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.

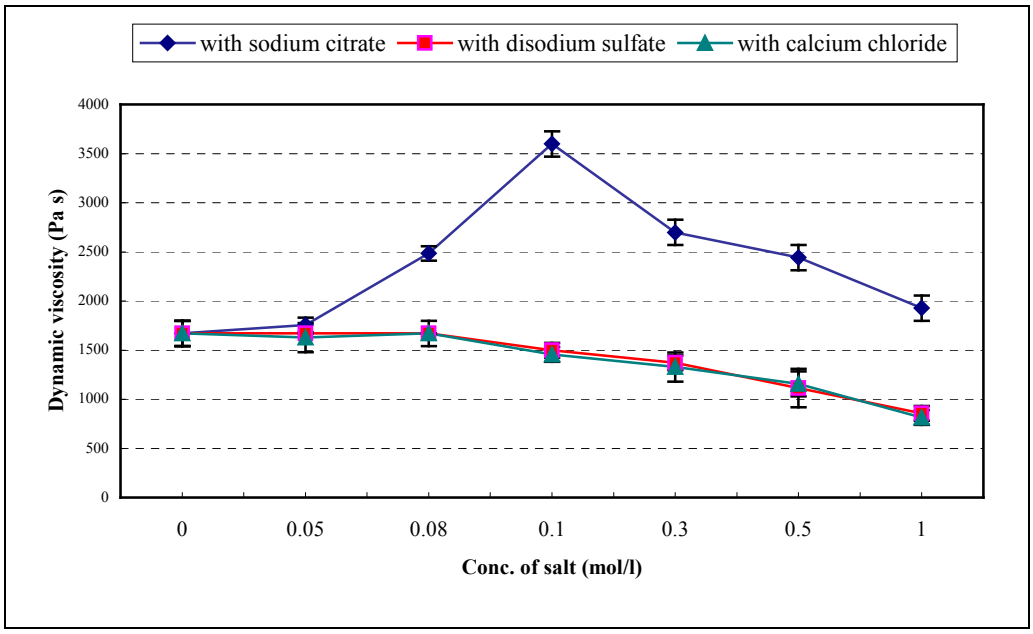


Fig. 3.1: Dynamic viscosity of 2%-carbomer 934P aqueous dispersion with salts

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).

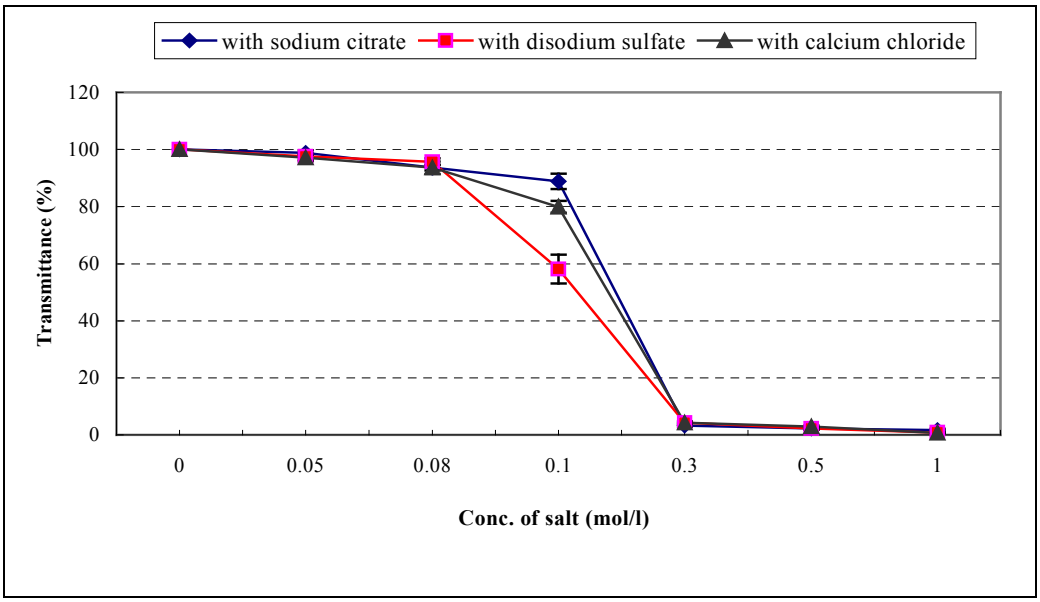


Fig. 3.2: Transmittance of carbomer 934P-aqueous dispersion with salts

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.

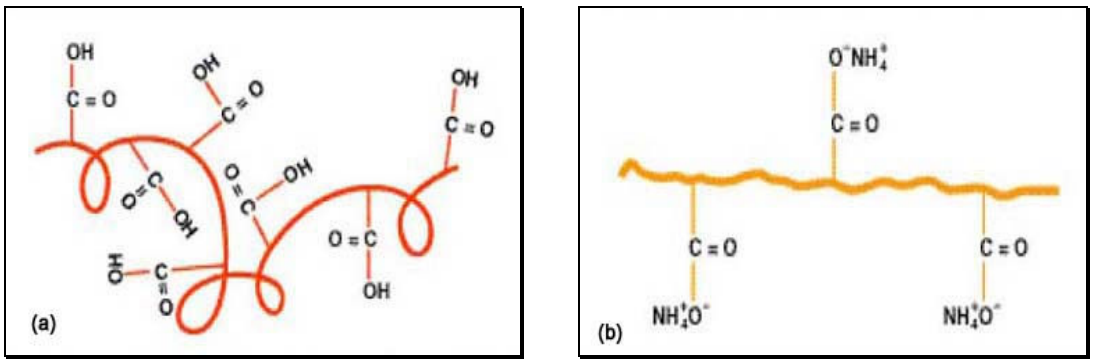


Fig. 3.3: Carbomer resin molecule: unneutrallized (a) and neutralized (b).

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].

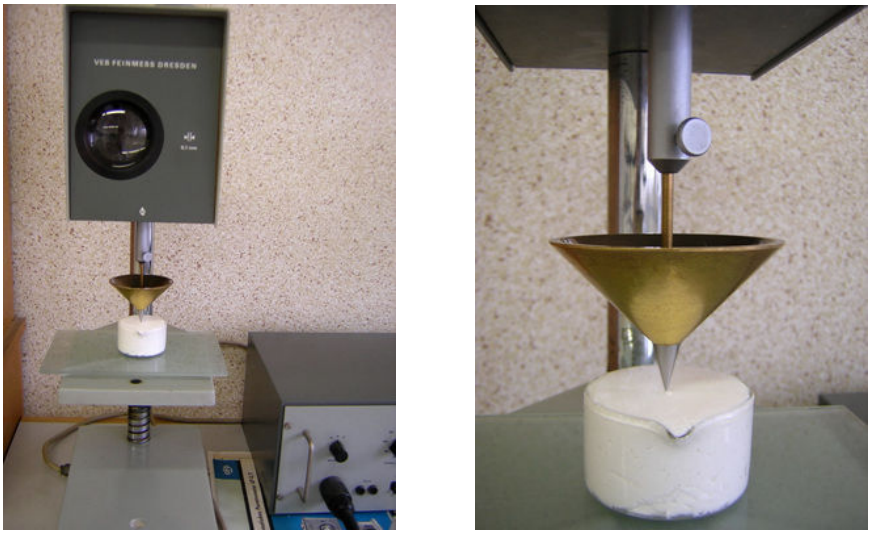


Fig. 3.4: Measurement of penetration depth by penetrometer

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 →	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)		**Wet mass prepared (60g)**
30g Powder mixture of Carbomer 934P (20%) MCC (80%) + Na_2SO_4-dissolved water (30ml)	0	Kneading in mortar →	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)		**Wet mass prepared (60g)**
30g Powder mixture of Carbomer 934P (20%) MCC (80%) + $CaCl_2$-dissolved water (30ml)	0	Kneading in mortar →	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)

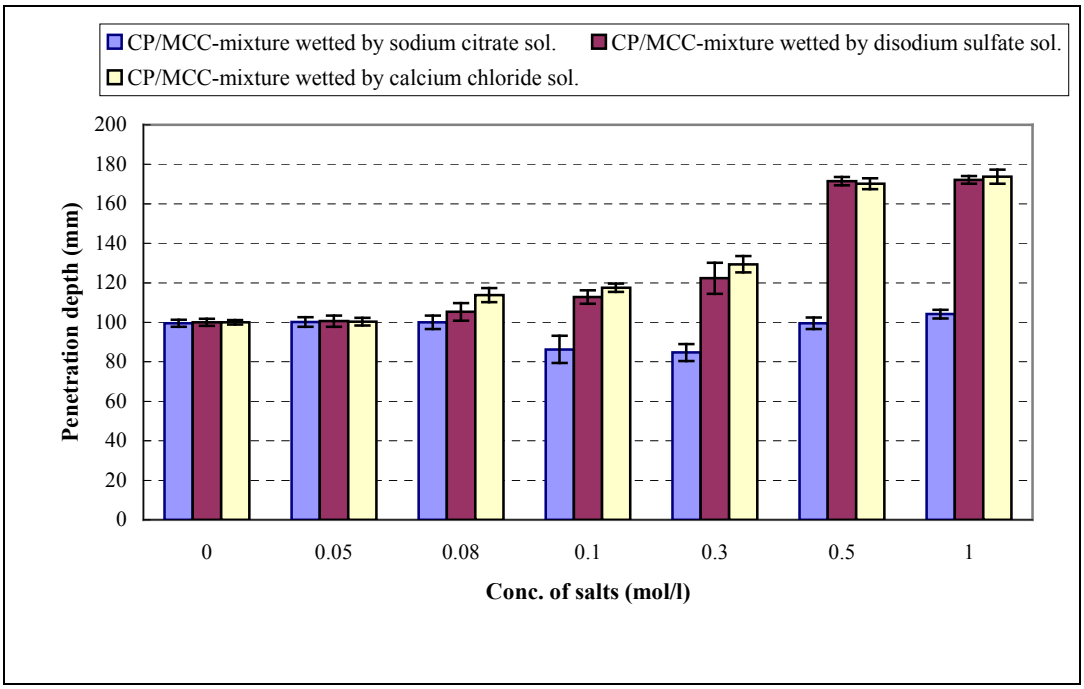


Fig. 3.5: Penetration depth of wet mass made with carbomer 934P/microcrystalline cellulose/salt-dissolved water (the concrete compositions of each wet mass are shown in table 3.1~3.3) (CP: carbomer 934P, MCC: microcrystalline cellulose) (Mean±S.D., n=5)

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'.

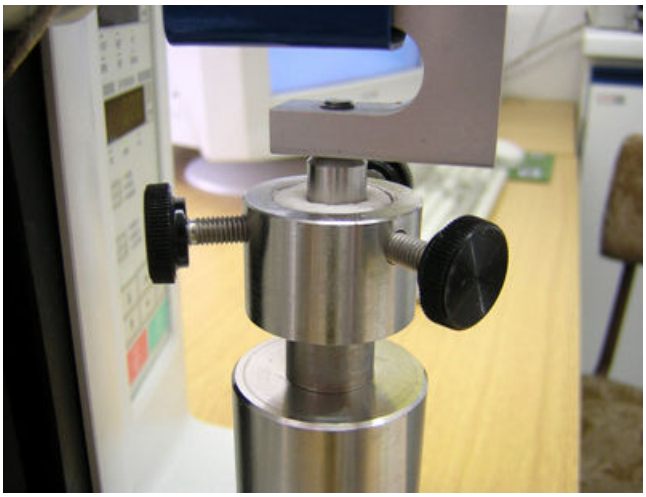


Fig. 3.6: Measurement of adhesion by texture analyzer

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.

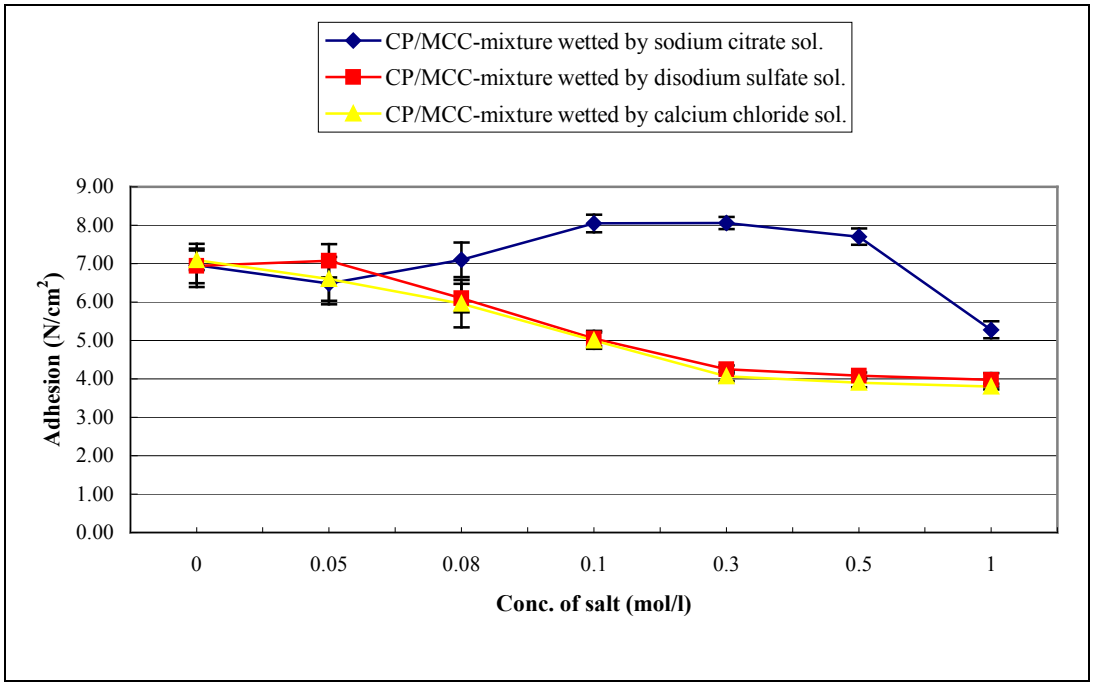


Fig. 3.7: Adhesion of wet mass made with carbomer 934P/microcrystalline cellulose/salt-dissolved water (the concrete compositions of each wet mass are shown in table 3.1~3.3)

(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

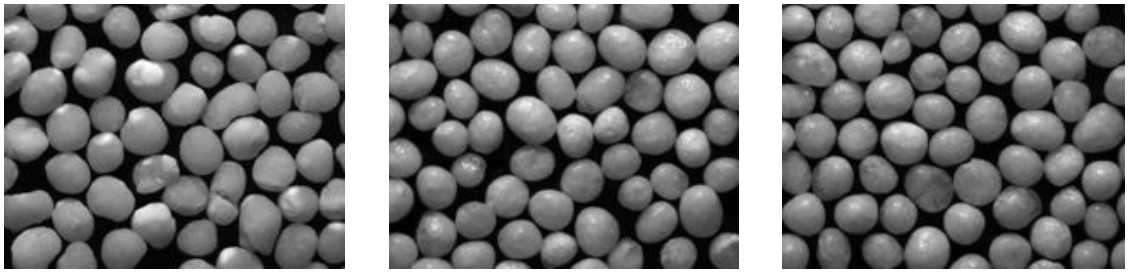
Parameter	Setting
Batch size (g)	400
Type of disc	Hatched
Inlet air volume (m^3/h)	60-70
Inlet air temperature (°C)	40

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)



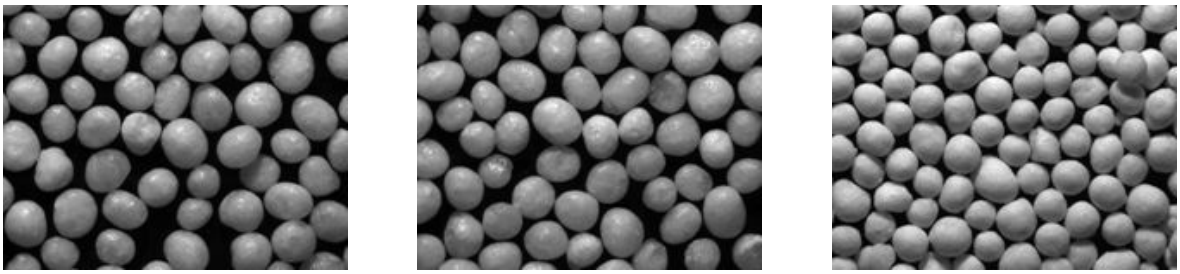
(a) (b) (c)

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.

