CHAPTER IV

RESULTS AND DISCUSSION

Part I. Study of drug loading

1. Characteristic of resins

The particle shape of ion exchange resins was observed by using Scanning Electron Microscope (SEM). Ion exchange resins were in spherical shape (Figure 10). The particle size of ion exchange resins were in the range of 707-841 microns (20-25 mesh). Physical properties of ion exchange resins were shown in Table 9. Flowability of both resins was free flowing because of the spherical shape of resins. The surface morphology of 4 % crosslinkage resins had more porous than 8 % crosslinkage resins. It was explained by the 4 % crosslinkage resins had lower amount of divinylbenzene, the copolymerization for crosslinking the polymer chains. This parameter influences the porosity property of resin. The higher degree crosslinkage resins had a tighter pore structure (Irwin et al., 1987).

Table 9 The physical properties of ion exchange resins (mean (SD), n=3)

Physical properties	Moisture content (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility (%)
4 % crosslinkage	6.43% (0.73)	0.677 (0.009)	0.685 (0.003)	1.20 (0.009)
8 % crosslinkage	10.31% (0.37)	0.905 (0.006)	0.915 (0.006)	1.01 (0.003)

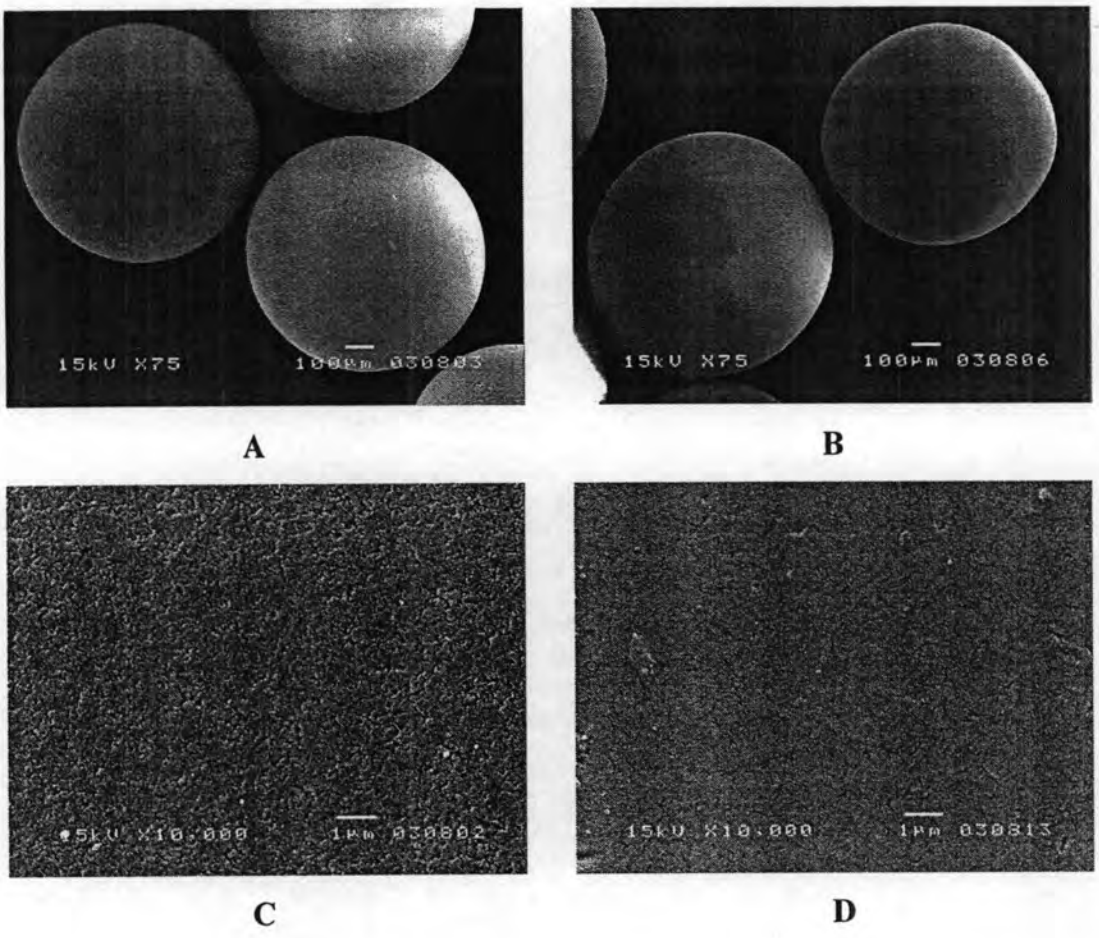


Figure 10 The photomicrograph (SEM) of particle shape and surface morphology of (A) 4 % crosslinkage(x75), (B) 8 % crosslinkage(x75), (C) 4 % crosslinkage(x10,000) and (D) 8 % crosslinkage(x10,000).

2. Preparation of diltiazem resinates

2.1 Effect of resin crosslinkage and quantity of resins

