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.

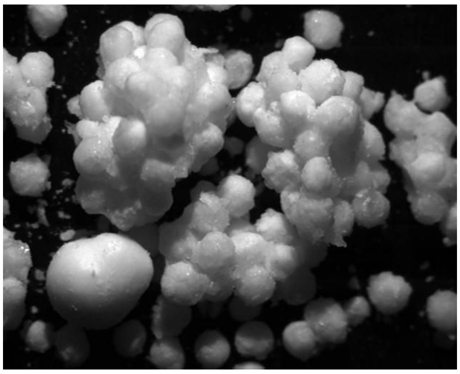

Fig. 4.1: Product of dry-coating trial using carbomer 934P

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.

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

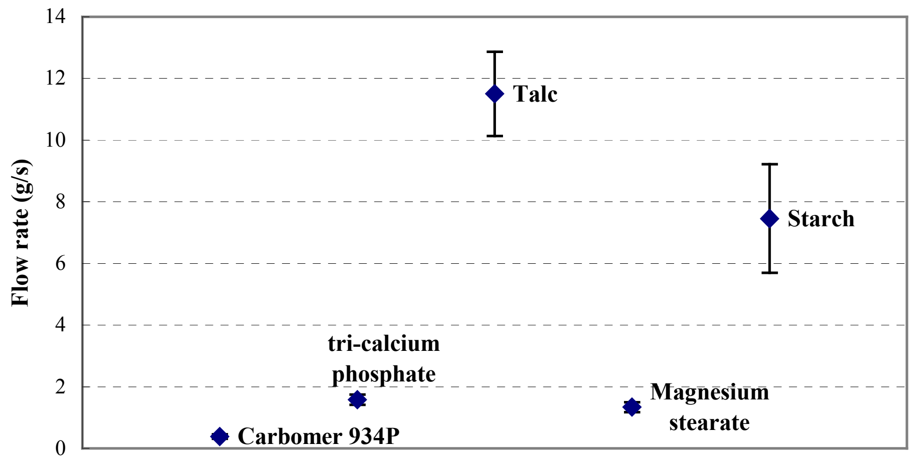

Fig. 4.2: Flow rate of carbomer 934P and other excipients (Mean±S.D., n=5)

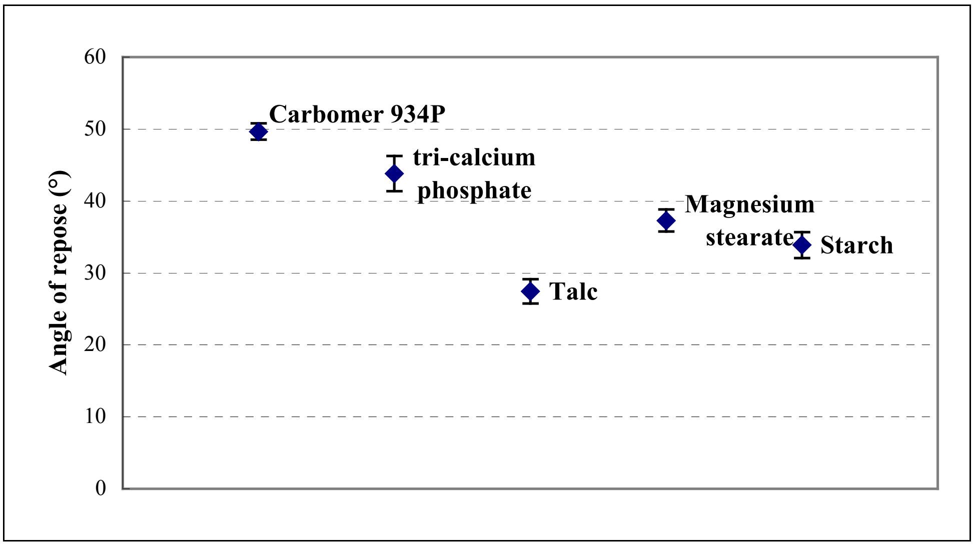

Fig. 4.3: Angle of repose of carbomer 934P and other excipients (Mean±S.D., n=5)

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.

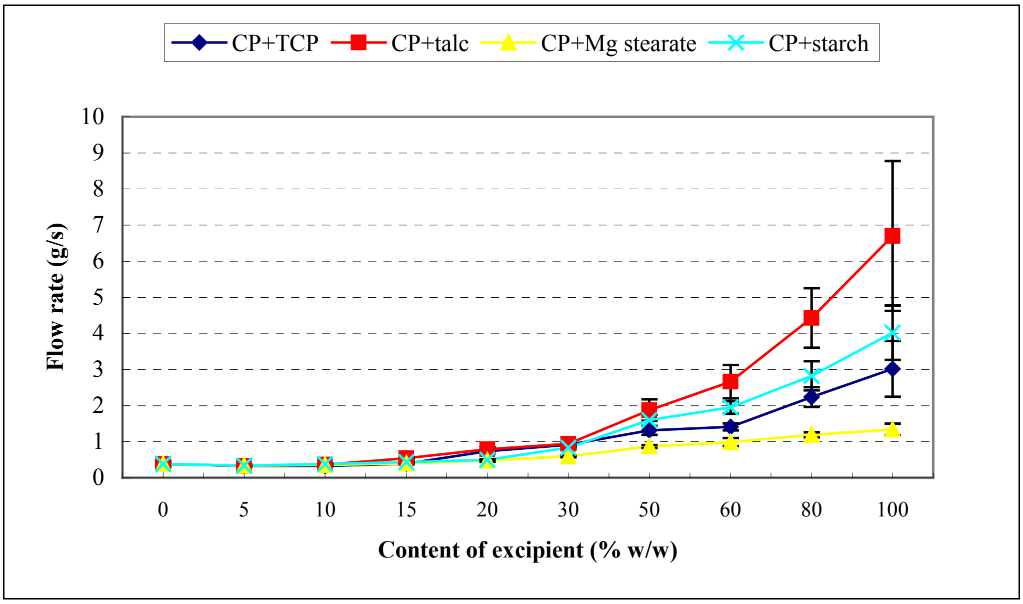

Fig. 4.4: Flow rate of carbomer 934P/excipient-mixtures (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

