate and talc were incorporated. The following composition was therefore used for further investigations: carbomer, tri-calcium phosphate and talc (2:1:1).

4.4.3 Influence of process parameters on the coated pellets

Three parameters- rotor rotation speed, spray rate of binder, and powder feed rate- were selected. Their influences were investigated on the yield, powder layering efficiency [183, 184], and image analysis result of produced pellets.

4.4.3.1 Investigations through a factorial design

The parameters were set as described in table 4.4~4.6.

Tab. 4.4: The fixed parameters

Inlet air temperature ($^\circ$C)	45
Drying air temperature ($^\circ$C)	60
Spray pressure (bar)	1.5
Inlet air volume (m^3/h)	20-30
Batch size (g)	500

Tab. 4.5: Factors and their settings in the factorial design

Factors	Level	
	Low (-1)	High (+1)
A: rotor speed (rpm)	200	650
B: spray rate of binder (g/min)	2	10
C: powder feed rate (g/min)	5	15

Tab. 4.6: Combination of factors (-, low level; +, high level)

	A	B	C
-1	-	-	-
a	+	-	-
b	-	+	-
ab	+	+	-
c	-	-	+
ac	+	-	+
bc	-	+	+
abc	+	+	+

4.4.3.2 Results

Tab. 4.7: Result of evaluation of produced granules

Batch	Yield (%)	Powder layering efficiency (%)	Sphericity (%)	Roughness	Aspect ratio
-1	71.8±1.83	80.9±4.15	68.5±1.31	1.04±0.02	1.17±0.07
a	67.2±3.05	64.6±2.21	60.1±0.95	1.08±0.01	1.20±0.02
b	47.2±2.70	43.7±0.81	56.4±0.80	1.11±0.02	1.23±0.04
ab	62.1±1.00	41.2±1.67	54.5±2.65	1.12±0.01	1.27±0.02
c	65.8±2.69	65.8±1.47	65.1±2.30	1.14±0.00	1.16±0.03
ac	58.0±2.46	70.7±0.32	63.5±0.46	1.09±0.02	1.11±0.04
bc	61.4±2.25	55.0±0.49	59.3±1.96	1.11±0.03	1.26±0.04
abc	56.1±3.16	56.6±1.22	56.8±3.90	1.10±0.01	1.26±0.01

(Mean ± S.D., n = 3)

Tab. 4.8: Effect and significance of process parameters (a)

	Yield (%)		Powder layering efficiency (%)	
	Effect	Significance	Effect	Significance
A	-0.7	-	-3.08	+
B	-9	+	-21.38	+
C	-1.75	-	4.43	+
AB	5.5	+	2.63	+
AC	-5.85	+	6.33	+
BC	5.85	+	8.93	+
ABC	-4.25	+	-4.28	+

A: rotor speed, **B**: spray rate, **C**: spheronization time, +, statistically significant ($P < 0.05$)

Tab. 4.9: Effect and significance of process parameters (b)

	Sphericity (%)		Roughness		Aspect ratio	
	Effect	Significance	Effect	Significance	Effect	Significance
A	-3.6	+	-0.003	-	0.005	-
B	-7.55	+	0.023	+	0.095	+
C	1.3	-	0.023	+	-0.02	-
AB	1.4	-	0.003	-	0.02	-
AC	1.55	-	-0.028	+	-0.03	-
BC	1.3	-	-0.033	+	0.03	-
ABC	-1.85	-	0.018	+	0.01	-

A: rotor speed, **B**: spray rate, **C**: spheronization time, +, statistically significant ($P < 0.05$)

4.4.3.2.1 Influence on the yield (%)

The high yield could be a first evidence of successful powder layering process [131, 132, 134]. It was indicated that in figure 4.21, three investigated parameters negatively affected on the yield. In particular, spray rate of binder had a remarkable negative effect.
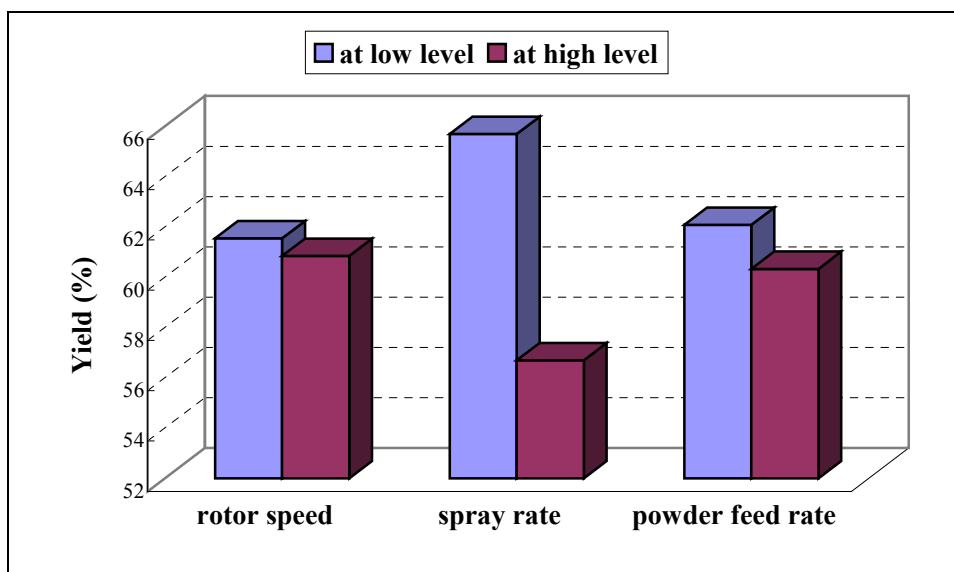
Fig. 4.21: Influence of parameters on the yield of pellets
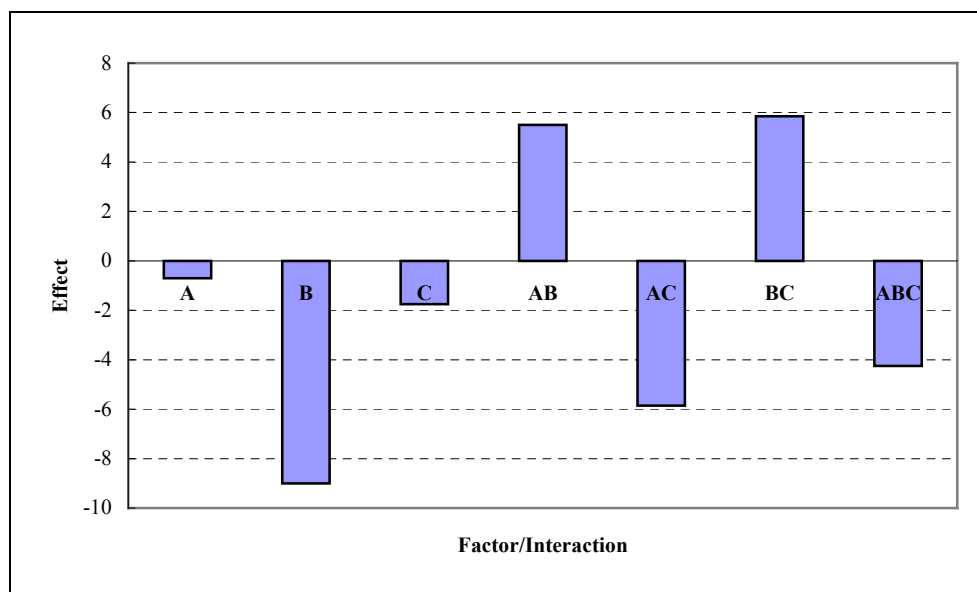
Fig. 4.22: Effect and interactions of parameters on yield

When the rotor rotation speed increased, the core pellets slides to the wall of rotating disk. That might cause a less chance to contact between the core pellets and coating powder. Thus, the core pellets were kept still uncoated and the powder was lost by the airflow. This resulted in a decreased yield. The increase in the spray rate of binder also caused a decreased yield. The high spray rate of binder resulted in a too wet bed. The core pellets were therefore agglomerated immediately due to the gel-forming of carbomer. On the contrary, the bed becomes too dry when the powder feed rate was high. The powder fed was partially adhered onto the core pellets, but the lost of excessive powder was occurred, therefore the final yield decreased.

4.4.3.2.2 Influence on the powder layering efficiency (%)

The rotor speed and the spray rate of binder affected negatively on the powder layering efficiency. By increasing rotor speed and spray rate, the powder layering efficiency was decreased for 15% and 30% respectively. On the contrary, the powder feed rate showed a positive effect. The positive interactions of AB, AC, BC, and negative ABC interaction was observed [Fig.4.23 and 4.24].
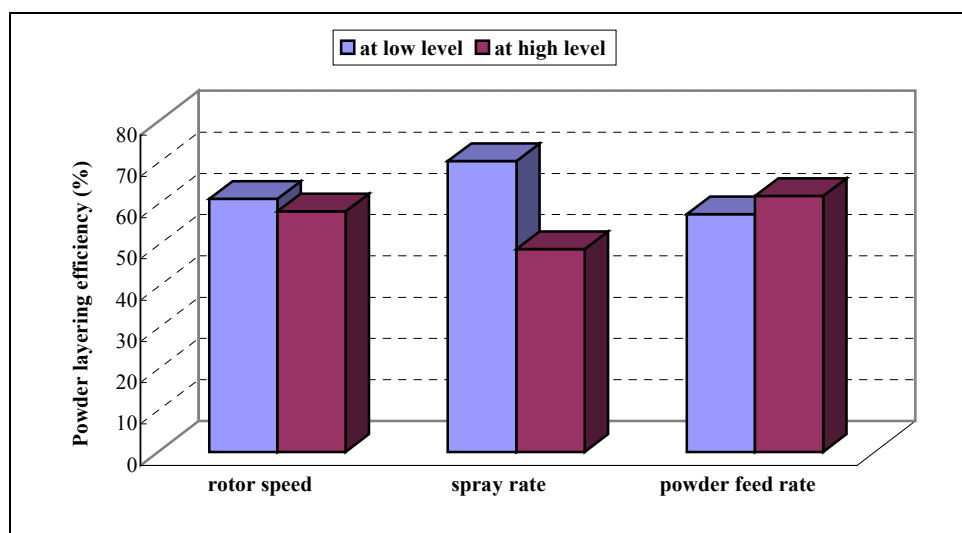
Fig. 4.23: Influence of parameters on powder layering efficiency
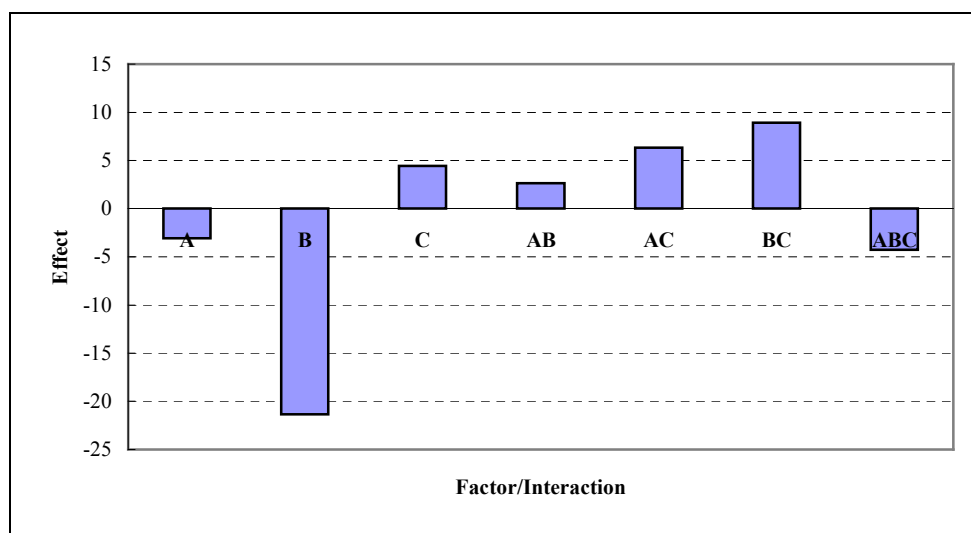
Fig. 4.24: Effect and interactions of parameters on powder layering efficiency

Balancing the application rate of layering powder and the binder solution was critical. When the spray rate of binder solution was too high, the pellet bed became so wet that it resulted in undesirable agglomeration. When the powder feed rate was too high, the bed became too dry, therefore the powder-layering efficiency decreased.

