

## 5. Investigations of Mucoadhesion and Dissolution

### 5.1 General

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

### 5.2 Determination of mucoadhesion

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



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

**Fig. 5.1:** Measurement of mucoadhesion by texture analyzer

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

### 5.2.1 Influence of carbomer 934P content on the mucoadhesion

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

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

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

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

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

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

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

### 5.2.2 Influence of pH value on the mucoadhesion

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

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

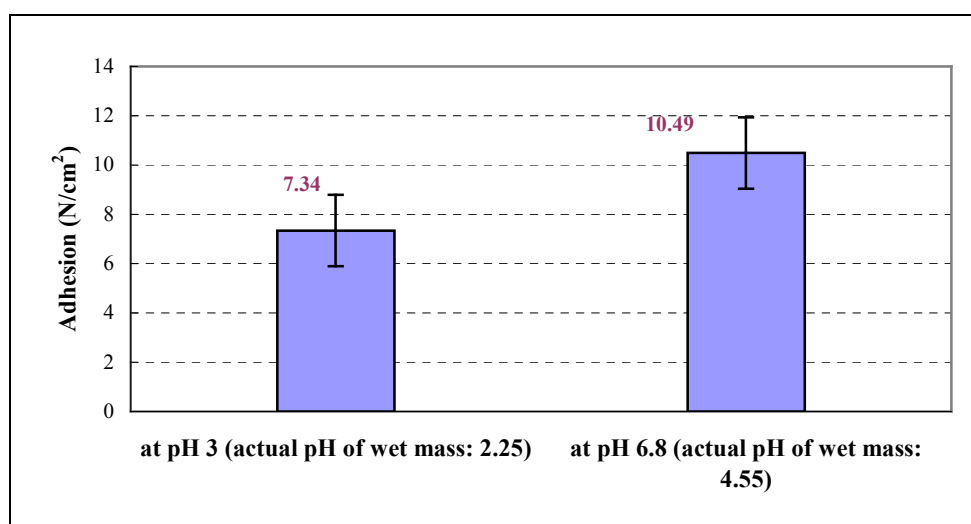
**Tab. 5.3:** Mucoadhesion of wet mass containing carbomer 934P 10.5%/theophylline 10.5%/microcrystalline cellulose 15.8%/tri-calcium phosphate 15.8%/ water 47.4% at different pH values

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

(Mean ± S.D., n=5)

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

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



**Fig. 5.2:** Difference in mucoadhesion at two pH levels (Mean  $\pm$  S.D., n = 5)

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

### 5.2.3 Influence of excipients on the mucoadhesion

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

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

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

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

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

**Tab. 5.5:** The actual compositions of prepared wet masses

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

**Tab. 5.6:** Mucoadhesion of all compositions

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

(Mean ± S.D., n = 5)