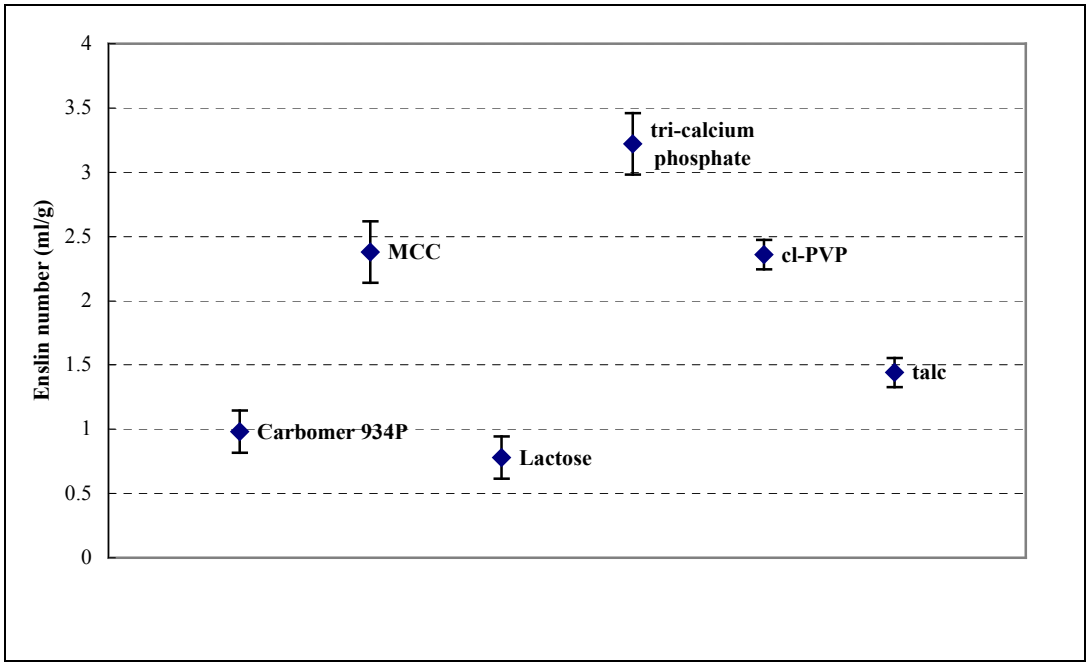


Fig. 3.10: Enslin number of investigated excipients (Mean±S.D., n=5)

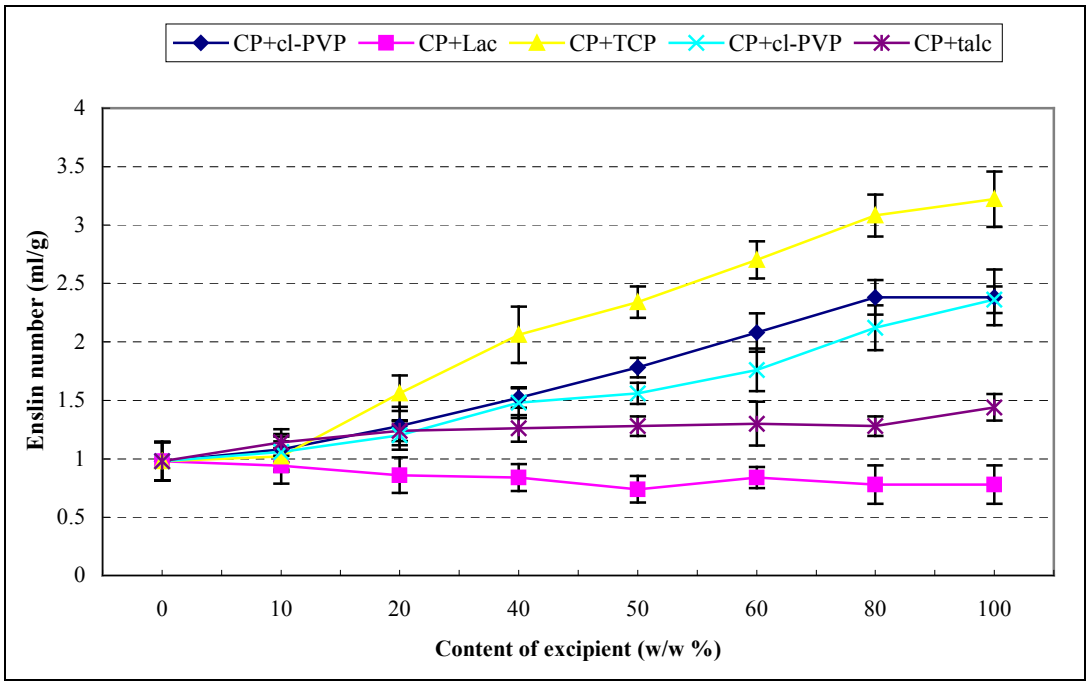


Fig. 3.11: Enslin number of carbomer 934P/excipient-mixtures (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

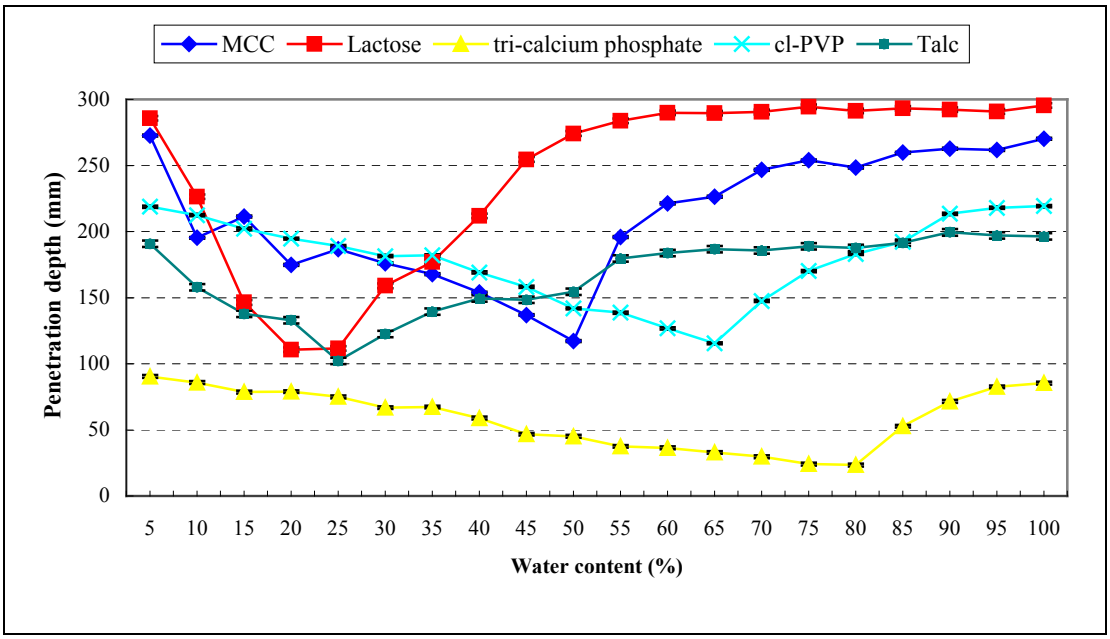


Fig. 3.12: Penetration depth of excipients (cl-PVP: cross-linked PVP, MCC: microcrystalline cellulose)

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.

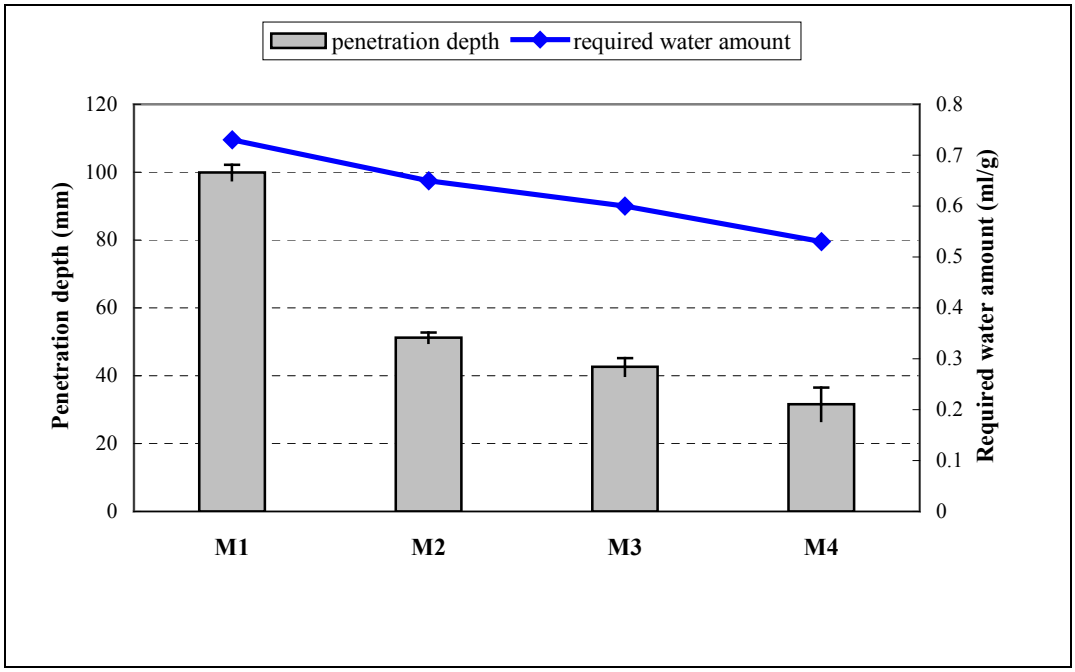


Fig. 3.13: Penetration depth and required water amount of carbomer 934P/microcrystalline cellulose-mixtures (Mean±S.D., n=5)

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 →	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.

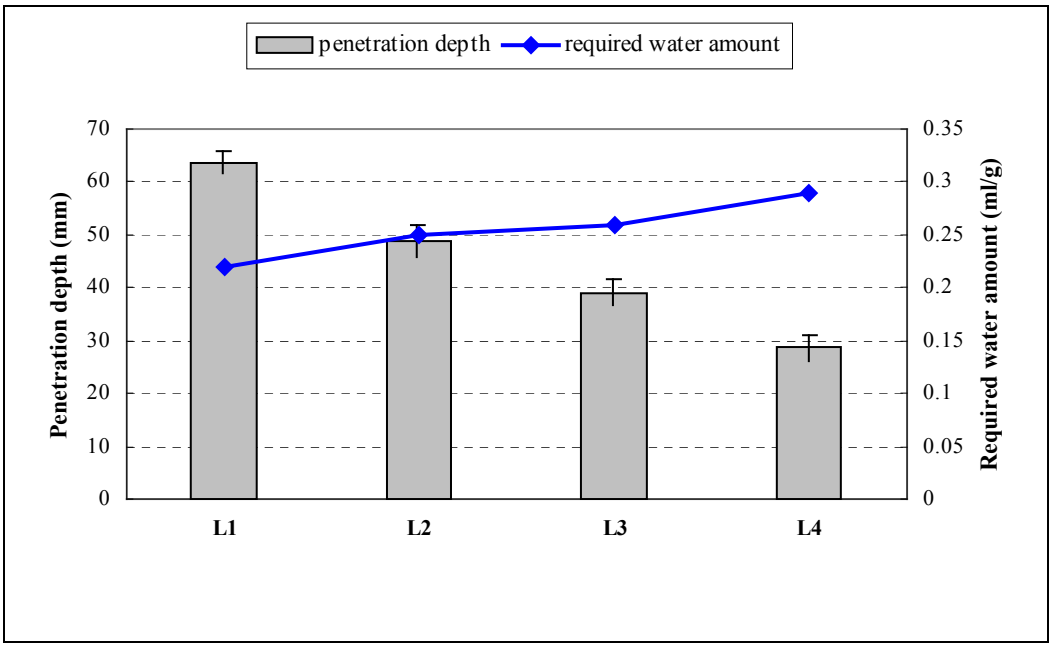


Fig. 3.14: Penetration depth of carbomer 934P/ lactose-mixture (Mean±S.D., n=5)

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

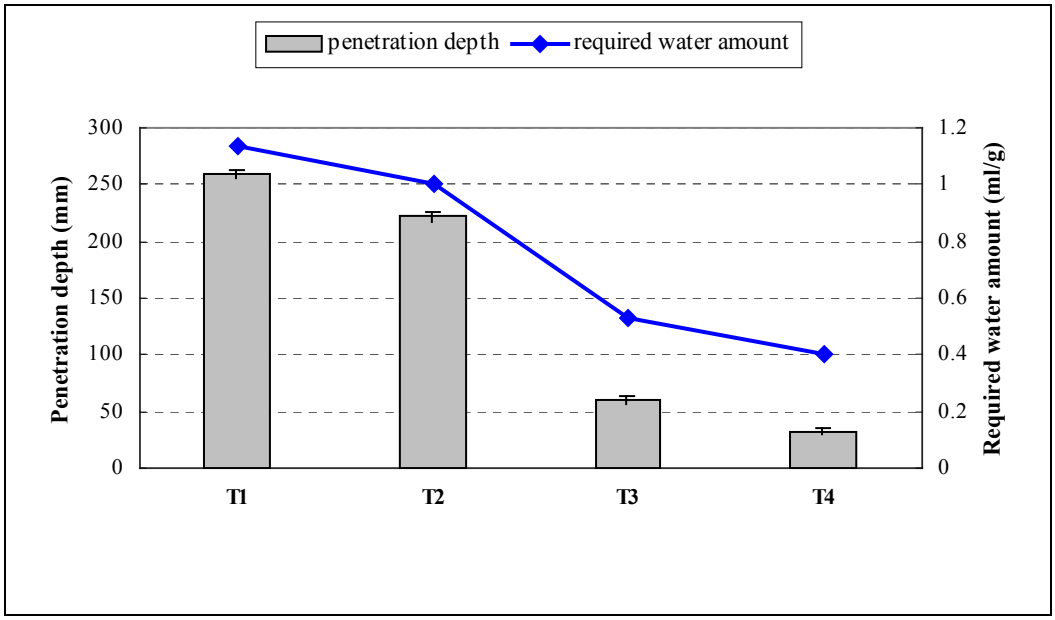


Fig. 3.15: Penetration depth of carbomer 934P/tri-calcium phosphate-mixture (Mean±S.D., n=5)