After system equilibrium was reached, which was about 24 hours, the amount of drug loading in the 4 % crosslinkage resins was 28.80 % higher than 8 % crosslinkage resins which had percentage of drug loading only 5.51 % (Table 10). Increasing in crosslinkage of the polymer network decreased the drug binding. Because low crosslinkage resins swelled upon hydration while the higher grade had a tight pore structure. This might cause a reduction in pore diameter and lead to the entrapment of large ions (Irwin et al., 1987).

The percentage of drug loading in the resins increased when the quantity of resin was decreased or when the initial drug amount in the drug loading solution was increased. It might be explained that the increasing in the ionized drug to exchange with the sodium ions at the binding site (sulfonate group) within the resin. It was observed that at the drug to resin in the ratio of 1:1, drug loading was unlikely to further increase (Figure 11). It might be caused by the limit of binding capacity. This ratio of drug and resin was used in further experiments.

Table 10 Percentage of drug loading (mean (SD), n=3)

resin amount (gm) per 0.25 gm drug	drug amount (gm) per 1 gm resin	% drug loading	
		4 % crosslinkage	8 % crosslinkage
12.50	0.02	2.67% (0.20)	1.31% (0.13)
5.00	0.05	4.75% (0.03)	2.66% (0.09)
2.50	0.10	8.88% (0.04)	4.94% (0.17)
1.25	0.20	15.78% (0.66)	4.95% (0.37)
0.50	0.50	25.30% (0.64)	5.08% (0.09)
0.25	1.00	28.26% (0.03)	5.32% (0.36)
0.167	1.50	28.75% (0.37)	5.33% (0.10)
0.125	2.00	28.80% (0.55)	5.51% (0.34)

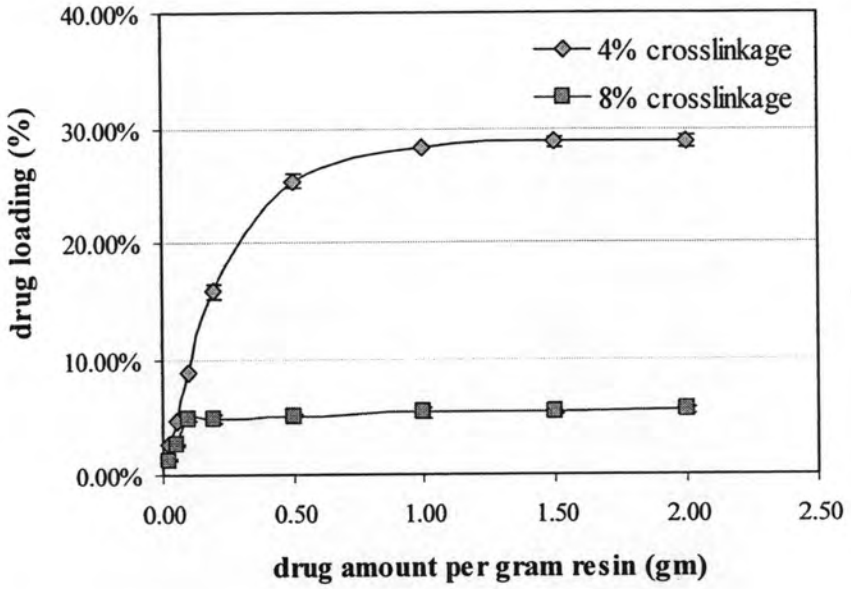


Figure 11 Effect of resin crosslinkage and quantity of resins.