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

#### 5.2.4 Influence of salts on the mucoadhesion

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

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

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

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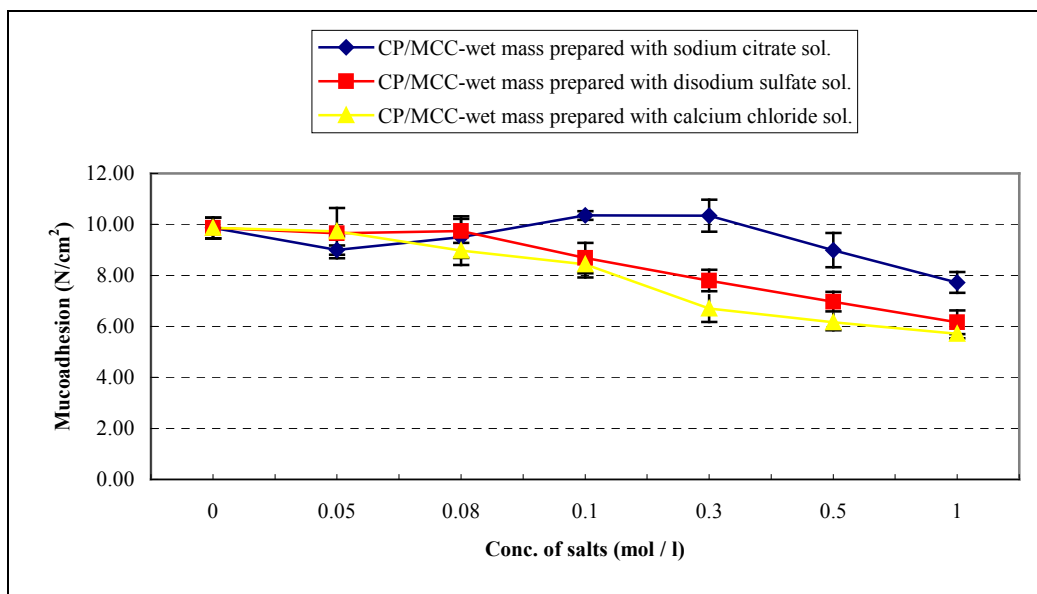
	0.3		CP (10%) / MCC (40%) / Na citrate (4.4%) / Water (45.7%)
	0.5		CP (10%) / MCC (40%) / Na citrate (7.3%) / Water (42.8%)
	1.0		CP (10%) / MCC (40%) / Na citrate (14.5%) / Water (35.5%)

**Tab. 5.8:** The actual composition of wet mass made with carbomer/MCC/Na<sub>2</sub>SO<sub>4</sub>-dissolved water

30g Powder mixture of Carbomer 934P (20%) MCC (80% w/w)  + Na <sub>2</sub> SO <sub>4</sub> -dissolved water (30ml)	Conc. of Na <sub>2</sub> SO <sub>4</sub> (mol/ml)	Kneading in mortar  →	The actual composition of prepared wet mass (60g)
	0		CP (10%) / MCC (40%) / Na <sub>2</sub> SO <sub>4</sub> (0%) / Water (50%)
	0.05		CP (10%) / MCC (40%) / Na <sub>2</sub> SO <sub>4</sub> (0.4%) / Water (49.6%)
	0.08		CP (10%) / MCC (40%) / Na <sub>2</sub> SO <sub>4</sub> (0.6%) / Water (49.4%)
	0.1		CP (10%) / MCC (40%) / Na <sub>2</sub> SO <sub>4</sub> (0.7%) / Water (49.3%)
	0.3		CP (10%) / MCC (40%) / Na <sub>2</sub> SO <sub>4</sub> (2.1%) / Water (47.9%)
	0.5		CP (10%) / MCC (40%) / Na <sub>2</sub> SO <sub>4</sub> (3.6%) / Water (46.4%)
	1.0		CP (10%) / MCC (40%) Na <sub>2</sub> SO <sub>4</sub> (7.1%) / Water (42.9%)

**Tab. 5.9:** The actual composition of wet mass made with carbomer/MCC/CaCl<sub>2</sub>-dissolved water

30g Powder mixture of Carbomer 934P (20%) MCC (80% w/w)  + CaCl <sub>2</sub> -dissolved water (30ml)	Conc. of CaCl <sub>2</sub> (mol/ml)	Kneading in mortar  →	The actual composition of prepared wet mass (60g)
	0		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (0%) / Water (50%)
	0.05		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (0.4%) / Water (49.6%)
	0.08		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (0.6%) / Water (49.4%)
	0.1		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (0.7%) / Water (49.3%)
	0.3		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (2.2%) / Water (47.8%)
	0.5		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (3.7%) / Water (46.3%)
	1.0		CP (10%) / MCC (40%) / CaCl <sub>2</sub> (7.4%) / Water (42.6%)