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)

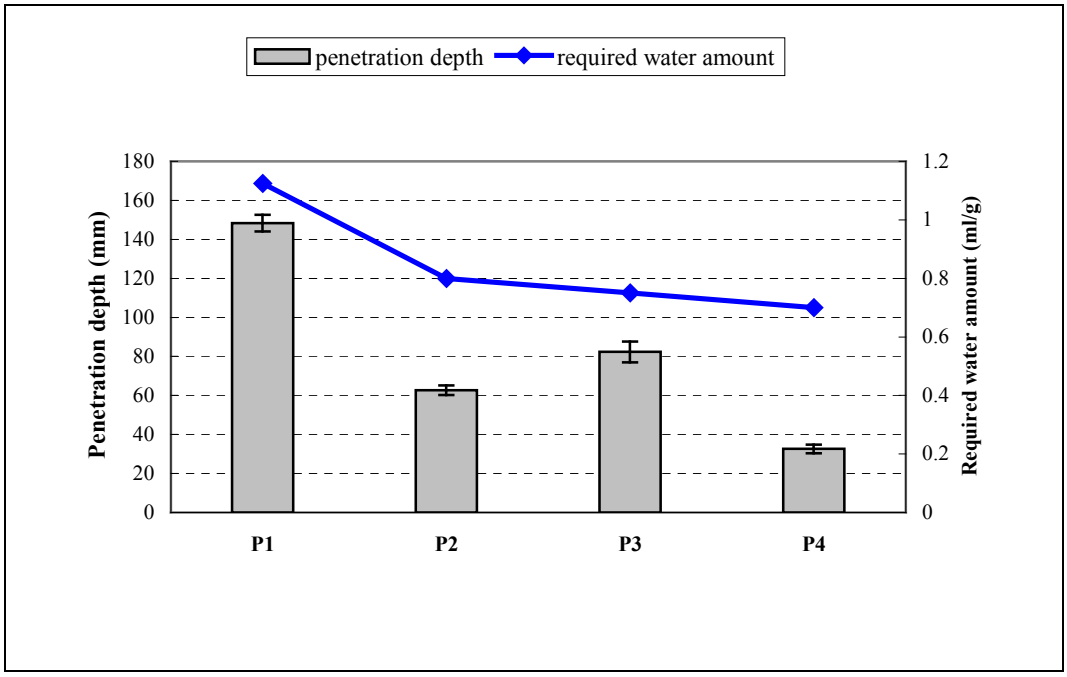


Fig. 3.16: Penetration depth of carbomer 934P/cross-linked PVP-mixture (cl-PVP: cross-linked PVP) (Mean±S.D., n=5)

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.

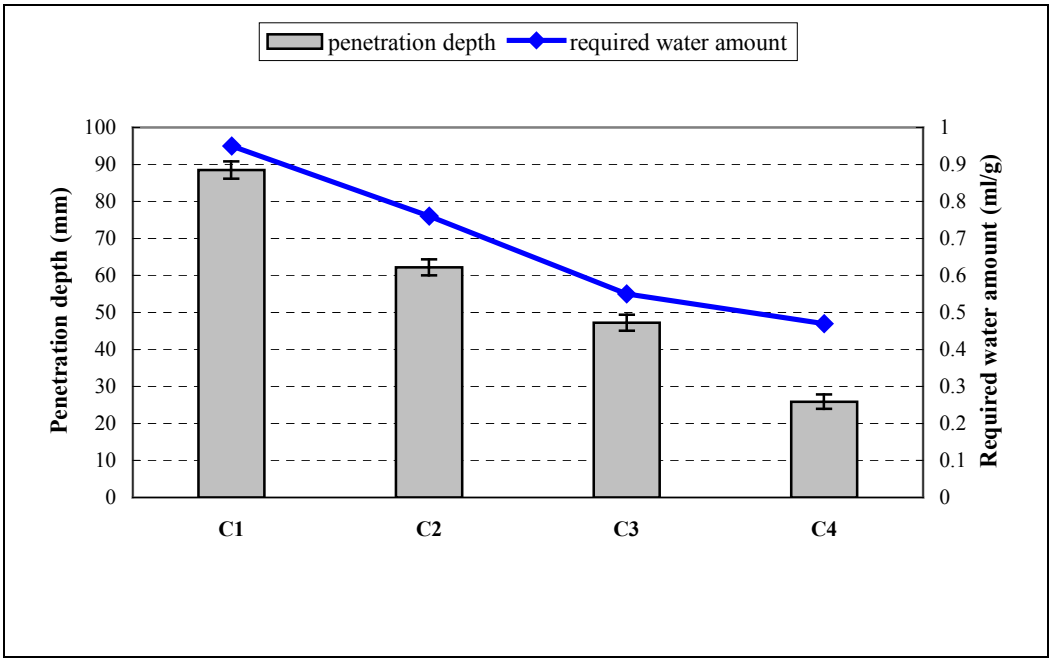


Fig. 3.17: Penetration depth of carbomer 934P/talc-mixture (Mean±S.D., n=5)

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.

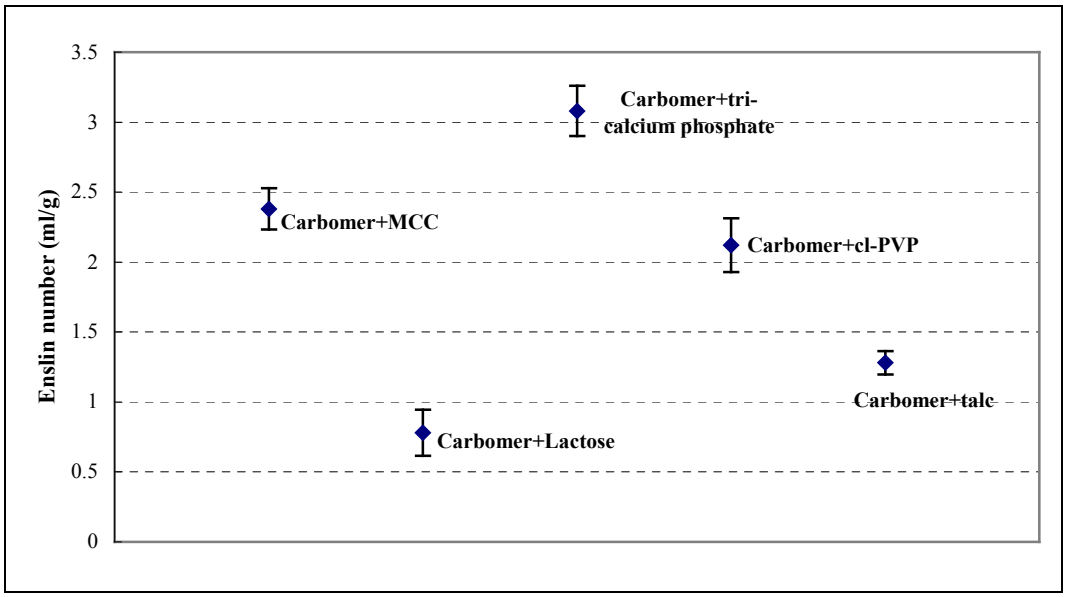


Fig. 3.18: Enslin number of binary mixtures (carbomer 934P/excipient) (Mean±S.D., n=5)

- 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.

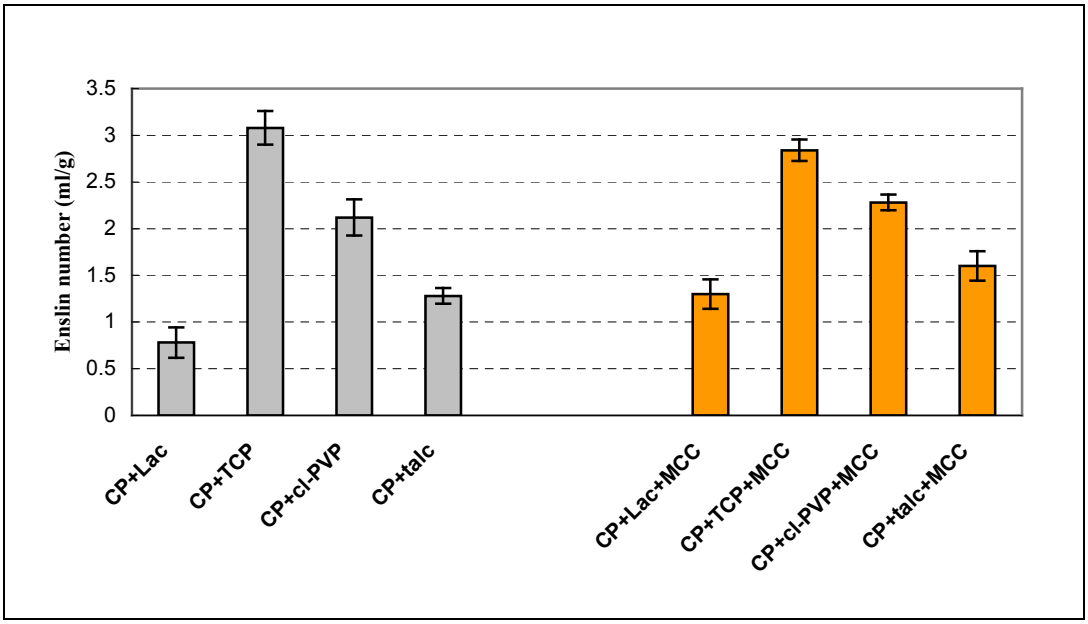


Fig. 3.19: Influence of microcrystalline cellulose on the enslin number (CP: carbomer 934P, cl-PVP: cross linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

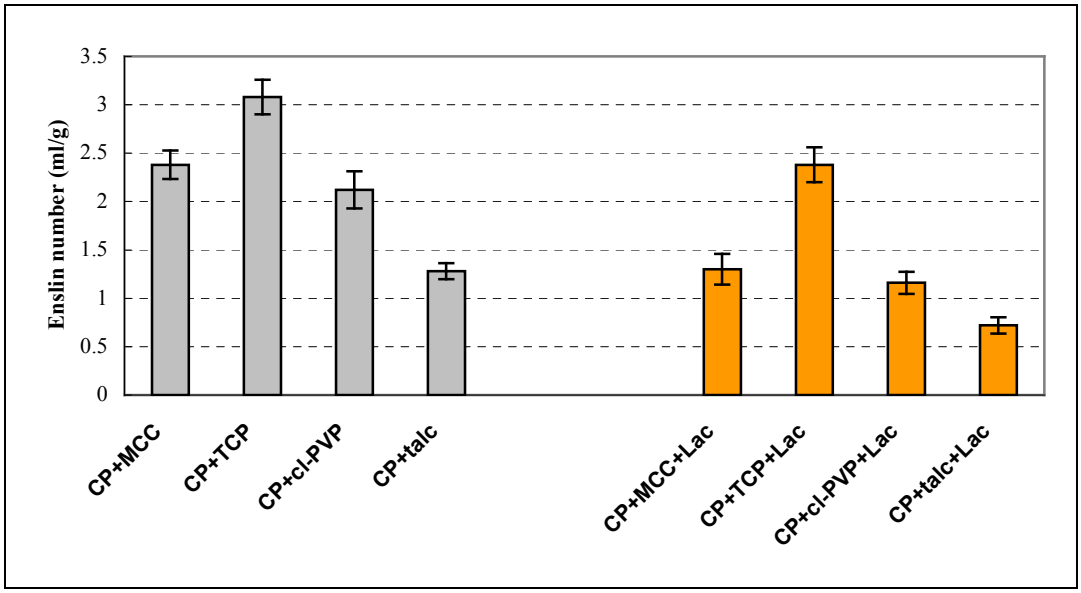


Fig. 3.20: Influence of lactose on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

c) Influence of tri-calcium phosphate

Tri-calcium phosphate caused a considerable increase in enslin number in all cases [Fig.3.21].

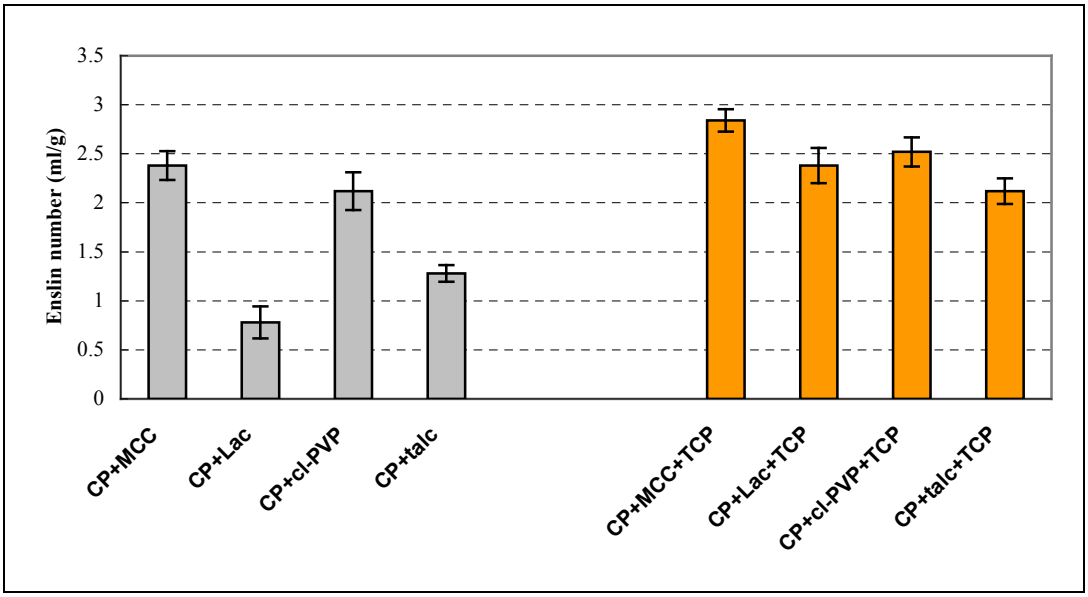


Fig. 3.21: Influence of tri-calcium phosphate on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

