CHAPTER IV

RESULTS AND DISCUSSION

1. Physical properties of acyclovir matrices

The physical properties of acyclovir matrices are summarized in Table 6.

1.1 Weight variation

The average weight of the tablets ranged from 576.03 to 585.42 mg. Since the acceptable limit of weight variation conforming to USP 24 is in the range of average weight ± 5% (551 - 609 mg), the weight variations of all formulations passed the specification. The weight variation was within acceptable limit, indicating the favourable flowability conferred by wet granulation method (Cheng et al., 1993).

1.2 Hardness

The hardness of the matrices was between 7.82 – 8.35 kp. This result indicated that the hardness of matrices could be controlled within a predetermining range (7–9 kp.

1.3 Thickness

The thickness of matrices was in the range of 5.81 – 6.88 mm. The variation of thickness of the matrices might be caused by the differences in granule properties including bulk density, particle size and particle size distribution in the different matrix formulations (Rosanske et al., 1990).

1.4 Friability

The average friability of the matrices ranged from 0.02 to 0.74%. Since the acceptable limit of friability conforming to USP 24 is not more than 1%, the percent friability of the prepared matrices passed the specifications.

Table 6 Physical properties of acyclovir matrices containing various amounts of hydroxypropyl methylcellulose, xanthan gum, sodium alginate or carbopol 934P (n=20)

Formulation	Weight variation (mg) (Mean ± SD)	Hardness (kp) (Mean ± SD)	Thickness (mm) (Mean ± SD)	Friability (%) (Mean ± SD)
FB1	582.45 ± 5.72	8.35 ± 0.49	6.07 ± 0.03	0.49 ± 0.02
FB2	581.19 ± 6.43	8.12 ± 0.51	6.39 ± 0.10	0.36 ± 0.12
F 1	582.18 ± 6.17	8.14 ± 0.58	6.37 ± 0.05	0.06 ± 0.02
F 2	581.33 ± 5.64	8.13 ± 0.60	6.18 ± 0.02	0.03 ± 0.03
F 3	579.50 ± 4.72	8.20 ± 0.63	6.03 ± 0.05	0.05 ± 0.02
F 4	578.89 ± 7.07	7.82 ± 0.52	6.37 ± 0.05	0.35 ± 0.05
F 5	579.18 ± 4.79	8.29 ± 0.53	6.12 ± 0.03	0.45 ± 0.15
F 6	576.73 ± 5.79	8.00 ± 0.59	6.08 ± 0.03	0.34 ± 0.03
F 7	585.42 ± 3.57	8.10 ± 0.69	6.18 ± 0.06	0.28 ± 0.10
F 8	581.8 ± 6.15	8.34 ± 0.47	6.08 ± 0.02	0.42 ± 0.09
F 9	584.33 ± 5.36	8.08 ± 0.55	6.07 ± 0.03	0.25 ± 0.04
F 10	576.03 ± 4.24	8.34 ± 0.44	6.88 ± 0.12	0.21 ± 0.04
F 11	580.91 ± 5.17	8.12 ± 0.43	6.50 ± 0.08	0.13 ± 0.04
F 12	579.17 ± 5.61	8.24 ± 0.47	6.53 ± 0.06	0.06 ± 0.02
F 13	578.54 ± 5.65	8.31 ± 0.41	6.01 ± 0.07	0.05 ± 0.02
F 14	581.40 ± 7.81	8.28 ± 0.43	6.42 ± 0.15	0.02 ± 0.02
F 15	580.91 ± 2.77	8.33 ± 0.49	6.40 ± 0.04	0.06 ± 0.02
F 16	578.53 ± 2.82	7.96 ± 0.39	5.81 ± 0.03	0.33 ± 0.12
F 17	581.61 ± 4.99	8.20 ± 0.52	6.07 ± 0.08	0.74 ± 0.07

Table 6 (Continued) Physical properties of acyclovir matrices containing various amounts of hydroxypropyl methylcellulose, xanthan gum, sodium alginate or carbopol 934P (n=20)

Formulation	Weight variation (mg) (Mean ± SD)	Hardness (kp) (Mean ± SD)	Thickness(mm) (Mean ± SD)	Friability (%) (Mean ± SD)
F 18	580.37 ± 4.01	8.08 ± 0.59	5.92 ± 0.02	0.39 ± 0.07
F 19	579.54 ± 3.64	8.11 ± 0.57	5.68 ± 0.04	0.30 ± 0.02
F 20	581.13 ± 3.84	8.17 ± 0.47	5.84 ± 0.04	0.37 ± 0.02
F 21	581.17 ± 3.96	8.14 ± 0.63	5.84 ± 0.04	0.38 ± 0.07
F 22	580.80 ± 3.67	8.08 ± 0.45	6.54 ± 0.04	0.08 ± 0.02
F 23	578.15 ± 6.91	8.35 ± 0.49	6.64 ± 0.11	0.23 ± 0.04
F 24	579.18 ±4.55	7.92 ± 0.44	6.39 ± 0.10	0.23 ± 0.12

2. Drug content of acyclovir matrices

The percentage drug content of acyclovir matrices are shown in table 7. The values of percentage drug content ranged from 97.11 to 102.87 %.

Table 7 The percentage drug content of acyclovir matrices (n=3)

Formulation	%Drug content (Mean ± SD)	Formulation	%Drug content (Mean ± SD)
FB1	99.62 ± 0.41	F 12	97.46 ± 0.87
FB2	97.64 ± 0.74	F 13	98.15 ± 0.62
F 1	98.99 ± 1.01	F 14	98.71 ± 1.16
F 2	98.85 ± 0.96	F 15	99.01 ± 1.55
F 3	102.87 ± 0.58	F 16	98.21 ± 0.78
F 4	98.86 ± 1.86	F 17	98.72 ± 0.29
F 5	100.49 ± 1.44	F 18	97.64 ± 0.07
F 6	97.20 ± 0.41	F 19	98.78 ± 0.93

Table 7 (Continued) The percentage drug content of acyclovir matrices (n=3)

Formulation	%Drug content (Mean ± SD)	Formulation	%Drug content (Mean ± SD)
F 7	97.50 ± 0.97	F 20	97.71 ± 0.25
F 8	97.14 ± 2.01	F 21	97.11 ± 0.82
F 9	97.56 ± 2.00	F 22	101.68 ± 0.85
F 10	100.47 ± 0.18	F 23	99.56 ± 0.79
F 11	98.54 ± 1.24	F 24	99.36 ± 0.94

3. Solubility of acyclovir

The solubilities of acyclovir in media with different pH or ionic strength values at 37 °C ± 0.5 °C are presented in Table 8. The solubility of acyclovir in 0.1 N HCl solution was highest. In other media, the solubilities were similar and were much less than that in 0.1 N HCl solution.

Table 8 The solubilities of acyclovir in various media at 37 °C ± 0.5 °C (n=3)

Medium	Solubility (mg/ml) (mean ± SD)
0.1 N HCl solution	18.34 ± 1.31
Phosphate buffer pH 6.8 solution	2.73 ± 0.01
Phosphate buffer pH 6.8 solution + NaCl[a]	2.74 ± 0.07
Deionized water	2.74 ± 0.11
0.05 M NaCl	2.89 ± 0.02
0.1 M NaCl	2.78 ± 0.02
0.2 M NaCl	2.83 ± 0.08

[a] The ionic strength was adjusted to 0.1 with sodium chloride.

4. Viscosity of polymer solution

Since the viscosity of the hydrated gel layer may critically influence drug release, the difference in viscosity of hydrated surface layer caused by differences in pH and ionic strength of the dissolution media is likely to influence drug release from hydrophilic matrices. Therefore, to elucidate the influence of pH and ionic strength of dissolution media on the viscosity of polymer solutions, the tests were performed in solutions with different pH values and salt concentrations.

In this study, the solutions with pH values of 1.2 and 6.8 were used to simulate the pH of the stomach and the intestine, respectively. In case of various ionic strengths, sodium chloride was used as an electrolyte in medium, since this is the major representative electrolyte of the gastrointestinal fluid (GI fluid) (Talukdar and Kinget, 1995). Since the range of ionic strength in GI fluid is 0.010 – 0.166 (Johnson et al., 1993), the range of ionic strength of 0.00 – 0.20 was chosen for this study.

4.1 Effect of pH on viscosity of polymer solutions

The viscosities of various polymers at two different pH values: pH 1.2 (0.1 N HCl solution) and phosphate buffer solution pH 6.8 (PBS pH 6.8) are illustrated in Figure 8. Moreover, the ionic strengths of these media were also different. The ionic strengths of 0.1 N HCl solution and PBS pH 6.8 were 0.1 and about 0.07, respectively. Therefore, the difference in viscosity of polymer solution in 0.1 N HCl solution and PBS pH 6.8 might due to the difference of pH and/or ionic strength of these media. In order to clarify the result, the viscosity of polymer solutions in PBS pH 6.8 with an ionic strength of 0.1 was also studied.

4.1.1 HPMC solutions

As shown in Figure 8, the viscosity of HPMC at pH 1.2 was less than that at pH 6.8 (either in PBS pH 6.8 or PBS pH 6.8 + NaCl). This result was probably due to the instability of HPMC solution at pH 1.2. The HPMC solution is generally stable in the pH range of 3 to 11. Below pH 3, acid–catalyzed hydrolysis of the glucose –

glucose linkage becomes significant (Greminger and Krumel, 1980). Therefore, the solution with pH 1.2 might destabilize the HPMC molecule resulting in instability of HPMC solution. The weak gel network occurred and consequently small extent of viscosity.

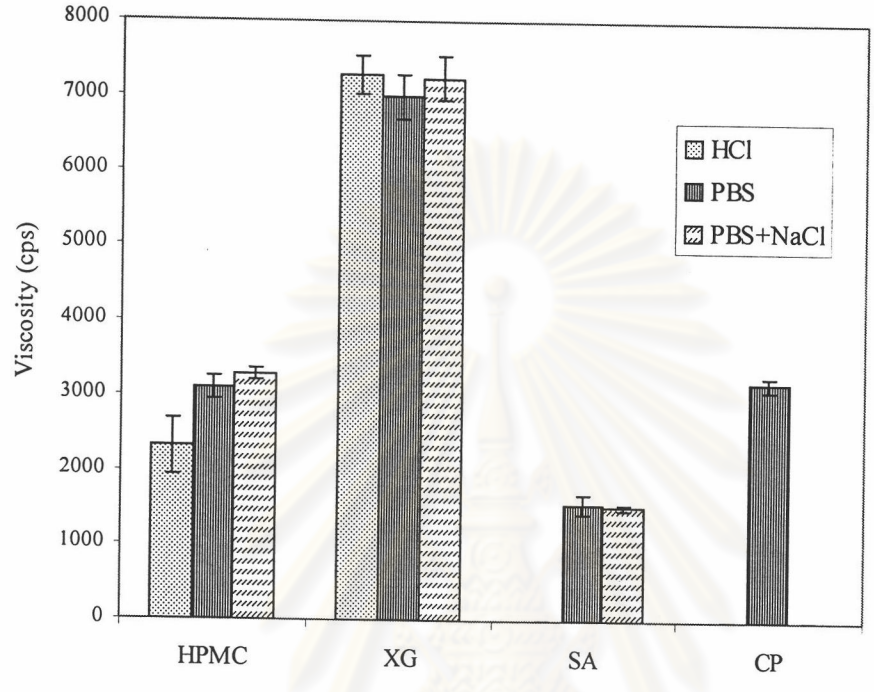


Figure 8 The viscosity of hydroxypropyl methylcellulose (HPMC), xanthan gum (XG), sodium alginate[a] (SA) and carbopol 934P[b] (CP) in media with different pH values: 0.1 N HCl solution (pH 1.2), phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 (PBS pH6.8 + NaCl)

[a] The viscosity measurement was only performed in PBS pH 6.8 and PBS pH 6.8 + NaCl.

[b] The viscosity measurement was only performed in PBS pH 6.8.

In order to clarity that the lower viscosity of HPMC in pH 1.2 was only due to the instability of HPMC solution at acidic pH and the difference in ionic strength of 0.1 N HCl and PBS pH 6.8 did not cause the difference in viscosity in these media.

The viscosity measurement of HPMC in PBS pH 6.8 + NaCl was performed. As illustrated in Figure 8, the viscosities of HPMC in PBS pH 6.8 and PBS pH 6.8 + NaCl were apparently similar. This result pointed out that the difference in viscosity of HPMC in 0.1 N HCl and PBS pH 6.8 + NaCl was due to the difference in pH of these media. The difference in ionic strength of 0.1 N HCl and PBS pH 6.8 had no significant effect on the viscosity of HPMC solution.

4.1.2 Xanthan gum solutions

As displayed in Figure 8, the viscosity of xanthan gum solution in 0.1 N HCl solution was comparable to that in PBS pH 6.8. This was an indication that pH of the medium had little effect on viscosity of xanthan gum solution. The previous report by Cottrell et al. (1980) may support the obtained result in this study. They reported that pH had little effect on the viscosity of industrial-grade xanthan gum solutions. In addition, the viscosity of xanthan gum in PBS pH 6.8 was similar to that in PBS pH 6.8 + NaCl . This finding indicated that within the range of ionic strength tested in this study, no influence of ionic strength on the viscosity of xanthan gum solution was observed. The effect of ionic strength on the viscosity of xanthan gum solution was discussed in the next topic.

4.1.3 Sodium alginate solutions

Since the pK_a values of alginic acid range between 3.4 and 4.4, water insoluble alginic acid is rapidly formed in 0.1 N HCl (Hodsdon et al., 1995). Therefore, the viscosity mesurement of the sodium alginate in 0.1 N HCl was not performed. As represented in Figure 8, the viscosities of the sodium alginate solutions in PBS pH 6.8 and PBS pH 6.8 + NaCl were not apparently different. This result pointed out that the viscosity of sodium alginate solution did not depend on the ionic strength of the medium. The influence of ionic strength of the medium on the viscosity of sodium alginate solution was also discussed in the next topic.

4.1.4 Carbopol 934P solutions

At pH 6.8, carbopol (pK_a = 6) is soluble and hydrated to form viscous solution. However, at pH 1.2, carbopol is virtually un–ionized and, due to its low solubility, unable to hydrate (Perez – Morcos et al., 1996). Moreover, since in the dissolution studies, the carbopol matrices could not produce sufficient sustained release, the effects of pH and ionic strength were not considered. Consequently, the viscosity measurement was only carried out in PBS pH 6.8. The viscosities of carbopol 934P and HPMC solutions in PBS pH 6.8 were comparable, as displayed in Figure 8. The viscosity of carbopol 934P in PBS pH 6.8 was intermediate between xanthan gum and sodium alginate solutions in the same medium.

4.2 Effect of various ionic strengths on viscosity of polymer solutions

The viscosities of HPMC, xanthan gum and sodium alginate solutions in media having different ionic strengths are presented in Figure 9. The effect of ionic strength on the viscosity of carbopol 934P solution was not studied. The media with various ionic strengths were sodium chloride solutions in concentrations of 0.05 M, 0.1 M and 0.2 M corresponding to ionic strengths of 0.05, 0.1 and 0.2, respectively. Moreover, deionized water was used as the medium with ionic strength approaching zero.

4.2.1 HPMC solutions

In case of HPMC solutions, the viscosities of HPMC solutions at various ionic strengths were apparently similar. This result indicated that the viscosity of HPMC solutions did not depend on the ionic strength of the medium. This finding is similar to a previous study (Talukdar et al., 1996). They studied the effect of the ionic strength of medium on the rheological properties of HPMC solution. They found that the presence of salt in the system had practically no effect on rheological properties of HPMC solution. This could be attributed to the non–ionic property of HPMC molecules. Being a non–ionic polymer, there was no salt screening effect on the molecules of HPMC

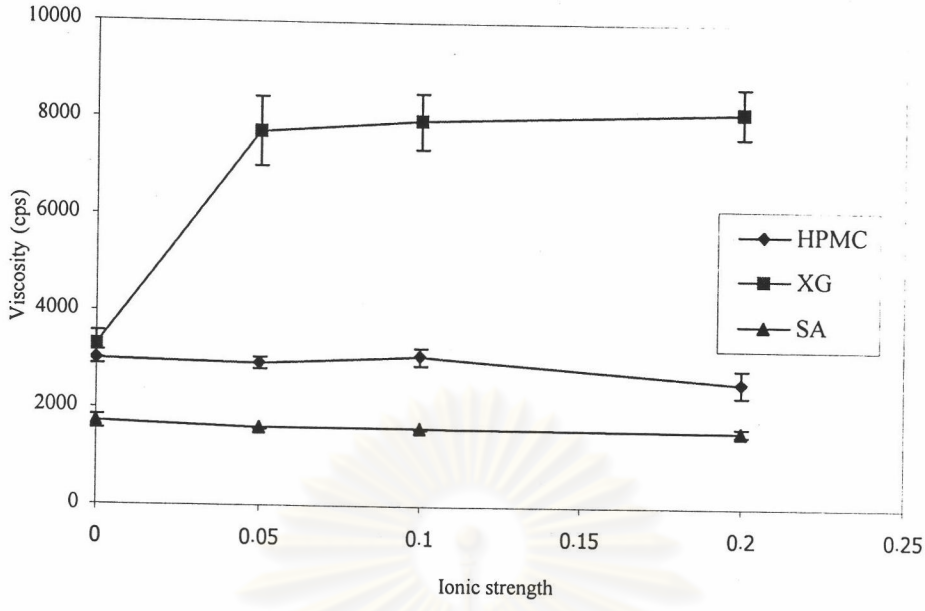


Figure 9 The viscosity of polymer solutions in media with various ionic strengths

4.2.2 xanthan gum solutions

For xanthan gum solutions, the influence of ionic strength of the medium on the viscosity of xanthan gum solution was observed. As shown in Figure 9, an increase in ionic strength from 0–0.05 resulted in an increase in the viscosity. The result agrees with a previous study in that the viscosity of xanthan gum in aqueous medium was influenced by ionic strength (Talukdar et al., 1996 and Talukdar and Kinget, 1995). The addition of salt to xanthan gum solution in the concentration range from 0.2 – 3.0 % causes the viscosity to increase (Talukdar and Kinget, 1995). The reason for this finding might be attributed to the salt dependent conformation of xanthan molecules. The existence of comformational transition of xanthan gum in aqueous solution was established. The disordered random coil conformation loses the ability to form a gel while the ordered elongated conformation is able to form a gel. An increase in concentration of added salt causes an increase in the rate of formation of an ordered structure (Talukdar and Kinget, 1995). In addition, it was also been found that the salt screens the electrostatic repulsions of pyruvate and acetate groups on the trisaccharide side chains, allowing the adoption of a helical backbone

conformation of xanthan gum. This in turn promotes the increased association of the ordered xanthan gum molecule in solution (Talukdar et al., 1996).

However, the present study found that the influence of ionic strength on viscosity of xanthan gum solution was limited up to ionic strength = 0.05. Above this value, further addition of salt had no effect. This finding is inconsistent with the result from previous studies (Talukdar et al., 1996 and Talukdar and Kinget, 1995) in which the influence of ionic strength of medium on the rheological properties of xanthan gum solution was observed up to a value of 0.1. These authors explained that under this condition (0.1 M NaCl) xanthan gum was in a stable form due to helix formation. Therefore, further addition of salts had no influence on the rheological properties. This deviated result might be caused by the difference in acetate and pyruvate content in xanthan gum molecules from different sources (Zatz and Knapp, 1984).

4.2.3 Sodium alginate solutions

As displayed in Figure 9, the viscosities of sodium alginate solutions in different ionic strengths of media were apparently unchanged. The finding pointed out that the independence of viscosity with respect to the ionic strength of the medium was observed. Nevertheless, this result disagrees with published report by Cottrell and Kovacs (1980) and Nussinovitch (1997). These authors described that monovalent salts depressed the viscosities of dilute sodium alginate solutions. The maximum effect on viscosity was attained at a salt level of 0.1 N in the solution (Cottrell and Kovacs, 1980). However, this effect can be reduced by increasing the alginate concentration (Nussinovitch, 1997). Since the polymer solutions in this study were prepared at a moderate concentration (2 % w/w) therefore the deviated result might be explained in terms of the higher concentration of alginate solution tested in this study. In addition, the influence of a salt on an alginate solution will also vary with the source of the alginate, as well as with its degree of polymerization and the type of salt (Cottrell and Kovacs, 1980).

5. Dissolution study

The dissolution experiment should be performed under the sink condition. When the drug concentration in the dissolution medium is equal or less than 15% of drug solubility in that medium, the sink condition is reassured (Carstensen, 1977). Since acyclovir was poorly soluble in all dissolution media studied, except for 0.1 N HCl solution (see Table 8), the sink condition occurred only at below 94% of accumulated percent drug release. Therefore, at the accumulated percent drug release above this value, the deviation of drug release profile might occur.

5.1 Dissolution study of blank matrices

The blank matrices containing no polymer were prepared. They were composed of major ingredients: acyclovir and a diluent. The blank A and B matrices contained lactose and dibasic calcium phosphate as the diluent, respectively.

5.1.1 Effect of dissolution medium on drug release

5.1.1.1 Effect of pH of dissolution medium on drug release

In order to study the effect of pH of the dissolution medium on drug release, the blank matrices were tested in 0.1 N HCl solution (pH 1.2) and phosphate buffer pH 6.8 solution (PBS pH 6.8). The releases profiles from blank A and B matrices in dissolution media with different pH values are displayed in Figures 10-11. For both blank A and B matrices, the drug releases in 0.1 N HCl solution were markedly faster than those in PBS pH 6.8. The blank A and B matrices dissolved completely in 0.1 N HCl solution at the 1st hour and 4th hour, respectively, while the release of acyclovir from those in PBS pH 6.8 were sustained over 12 hours. The reason for this finding might be due to the higher solubility of acyclovir in 0.1 N HCl solution. As displayed in Table 8, the solubilities of acyclovir in 0.1 N HCl solution and PBS pH 6.8 were 18.34 and 2.73 mg/ml, respectively. Therefore, when the matrices were exposed to 0.1 N HCl solution, acyclovir readily dissolved which led to an apparant faster drug release.

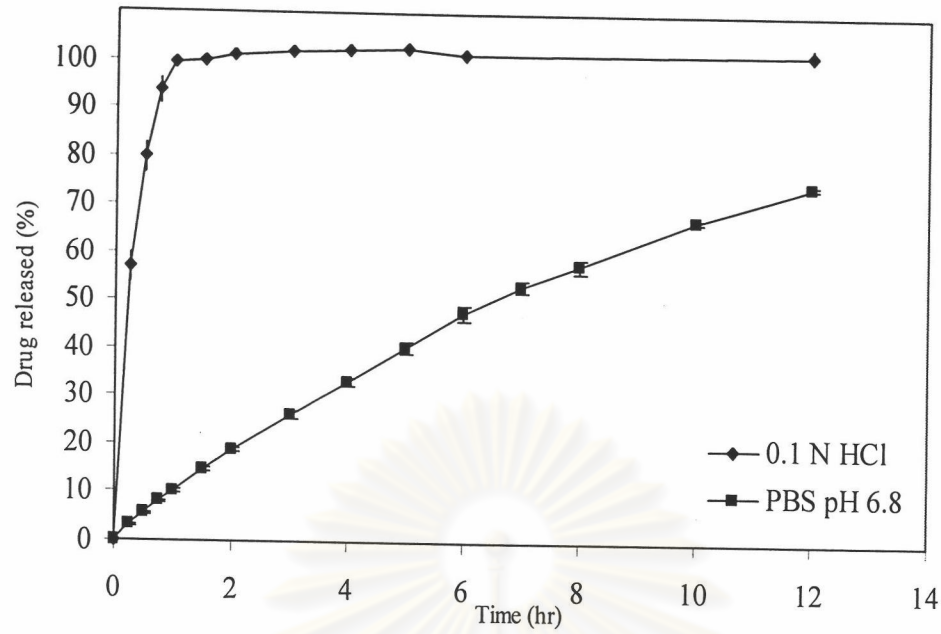


Figure 10 The release profiles of blank A matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

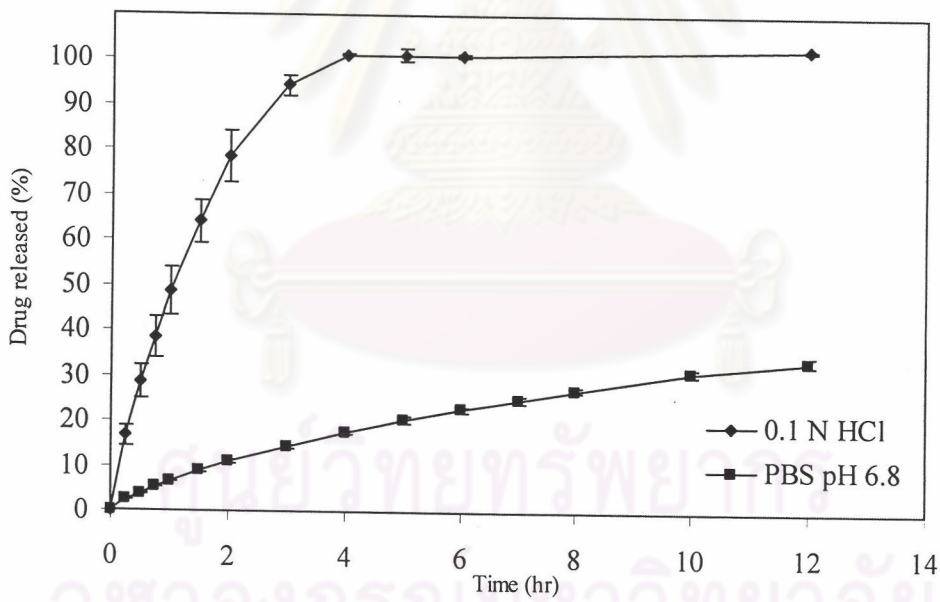


Figure 11 The release profiles of blank B matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

5.1.1.2 Effect of ionic strength of dissolution medium on drug release

The release profiles from blank matrices at different ionic strengths of the dissolution medium are shown in Figures 12-13. The blank A and B matrices were investigated for drug releases in deionized water and 0.2 M sodium chloride solution corresponding to the ionic strengths of 0 and 0.2, respectively. For both blank A and B matrices, the release profiles at different ionic strengths were similar. They were sustained over 12 hours. The reason for this finding might be explained in terms of the solubility of acyclovir in these media. As the result from drug solubility determination, the solubilities of acyclovir at different ionic strengths were apparently similar. Therefore, the influence of ionic strength of dissolution medium on drug release profile was not observed. On the other hand, the sustained release property of blank matrices was probably due to the low solubility of acyclovir in deionized water and 0.2 M sodium chloride solution.

5.1.2 Effect of type of diluent on drug release

The blank matrices were tested at various pH values and ionic strengths of the dissolution medium. When the release profiles of blank A and B matrices in the same dissolution medium were compared, the drug releases from blank A matrices which contained lactose as diluent were faster than those from blank B matrices which contained dibasic calcium phosphate as diluent in all dissolution media as shown in Figures 14-15. From the data obtained, it was found that the solubility of the diluent played an important role on the drug release. Dibasic calcium phosphate was used as a water-insoluble excipient, whereas lactose was used as a water-soluble excipient. Therefore, when the matrices were immersed in the dissolution medium, lactose in the matrices readily dissolved which led to pore generation in the matrices. Consequently, the dissolution medium could penetrate into the matrices and the drug could readily dissolve and diffuse out from the matrices.

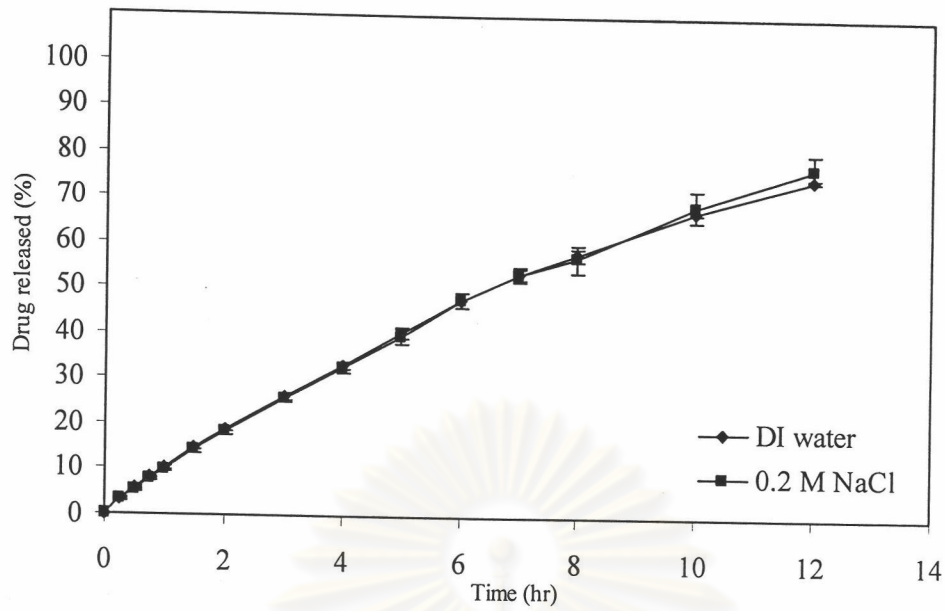


Figure 12 The release profiles of blank A matrices in deionized water (DI water) and 0.2 M sodium chloride solution (0.2 M NaCl)

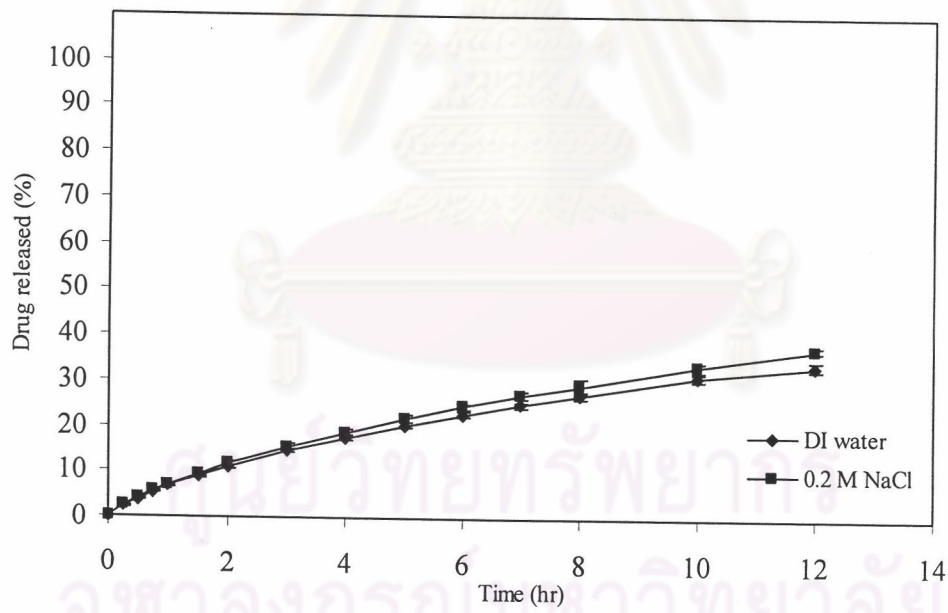


Figure 13 The release profiles of blank B matrices in deionized water (DI water) and 0.2 M sodium chloride solution (0.2 M NaCl)

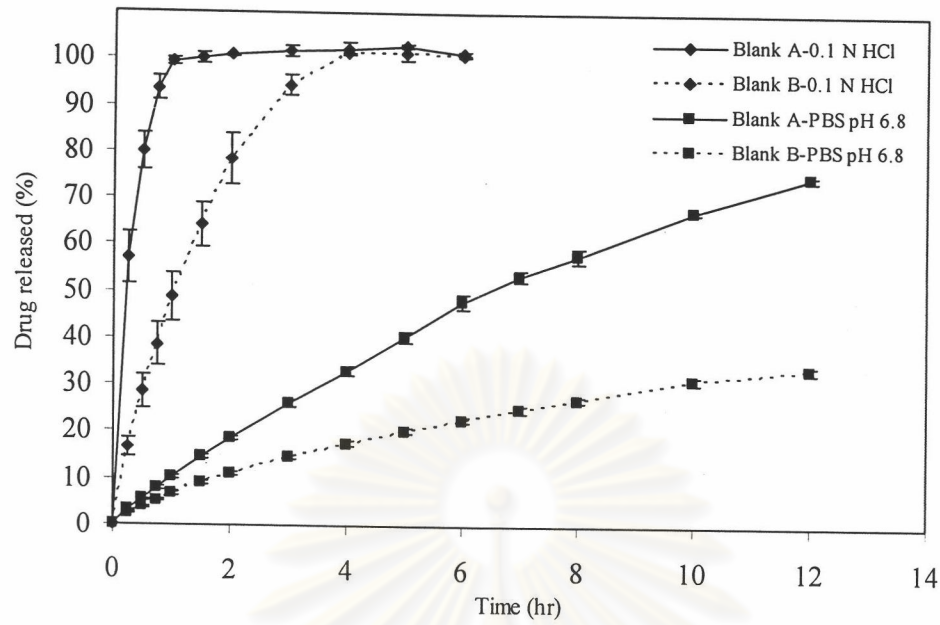


Figure 14 The release profiles of blank A and blank B matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

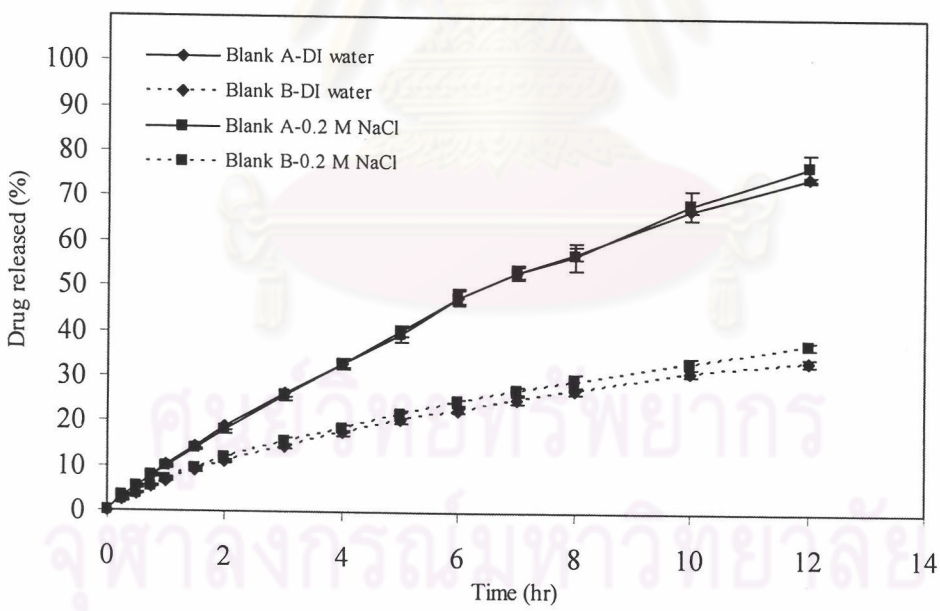


Figure 15 The release profiles of blank A and blank B matrices in deionized water (DI water) and 0.2 M sodium chloride solution (0.2 M NaCl)

Since dibasic calcium phosphate could only slowly dissolve in 0.1 N HCl solution, the drug release from blank A matrices in 0.1 N HCl solution was still faster than from blank B matrices.