4.4.3.2.3   Influence on the sphericity, roughness and aspect ratio

The sphericity of coated pellets was considerably decreased by the increase in rotor speed and spray rate of binder [Fig. 4.25].
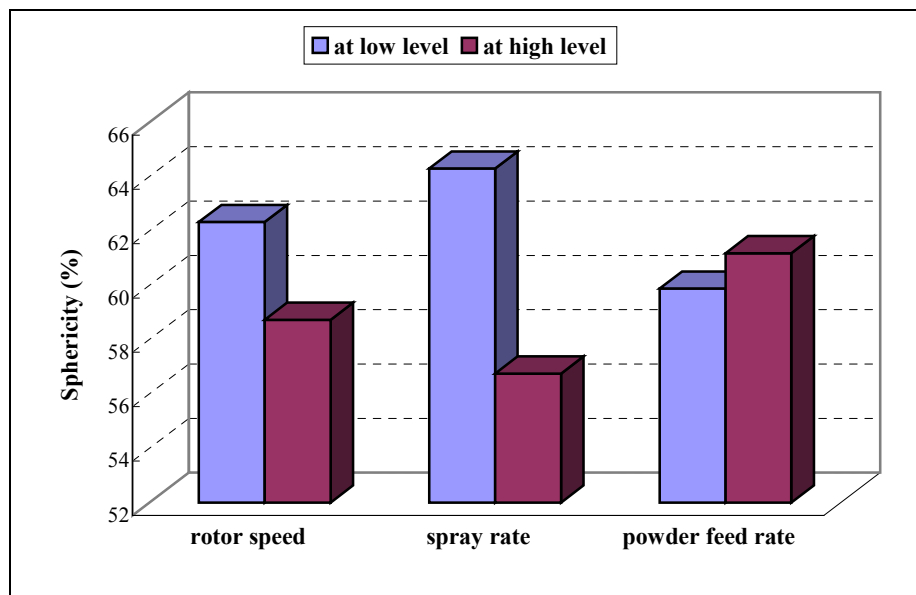
Fig. 4.25: Influence of parameters on sphericity
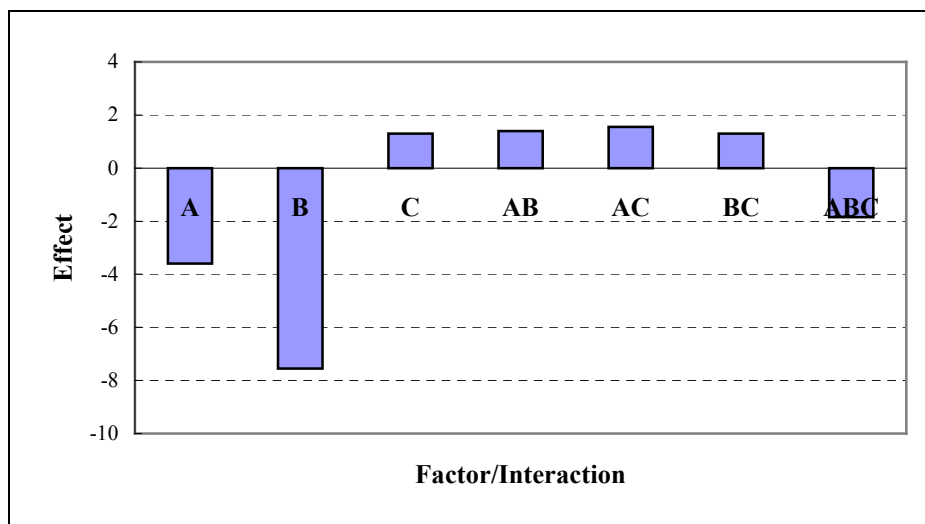
Fig. 4.26: Effect and interactions of parameters on sphericity

The contact chance was decreased between the core pellets and coating powder due to the intensive rolling action of higher rotor speed. As a consequence, the provided powder could not cover the whole surface of core pellets. That resulted in the ununiform adhering of coating powder onto pellets. The higher spray rate led to the over-wetting of pellet surface, thus the carbomer particle in powder blend could more chance to form a gel. Although the core pellets were not fully

agglomerated, some partial aggregate could occur. Therefore, the less spherical and oversized pellets were produced [Fig.4.27]. The positive interactions of AB, AC and BC were also found, whereas a negative interaction of ABC was observed [Fig.4.26]. These interactions were not significant.
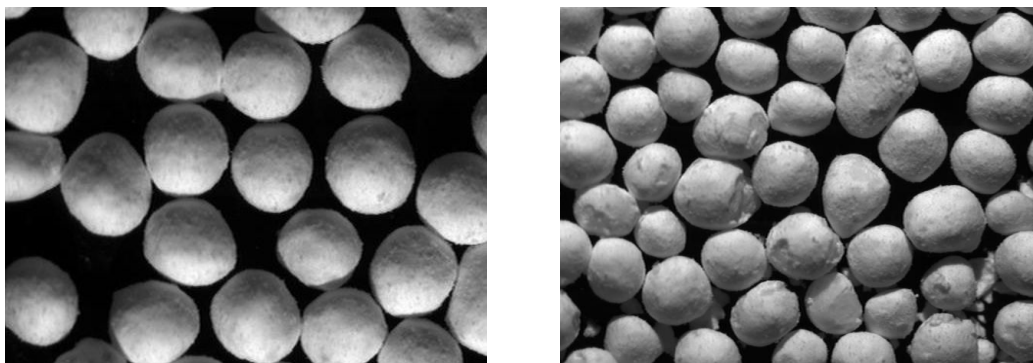
Fig. 4.27: Carbomer 934P-coated granules at different level of spray rate of binder: at low level (left) and at high level (right)

The roughness and aspect ratio [Fig.4.28~4.31] were closely correlated with the sphericity. When the sphericity was decreased, the roughness and the aspect ratio were increased at the same time. It was found that the spray rate of binder and powder feed rate were the critical parameters on the roughness and aspect ratio.
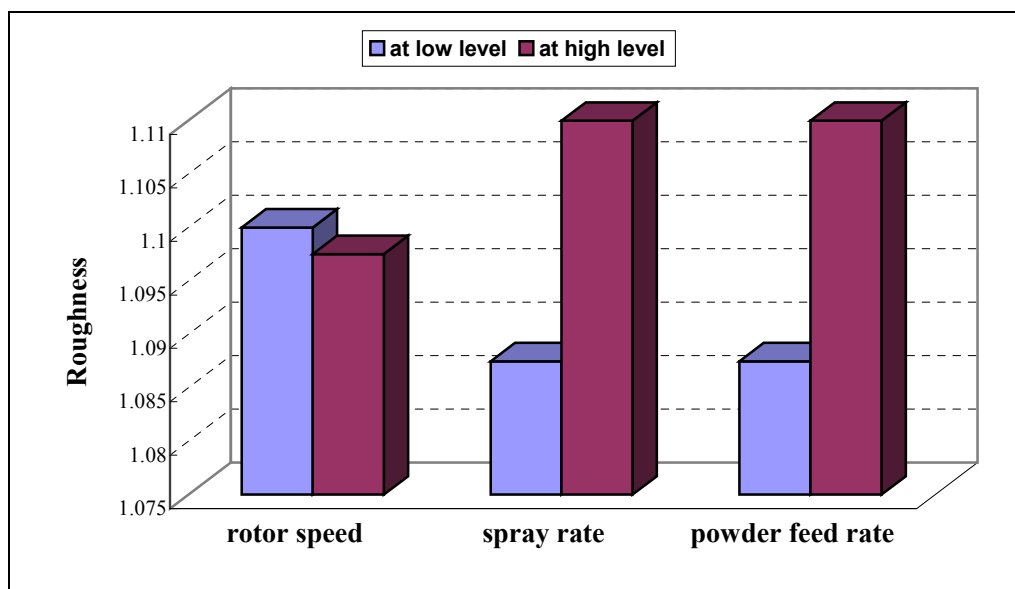
Fig. 4.28: Influence of parameters on roughness of pellets
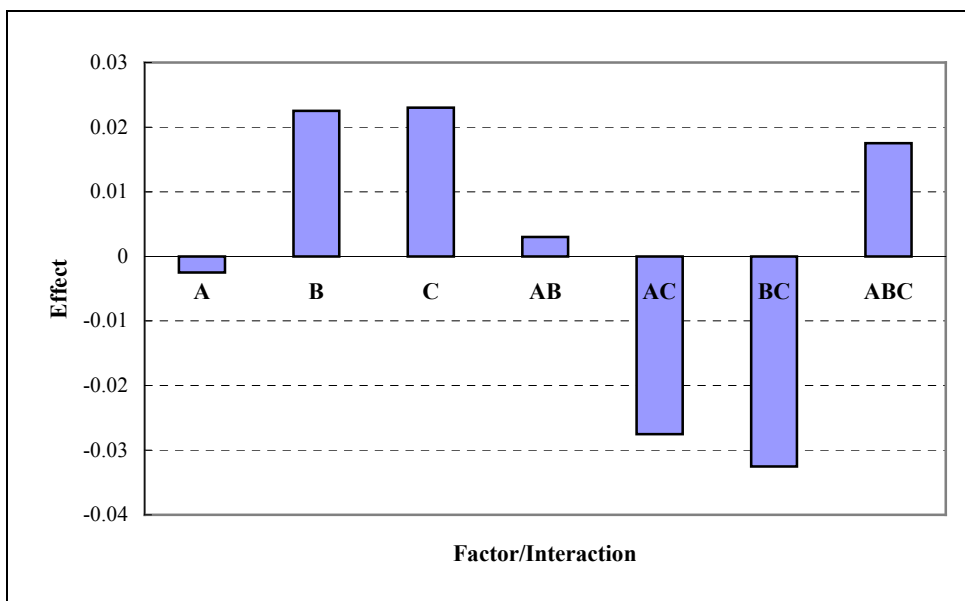
Fig. 4.29: Effect and interactions of parameters on the roughness of pellets
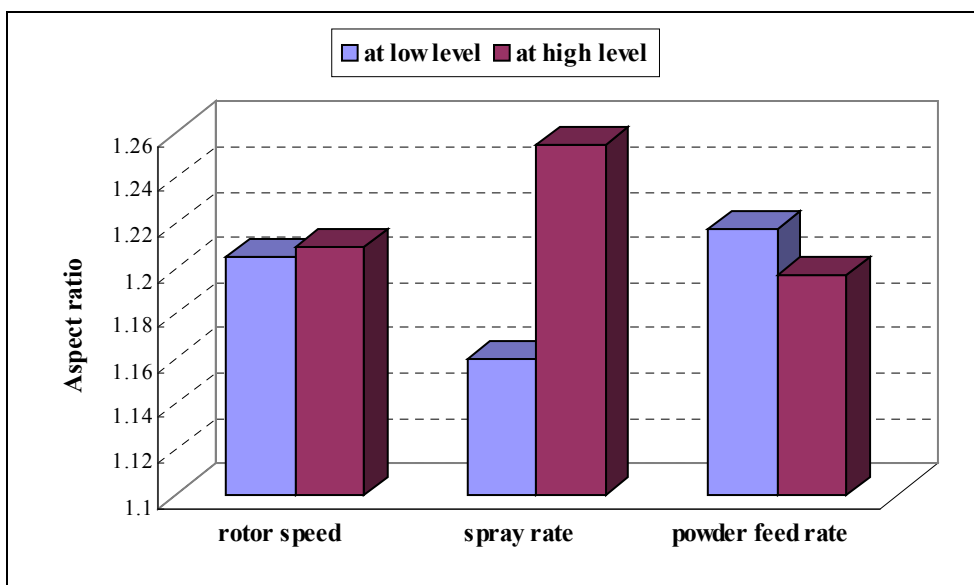
Fig. 4.30: Influence of parameters on the aspect ratio of pellets
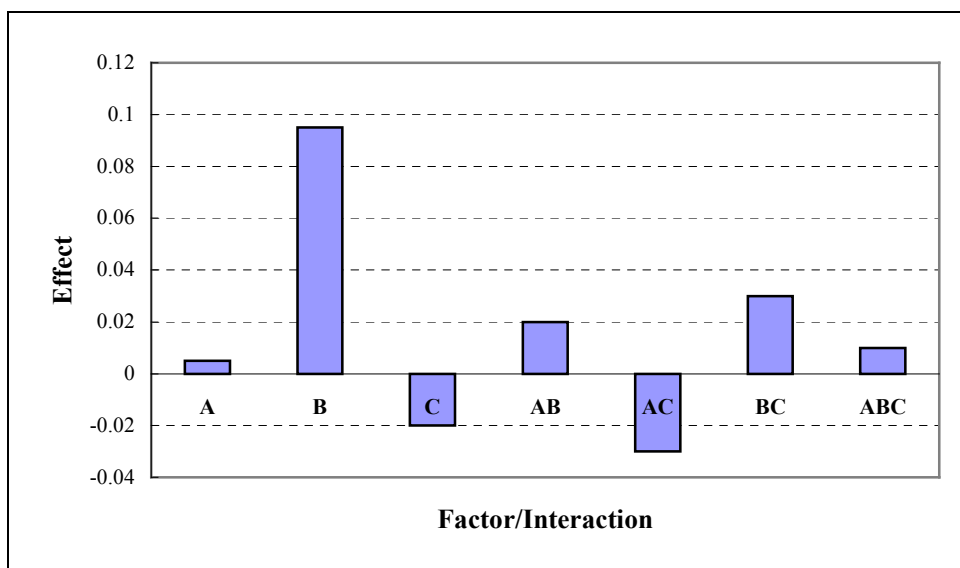
Fig. 4.31: Effect and interactions of parameters on the aspect ratio of pellets