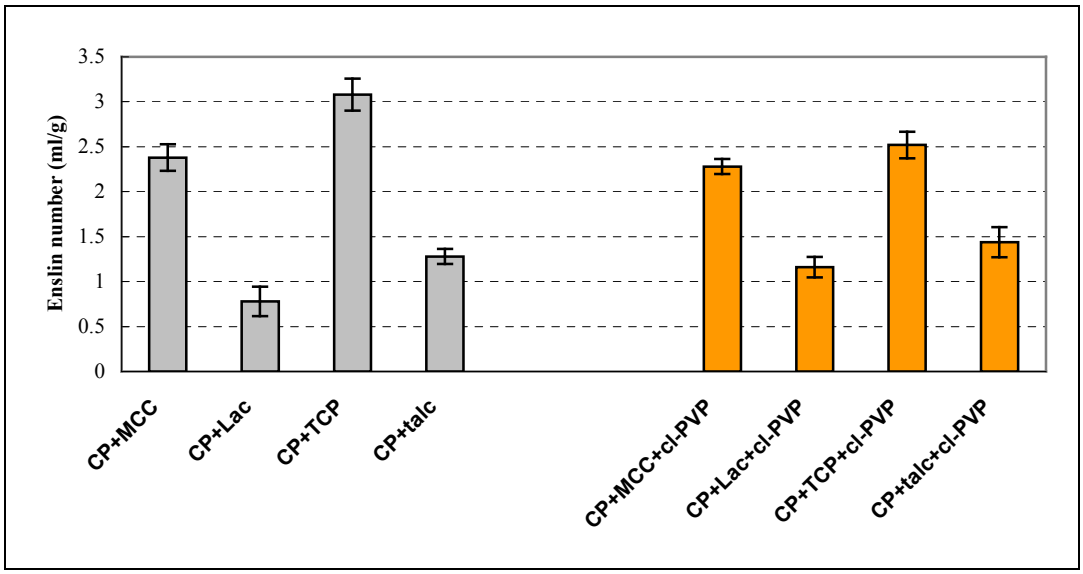


Fig. 3.22: Influence of cross-linked PVP on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

e) Influence of talc

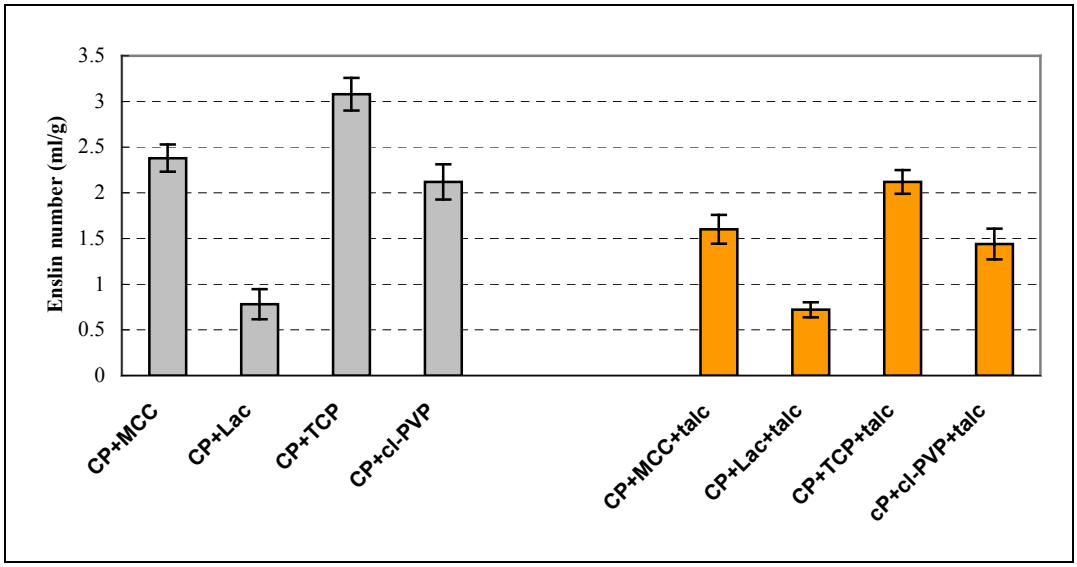


Fig. 3.23: Influence of talc on the enslin number (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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	Kneading in mortar →	CP (11.6%) / MCC (46.2%) / Water (42.2%)	B1
CP (20%) / Lac (80%)	6.6		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

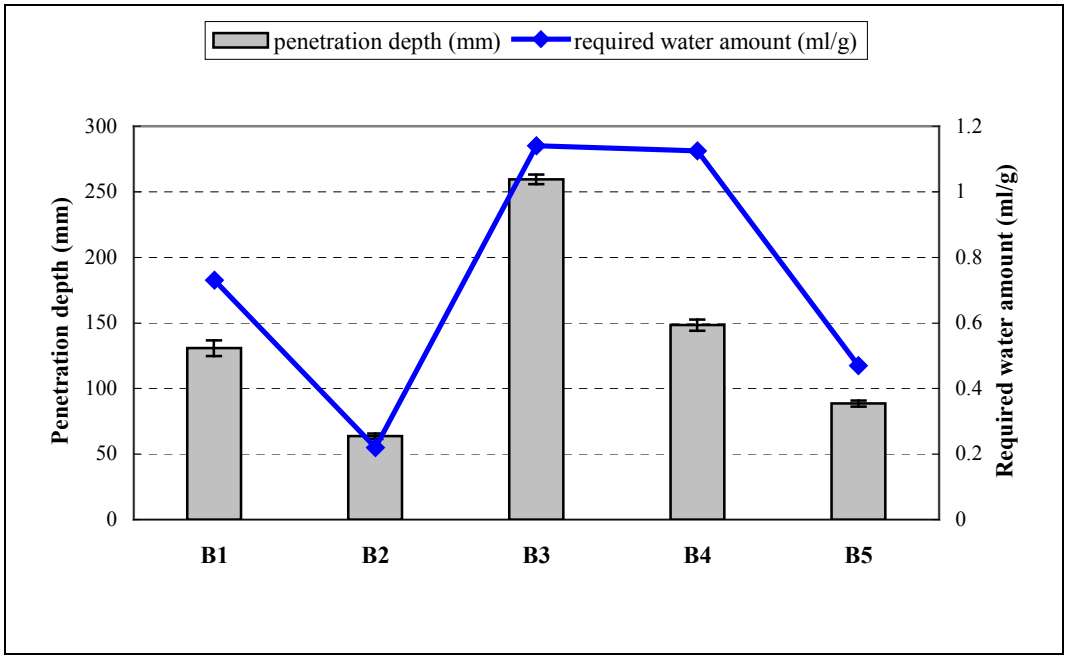


Fig. 3.24: Penetration depth of carbomer 934P/ other excipient-mixtures (CP: carbomer 934P, cl-PVP: cross-linked PVP, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

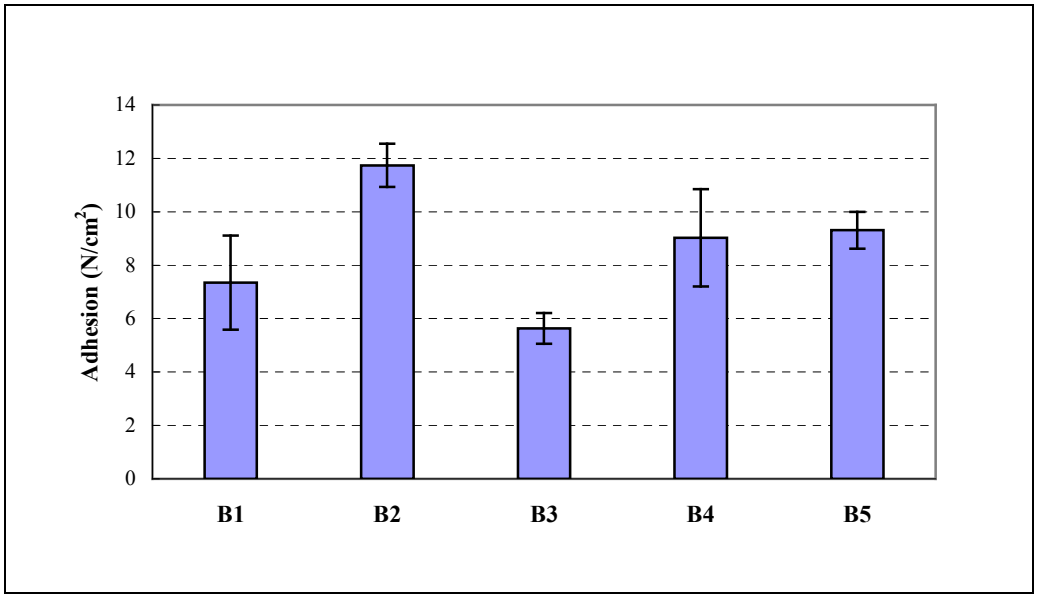


Fig. 3.25: Adhesion of carbomer 934P/ other excipient-mixtures (CP: carbomer 934P, cl-PVP: cross-linked PVP, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

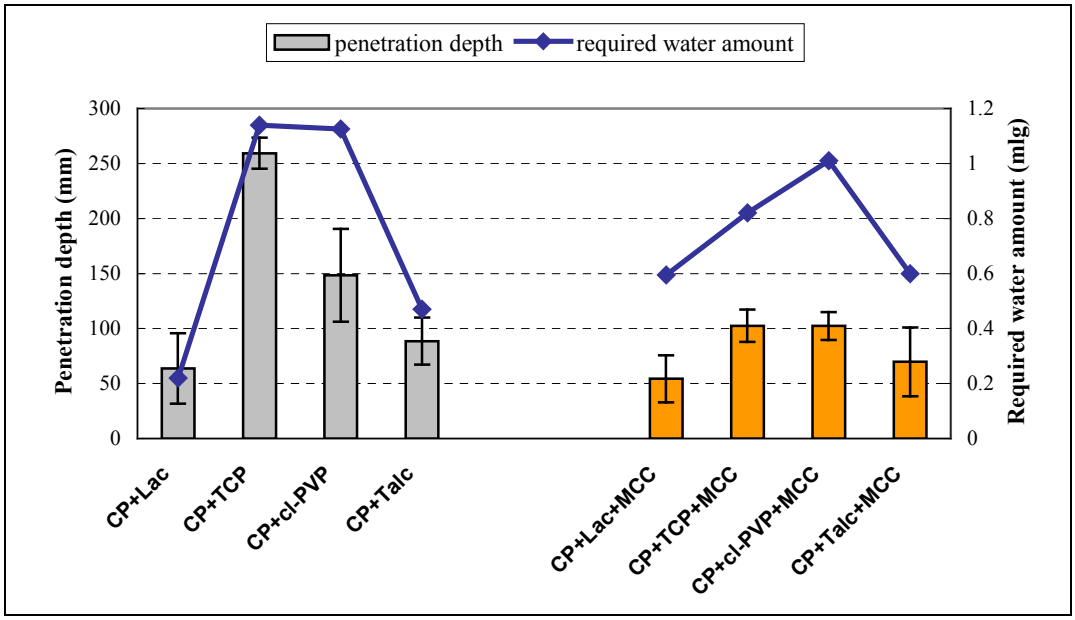


Fig. 3.26: Influence of microcrystalline cellulose on penetration depth (CP: carbomer 934P, cl PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean± S.D., n=5)

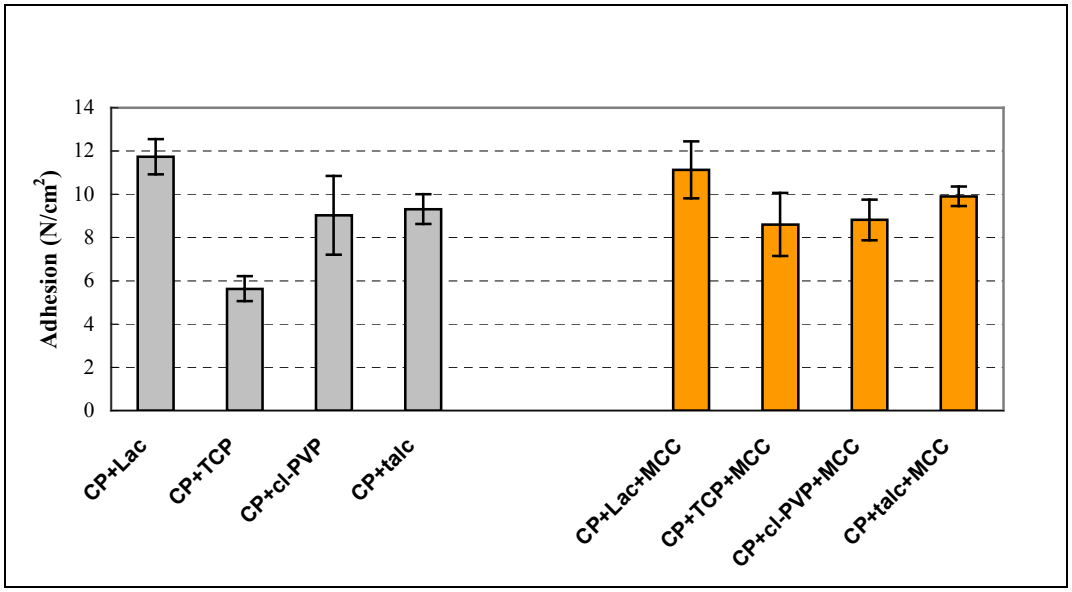


Fig. 3.27: Influence of microcrystalline cellulose on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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].