5.2 Dissolution study of acyclovir matrices in dissolution media with different pH values

5.2.1 Effect of polymer concentration on drug release

The four hydrophilic polymers were used as release-regulating polymers in hydrophilic matrices. The polymer concentrations in the matrices containing HPMC, xanthan gum, sodium alginate or carbopol 934P as hydrophilic polymers were 10%, 15% and 20%. In each polymer concentration, matrices were composed of lactose or dibasic calcium phosphate as diluent. The drug release experiments were performed using 0.1 N HCl solution (pH 1.2) and phosphate buffer pH 6.8 solution (PBS pH 6.8) as dissolution media in order to simulate the pH in the gastro-intestinal tract.

5.2.1.1 HPMC matrices

The releases profiles of lactose matrices in 0.1 N HCl solution and PBS pH 6.8 (see Figures 16 and 18) and dibasic calcium phosphate matrices in 0.1 N HCl solution (see Figure 17) clearly illustrate that the drug release rate was influenced by the polymer concentration of the matrices. An increase in the polymer concentration exhibited a decline in the drug release rate.

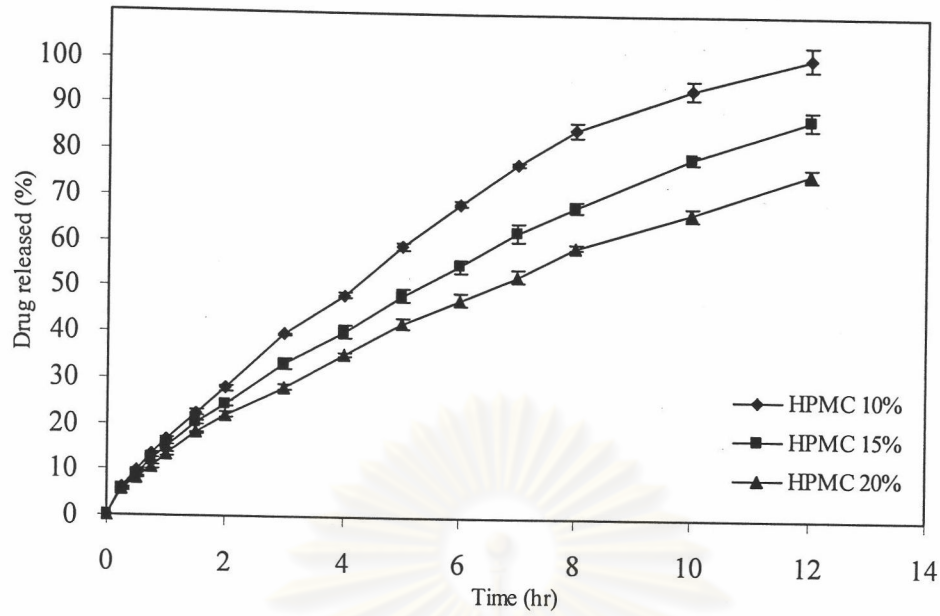


Figure 16 The release profiles of matrices containing lactose and hydroxypropyl methylcellulose (HPMC) in various amounts in 0.1 N HCl solution

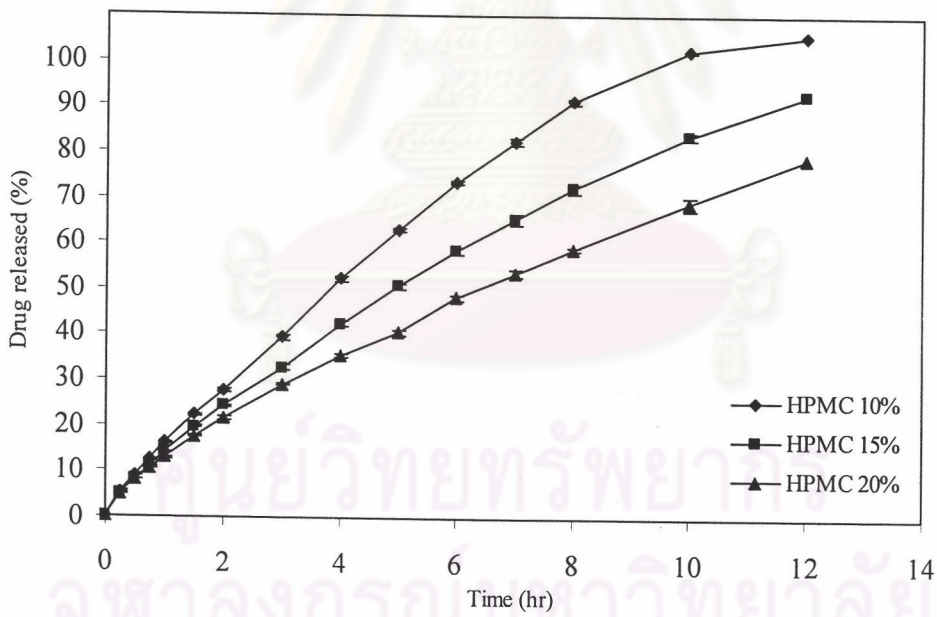


Figure 17 The release profiles of matrices containing dibasic calcium phosphate and hydroxypropyl methylcellulose (HPMC) in various amounts in 0.1 N HCl solution

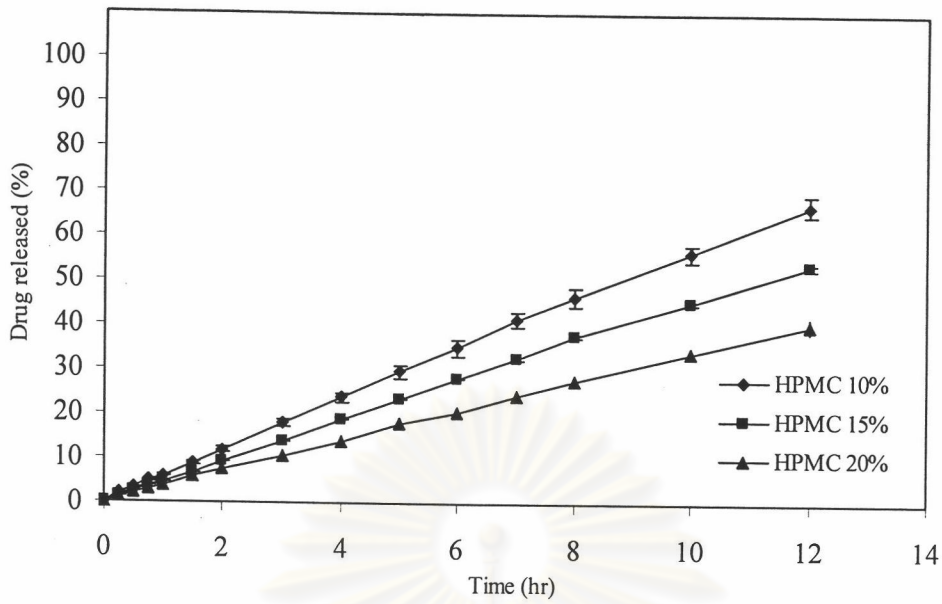


Figure 18 The release profiles of matrices containing lactose and hydroxypropyl methylcellulose (HPMC) in various amounts in phosphate buffer pH 6.8 solution

This could also be shown by plotting the relative dissolution times (RDT values) against the percentage of polymer in the formulation (see Figures 19-20). The higher RDT value indicates the slower drug release. Conversely, The lower RDT value indicates the faster drug release. The RDT values of lactose matrices in 0.1 N HCl solution and PBS pH 6.8 (see Figure 19) and dibasic calcium phosphate matrices in 0.1 N HCl solution (see Figure 20) increased with increasing percentages of the polymer in the matrices. This result indicated that the drug release of matrices composed of lower percentage of the polymer was faster than that of matrices containing higher polymer concentration.

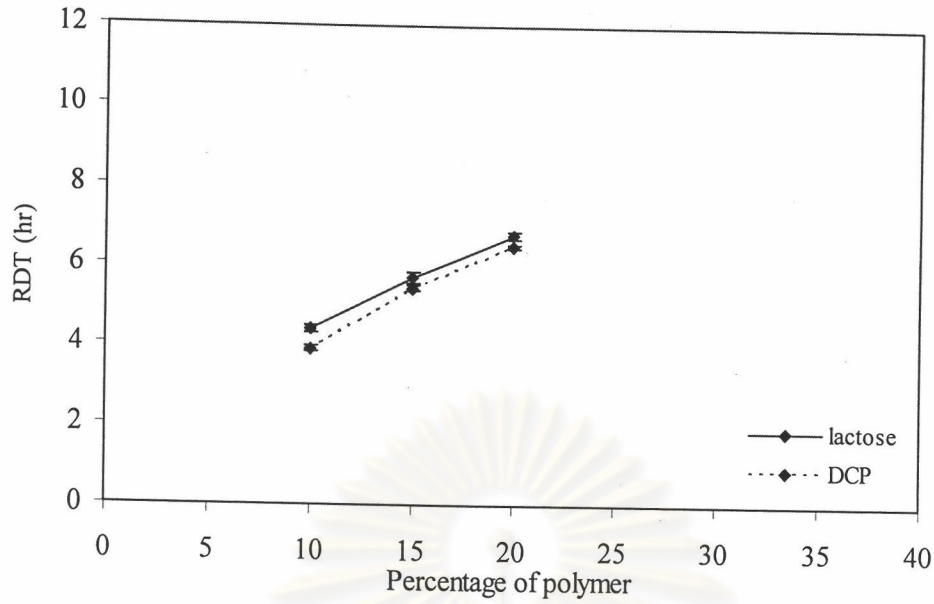


Figure19 The relationship between the relative dissolution time (RDT value) and the percentage of hydroxypropyl methylcellulose contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in 0.1 N HCl solution

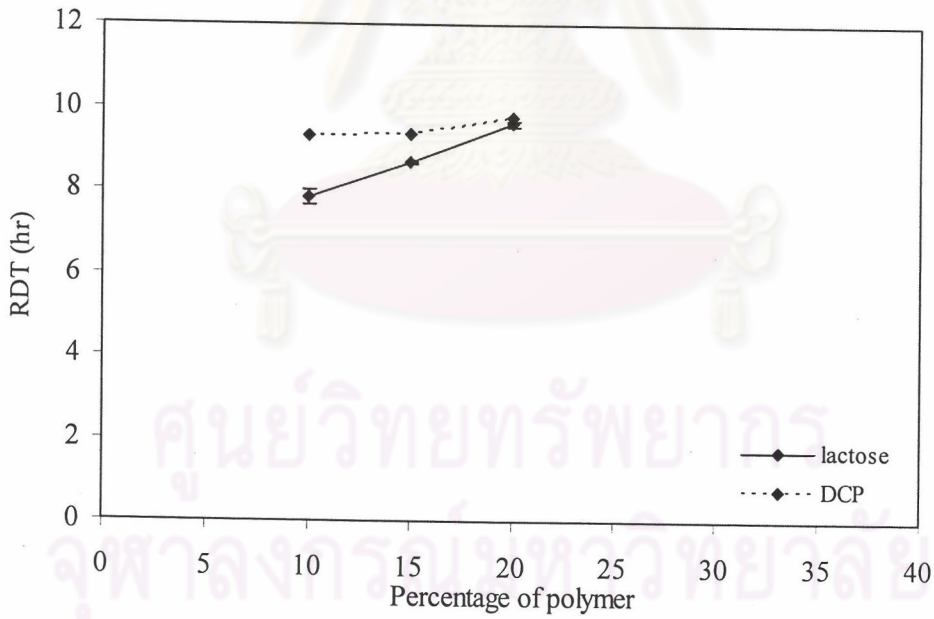


Figure 20 The relationship between the relative dissolution time (RDT value) and the percentage of hydroxypropyl methylcellulose contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in phosphate buffer pH 6.8 solution

This finding agreed with previous studies by Ford et al. (1985), Mitchell et al. (1993) and Velesco et al. (1999). They studied the effect of HPMC content on the drug release rate. Although their studies used different test drugs and grades of HPMC, their results were consistent. They concluded that an increase in polymer concentration resulted in a decrease in drug release rate. This might be due to an augmentation of polymer chain entanglement in hydrated gel layer around the matrices comprising higher HPMC content. This resulted in a more concentrated gel and increased gel tortuosity. Consequently, the diffusion path became more convoluted and thus the diffusion rate decreased. Moreover, a concentrated or strong protective gel-barrier would be less susceptible to erosion, resulting in decreased drug release. This finding pointed out that the physical and mechanical properties of the surface-hydrated gelatinous barrier played an important role in overall drug release rate (Talukdar et al., 1996).

In case of drug release profiles of matrices prepared using dibasic calcium phosphate as diluent in phosphate buffer pH 6.8 solution (see Figure 21), the slower drug release rate was observed. This result could be explained in terms of drug and diluent solubilities in the dissolution medium. Acyclovir was slightly soluble in phosphate buffer pH 6.8 solution (2.73 mg/ml; see Table 8). Moreover, dibasic calcium phosphate did not dissolve in PBS pH 6.8. Therefore, the release profiles of matrices using dibasic calcium phosphate as diluent in phosphate buffer pH 6.8 solution displayed slow drug release rate. At 12 hours, the accumulated release was only about 40%.

Polymer concentration had practically no effect on drug release rate in some cases. Figure 21 is an indication that the drug and diluent solubilities played a major role in controlling drug release, whereas the polymer concentration played a minor role. The independence of drug release rate on polymer concentration could be noted in the range of concentration studied. As shown in Figure 20, this finding was also reflected in the RDT value.

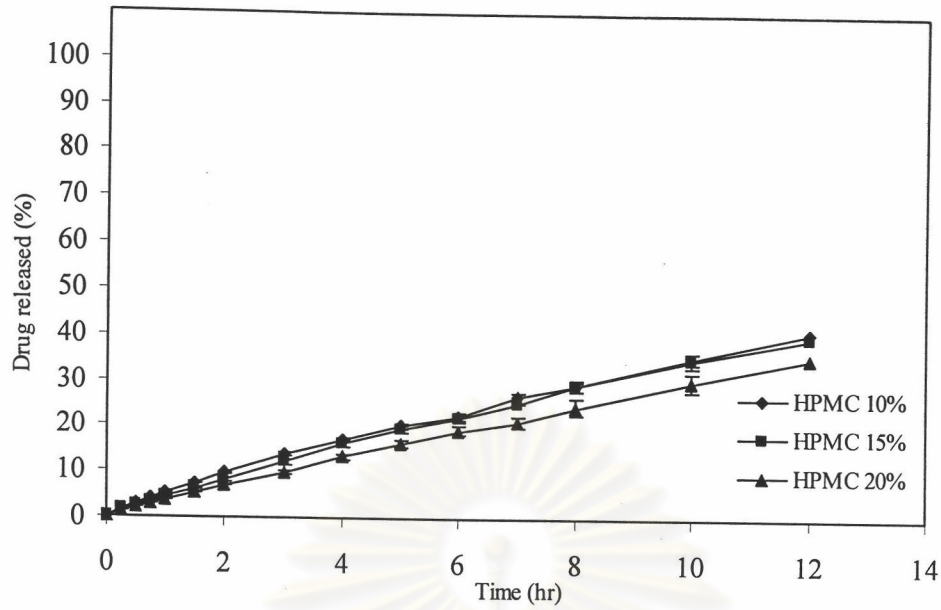


Figure 21 The release profiles of matrices containing dibasic calcium phosphate and hydroxypropyl methylcellulose (HPMC) in various amounts in phosphate buffer pH 6.8 solution

5.2.1.2 Xanthan gum matrices

For the xanthan gum matrices, the release profiles of matrices comprising lactose and dibasic calcium phosphate as diluent in dissolution media with different pH values are displayed in Figures 22-25, respectively.

In case of using 0.1 N HCl solution as the dissolution medium, an increase in the polymer concentration trended a decrease in the drug release rate (see Figures 22-23). The release profiles of matrices containing 10% polymer showed superior release profiles, whereas the release profiles of matrices containing 15% and 20% polymer were comparable. This result was an indication that the influence of polymer concentration on drug release rate was limited up to the concentration of 15%. The further increase in polymer concentration had little effect on drug release. This pointed out that matrices containing 15% polymer had a strong enough gel barrier to sustain drug release.

The effect of xanthan gum concentration on the relative dissolution time (RDT value) of matrices in 0.1 N HCl solution is also displayed in Figure 26. The matrices containing 10% polymer displayed the lower RDT value, while the RDT values of 15% and 20% polymer content matrices were apparently similar.

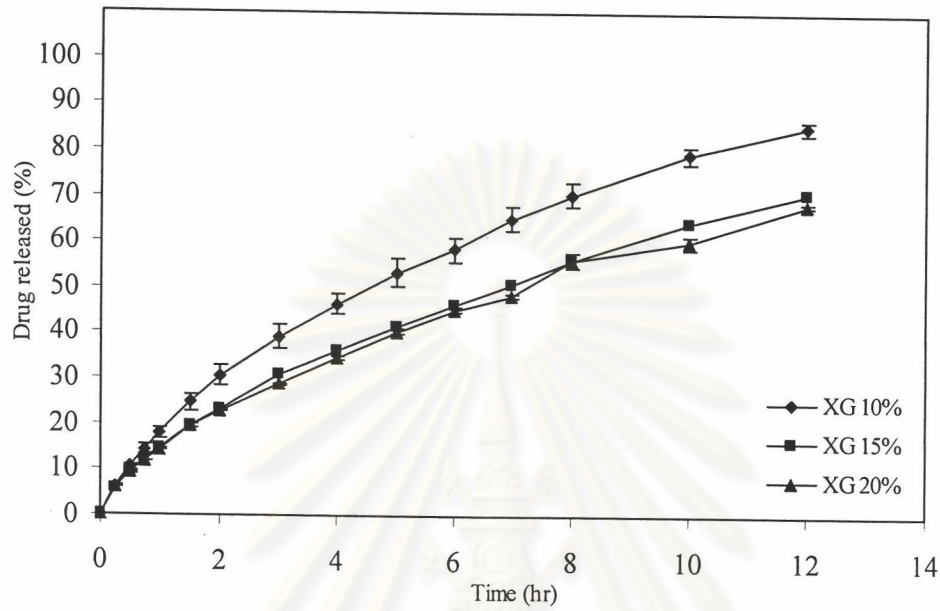


Figure 22 The release profiles of matrices containing lactose and xanthan gum (XG) in various amounts in 0.1 N HCl solution

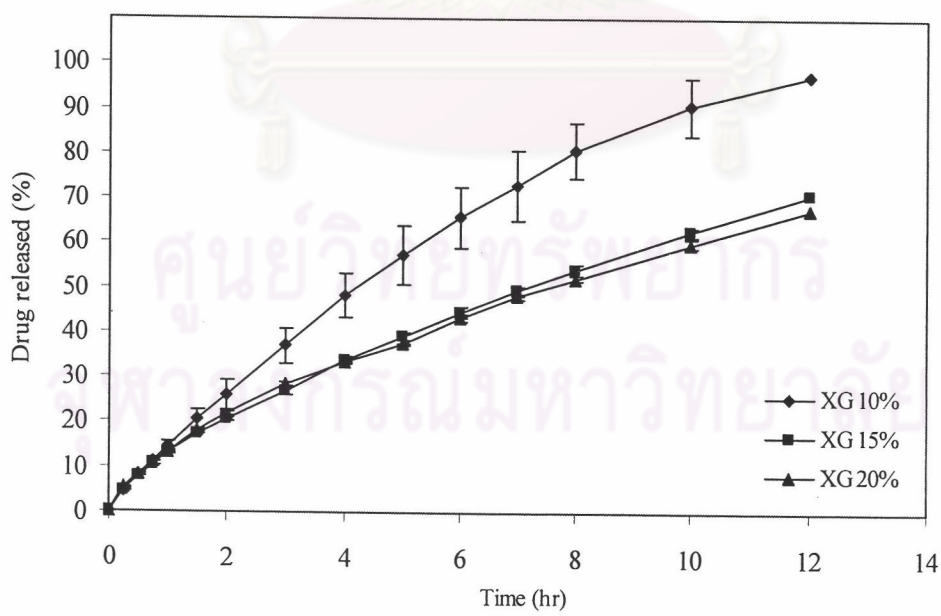


Figure 23 The release profiles of matrices containing dibasic calcium phosphate and xanthan gum (XG) in various amounts in 0.1 N HCl solution

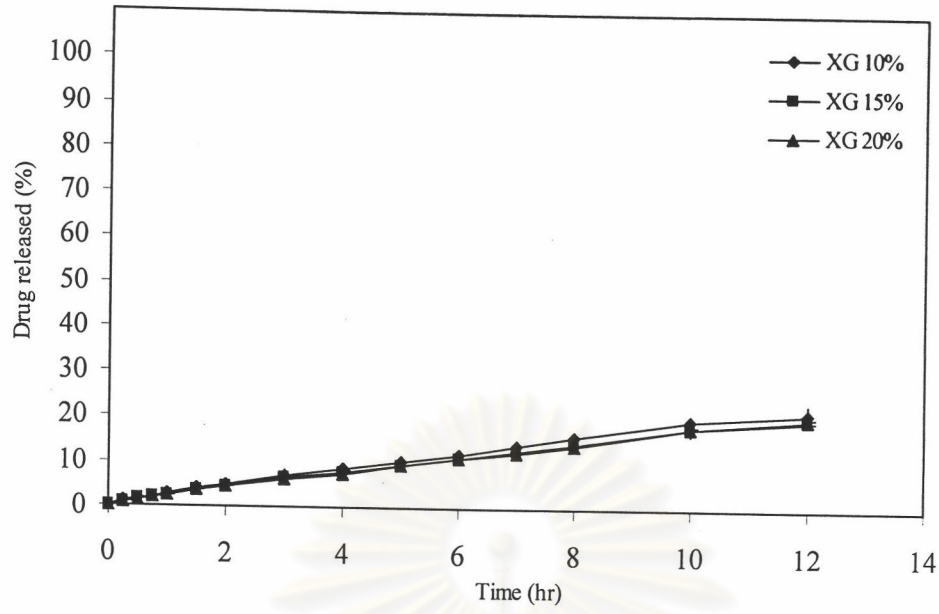


Figure 24 The release profiles of matrices containing lactose and xanthan gum (XG) in various amounts in phosphate buffer pH 6.8 solution

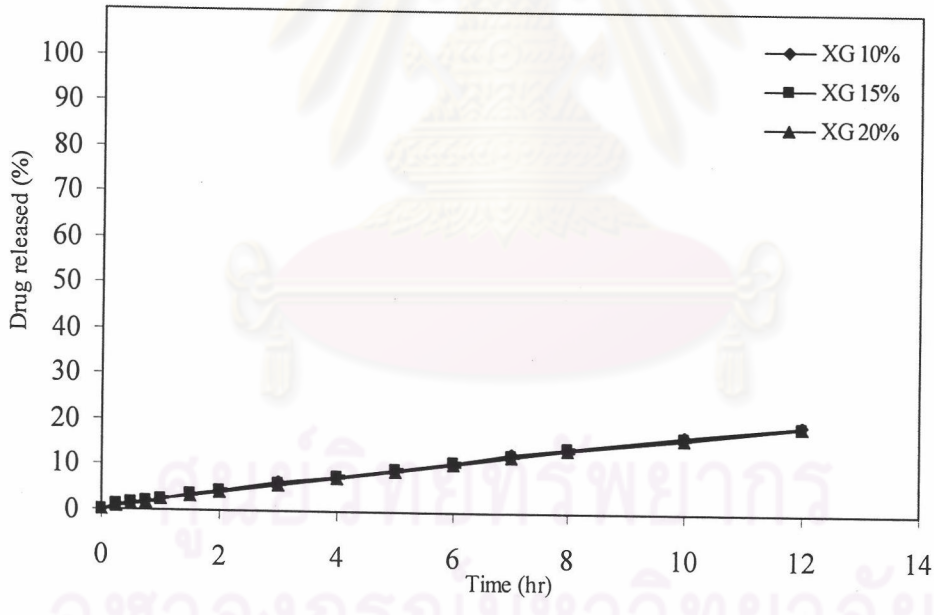


Figure 25 The release profiles of matrices containing dibasic calcium phosphate and xanthan gum (XG) in various amounts in phosphate buffer pH 6.8 solution

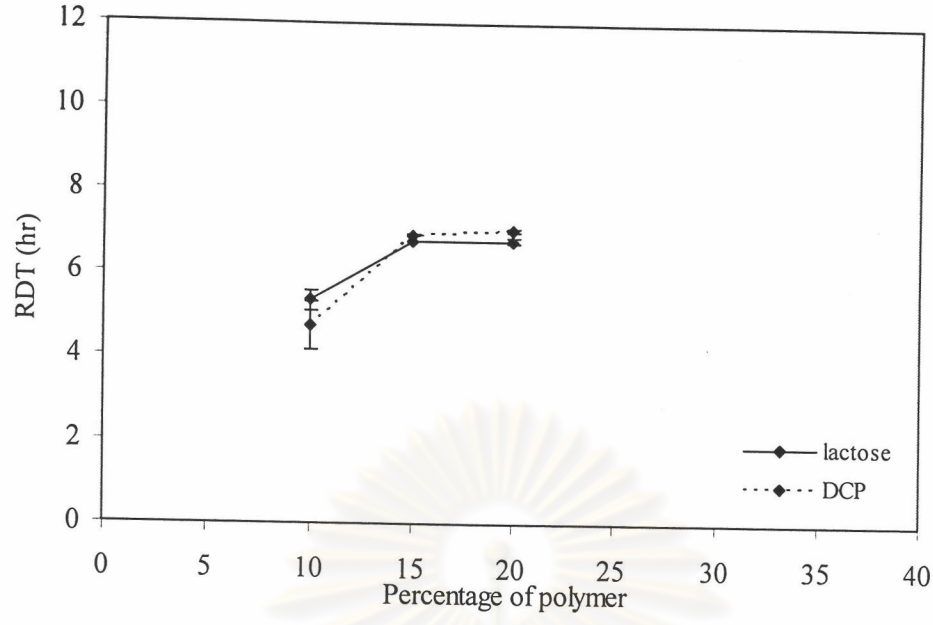


Figure 26 The relationship between the relative dissolution time (RDT value) and the percentage of xanthan gum contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in 0.1 N HCl solution

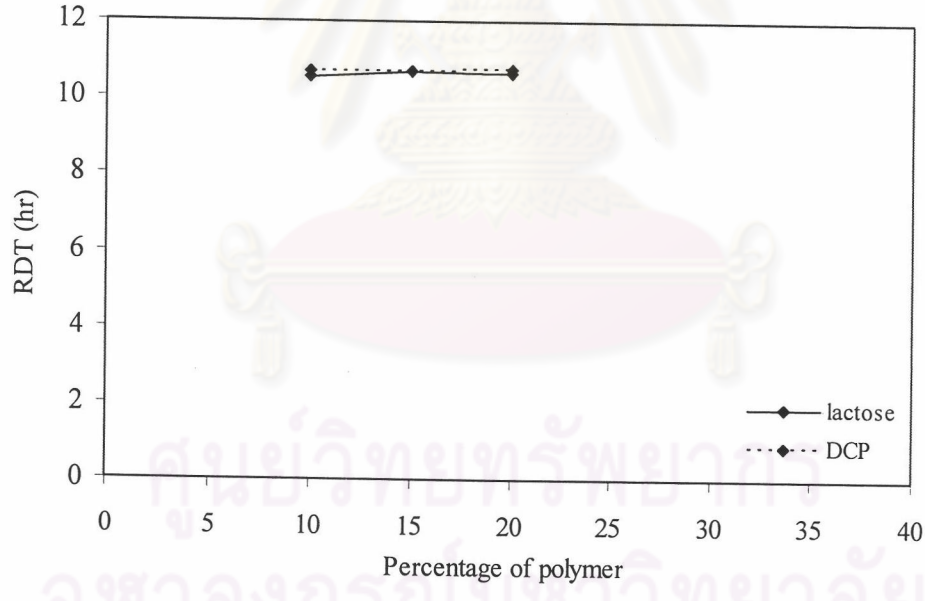


Figure 27 The relationship between the relative dissolution time (RDT value) and the percentage of xanthan gum contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in phosphate buffer pH 6.8 solution

As presented in Figures 24-25, the drug release rates of xanthan gum composed of lactose or dibasic calcium phosphate as diluent in PBS pH 6.8 were very slow. The maximum amount of accumulated drug release at 12 hours was only about 20%. This result might be caused by the important role of swelling property of the xanthan gum matrices and the viscosity of the xanthan gum gel around the matrices.

Visual observation of matrices during dissolution test revealed that xanthan gum matrices had highly swellable property. This could be confirmed by the matrices swelling determination, which was discussed in the next topic. More swelling of the matrix, the longer the diffusional pathlength required for the drug to came out, which resulted in decreasing drug release rate (Talukdar et al., 1996). Moreover, as in the result of viscosity measurement in this study, the viscosity of xanthan gum solution in PBS pH 6.8 was markedly different from other polymer solutions. The viscosity of xanthan gum solution was the highest. This indicated that the xanthan gum matrices were less susceptible to erosion, which caused a decrease in drug release rate. In addition, the drug solubility is one of the important factors that affect drug release. As the result of this study, acyclovir was slightly soluble in PBS pH 6.8 which led to decrease drug release rate. Consequently, the highly swellable property of xanthan gum matrices, the formation of the stronger swollen gel layer around the matrices, and the poor solubility of the drug in the dissolution medium caused very slow drug release rate of xanthan gum matrices in PBS pH 6.8.

On the other hand, the polymer concentration had practically no effect on drug release rate of xanthan gum matrices in phosphate buffer pH 6.8 solution regardless of the diluent used, as illustrated in Figures 24-25. An increase in drug release rate did not occur with decreasing polymer concentrations in the matrices. This finding indicated that the properties of hydrated gel layer around the matrices and the drug solubility in dissolution medium played the major role in regulating drug release. This might obscure the effect of polymer concentration on drug release rate. Therefore, no influence of polymer concentration on drug release rate was occurred. As shown in Figure 27, the independence of polymer content on RDT value could support the obtained result.

5.2.1.3 *Sodium alginate matrices*

The release profiles of sodium alginate matrices containing lactose or dibasic calcium phosphate as diluent in 0.1 N HCl and PBS pH 6.8 are shown in Figures 28-31. The relationship between the relative dissolution time (RDT value) and the percentage of sodium alginate contained in each formulation in various dissolution media are displayed in Figures 32-33.

Since the pK_a of alginic acid is about 3.4 - 4.4, sodium alginate is rapidly converted to the insoluble alginic acid in 0.1 N HCl solution (pH 1.2) (Hodsdon et al., 1995). However, even under acidic condition, some of the polymer has dissolved and appeared to form an interstitial glue between the poorly hydrated regions. This structure can explain why sodium alginate matrices form a coherent surface barrier layer which hold together, in an environment in which disintegration can otherwise be expected (Hodsdon et al., 1995). As shown in Figures 28 and 29 an increase in drug release rate seemed to occur with decreasing polymer concentrations. In consideration of RDT value, Figure 32 illustrates that an increase in percentage of polymer in the formulation caused a little increase in RDT value. The reason for this finding might be due to the rapid conversion of sodium alginate to alginic acid in 0.1 N HCl solution. The insoluble alginic acid appeared to impede the penetration of the dissolution medium into the matrices. Consequently, the higher polymer concentration led to the lower medium penetration into the matrices, resulted in decreasing drug release rate.

In case of drug release in PBS pH 6.8, the release profiles are shown in figures 30-31. When using lactose as diluent, the influence of polymer concentration on drug release rate could be noted as shown in Figure 30. An increase in polymer concentration exhibited a decrease in drug release rate. This could be confirmed by an increase in RDT value with increasing amount of polymer in the matrices containing lactose as diluent (see Figure 33). The decline in drug release rate of matrices with higher polymer content was probably due to the more concentrated gel and the augmentation of polymer chain entanglement of hydrated gel layer around the matrices. However, the release profiles of matrices with dibasic calcium phosphate as

diluent were similar during the initial 3 hours of the dissolution test but during the 3rd and the10th hours, the drug release from matrices containing 15% and 20% polymer graduately increased over that from matrices containing 10% polymer, as shown in Figure 31. This result might be explained by visual observation over the course of dissolution test that the matrices containing 10% polymer could adhere to the perforated plates at the bottom of the dissolution vessels over the dissolution period, whereas the matrices containing 15% and 20% polymer could adhere to the perforated plated at initial 3 hours of dissolution test. After that, the movement of these matrices around the perforated plates occurred. Therefore, the attrition of the matrices caused by the movement of the matrices around the perforated plates resulted in an increase in drug release rate of the matrices comprising15% and 20% polymer. This resulted in the higher release profiles of the matrices containing 15% and 20% sodium alginate over that of matrices containing 10% polymer at the intermediate and last portions of the dissolution profile. In the consideration of RDT value, the higher RDT value of matrices containing 10% polymer was observed, while the RDT values of the matrices containing 15% and 20% polymer content matrices were similar (see Figure 33).