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

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

### 5.3 Dissolution test

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

#### 5.3.1 Pellets produced by the spraying of salt solution

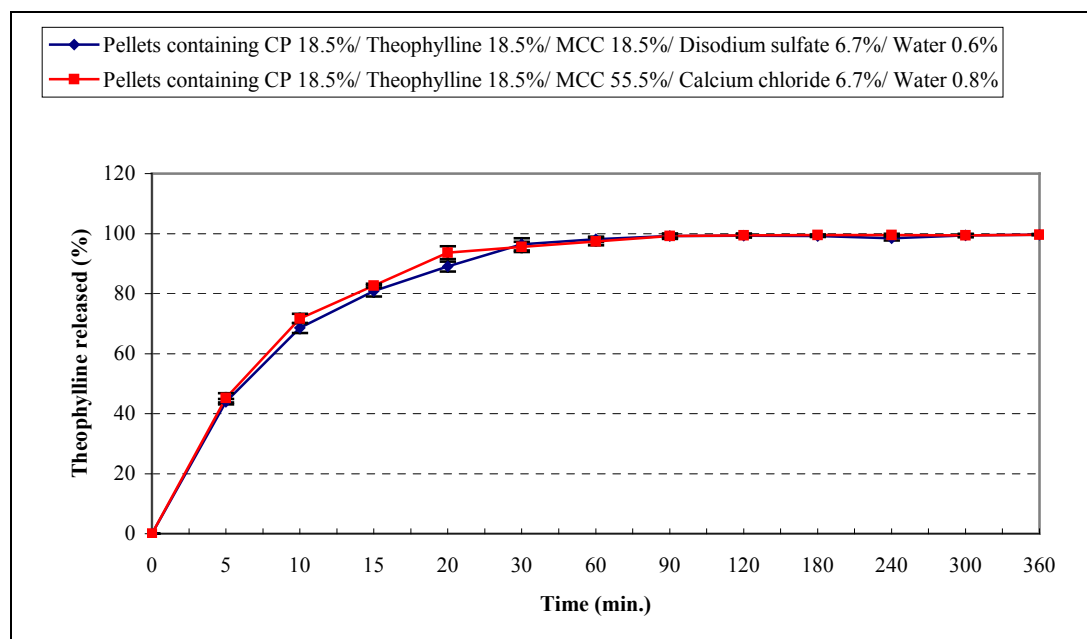
Three kinds of salts- sodium citrate, disodium sulfate, and calcium chloride- were tried to produce pellets. It was failed to prepare pellets by the spraying of sodium citrate solution, since it could not reduce the tack of carbomer 934P. Therefore, only disodium sulfate and calcium chloride were practically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



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

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

Powder mixture (400g)		Sprayed salt solution for granulation (ml)	Moisture content of produced pellets (%)	The actual composition of produced pellets	
Carbomer 934P	20%	Na <sub>2</sub> SO <sub>4</sub> sol. 680ml	0.6%	Carbomer 934P	18.5%
Theophylline	20%			Theophylline	18.5%
MCC	60%	CaCl <sub>2</sub> sol. 655ml	0.8%	MCC	55.7%
				Na <sub>2</sub> SO <sub>4</sub>	6.7%
				Water	0.6%
				Carbomer 934P	18.5%
				Theophylline	18.5%
				MCC	55.5%
		CaCl <sub>2</sub>	6.7%		
		PVP	1.7%		
		Water	0.8%		