5. Investigations of Mucoadhesion and Dissolution

5.1 General

The important role of mucoadhesive dosage forms is to help the controlled-release of an active ingredient through increasing of the residence time of dosage forms in gastrointestinal tract [1-3]. Thus, the mucoadhesion test can be an important step in the development of mucoadhesive drug delivery system. In order to investigate the bioadhesion phenomena, a large number of different methods have been used in the study of bioadhesive materials. The test methods can broadly be classified in two major categories: *in vitro /ex vivo* methods and *in vivo* methods. However, most of the available information on bioadhesives has come from *in vitro* experimentation. Several techniques for *in vitro* determination of bioadhesion have been reported, which included tensile testing (Park and Robinson, 1987), shear stress testing (Smart *et al.*, 1984), adhesion weight method (Smart and Kellaway, 1982), fluorescent probe method (Park and Robinson, 1984), flow channel technique (Mikos and Peppas, 1986), and colloidal gold staining method (Park, 1989) [307]. Most *in vitro* methods are based on the measurement of either tensile or shear stress [227-229]. Methods using tensile strength usually measure the force required to break the adhesive bond between a model membrane and the test polymers [230, 241, 260]. The instruments usually employed are modified balance or tensile tester. Shear stress measures the force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact [261, 304, 305]. In current study, a texture analyzer was employed to measure the mucoadhesive force. The measurement of mucoadhesive force is one of the most commonly employed *in vitro* techniques [4]. The use of texture analyzer was reported by Tobyn *et al.* (1995) for mucoadhesive studies using porcine stomach tissue under simulated gastric conditions. This method was also applied by Wong *et al.* [307] to evaluate the bioadhesive properties of some polymers under simulated buccal conditions. The procedures of the method applied in this study are described in 5.2 in detail.

5.2 Determination of mucoadhesion

The mucoadhesion was determined by measuring the maximal force required to separate the test material from the mucosal surface. The mucosal surface of rat's small intestine was used in the test. The rat small intestine is relatively free of intestinal content, and provided a macroscopically flat and uniform surface [227-229]. The middle section, discarding the first 40-50 mm at either ends of fresh intestine from male Wistar rats was used. This was cut into 2 cm lengths, opened longitudinally to expose the inner mucosal surface, and fixed at the upper plate of instrument with a two-sided adhesive tape [Fig.5.1]. The intestine was kept in phosphate buffer solution of pH 6.0 during the preparation time.

The texture analyzer (EZ-test, Shimadzu, Japan) and associated software was introduced for the measurement of mucoadhesion. Wet mass of test material was filled in a metal cup (height 7mm, diameter 20.2mm), and the mucosa was placed to the upper stamp (diameter 14mm). 30µl of pH 6.0 isotonic phosphate buffer solution was spread with a pipette on the mucosa to standardize hydration prior to testing, and then the mucosa was brought into contact with the test material. After a preload of 1~2N for 2 min of contact time, the mucosa was raised at a constant speed of 1 mm/s and the detachment force was recorded.

Fig. 5.1: Measurement of mucoadhesion by texture analyzer

Since this value is for the contact area 1.54cm^2 between the upper stamp and test material, the mucoadhesive force per area was calculated and expressed as 'mucoadhesion' (N/cm^2).

5.2.1 Influence of carbomer 934P content on the mucoadhesion

Tab. 5.1: Preparation of binary mixtures (carbomer/MCC) and their actual compositions

Powder mixture (30g)	Added water amount (ml)		The actual composition of prepared wet mass	Name of wet mass
CP (20%) / MCC (80%)	21.9	Kneading in mortar →	CP (11.6%) / MCC (46.2%) / Water (42.2%)	M1
CP (40%) / MCC (60%)	19.5		CP (24.2%) / MCC (36.4%) / Water (39.4%)	M2
CP (60%) / MCC (40%)	18		CP (37.5%) / MCC (25%) / Water (37.5%)	M3
CP (80%) / MCC (20%)	15.9		CP (52.3%) / MCC (13.1%) / Water (34.6%)	M4

Table 5.2 describes the influence of carbomer 934P content on the mucoadhesion. The results are mean of five replicates.

Tab. 5.2: Influence of carbomer content in carbomer 934P/MCC-mixtures

Wet mass tested	Mucoadhesion (N/cm^2)
M1	7.92 $\pm$ 1.15
M2	10.10 $\pm$ 0.59
M3	11.56 $\pm$ 1.08
M4	13.69 $\pm$ 1.00

(Mean±S.D., n=5)

When the content of carbomer increased, wet mass showed the higher mucoadhesion. This results was as expected, since the overall adhesion of wet mass was dependent on the gel-forming of carbomer. As more carbomer was incorporated, it provides the more chance to carbomer particles to form a gel-structure. Therefore, the mucoadhesion of wet mass becomes stronger. Although the stronger mucoadhesion was obtained in the investigated range (20~80% w/w, in dry state) of carbomer 934P, but carbomer content cannot be extremely maximized for the stronger mucoadhesion due to the limitations during a granulation process. The content of carbomer 934P was fixed as 20% (w/w, in dry state) in composition in current study.

5.2.2 Influence of pH value on the mucoadhesion

It should be noticed that the gel-forming of carbomer 934P is very highly dependent on the environmental pH value [8, 47, 54, 57, 59, 60, 62, 65]. Moreover, it was indicated that there is a difference between the pH value of wetting liquid and that of wet mass prepared, since carbomer 934P is an acidic substance (pH 2~3 for a 1% w/v aqueous dispersion). The actual pH value of wet mass was therefore investigated by differing pH of wetting agent. Wet masses were prepared with the wetting solutions of various pH values (1~13), and pH values of prepared wet mass were measured by pH meter.

The composition was: carbomer 934P 20% + theophylline 20% + microcrystalline cellulose 30% + tri-calcium phosphate 30% (w/w in dry state). 1.9ml of demineralized water per 1g of powder was used as the wetting agent and its pH was adjusted with 1N-HCl or 1N-NaOH by a titrator to 1, 3, 5, 7, 9, 11, and 13, respectively. Therefore, the actual composition of prepared wet mass after the addition of wetting liquid was as follows: carbomer 934P 10.5% + theophylline 10.5% + microcrystalline cellulose 15.8% + tri-calcium phosphate 15.8% + water 47.4%. The pH of wet mass and its mucoadhesion are described in table 5.3.

Tab. 5.3: Mucoadhesion of wet mass containing carbomer 934P 10.5%/theophylline 10.5%/microcrystalline cellulose 15.8%/tri-calcium phosphate 15.8%/ water 47.4% at different pH values

pH of wetting agent	pH of wet mass	Mucoadhesion (N/cm^2)
1	1.02	6.92 $\pm$ 0.62
3	2.25	7.34 $\pm$ 1.45
5	2.87	7.27 $\pm$ 0.64
7	4.55	10.49 $\pm$ 1.66
9	5.11	12.40 $\pm$ 0.77
11	6.28	12.83 $\pm$ 1.92
13	6.43	12.08 $\pm$ 1.83

(Mean $\pm$ S.D., n=5)

It was indicated that actual pH of wet mass was lower than that of wetting liquid, because of the acidity of carbomer 934P. There was no considerable differences in mucoadhesion at pH range of 1~5 of added liquid, but at pH 7 it was increased for 45%. The pH value of wet mass reached about 4.5 at this point. It was considered that the gel-formation of carbomer 934P became more active above pH 7, due to the neutralizing effect. Maximum mucoadhesion was observed from pH 9 (pH of wet masses were about 5), and it showed no continuous increase till pH 13 [Tab. 5.3].