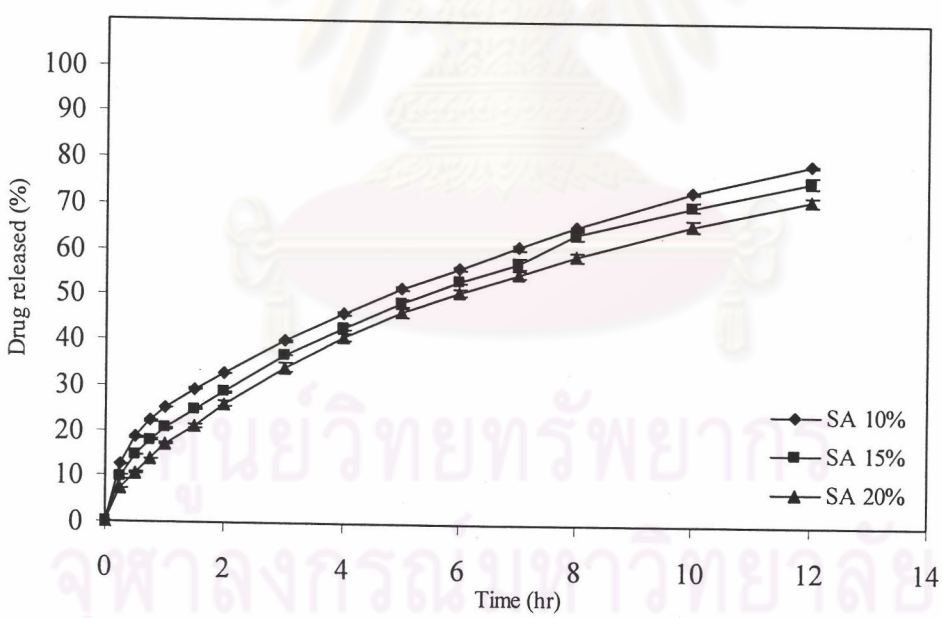


Figure 28 The release profiles of matrices containing lactose and sodium alginate (SA) in various amounts in 0.1 N HCl solution

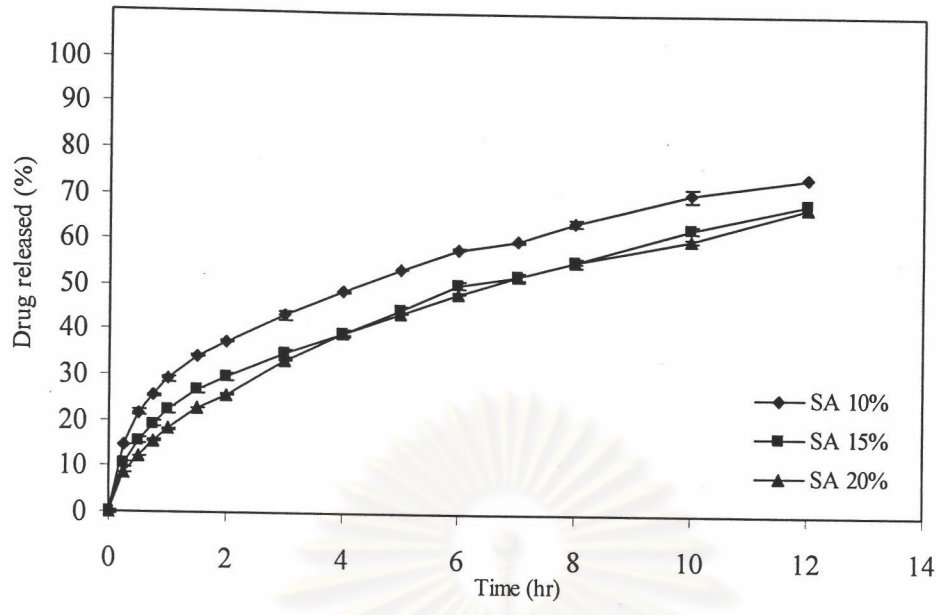


Figure 29 The release profiles of matrices containing dibasic calcium phosphate and sodium alginate (SA) in various amounts in 0.1 N HCl solution

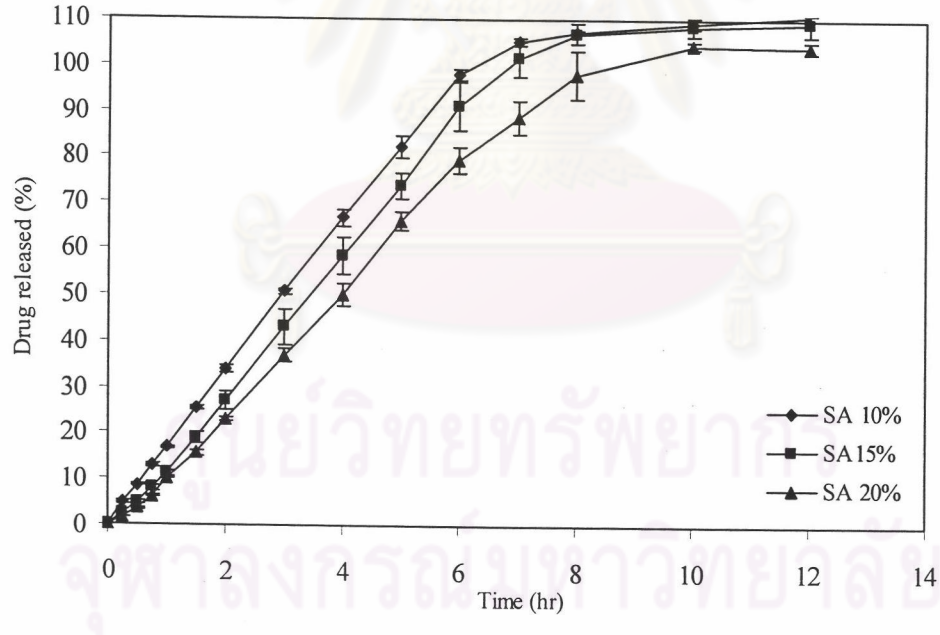


Figure 30 The release profiles of matrices containing lactose and sodium alginate (SA) in various amounts in phosphate buffer pH 6.8 solution

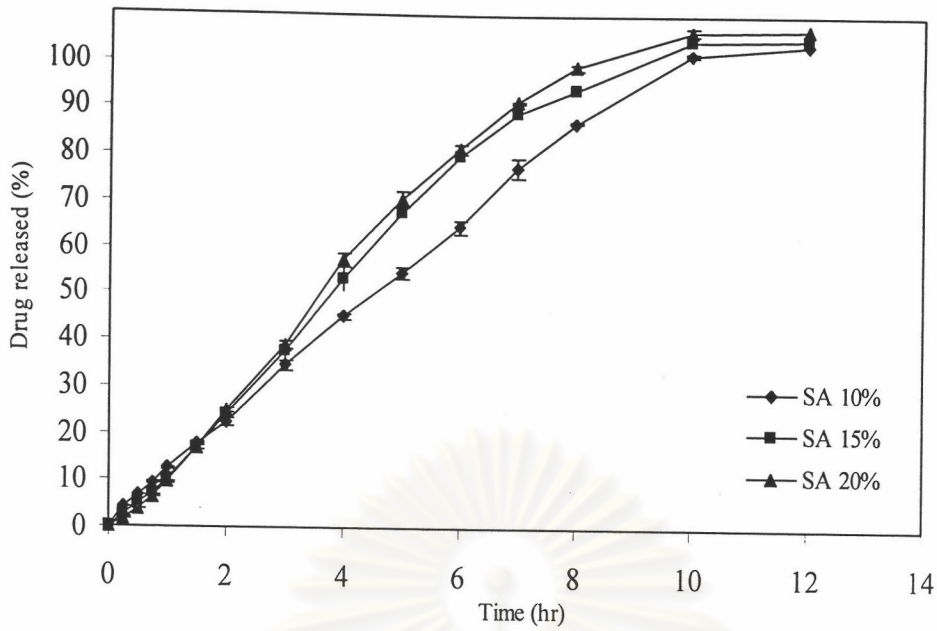


Figure 31 The release profiles of matrices containing dibasic calcium phosphate and sodium alginate (SA) in various amounts in phosphate buffer pH 6.8 solution

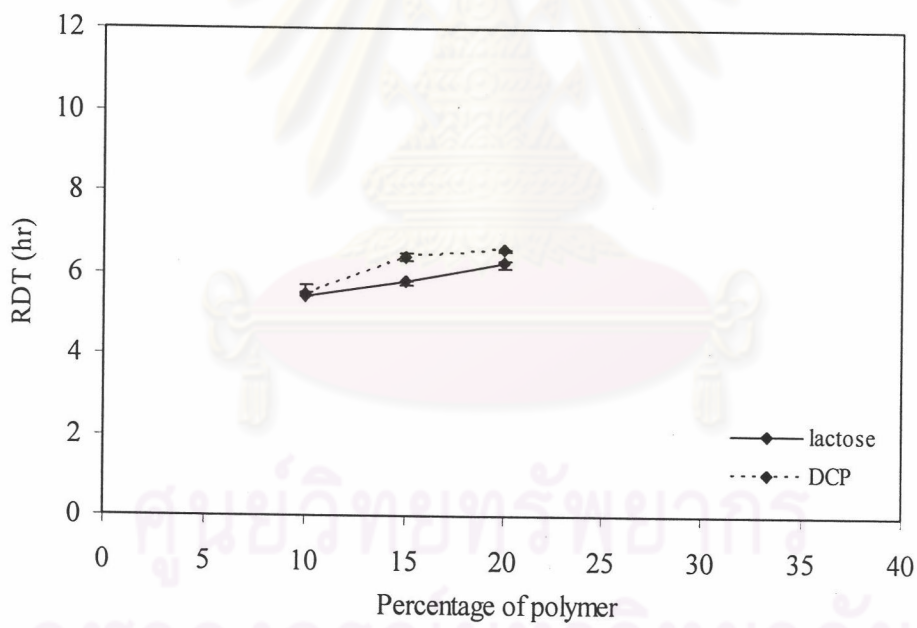


Figure 32 The relationship between the relative dissolution time (RDT value) and the percentage of sodium alginate contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in 0.1 N HCl solution

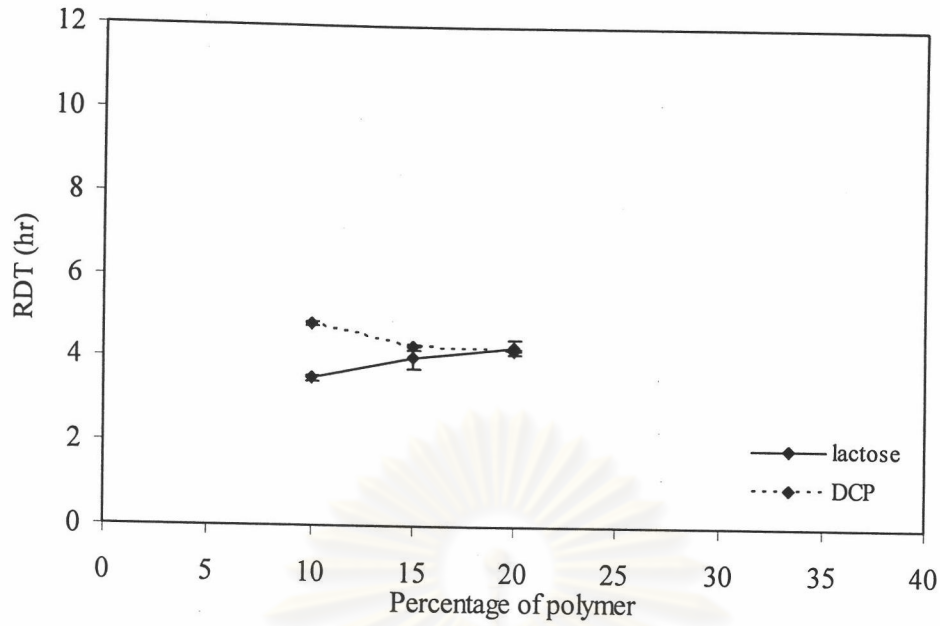


Figure 33 The relationship between the relative dissolution time (RDT value) and the percentage of sodium alginate contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in phosphate buffer pH 6.8 solution

5.2.1.4 Carbopol 934P matrices

The releases profiles of matrices containing carbopol 934P with lactose or dibasic calcium phosphate as diluent in 0.1 N HCl solution and PBS pH 6.8 are shown in Figures 34-37.

As seen in Figures 34-37, the matrices containing carbopol 934P as release–regulating polymer did not produce sustained releases. The matrices completely dissolved within about 1-2 hours. By visual observation during the dissolution test, the matrices exploded immediately when they exposed to the dissolution medium. Since the pK_a of carbopol is about 6.0, it is insoluble in 0.1 N HCl solution (pH 1.2). However, it can dissolve and swell in PBS pH 6.8 (Perez-Marcos et al., 1996).

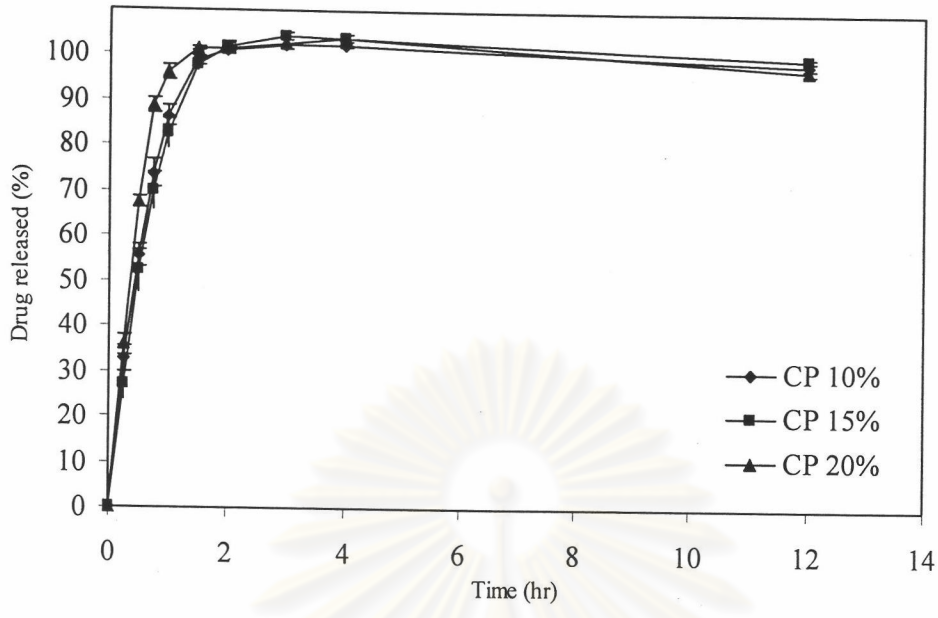


Figure 34 The release profiles of matrices containing lactose and carbopol 934P (CP) in various amounts in 0.1 N HCl solution

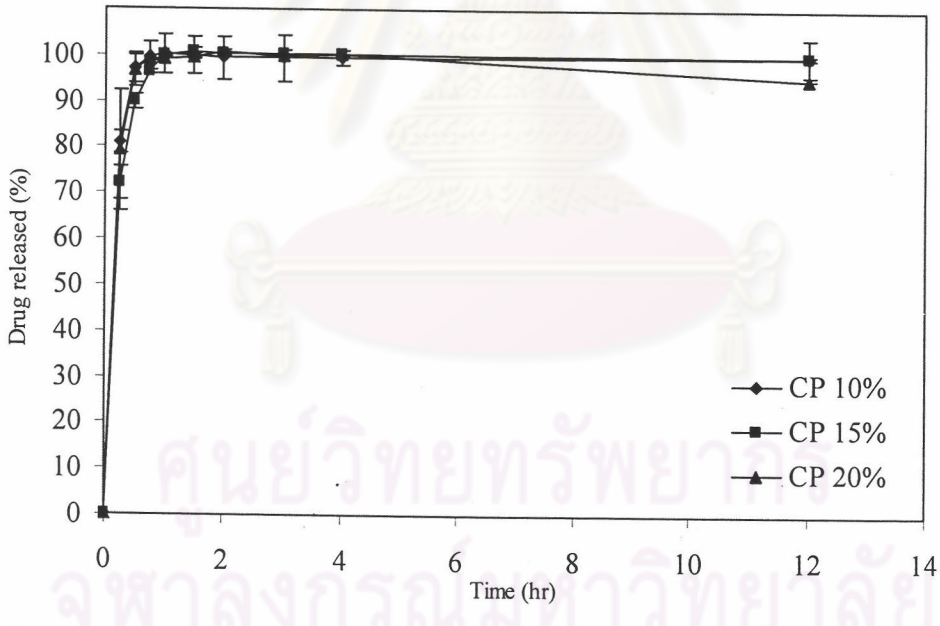


Figure 35 The release profiles of matrices containing dibasic calcium phosphate and carbopol 934P (CP) in various amounts in 0.1 N HCl solution

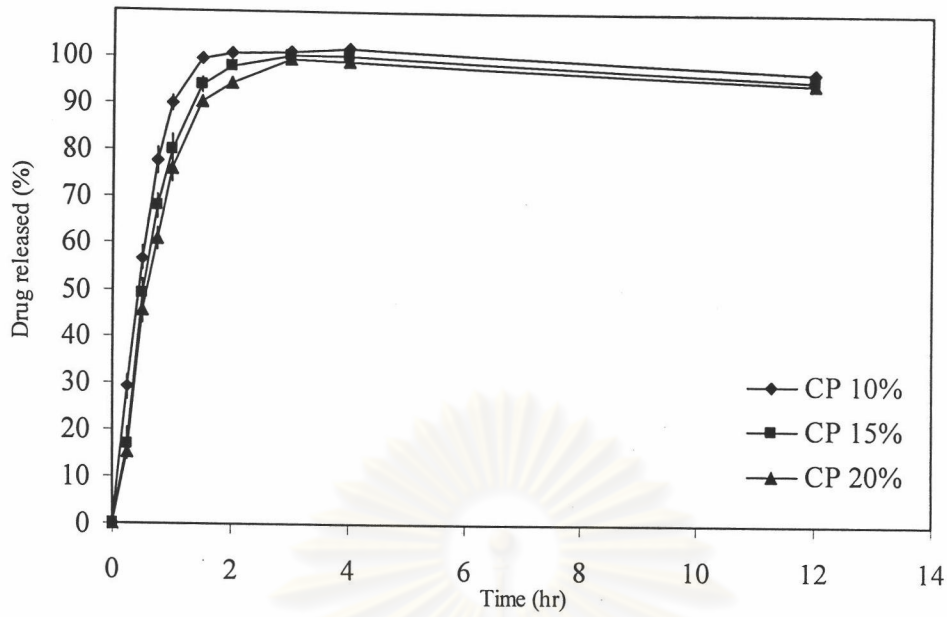


Figure 36 The release profiles of matrices containing lactose and carbopol 934P (CP) in various amounts in phosphate buffer pH 6.8 solution

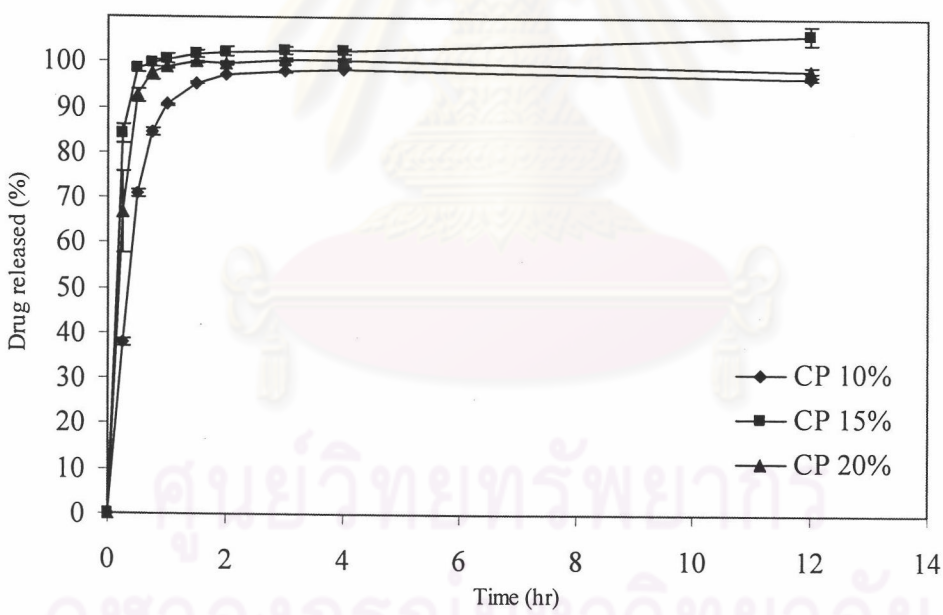


Figure 37 The release profiles of matrices containing dibasic calcium phosphate and carbopol 934P (CP) in various amounts in phosphate buffer pH 6.8 solution

Therefore, the carbopol 934P matrices could not form the protective gel barrier when immersed in 0.1 N HCl solution. In contrary, they had ability to produce the gelatinous barrier around them in PBS pH 6.8. Moreover, as the result of viscosity measurement, the viscosities of carbopol 934P and HPMC solutions in phosphate buffer pH 6.8 solution were comparable (see Figure 8). This result indicated that the strength of protective gel barrier around the matrices should be strong enough to sustain drug release. Nevertheless, the matrices rapidly eroded when exposed to both dissolution media. This result pointed out that although the matrices had ability to produce the protective gel barrier, they lost shape and integrity rapidly during the dissolution test. However, the release particles in PBS pH 6.8 did slowly gel, which was observed visually. This finding indicated that the polymer hydration had not been prevent but merely retarded. This demonstrated how essential the rapid production of a gel around the tablet was in maintaining the integrity of the matrices.

The rapid explosion of the matrices might be due to the relative lack of polymer in the matrices. At such low quantities of carbopol 934P, there were likely to be areas where there was an absence of polymer throughout the matrices. Water would enter into the inner layers of the matrices through the polymer-poor areas at the surface and would hydrate the inner layers . Because the protective gel surrounding the matrices took a finite time to form, water would continue to enter into the inner layers of the matrices before the protective gel coat could be completely formed. The pressure caused by hydration of the inner layers would result in pores within the matrices which would eventually disintegrate or explode if the surface gel layer had not completely formed. If there is a sufficient quantity of polymer in the matrices, there will be fewer pores and a protective coat can form without water penetrating too far into the matrices (Mitchell et al., 1993). This result implied that the hydration rate of the polymer to form the protective gel barrier around the matrices played an important role in controlling drug release from the matrices, especially at the beginning of the release profile.

Consequently, in order to prepare the matrices that can produce sufficient sustained drug release, the increase in polymer concentration is necessary. Therefore, the use of carbopol 934P as retarding polymer is not suitable for matrices containing

high dose drug such as acyclovir. Since carbopol 934P matrices failed to produce sustained drug release, the influence of other factors on drug release was not studied and discussed.

5.2.2 The effect of type of diluent on drug release

Lactose and dibasic calcium phosphate are commonly used as diluents in tablet formulations. Lactose is used as water–soluble diluent, while the dibasic calcium phosphate is used as water insoluble-diluent. The effect of different diluents at the polymer levels of 10%, 15% and 20% on drug release from HPMC, xanthan gum and sodium alginate matrices were studies. The dissolution studies were performed using 0.1 N HCl solution and PBS pH 6.8 as the dissolution media.

5.2.2.1 The dissolution studies in 0.1 N HCl solution

a) HPMC matrices

The release profiles of HPMC matrices containing different diluents in 0.1 N HCl solution are represented in Figure 38. The influence of the type of diluent on drug release rate of low polymer containing (corresponding to high level of diluent) matrices could be observed. The drug release rate of dibasic calcium phosphate matrices was slightly faster than that of lactose matrices, especially during the last portion of dissolution profile. However, the type of diluent had practically no effect on drug release rate of high polymer containing matrices (corresponding to low level of diluent). For high polymer content matrices, the drug release profiles of lactose and dibasic calcium phosphate matrices were similar. This result indicated that the difference in drug release rate between lactose and dibasic calcium phosphate content matrices occurred only with matrices containing high level of diluent.

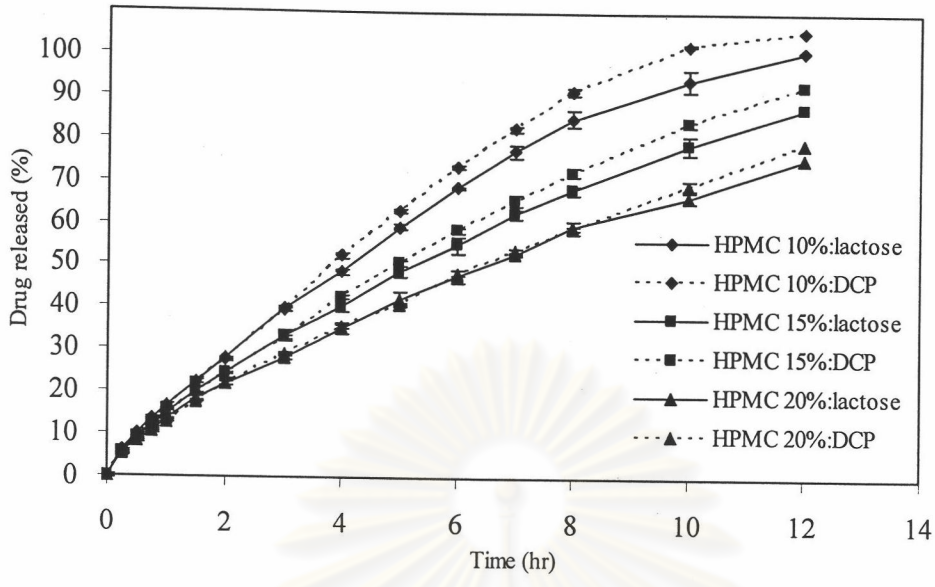


Figure 38 The release profiles of matrices containing lactose or dibasic calcium phosphate (DCP) and hydroxypropyl methylcellulose (HPMC) in various amounts in 0.1 N HCl solution

Lapidus and Lordi (1966) found that replacement of HPMC by either a soluble or insoluble diluent increased dissolution rate. Additionally, they concluded that only at high diluent level, there was difference in drug release between soluble and insoluble excipients. This can support the obtained result in this study in that the difference in drug release rate between lactose and dibasic calcium phosphate containing matrices was only observed at high diluent level. This study again agreed with previous study by Ford et al. (1987). They concluded that the difference in release rates between lactose and calcium phosphate replacement occurred only when matrices contained high levels of the diluents.

The effect of the type of diluent on drug release rate could be attributed to the different solubilities of the diluent in the dissolution medium. Lactose is water-soluble diluent and can dissolve in 0.1 N HCl solution. On the other hand, though dibasic calcium phosphate is water-insoluble diluent but it can slowly dissolve in 0.1 N HCl solution. This result agreed with the visual observation over the course the dissolution test that no particles of dibasic calcium phosphate were found in 0.1

N HCl, whereas the particles of dibasic calcium phosphate were found in phosphate buffer solution pH 6.8.

Both soluble and insoluble–diluents might cause the occurrence of non-uniformity of the gel layer around the matrices (Ford et al., 1987). In case of using dibasic calcium phosphate as diluent, when dissolution medium penetrated into the matrices, the insoluble dibasic calcium phosphate particles caused the discontinuous gel layer. Moreover, the erosion of the matrices occurred when dibasic calcium phosphate slowly dissolved. Therefore, an augmentation in the drug release rate appeared. Although lactose could also cause the non–uniform hydrated gel layer by the formation of water–filled pores or microvoids, the drug release from lactose-containing matrices was lower than that from dibasic calcium phosphate containing matrices. This might be attributed to the higher degree of matrix integrity appearing with matrices composed of lactose. The lower RDT values of dibasic calcium phosphate matrices supported the obtained result (see Figure 19).

b) xanthan gum matrices

As illustrated in Figure 39, the release profiles of matrices containing 15% and 20% polymer were similar. However, in case of matrices composed of 10% polymer, the drug release rate of dibasic calcium phosphate matrices were faster than that of lactose matrices, especially at the last portion of release profile. Moreover, the high standard deviation values of percent drug released were observed with dibasic calcium phosphate matrices containing 10% polymer.

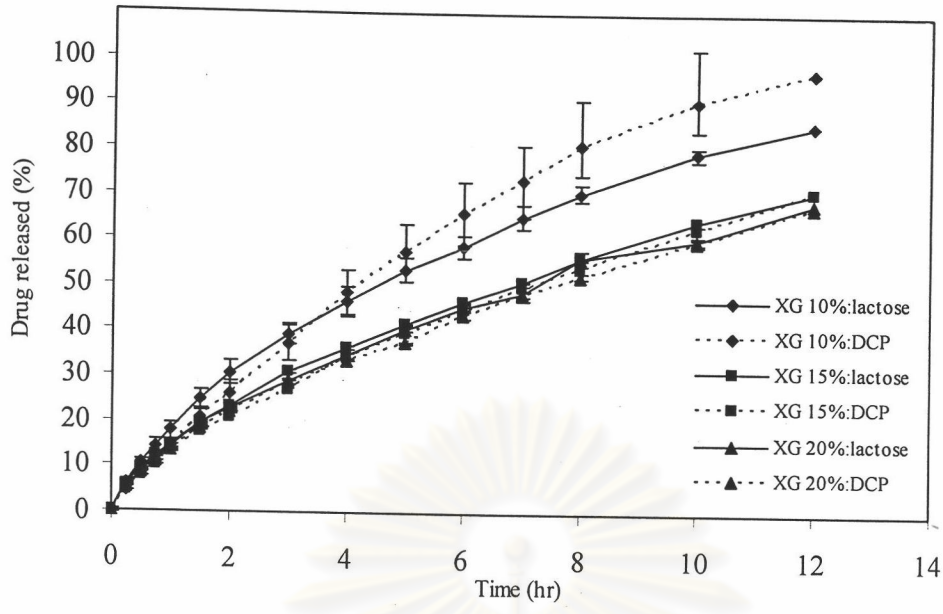


Figure 39 The release profiles of matrices containing lactose or dibasic calcium phosphate (DCP) and xanthan gum (XG) in various amounts in 0.1 N HCl solution

Nevertheless, by visual inspection over the course of dissolution test, the movement of the matrices around the perforated plates was observed with dibasic calcium phosphate matrices containing 10% polymer. This caused the attrition of the surface gel layer around the matrices that resulted in the higher drug release rate and standard deviation values of percent drug released. Consequently, the matrix erosion caused by the slow dissolution of dibasic calcium phosphate in 0.1 N HCl solution and the gel layer destruction might cause the faster drug release rate of dibasic calcium phosphate matrices containing 10% polymer.

c) Sodium alginate matrices

Since pK_a values of alginic acid range between 3.4 and 4.4, sodium alginate is rapidly converted to alginic acid in 0.1 N HCl solution (Hodsdon et al., 1995). Consequently, by visual inspection over the course of dissolution test, the continuous gel layer did not form around the sodium alginate matrices hydrated in 0.1 N HCl solution. Instead the porous, tough and rubbery texture was observed. The drug release rates of dibasic calcium phosphate matrices containing 15% and 20% polymer were slower than that of lactose matrices containing the same polymer concentration (see Figure 40).

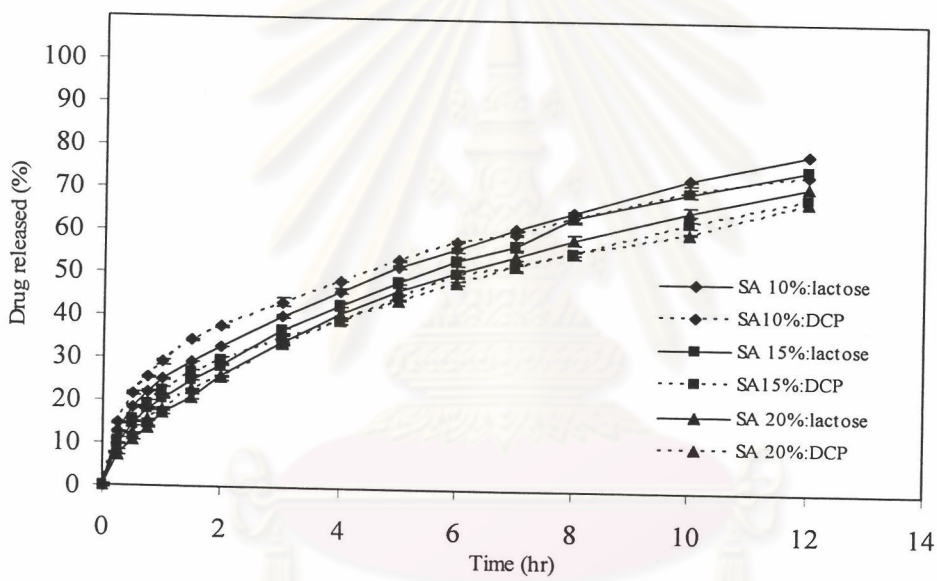


Figure 40 The release profiles of matrices containing lactose or dibasic calcium phosphate (DCP) and sodium alginate (SA) in various amounts in 0.1 N HCl solution

This finding might be the result of a raised pH within the matrices as a result of the slowly dissolved of dibasic calcium phosphate in the matrices which is a basic material. This resulted in some dissolution of sodium alginate within the matrices and then the formation of the interstitial glue between the poorly hydrated regions. The interstitial glue acted as a barrier of drug molecule to diffuse out. Therefore, the drug release rate of dibasic calcium phosphate matrices was slower than that of lactose matrices in 0.1 N HCl solution. The higher RDT value of dibasic calcium phosphate matrices, especially at 15% polymer level may support the obtained result (see Figure 32).

5.2.2.2 The dissolution studies in phosphate buffer pH 6.8 solution

a) HPMC matrices

The dependence of drug release rate on the type of diluent was observed, as shown in Figure 41. There was a great difference between lactose and dibasic calcium phosphate containing matrices release profiles in term of drug release rate from the low polymer content formulation, while little difference was observed with the high polymer content formulation. This result confirmed that the difference in drug release rate between the matrices using lactose or dibasic calcium phosphate as diluent were dominately observed only at high diluent levels (corresponding to low polymer content).

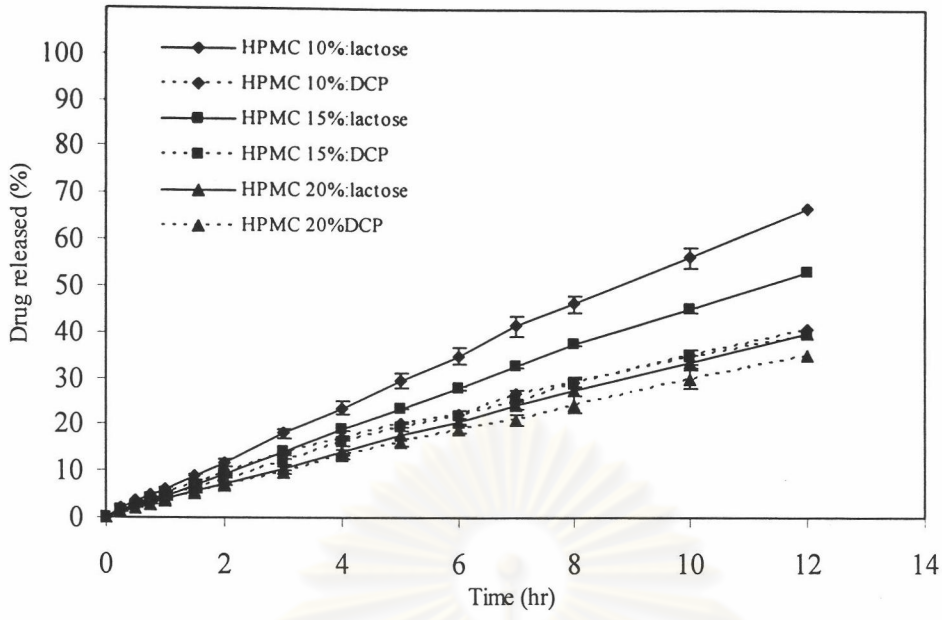


Figure 41 The release profiles of matrices containing lactose or dibasic calcium phosphate (DCP) and hydroxypropyl methylcellulose (HPMC) in various amounts in phosphate buffer pH 6.8 solution

lactose was higher than dibasic calcium phosphate matrices. This could result from the different solubilities of diluent in the dissolution medium. The lactose is used as water-soluble diluent which can dissolve in phosphate buffer pH 6.8 solution, while dibasic calcium phosphate is water-insoluble diluent. Therefore, the influence of lactose on drug release was attributed to the facilitation of dissolution medium penetration by increasing porosity of the matrices after hydration. Contrarily to lactose, the dibasic calcium phosphate did not dissolve in dissolution medium and thus caused a decrease in porosity of the hydrated matrices. Moreover, the visual observation of matrices during dissolution test revealed that higher degree of matrix integrity was observed with dibasic calcium phosphate matrices than with lactose matrices. Consequently, the matrices containing lactose displayed the higher erosion resulting in the higher drug release rate.

The obtained result could be supported by the relationship between percentage of polymer and the relative dissolution time (RDT value) of lactose and dibasic calcium phosphate matrices (see Figure 20). The marked lower RDT value of lactose

matrices than that of dibasic calcium phosphate matrices at 10% polymer level was observed. Moreover, when increasing the percentage of polymer in the formulation, the less difference in RDT value of lactose and dibasic calcium phosphate matrices was found. The RDT value of lactose and dibasic calcium phosphate matrices containing 20% polymer were comparable.

b) Xanthan gum matrices

Unexpectedly for xanthan gum matrices, no difference in drug release rate between lactose and dibasic calcium phosphate matrices was observed despite the solubilities of these diluents were different (see Figure 42). At 10%, 15% and 20% polymer levels, the RDT values of lactose and dibasic calcium phosphate matrices were similar, as presented in Figure 27. This finding indicated that the solubility of diluent played a minor role in controlling drug release from xanthan gum matrices in PBS pH 6.8. The major factors regulating drug release might be the swelling property of the matrices, the strength of the gel barrier around the matrices and the solubility of the drug in dissolution medium, as previously mentioned in section 5.2.1.2.