**Fig. 5.4:** Influence of salts on the release of theophylline in water of pH 4.1~4.9 (Mean±S.D., n=3)

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

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

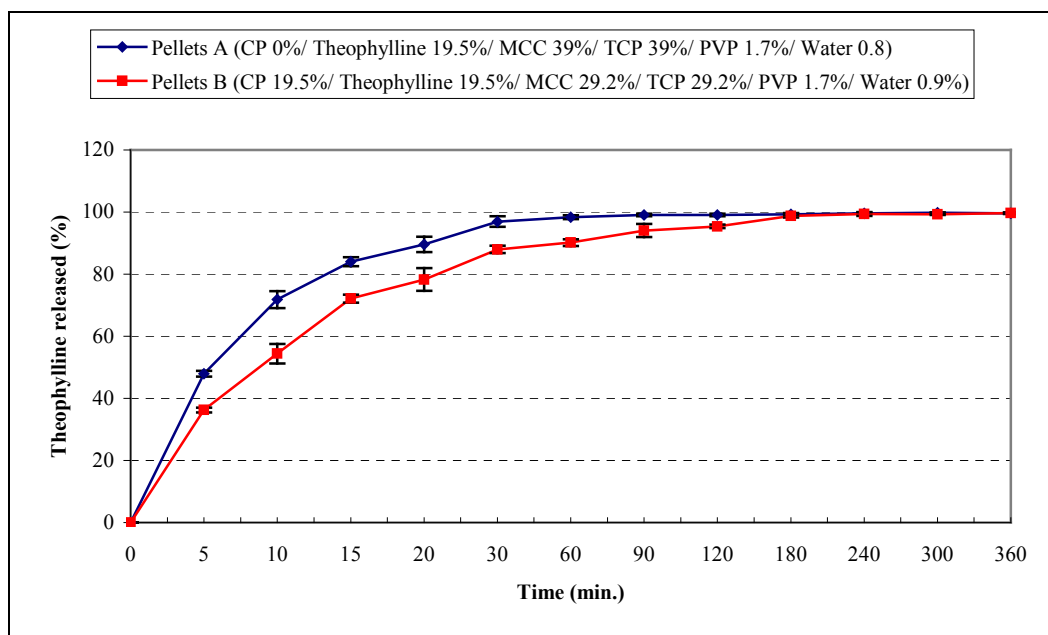
#### 5.3.2.1 Influence of carbomer 934P

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

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

**Tab. 5.11:** The actual composition of produced pellets

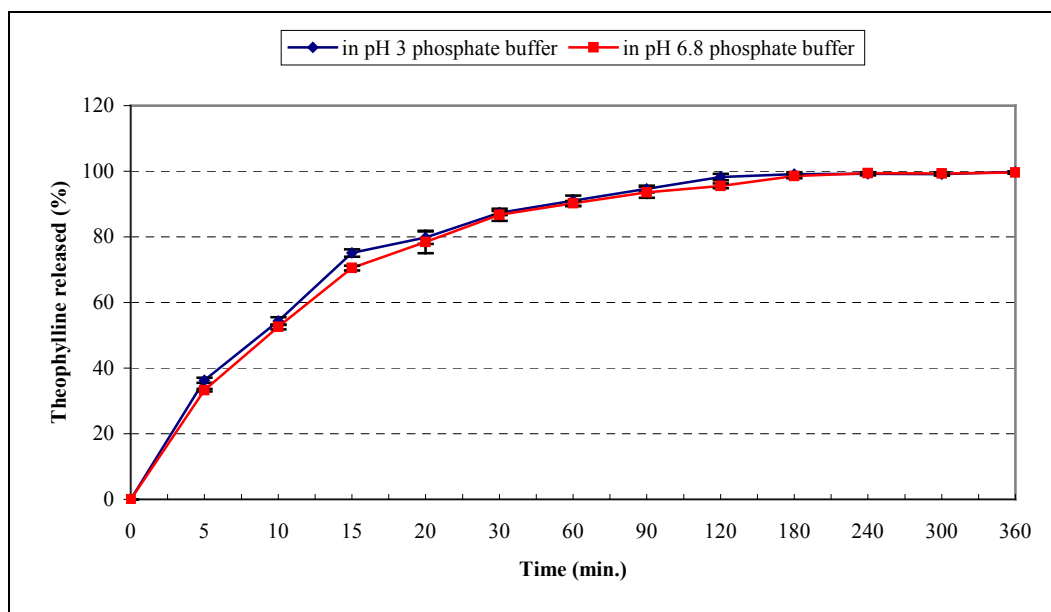
	Powder mixture (400g)	Sprayed binder solution for granulation (ml)	Moisture content of produced pellets (%)	The actual composition of produced pellets
Pellets A	Carbomer 934P 0% Theophylline 20% MCC 40% TCP 40%	1%-PVP K90 sol. 686ml	0.8%	Carbomer 934P 0% Theophylline 19.5% MCC 39% TCP 39% PVP 1.7% Water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



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

### 5.3.2.2 Influence of pH value

In order to evaluate the influence of pH value of dissolution medium, the release from the pellets containing 20% of carbomer 934P was compared in the medium of different pH (3 and 6.8).