This behavior can be explained by the molecular structure of the gel. The polymer chains are initially (i.e. at pH 1-3) coiled into a spiral form [8, 47, 54, 57, 59, 60, 62, 65], thus affording a relatively low viscosity. As neutralization progresses, the carboxyl groups of carbomer become ionized, leading to an increasing repulsion of negative charges that causes the molecular structure to unwind, thus inducing a gradual rise in viscosity. When the pH of wetting liquid was under 7, the pH value of wet mass was kept still low (under pH 4). Therefore, a relative low mucoadhesion was observed. At pH 7 of added liquid, the mucoadhesion increased up to a middle level ($10.49 N/cm^2$). It was shown that the higher mucoadhesion could be obtained above pH 9. However, wet mass became too sticky to handle at this level.
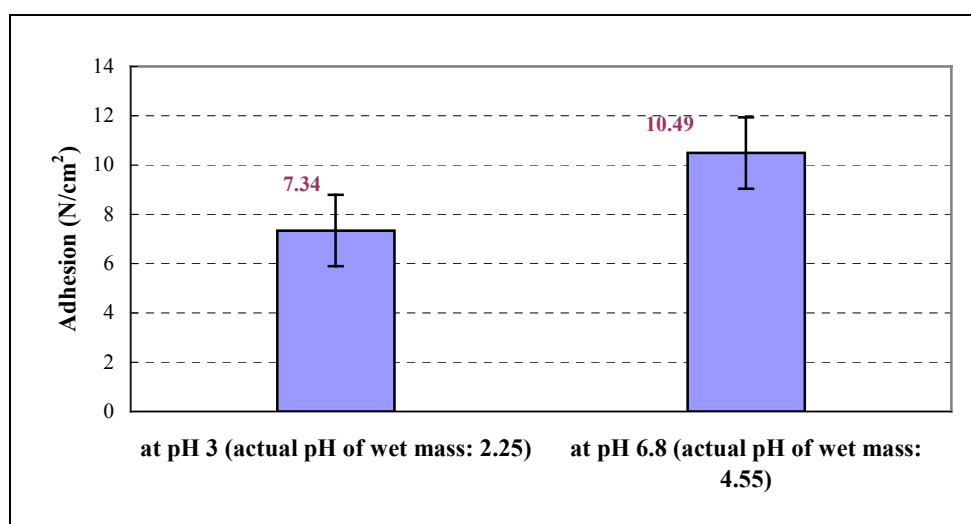
Fig. 5.2: Difference in mucoadhesion at two pH levels (Mean $\pm$ S.D., n = 5)

At pH 3, wet mass was not sticky, that makes it possible to produce the pellets by the fluid-bed granulation. The pH value of binding liquid in this study was about pH 4~5, it was relative acidic. It assumed that therefore, somewhat different result could be obtained, if the granulation is carried out under other experimental conditions. For example, when the water of higher pH value was introduced, wet mass could become tackier than that of this study. However, it could not be regarded as 'extremely tacky' making the granulation process impossible. Optimization will be required, for example, by differing the content of polymer and excipients, and process parameters, etc. This result describes that pH value is a highly important factor in the mucoadhesion of carbomer 934P. For this reason, the pH values of wet masses were noticed during investigations.

5.2.3   Influence of excipients on the mucoadhesion

The mucoadhesion of following compositions was investigated. Table 5.4 shows all compositions in dry state (powder mixtures), and the actual compositions of prepared wet masses after wetting are described in table 5.5. The pH values of wet masses were determined by pH meter and the mucoadhesion was measured. The results are shown in table 5.6.

Tab. 5.4: Compositions of trials (% w/w in dry state)

	C1	C2	C3*	C4	C5	C6	C7*	C8	C9	C10	C11	C12	C13	C14	C15
CP	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
MCC	80					40	40	40	40						
Lac		80				40				40	40	40			
TCP			80				40			40			40	40	
cl-PVP				80				40			40		40		40
Talc					80				40			40		40	40

(CP: carbomer 934P, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate,

* : showed possibility to produce pellets in fluid-bed granulation)

Tab. 5.5: The actual compositions of prepared wet masses

Composition	Added water amount (ml/g)	The actual composition of prepared wet mass
C1	0.73	CP (11.6%) / MCC (46.2%) / Water (42.2%)
C2	0.22	CP (16.4%) / Lac (65.6%) / Water (18%)
C3*	1.14	CP (9.3%) / TCP (37.4%) / Water (53.3%)
C4	1.13	CP (9.4%) / cl-PVP (37.6%) / Water (53%)
C5	0.47	CP (13.6%) / Talc (54.4%) / Water (32%)
C6	0.60	CP (12.5%) / MCC (25.1%) / Lac (25.1%) / Water (37.3%)
C7*	0.82	CP (11%) / MCC (22%) / TCP (22%) / Water (45.1%)
C8	1.01	CP (10%) / MCC (19.9%) / cl-PVP (19.9%) / Water (50.2%)
C9	0.60	CP (12.5%) / MCC (25%) / Talc (25%) / Water (37.5%)
C10	0.93	CP (10.4%) / Lac (20.7%) / TCP (20.7%) / Water (45%)
C11	0.64	CP (12.2%) / Lac (24.4%) / cl-PVP (24.4%) / Water (45%)
C12	0.51	CP (13.2%) / Lac (26.5%) / Talc (26.5%) / Water (45%)
C13	1.06	CP (9.7%) / TCP (19.4%) / cl-PVP (19.4%) / Water (51.5%)
C14	0.68	CP (11.9%) / TCP (23.8%) / Talc (23.8%) / Water (40.5%)
C15	0.88	CP (10.6%) / cl-PVP (21.3%) / Talc (21.3%) / Water (46.9%)

Tab. 5.6: Mucoadhesion of all compositions

Composition	Mucoadhesion (N/cm^2)	pH of wet mass
C1	9.71 $\pm$ 0.82	3.16
C2	14.07 $\pm$ 1.21	3.02
C3*	7.45 $\pm$ 0.79	2.86
C4	11.02 $\pm$ 0.73	2.91
C5	12.14 $\pm$ 2.10	3.11
C6	14.63 $\pm$ 1.11	3.28
C7*	8.95 $\pm$ 0.90	3.87
C8	10.79 $\pm$ 1.18	2.67
C9	13.41 $\pm$ 0.69	2.22
C10	12.91 $\pm$ 1.42	3.66
C11	14.36 $\pm$ 1.04	2.36
C12	14.93 $\pm$ 1.23	2.29
C13	7.90 $\pm$ 1.10	3.58
C14	11.82 $\pm$ 1.19	3.61
C15	10.19 $\pm$ 1.31	2.60

(Mean $\pm$ S.D., n = 5)

It was observed that the compositions containing tri-calcium phosphate (C3, C7) showed a relative low mucoadhesion. According to the results of chapter 3.2.4, only these compositions showed a possibility to produce pellets by fluid-bed granulation. .

5.2.4 Influence of salts on the mucoadhesion

To investigate the influence of selected salts (sodium citrate, disodium sulfate and calcium chloride) on mucoadhesion, wet masses were prepared and their mucoadhesion was determined. The concrete compositions of wet masses are shown in table 5.7~5.9. The results of mucoadhesion test are illustrated in figure 5.3.

Tab. 5.7: The actual composition of wet mass made with carbomer /MCC/Na citrate-dissolved water

30g Powder mixture of Carbomer 934P (20%) MCC (80% w/w) $+$ Na citrate-dissolved water (30ml)	Conc.of Na citrate (mol/ml)	Kneading in mortar $\rightarrow$	The actual composition of prepared wet mass (60g)
	0		CP (10%) / MCC (40%) / Na citrate (0%) / Water (50%)
	0.05		CP (10%) / MCC (40%) / Na citrate (0.7%) / Water (49.3%)
	0.08		CP (10%) / MCC (40%) / Na citrate (1.2%) / Water (48.8%)
	0.1		CP (10%) / MCC (40%) / Na citrate (1.5%) / Water (48.6%)

	0.3		CP (10%) / MCC (40%) / Na citrate (4.4%) / Water (45.7%)
	0.5		CP (10%) / MCC (40%) / Na citrate (7.3%) / Water (42.8%)
	1.0		CP (10%) / MCC (40%) / Na citrate (14.5%) / Water (35.5%)

Tab. 5.8: The actual composition of wet mass made with carbomer /MCC/ Na_2SO_4 -dissolved water

	Conc.of Na_2SO_4 (mol/ml)		The actual composition of prepared wet mass (60g))
	0		CP (10%) / MCC (40%) / Na_2SO_4 (0%) / Water (50%)
30g Powder mixture of	0.05		CP (10%) / MCC (40%) / Na_2SO_4 (0.4%) / Water (49.6%)
Carbomer 934P (20%) MCC (80% w/w)	0.08	Kneading in mortar	CP (10%) / MCC (40%) / Na_2SO_4 (0.6%) / Water (49.4%)
+	0.1	$\rightarrow$	CP (10%) / MCC (40%) / Na_2SO_4 (0.7%) / Water (49.3%)
Na_2SO_4-dissolved water (30ml)	0.3		CP (10%) / MCC (40%) / Na_2SO_4 (2.1%) / Water (47.9%)
	0.5		CP (10%) / MCC (40%) / Na_2SO_4 (3.6%) / Water (46.4%)
	1.0		CP (10%) / MCC (40%) Na_2SO_4 (7.1%) / Water (42.9%)

Tab. 5.9: The actual composition of wet mass made with carbomer /MCC/$CaCl_2$-dissolved water

	Conc.of $CaCl_2$ (mol/ml)		The actual composition of prepared wet mass (60g)
	0		CP (10%) / MCC (40%) / $CaCl_2$ (0%) / Water (50%)
30g Powder mixture of	0.05		CP (10%) / MCC (40%) / $CaCl_2$ (0.4%) / Water (49.6%)
Carbomer 934P (20%) MCC (80% w/w)	0.08	Kneading in mortar	CP (10%) / MCC (40%) / $CaCl_2$ (0.6%) / Water (49.4%)
+	0.1	$\rightarrow$	CP (10%) / MCC (40%) / $CaCl_2$ (0.7%) / Water (49.3%)
$CaCl_2$-dissolved water (30ml)	0.3		CP (10%) / MCC (40%) / $CaCl_2$ (2.2%) / Water (47.8%)
	0.5		CP (10%) / MCC (40%) / $CaCl_2$ (3.7%) / Water (46.3%)
	1.0		CP (10%) / MCC (40%) / $CaCl_2$ (7.4%) / Water (42.6%)

Fig. 5.3: Influence of salts in carbomer 934P/microcrystalline cellulose-wet mass prepared with salt solution (CP: carbomer 934P, MCC: microcrystalline cellulose) (Mean $\pm$ S.D., n = 5)

Sodium citrate could not reduce considerably the tack of wet mass [Fig. 5.3]. As described in chapter 3.1, this result could be attributed by the pH value of sodium citrate solution (pH 7-9 for 5w/v aqueous solution). Sodium citrate solution of high concentration showed the pH value above 7. The wet mass prepared with this solution had the pH value above 4.5. That is, sodium citrate acted as a neutralizing agent to carbomer 934P, thus the gel-formation of carbomer 934P could not be effectively blocked than adding disodium sulfate or calcium chloride.

5.3   Dissolution test

Dissolution test was performed according to USP paddle method in 900ml of dissolution medium (purified water, pH 3 and pH 6.8 phosphate buffer solution). 50mg of pellets were used for test. The temperature of the medium was kept $37\pm0.5°C$ while the rotational speed of the paddles was set at 50rpm. 5ml samples were withdrawn at regular time intervals and spectrophotometrically determined at 271nm. The results are mean of three replicates.