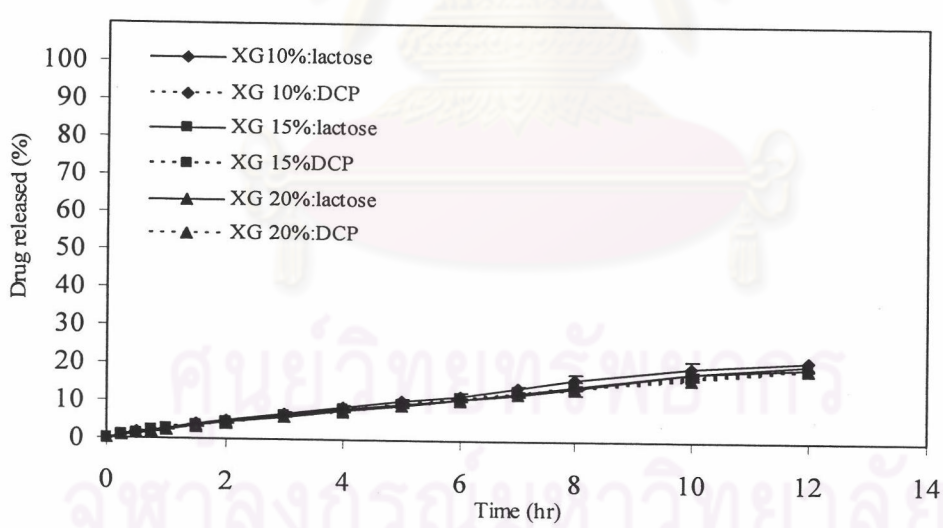


Figure 42 The release profiles of matrices containing lactose or dibasic calcium phosphate (DCP) and xanthan gum (XG) in various amounts in phosphate buffer pH 6.8 solution

c) Sodium alginate matrices

The dependence of drug release rate on the type of diluent could be seen in Figure 43. The type of diluent affected the drug release rate of the low polymer content (corresponding to high diluent content) sodium alginate matrices. The drug release rate of lactose matrices was higher than that of dibasic calcium phosphate matrices. However, the drug release rates of lactose and dibasic calcium phosphate matrices at 15% and 20% polymer concentrations were comparable. Therefore, in support of previous studies (Ford et al.,1987; Lapidus and Lordi, 1996), this study found that only at high diluent concentration, the difference in drug release rate between soluble- and insoluble-diluents containing matrices was observed.

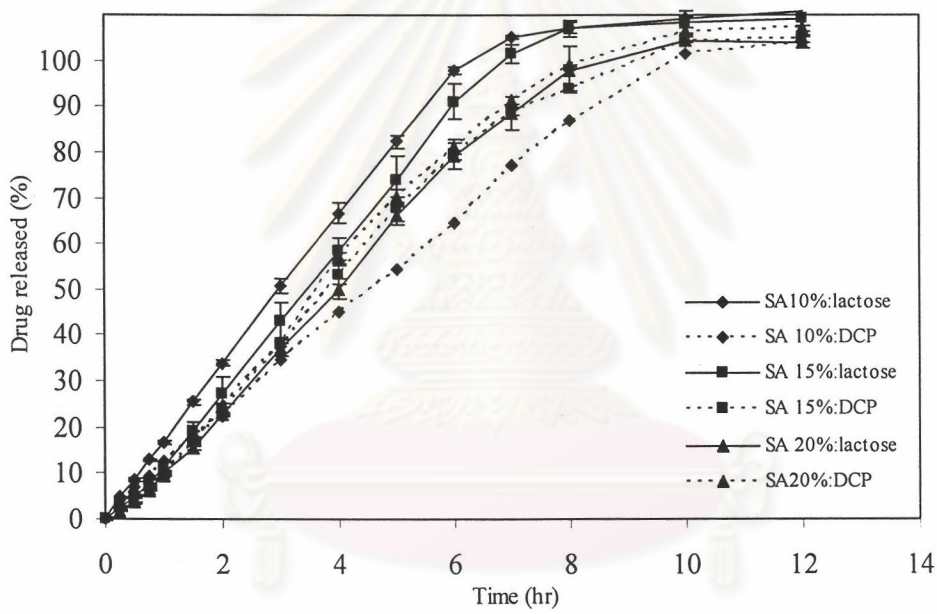


Figure 43 The release profiles of matrices containing lactose or dibasic calcium phosphate (DCP) and sodium alginate (SA) in various amounts in phosphate buffer pH 6.8 solution

Generally, the lactose matrices exhibited a faster drug release rate than dibasic calcium phosphate matrices in phosphate buffer pH 6.8 solution, as discussed previously. Nevertheless, as mentioned and discussed in section 5.2.1.3, the movement of dibasic calcium phosphate matrices comprised of 15% and 20% polymer around the perforated plates at the bottom of the dissolution vessels resulted in an increase in drug release rate. This augmentation in drug release rate of dibasic calcium phosphate matrices might cause the similar release profiles of lactose and dibasic calcium phosphate matrices containing 15% and 20% polymer. Consequently, this finding might also cause the independence of drug release rate on the type of diluent at 15% and 20% polymer level.

When the relative dissolution time (RDT value) of lactose and dibasic calcium phosphate matrices were compared, the RDT value of lactose matrices was markedly lower than that of dibasic calcium phosphate matrices at 10% polymer level (see Figure 33). This supports the obtained result in that the faster drug release rate was observed with lactose matrices at low polymer level. At 15% and 20% polymer levels, the RDT values of lactose and dibasic calcium phosphate matrices were similar. This also support the result in this study in that the difference in drug release rate of lactose and dibasic calcium phosphate matrices appeared only at low polymer content, but at high polymer content the drug release rates of those were similar.

5.2.3 Effect of pH of the dissolution medium on drug release

The influence of pH of the dissolution medium on the drug release from HPMC, xanthan gum and sodium alginate matrices was examined. The 10, 15 and 20% polymer content matrices with different fillers; lactose and dibasic calcium phosphate were investigated for the release profiles in different pH dissolution media. The dissolution media were 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8), which were corresponding to the pH of 1.2 and 6.8, respectively.

5.2.3.1 HPMC matrices

Figures 44 and 45 illustrate the effect of pH of the dissolution medium on drug release profile of HPMC matrices containing lactose or dibasic calcium phosphate as diluent, respectively. The strong influence of the pH of dissolution media on the drug release rate could be observed. The drug release rates in 0.1 N HCl solution were markedly greater than those in phosphate buffer pH 6.8 solution, which could be confirmed from the lower RDT values in 0.1 N HCl solution and higher RDT values in PBS pH 6.8 (see Figure 46).

This result might be caused by the different strengths of gel layer of the matrices hydrated in 0.1 N HCl solution and phosphate buffer pH 6.8 solution. The viscosity determination of polymer solution revealed that the viscosity of the HPMC solution in 0.1 N HCl solution was less than that in phosphate buffer pH 6.8 solution (see Figure 8). Therefore the stronger gel layer around the matrices which immersed in phosphate buffer pH 6.8 solution was formed. This also caused the slower drug release rate in phosphate buffer pH 6.8 solution. This result pointed out that the pH of the dissolution medium was a critical factor in determining the dissolution rate of acyclovir from HPMC matrices.

In addition, this result might be due to the different solubilities of acyclovir in 0.1 N HCl solution and phosphate buffer pH 6.8 solution. According to the result of this study, acyclovir was slightly soluble in phosphate buffer pH 6.8 solution, whereas in 0.1 N HCl solution the solubility improved dramatically.

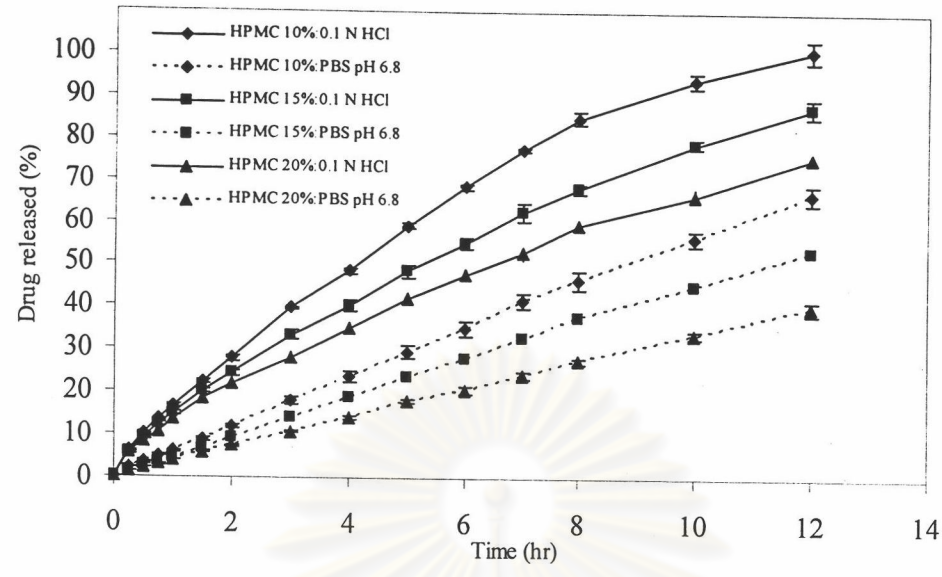


Figure 44 The release profiles of matrices containing lactose and hydroxypropyl methylcellulose (HPMC) in various amounts in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

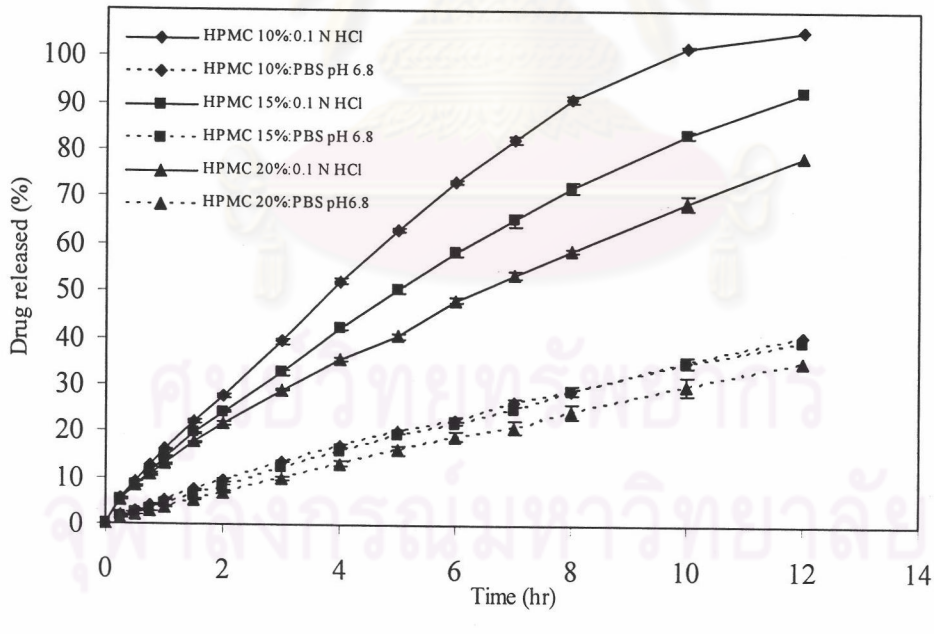


Figure 45 The release profiles of matrices containing dibasic calcium phosphate and hydroxypropyl methylcellulose (HPMC) in various amounts in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

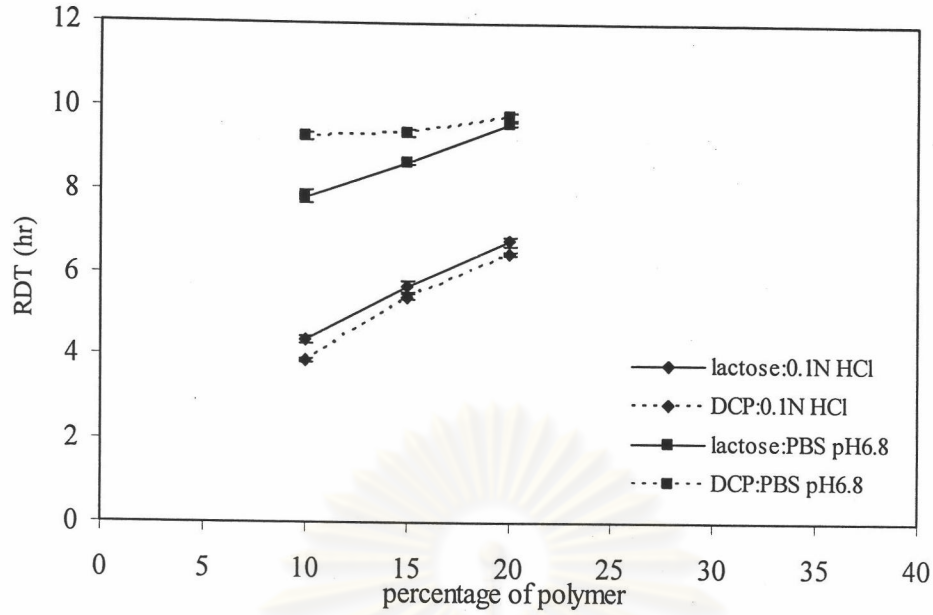


Figure 46 The relationship between the relative dissolution time (RDT value) and the percentage of hydroxypropyl methylcellulose contained in each formulation when using lactoseor dibasic calcium phosphate (DCP) as diluent in different dissolution media

5.2.3.2 *xanthan gum matrices*

The influence of pH of the dissolution medium on drug release profile of xanthan gum matrices containing lactose or dibasic calcium phosphate as diluent is shown in Figures 47 and 48, respectively. The drug release profiles of xanthan gum matrices containing either lactose or dibasic calcium phosphate depended on pH of the dissolution medium. The drug release rate was faster in 0.1 N HCl solution than in PBS pH 6.8. This result is quite consistent with the reported higher RDT values of xanthan gum matrices on PBS pH 6.8 than in 0.1 N HCl solution (see Figure 49). This finding could be attributed to the poor solubility of acyclovir in phosphate buffer pH 6.8 solution.

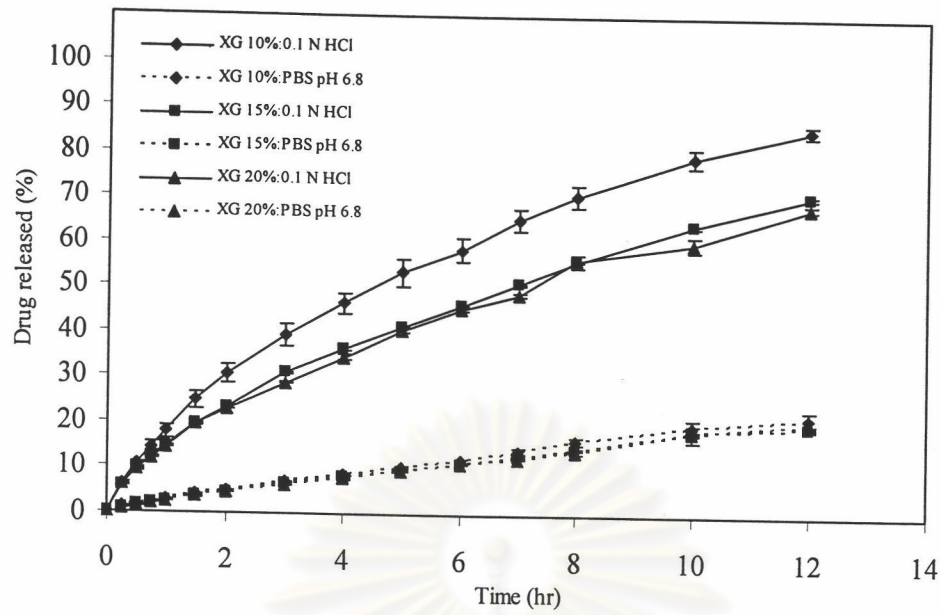


Figure 47 The release profiles of matrices containing lactose and xanthan gum (XG) in various amounts in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

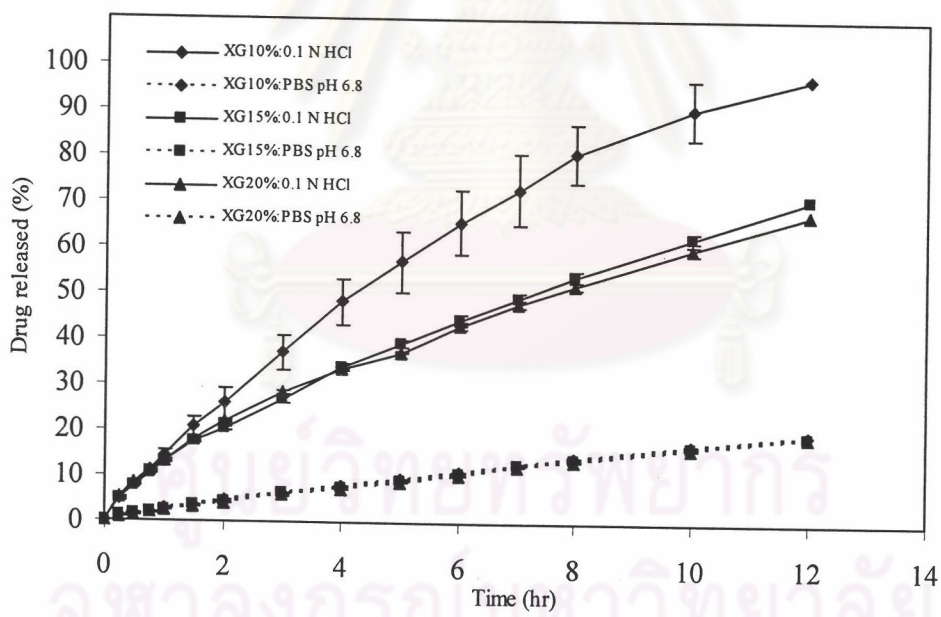


Figure 48 The release profiles of matrices containing dibasic calcium phosphate and xanthan gum (XG) in various amounts in 0.1N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

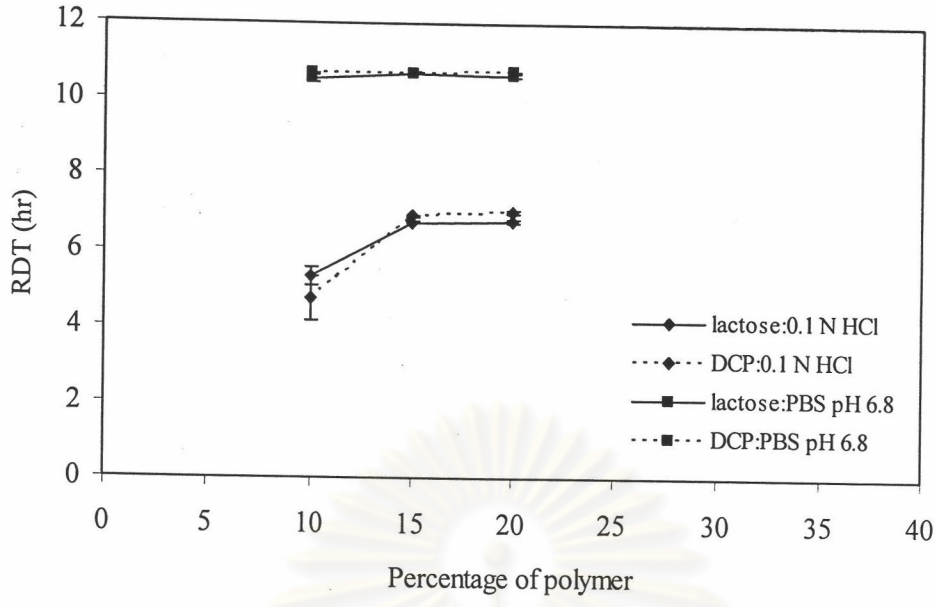


Figure 49 The relationship between the relative dissolution time (RDT value) and the percentage of xanthan gum contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in different pH dissolution media

The matrices swelling rate is one of the important factors that affects drug release rate of hydrophilic matrices. Talukdar and Kinget (1995) studied the relationship between the swelling rate and the drug release rate of the matrices. They concluded that the swelling of the matrices and the release of soluble drug displayed a reciprocal relationship, while the insoluble drug exhibited a direct relationship. This difference in relationship can be explained by the difference in the release mechanism of drugs. The soluble drug is released via diffusion mechanism, whereas the insoluble drug is released by the mechanism of erosion (Alderman, 1984).

For diffusion–controlled mechanism, as the gel thickness increases, the diffusion path length increases, which in turn causes the decrease in drug release from the matrices. Conversely, in case of erosion-controlled mechanism, the swelling of the matrices leads to more susceptibility of the matrices to erosion, resulting in an increase in drug release rate.

The previous published report by Talukdar and Kinget (1995) may support the obtained result in this study. They studied the influence of pH of dissolution medium in the swelling rate of xanthan gum tablet. They reported that the swelling rate of xanthan gum single compact in extreme acidic medium was significantly lower than in neutral or alkaline solutions. This is also consistent with the result of matrices swelling determination in this study, which was discussed in the next topic. The result of this study indicated that the swelling and drug release in 0.1 N HCl solution followed a reciprocal relationship. As the swelling rate decreased, the diffusion path length decreased, resulting in an increase in drug release rate in 0.1 N HCl solution. This was clearly evident since the release of acyclovir which could dissolve in 0.1 N HCl solution from hydrophilic matrices, should mainly proceed through the gel layer (boundary layer control) formed around the matrices upon contact with the medium (Alderman, 1984).

Conversely, the poor solubility of acyclovir in phosphate buffer pH 6.8 solution resulted in the drug release via the large contribution of erosion process. Thus, the rapid swelling rate in phosphate buffer pH 6.8 solution caused the more susceptibility of the matrices to erosion. However, according to the result of this study, the drug release rate in phosphate buffer pH 6.8 solution was markedly lower than that in 0.1 N HCl solution. This deviated result might be explained in terms of the viscosity of the hydrated gel around the matrices and the tablet integrity. Not only the swelling rate of the matrices but also the viscosity of the gel barrier around the matrices affected the erosion of the gel layer. As the result of viscosity measurement in this study, the viscosity of xanthan gum solution was dramatically higher than those of carbopol 934P, HPMC and sodium alginate solutions in phosphate buffer pH 6.8 solution (see Figure 8). Thus, as the result of high viscosity of xanthan gum solution, the gel layer around the matrices was not susceptible to erosion. In addition, the high

viscosity of polymer gel around the matrices led to maintenance of the matrix integrity, which observed visually over the course of the dissolution test.

In conclusion, the differences in drug solubility and swelling rate in dissolution media with different pH values affected the drug release rate of the xanthan gum matrices.

5.2.3.3 *sodium alginate matrices*

In the case of matrices containing sodium alginate as retarding polymer, the dependence of the release profiles of lactose and dibasic calcium phosphate matrices on the pH of the dissolution medium is shown in Figures 50 and 51, respectively. The different dissolution media also produced the difference in the drug release pattern. This result agreed with the published report by Fu Lu et al. (1991). They found that the pH of the dissolution medium had a great effect on the dissolution profile of alginate matrices. In addition, the change in the type of diluent from lactose to dibasic calcium phosphate did not appear to modify the response of the matrices to pH changes.

The difference in drug release patterns of sodium alginate matrices in different dissolution media could be explained by the difference in drug release mechanisms. In 0.1 HCl solution, drug release was linear with the square root of time. This finding suggested that in acidic pH the release mechanism was predominantly diffusion-controlled (Touitou and Donbrow, 1982), whereas at pH 6.8, drug release was linear with time. This was an indication that the drug release in phosphate buffer pH 6.8 solution followed zero-order kinetics where the erosion mechanism was predominated. The drug release rates of sodium alginate matrices in 0.1 N HCl solution ($\%hr^{-1/2}$) and that in phosphate buffer pH 6.8 solution ($\%hr^{-1}$) are illustrated in Table 9.

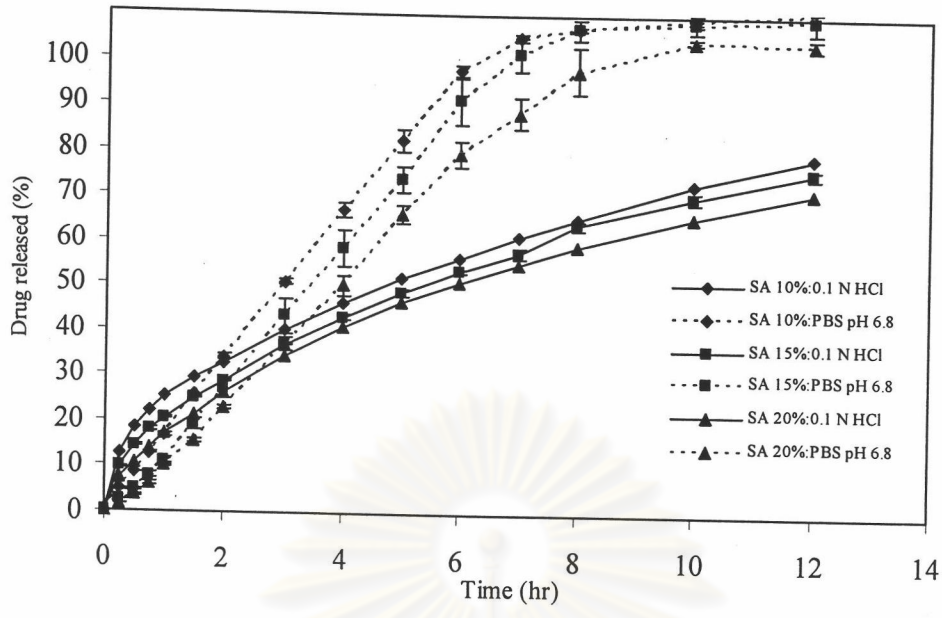


Figure 50 The release profiles of matrices containing lactose and sodium alginate (SA) in various amounts in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

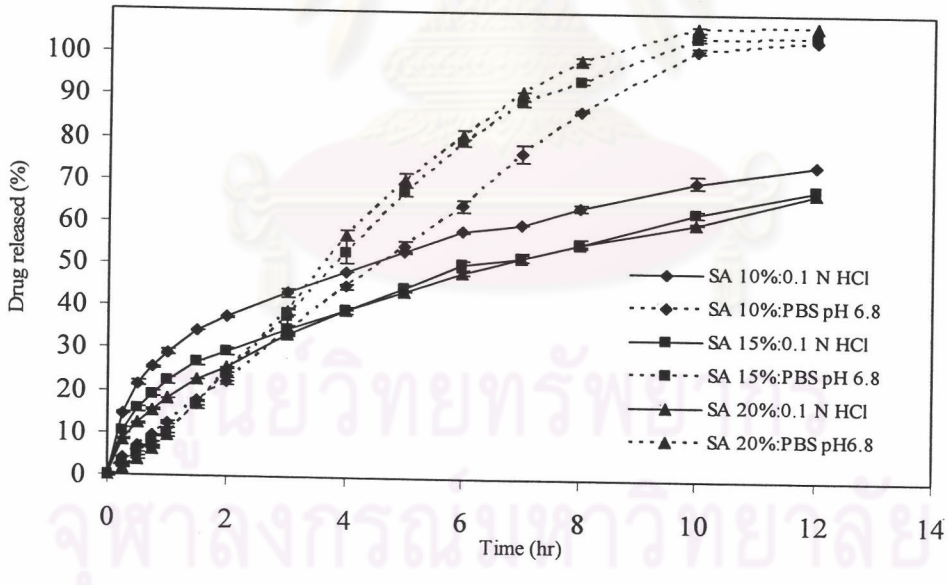


Figure 51 The release profiles of matrices containing dibasic calcium phosphate and sodium alginate (SA) in various amounts in 0.1 N HCl solution and phosphate buffer solution pH 6.8

Table 9 The drug release rate of sodium alginate matrices with different polymer content and diluents in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8) at 37 °C ± 0.5 °C (mean (SD); n=3)

Formulation	Sodium alginate content	Diluent	Dissolution medium			
			0.1 N HCl		PBS pH 6.8	
			Release rate (% $min^{-1/2}$) (mean (SD))	r^2	Release rate (% min^{-1}) (mean (SD))	r^2
F7	10%	Lactose	22.43 (0.21)	0.9982	16.73 (0.25)	0.9999
F8	15%	Lactose	22.22 (0.36)	0.9986	15.02 (0.98)	0.9973
F9	20%	Lactose	22.06 (0.43)	0.9949	13.21 (0.47)	0.9961
F19	10%	DCP	21.58 (0.25)	0.9858	10.70 (0.15)	0.9989
F20	15%	DCP	19.31 (0.25)	0.9972	13.58 (0.51)	0.9963
F21	20%	DCP	20.02 (0.12)	0.9983	14.67 (0.18)	0.9931

In order to clarify the pH dependent release mechanism of sodium alginate matrices, the internal microscopic structure of the hydrated surface layer formed on matrices hydration in different pH dissolution media reported by Hodsdon et al.(1995) was relevant. Hodsdon et al. (1995) studied the effect of pH of the dissolution medium on the release kinetics of sodium alginate matrices. Their result could be explained in terms of the difference in internal morphology of sodium alginate matrices after hydration in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.5).

The cryogenic electron microscopy revealed the hydrated surface layer formed by alginate matrices in SGF to be particulate and porous in nature, in contrast to the highly hydrated continuous gel layer formed in SIF. This may support the obtained result in this study. In this study, the difference in consistency of hydrated matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution was observed. In the case of hydration of matrices in phosphate buffer pH 6.8 solution, on retrieval of this type of matrices from the dissolution vessel, the viscous hydrated surface layer formed

around the matrices could be seen by visual observation. In contrast, the hydrated layer of matrices in 0.1 N HCl solution was not viscous nor adhesive in nature, but possessed a tough and rubbery texture. The reason for this finding might be due to the difference in hydration characteristics of the sodium alginate in acidic and neutral pH values. At pH 1.2, sodium alginate is rapidly converted to alginic acid which has the ability to swell on hydration but which virtually insoluble (Hodsdon et al., 1995). This caused the porous, tough and rubbery texture of sodium alginate matrices hydrated in 0.1 N HCl solution. On the other hand, at neutral pH, sodium alginate was soluble and hydrated to form viscous solutions (Hodsdon et al., 1995). This resulted in the consistent gelatinous layer formed around the matrices in PBS pH 6.8.

Since the hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release, any change in the properties of the hydrated surface layer caused by a change in pH, is likely to influence the performance of the drug release from sodium alginate matrices (Hodsdon et.,1995). In 0.1 HCl solution, the drug release was predominantly diffusion-controlled mechanism. This could be explained in term of internal structure of the hydrated matrices in acid pH. At pH 1.2, the porous, tough and rubbery texture of hydrated matrices which did not act as the diffusional barrier in contrast to the continuous gel layer formed at pH 6.8. Moreover, the tough mechanical property of the particulate hydrated layer formed at acidic pH rendered the matrices very resistant to erosion. Therefore, the drug release of matrices in 0.1 N HCl solution followed diffusion-controlled mechanism. Conversely, the viscous gelatinous layer formed around the matrices at pH 6.8 also possessed markedly different mechanical properties to that produced at pH 1.2. This difference in gel barrier integrity exhibited itself as the difference in the susceptibility of the hydrated layer to erosion. The outer layer of the viscous gel barrier that was formed in PBS pH 6.8 was much less resistant to attrition and played a strong diffusional barrier role against drug diffusion through the gelatinous layer around the matrices. Consequently, the matrices in phosphate buffer pH 6.8 solution depended predominantly on surface erosion for their release.

As shown in Figures 50 and 51, the release profiles of the matrices in 0.1 N HCl solution displayed the initial burst drug release, whereas this was absent in PBS pH 6.8. Since the formation of continuous gel barrier around the matrices in 0.1 N HCl solution did not occur, the initial burst drug release might be caused by the rapid dissolution of the drug particles at the outer surface of the matrices immersed in 0.1 N HCl solution. For drug release in PBS pH 6.8, the absence of the rapid drug release rate at the initial dissolution time indicated that the hydration rate of sodium alginate in PBS pH 6.8 was rapid enough to prevent the dissolution of the drug particles, which deposited at the outer surface of matrices. This result pointed out that the hydration rate of the polymer to form the protective gel barrier around the matrices played an important role in controlling drug release, especially at the beginning of the dissolution process.

However, the drug release rate was dramatically faster in phosphate buffer pH 6.8 solution during the intermediate and last parts of the dissolution profile. The reason for this finding might be explained in terms of the low strength of hydrated gel barrier around the matrices. As the result of viscosity measurement, the viscosity of sodium alginate solution was lower than that of HPMC and xanthan gum solutions in the same medium (see Figures 8 and 9). The low viscosity of the hydrated gel barrier resulted in an increased susceptibility of the matrices to erosion. Consequently, the faster drug release was observed in phosphate buffer pH 6.8 solution during the intermediate and last portions of dissolution profile, although the solubility of acyclovir was higher in 0.1 N HCl solution than in PBS pH 6.8. This result could confirm by the RDT values in which the RDT values of sodium alginate matrices in 0.1 HCl solution were greater than those in PBS pH 6.8 (see Figure 52).

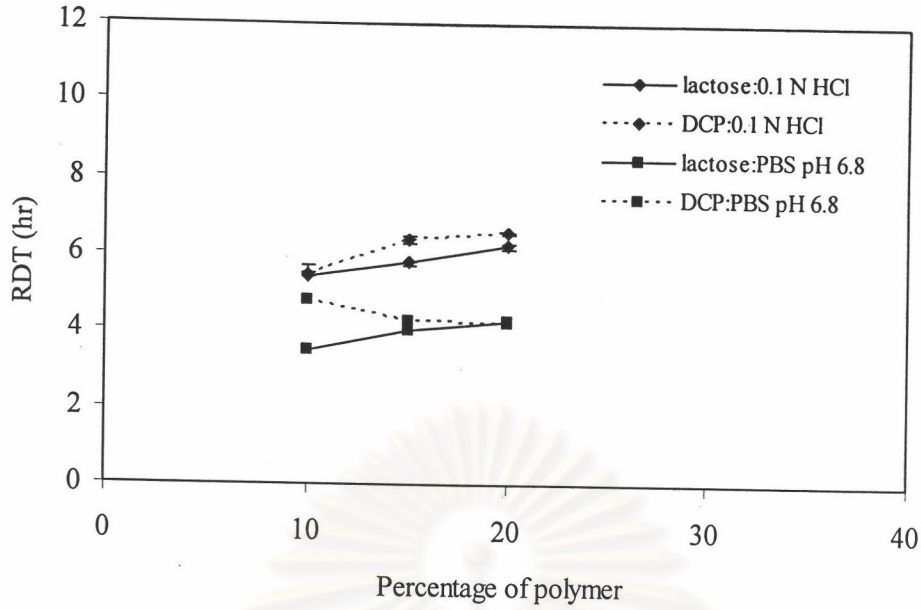


Figure 52 The relationship between the relative dissolution time (RDT value) and the percentage of sodium alginate contained in each formulation when using lactose or dibasic calcium phosphate (DCP) as diluent in different pH dissolution media

In order to study the effect of pH of dissolution medium on drug release, the dissolution test using 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8) was performed. Nevertheless, the difference in ionic strengths of these dissolution media was also noted. The ionic strengths of 0.1 N HCl solution and phosphate buffer pH 6.8 solution were 0.1 and about 0.07, respectively. Consequently, in order to confirm that either the difference in pH or ionic strength of dissolution medium caused the different drug release profiles in 0.1 N HCl solution and phosphate buffer pH 6.8 solution, the release profile in phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8 + NaCl) was investigated. The ionic strength of 0.1 N HCl solution, PBS pH 6.8 and PBS pH 6.8+NaCl were 0.1, approximately 0.07 and 0.1, respectively. The pH and ionic strength of these dissolution media are illustrated in Table 10.