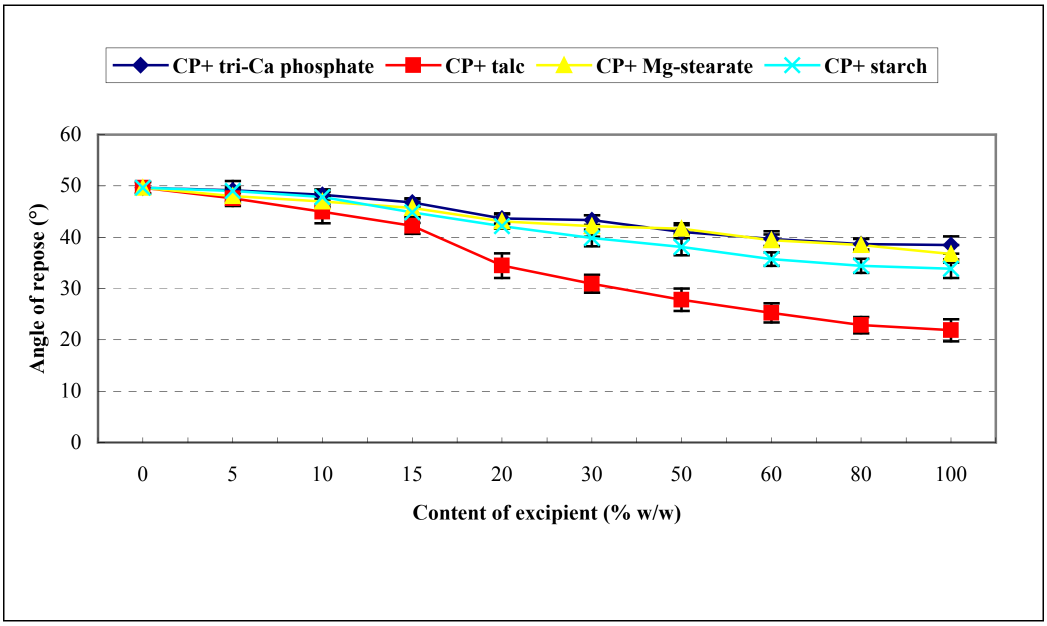

Fig. 4.5: Angle of repose of carbomer 934P/excipient-mixtures (CP: carbomer 934P) (Mean±S.D., n=5)

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.

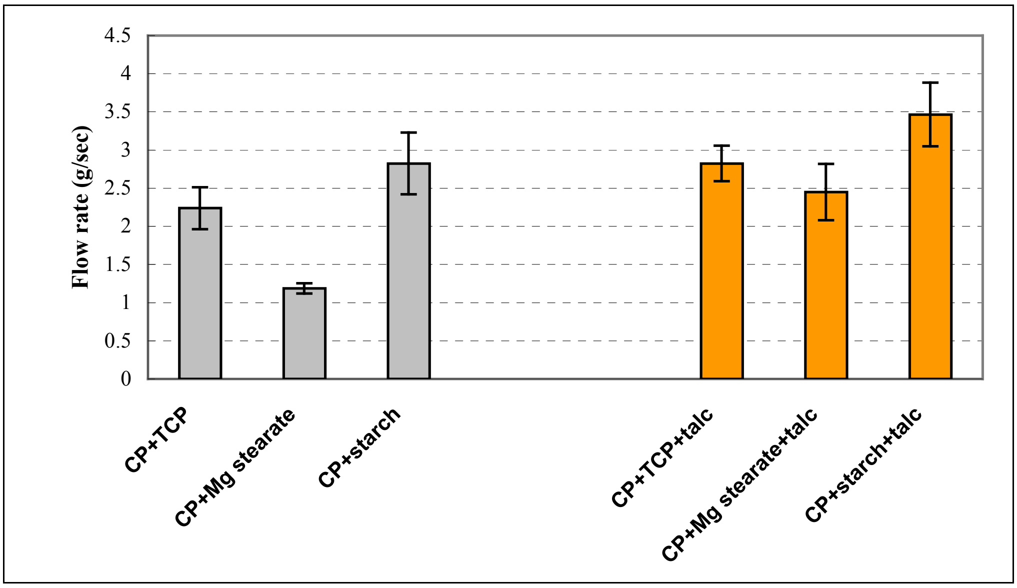

Fig. 4.6: Influence of talc on the flow rate of powder in carbomer 934P:talc:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

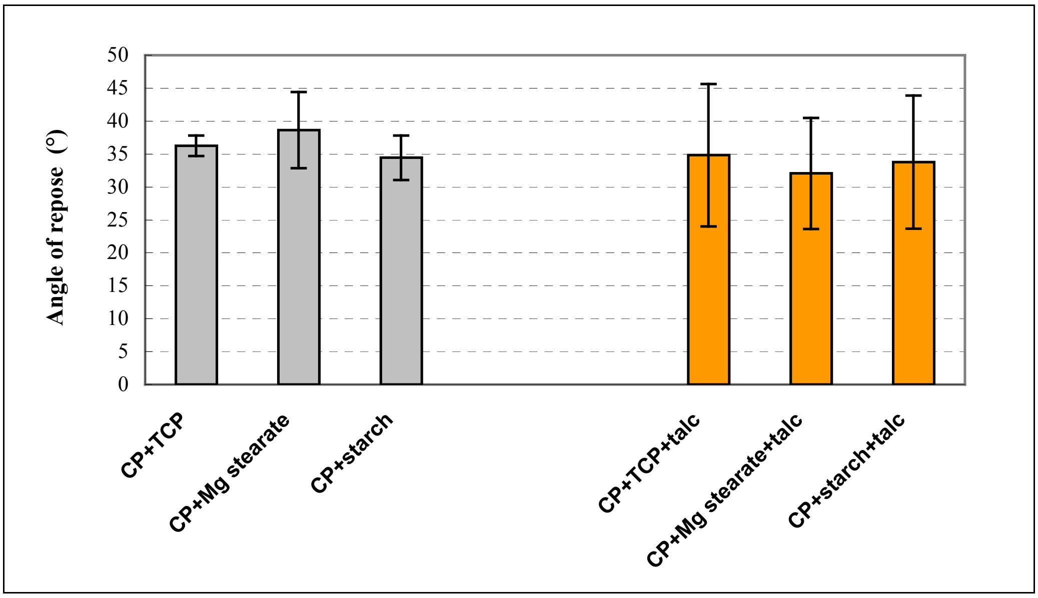

Fig. 4.7: Influence of talc on the angle of repose of powder in carbomer 934P:talc:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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].

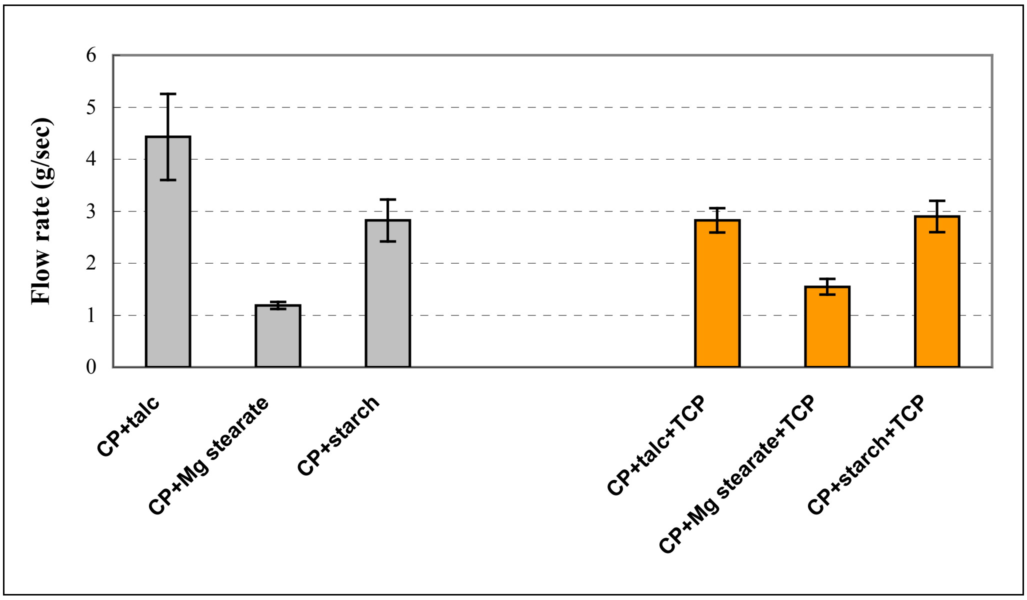

Fig. 4.8: Influence of tri-calcium phosphate on the flow rate of powder in carbomer 934P:tri-calcium phosphate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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].