5.3.1   Pellets produced by the spraying of salt solution

Three kinds of salts- sodium citrate, disodium sulfate, and calcium chloride- were tried to produce pellets. It was failed to prepare pellets by the spraying of sodium citrate solution, since it could not reduce the tack of carbomer 934P. Therefore, only disodium sulfate and calcium chloride were practically employed in pellet production. The composition was: carbopol[®] 934P 20%, theophylline 20%, and microcrystalline cellulose 60% (w/w, in dry state). 0.3 mol/l of salt solution (disodium sulfate or calcium chloride) was sprayed as a binding agent. The concrete compositions of pellets

used in the dissolution test are shown in table 5.10. Their release profiles are illustrated in figure 5.4.

Tab. 5.10: The actual composition of pellets prepared by the spraying of salt solution

Powder mixture (400g)		Sprayed salt solution for granulation (ml)	Moisture content of produced pellets (%)	The actual composition of produced pellets	
Carbomer 934P	20%	Na_2SO_4 sol. 680ml	0.6%	Carbomer 934P	18.5%
				Theophylline	18.5%
				MCC	55.7%
				Na_2SO_4	6.7%
				Water	0.6%
Theophylline	20%	$CaCl_2$ sol. 655ml	0.8%	Carbomer 934P	18.5%
				Theophylline	18.5%
MCC	60%			MCC	55.5%
				$CaCl_2$	6.7%
				PVP	1.7%
				Water	0.8%
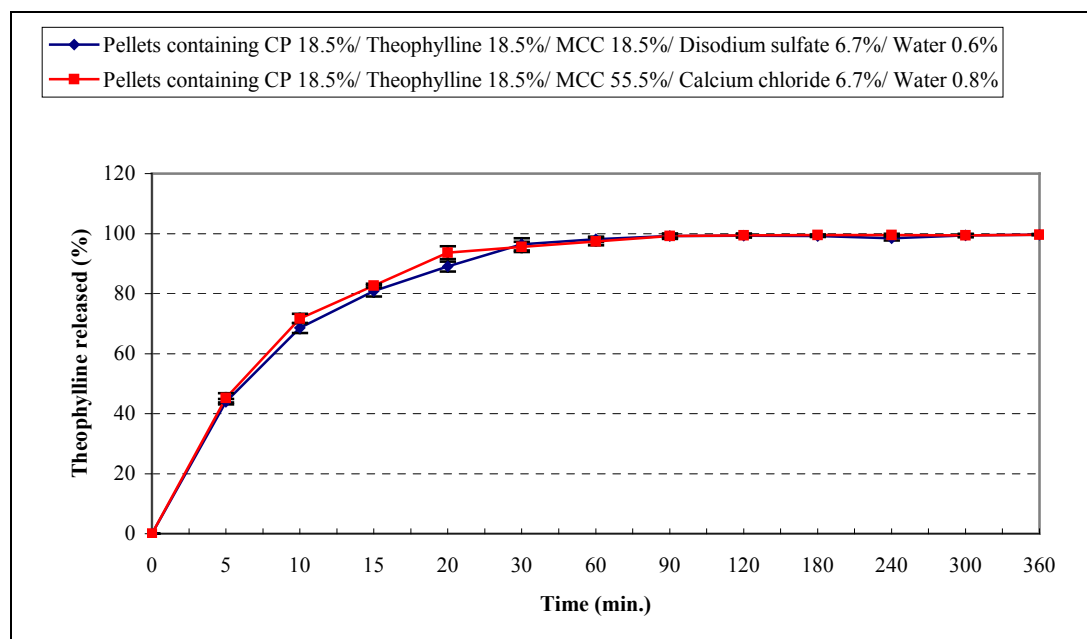
Fig. 5.4: Influence of salts on the release of theophylline in water of pH 4.1~4.9 (Mean±S.D., n=3)

From figure 5.4, no considerable difference in theophylline release between two groups of pellets containing disodium sulfate and calcium chloride. As indicated in table 5.10, the compositions of these pellets were very similar, therefore it might result in no remarkable difference in dissolution pattern.

5.3.2 Pellets produced with carbomer 934P/ theophylline/ MCC/ tri-calcium phosphate

5.3.2.1 Influence of carbomer 934P

To investigate the influence of carbomer 934P, two kinds of pellets were tested. The one contained carbomer 934P (Pellets A), another one was the control-pellets without carbomer 934P (Pellets B). The concrete compositions of pellets were as described in table 5.11. The results of dissolution test are illustrated in figure 5.5.

Pellets containing carbomer 934P showed a slower release of theophylline, whereas the control pellets without carbomer showed about 100% release at 30min. [Fig.5.5]. This result was as expected due to the gel-forming of carbomer. The pellets containing carbomer 934P formed a thin gel-barrier in dissolution medium, that led to the less penetration of medium liquid into the pellets [265, 275-279, 289, 290, 293, 294, 301]. The delay of theophylline release was occurred due to this gel barrier.

Tab. 5.11: The actual composition of produced pellets

	Powder mixture (400g)		Sprayed binder solution for granulation (ml)	Moisture content of produced pellets (%)	The actual composition of produced pellets	
Pellets A	Carbomer 934P	0%	1%-PVP K90 sol. 686ml	0.8%	Carbomer 934P	0%
	Theophylline	20%			Theophylline	19.5%
	MCC	40%			MCC	39%
	TCP	40%			TCP	39%
					PVP	1.7%
					Water	0.8%
Pellets B	Carbomer 934P	20%	1%-PVP K90 sol. 702ml	0.9%	Carbomer 934P	19.5%
	Theophylline	20%			Theophylline	19.5%
	MCC	30%			MCC	29.2%
	TCP	30%			TCP	29.2%
					PVP	1.7%
					Water	0.9%

Fig. 5.5: Influence of carbomer 934P on the release of theophylline in water of pH 3.8 (Mean±S.D., n=3)

5.3.2.2   Influence of pH value

In order to evaluate the influence of pH value of dissolution medium, the release from the pellets containing 20% of carbomer 934P was compared in the medium of different pH (3 and 6.8).
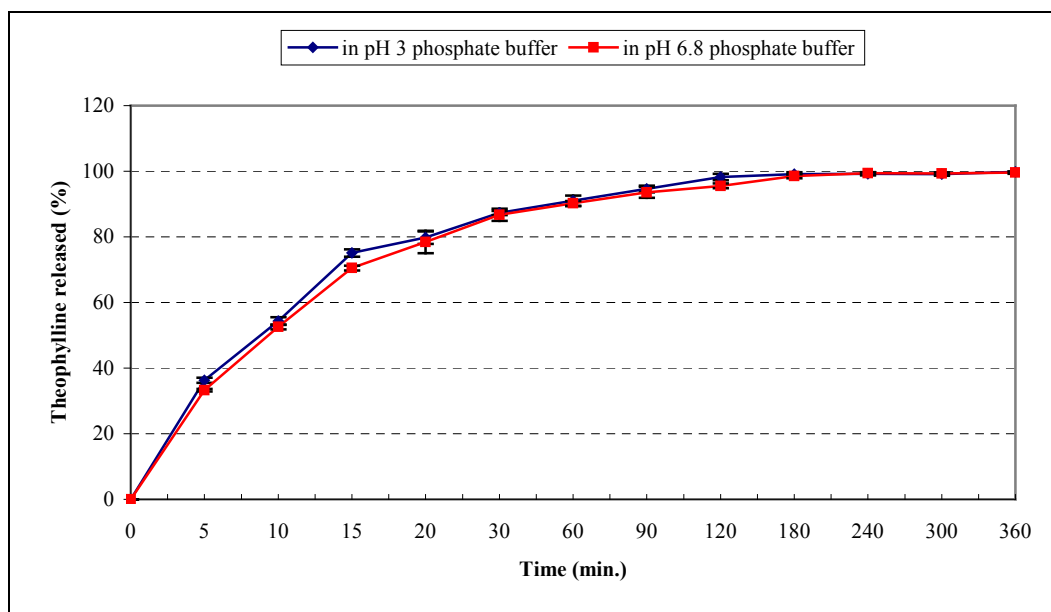
Fig. 5.6: Influence of pH on the release of theophylline from the pellets containing CP 19.5%/Theophylline 19.5%/MCC 29.2%/TCP 29.2%/PVP 1.7%/Water 0.9% (CP: carbomer 934P, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate, cl-PVP: cross-linked PVP) (Mean±S.D., n=3)

As indicated in figure 5.6, theophylline release patterns at pH 3 and 6.8 showed no considerable difference. Principally, carbomer forms a strong gel-structure at pH 4~9 [8-10], thus a remarkable difference of dissolution profile was expected. However, no considerable differences in dissolution pattern were found from the result. It might be caused by the content of carbomer 934P. It was fixed as 20% (w/w, in dry state), since it could not be fully maximized to avoid the handling difficulty in pelletization process. This amount could be probably not sufficient to show any remarkable differences in dissolution pattern. Only a slight delay was observed by differing pH of medium from 3 to 6.8.

5.3.3 Pellets produced through dry-coating technique

5.3.3.1 Influence of coating level

The release profiles of uncoated and carbomer 934P-layered pellets are illustrated in figure 5.7.
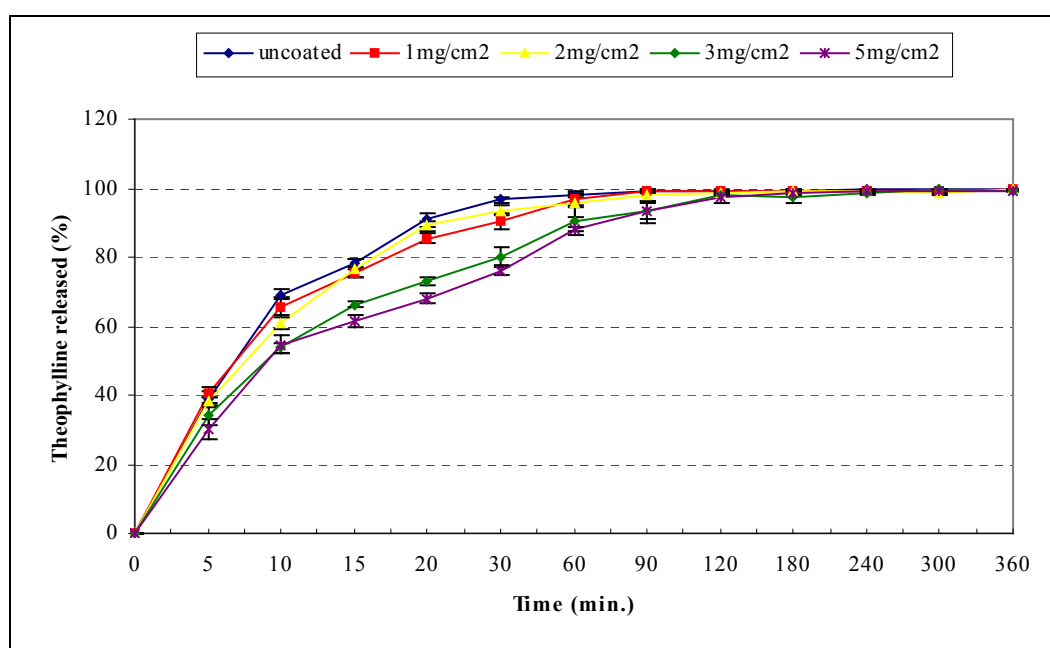
Fig. 5.7: Influence of coating level on the release of theophylline from carbomer 934P-coated pellets (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) in water of pH 4~5 (Mean±S.D., n=3)

Theophylline release from uncoated and coated pellets with the coating level of 1 mg/cm^2 and 2 mg/cm^2 was almost 100% at 30 min. The delay of drug release was indicated only at the higher coating level (3 and 5 mg/cm^2). Below the coating level of 3 mg/cm^2, carbomer could not delay the drug release considerably. It was considered that this coating level could not guarantee the formation of a gel-layer providing the sustained release of drug.