Table 10 The pH and ionic strength of dissolution medium

Dissolution medium	pH	Ionic strength
0.1 N HCl	1.2	0.1
PBS pH 6.8 [a]	6.8	about 0.07
PBS pH 6.8+NaCl [b]	6.8	0.1

[a] Phosphate buffer pH 6.8 solution

[b] Phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride

Since the ionic strengths of 0.1 N HCl solution and PBS pH 6.8+NaCl were identical, the different release profiles in these dissolution media indicated the effect of pH of dissolution medium on drug release. Conversely, in order to evaluate the influence of ionic strength of dissolution medium on drug release, the release profiles in PBS pH 6.8 and PBS pH 6.8+NaCl were compared.

The matrices containing 15 % polymer and using lactose or dibasic calcium phosphate as diluent were investigated for release profiles. For HPMC matrices, the release profiles of lactose or dibasic calcium phosphate containing matrices are shown in Figures 53 and 54, respectively. The relationship between pH and ionic strength of dissolution medium and the relative dissolution time (RDT value) is displayed in Figure 55. As illustrated in Figures 53-55, the drug release profiles and RDT values of HPMC matrices of PBS pH 6.8 and PBS pH 6.8+NaCl were comparable and greatly different from those in 0.1 N HCl solution. The result of this study pointed out that the rate of drug release from HPMC matrices was mainly controlled by the pH of the dissolution medium. The ionic strength of the dissolution medium had little effect on drug release rate. The influence of ionic strength of dissolution medium on the drug release from HPMC matrices was discussed in the next topic.

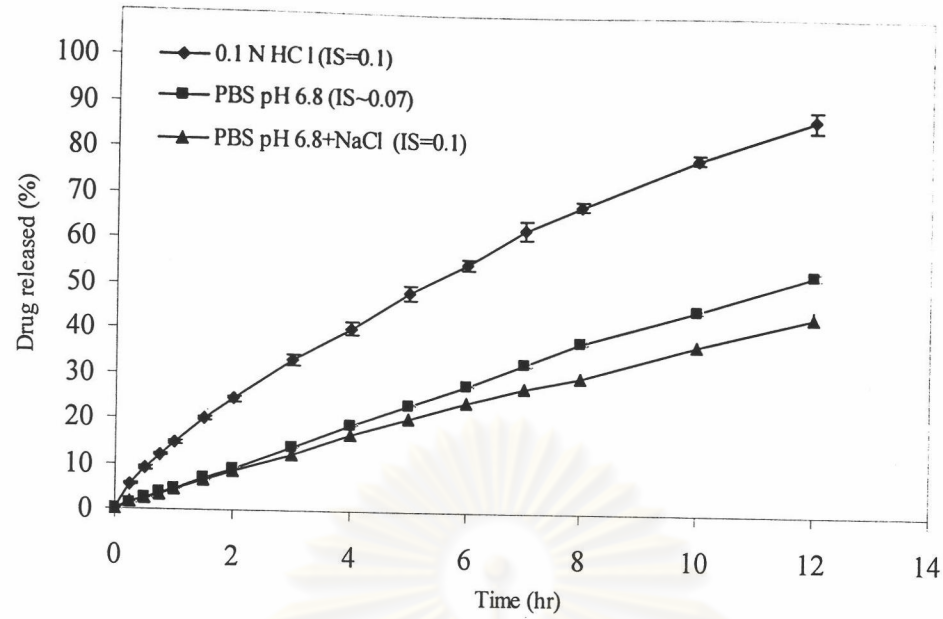


Figure 53 The release profiles of matrices containing lactose and 15% hydroxypropyl methylcellulose in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

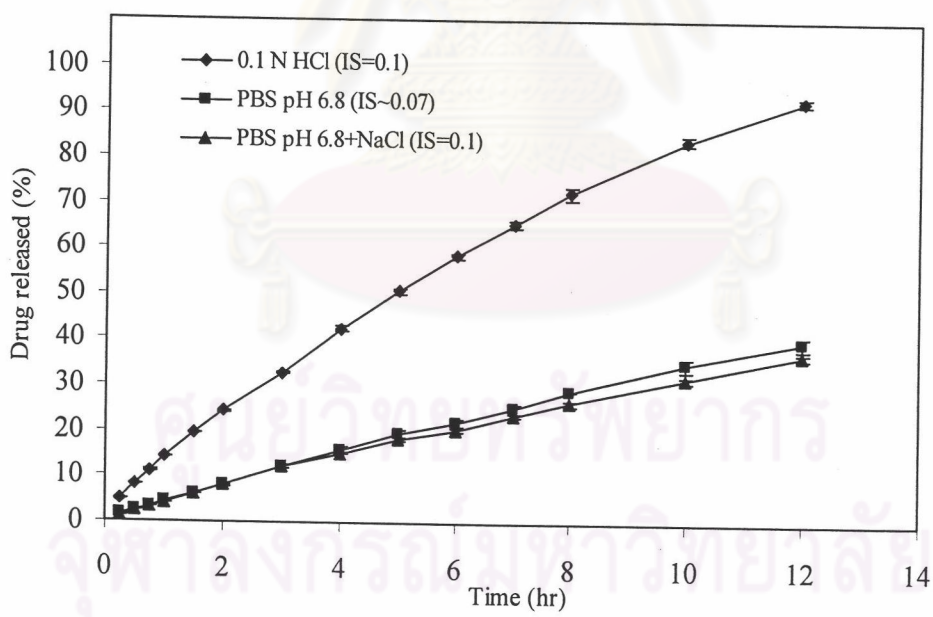


Figure 54 The release profiles of matrices containing dibasic calcium phosphate and 15% hydroxypropyl methylcellulose in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

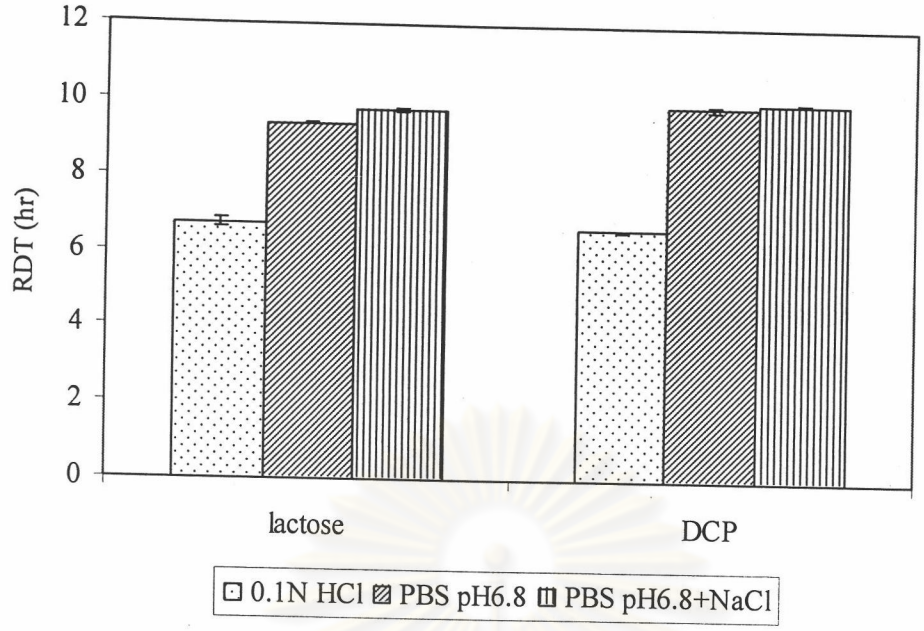


Figure 55 The relative dissolution times (RDT values) of hydroxypropyl methylcellulose matrices containing lactose or dibasic calcium phosphate (DCP) as diluent in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

In the case of xanthan gum matrices, the release profiles of matrices containing lactose or dibasic calcium phosphate as diluent are shown in Figures 56 and 57, respectively. The influences of pH and ionic strength of dissolution medium on RDT value are illustrated in Figure 58. The release profiles in 0.1 N HCl solution were dramatically higher than those in PBS pH 6.8 and PBS pH 6.8+NaCl. The drug release profiles and RDT values in PBS pH 6.8 and pH 6.8+NaCl were similar. This result indicated that the independence of drug release profile and RDT value with respect to the ionic strength of dissolution medium was observed. Therefore, the difference in release profile in 0.1 N HCl solution and PBS pH 6.8 could be attributed to the different pH values of dissolution medium .

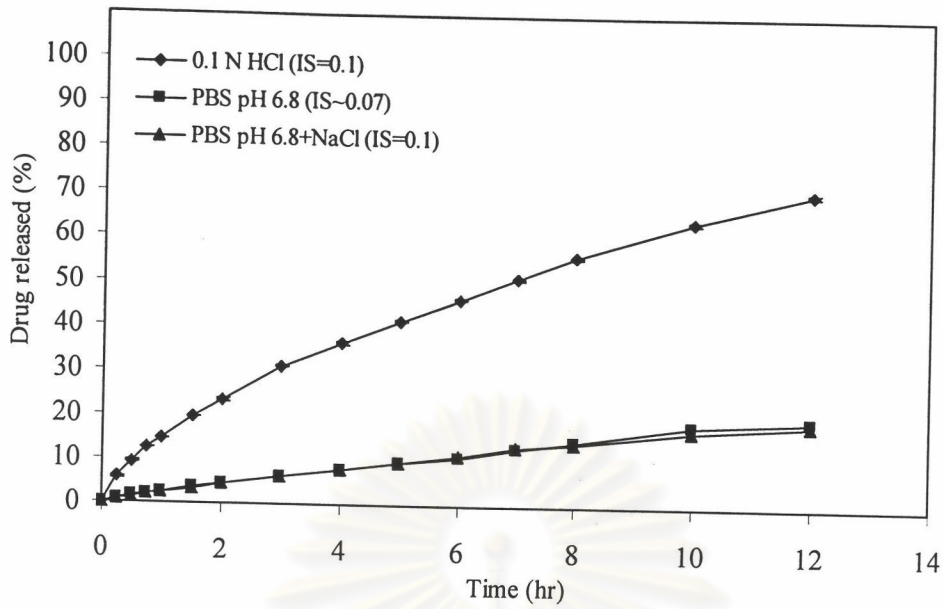


Figure 56 The release profiles of matrices containing lactose and 15% xanthan gum in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

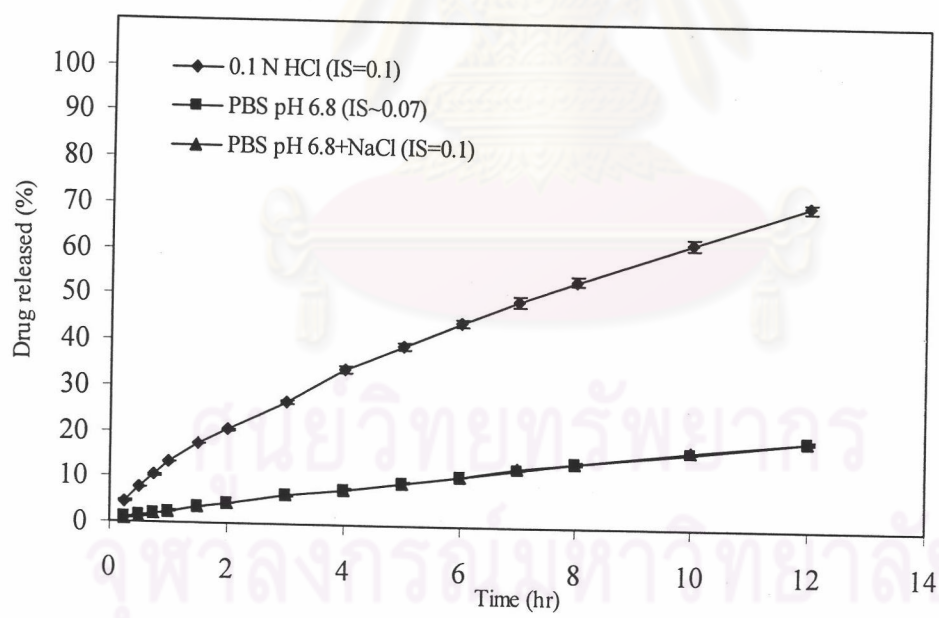


Figure 57 The release profiles of matrices containing dibasic calcium phosphate and 15% xanthan gum in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

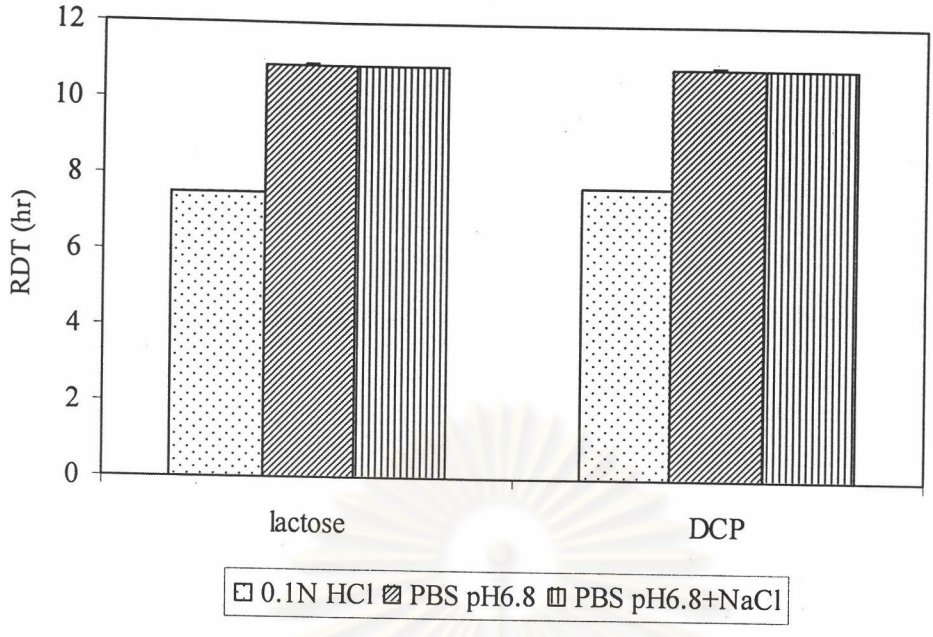


Figure 58 The relative dissolution times (RDT values) of xanthan gum matrices containing lactose or dibasic calcium phosphate (DCP) as diluent in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

For sodium alginate matrices, Figures 59 and 60 present the release profiles of sodium alginate matrices containing lactose or dibasic calcium phosphate as diluent, respectively. The dissolution profiles in different dissolution media (0.1 N HCl solution (pH 1.2) and PBS pH 6.8) displayed the difference in drug release patterns. This result was the indication that the drug release mechanisms in acidic and neutral pH values dissolution media were different.

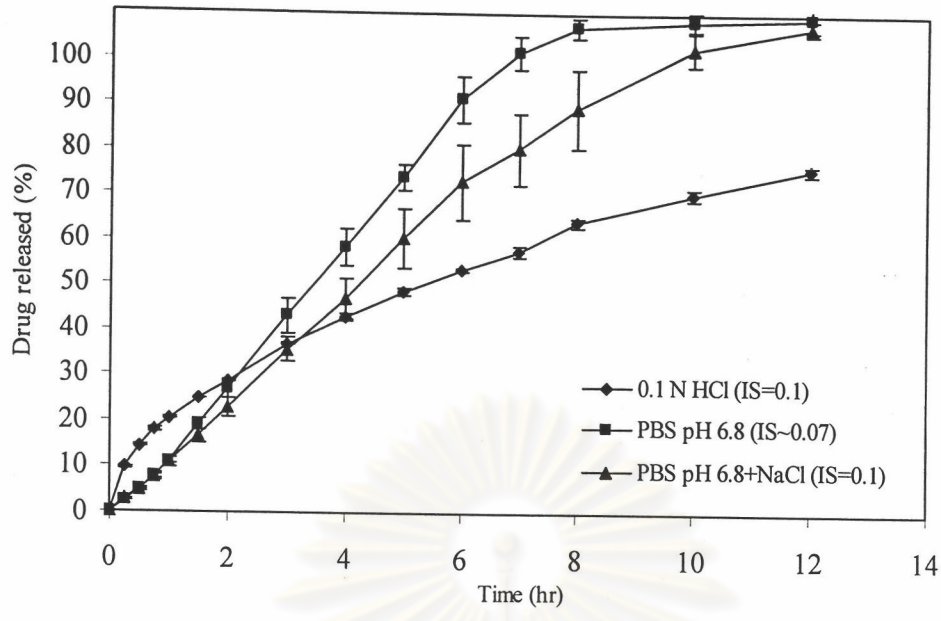


Figure 59 The release profiles of matrices containing lactose and 15% sodium alginate in 0.1 N HCl solution, phosphate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

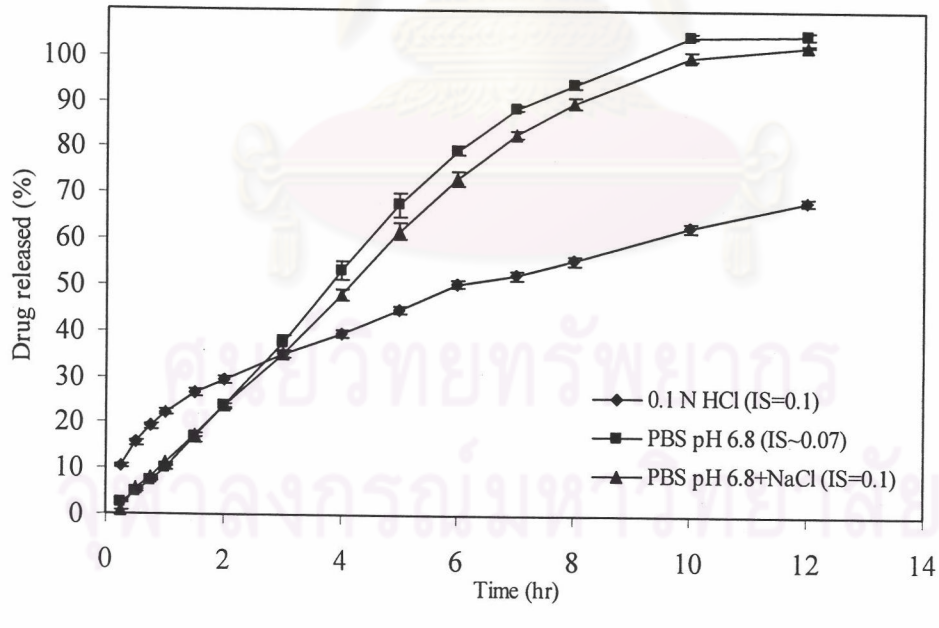


Figure 60 The release profiles of matrices containing dibasic calcium phophate and 15% sodium alginate in 0.1 N HCl solution , phophate buffer pH 6.8 solution (PBS pH 6.8) and phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8+NaCl)

The release profiles in PBS pH 6.8 and PBS pH 6.8+NaCl were apparently related. This finding indicated that the mechanism of drug release and, hence, the drug release pattern depended on the pH of dissolution medium. The difference in ionic strength of dissolution medium did not cause the difference in drug release pattern. Therefore, the major factor causing the different patterns of drug release profile and also drug release rate in 0.1 N HCl solution and PBS pH 6.8 was the pH of dissolution medium. The influence of ionic strength of dissolution medium on drug release profile was also discussed in section 5.3.1.3.

5.3 Dissolution study of acyclovir matrices in dissolution media having different ionic strengths

5.3.1 Effect of ionic strength of the dissolution medium on drug release

The effect of ionic strength of the dissolution medium on the drug release profile of HPMC, xanthan gum and sodium alginate matrices was investigated. The formulations containing 15% polymer with different diluents (lactose and dibasic calcium phosphate) were chosen for drug release study. The dissolution media used were deionized water, 0.05 M, 0.1 M and 0.2 M sodium chloride solutions corresponding to the ionic strengths of 0, 0.05, 0.1 and 0.2, respectively.

In general, drug solubility is one of the important factors that affects drug release. As the result of solubility determination in this study, the solubilities of acyclovir in media with various ionic strengths were similar (see Table 8). Therefore, the drug solubility might not be a major factor in the difference in drug release rates in various dissolution media studied. The difference in drug release rate might be explained in terms of the difference in physical and mechanical properties of hydrated gel layer around the matrices instead.

5.3.1.1 HPMC Matrices

The influence of ionic strength of the dissolution medium on drug release profile could be seen in Figures 61 and 62. The drug release rate trended to decrease with increases in ionic strength of the dissolution medium, especially that in 0.2 M sodium chloride solution. In 0.2 M sodium chloride solution, the slowest drug release rate was observed. In the cases of matrices containing different diluents (lactose and dibasic calcium phosphate), the effects of ionic strength were similar.

This result could also be shown by plotting the RDT value against the ionic strength of dissolution medium, as presented in Figure 63. The highest RDT value was observed at the ionic strength of 0.2, indicating the slowest drug release rate.

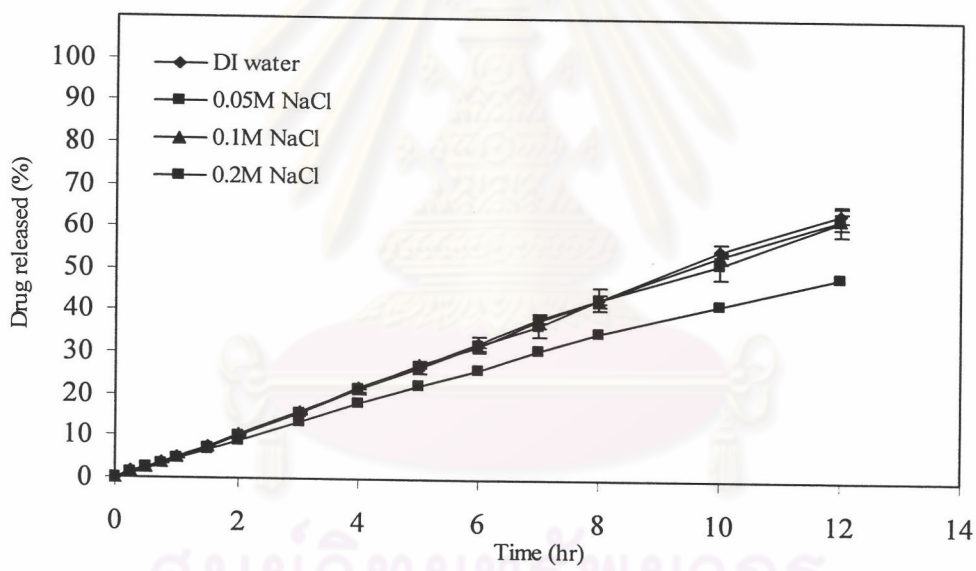


Figure 61 The release profiles of matrices containing lactose and 15% hydroxypropyl methylcellulose in various ionic strengths of the dissolution medium

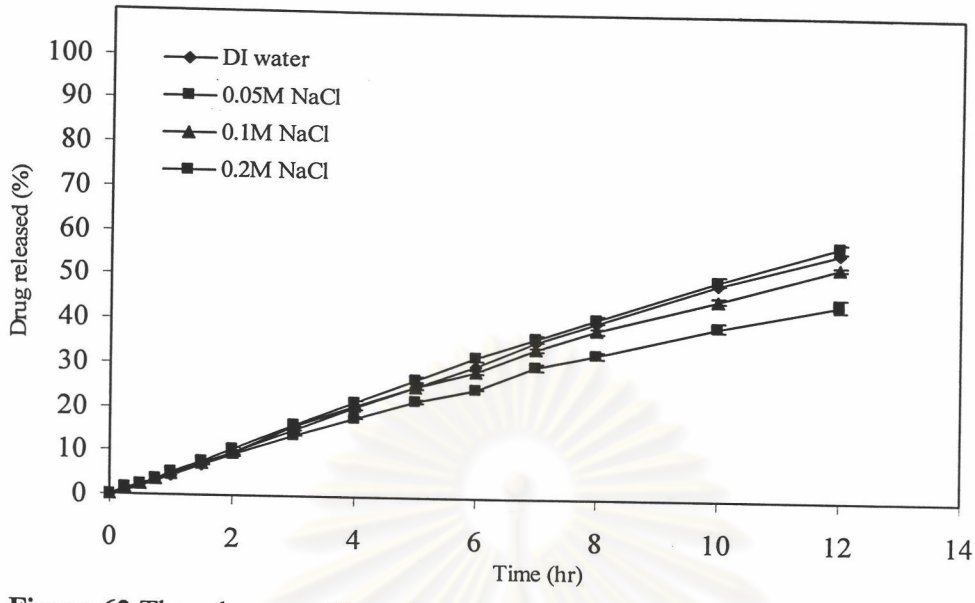


Figure 62 The release profiles of matrices containing dibasic calcium phosphate and15% hydroxypropyl methylcellulose in various ionic strengths of the dissolution medium

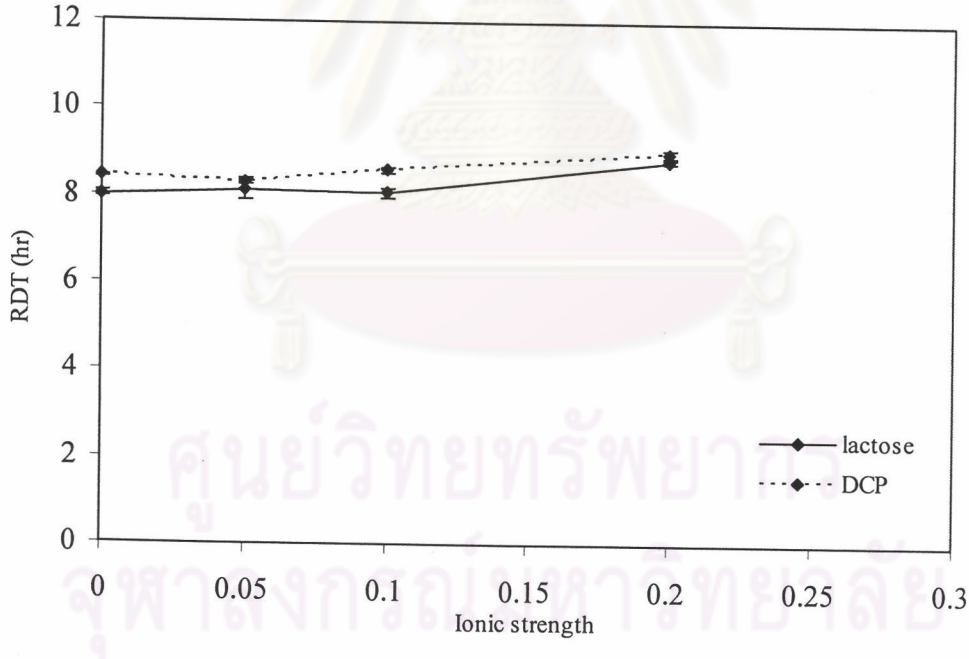


Figure 63 The relationship between the relative dissolution time (RDT value) of hydroxypropyl methylcellulose matrices containing lactose or dibasic calcium phosphate (DCP) and ionic strength of the dissolution medium

Although there is no salt screening effect on the molecules of HPMC because of the non-ionic characteristic of the polymer, the dependence of drug release rate on ionic strength of dissolution medium from HPMC matrices still occurred. This could be attributed to the dehydration or salting out of polymer in the electrolyte solution. Solutes, such as sodium chloride, that have greater affinity for water than HPMC compete for the available water in the gel layer and thereby reduce the hydration of polymer (Abrahamsson, et al., 1998, Jalil and Ferdous, 1993, Lapidus and Lordi, 1996, Mitchell et al., 1990, Smitch et al., 1996 and Touitou and Donbrow, 1982). Increased salt concentrations in this study could thereby lead to a stronger gel due to an increased extent of hydrophobic HPMC-HPMC interaction primarily between methoxy-substituents (Abrahamsson et al., 1998).

Although the presence of salt in dissolution medium causes the decrease in dissolution rate, further increases in salt concentration result in augmentation of drug release rate. It has been observed previously that the drug release rate initially decreased and then increased with the increase in ionic strength (Jalil and Ferdus, 1993, Lapidus and Lordi, 1966 and Smitch et al., 1996). This apparent inconsistency might be explained by considering that when the salt concentration is increased beyond a certain point, the activity of water becomes so greatly reduced as to prevent uniform hydration of the polymer. This then results in a massive discontinuity in the gel structure (Lapidus and Lordi, 1966). Furthermore, the catastrophic disintegration and the dose dumping of the matrices can ultimately occur at the higher salt concentration (Mitchell et al. 1990 and Smitch et al., 1996). This indicated that the integrity of HPMC matrices is also affected by ionic strength. Nevertheless, the value of ionic strength reported to cause disintegration of HPMC matrices was much higher than the ionic strength of sodium chloride solution tested in this study. Consequently, disintegration of the matrices was not observed. The matrices remained intact over the course of dissolution test. This result pointed out that the disintegration of the HPMC matrices might not occur in the gastro-intestinal environment in the fasting state the ionic strength of which is in the same range of that tested in this study. (Johnson et al.,1993 and Waaler et al., 1992). However, an increase in ionic strength

in the gastro-intestinal tract appears at fed-state (Waaler et al., 1992). Therefore, at the fed-state, the matrix disintegration might occur.

5.3.1.2 *Xanthan gum matrices*

Figures 64 and 65 illustrate the release profiles of xanthan gum matrices containing lactose or dibasic calcium phosphate as diluent in dissolution media with different ionic strengths, respectively. The type of diluent (lactose and dibasic calcium phosphate) did not apparently modify the pattern of release profiles in various media. For both lactose and dibasic calcium phosphate containing matrices, the strong influence of the addition of salt on the pattern of drug release profile was observed. The pattern of release profile in deionized water was markedly different from those in sodium chloride solutions (0.05 M, 0.1 M and 0.2 M NaCl). The release profile in deionized water followed biphasic release profile, whereas those in sodium chloride solutions manifested slow drug release rates and approached linear profiles over the course of the dissolution tests. During the initial time, the dissolution profiles in deionized water and sodium chloride solutions were similar. Interestingly, at the intermediate and last portions of the dissolution profile, the drug release rate in deionized water dramatically higher than those in sodium chloride solutions. This finding indicated the strong influence of the added salt in the dissolution medium on the drug release rate.

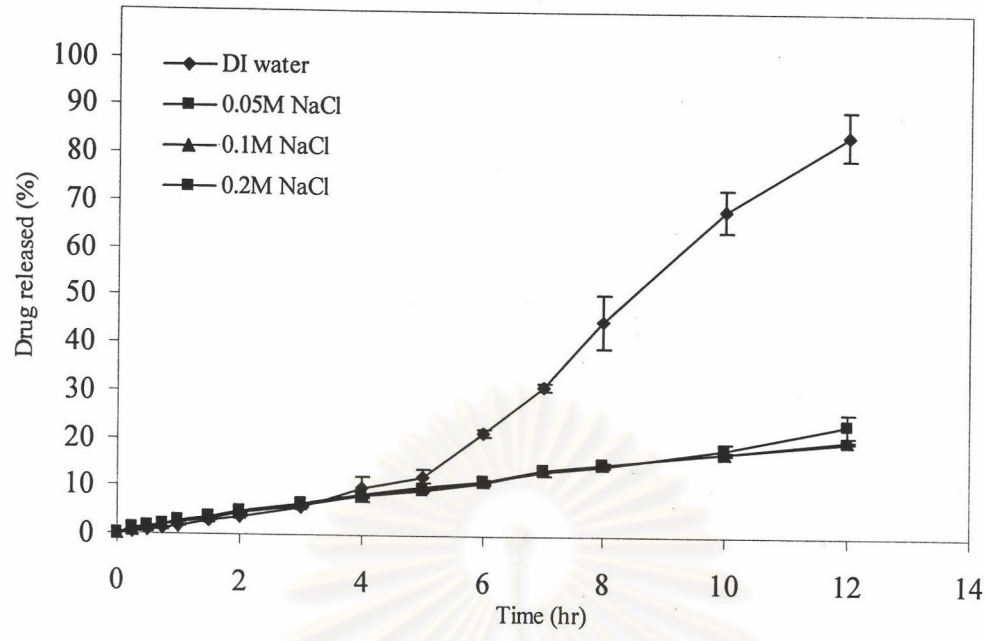


Figure 64 The release profiles of matrices containing lactose and 15% xanthan gum in various ionic strengths of the dissolution medium

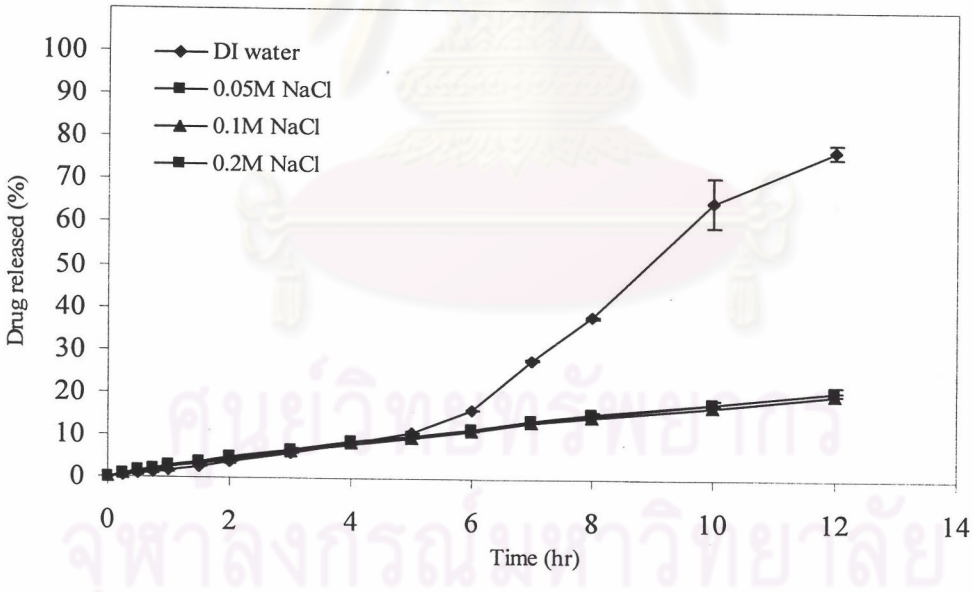


Figure 65 The release profiles of matrices containing dibasic calcium phosphate and 15% xanthan gum in various ionic strengths of the dissolution medium

However, the increasing concentrations of sodium chloride solution had no effect on drug release rate. The drug release profiles of various concentrations of sodium chloride solution were similar. This could also be shown by the different relative dissolution times (RDT values) of xanthan gum matrices in the dissolution medium having various ionic strengths, as displayed in Figure 66. As expected, the RDT value in deionized water was much lower than those in sodium chloride solutions. The RDT values of matrices in various concentrations of sodium chloride solution were similar, indicating the similar drug release rates. These results agreed with the previous studies by Talukdar et al. (1996), Talukdar and Kinget (1995) and Talukdar and Plaizier-Vercammen (1993). They concluded that drug release from xanthan gum matrix tablet depended on the ionic strength of dissolution medium.