2.2 Effect of concentration of drug loading solution

For 8 % crosslinkage resins, the percentage of drug loading in the resins slightly increased as the initial drug concentration in the solution was increased, whereas the drug loading of 4 % crosslinkage resins were not increased (Table 11). It was explained that the concentration of drug loading solution concentration between 0.5-8 % w/v did not influence the drug loading in the resins. Therefore, 8 % w/v drug loading concentration was employed for preparing resinates because at the high concentration need the smaller volume of drug solution when scale up the batch size.

Table 11 Percentage of drug loading at different concentrations of drug loading solution (mean (SD), n=3)

drug concentration (%w/v)	% drug loading	
	4 % crosslinkage	8 % crosslinkage
0.5%	28.26% (0.03)	5.32% (0.36)
1%	27.96% (0.24)	5.34% (0.48)
4%	28.18% (0.92)	5.36% (0.02)
8%	27.35% (0.05)	5.40% (0.48)

2.3 Effect of temperature during drug loading

In Table 12, the percentage of drug loading of both resin types increased at all drug loading concentrations when the controlled temperature increased. However, increasing in the temperature from 30°C to 50°C seemed to have more influence on 8 % crosslinkage resins than on 4 % crosslinkage resins. The drug ions were difficult to diffuse through the tight pore structure of 8 % crosslinkage resins. Higher temperature could expand the pore diameter facilitating diffusion of drug ions onto resin.

However, increasing in temperature not only increased the percentage of drug loading but also reduced the time required for system equilibrium (Table 13 and Figure 12). This was due to pore expansion of resin by heat affording ions to enter into exchange sites (Irwin et al., 1987). From the result of this study, the suitable temperature should be 50°C.

Table 12 Effect of temperature during drug loading (mean (SD), n=3)

drug concentration (%w/v)	% drug loading		
	30°C	40°C	50°C
4 % crosslinkage 1%	27.96% (0.24)	29.47% (0.57)	30.54% (0.84)
4%	28.18% (0.92)	29.78% (0.46)	29.90% (0.28)
8%	27.35% (0.05)	29.22% (0.46)	29.95% (0.95)
8 % crosslinkage 1%	5.34% (0.48)	8.32% (0.27)	11.57% (0.44)
4%	5.36% (0.02)	8.69% (0.19)	11.90% (0.38)
8%	5.40% (0.48)	9.45% (0.04)	11.81% (0.81)

Table 13 Effect of temperature during drug loading of 4 % crosslinkage resin in 8 % w/v drug loading solution (mean (SD), n=3)

time (hr)	% drug loading		
	30°C	40°C	50°C
0.5	10.94% (1.10)	11.24% (1.57)	18.48% (2.01)
1	15.60% (0.57)	15.07% (0.29)	22.54% (1.66)
3	22.91% (0.93)	25.60% (1.12)	26.86% (1.10)
6	24.60% (0.50)	27.29% (0.65)	28.32% (0.97)
12	26.40% (0.61)	27.38% (0.40)	28.70% (0.90)
24	27.52% (1.15)	28.54% (0.24)	28.74% (0.96)
28	28.75% (0.76)	27.83% (0.94)	29.34% (0.48)