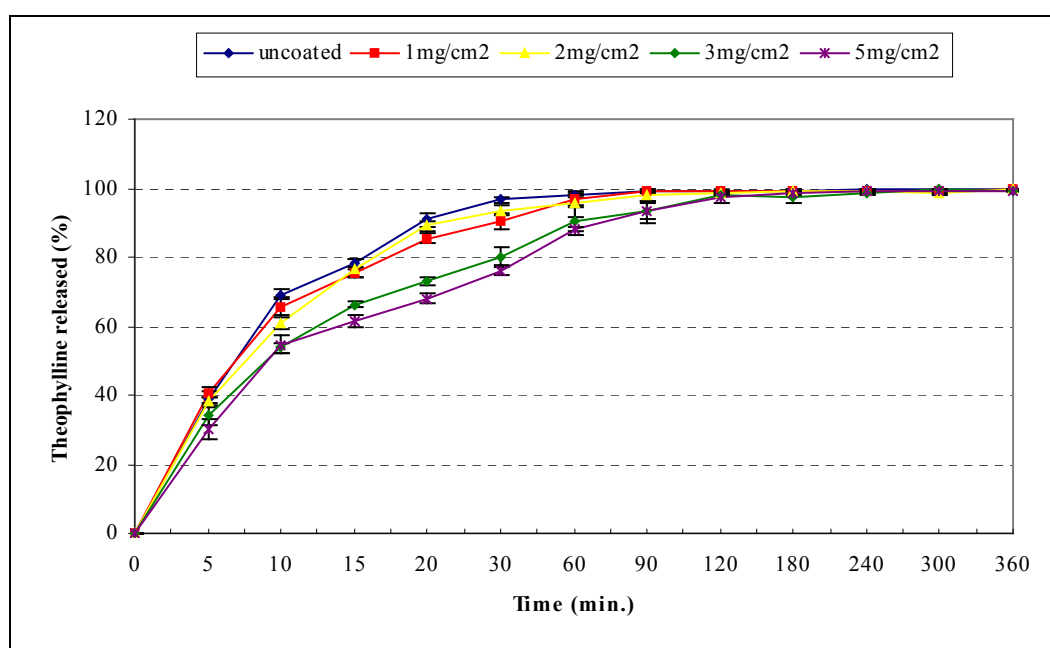
**Fig. 5.6:** Influence of pH on the release of theophylline from the pellets containing CP 19.5%/Theophylline 19.5%/MCC 29.2%/TCP 29.2%/PVP 1.7%/Water 0.9% (CP: carbomer 934P, MCC: microcrystalline cellulose, TCP: tri-calcium phosphate, cl-PVP: cross-linked PVP) (Mean $\pm$ S.D., n=3)

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

### 5.3.3 Pellets produced through dry-coating technique

#### 5.3.3.1 Influence of coating level

The release profiles of uncoated and carbomer 934P-layered pellets are illustrated in figure 5.7.