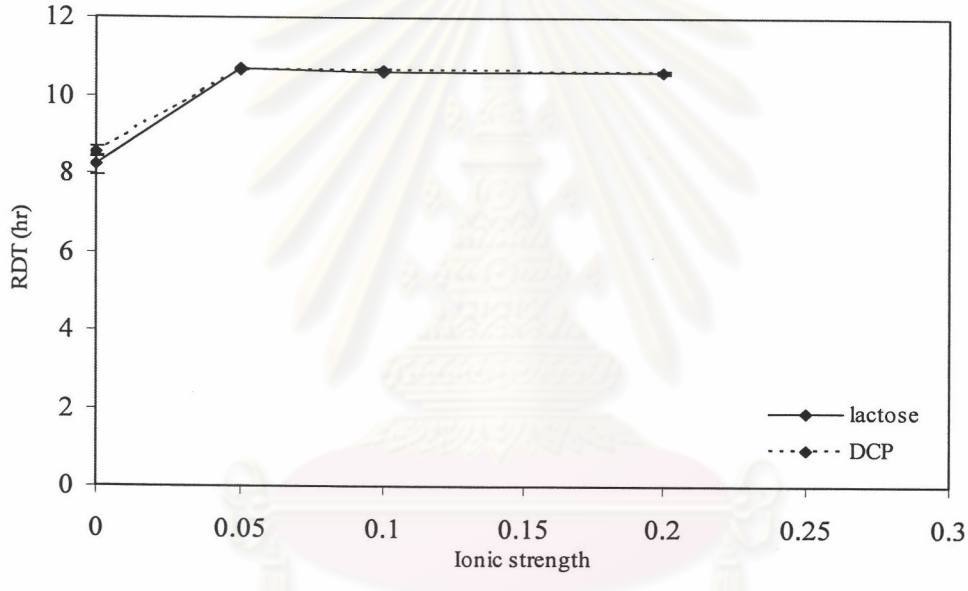


Figure 66 The relationship between the relative dissolution time (RDT value) of xanthan gum matrices containing lactose or dibasic calcium phosphate (DCP) as diluent and ionic strength of the dissolution medium

From the result of matrix swelling measurement in this study, the absence of salt in the dissolution medium (deionized water) caused the formation of fully hydrated matrices. This is again in accordance with the published data, where the swelling of xanthan gum matrix tablet displayed a reciprocal relationship with ionic

strength of dissolution medium (Talukdar and Kinget, 1995). An increase in matrix swelling was corresponding with a decrease in ionic strength of dissolution medium. The influence of electrolyte on swelling behavior could be explained as a consequence of salt dependence of the conformation of xanthan molecules (Talukdar and Kinget, 1995).

Earlier researchers (Talukdar and Kinget, 1995) studied the swelling and drug release behavior of xanthan gum matrix tablets using three drugs having different water solubilities in dissolution media with various ionic strengths. They found that the swelling of matrix and the release of soluble drug showed a reciprocal ralationship, while the insoluble drug exhibited a direct relationship. This difference can be explained by the different drug release mechanisms. The soluble drug is released by diffusion process, whereas the insoluble drug is release via an erosion mechanism (Alderman,1984, Dhopeshwarkar and Zatz, 1993, Ford et al., 1987 and Hodsdon et al., 1995). In the case of soluble drug, the more the matrix swells, the more the diffusion path length increases, resulting the decrease in drug release from the matrix. On the contrary, the erosion-controlled mechanism of insoluble drug release can be explained in terms of the susceptibility of matrix to erosion. For the matrix system, the swelling process leads to the polymer chain disentanglement, the polymer dissolution and drug liberation, respectively. Therefore, the more matrix swelling causes the matrix to be more susceptible to erosion, leading to an increase in the release of insoluble drug. Consequently, depending on the solubility of the drug, the release from matrix is regulated by its swelling behavior. This finding may support the obtained result in this study. Since acyclovir is slightly soluble in deionized water (see Table 8), it follows the erosion-controlled mechanism. This could be confirmed by the drug release mechanism analysis which was discussed in the next topic.

Moreover, from the results of viscosity measurement in this study, the viscosity of polymer solution in deionized water was much less than those in sodium chloride solutions. This result indicated that the gel barrier around the matrices in sodium chloride solutions were much stronger than that in deionized water. Therefore, the gelatinous layer around the matrix in deionized water was much more susceptible

to erosion than those in sodium chloride solutions. In addition, by visual inspection at the intermediate and the last portions of dissolution time, floatation and movement of matrices around the perforated plates at the bottom of the dissolution vessels were observed in deionized water. In contrast, these did not occur with the matrices hydrated in sodium chloride solutions. This result could be explained in terms of the density of the matrices. The increased matrix swelling in deionized water led to the decrease in matrix density, resulting in the floatation and the movement of the matrices. This mechanical motion caused the destruction of the gel layer around the matrices, which might accelerate drug release during the intermediate and the last portions of dissolution period.

In conclusion, the rapid increase in drug release of the matrices in DI water during the intermediate and the last portions of the release profile, which caused two-phase release pattern might be due to the swelling behavior of matrices, the more susceptibility of the matrices to erosion and the destruction of the gel barrier.

In the case of drug release in sodium chloride solutions, the relevance of the concentrations of sodium chloride solution (0.05 M, 0.1 M and 0.2 M NaCl) on their release profiles was not observed. The release profiles in different ionic strengths of sodium chloride solutions were similar. This result indicated that there was no salt effect on the release profiles in sodium chloride solutions in terms of both drug release rate and drug release pattern. This finding implied that the ionic strength of dissolution medium had a marked influence on the drug release up to a value of 0.05. The obtained result agreed well with the data from viscosity measurement in this study. The effect of ionic strength on the viscosity of xanthan gum gel was limited up to ionic strength of 0.05. Further increase in ionic strength had no influence on the viscosity of xanthan gum gel, resulting in a constant viscosity. However a different result was reported by Talukdar and Kinget (1995). They concluded that the ionic strength of the dissolution medium had a significant influence on the swelling rate of xanthan gum matrices up to a value of 0.1, which could be attributed to the formation of stable helix form in dissolution medium having ionic strength of 0.1. This discrepancy in limitation of ionic strength level between the previous and this present

studies may be due to differences in acetate and/or pyruvate content in the xanthan gum supplied by different manufacturers (Zatz and Knapp, 1984).

Moreover, by visual inspection over the course of the dissolution time, the matrices in each concentration of sodium chloride solution did not move around the perforated plates during the course of dissolution test. The loss of matrices integrity was not observed. As a consequence, the release profiles in sodium chloride solutions displayed slow drug release rates, and the rapid drug released caused by the destruction of the gel barrier around the matrices did not occur.

5.3.1.3 sodium alginate matrices

The release profiles of sodium alginate matrices containing lactose or dibasic calcium phosphate as diluent in dissolution media with various ionic strengths are displayed in Figures 67 and 68, respectively. The relationship between the RDT value and the ionic strength of the dissolution medium is also presented in Figure 69. As shown in Figures 67-69, the strong influence of ionic strength on the drug release profile and RDT value was observed. A decrease in drug release rate occurred with increasing the ionic strength of dissolution medium. As expected, the higher ionic strength led to a greater RDT value (see Figure 69).

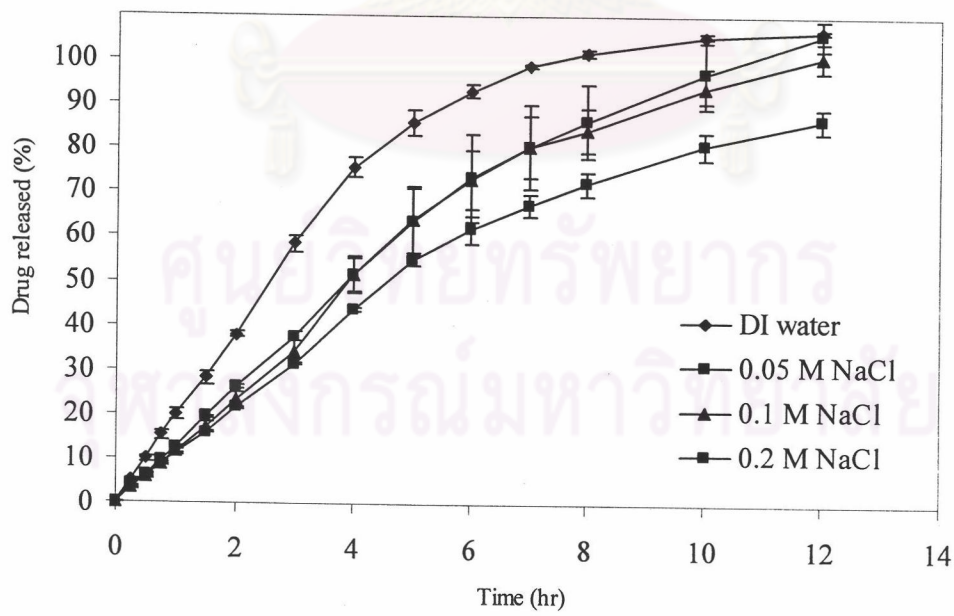


Figure 67 The release profiles of matrices containing lactose and 15%sodium alginate in various ionic strengths of the dissolution medium

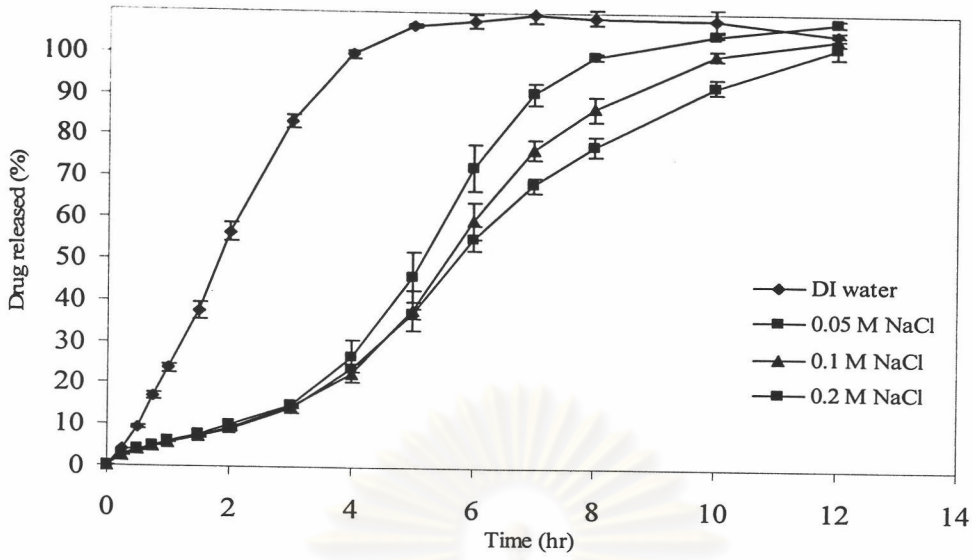


Figure 68 The release profiles of matrices containing dibasic calcium phosphate and 15%sodium alginate in various ionic strengths of the dissolution medium

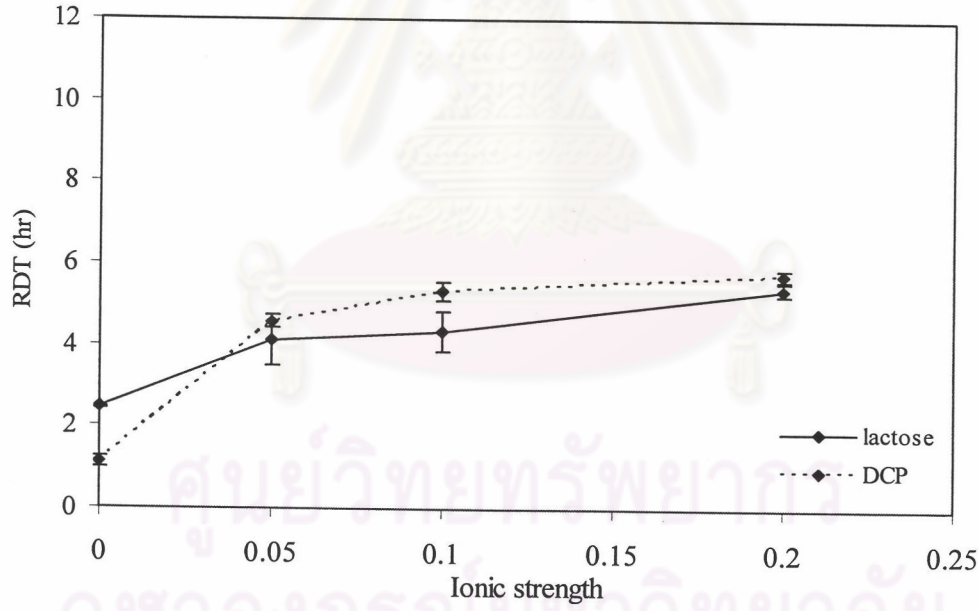


Figure 69 The relationship between the relative dissolution time (RDT value) of sodium alginate matrices containing lactose or dibasic calcium phosphate (DCP) as diluent and ionic strength of the dissolution medium

The obtained results from this study might be explained in terms of added salt effect on the polyelectrolyte chain conformation. Zheng et al. (1998) discussed that the highly charged polyelectrolyte chain in a salt-free aqueous solution would be nearly fully stretched due to strong electrostatic repulsions, which would be screened out with the increase of added salt concentration. This indicated that the reduced electrostatic interaction between the alginate polyanions and the counterion led to the tighter polymer network at increased ionic strength (Bonferoni et al., 1995 and Larsen et al., 2003). This again agreed with the reported contraction of alginate polymer in solutions with increased ionic strength (Nussinovitch, 1997). Consequently, the tighter polymer network caused by an increase in ionic strength resulted in a decrease in drug release rate.

Moreover, It was observed previously that sodium alginate dissolved at a slower rate with increased salt concentration in the medium (Larsen et al., 2003). In addition, Draget (2000) reported that the drive of the dissolution process of alginate became severely reduced when alginate was attempted to be dissolved in an aqueous solvent already containing ions. The slower rate of sodium alginate dissolution in sodium chloride solution might be caused by the tighter polymer network at increased ionic strength of dissolution medium. These findings may also support the obtained result in this study.

5.4 Dissolution study of acyclovir matrices in pH change medium

In order to simulate the environment of the gastro-intestinal tract, the dissolution test was carried out by using pH change dissolution method. The drug release study was performed by using 0.1 N HCl solution as the dissolution medium for initial 2 hours of dissolution test. After that phosphate buffer pH 6.8 solution was used as the dissolution medium. The drug release study was performed for 12 hours.

In order to select the appropriate formulation for investigating the sustained release property in pH change medium, the following criteria were considered.

1. The suitable formulation should produce sufficient sustained release. The drug release rate should not be too rapid or too slow.

2. The suitable formulation should be less sensitive to ionic strength of dissolution medium in order to receive precise and reproducible drug release *in vivo*. Since food and beverage cause an increase in ionic strength of the gastro-intestinal contents (Waaler et al., 1992).

According to the above criteria, the formulation containing 10% HPMC and using lactose as diluent (formulation F1) was chosen for investigating drug release in pH change medium since this formulation could produce sufficient and suitable sustained release. Although the influence of the ionic strength of dissolution medium on drug release from HPMC matrices hydrated in 0.2 M NaCl could be observed, the ionic strength had little effect on drug release in the dissolution medium with ionic strength up to 0.1. Carbopol 934P, xanthan gum and sodium alginate matrices were not chosen because of the following reasons.

1. The carbopol 934P matrices could not produce sustained release.

2. Although the influence of concentration of sodium chloride solution on drug release rate of xanthan gum matrices did not occur in the range of concentrations studied, the very slow drug release rate was observed with xanthan gum matrices. The percent drug release in phosphate buffer pH 6.8 solution was only about 20%. Therefore, xanthan gum matrices were not selected for pH change dissolution study.

3. The strong influence of ionic strength of dissolution medium on drug release rate of sodium alginate matrices was observed.

The release profile of matrices containing 10% HPMC with lactose as diluent (formulation F1) in pH change medium is shown in Figure 70.

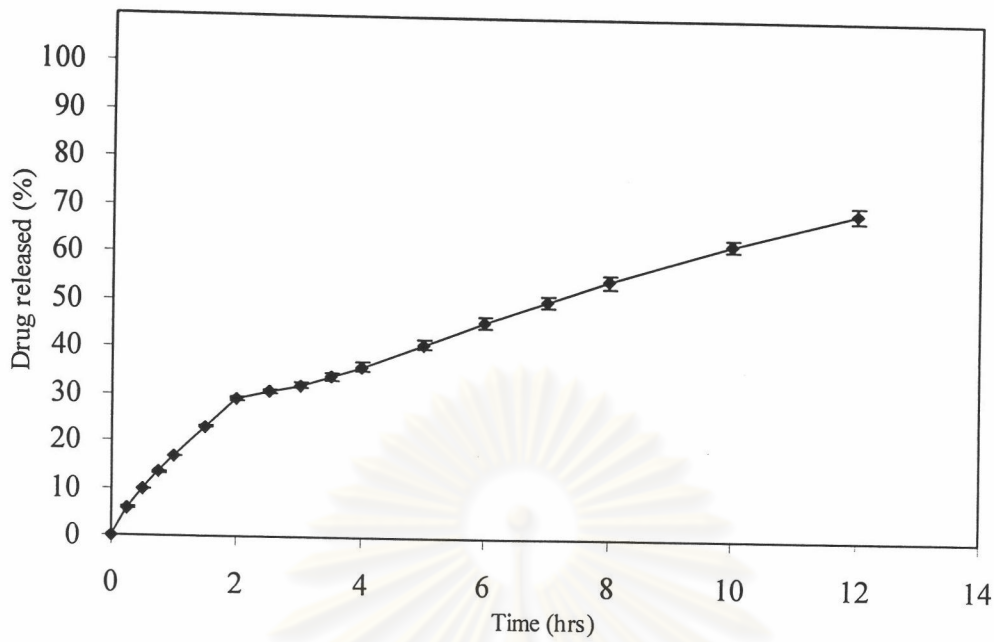


Figure 70 The release profile of matrices containing 10% HPMC and using lactose as diluent (Formulation F1) in pH change medium

As illustrated in Figure 70, the matrices could produce sustained release for 12 hours. The biphasic drug release profile was observed. The drug release rate in 0.1 N HCl solution at the initial 2 hours of dissolution study was faster than that in phosphate buffer pH 6.8 solution during the last 10 hours of dissolution test. This result agreed well with the previous result of this study in which pH of dissolution medium affected drug release rate of HPMC matrices. The drug release rate in 0.1 N HCl solution was faster than that in phosphate buffer pH 6.8 solution (see Figure 44). The rapid erosion rate due to the lower viscosity of hydrated gel layer and the higher solubility of acyclovir in 0.1 N HCl solution might potentially explained this finding. From this result it could be predicted that drug release rate of the matrices would be different in the stomach and the small intestine. Consequently, the precise and reproducible drug release *in vivo* might not occur because of the variation of gastric emptying time. The relative dissolution time (RDT value) was 6.7135 hr ± 0.1210 hr. The RDT value of matrices hydrated in pH change medium was in the range of that in 0.1 N HCl solution (4.3863 hr ± 0.0941 hr) and phosphate buffer pH 6.8 solution (7.8198 hr ± 0.1677 hr).

6. The swelling and erosion of the matrices

In hydrophilic matrix systems, the polymer at the surface of the matrices swells initially during dissolution test to generate an outer viscous gel layer. This phase is then sequentially followed by matrix bulk hydration, swelling and erosion. The overall dissolution rate is controlled by the rate of matrices swelling, drug diffusion through the gel layer and/or matrix erosion. Therefore, the matrix swelling and matrix erosion might be the useful clues to explain the difference in dug release rate of the matrices under the different experimental conditions.

HPMC, xanthan gum and sodium alginate matrices containing 15% polymer and lactose were chosen for investigating the swelling and erosion of the matrices. The determinations of swelling and erosion of the matrices were carried out in dissolution media with differences in pH value and ionic strength. The dissolution media with difference in pH value were 0.1 N HCl solution (pH 1.2) and phosphate buffer pH 6.8 solution. The dissolution media with difference in ionic strength were deionized water and 0.2 M sodium chloride solution, corresponding to ionic strength of 0 and 0.2, respectively. In order to explain the swelling and erosion behaviors of the matrices during drug release study, the experimental conditions applied to determine the swelling and erosion of the matrices were similar to those of the dissolution testing. The experiments were performed at the time intervals of 0.5, 1, 2, 4, 6, 8 and 12 hours. The swelling measurement was not performed in some cases because irregular shapes of the matrices were observed. Consequently, the dimension and estimated the percent swelling of the matrices could not be determined. Therefore, in this case the percent erosion of the matrices was investigated only.

6.1 HPMC matrices

6.1.1 The effect of pH of the dissolution medium on swelling and erosion profiles

The swelling and erosion profiles of HPMC matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution are shown in Figure 71. The percent swelling of the matrices hydrated in both 0.1 N HCl solution and phosphate buffer pH 6.8 solution increased during the initial 2 hours of swelling test. The maximum percent swelling of matrices in both media was about 25%. After that, the percent swelling of the matrices hydrated in 0.1 N HCl solution decreased considerably, indicating that the erosion process began to prevail. The swelling profile of the matrices immersed in phosphate buffer pH 6.8 solution showed a prolonged increase in percent swelling if compared to that in 0.1 N HCl solution. This result indicated that the stronger gel layer was formed around the matrices hydrated in phosphate buffer pH 6.8 solution. This finding was also consistent with the result of viscosity measurement in which the viscosity of HPMC solution in 0.1 N HCl solution was lower than that in phosphate buffer pH 6.8 solution (see Figure 8). However, the percent swelling of the matrices immersed in phosphate buffer pH 6.8 solution trended to decrease after 6 hours of the swelling test, indicating that the erosion process began to predominate.

Since a decrease in percent swelling resulted in a shorter diffusional path length, then faster drug release could occur. Therefore, a decrease in percent swelling of the matrices immersed in 0.1 N HCl solution might be one of the factors that caused the higher drug release rate of the matrices hydrated in 0.1 N HCl solution than those in phosphate buffer pH 6.8 solution.

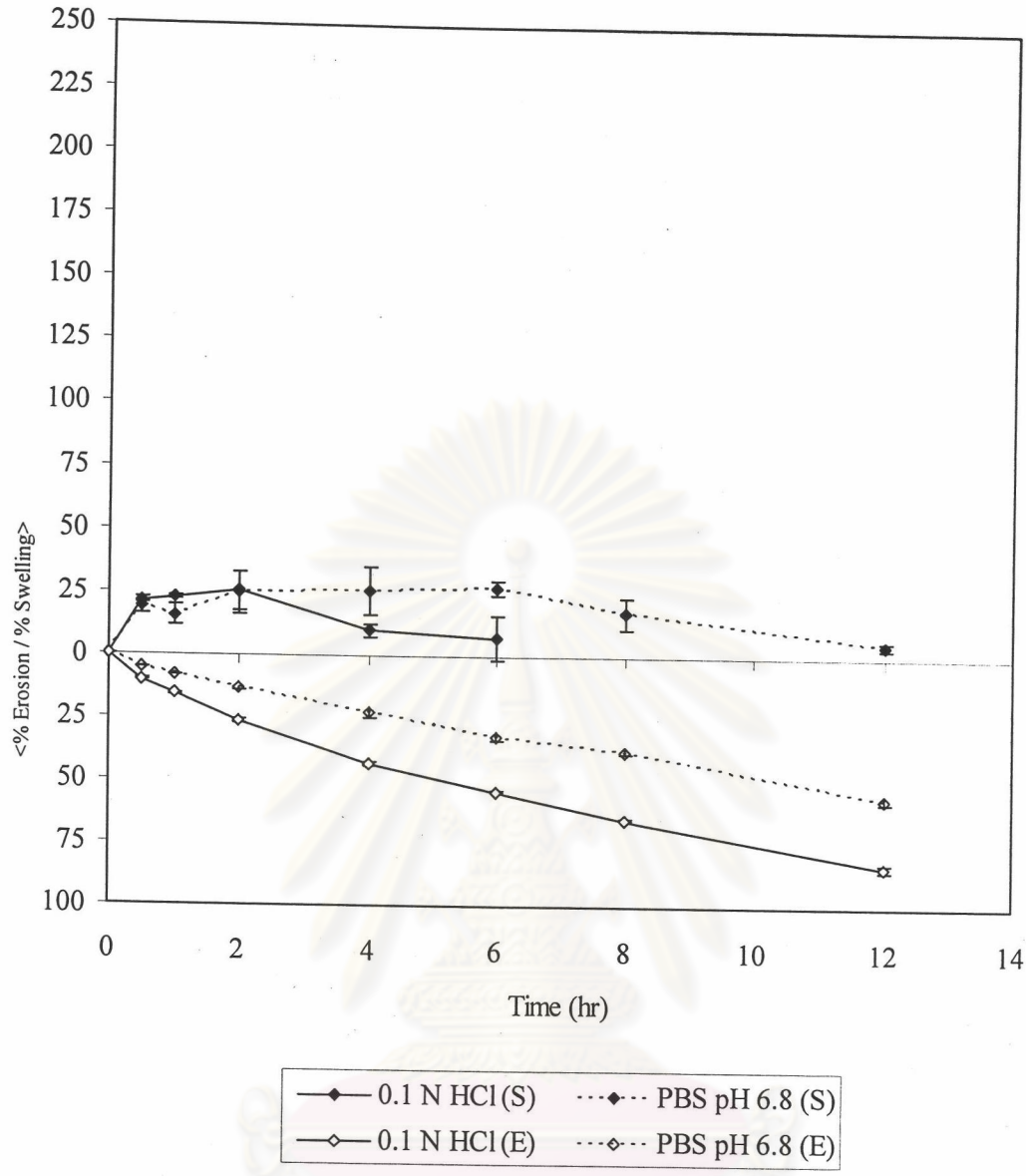


Figure 71 The percent swelling (S) and percent erosion (E) of matrices containing 15% HPMC and lactose in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

According to the erosion profile, the dependence of the erosion rate on the pH of the dissolution medium was observed. The erosion rate of matrices hydrated in 0.1 N HCl solution was much greater than that in phosphate pH 6.8 solution. This might be caused by the lower strength of the gel barrier around the matrices due to the low viscosity of HPMC gel in 0.1 N HCl solution (see Figure 8). Therefore, the hydrated gel barrier around the matrices immersed in 0.1 N HCl solution was more susceptible to erosion than that in phosphate buffer pH 6.8 solution. This result agreed well with the result of the drug release study (see Figure 44). The drug release rate in 0.1 N HCl solution was faster than that in phosphate buffer pH 6.8 solution. This result indicated that the drug release rate was directly correlated to the erosion rate. The more rapid matrix erosion resulted in the higher percent drug release.

6.1.2 The effect of ionic strength of the dissolution medium on drug release

The swelling and erosion profiles of HPMC matrices in deionized water and 0.2 M sodium chloride solution are displayed in Figure 72. The swelling and erosion profiles of HPMC matrices in these dissolution media were almost comparable and displayed the nearly constant swelling rate. This result indicated that the synchronization of matrices swelling and erosion occurred. The high standard deviation values might be caused by the error in estimating tablet dimension due to the irregular shape of the hydrated matrices. However, the dependence of the erosion rate on the ionic strength of dissolution medium was observed. The erosion rate of matrices in deionized water was slightly faster than that in 0.2 M sodium chloride solution. The slower erosion rate of the matrices hydrated in 0.2 M sodium chloride solution might be caused by a stronger gel layer due to increasing extent of hydrophibic HPMC-HPMC layer interaction primarily between methoxy-substituents (Abrahamsson et al., 1998). This finding is consistent with the result of drug release study in which the drug release rate of the matrices in deionized water was faster than that in 0.2 M sodium chloride solution. This result again implied that the drug release rate was directly correlated with the erosion rate.

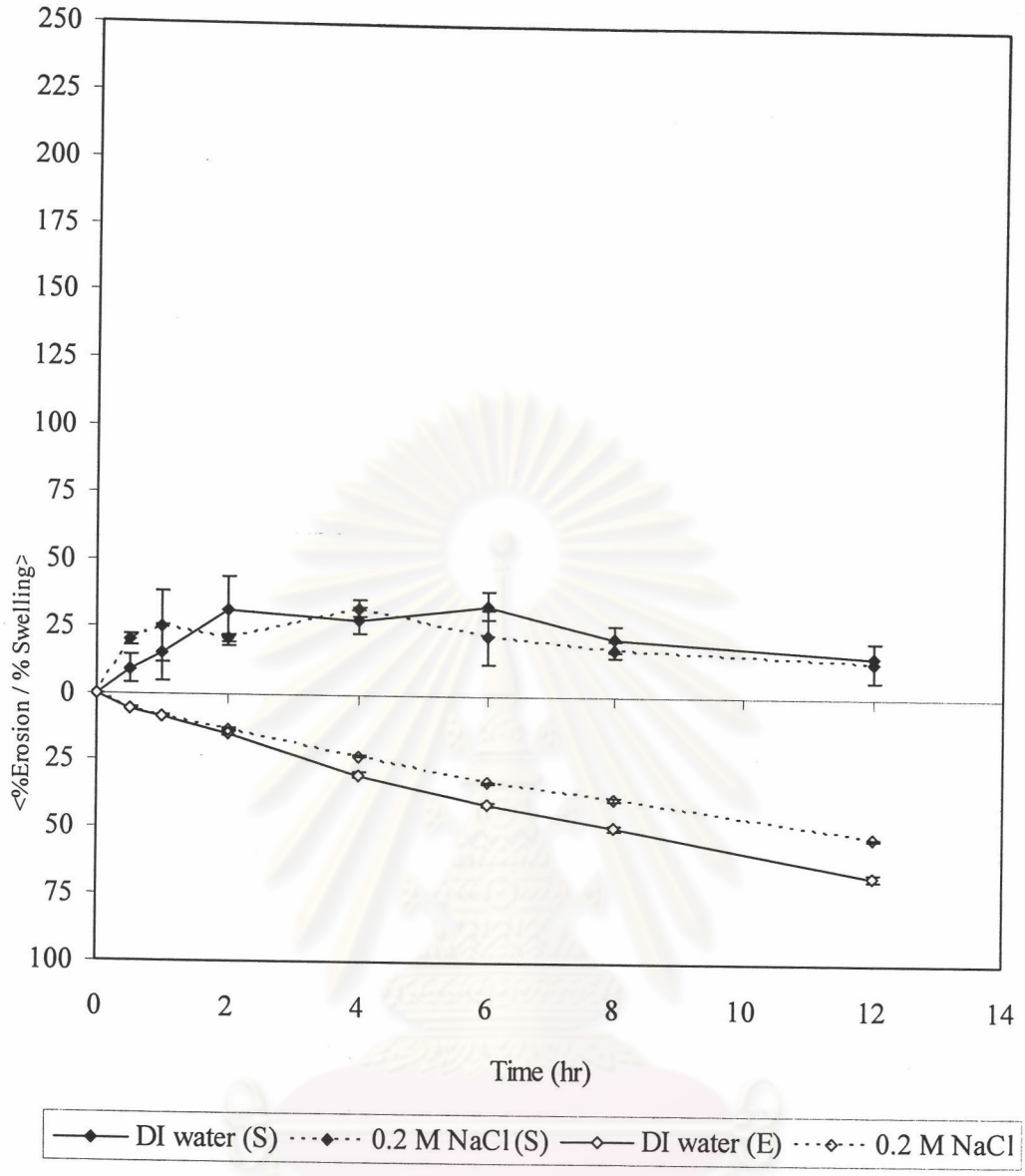


Figure 72 The percent swelling (S) and percent erosion (E) of matrices containing 15% HPMC and lactose in deionized water (DI water) and 0.2 M sodium chloride solution (0.2 M NaCl)

6.2 Xanthan gum matrices

6.1.1 The effect of pH of the dissolution medium on swelling and erosion profiles

Figure 73 presents the swelling and erosion profiles of xanthan gum matrices in dissolution media with difference in pH value. As shown in Figure 73, the xanthan gum matrices immersed in both 0.1 N HCl solution and phosphate buffer pH 6.8 solution underwent rapid swelling as soon as the matrices came in contact with the medium. No lag time could be detected which indicated that the polymer was hydrated quickly and a sufficient boundary gel formed immediately.

This may be supported by the visual observation in which xanthan gum matrices appeared swollen almost from the beginning, and a viscous gel mass was produced when they came in contact with the dissolution medium. In these media, the swelling continued even at the end of the matrices swelling test. This result indicated that gel layer formed was strong enough to avoid matrices erosion. The reason for this finding might be due to the high viscosity of the xanthan gum solution in these media. In addition, these findings agreed with previous study by Talukdar and Kinget (1995). They found that the tablet containing xanthan gum could instantly form a gel layer upon contact with the medium, which would be strong enough to avoid matrices erosion and would significantly retard drug release for a long period of time. The strong influence of pH of dissolution medium on the swelling rate could be noted. The swelling rate of the matrices in phosphate buffer pH 6.8 solution was faster than that in 0.1 N HCl solution. This result is again consistent with previous study by Talukdar and Kinget (1995). They concluded that the swelling rate in acidic medium was significantly lower than in neutral or alkaline solutions. This might be explained in terms of the acidity of xanthan gum molecule. Being an acidic polymer with a pk_a of 3.1, xanthan gum becomes less soluble at such a low pH value.

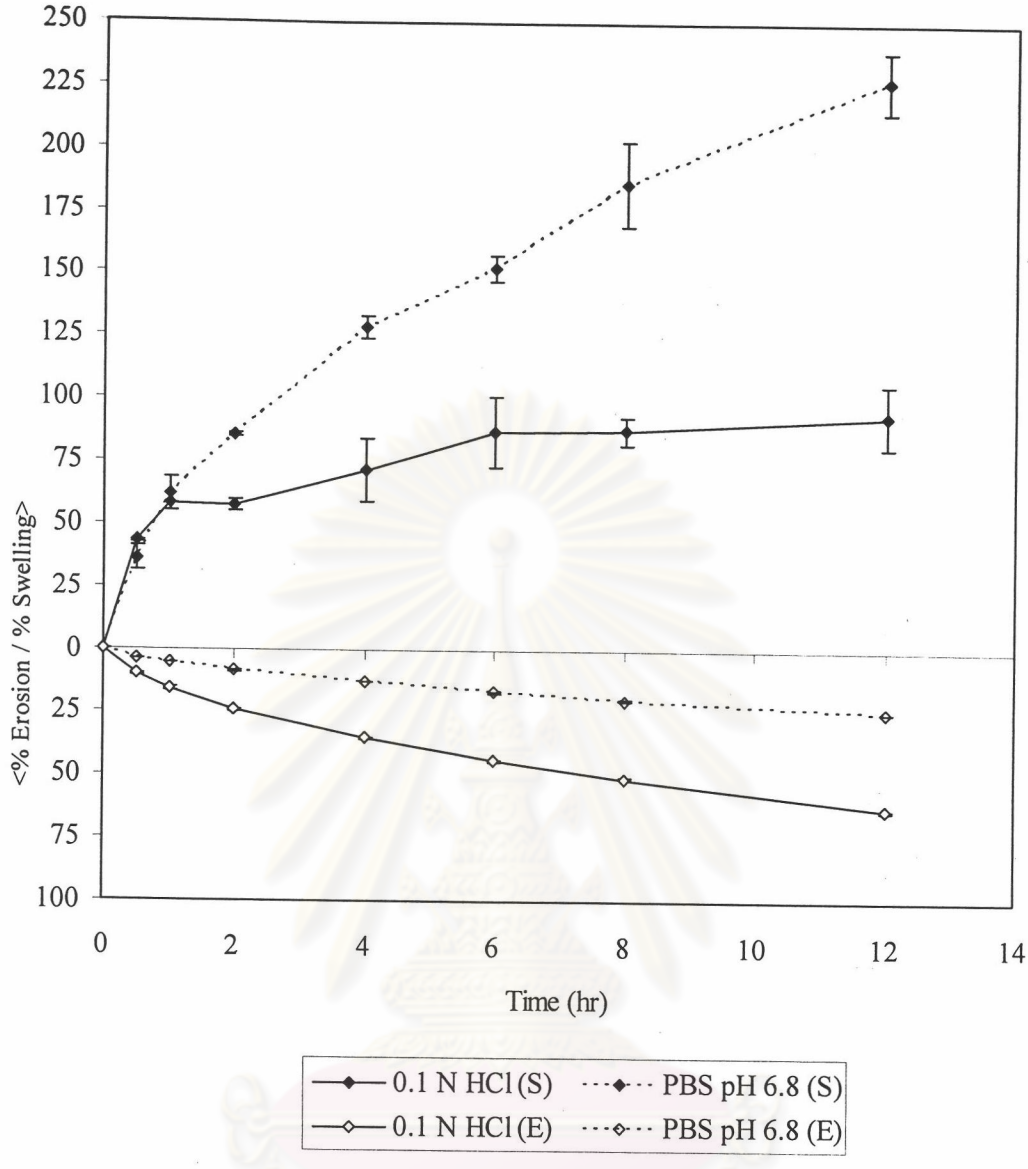


Figure 73 The percent swelling (S) and percent erosion (E) of matrices containing 15% xanthan gum and lactose in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

From the erosion profile, the influence of pH of dissolution medium on erosion rate was also observed. Contrary to matrix swelling, the erosion rate of the matrices in 0.1 N HCl solution was more rapid than in that in phosphate buffer pH 6.8 solution. This pointed out that the erosion profile was inversely related to the swelling profiles. Although the highly swellable property of xanthan gum in phosphate buffer pH 6.8 solution was observed, which might cause the susceptibility of the matrices to erosion, the erosion of the matrices in phosphate buffer pH 6.8 solution was much lower than that in 0.1 N HCl solution. This result indicated that the hydrated gel layer around the matrices was very strong. This finding might be supported by the high viscosity of xanthan gum solution, as in the result of viscosity measurement in this study.