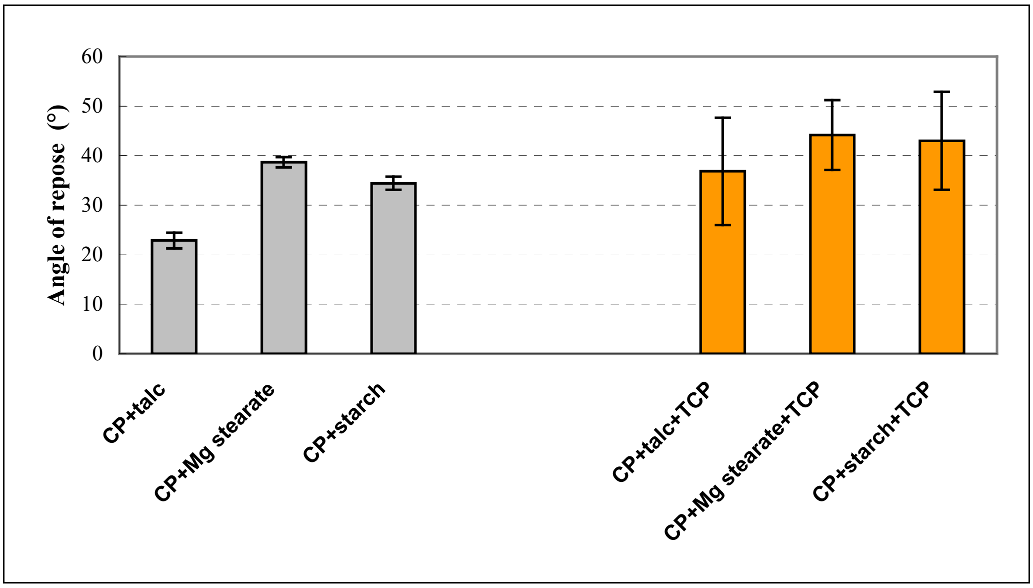

Fig. 4.9: Influence of tri-calcium phosphate on the angle of repose of powder in carbomer 934P:tri-calcium phosphate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

c) Influence of magnesium stearate

Flow rate was decreased magnesium stearate in all cases [Fig.4.10].

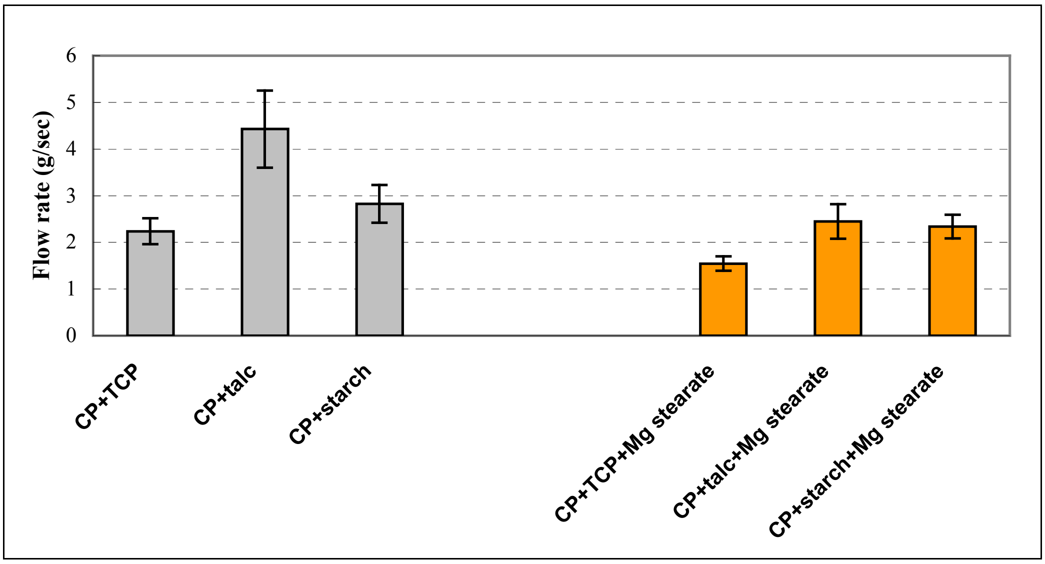

Fig. 4.10: Influence of magnesium stearate on the flow rate in carbomer 934P:magnesium stearate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

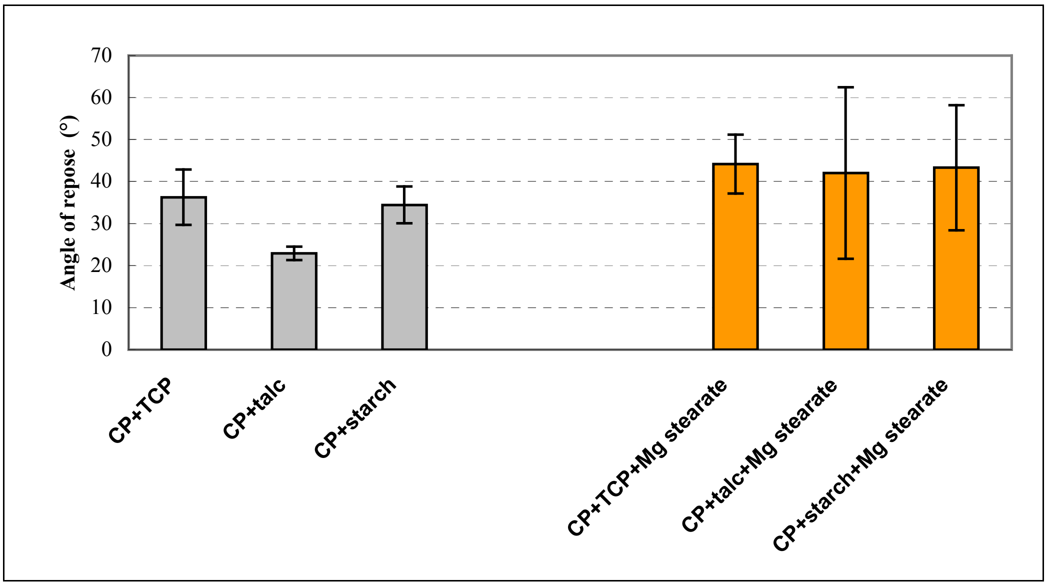

Fig. 4.11: Influence of magnesium stearate on the angle of repose in carbomer 934P:magnesium stearate:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