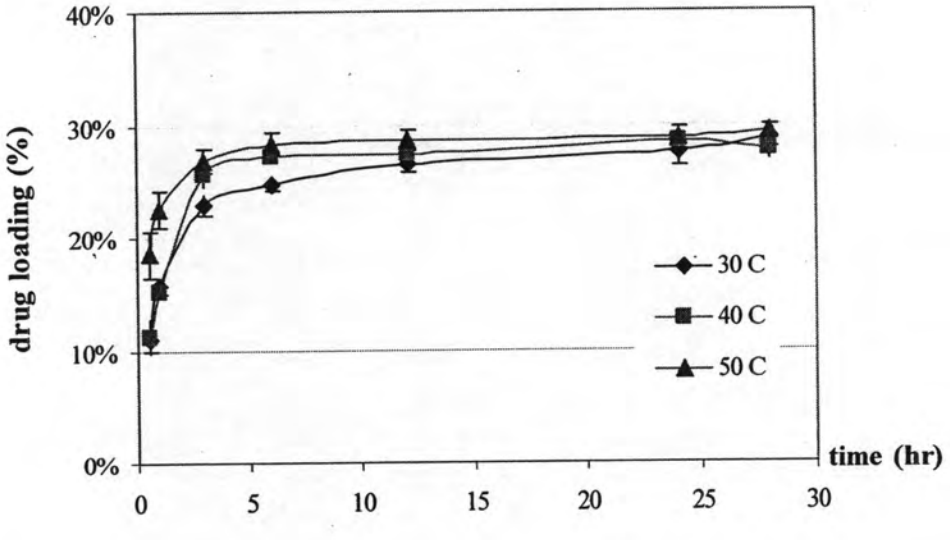
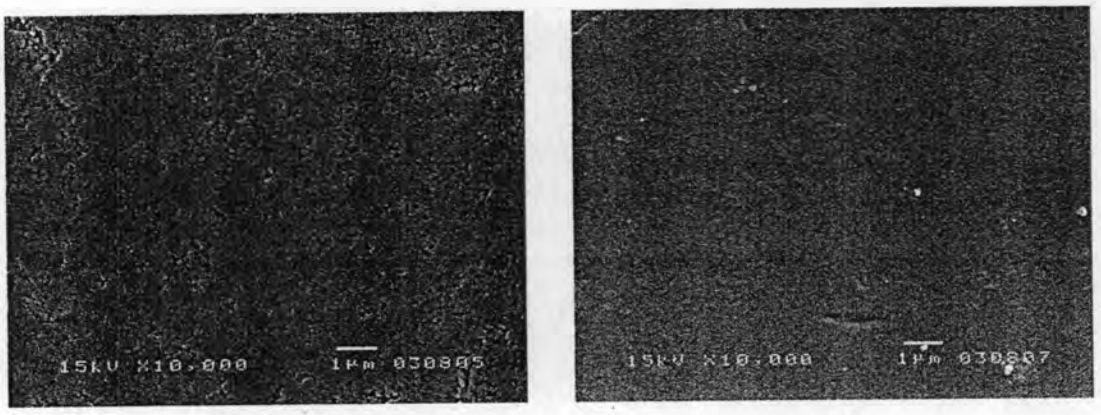


Figure 12 Effect of temperature during drug loading of 4 % crosslinkage resin in 8 % w/v drug loading solution.

In conclusion, the loading of drug onto resins was found to be influenced by resin crosslinkage, the quantity of resins and the temperature during drug loading. The concentration of drug solution had less effect to the percentage of drug loading. From the result of this study, the suitable conditions for resinate preparation are drug to resin ratio of 1:1 in 8 % w/v drug loading solution at 50°C.

3. Characteristic of diltiazem resinates

The surface morphology of resinates were not different from the resins before drug loading (Figure 13). The physical properties of prepared resinates are shown in Table 14. Flowability of both resinates was also free flowing. The diltiazem bound in 4 % crosslinkage resins was 27.92 % higher than in 8 % crosslinkage resins which was only 5.40 %.



A B

Figure 13 The photomicrograph (SEM x10,000) of surface morphology of resinates (A) 4 % crosslinkage resinate and (B) 8 % crosslinkage resinate.