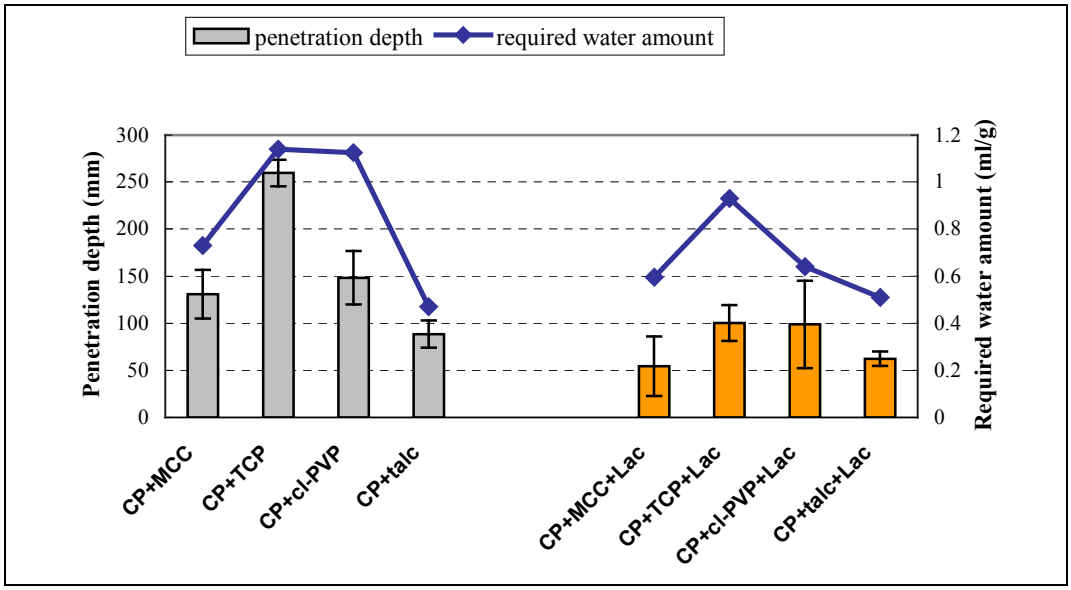


Fig. 3.28: Influence of lactose on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

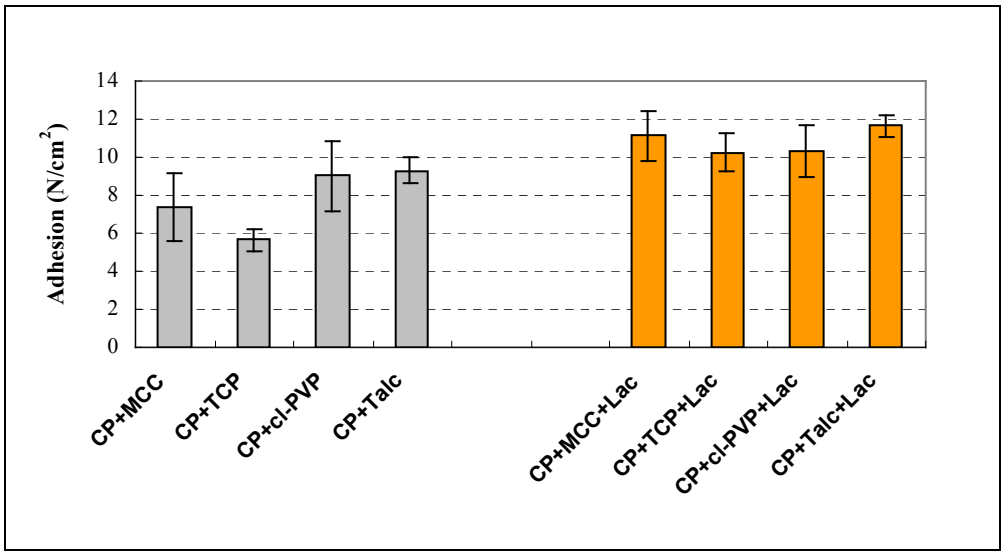


Fig. 3.29: Influence of lactose on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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%)

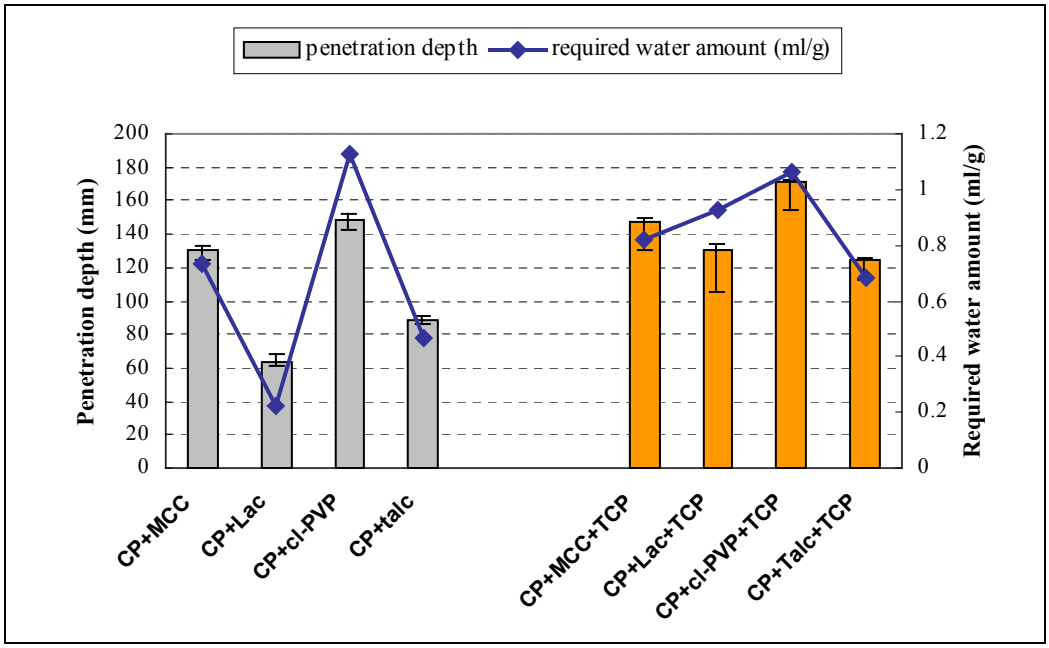


Fig. 3.30: Influence of tri-calcium phosphate on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean ±S.D., n=5)

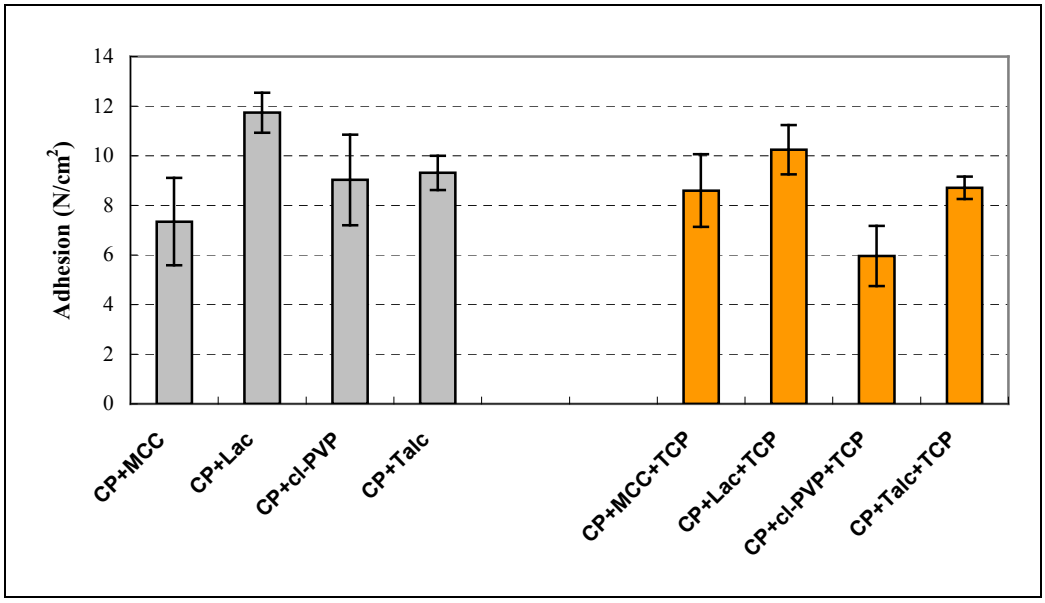


Fig. 3.31: Influence of tri-calcium phosphate on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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%)

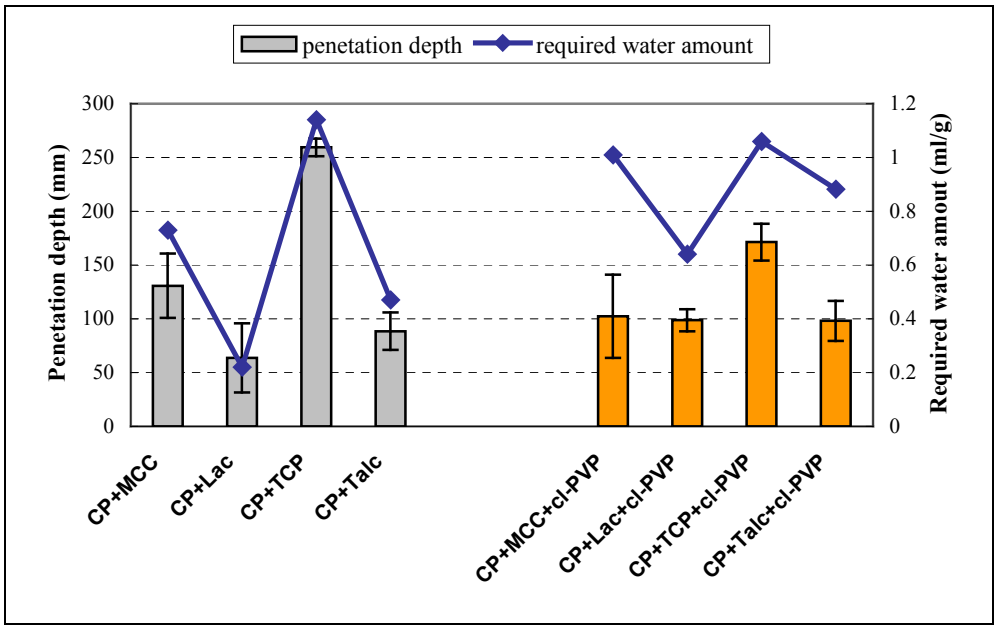


Fig. 3.32: Influence of cross-linked PVP on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean± S.D., n=5)

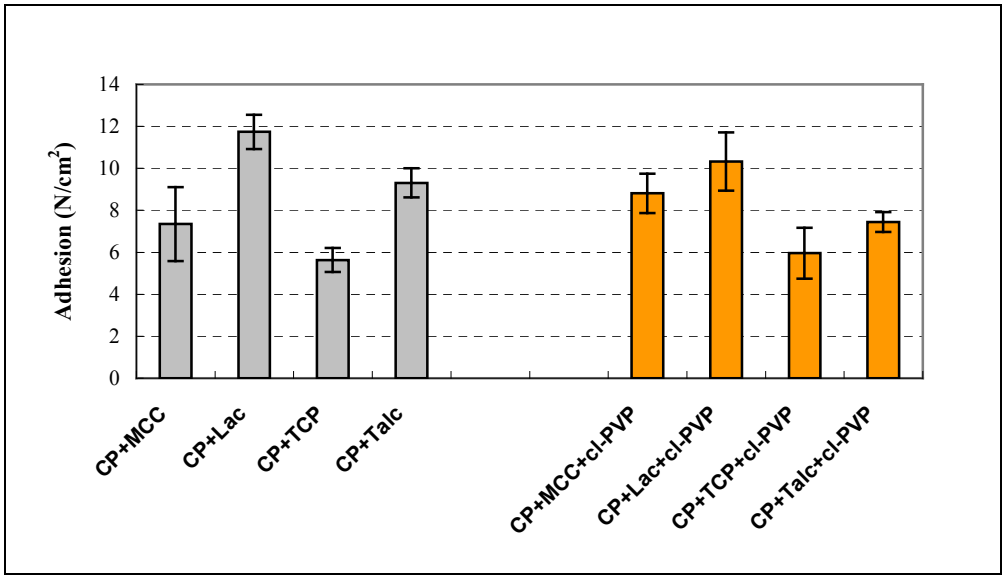


Fig. 3.33: Influence of cross-linked PVP on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

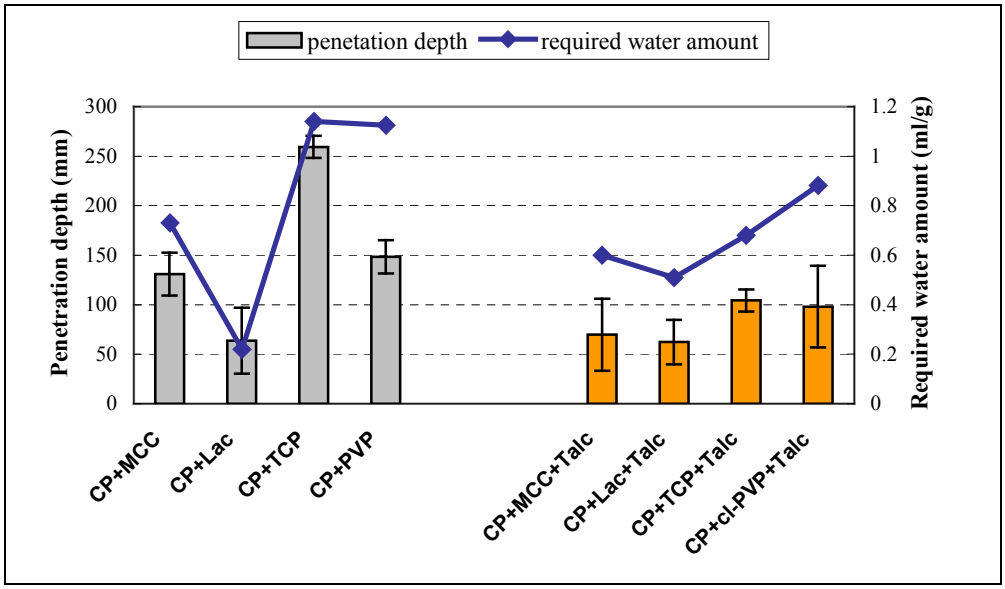


Fig. 3.34: Influence of talc on penetration depth (CP: carbomer 934P, cl-PVP: cross-linked PVP, Lac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

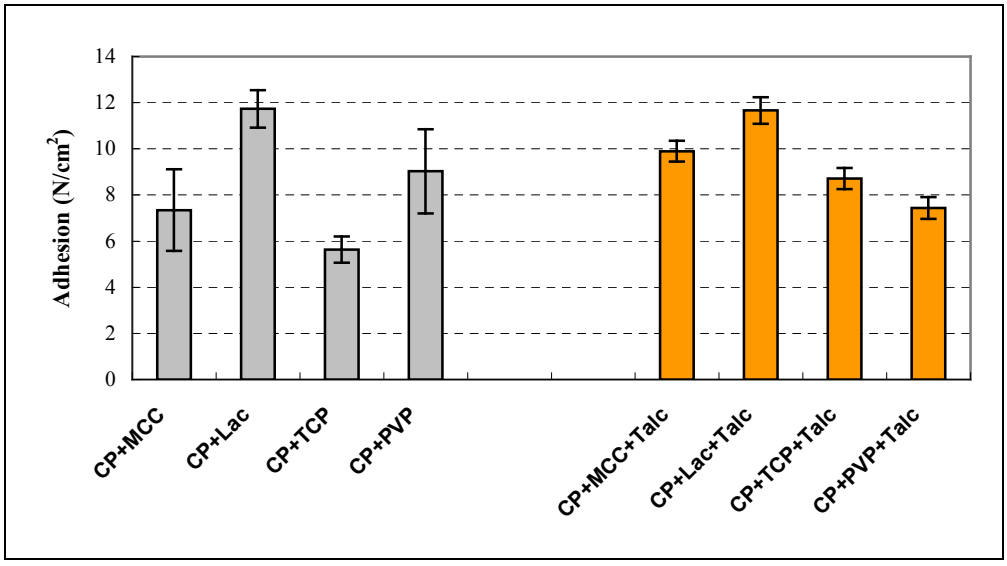


Fig. 3.35: Influence of talc on adhesion (CP: carbomer 934P, cl-PVP: cross-linked PVP, ac: lactose, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

3.1.4.3.3 Investigations through the fluid-bed granulation

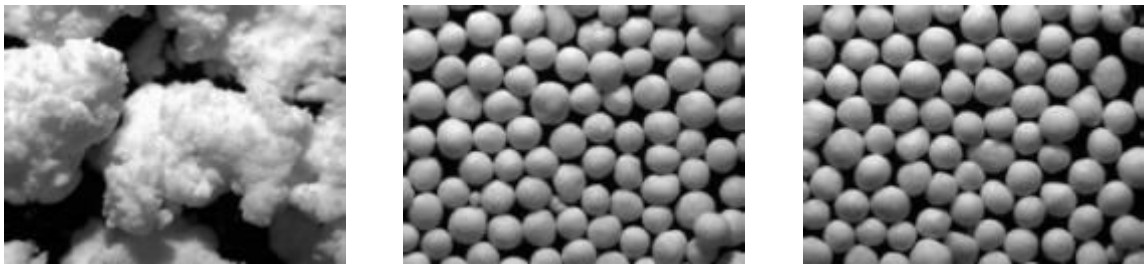
Trial batches were prepared with various combinations [Tab.3.18] using a fluid-bed granulator (GPCG 1, Glatt, Germany) to find a proper composition for granulation. The process parameters were arranged as described in table 3.4.