d) Influence of starch

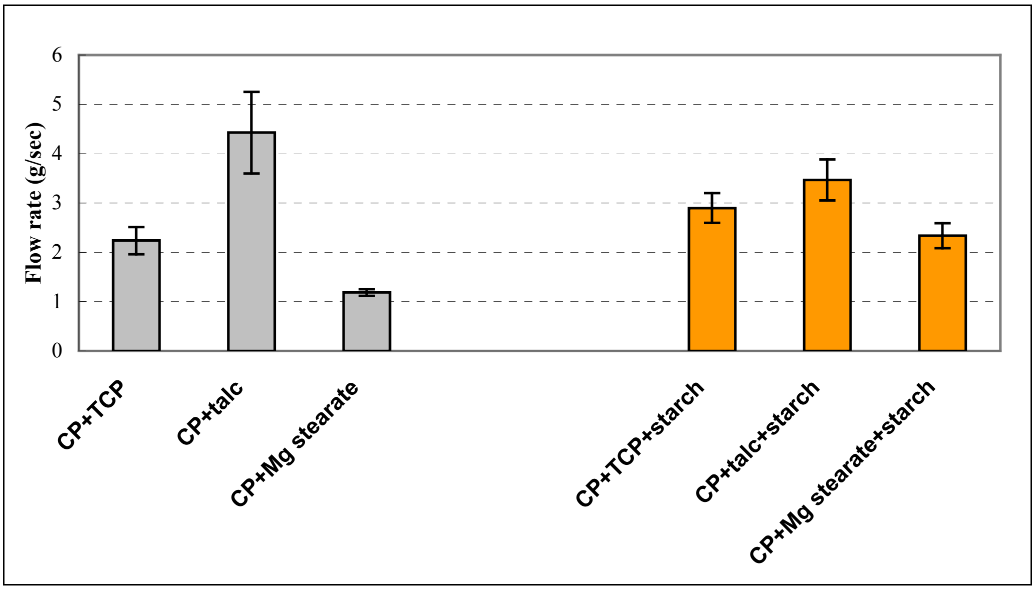

Fig. 4.12: Influence starch on the flow rate in carbomer 934P:starch:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

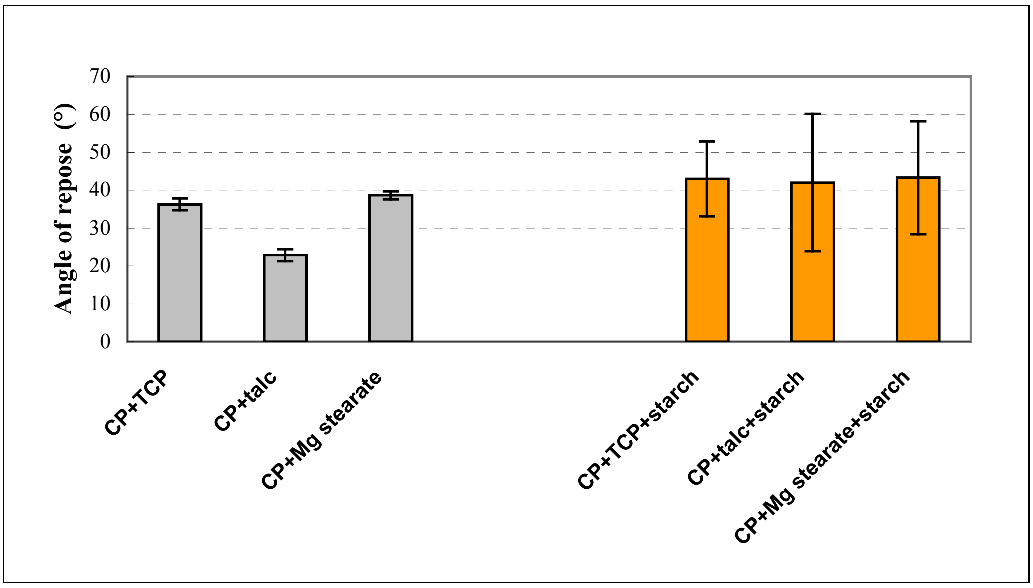

Fig. 4.13: Influence of starch on the angle of repose in carbomer 934P:starch:other excipient=1:2:2 mixtures (TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

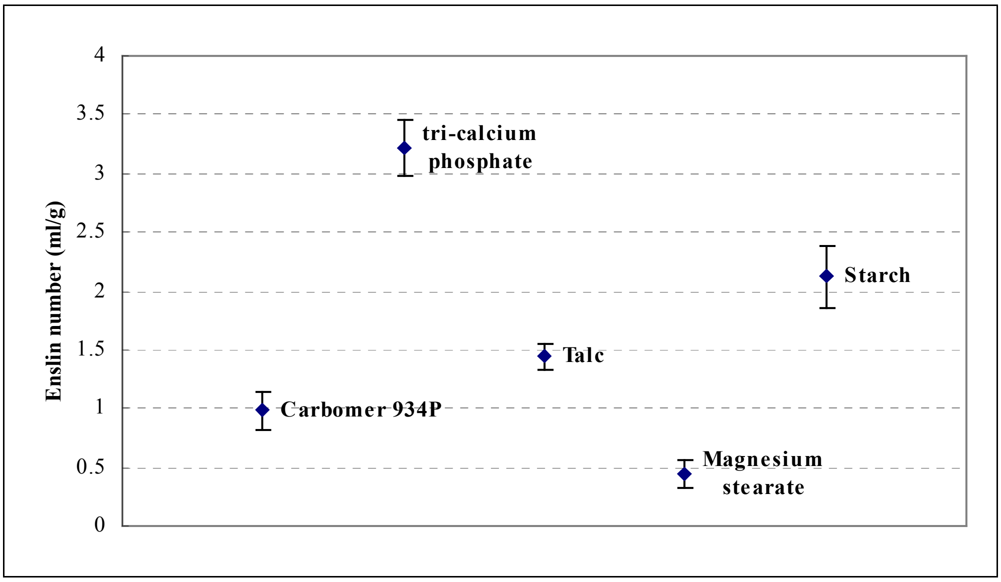

Fig. 4.14: Enslin number of carbomer 934P and other excipients (Mean±S.D., n=5)

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.

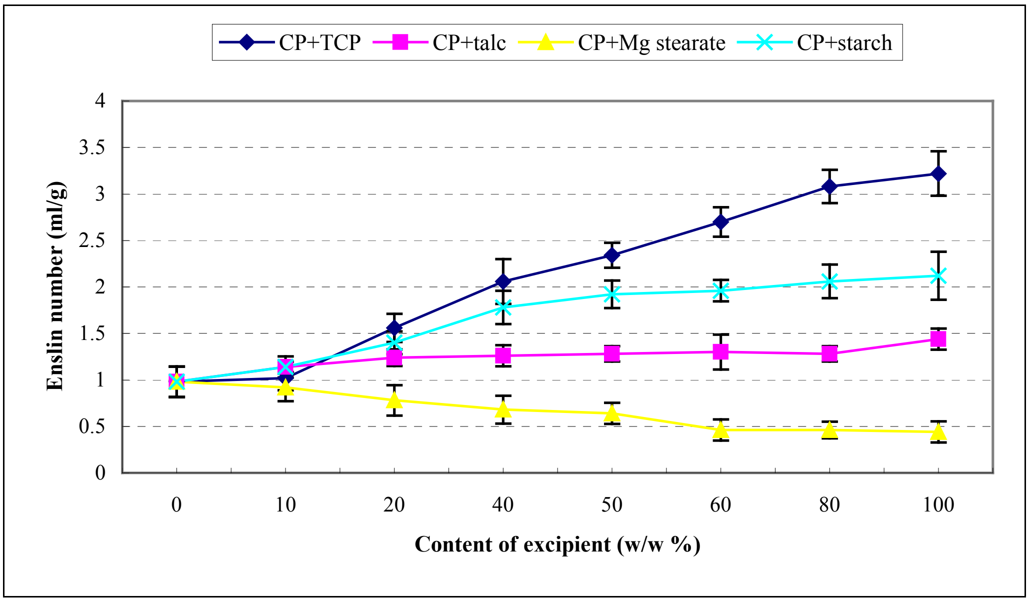

Fig. 4.15: Enslin number of binary mixtures (carbomer 934P/other excipient-mixtures) (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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