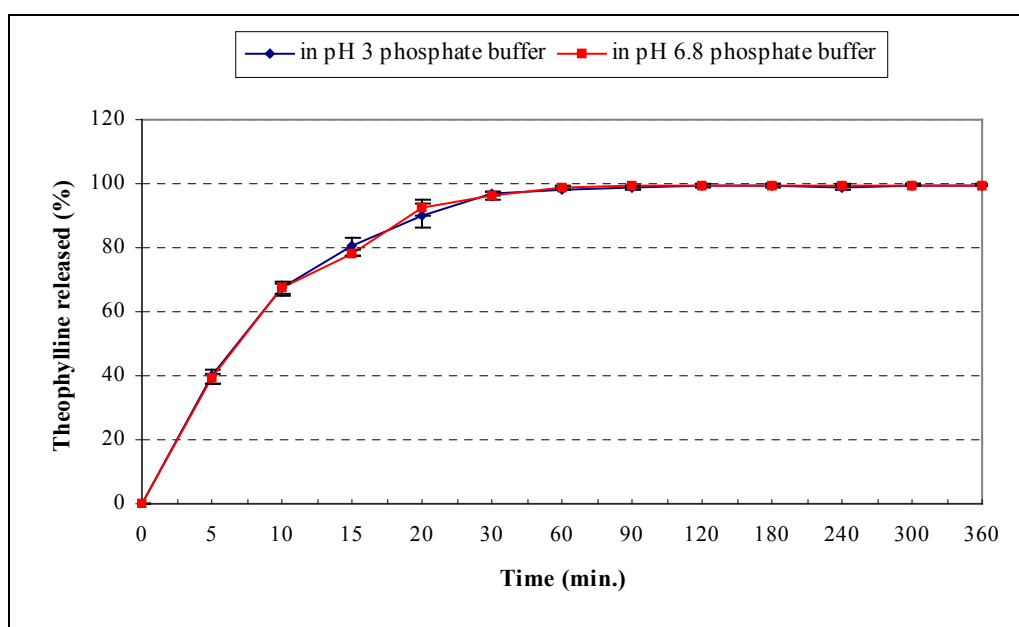


**Fig. 5.7:** Influence of coating level on the release of theophylline from carbomer 934P-coated pellets (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) in water of pH 4~5 (Mean±S.D., n=3)

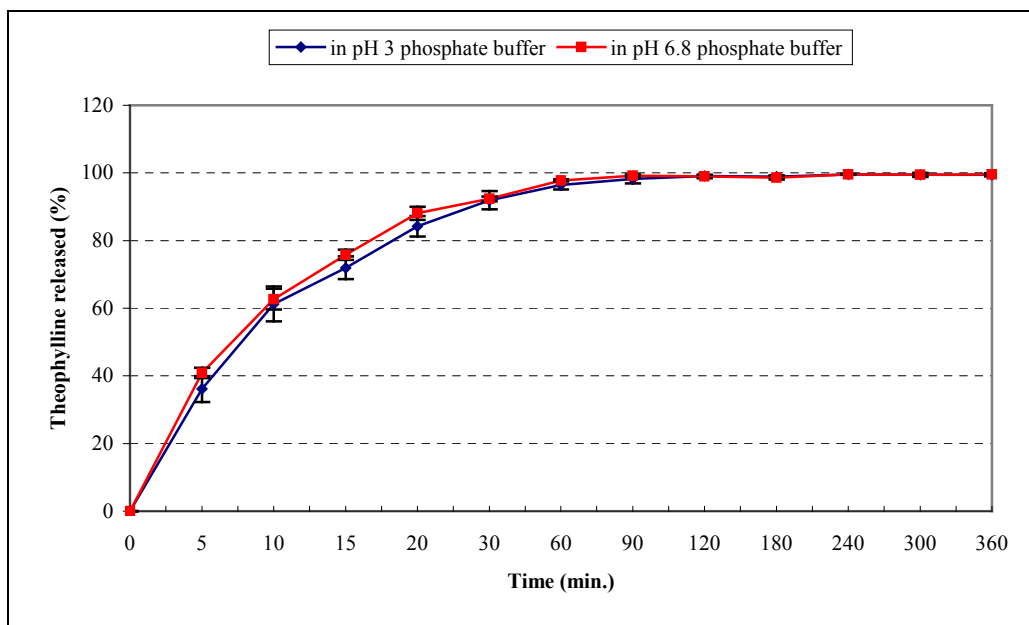
Theophylline release from uncoated and coated pellets with the coating level of 1 mg/cm<sup>2</sup> and 2 mg/cm<sup>2</sup> was almost 100% at 30 min. The delay of drug release was indicated only at the higher coating level (3 and 5 mg/cm<sup>2</sup>). Below the coating level of 3 mg/cm<sup>2</sup>,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