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.

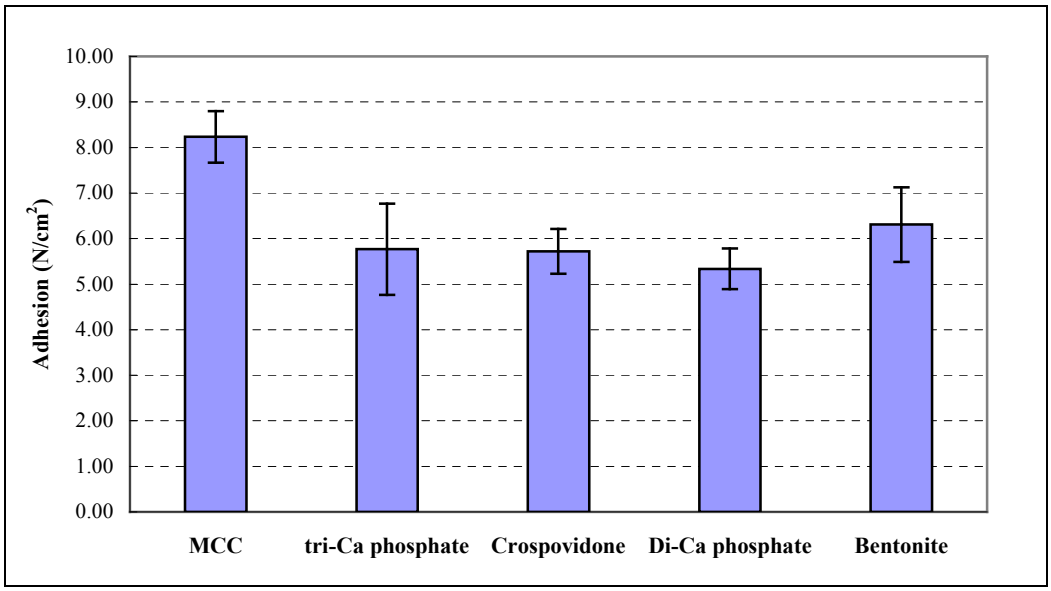


Fig. 3.37: Adhesion of wet mass containing tri-calcium phosphate and other excipients instead of tri-calcium phosphate (Mean ± S.D., n =5)

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].

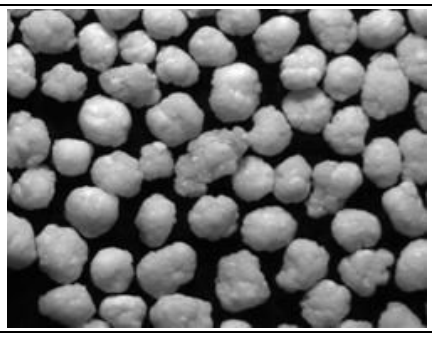


Fig. 3.38: Product made with carbomer 934P 20% + theophylline 20% + MCC + **Crospovidone** 30%-mixtures

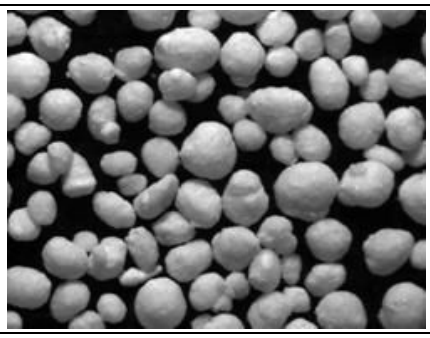


Fig. 3.39: Product made with carbomer 934P 20%+ theophylline 20%+ MCC 30% + **di-calcium phosphate** 30%-mixtures

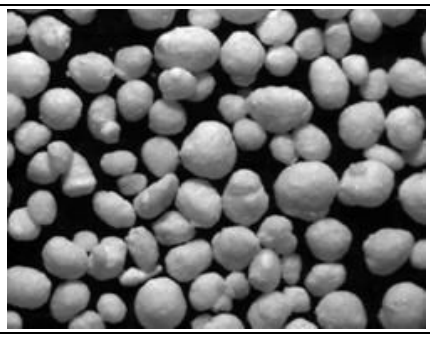


Fig. 3.40: Product made with carbomer 934P 20%+ theophylline 20%+ MCC 30% + **Bentonite** 30%-mixtures

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].

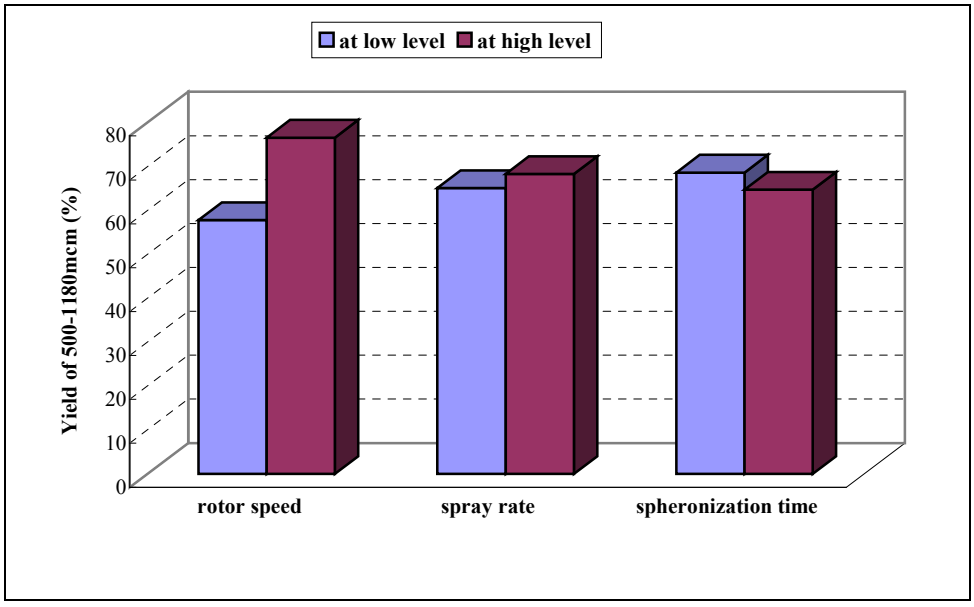


Fig. 3.41: Influence of parameters on the yield of 500~1180 µm of fraction

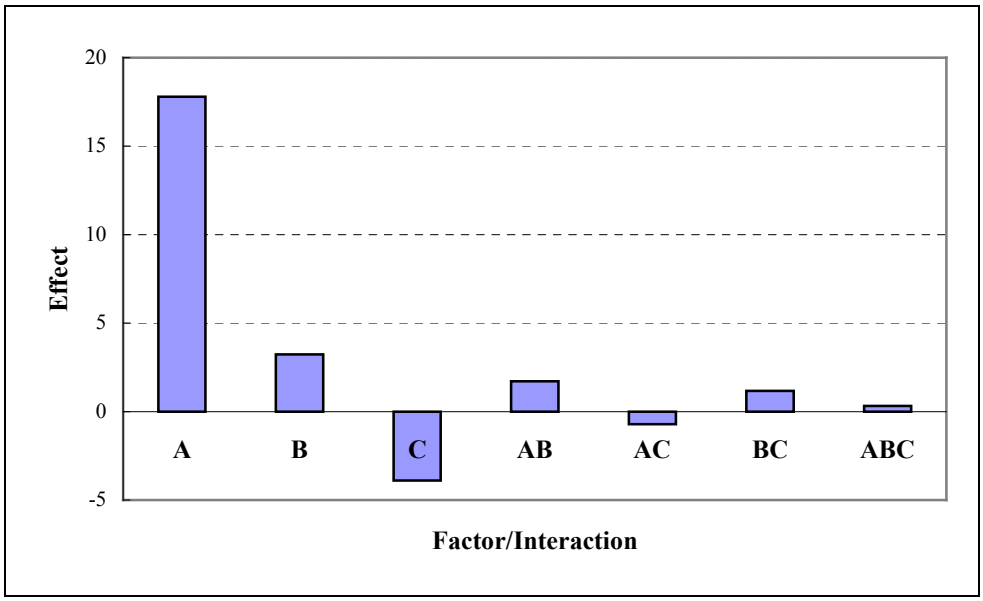


Fig. 3.42: Effect and interactions of parameters on the yield of 500~1180 µm of fraction

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.

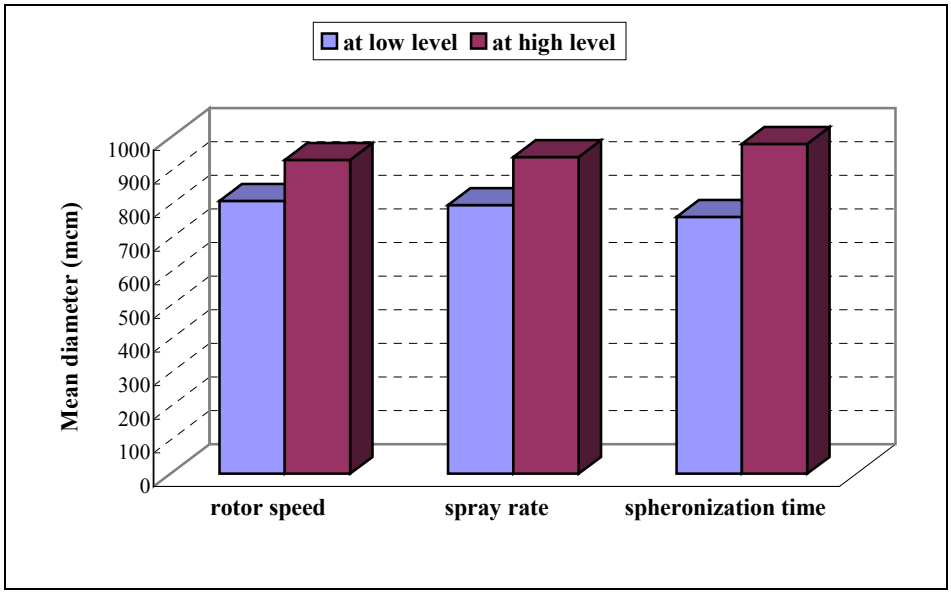


Fig. 3.43: Influence of parameters on mean diameter of pellets

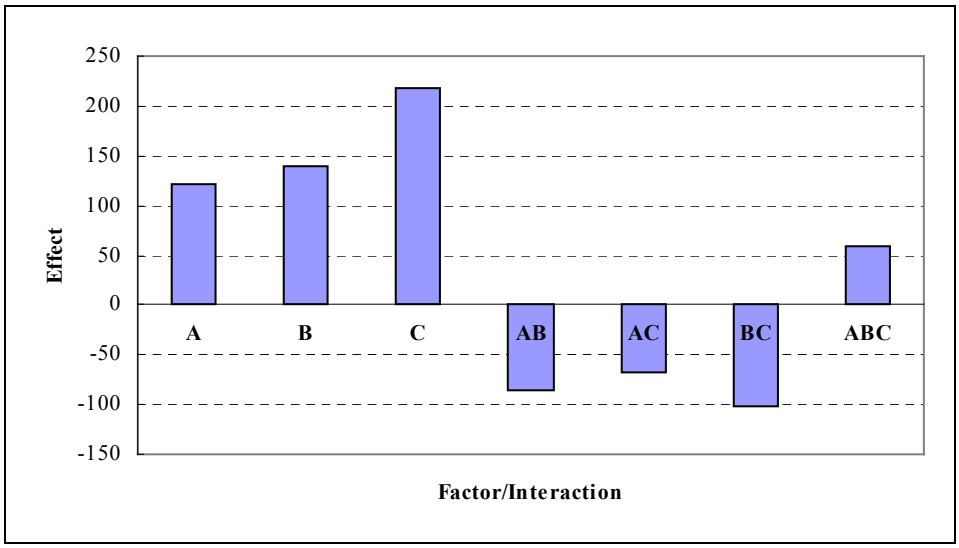


Fig. 3.44: Effect and interactions of parameters on mean diameter of pellets

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.