a) <u>Influence of talc</u>

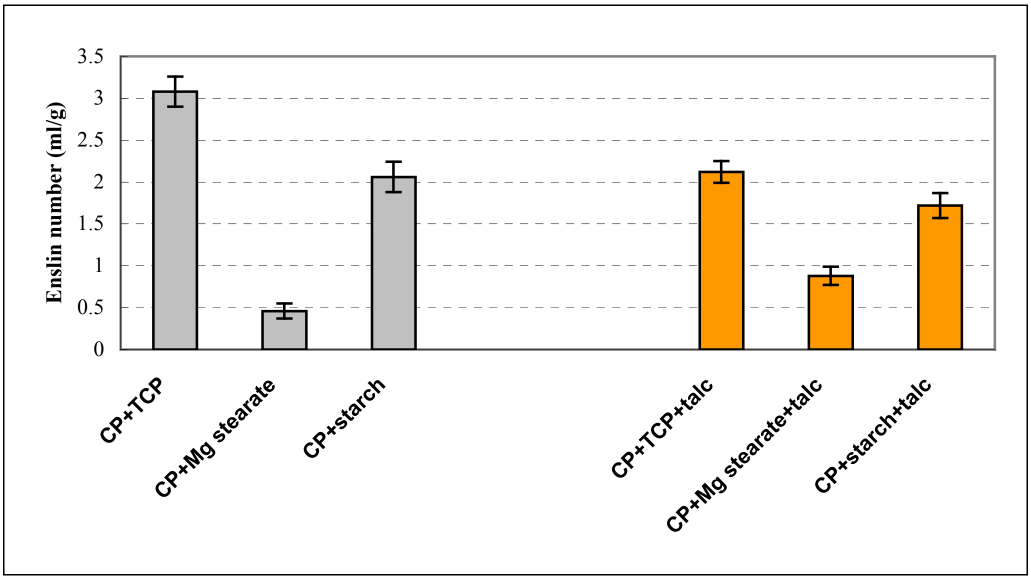

Fig. 4.16: Influence of talc on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

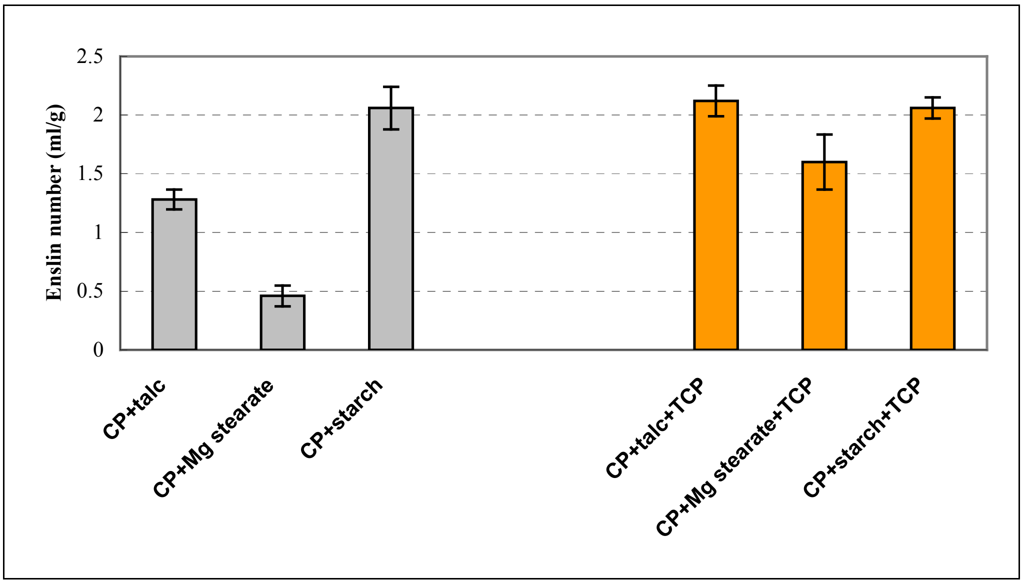

Fig. 4.17: Influence of tri-calcium phosphate on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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.

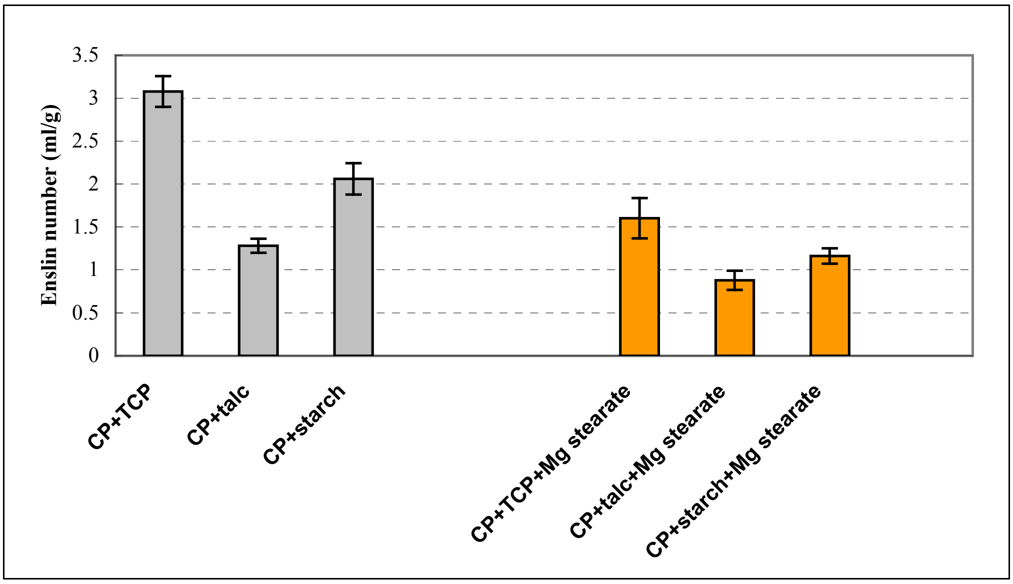

Fig. 4.18: Influence of magnesium stearate on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