Table 14 The physical properties of ion exchange resinates (mean (SD), n=3)

Physical properties	Moisture content (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility (%)	Diltiazem content (%)
4 % crosslinkage	5.54% (0.78)	0.650 (0.003)	0.659 (0.002)	1.30 (0.007)	27.92% (0.06)
8 % crosslinkage	4.84% (0.05)	0.867 (0.004)	0.906 (0.005)	4.33 (0.008)	5.40% (0.48)

4. Study of drug release

The study in previous section indicated that using 4 % crosslinkage resins was more suitable for prepared diltiazem resinates because of the higher percentage of drug loading onto the resins. It was therefore used for release study.

4.1 Effect of ionic strength and counter ions of dissolution medium

In order to study the drug release kinetics of the investigated resinates, the first 60 % of dissolution profiles were calculated following to the mathematical kinetic models (Appendix E). The release kinetic was analyzed according to the matrix controlled release model, Higuchi model which are shown in equation 17. The drug release rate constant (K) was the slope of percentage cumulative drug release and a square root time (Figure 14 and 15).

Figure 16 shows that increasing ionic strength enhanced the release rate of drug from resinates. It was explained by increasing in the cation at the binding site in the resin, but at 0.3 M KCl exhibited no further increasing in release rate. It might be caused by the limit of the ionic site and the pore size in the resinate. The release rate in sodium chloride was slightly lower than in potassium chloride when compared at the same ionic strength (Table15). This might be explained by the hydrated size of potassium ion was smaller than sodium ion (Kunin, 1958).

In previous study of comparing the effect of different counter ions on drug release from coated resinates, Sprockel and Prapaitrakul (1988) reported that the hydrogen ion caused the fastest release of the phenylpropanolamine from resinates coated with cellulose acetate butyrate follow by the sodium and the calcium ion. The affinity of the sulfonic acid functional groups for the sodium and calcium ion is lower than hydrogen ion might cause a slower drug release by retarding drug displacement from the binding site.

In this study, diltiazem release exhibited fastest release in potassium chloride followed by sodium chloride, calcium chloride and hydrochloric acid (Figure 17). This result was different from the previous report. The diltiazem release from

resinates in 0.1 M HCl was slowest. In the preliminary study, the solubility of diltiazem hydrochloride in 0.1 M KCl was 578 mg/ml, 0.1 M NaCl was 564 mg/ml, 0.04 M $CaCl_2$ was 606 mg/ml and 0.1 M HCl was 588 mg/ml. It indicated that, this result did not affect by solubility of drug. The other factors might be influent drug release was the swelling property of resins in each dissolution medium. The swelling property affected the rate of hydration, the volume expansion and the rate of ion exchange (Swarbrick and Boylan, 1988). Shrinkage of the resin when the cationic form was brought into contact with acid solutions might also occur (Irwin et al., 1987). This might cause a reduction in pore diameter and lead to the entrapment of ions in 0.1 M HCl.

Table 15 The diltiazem released from resinates in dissolution mediums having different ionic strength and counter ions

Dissolution medium	Ionic strength (M)	pH	R^2	K ($\%t^{-1/2}$)	% drug release at 12 hr
Potassium chloride	0.01	5.66	0.9930	0.1678	53.46% (1.10)
	0.05	5.83	0.9921	0.2765	75.42% (0.69)
	0.1	5.73	0.9918	0.3289	84.20% (0.30)
	0.2	5.94	0.9902	0.4273	89.03% (0.20)
	0.3	5.90	0.9876	0.4978	89.74% (0.22)
	0.4	5.86	0.9924	0.4905	93.94% (0.54)
	0.5	5.87	0.9909	0.4938	94.71% (1.01)
Sodium chloride	0.01	6.02	0.9899	0.1516	48.18% (0.38)
	0.05	6.04	0.9930	0.2329	68.47% (0.86)
	0.1	5.88	0.9951	0.3005	79.82% (0.69)
	0.2	5.98	0.9881	0.3374	84.49% (0.74)
	0.3	6.22	0.9878	0.4065	86.56% (1.01)
	0.4	6.32	0.9882	0.4316	88.09% (0.23)
	0.5	6.32	0.9900	0.4718	92.88% (0.51)
Calcium chloride (0.04 M)	0.1	5.69	0.9931	0.2601	75.46% (1.19)
Hydrochloric acid	0.1	1.2	0.9951	0.2487	71.52% (0.45)