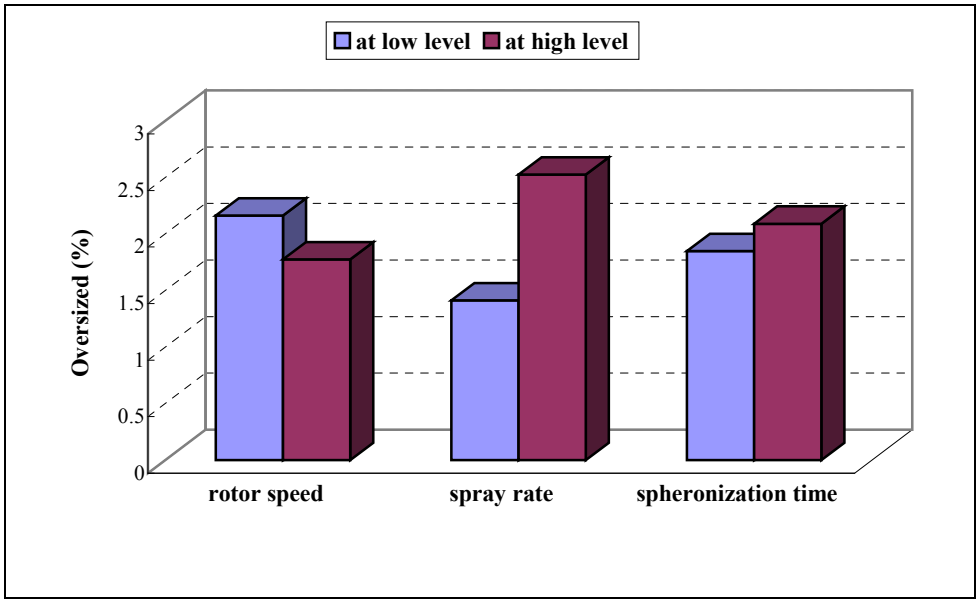


Fig. 3.45: Influence of parameters on % oversized

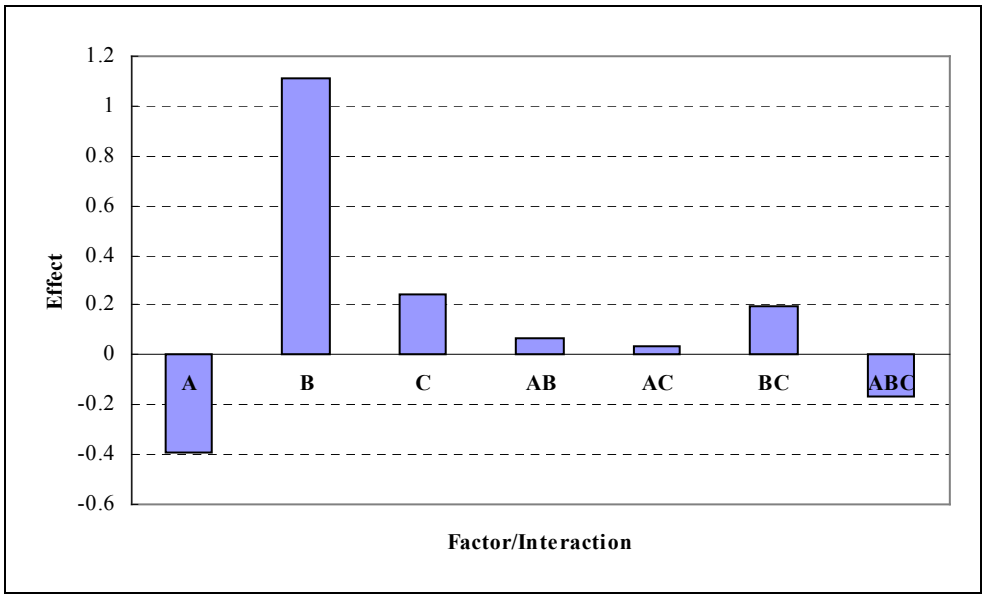


Fig. 3.46: Effect and interactions of parameters on % oversized

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].

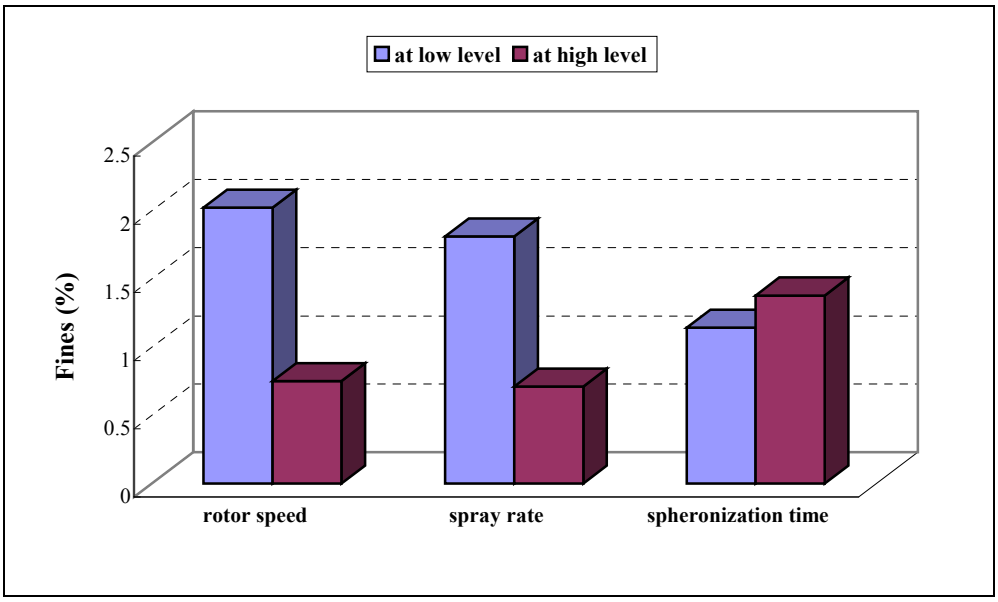


Fig. 3.47: Influence of parameters on % fines

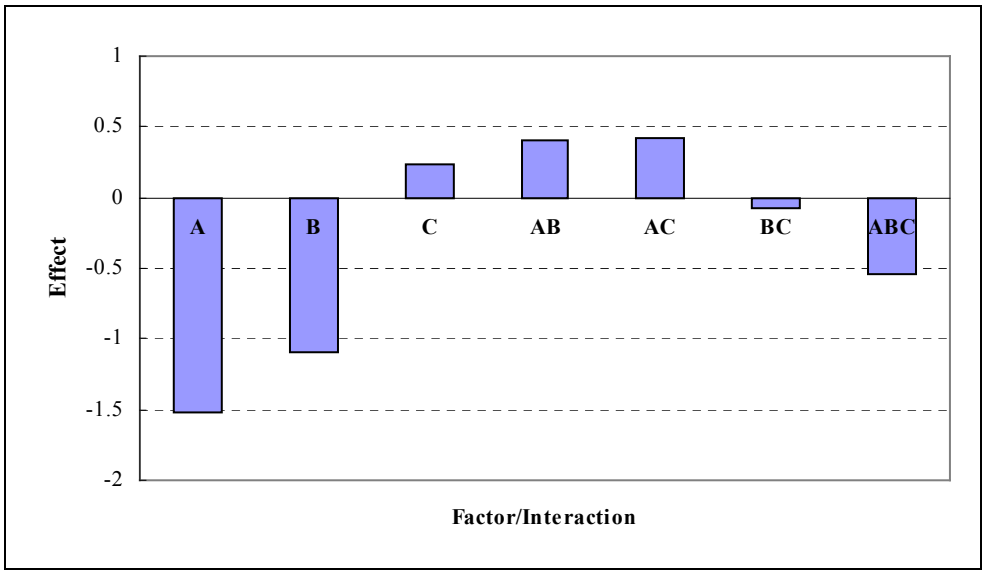


Fig. 3.48: Effect and interactions of parameters on % fines

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

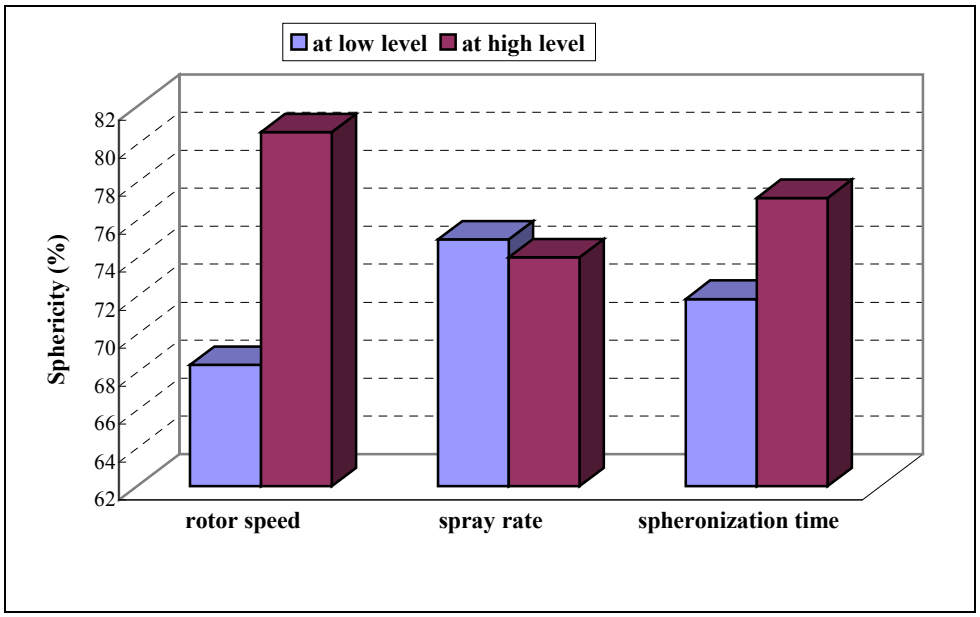


Fig. 3.49: Influence of parameters on sphericity of pellets

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.

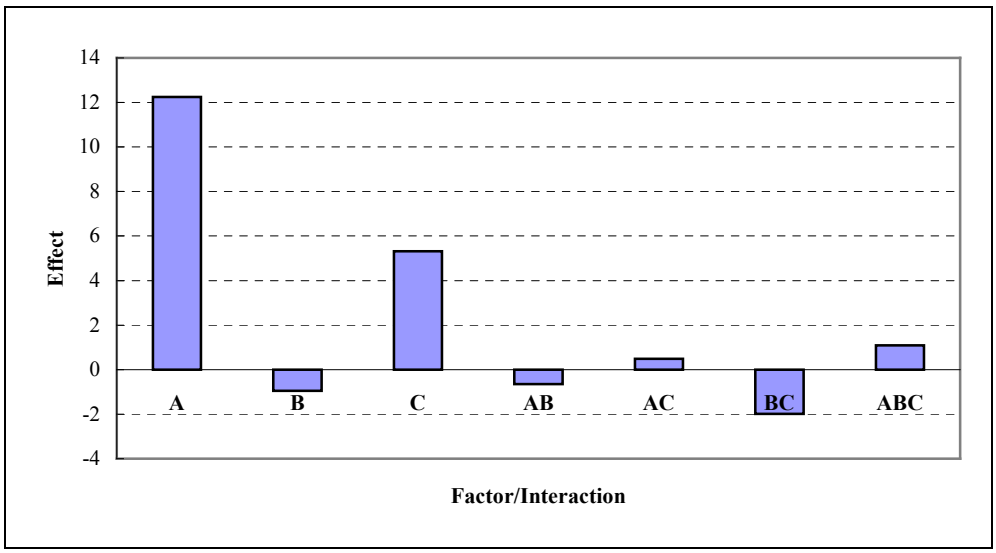


Fig. 3.50: Effect and interactions of parameters on sphericity of pellets

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**

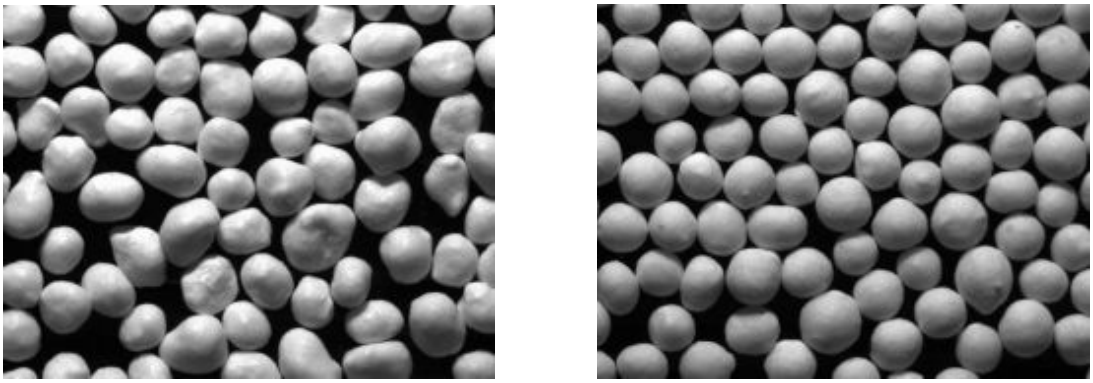


Fig. 3.51: Granules produced at different rotor speed

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].

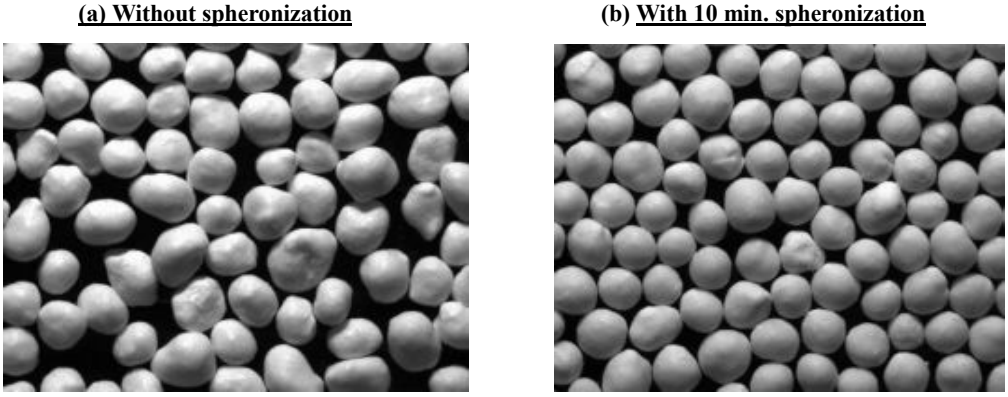


Fig. 3.52: Granules produced with at different spheronization time

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.

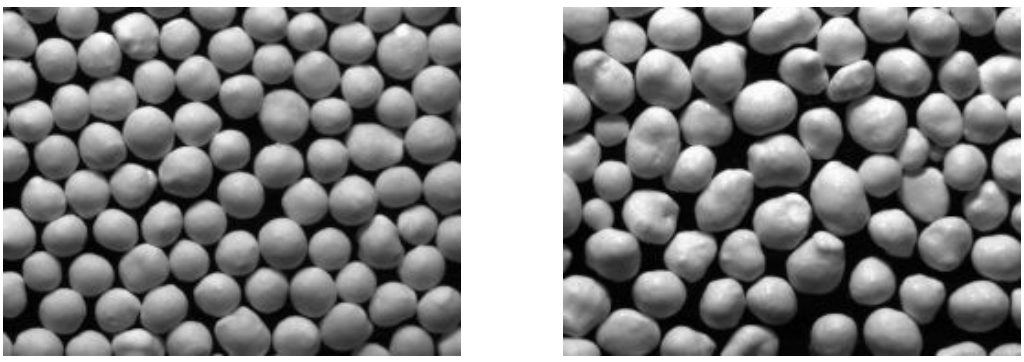


Fig. 3.53: Granules produced at different level of spray rate and spheronization time: at low spray rate + spheronization time (left), at high spray rate + spheronization time (right)

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.