e) Influence of starch

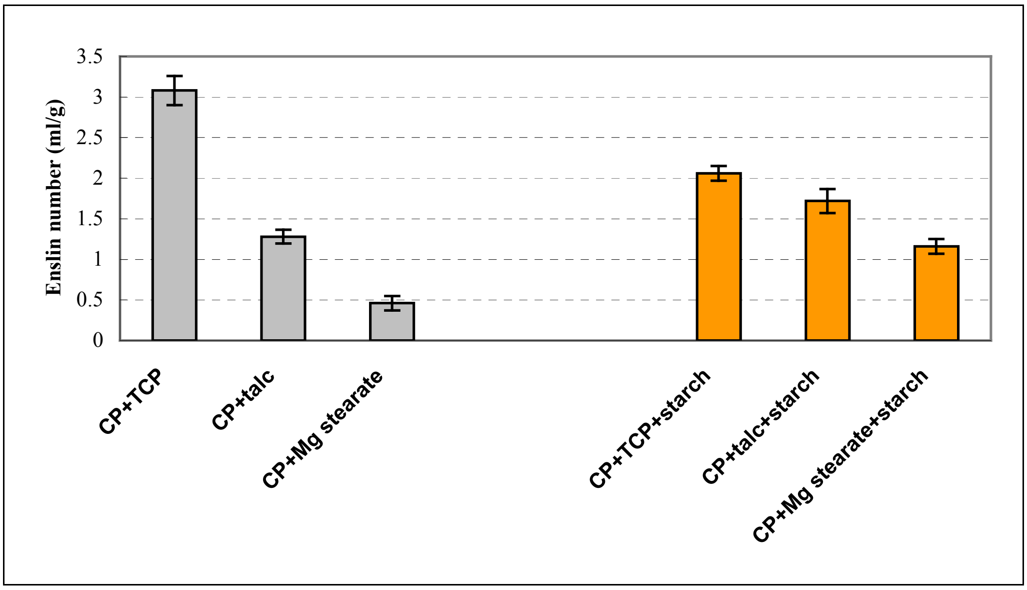

Fig. 4.19: Influence of starch on enslin number (CP: carbomer 934P, TCP: tri-calcium phosphate) (Mean±S.D., n=5)

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 (°C)	45
Drying air temperature (°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.

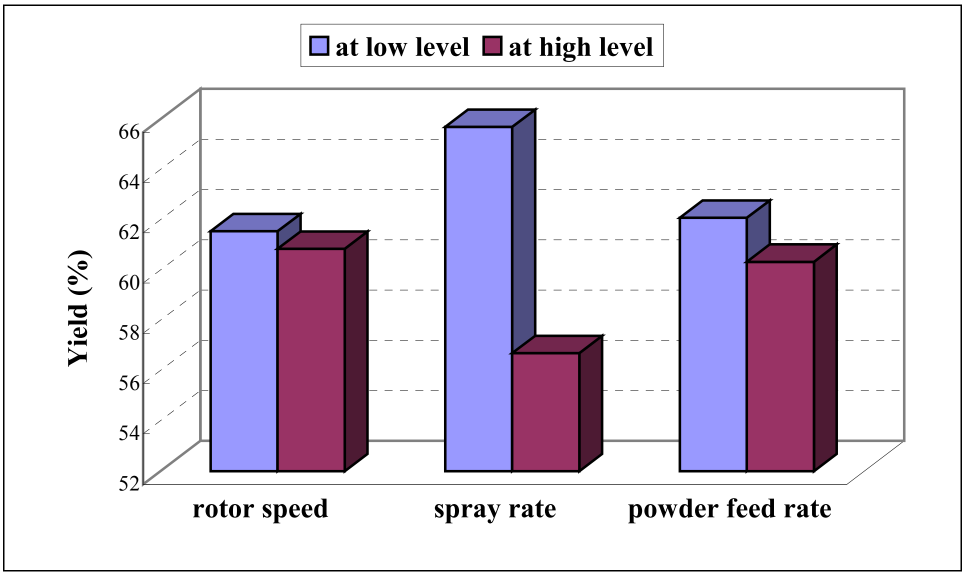

Fig. 4.21: Influence of parameters on the yield of pellets

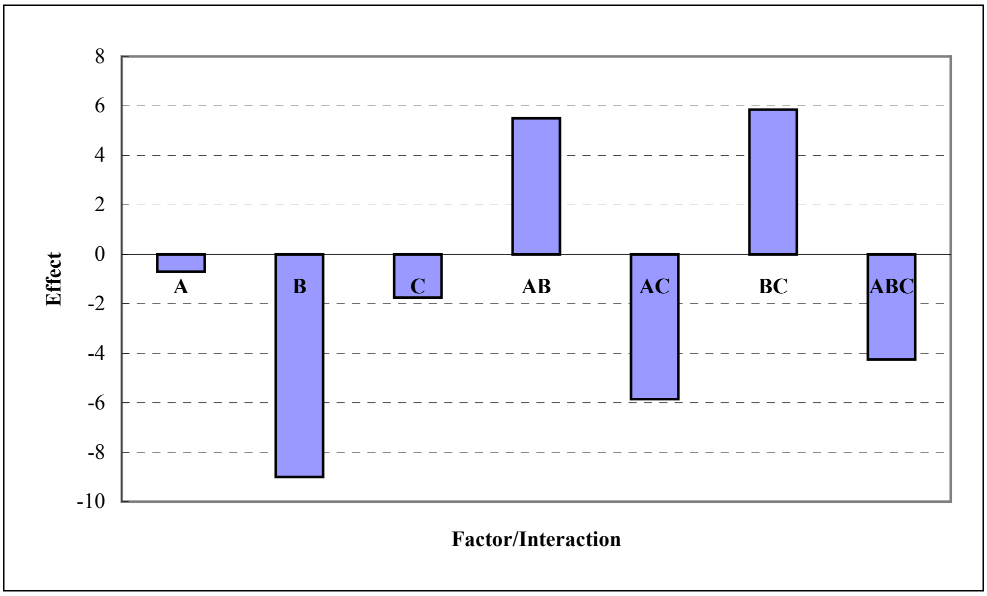

Fig. 4.22: Effect and interactions of parameters on yield

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].