5.3.3.2 Influence of pH value

Uncoated pellets and the pellets with low coating level (1 and 2 mg/cm^2) showed no considerable differences by differing pH [Fig.5.8~5.10]. However, in case of the pellets with the high coating level (3 and 5 mg/cm^2), theophylline release was slightly delayed at pH 6.8 [Fig.5.11 and 5.12]. This result can be explained through the gel-barrier formed at surface of pellets [265, 275-279, 289, 290, 293, 294, 301]. Whereas the uncoated and the low-level coated pellets were not influenced by the gel-formation of carbomer, the pellets coated with 3 and 5 mg/cm^2 could be dependent on the gel-forming of carbomer by varying pH. In the medium of pH 6.8, carbomer could swell promptly at the surface of pellets. This gel-barrier could prohibit the dissolution of theophylline from pellets into dissolution medium. That resulted in the delay of theophylline release.
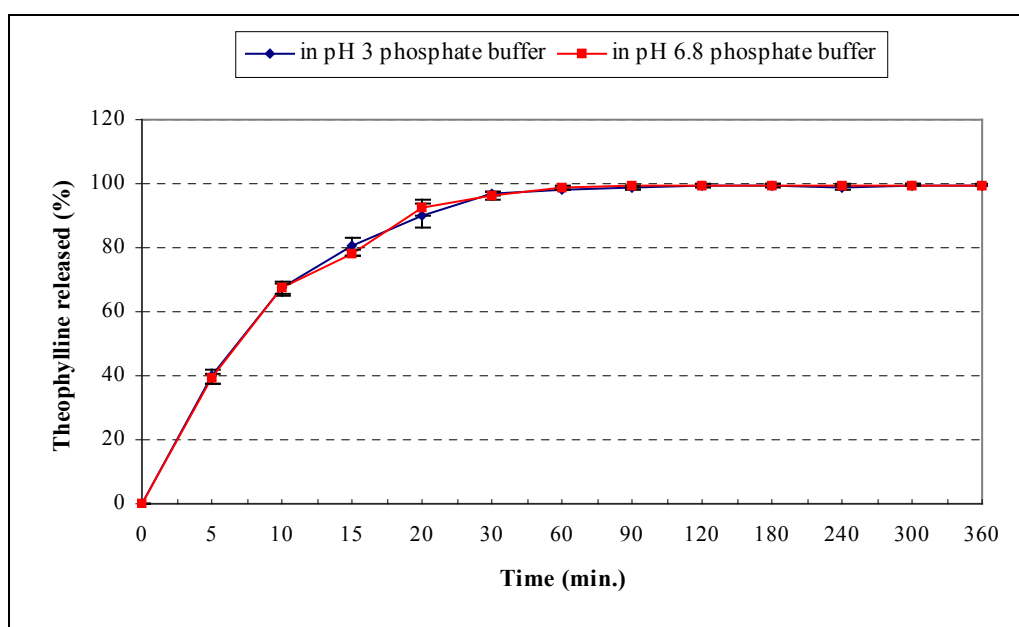
Fig. 5.8: Theophylline release from uncoated pellets containing theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%at different pH (Mean±S.D., n=3)
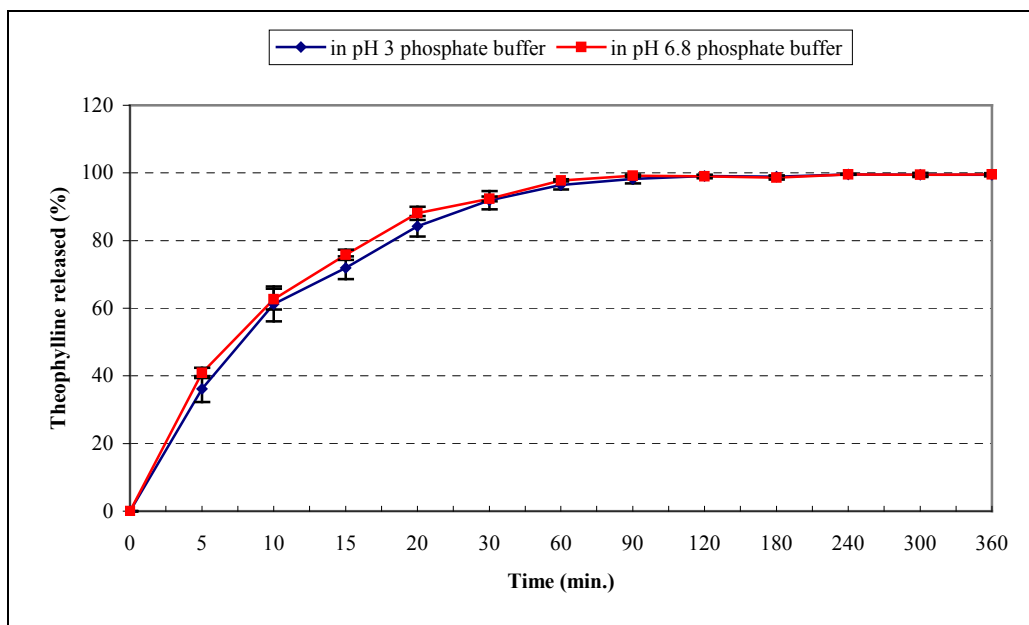
Fig. 5.9: Theophylline release from the pellets with 1mg/cm^2 of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean±S.D., n=3)
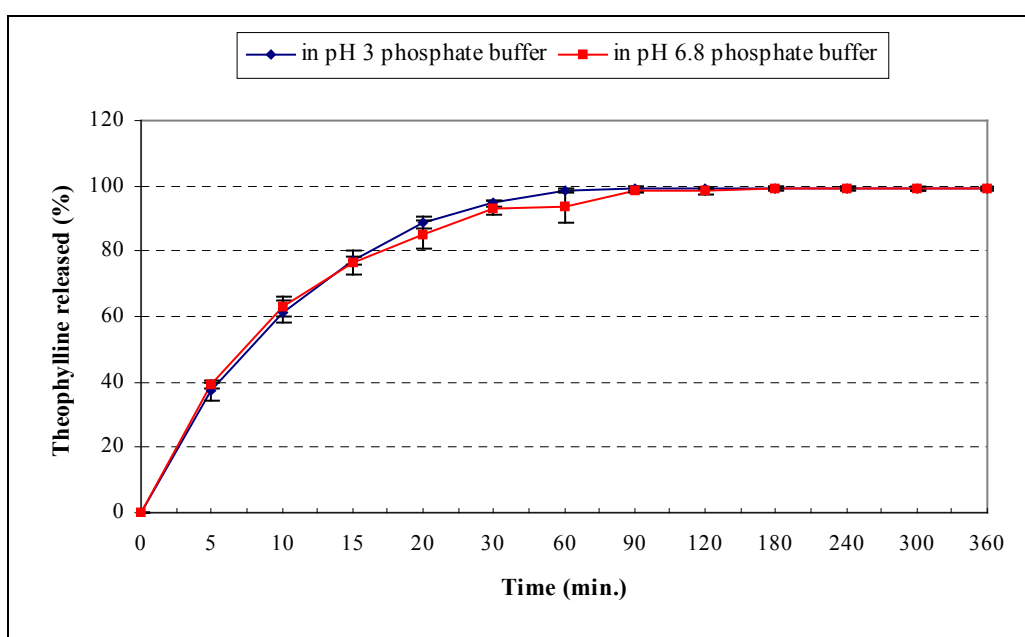
Fig. 5.10: Theophylline release from pellets with 2mg/cm^2 of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean±S.D., n=3)
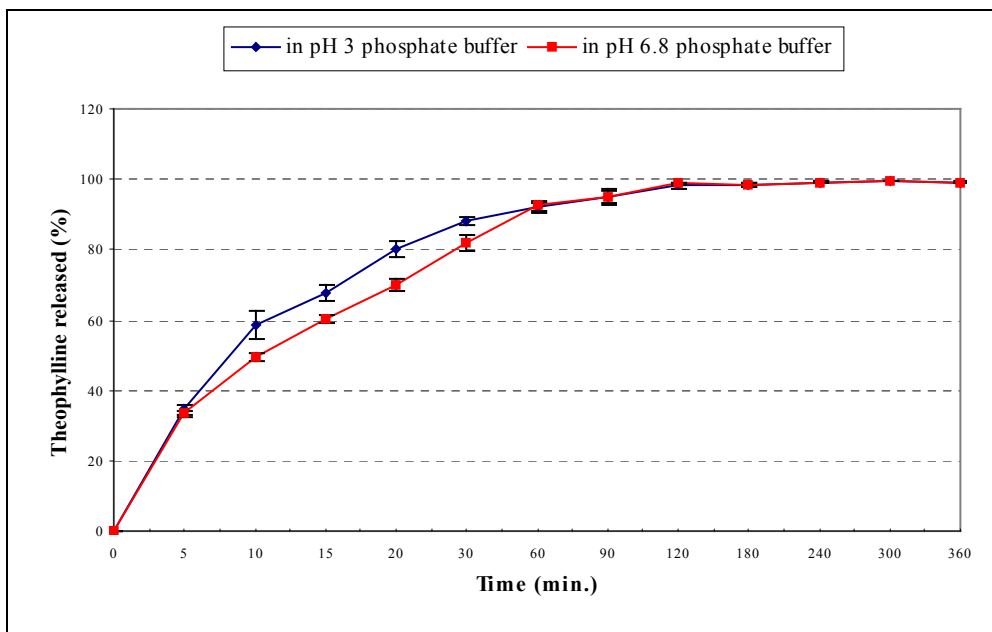
Fig. 5.11: Theophylline release from pellets with 3mg/cm^2 of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean±S.D., n=3)
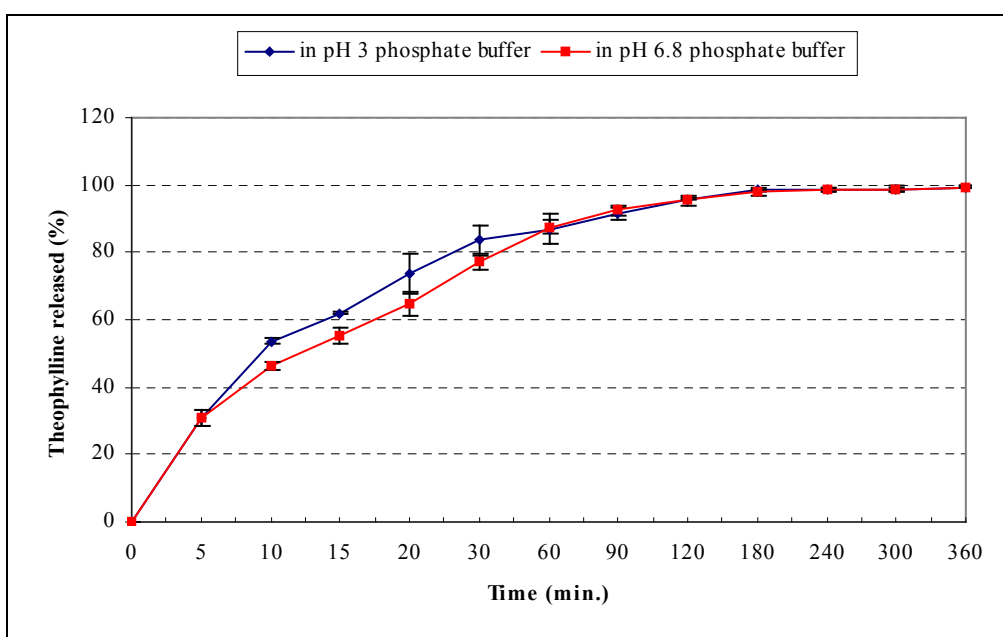
Fig. 5.12: Theophylline release from pellets with 5mg/cm^2 of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean±S.D., n=3)

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.