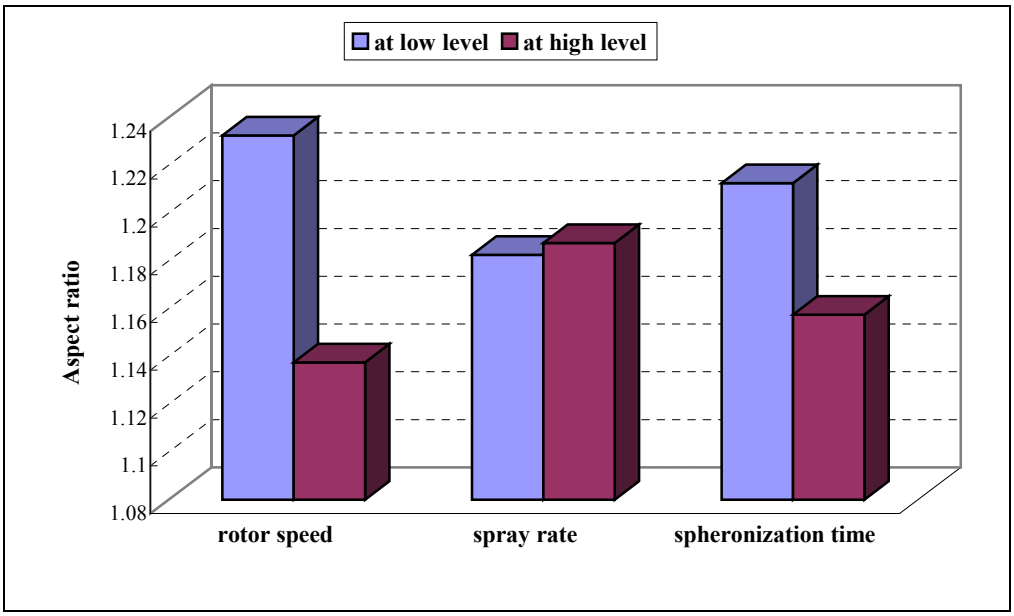


Fig. 3.54: Influence of parameters on aspect ratio of pellets

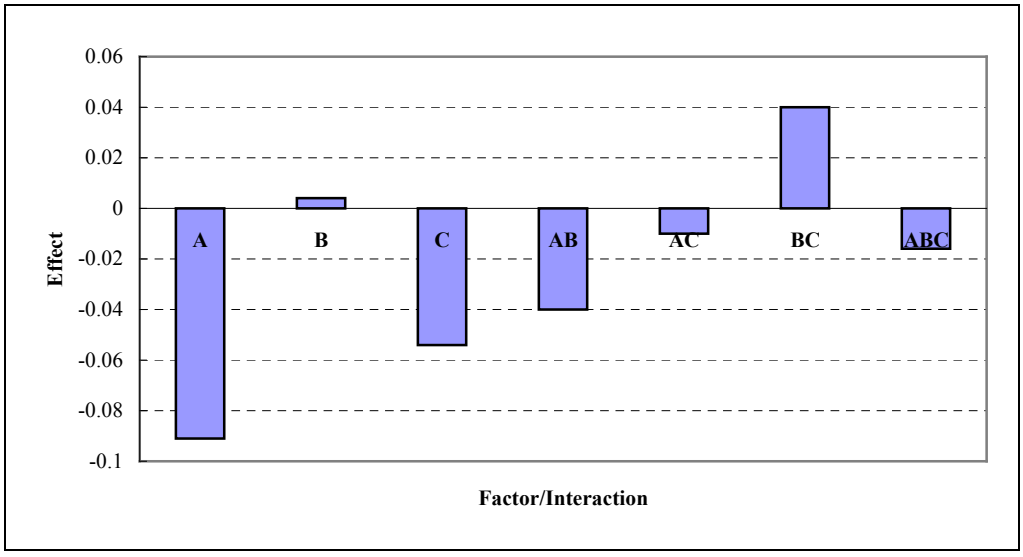


Fig. 3.55: Effect and interactions of parameters on aspect ratio of pellets

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.

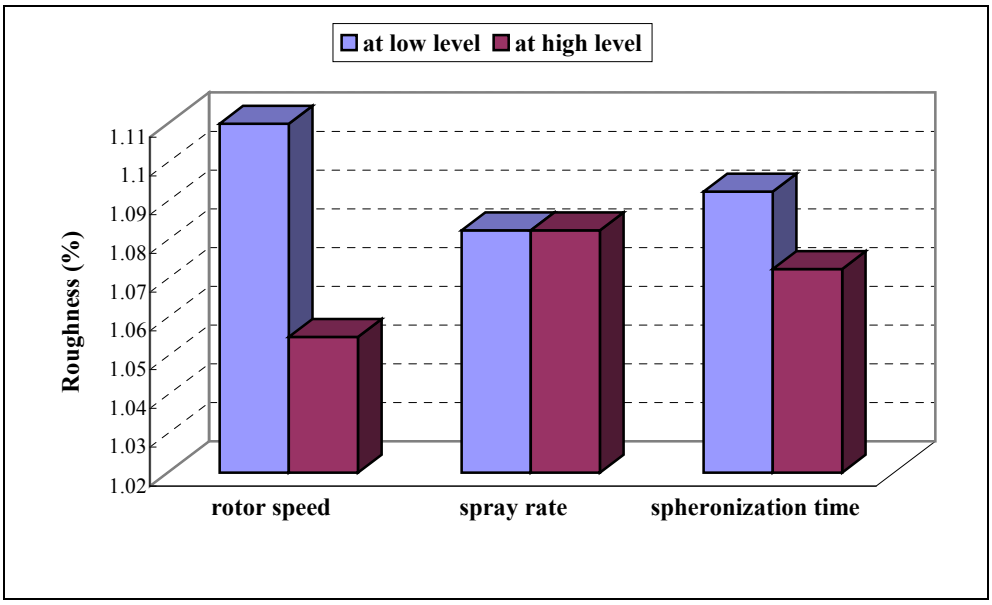


Fig. 3.56: Influence of parameters on roughness of pellets

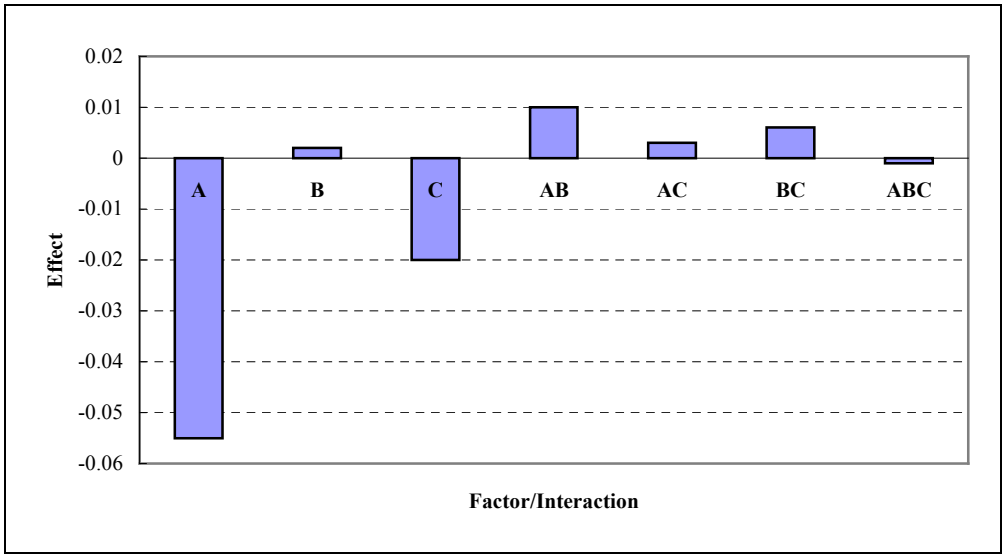


Fig. 3.57: Effect and interactions of parameters on the roughness of pellets

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.

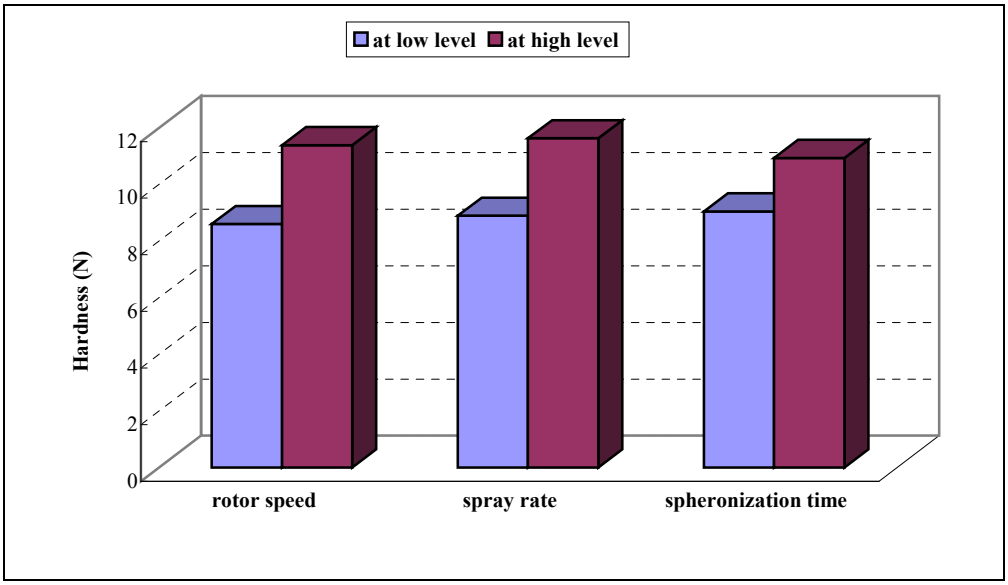


Fig. 3.58: Influence of parameters on the hardness of pellets

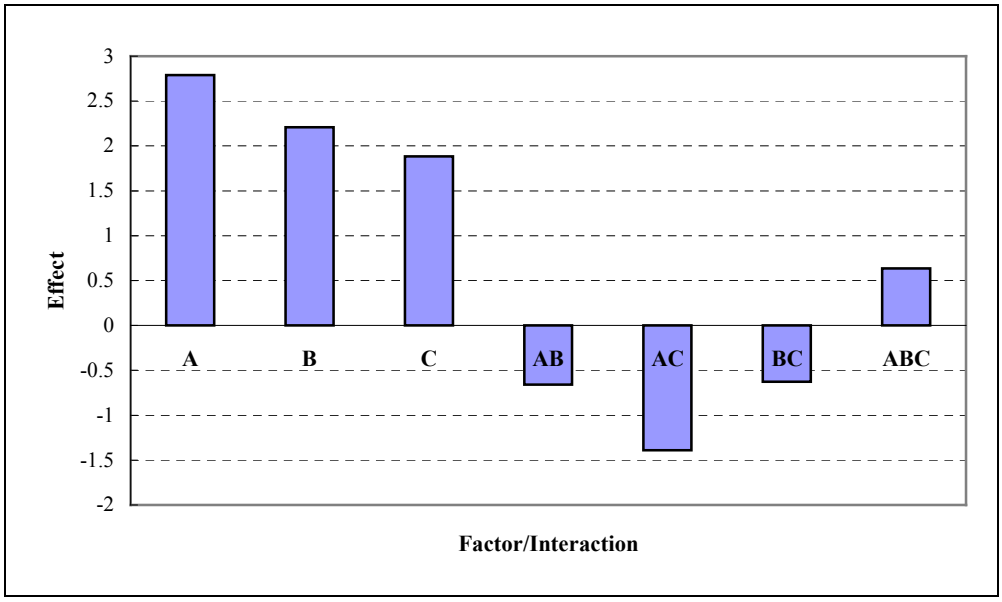


Fig. 3.59: Effect and interactions of parameters on the hardness of pellets

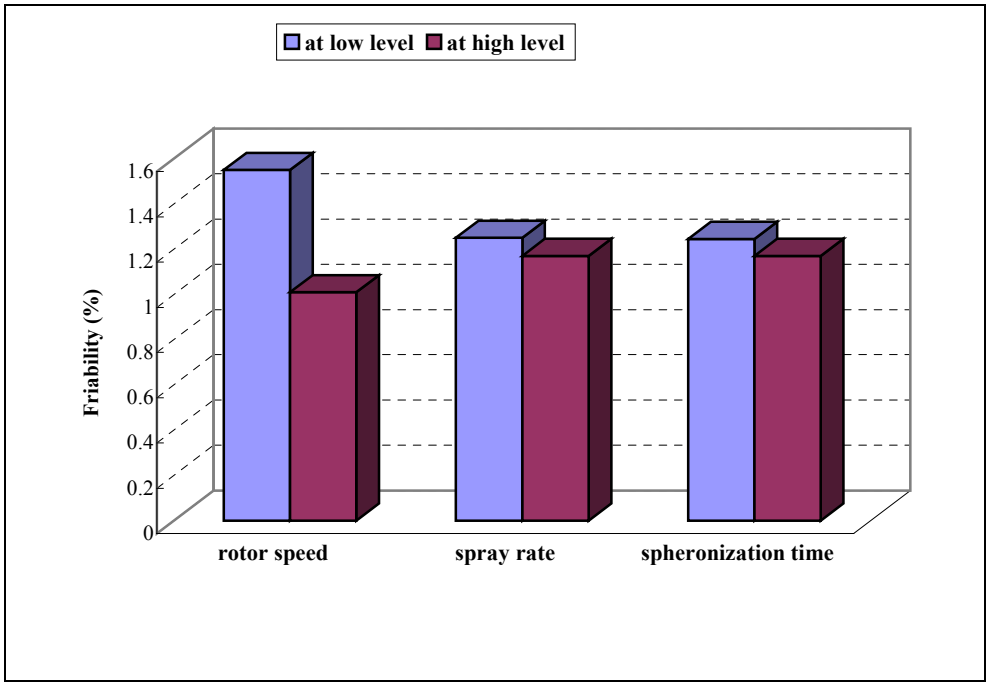


Fig. 3.60: Influence of parameters on the friability of pellets

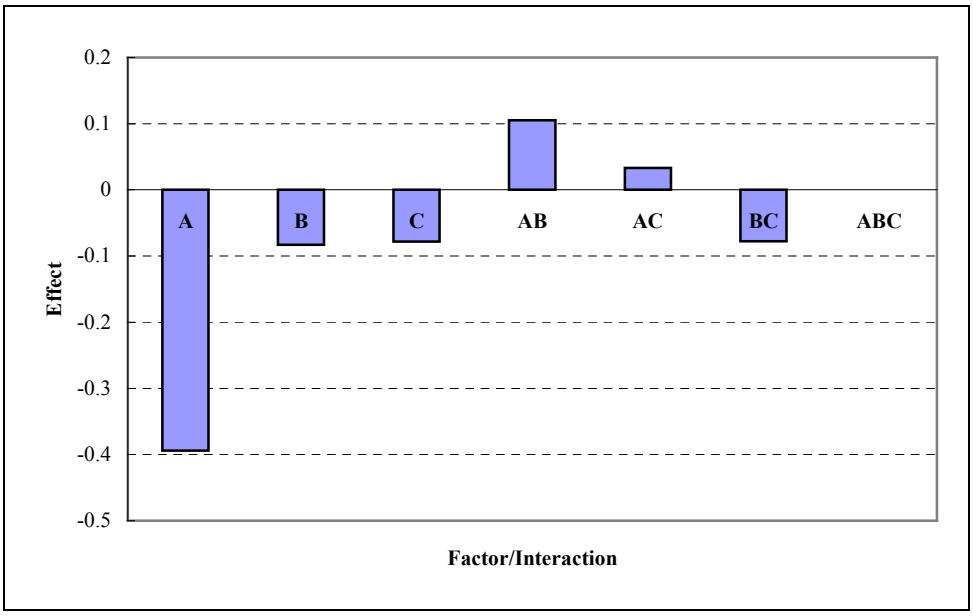


Fig. 3.61: Effect and interactions of parameters on the friability of pellets