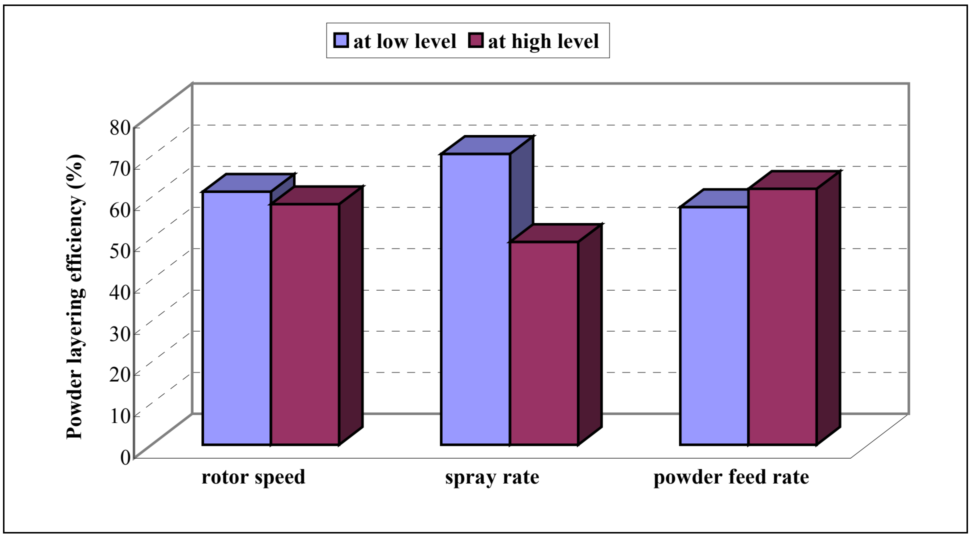

Fig. 4.23: Influence of parameters on powder layering efficiency

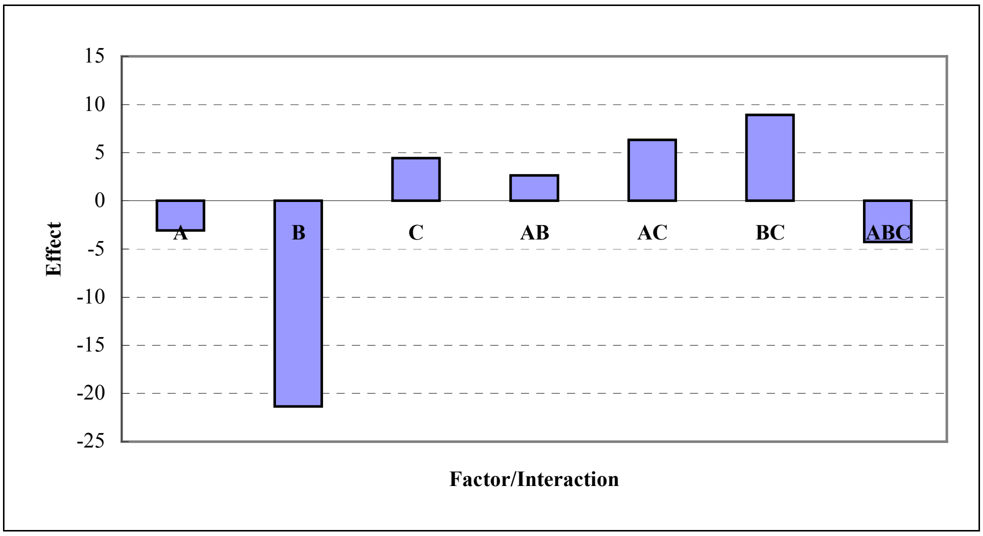

Fig. 4.24: Effect and interactions of parameters on powder layering efficiency

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].

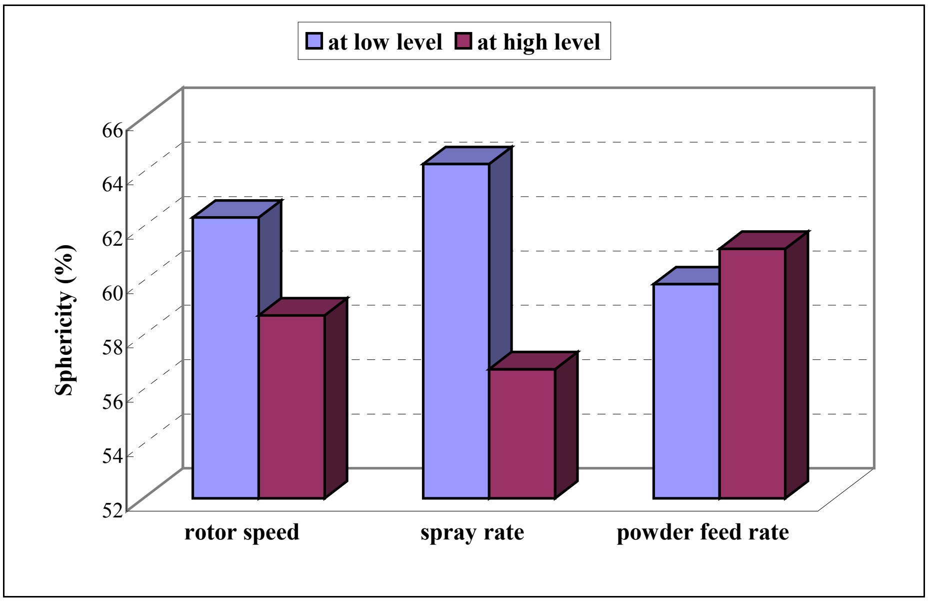

Fig. 4.25: Influence of parameters on sphericity

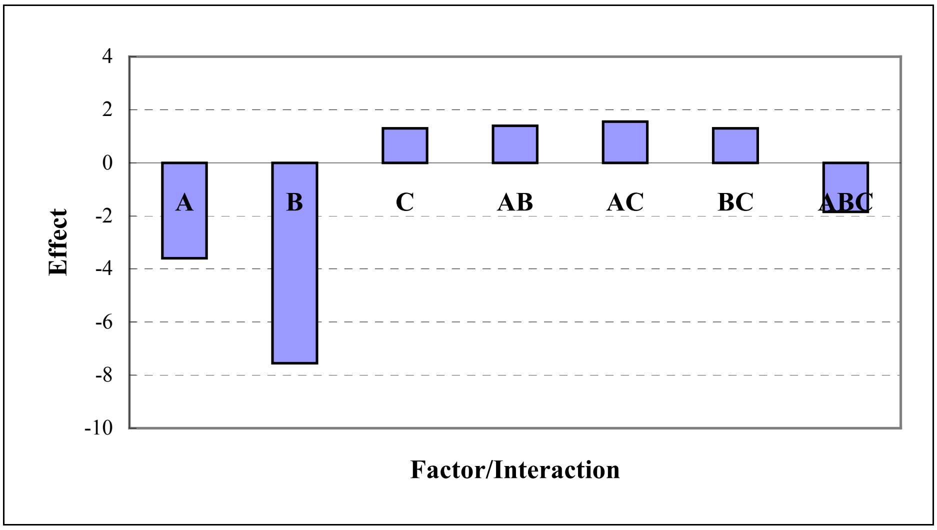

Fig. 4.26: Effect and interactions of parameters on sphericity

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.

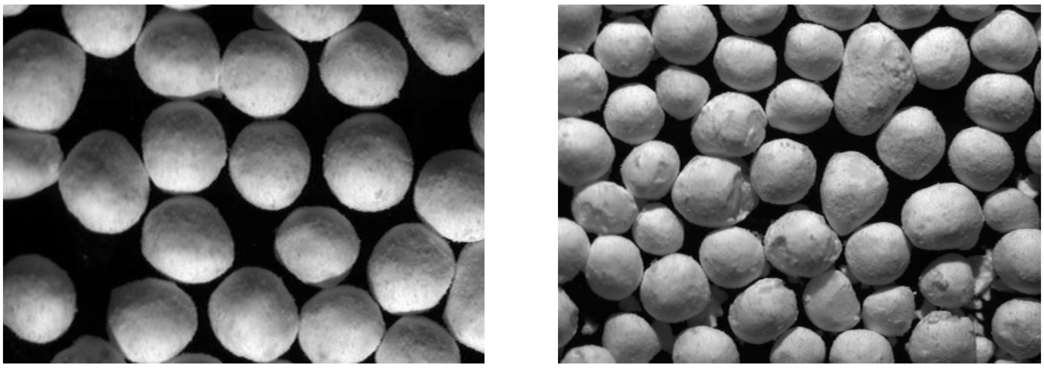

Fig. 4.27: Carbomer 934P-coated granules at different level of spray rate of binder: at low level (left) and at high level (right)

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.