Appendix I

I.1 Related materials

I.1.1 Carbomer 934P

Carbomers are carboxyvinyl polymers of extremely high molecular weight that are available as dry fluffy powders. Various grades of carbomers are commercially available that different from each other depending on their molecular weight and a architecture as well as on the use of either allylsucrose or allylethers of pentaerythritol for cross-linking acrylic acid. The chemical structure of carbomer is illustrated in Fig. I.1.
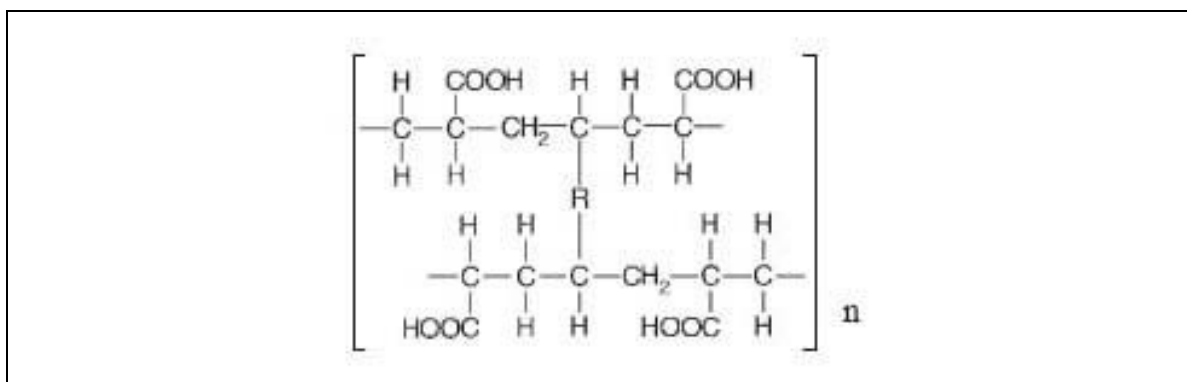
Fig. I.1: The structure of Carbomer (R= allylsucrose or allyl pentaerythritol) [8]

Carbomer resins intended for oral and mucosal applications are designated by a 'P' (934P, 974P, 971P) [5, 8-11]. They contain between 56-58% of the carboxylic groups calculated on dry basis. A high percentage of carboxylic acid groups allow the polymer to be water swellable. When dispersed in water, carbomer resin molecules partially swell and become viscous. On neutralization with a water-soluble base, the resin molecules swell completely, with a dramatic increase in their viscosity [47, 54, 57].

Carbomers are extensively being used in the pharmaceutical and cosmetic industry due to:

a) excellent thickening efficiency even at low resin concentration, allowing it to be used for suspending insoluble substances and viscosifying and stabilizing emulsions, pastes, ointments, jellies, and the like

b) excellent temperature stability even when subjected to heating and cooling cycles

c) microbial resistance since dry powder forms of the resin do not support the growth of molds and fungi [5, 8-13].

I.1.2 Microcrystlline cellulose (MCC)

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white-colored, odorless, tasteless, crystalline powder composed of porous particles [85, 100]. It is commercially available in different particle size grades which have different properties and applications. The structure of microcrystalline cellulose is shown in Fig. I.2.
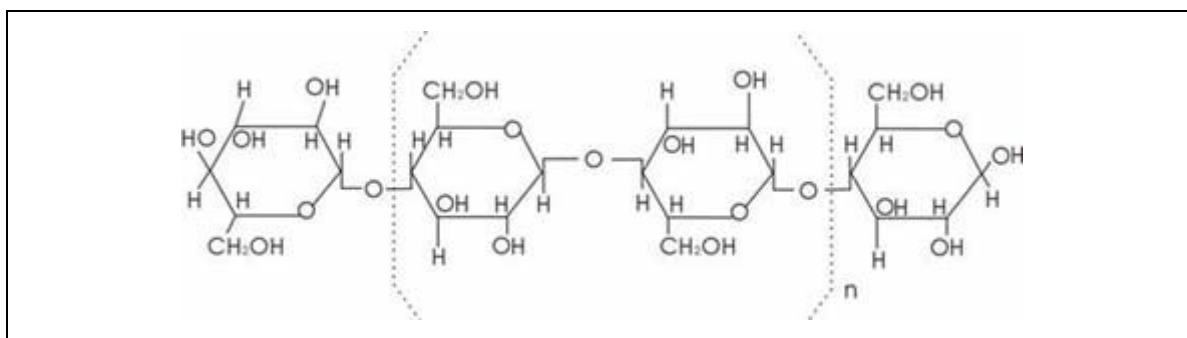
Fig. I.2: The structure of microcrystalline cellulose (MCC) [85]

It is manufactured by the controlled hydrolysis, with dilute mineral acid solutions, of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution. Several different grades of microcrystalline cellulose are commercially available which differ in their method of manufacture, particle size, moisture, flow and other physical properties. The larger particle size grades generally provide better flow properties in pharmaceutical machinery. Low moisture grades are used with moisture-sensitive materials [100].

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and nonirritant material. It is not absorbed systemically following oral administration and thus has little toxic potential.
In pharmaceuticals, it is widely used primarily as a diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting [85, 100].

7.1.3 Other substances

Other substances used in all investigations are listed in table I.1.

Tab. I.1: Other substances used

Name	Abbreviation	Supplier
Bentonite	Bentonite	Carl Roth GmbH (Quellton)
Calcium chloride Hexahydrate	$CaCl_2$ x 6 H_2O	Merck AG
Corn starch	Corn starch	Cerestar
Crospovidone	Polyplasdone XL	Polyplasdone XL 10, ISP
Di-Calcium phosphate	Di-Ca-Phosph.	Dicalciumphosphat, Budenheim
Lactose	Lactose	Tablettose 80, Meggle
Magnesium stearate	Mg-Stearate	Merk AG
Polyethylene glycol	PEG 6000	PEG 6000, Merk-Schuchardt
Polyvinylpyrrolidone K 90	PVP K 90	Polyvinylpyrrolidone 350, Serva
Sodium chloride	NaCl	Merck AG
Sodium citrate	Na citrate	Isocommerz
Sodium sulfate Decahydrate	Na_2SO_4 x 10 H_2O	Isocommerz
Talc	Talc	VEB Laborchemie Apolda
Theophylline	Theophylline anhydrous	Boehringer Ingelheim
Tricalciumphosphat	Tri-Ca-Phosph.	Tricalciumphosphat, Budenheim

I.2 Methods

I.2.1 Chelate titration method

Since tri-calcium phosphate is almost insoluble in water, it was assumed that its anti-tack action to carbomer is not because the influence of its Ca ions. In order to elucidate this hypothesis, the amount of Ca ions in the composition was measured by the chelate titration method.

The composition contains 30% (w/w) of tri-calcium phosphate, and 1ml of water / 1g of powder were required to prepare wet mass. That is, 1ml of water contains 0.3g of tri-calcium phosphate. Therefore, 0.3 g/ml of tri-calcium phosphate dispersion was prepared and stirred for 30min. After centrifugation, 300ml of solution was prepared and 1N-NaOH was added. This solution was titrated with 0.1N-EDTA solution. Eriochrome black T was used as an indicator. 0.5ml of EDTA solution was required to reach the endpoint (pink $\rightarrow$ blue color).

1ml of EDTA solution = 4.008 mg Ca

Therefore, 0.5 X 4.008 = 2.004 mg Ca in 300 ml solution

Finally, 1ml of this solution contains 0.006 mg Ca.

I.2.2 Determination of flow rate of powder

50g of powder blends were filled in a glass funnel fixed on a clamp. The time was recorded from when the powder started to flow until finish. Flow rate was calculated as g/s [306]. The mean of five replicates was used as the result.

I.2.3 Determination of angle of repose of powder
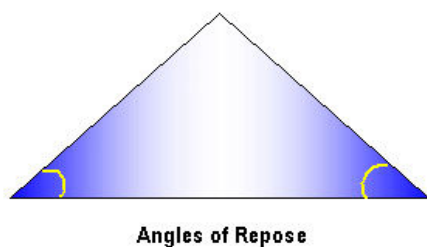
Angles of Repose

Angle of repose is defined as the angle of the free surface of a pile of powder to the horizontal plane [Fig. I.3] [221, 306]. 50g of powder blends were flown from a funnel and the height (h) of the powder cone and radius (r) was measured. Angle of repose was calculated using the equation: $\tan\alpha = h/r$. The mean of five replicates was used as the result.

Fig. I.3: Angle of repose

I.2.4 Determination of enslin number of powder

Enslin number is defined as the absorbed water amount (g or ml) by 1g of substance powder for 15 min. 1g of sample powder was placed in an enslin-apparatus [Fig. I.4], the absorbed water amount was written in 15min [306].
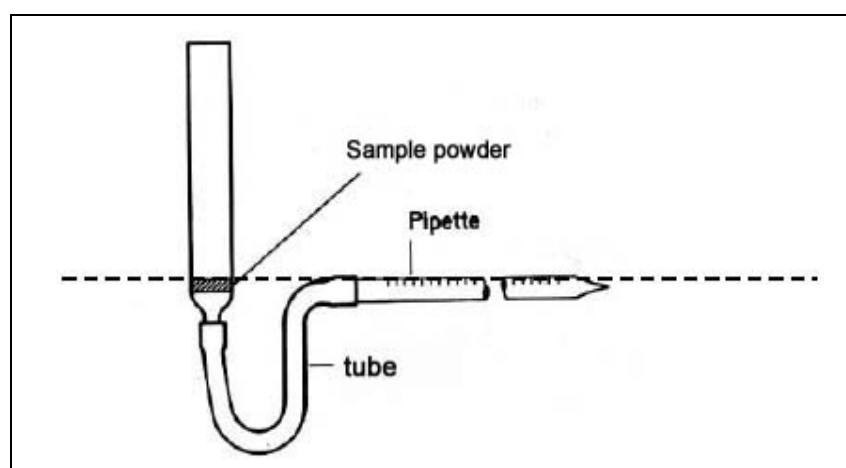
Fig. I.4: Measurement of enslin numer by Enslin-apparatus [306]

I.2.5 Evaluation of pellets

I.2.5.1 Sieve analysis

Particle size distribution was determined by sieve analysis. 100g of sample was sieved using a vibratory sieve shaker (Vibro, Retsch, Germany) at an amplitude 50 for 10min. 2000, 1700, 1400, 1180, 1000, 710, 500, 355, 250, 125, and 90μm sieves were used and the fraction retaining on each screen was weighed and expressed as a percentage of the total weight.

Total yield and the yield of sieve fraction 500~1180 μm were calculated. All results presented are the mean of three determinations. Mass median diameter was the spheroid diameter at the 50-percentile mark on a cumulative percent oversize plot.