In accordance with the drug release profiles of xanthan gum matrices containing lactose as diluent in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (see Figure 47), the drug release rates were inversely correlated with the swelling rate. Due to the longer diffusional path length of drug, higher matrix swelling resulted in less drug release rate. In contrast, the erosion rate was directly related to the drug release rate. The more matrices erosion led to the more percent drug release. Consequently, both swelling and erosion of matrices controlled the drug release from the matrices.

6.2.2 The effect of ionic strength of the dissolution medium on drug release

As presented in Figure 74, the swelling and erosion of xanthan gum matrices were also examined in dissolution media with difference in ionic strength (deionized water and 0.2 M sodium chloride solution). The determinations of matrix swelling and matrix erosion in deionized water were performed only 2 hours because, after that, the matrices were not intact. Therefore, actual weight and dimensions of the matrices for estimating the percent erosion and swelling of the matrices, respectively, could not be determined.

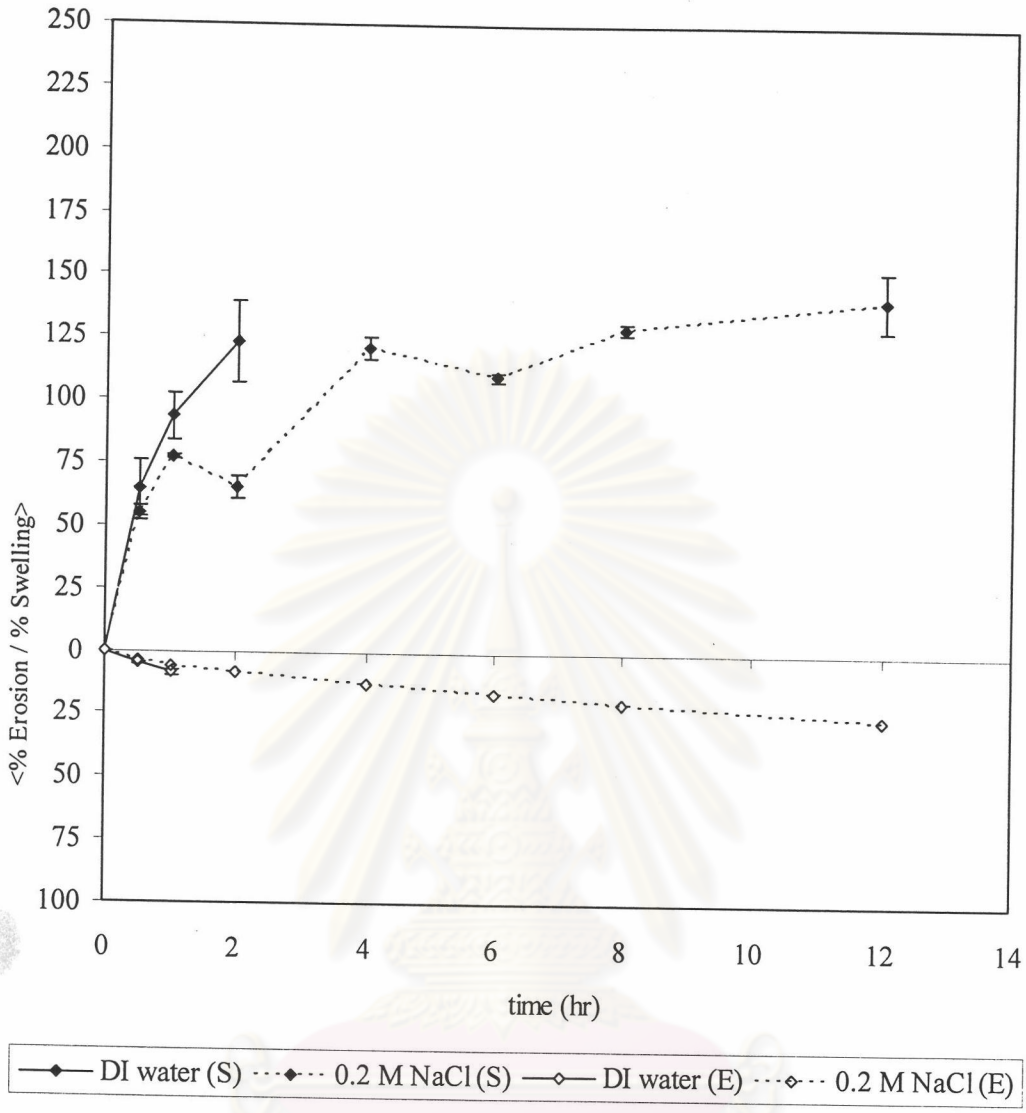


Figure 74 The percent swelling (S) and percent erosion (E) of matrices containing 15% xanthan gum and lactose in deionized water (DI water) and 0.2 M sodium chloride solution (0.2 M NaCl)

Similar to the swelling of the matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution, no lag time was observed for swelling profiles of xanthan gum matrices in deionized water and 0.2 M sodium chloride solution. For matrix swelling in deionized water, at the first 2 hours of swelling profile, the swelling rate of the matrices in deionized water was faster than that in 0.2 M sodium chloride solution. Moreover, by visual observation during the experiment, it was observed that although the matrices immersed in deionized water were intact under the dissolution test conditions, they did not retain their shape when removed from the dissolution vessels to estimate the dimension. This was an indication that fully hydrated matrices were formed. This result was similar to a previous study, Talukdar and Kinget (1995) found that in the absence of salt, xanthan gum swelled to the maximum extent, resulting the presence of fewer or smaller regions of low microviscosity (water-filled pores or microvoids) in the gel microstructure of the hydrated xanthan gum tablet. Therefore, the longer diffusion path length due to the maximum extent of swelling and the formation of fewer or smaller regions of water-filled pores resulted in the lower extent of drug diffusion through the gel layer. This finding could be confirmed by drug release mechanism analysis discussed in the next topic.

In case of matrix swelling in 0.2 M sodium chloride solution, a large extent of swelling was observed even at 12 hours of swelling test. The percent swelling of the matrices at 12 hours was about 140%. This indicated that the very strong gel layer was formed. This result was consistent with the viscosity measurement in this study in which the viscosity of xanthan gum solution was dramatically increase with an addition of salt. Furthermore, the stronger gel layer made the matrices more resistant to erosion. As shown in Figure 74, the percent erosion of the matrices at 12 hours was only about 26%.

6.3 sodium alginate matrices

6.3.1 The effect of pH of the dissolution medium on swelling and erosion profiles

The swelling and erosion profiles of sodium alginate matrices in 0.1 N HCl solution is shown in Figure 75. The swelling profile of sodium alginate matrices in phosphate buffer pH 6.8 solution was not shown because the rough surface and irregular shape of matrices was observed. Therefore, only the matrix erosion was investigated.

As presented in Figure 75, the swelling of the sodium alginate matrices hydrated in 0.1 N HCl solution was observed. The percent swelling of the matrices between 2-12 hours seemed to be constant. This result confirms that alginic acid which converts from sodium alginate in 0.1 N HCl solution has the ability to swell on hydration (Hodsdon et al., 1995). However, the intact but porous structure in which much of undissolved polymer is formed (Hodsdon et al., 1995). Moreover, by visual observation during the matrix swelling test, the porous, tough and rubbery texture of the matrices, which caused the matrices more resistant to erosion, was observed. This resulted in the constant percent swelling of the sodium alginate matrices hydrated in 0.1 N HCl solution. This was also supported by visual observation in which the sodium alginate matrices remained intact at 12 hours of matrix erosion test. Consequently, the contribution of the matrix erosion merely occurred. However, the percent erosion of the matrices in 0.1 N HCl solution even at 12 hours was about 50%. Therefore, the weight loss of the matrices during the erosion test might be due to the diffusion of drug molecules to the dissolution medium.

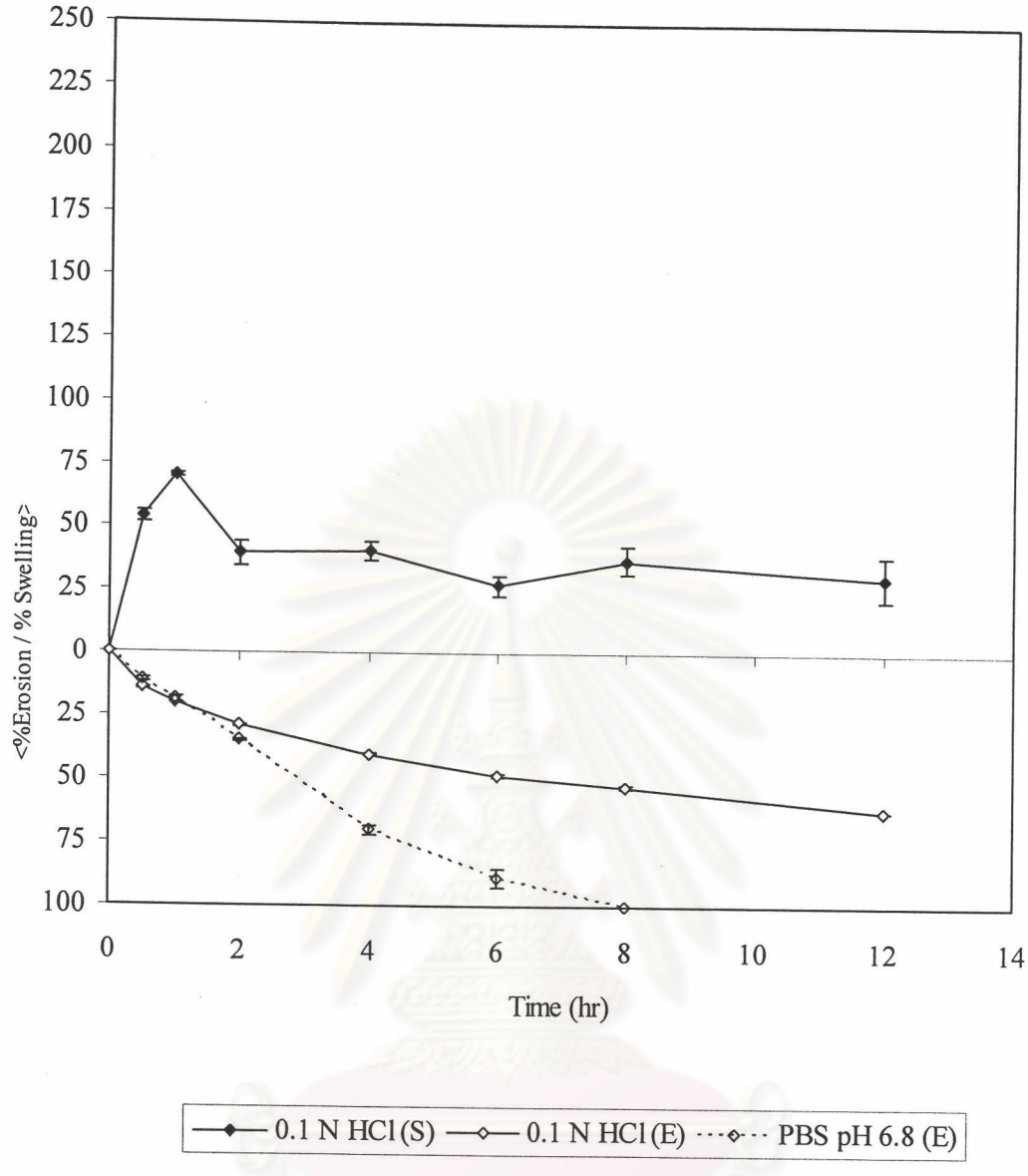


Figure 75 The percent swelling (S) and percent erosion (E) of matrices containing 15% sodium alginate and lactose in 0.1 N HCl solution and phosphate buffer pH 6.8 solution (PBS pH 6.8)

In case of sodium alginate matrices hydrated in phosphate buffer pH 6.8 solution, the erosion rate of the matrices was very rapid. They completely eroded at about 8 hours of matrix erosion test. The rapid erosion was reflected well the fast drug release rate from sodium alginate matrices in phosphate buffer solution pH 6.8 (see Figure 50). Therefore, the erosion of the matrices could be used as a evidence to elucidate the dissolution performance.

6.3.2 The effect of ionic strength of the dissolution medium on drug release

The swelling and erosion profiles of the matrices were also investigated in dissolution media with difference in ionic strength, as shown in Figure 76. The matrix swelling measurement of sodium alginate matrices hydrated in deionized water was performed for 2 hours only because, after that, the rough surface and irregular shape of the matrices was observed. At first 2 hours of the experiment, the percent swelling of the matrices in 0.2 M sodium choloride solution seemed to be higher than that in deionized water. However, after the first hours of the test, percent swelling of the matrices in 0.2 M sodium chloride solution trended to decrease with time.

This was an indication that the low strength of gel layer was formed, resulting in less resistance of the matrices to erosion. This finding might be supported by the result of viscosity measurement in this study in which the viscosity of sodium alginate solution was less than that of HPMC and xanthan gum solutions in the same medium.

In the consideration of erosion profiles, the strong dependence of the erosion rate on the ionic strength of dissolution medium was observed. An increase ionic strength of dissolution medium exhibited a decrease in matrix erosion rate. The matrices hydrated in deionized water completely eroded at about 6 hours. It is important to indicate that an increase in ionic strength of dissolution medium led to a decrease in drug release rate of sodium alginate matrices (see Figure 67). This might be caused by the slower erosion rate of gel layer around the matrices hydrated in higher ionic strength of dissolution medium. This result again indicated that the matrices erosion rate was directly related to the drug release rate. The more matrix

erosion resulted in the more drug release from the matrices. The slower erosion rate of the matrices hydrated in 0.2 M sodium chloride solution might be due to a stronger gel layer caused by the tighter polymer network at higher ionic strength of the dissolution medium.

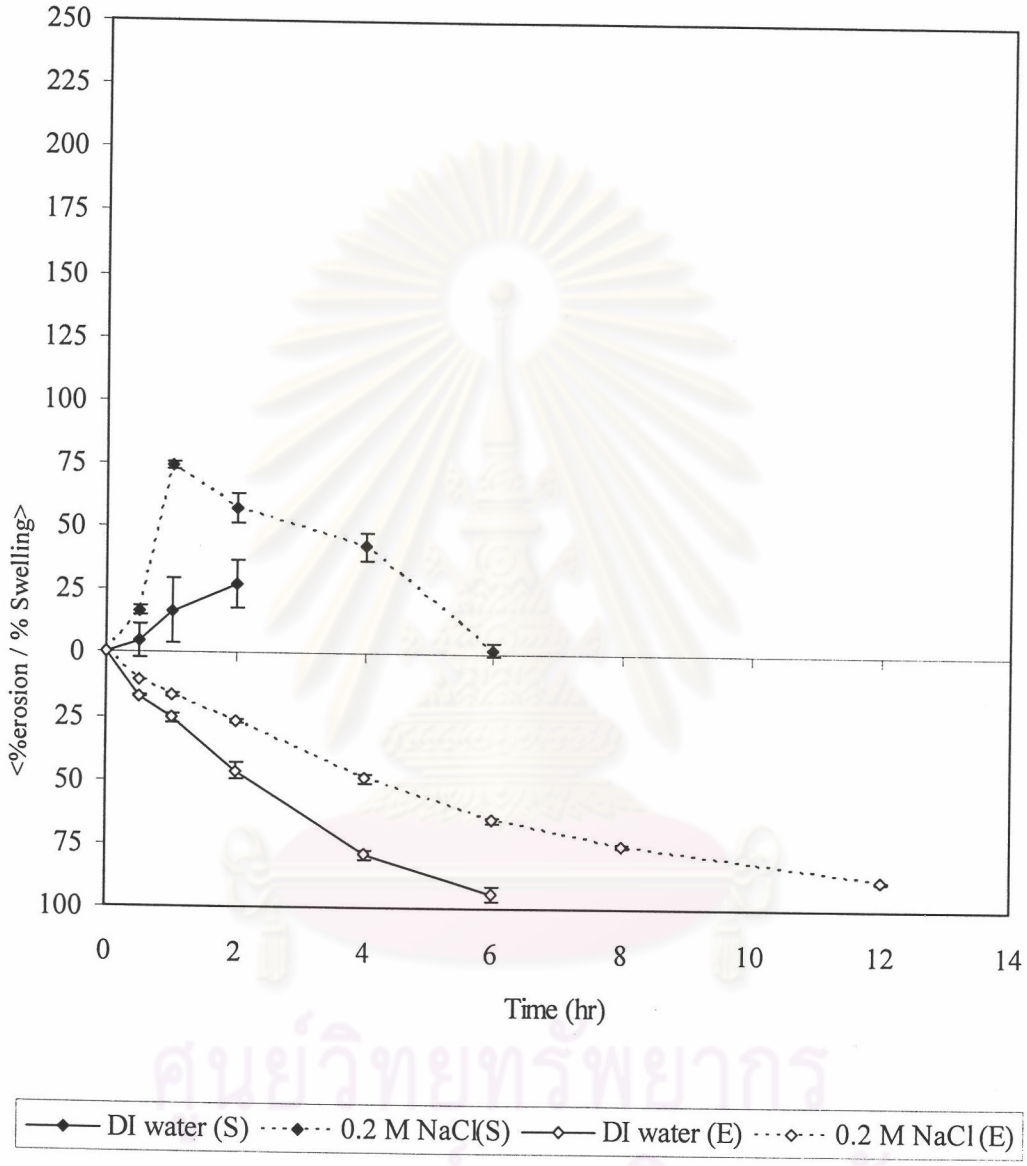


Figure 76 The percent swelling (S) and percent erosion (E) of matrices containing 15% sodium alginate and lactose in deionized water (DI water) and 0.2 M sodium chloride solution (0.2 M NaCl)

7. Release mechanism analysis

The drug release mechanism of polymeric matrix was investigated by fitting the dissolution data into the exponential equation given below:

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is the fraction of drug released (0-0.60), t is the release time, k is a kinetic constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of drug release. In case of a tablet, n = 0.45 for Case I or Fickian diffusion, n = 0.89 for Case II transport, $0.45 < n < 0.89$ for anomalous or non–Fickian transport and $n > 0.89$ for super Case II transport (Ritger and Peppas, 1987).

The drug release mechanism of HPMC, xanthan gum and sodium alginate matrices containing lactose or dibasic calcium phosphate as diluent in various dissolution media was investigated. The effects of pH (0.1 N HCl solution, pH 1.2 and phosphate buffer pH 6.8 solution) and ionic strength (deionized water, 0.05 M, 0.1 M and 0.2 M sodium chloride solutions corresponding to ionic strength of 0, 0.05, 0.1 and 0.2, respectively) of dissolution medium and the type of diluent (lactose and dibasic calcium phosphate) on drug release mechanism were discussed. Moreover, in case of drug release in 0.1 N HCl solution and phosphate buffer pH 6.8 solution, the influence of polymer concentration on drug release mechanism was also discussed.

7.1 HPMC matrices

The values of release exponent (n) and coefficient of determination (r^2) following linear regression of dissolution data of HPMC matrices in various dissolution media are shown in Table 11.

Table 11 Values of release exponent (n) and coefficient of determination (r^2) of hydroxypropyl methylcellulose (HPMC) matrices in various dissolution media (mean (SD), n=3)

Diluent	Dissolution media	% Polymer					
		10%		15%		20%	
		n	r^2	n	r^2	n	r^2
Lactose	0.1 N HCl	0.7666 (0.0087)	0.9993	0.7273 (0.0035)	0.9999	0.6970 (0.0083)	0.9988
	PBS pH 6.8	0.9276 (0.0027)	0.9977	0.9667 (0.0059)	0.9988	0.9010 (0.0046)	0.9969
	Deionized water	-	-	1.0024 (0.0036)	0.9984	-	-
	0.05 M NaCl	-	-	1.0070 (0.0097)	0.9979	-	-
	0.1 M NaCl	-	-	0.9930 (0.0050)	0.9984	-	-
	0.2 M NaCl	-	-	0.9400 0.0065	0.9985	-	-
Dibasic calcium phosphate	0.1 N HCl	0.8219 (0.0061)	0.9988	0.7781 (0.0053)	0.9996	0.7143 (0.0037)	0.9996
	PBS pH 6.8	0.8947 (0.0027)	0.9994	0.8975 (0.0094)	0.9983	0.8915 (0.0239)	0.9987
	Deionized water	-	-	0.9998 (0.0108)	0.9984	-	-
	0.05 M NaCl	-	-	0.9848 (0.0055)	0.9989	-	-
	0.1 M NaCl	-	-	0.9606 (0.0040)	0.9987	-	-
	0.2 M NaCl	-	-	0.9097 (0.0066)	0.9991	-	-

7.1.1 The effect of pH of dissolution medium on drug release mechanism

As shown in Table 11, the values of release exponent (n) of HPMC matrices containing lactose or dibasic calcium phosphate as diluent in 0.1 N HCl solution were in the range of 0.6970-0.8219, indicating the mechanism of anomalous transport. This result pointed out that the HPMC matrices released the drug in 0.1 N HCl solution via the combination of diffusion and polymer relaxation mechanism. In phosphate buffer pH 6.8 solution, the drug release mechanism of lactose and dibasic calcium phosphate containing matrices was super Case II transport with n values of 0.8915-0.9667. This was an indication that the polymer relaxation acted as dominant mechanism in controlling drug release from the matrices.

Therefore, the obtained results indicated that the pH of dissolution medium affected the release mechanism of HPMC matrices. In acidic pH, the release mechanisms were a combination of diffusion and polymer relaxation, while only the polymer relaxation or matrix erosion controlled drug release in PBS pH 6.8. The reason for this finding might be due to the difference in solubility of acyclovir in media with difference in pH value. From the solubility determination in this study, acyclovir was soluble in 0.1 N HCl solution, whereas the poor solubility was observed in phosphate buffer pH 6.8 solution. Consequently, when the dissolution medium penetrated into the matrices immersed in 0.1 N HCl solution, the dissolved drug could diffuse out. Moreover, drug might also be released by erosion of the gel. Conversely, the poor solubility of acyclovir in phosphate buffer pH 6.8 solution caused relative low ability of the drug to diffuse out when the dissolution medium moved toward the center of the matrices. Therefore, the drug release in phosphate buffer pH 6.8 solution was mainly controlled by polymer relaxation. This finding is consistent with a previous report by Alderman (1984). The author concluded that the water-soluble drugs were released by diffusion and/or erosion mechanism, while the drug released of water-insoluble drug controlled mainly by polymer relaxation or erosion mechanism.

7.1.2 The effect of ionic strength of dissolution medium on drug release mechanism

In case of drug release in dissolution media with various ionic strengths, no influence of drug release mechanism on the ionic strength of dissolution medium could be noted for both lactose and dibasic calcium phosphate containing matrices. The values of release exponent (n) were more than 0.89, expressing release mechanism of Super Case II transport. This was an indication that drug release in these dissolution media was governed by polymer relaxation. This result could be explained in terms of the poor solubility of acyclovir in these media. From the result of solubility determination, acyclovir was slightly soluble in deionized water and sodium chloride solutions (see Table 8).

7.1.3 The effect of polymer concentration on drug release mechanism

The independence of drug release mechanism with respect to the polymer concentration was evident. The drug release mechanism of 10%, 15% and 20% polymer containing matrices in the same dissolution medium was similar.

7.1.4 The effect of type of diluent on drug release mechanism

The type of diluent (lactose and dibasic calcium phosphate) had no effect on drug release mechanism. For both lactose and dibasic calcium phosphate containing matrices, the mechanism of drug release in 0.1 N HCl solution was anomalous transport which the combination of diffusion and polymer relaxation controlled the drug release from the matrices. The predominant polymer relaxation was mainly regulated drug release in phosphate buffer pH 6.8 solution, deionized water and sodium chloride solutions with various ionic strengths.

7.2 xanthan gum matrices

The values of release exponent (n) and coefficient of determination (r^2) following linear regression of dissolution data of xanthan gum metrices in various dissolution media are shown in Table 12.

Table 12 Values of release exponent (n) and coefficient of determination (r^2) of xanthan gum matrices in various dissolution media (mean (SD), n=3)

Diluent	Dissolution media	% Polymer					
		10%		15%		20%	
		n	r^2	n	r^2	n	r^2
Lactose	0.1 N HCl	0.7050 (0.0238)	0.9963	0.6513 (0.0027)	0.9991	0.6293 (0.0080)	0.9989
	PBS pH 6.8	0.7927 (0.0061)	0.9965	0.8049 (0.0073)	0.9973	0.8104 (0.0018)	0.9955
	Deionized water	-	-	1.0837 (0.0423)	0.9909	-	-
	0.05 M NaCl	-	-	0.8366 (0.0044)	0.9977	-	-
	0.1 M NaCl	-	-	0.8050 (0.0057)	0.9987	-	-
	0.2 M NaCl	-	-	0.7964 0.0155	0.9960	-	-
Dibasic calcium phosphate	0.1 N HCl	0.8465 (0.0317)	0.9996	0.7008 (0.0057)	0.9992	0.6560 (0.0034)	0.9993
	PBS pH 6.8	0.7792 (0.0096)	0.9977	0.7792 (0.0096)	0.9977	0.8195 (0.0082)	0.9979
	Deionized water	-	-	1.0722 (0.0088)	0.9972	-	-
	0.05 M NaCl	-	-	0.8638 (0.0054)	0.9995	-	-
	0.1 M NaCl	-	-	0.8038 (0.0050)	0.9992	-	-
	0.2 M NaCl	-	-	0.7886 (0.0112)	0.9993	-	-

7.2.1 The effect of pH of dissolution medium on drug release mechanism

There was no effect of pH of dissolution medium on drug release mechanism from xanthan gum matrices. The drug release mechanisms of xanthan gum matrices in 0.1 N HCl solution and phosphate buffer pH 6.8 solution were anomalous transport because the n values were in the limits of 0.45-0.89. This indicated that the drug releases in these dissolution media were governed by both diffusion and polymer relaxation. Although the drug release mechanisms in both dissolution media were similar (anomalous transport), the n values ranged between 0.6293-0.8465. This difference in n value indicated that the quantitative contribution of drug released by diffusion and polymer relaxation was different (Peppas and Sahlin, 1989).

Generally, water insoluble drugs are released by mechanism of polymer relaxation (Alderman, 1984). However, in this study, the mechanism of drug release in phosphate buffer pH 6.8 solution was anomalous transport with the contribution of both diffusional transport and polymer relaxation. This indicated that the drug was partly released by diffusion mechanism. From viscosity measurement in this study, the high viscosity of xanthan gum solution resulted in the formation of stronger protective gel barrier around the matrices. Thus, the matrices were less susceptible to erosion. Therefore, the role of the diffusion mechanism in controlling drug release from the matrices could increase. Moreover, acyclovir was partially soluble in phosphate buffer pH 6.8 solution (2.73 mg/ml, see Table 8). Consequently, the contribution of diffusion release mechanism could slightly occur. This finding pointed out that the drug release mechanism not only depended on the solubility of drug in dissolution medium but also the mechanical property of the protective gel barrier. However, the poor solubility of acyclovir and the less susceptibility of the matrices to erosion resulted in very slow drug release rate of the xanthan gum matrices hydrated in phosphate buffer pH 6.8 solution (see Figures 24 and 25).

7.2.2 The effect of ionic strength of dissolution medium on drug release mechanism

The biphasic release profiles of xanthan gum matrices containing lactose or dibasic calcium phosphate as diluent are shown in Figures 64 and 65. The marked increase in drug release rate during the 5^{th} – 12^{th} hours of dissolution test might be caused by the attrition of outer gel layer around the matrices due to the movement of the matrices around the perforated plates at the bottom of dissolution vessels, which was observed visually. Therefore, in order to investigate the drug release mechanism, the dissolution data during the first 5 hours of dissolution test were only fitted into the equation of Ritger and Peppas (1987).

The drug release mechanism of xanthan gum matrices in deionized water was Super Case II transport with n values of 1.0837 and 1.0722 for lactose and dibasic calcium phosphate containing matrices, respectively. This was an indication that the drug release was predominately controlled by polymer relaxation. The obtained n values of drug release in sodium chloride solutions with various concentrations (0.05 M, 0.1 M and 0.2 M NaCl) expressed the anomalous transport ($0.45 < n < 0.89$), indicating the contribution of both diffusion and polymer relaxation in drug release from the matrices. Therefore, these results pointed out that addition of salt into the dissolution medium resulted in the change of drug release mechanism. The drug release mechanism of xanthan gum was shifted from Super Case II transport to anomalous transport when the salt was added into the dissolution medium. However, in the presence of salt in dissolution medium, and increase in ionic strength of dissolution medium did not further affect the mechanism of drug release. The drug release mechanism in sodium chloride solutions with various ionic strengths was an anomalous transport. Nevertheless, since the difference in n value was observed, the drug release mechanism in various concentrations of sodium chloride solution was different in terms of extents of contribution between diffusion and polymer relaxation.

This finding is consistent with previous investigation by Talukdar and Kinget (1995). They found that in the absence of salt, the polymer swelled to the maximum extent, resulting in fewer or smaller regions of low microviscosity (water-filled pores or microvoids) present in the gel microstructure of the hydrated xanthan gum tablet. In this case the drug release is controlled by the degree of swelling of the polymer, the polymer relaxation and matrix erosion. Therefore, the drug release mechanism follows Super Case II transport. In contrast, in the presence of salt, the polymer partially swells and there are larger regions of low microviscosity, which results in an increase in the free volume due to the presence of the micropores. This may manifest itself as a shift in the release mechanism (Talukdar and Kinget, 1995).

7.2.3 The effect of polymer concentration on drug releasse mechanism

The polymer concentration had no effect on drug release mechanism. The drug release from the matrices with difference in polymer concentration in 0.1 N HCl solution and phosphate buffer pH 6.8 solution followed the same drug release mechanism (anomalous transport, $0.45 < n < 0.89$). However, the difference in n value was observed. Therefore, although no influence of polymer concentration on drug release mechanism could be noted, the quantitative contributions of diffusion and polymer relaxation might be different.

7.2.4 The effect of type of diluent on drug release mechanism

No influence of the type of diluent on drug release mechanism was observed. The drug release mechanism of lactose and dibasic calcium phosphate containing matrices in 0.1 N HCl solution, phosphate buffer pH 6.8 solution and sodium chloride solutions was anomalous transport with different n values. Consequently, the quantitative contributions of diffusion and polymer relaxation might be different, although these matrices followed the same anomalous transport mechanism. The drug release mechanism of both lactose and dibasic calcium phosphate containing matrices in deionized water was Super case II transport, in which the contribution of polymer relaxation predominately controlled the drug release.

7.3 sodium alginate matrices

The values of release exponent (n) and coefficient of determination (r^2) of sodium alginate matrices in various dissolution media are presented in Table 13.

7.3.1 The effect of pH of dissolution medium on drug release mechanism

The dependence of drug release mechanism on pH of the dissolution medium was observed. In case of drug release in acidic pH (0.1 N HCl solution, pH 1.2), the drug release mechanism was Fickian diffusion or anomalous transport, depending on the polymer concentration in the matrices. On the contrary, the large contribution of polymer relaxation controlled the drug release in phosphate buffer pH 6.8 solution. This result might be due to the difference in sodium alginate solubility in media with different pH values. In phosphate buffer pH 6.8, sodium alginate was soluble and hydrated viscous protective gel layer around the matrices could be formed. The continuous gel layer formed in phosphate buffer pH 6.8 solution acted as the diffusion barrier. Moreover, from the result of the viscosity measurement in this study, the low viscosity of sodium alginate solution caused the lower gel strength of the gel layer around the matrices, resulting in more susceptibility of the matrices to erosion. Therefore, the drug release from sodium alginate matrices in phosphate buffer pH 6.8 solution occurred mainly from matrix erosion or polymer relaxation.

On the other hand, sodium alginate is rapidly converted to alginic acid in 0.1 N HCl solution (Hodsdon et al., 1995). Thus, in acidic pH, the porous, tough and rubbery texture of hydrated matrices was formed instead of the continuous gel barrier formed at pH 6.8. In addition, the tough mechanical property of the hydrated matrices formed at acidic pH made the matrices less susceptible to erosion in 0.1 N HCl solution. Moreover, from the result of solubility determination in this study, acyclovir was soluble in 0.1 N HCl solution. These results indicated that the drug could diffuse out of the matrices when dissolution medium penetrated into the matrices.

Table 13 Values of release exponent (n) and coefficient of determination (r^2) of sodium alginate matrices in various dissolution media (mean (SD), n=3)

	Dissolution media	% Polymer					
		10%		15%		20%	
		n	r^2	n	r^2	n	r^2
Lactose	0.1 N HCl	0.4585 (0.0035)	0.9980	0.5332 (0.0028)	0.9992	0.6139 (0.0075)	0.9987
	PBS pH 6.8	0.9621 (0.0187)	0.9989	1.1710 (0.0147)	0.9986	1.2496 (0.0307)	0.9978
	PBSpH6.8+ NaCl	-	-	1.0546 (0.0113)	0.9994	-	-
	Deionized water	-	-	0.9813 (0.0106)	0.9994	-	-
	0.05 M NaCl	-	-	1.0046 (0.0268)	0.9997	-	-
	0.1 M NaCl	-	-	1.0008 (0.0367)	0.9971	-	-
	0.2 M NaCl	-	-	0.9252 0.0091	0.9963	-	-
Dibasic calcium phosphate	0.1 N HCl	0.4060 (0.0045)	0.9939	0.4661 (0.0064)	0.9968	0.5444 (0.0012)	0.9991
	PBS pH 6.8	0.8844 (0.0054)	0.9977	1.1154 (0.0069)	0.9972	1.2679 (0.0027)	0.9981
	PBSpH6.8+ NaCl	-	-	1.2689 (0.0222	0.9554	-	-
	Deionized water	-	-	1.2673 (0.0224)	0.9993	-	-
	0.05 M NaCl	-	-	0.9931 (0.0333)	0.9280	-	-
	0.1 M NaCl	-	-	0.9876 (0.0221)	0.9251	-	-
	0.2 M NaCl	-	-	0.9579 (0.0012)	0.9158	-	-

Consequently, the drug release mechanism in 0.1 N HCl solution did not corresponding to a large contribution of polymer relaxation or matrices erosion, but the mechanism of drug release followed Fickian diffusion or anomalous transport in which the contribution of both diffusion and polymer relaxation controlled drug release.This difference in drug release mechanism of the matrices immersed in 0.1 N HCl solution and phosphate buffer pH 6.8 solution was reflected well in the difference in pattern of drug release profile of sodium alginate matrices in these dissolution media (see Figures 50 and 51).