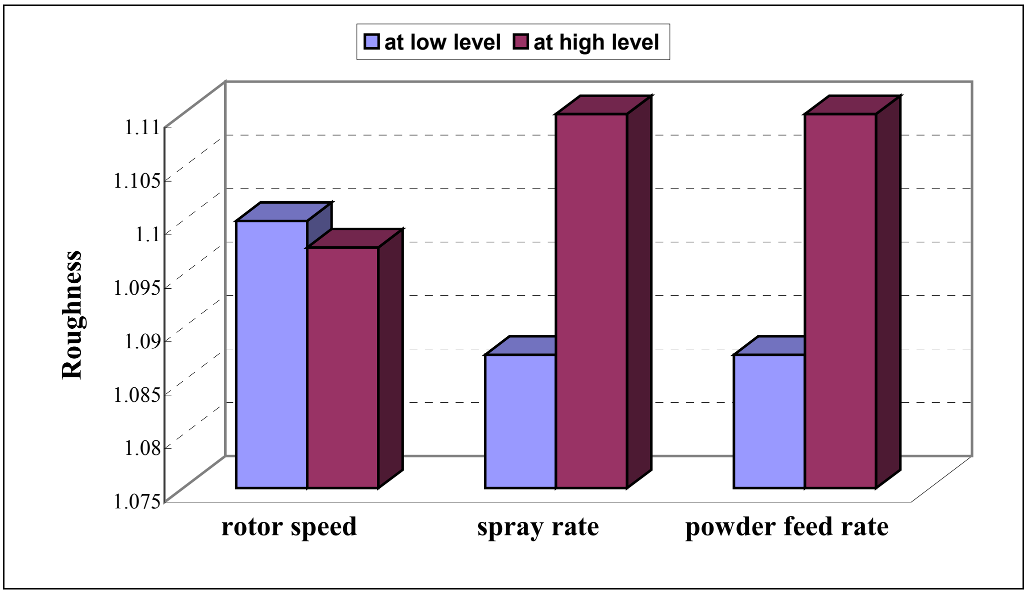

Fig. 4.28: Influence of parameters on roughness of pellets

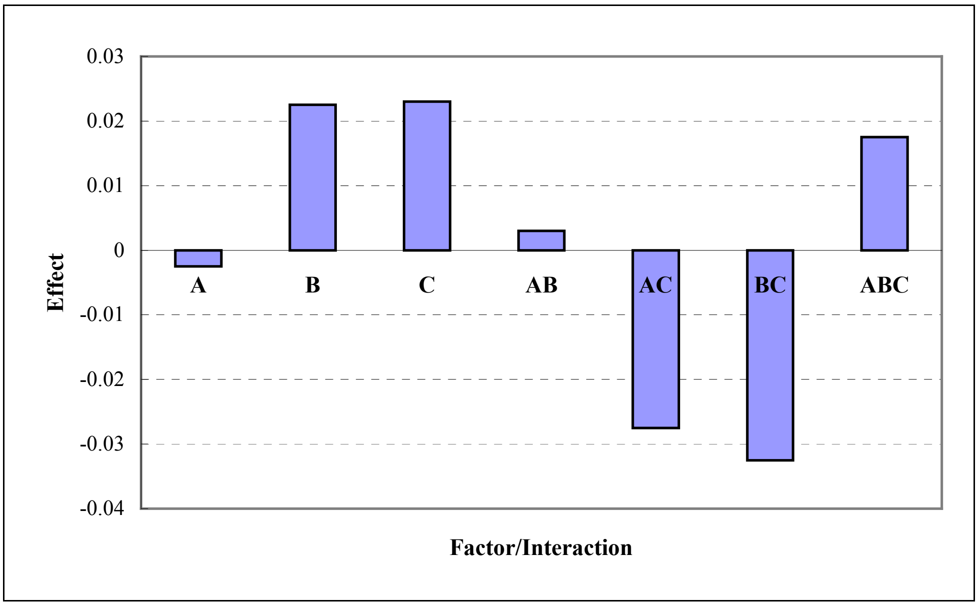

Fig. 4.29: Effect and interactions of parameters on the roughness of pellets

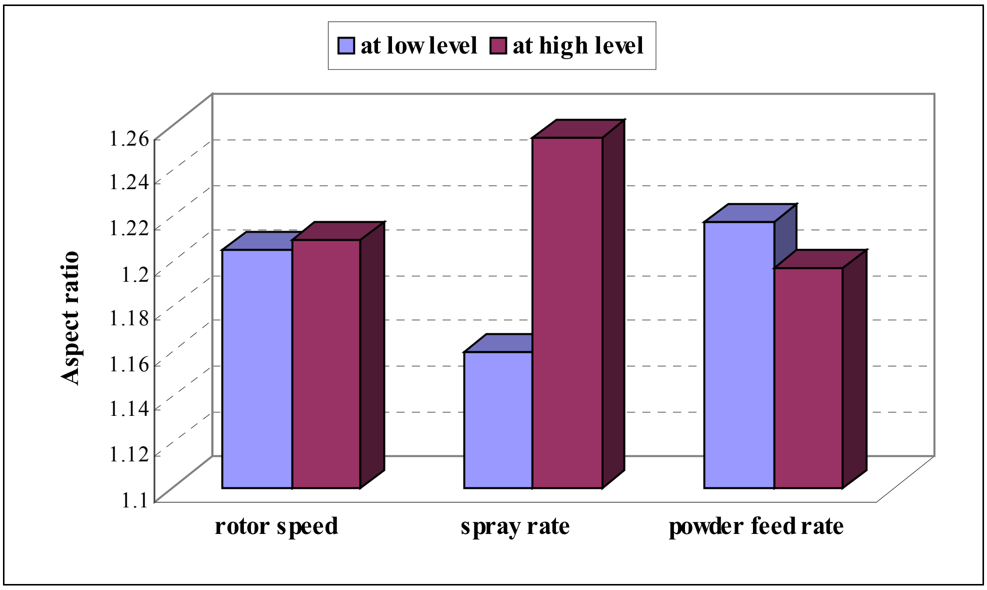

Fig. 4.30: Influence of parameters on the aspect ratio of pellets

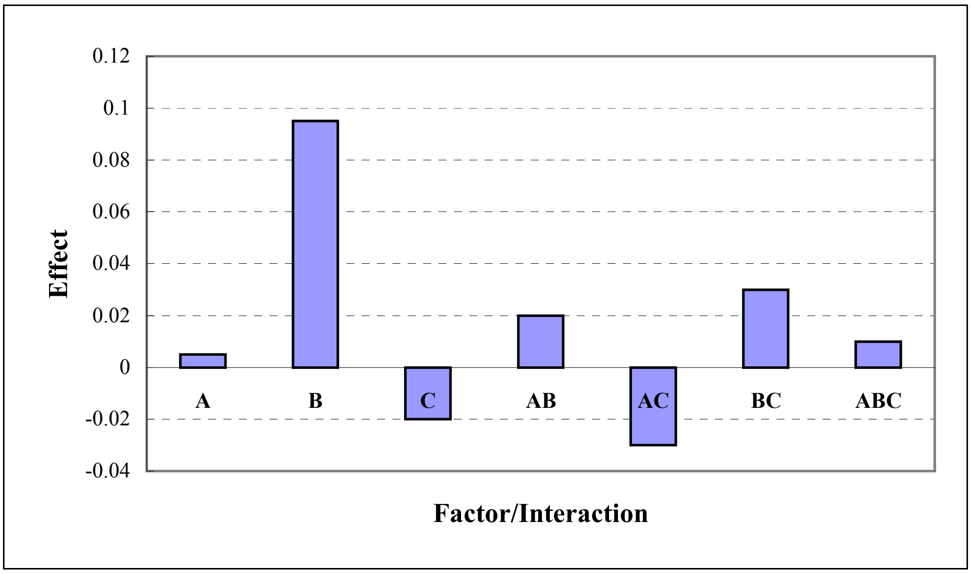

Fig. 4.31: Effect and interactions of parameters on the aspect ratio of pellets