Granule yield is involved to determine the quantity of granulated product actually available, thus excluding losses due to sticking to the sides of the bowl (related to static electricity) and the fine particles clogging the filters. The mass of granules obtained at the end of the operation was related to the theoretical quantity.

I.2.5.2 Image analysis

The sphericity, roughness, and aspect ratio of pellets were determined by optical microscopic image analysis using the system Leco IA 3.11(Leco Instrumente GmbH, D-Kirchheim). The basic principles of image analysis system are described in detail in the study of LINDNER und KLEINEBUDDE [307].

400~600 pellets from every batch (sieve fraction 710~1000μm) were collected and analyzed. Pellets were dispersed carefully on the microscope slides and a top light source was used to reduce the influence of shadow on the image processing. The image analyzer consisted of a computer system linked to a black/white-video camera, and a stereomicroscope. The digitized images were analyzed by Scion image analyzing software. The Sphericity or roundness (R), and the aspect ratio are defined as follows:

$$R= 4\pi A/C^2 \qquad \text{(A= area, C= circumference)}$$

$$\text{Aspect ratio}= d_{max}/d_{min} \qquad \text{(d_{max}: the longest Feret diameter, d_{min}: the hortest Feret diameter)}$$

For a perfect spherical shape, aspect ratio is equal to 1.

I.2.5.3 Determination of density

The bulk density of each batch of pellets was measured by carefully pouring an accurately weighed 50g sample through a funnel into a graduated 250ml cylinder and was calculated by dividing the

weight of the material (g) by the volume (ml) occupied in the cylinder. The cylinder was then tapped 10, 500, 1250 times on a tapping device and the tapped density was also determined in g per ml. The tap setting was sufficient in all cases to reach a constant volume [306].

I.2.5.4   Friability

10g pellets of 710~1000μm fraction were rotated with 200 glass beads (4mm in diameter) in friabilator (TAR, Erweka, Germany) at 20rpm for 30min [165]. The glass beads were then removed, and the fine particles were sieved off, the weight loss was calculated as % friability. The results were mean of triplicates.

I.2.5.5   Hardness

Hardness test was performed by measuring of required crushing force using texture Analyzer (EZ-tester, Shimadzu, Japan). 10 pellets of each batch (710~1000 μm fraction) were tested at following test conditions: a speed to perforce of 1mm/min, speed of 10mm/min during the test.

I.2.5.6   Moisture content

Moisture content of pellets were measured during and after granulation process using IR-balance (Type MA 40, Sartorius, Germany) set a temperature of 105ºC. The sample was heated to 105ºC, and evaporative moisture losses were recorded by the internal balance and automatically reported as percent moisture content.

I.2.5.7   Powder layering efficiency

Powder layering efficiency was calculated by dividing the actual weight gain of coated samples divided by the theoretical weight gain and multiplying by 100 [183, 184]. Theoretical drug content was calculated by dividing the amount of drug present in the layering powder with the total of charge load and the amount of the powder layering composition used.

I.2.5.8   Assay of drug content

Quantities (400 mg) of each batch of pellets were accurately weighed, ground to a fine powder using a pestle and mortar and made up to 1000 ml of water and allowed to stand for 1h. Aliquots of the solutions were filtered and assayed spectrophotometrically for theophylline at 271.

I.2.5.9 Dissolution test

I.2.5.9.1 Standard curve of model drug (theophylline)

10mg of theophylline was dissolved in 1L of medium (demineralized water, pH 3 and pH 6.8 phosphate buffer solution). This solution was diluted to 0.2×10^{-2}, 0.3×10^{-2}, 0.5×10^{-2}, and 0.8×10^{-2} mg/ml and UV absorbance was measured. The mean of three replicates was used as the result. The results are shown in Fig. I.5~ I.7.

I.2.5.9.2 Dissolution test

Dissolution test was performed according to USP paddle method in 900ml of dissolution medium (purified water, pH 3 and pH 6.8 phosphate buffer solution). 50mg of pellets were used for test. The temperature of the medium was kept $37 \pm 0.5°C$ while the rotational speed of the paddles was set at 50rpm. 5ml samples were withdrawn at regular time intervals and spectrophotometrically determined at 271nm. The mean of three replicates was used as the result.

I.2.5.9.3 Preparation of buffer solution

pH 3 phosphate buffer solution
3.40g of potassium dihydrogen phosphate were dissolved in demineralized water, and the pH value was adjusted with phosphoric acid. This solution was made up to 1000ml by the addition of demineralized water.

pH 6.8 phosphate buffer solution
5.94g of disodium hydrogen phosphate dihydrate and 4.54g of potassium dihydrogen phosphate were dissolved in demineralized water. This solution was made up to 1000ml by the addition of demineralized water.
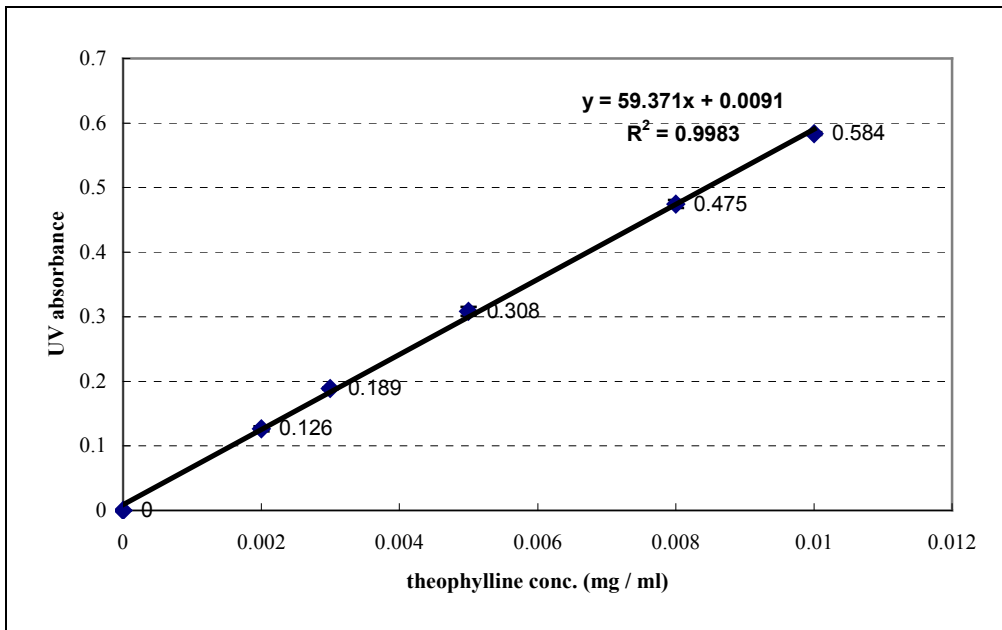
Fig. I.5: standard curve of theophylline in water (pH 3.8) (Mean±S.D., n=3)
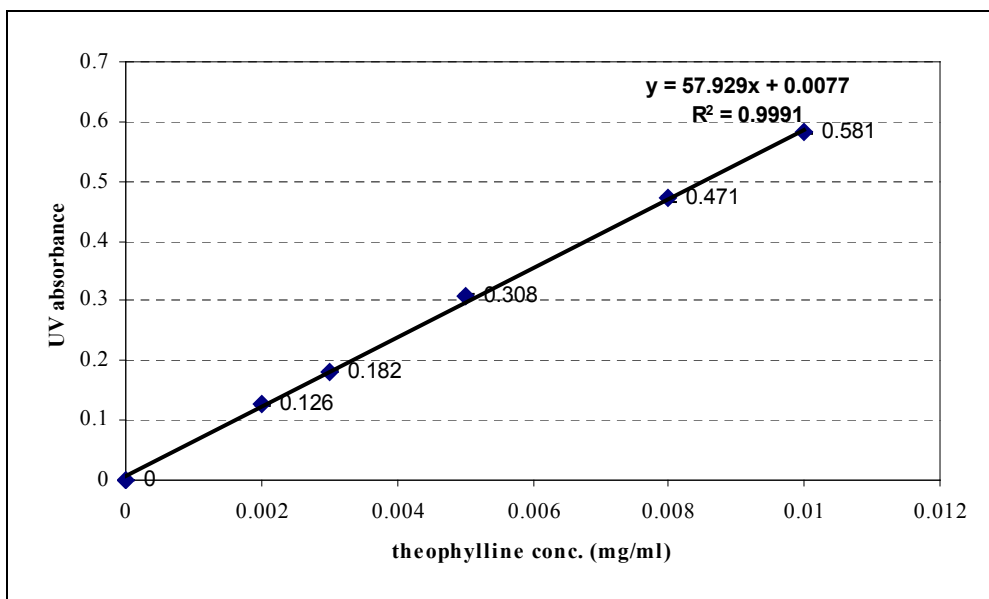
Fig. I.6: standard curve of theophylline in pH 3 phosphate buffer solution (Mean±S.D., n=3)
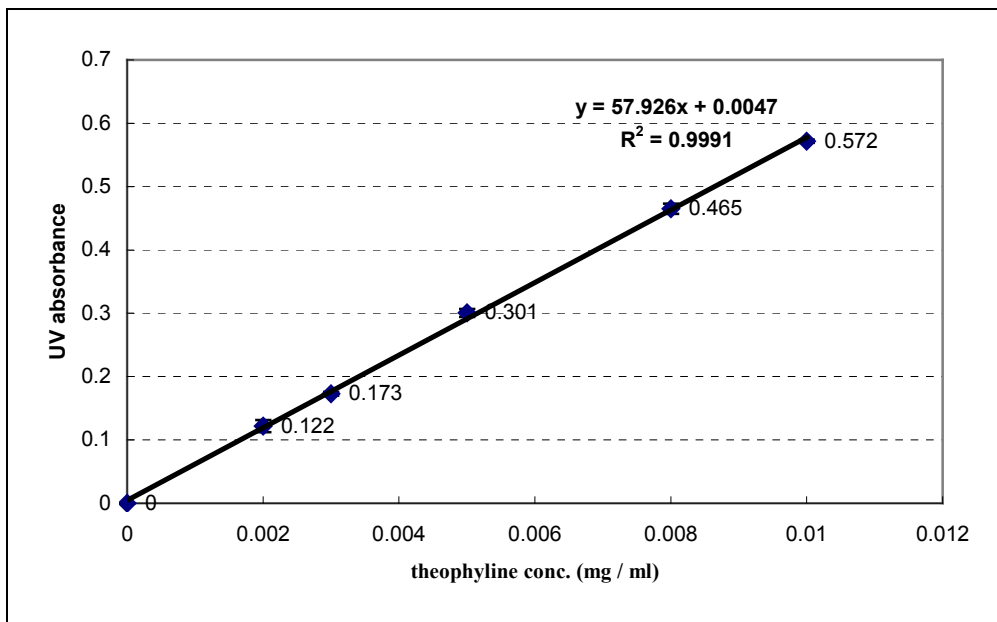
Fig. I.7: standard curve of theophylline in pH 6.8 phosphate buffer solution (Mean±S.D., n=3)

Appendix Ⅱ

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Erklärung

Ich erkläre hiermit, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst, andere als die angegebenen Quellen und Hilfsmittel nicht benutzt und die den benutzten Quellen entnommenen Stellen als solche kenntlich gemacht habe. Ich habe bisher an keiner in- oder ausländischen Fakultät ein Gesuch um Zulassung zur Promotion eingereicht, noch diese oder eine andere Arbeit als Dissertation vorgelegt.

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