Additionally, the drug release mechanism of sodium alginate matrices in phosphate buffer pH 6.8 solution with ionic strength adjusted to 0.1 with sodium chloride (PBS pH 6.8 + NaCl) was also investigated and the result is presented in Table 13.

The difference in drug release mechanism of the matrices hydrated in dissolution media with different pH values but equal ionic strength (0.1 N HCl solution (pH 1.2, ionic strength = 0.1) and PBS pH 6.8 + NaCl (ionic strength = 0.1)) was observed. The obtained n values of drug release in dissolution media with different ionic strengths but equal pH values (PBS pH6.8 (ionic strength about 0.07) and PBS pH 6.8 + NaCl (ionic strength = 0.1)) expressed the same drug release mechanism, which was mainly controlled by a large contribution of polymer relaxation or matrix erosion. This result indicated that the drug release mechanism depended on pH of the dissolution medium, while the ionic strength of dissolution medium had no effect on drug release mechanism. This support the obtained result in this study where the dissolution media with difference in pH value caused the difference in drug release pattern, while the dissolution media with difference in ionic strength gave the same drug release pattern but with different drug release rates (see Figures 59 and 60).

7.3.2 The effect of ionic strength of the dissolution medium on drug release mechanism

For drug release in dissolution media with various ionic strengths, there was no effect of ionic strength of dissolution medium on drug release mechanism. The drug release mechanism was Super Case II transport because the values of release exponent (n) were more than 0.89. This was an indication that the drug release was predominately controlled by polymer relaxation. The reason for this finding might be explained in terms of the low viscosity of sodium alginate solution and the poor solubility of acyclovir in these dissolution media, as in the result of viscosity and solubility determinations, respectively. The low viscosity of hydrated gel layer around the matrices caused the higher susceptibility of the matrices to erosion. In addition, since sodium alginate could dissolve and form continuous gel barrier around the matrices, which acted as barrier for the drug to diffuse out. Moreover, the poor solubility of acyclovir also resulted in the low ability of the drug to diffuse out of the matrices. Therefore, the mechanism of drug release was mainly controlled by polymer relaxation or matrix erosion. This result pointed out that the solubility of the drug in dissolution medium and the physical and mechanical properties of the hydrated surface gel layer around the matrices played an important role in determining drug release mechanism.

7.3.3 The effect of polymer concentration on drug release mechanism

In case of drug release in 0.1 N HCl solution, the influence of polymer concentration on drug release mechanism was observed. The release mechanism of 15% and 20% polymer containing matrices was anomalous transport while that of matrices comprising 10% polymer was close to Fickian diffusion with n values of 0.4585 and 0.4060 for lactose and dibasic calcium phosphate containing matrices, respectively. This result indicated that the contribution of polymer relaxation was not observed with 10% polymer containing matrices. This finding was possibly attributed to the differences in porosity and tortuosity in the matrices. Lactose is a soluble diluent and dibasic calcium phosphate can slowly dissolve in 0.1 N HCl solution. Therefore, the high diluent containing matrices (corresponding to low polymer

concentration) had higher porosity and lower tortuosity in the matrices so that the large contribution of drug diffusion might occur.

No influence of polymer concentration on drug release mechanism in phosphate buffer pH 6.8 solution could be noted. The obtained n values indicated that a large contribution of polymer relaxation controlled drug release form the matrices with different polymer concentrations in phosphate buffer pH 6.8 solution.

7.3.4 The effect of the type of diluent on drug release mechanism

No influence of the type of diluent on drug release mechanism was observed. For both lactose and dibasic calcium phosphate containing matrices, the drug release from sodium alginate matrices in phosphate buffer pH 6.8 solution and various ionic strengths of dissolution medium was mainly controlled by polymer relaxation or matrix erosion. The drug release mechanism of the matrices with 10% polymer content in 0.1 N HCl solution was close Fickian diffusion, while the higher polymer containing matrices displayed the anomalous transport mechanism.

8. Surface morphology of acyclovir matrices

Since the appearances of matrices after being immersed in the dissolution medium might be the important clues to predict and determine the predominant mechanism of drug release from the matrices, the surface morphology of HPMC, xanthan gum and sodium alginate matrices containing lactose as diluent was monitored via scanning electron microscopy. The matrices were investigated both before and after contacting with the dissolution medium. The dissolution media used for investigating surface morphology of matrices after dissolution test were 0.1 N HCl solution, phosphate buffer pH 6.8 dissolution, deionized water and 0.2 M sodium chloride solution. In case of HPMC and xanthan gum matrices, they were investigated after immersing in dissolution medium for 2, 6 and 12 hours. Sodium alginate matrices were evaluated after contacting with dissolution medium for 2, 4 and 6 hours since they displayed faster drug release rates and completely dissolved at 12 hours.

The photomicrographs of surface morphology of matrices before and after dissolution test at various time intervals are shown in Figures 77 - 83. These illustrate the microscopic structure of surface of the matrices.

8.1 The surface morphology of the matrices before dissolution test

Figure 77 illustrates the surface morphology of HPMC, xanthan gum and sodium alginate matrices before dissolution test. The surfaces of all matrices were dense and smooth.

8.2 The surface morphology of the matrices after dissolution test

8.2.1 HPMC matrices

The photomicrographs of HPMC matrices after dissolution test in dissolution media with difference in pH values and ionic strengths are displayed in Figures 78 and 79, respectively.

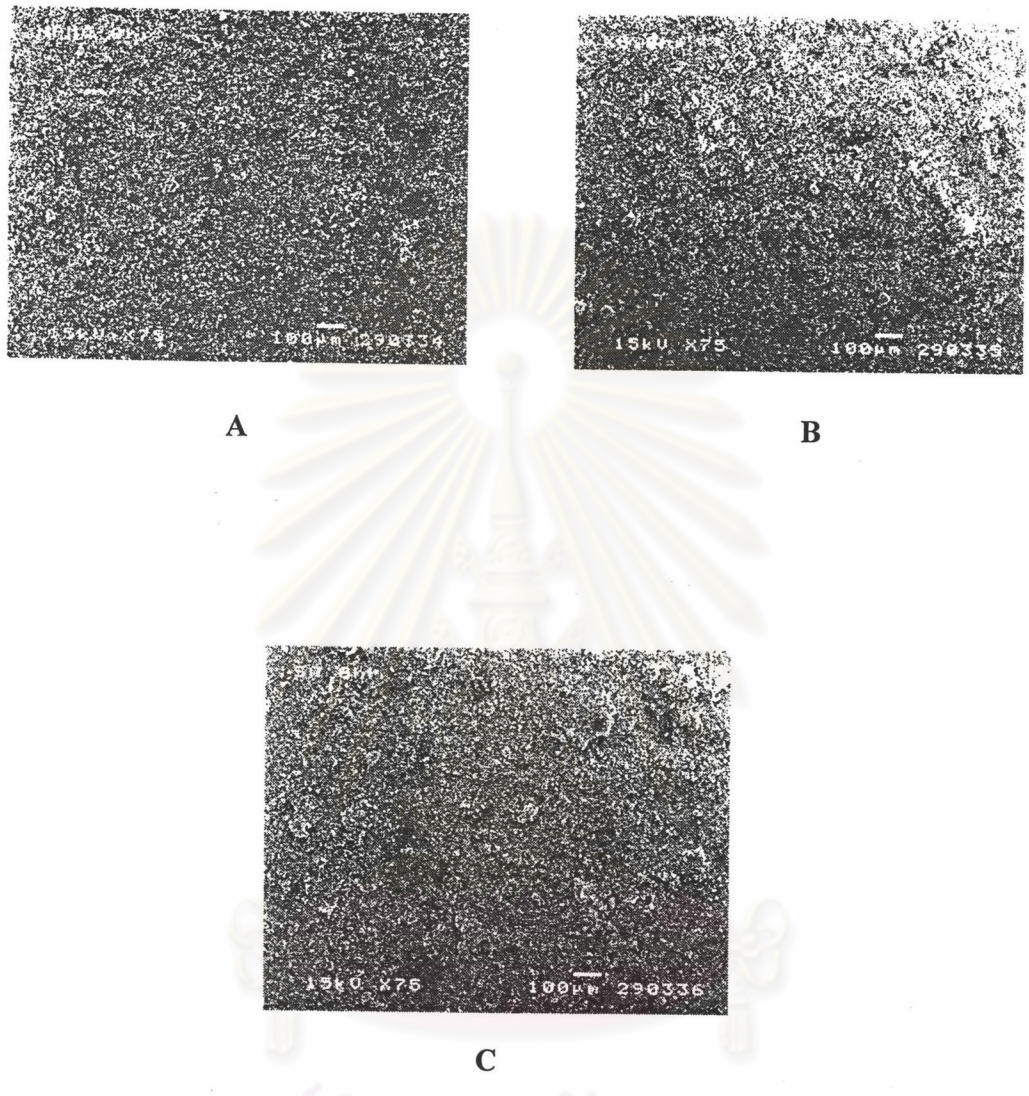
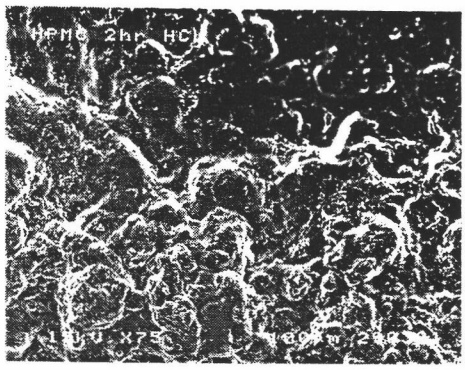
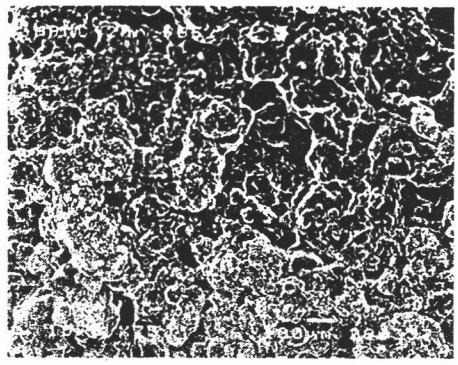


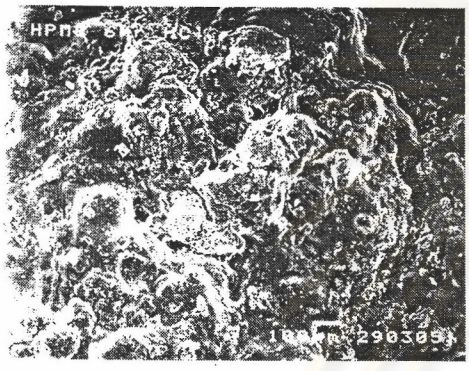
Figure 77 Surface morphology of HPMC (A), xanthan gum (B) and sodium alginate matrices (C) before dissolution test (X75)



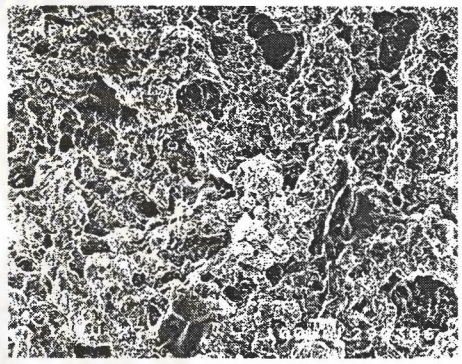
1A



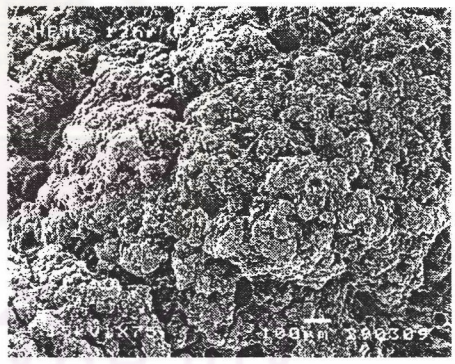
2A



1B

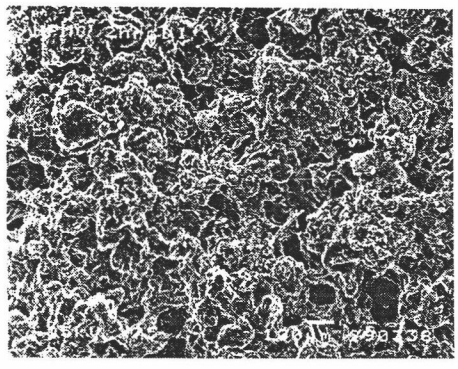


2B

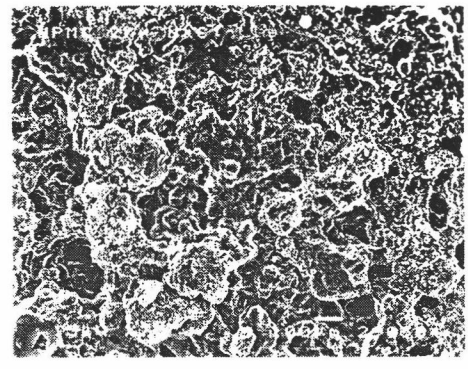


2C

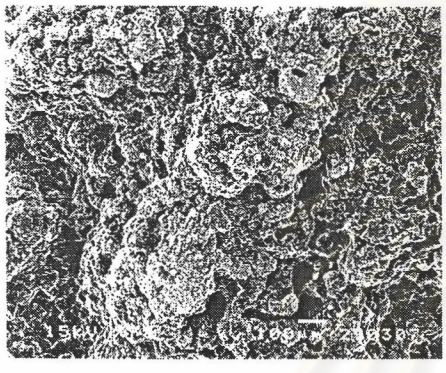
Figure 78 Surface morphology of HPMC matrices containing lactose as diluent, hydrated in 0.1 N HCl solution (left column) and phosphate buffer pH 6.8 solution (right column) for 2 hr (1A, 2A), 6 hr (1B, 2B) and 12 hr (2C) (x75)



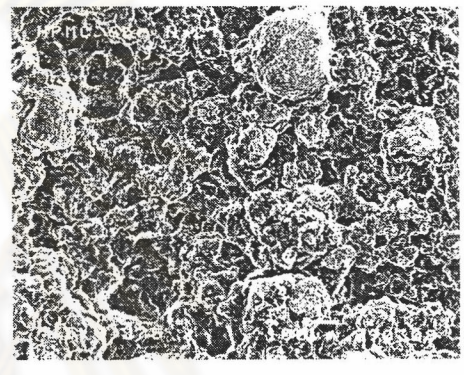
1A



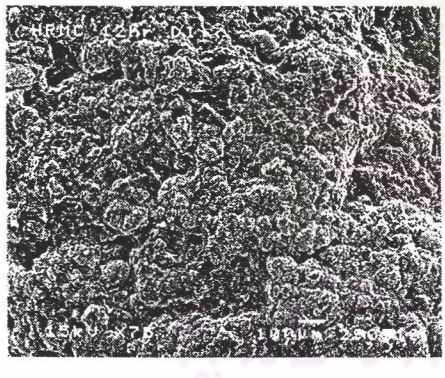
2A



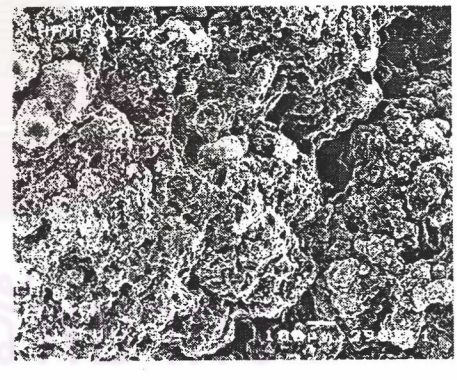
1B



2B



1C



2C

Figure 79 Surface morphology of HPMC matrices containing lactose as diluent, hydrated in deionized water (left column) and 0.2 M sodium chloride solution (right column) for 2 hr (1A, 2A), 6 hr (1B, 2B) and 12 hr (1C, 2C) (x75)

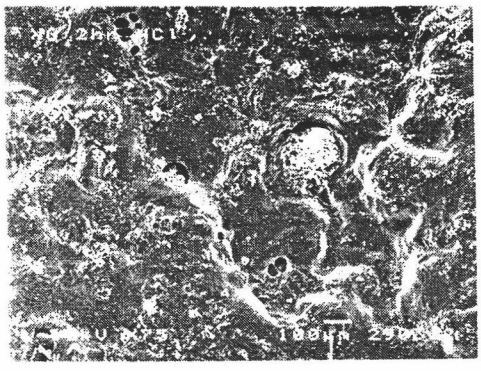
As illustrated in Figure 78 (1A, 1B), the photomicrographs show the slightly rough surface of the HPMC matrices immersed in 0.1 N HCl solution. The photomicrograph of HPMC matrices hydrated in 0.1 N HCl solution for 12 hours was not shown since the matrices dissolved completely. In contrast, the greater rough surface was observed with the surface of the matrices immersed in phosphate buffer pH 6.8 solution (see Figure 78 (2A, 2B and 2C)), deionized water and 0.2 M sodium chloride solution. (see Figure 79).

This clearly indicated that the greater surface erosion of the matrices hydrated in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution occurred. Consequently, the drug releases in these dissolution medium might be mainly controlled by polymer relaxation. The polymer relaxation or matrix erosion might also occur with matrices hydrated in 0.1 N HCl solution, although to a lesser extent.

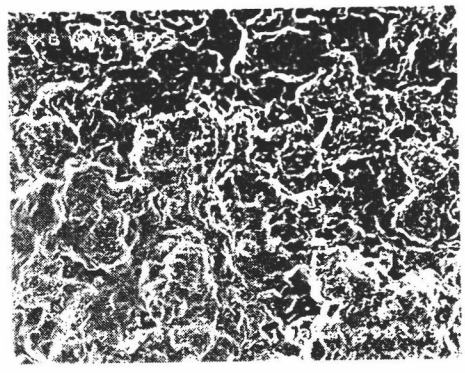
These results supported the result of drug release mechanism analysis in this study in that the mechanism of drug release from HPMC matrices in 0.1 N HCl solution was anomalous transport. On the contrary, large contribution from polymer relaxation controlled drug release from HPMC matrices in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution.

8.2.2 xanthan gum matrices

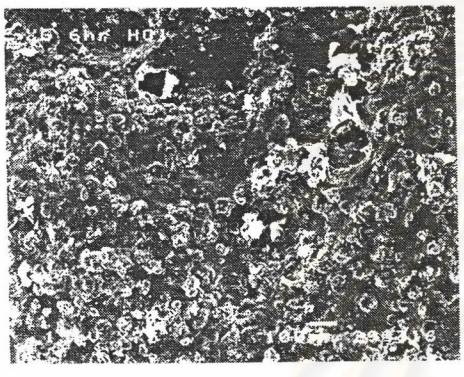
Figures 80 and 81 display the photomicrographs of surface of the xanthan gum matrices after dissolution test in dissolution media with difference in pH value and ionic strength, respectively. The photomicrographs of the matrices hydrated in deionized water at 6 and 12 hours were not shown because the matrices lost their integrity when they were removed from the dissolution vessels. As shown in Figure 80 (1A-1C), the rough surface occurred with matrices immersed in 0.1 N HCl solution. However, the surface of the matrices after hydration in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution seemed rougher than that of hydrated matrices in 0.1 N HCl solution.



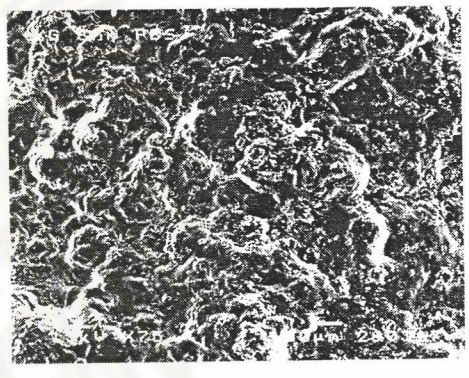
1A



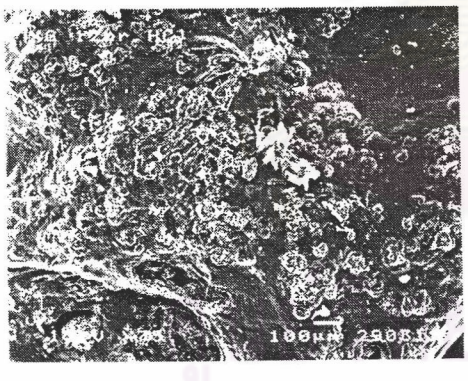
2A



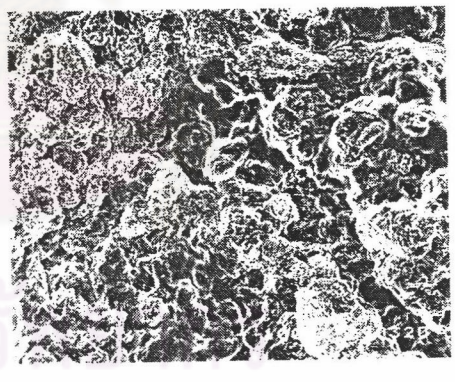
1B



2B

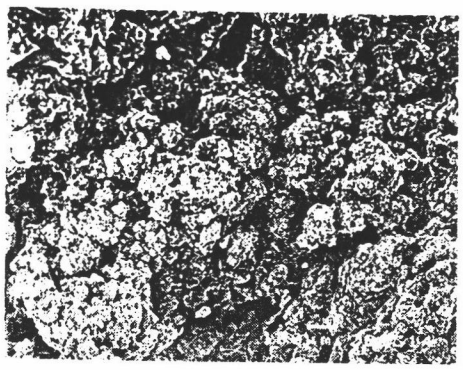


1C

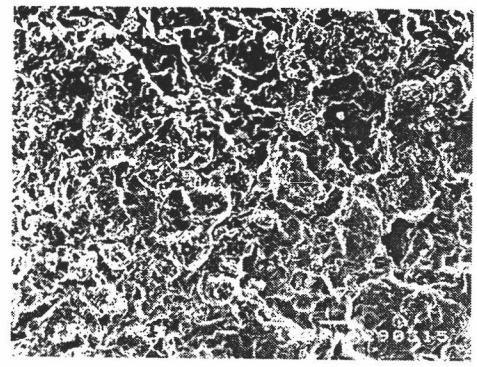


2C

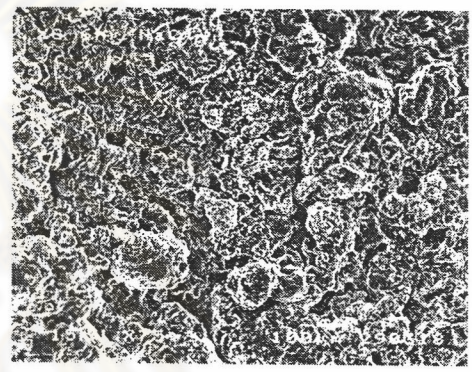
Figure 80 Surface morphology of xanthan gum matrices containing lactose as diluent, hydrated in 0.1 N HCl solution (left column) and phosphate buffer pH 6.8 solution (right column) for 2hr (1A,2A), 6hr (1B,2B) and 12hr (1C,2C) (x75)



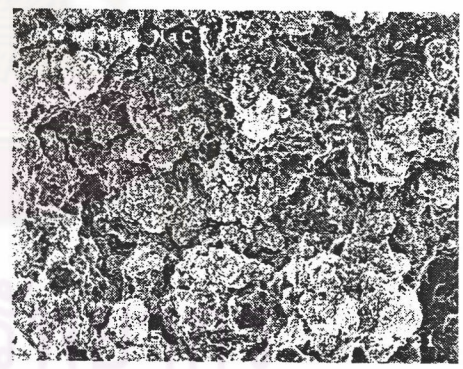
1A



2A



2B



2C

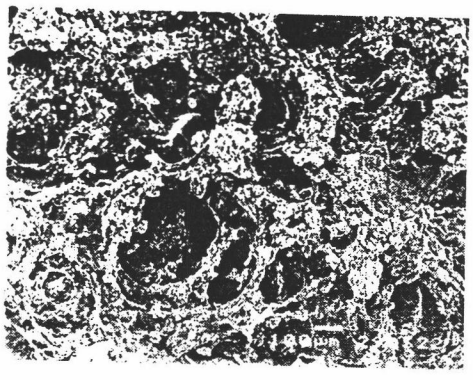
Figure 81 Surface morphology of xanthan gum matrices containing lactose as diluent, hydrated in deionized water for 2hr (1A) and 0.2 M sodium chloride solution for 2 hr (2A), 6hr (2B) and 12hr (2C) (x75)

The lesser rough surface of matrices hydrated in 0.1 N HCl solution pointed out that the drug release was less controlled by the contribution of polymer relaxation or matrix erosion. Conversely, The rougher surface of hydrated matrices in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution indicated that the drug release from matrices in these dissolution media was regulated by the contribution from polymer relaxation. The dramatically rougher surface of hydrated matrices in deionized water was an indication that the main drug release mechanism might be polymer relaxation or matrix erosion.

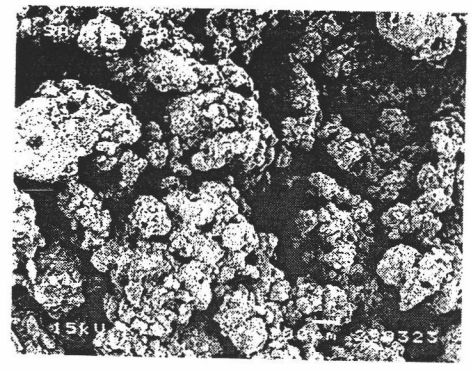
These results agreed well with the drug release mechanism, which was analyzed and reported in this study. The drug release mechanism analysis indicated that the drug release from xanthan gum matrices in deionized water was super Case II transport ($n>0.89$), in which the polymer relaxation mainly controlled the drug release from the matrices. The mechanism of drug release from xanthan gum matrices in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution was anomalous transport ($0.45<n<0.89$) with difference in the value of release exponent (n). This might explain the difference in surface morphology of these matrices in terms of the difference in quantitative contribution of diffusion and polymer relaxation. The more contribution from the polymer relaxation resulted in the rougher surface, while the more contribution of drug diffusion resulted in the smoother surface. Therefore, the drug release mechanism of xanthan gum matrices hydrated in 0.1 N HCl solution might be controlled by the more contribution of drug diffusion because the smoother surface was observed.

8.2.3 sodium alginate matrices

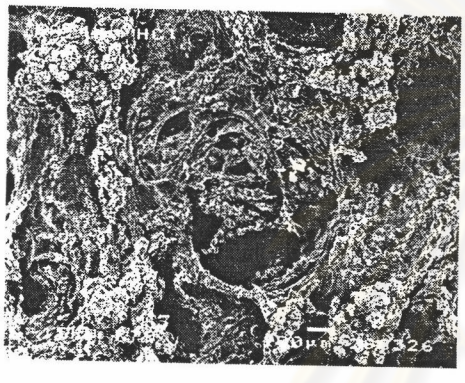
The photomicrographs of the surface of sodium alginate matrices hydrated in dissolution media with difference in pH value and ionic strength are shown in Figures 82 and 83, respectively.



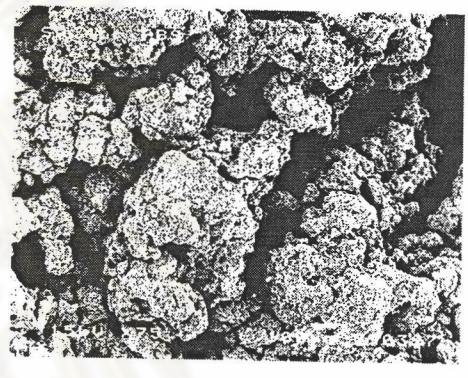
1A



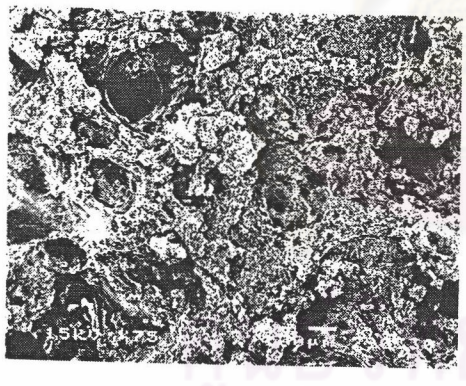
2A



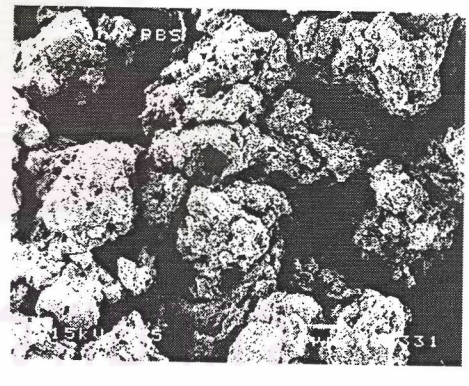
1B



2B

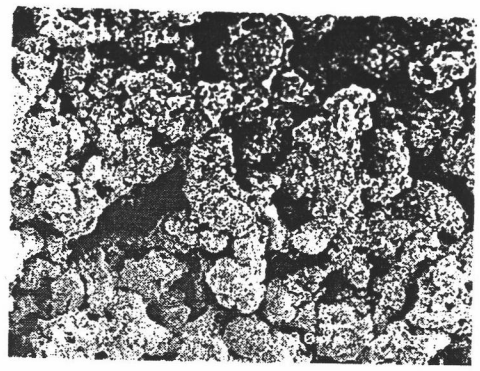


1C

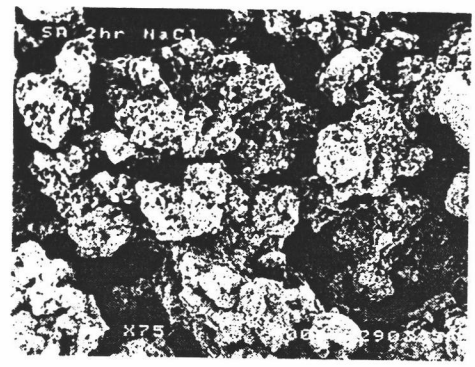


2C

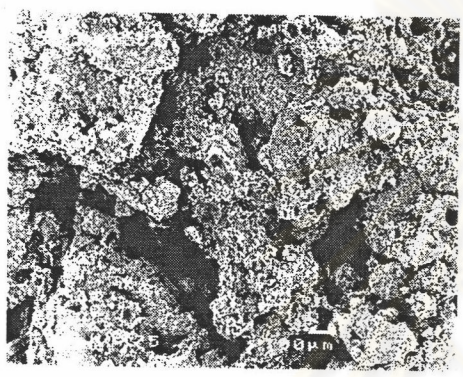
Figure 82 Surface morphology of sodium alginate matrices containing lactose as diluent, hydrated in 0.1 N HCl solution (left column) and phosphate buffer pH 6.8 solution (right column) for 2 hr (1A,2A), 4 hr (1B,2B) and 6 hr (1C,2C) (x75)



1A

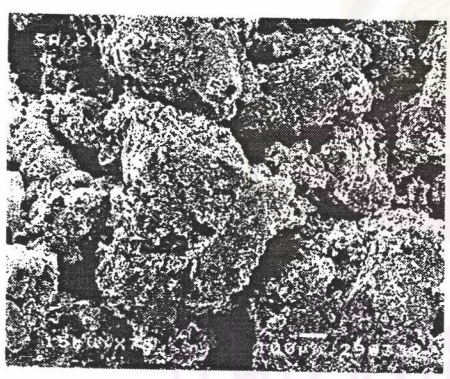


2A

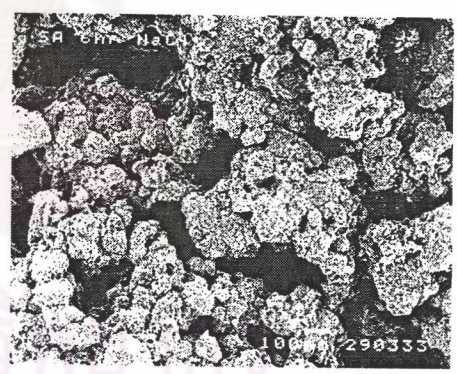


1B

2B



1C



2C

Figure 83 Surface morphology of sodium alginate matrices containing lactose as diluent, hydrated in deionized water (left column) and 0.2 M sodium chloride solution (right column) for 2 hr (1A, 2A), 4 hr (1B, 2B) and 6 hr (1C, 2C) (x75)

In case of matrices hydrated in 0.1 N HCl solution, the photomicrographs display the porous and rough surface morphology of the matrices. Since sodium alginate is insoluble in acidic pH, the insoluble alginic acid is rapidly formed in 0.1 N HCl solution (pH 1.2). Alginic acid has an ability to swell on hydration but virtually insoluble (Hodsdon et al., 1995). Therefore, when sodium alginate matrices were immersed in 0.1 N HCl solution, the relative porous and composite hydrated layer, in which much of polymer was undissolved and did not contribute to the diffusional barrier, was formed. Therefore, the large contribution of drug diffusion might mainly regulate the drug release from sodium alginate matrices hydrated in 0.1 N HCl solution

In contrast, for matrices hydrated in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution, the photomicrographs of matrices immersed in these dissolution media display very rough matrix surface, indicating an extensive erosion of the matrices. This result could be explained in terms of the weaker strength of the hydrated gel barrier. Since sodium alginate could dissolve and swell in phosphate buffer pH 6.8 solution, deionized water and 0.2 M sodium chloride solution, the continuous hydrated layer was formed when sodium alginate matrices were hydrated in these dissolution media. However, from the result of viscosity measurement, the viscosities of sodium alginate solution in these media were lower than those of HPMC and xanthan gum solutions in the same medium. The low viscosity of sodium alginate solution resulted in the low strength of protective gel barrier and thus made the matrices more susceptible to erosion. Therefore, the very rough surface was observed when matrices were hydrated in these dissolution media. Moreover, when the sodium alginate matrices were immersed in these dissolution media, a continuous gel layer was formed and acted as diffusional barrier. These results implied that the main drug release mechanism that controlled release from sodium alginate matrices in phosphate buffer pH 6.8 solution, deionized water and 0.2M sodium chloride solution was polymer relaxation.

The obtained result was consistent with the drug release mechanism analysis in this study. This study revealed that the mechanism of drug release from sodium alginate matrices in phosphate buffer pH 6.8, deionized water and 0.2 M sodium

chloride solution was Super Case II transport, in which the polymer relaxation or matrix erosion was the main mechanism in controlling drug release. On a contrary, the drug release from sodium alginate matrices in 0.1 N HCl solution was relatively controlled by a large contribution of drug diffusion.

In conclusion, this study showed that the surface morphology of the matrices was consistent with the result of the drug release mechanism analysis. Consequently, the surface morphology of the matrices after being hydrated in the dissolution medium could be used as an important evidence to support and/or determine the main mechanism of drug release from the hydrated matrices.