### 5.3.3.2 Influence of pH value

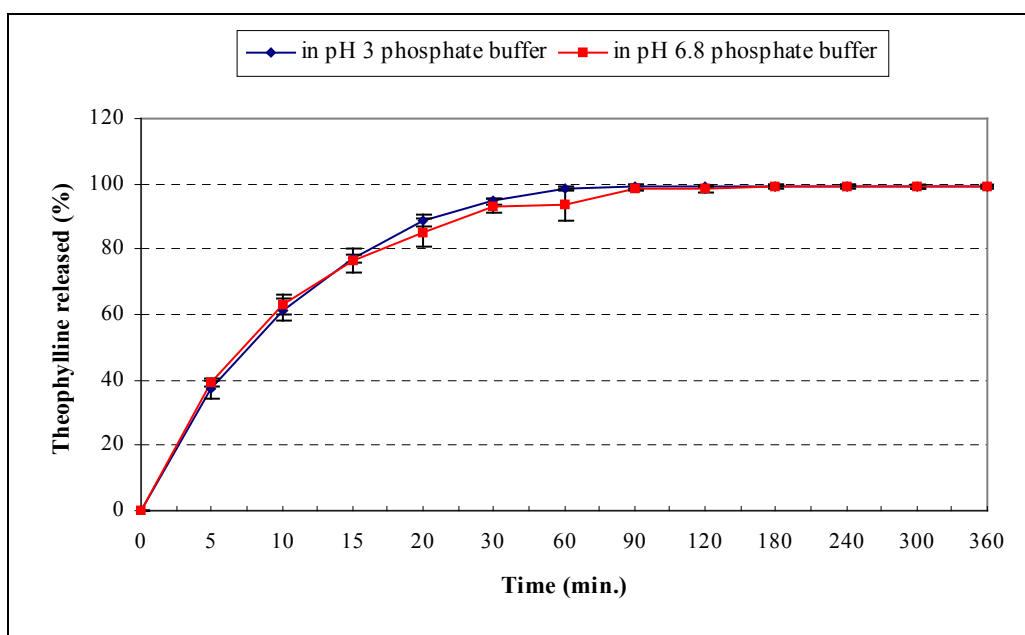
Uncoated pellets and the pellets with low coating level (1 and 2 mg/cm<sup>2</sup>) showed no considerable differences by differing pH [Fig.5.8~5.10]. However, in case of the pellets with the high coating level (3 and 5 mg/cm<sup>2</sup>), theophylline release was slightly delayed at pH 6.8 [Fig.5.11 and 5.12]. This result can be explained through the gel-barrier formed at surface of pellets [265, 275-279, 289, 290, 293, 294, 301]. Whereas the uncoated and the low-level coated pellets were not influenced by the gel-formation of carbomer, the pellets coated with 3 and 5 mg/cm<sup>2</sup> could be dependent on the gel-forming of carbomer by varying pH. In the medium of pH 6.8, carbomer could swell promptly at the surface of pellets. This gel-barrier could prohibit the dissolution of theophylline from pellets into dissolution medium. That resulted in the delay of theophylline release.



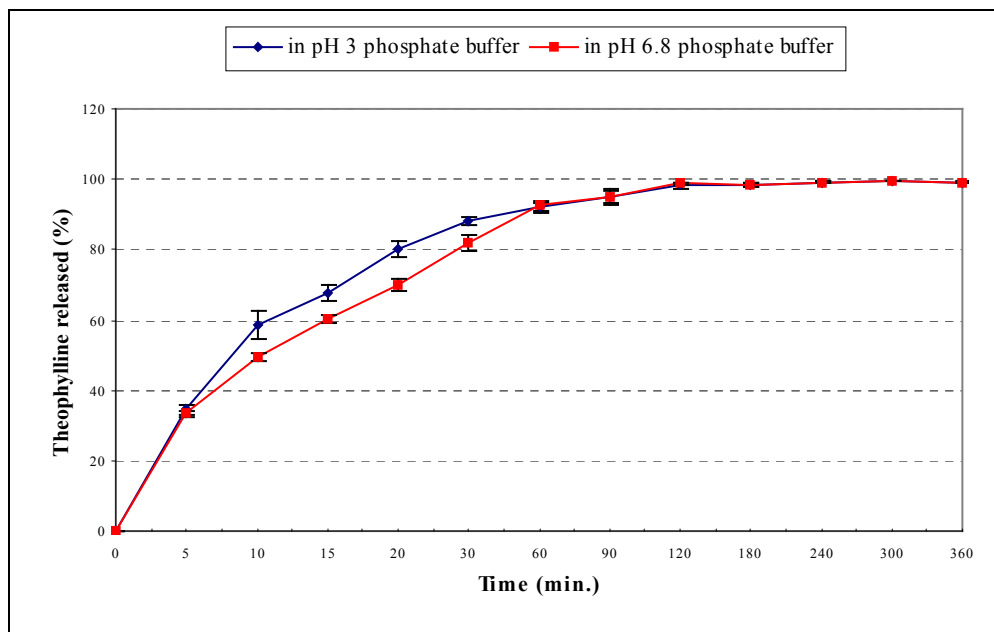
**Fig. 5.8:** Theophylline release from uncoated pellets containing theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8% at different pH (Mean±S.D., n=3)



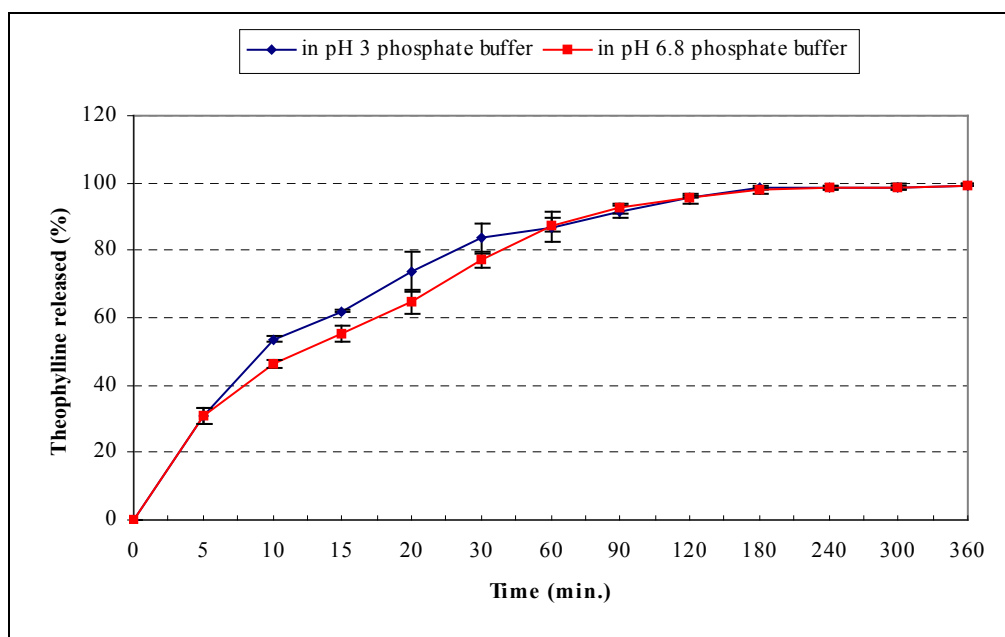
**Fig. 5.9:** Theophylline release from the pellets with  $1\text{mg}/\text{cm}^2$  of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean $\pm$ S.D., n=3)



**Fig. 5.10:** Theophylline release from pellets with  $2\text{mg}/\text{cm}^2$  of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean $\pm$ S.D., n=3)



**Fig. 5.11:** Theophylline release from pellets with 3mg/cm<sup>2</sup> of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean±S.D., n=3)



**Fig. 5.12:** Theophylline release from pellets with 5mg/cm<sup>2</sup> of coating level at different pH (core pellets contained theophylline 19.5%/MCC 39%/TCP 39%/PVP 1.7%/Water 0.8%) (Mean±S.D., n=3)