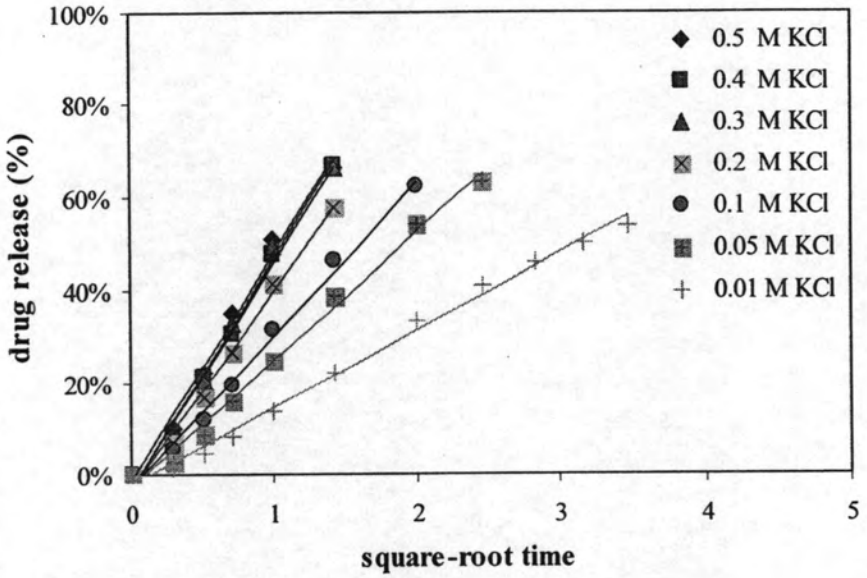


Figure 14 The Higuchi plot of diltiazem release from resinates in potassium chloride solution.

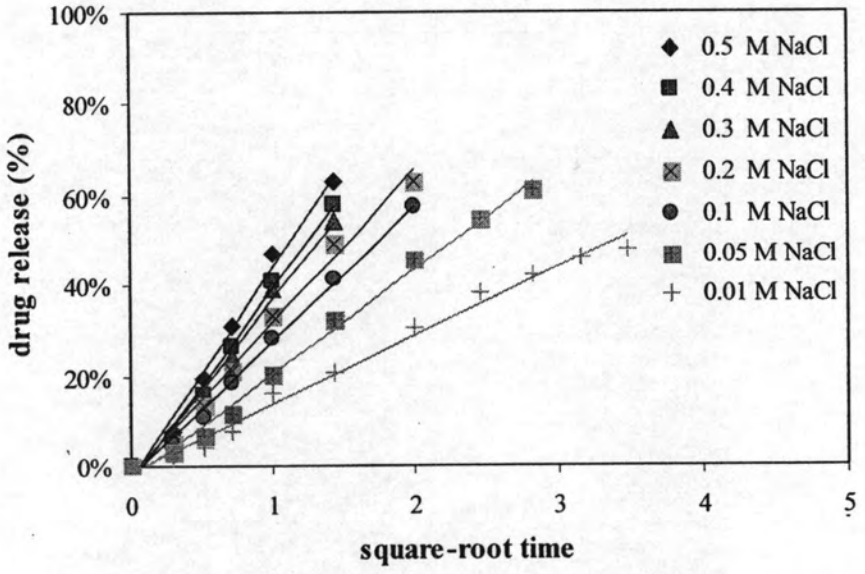


Figure 15 The Higuchi plot of diltiazem release from resinates in sodium chloride solution.

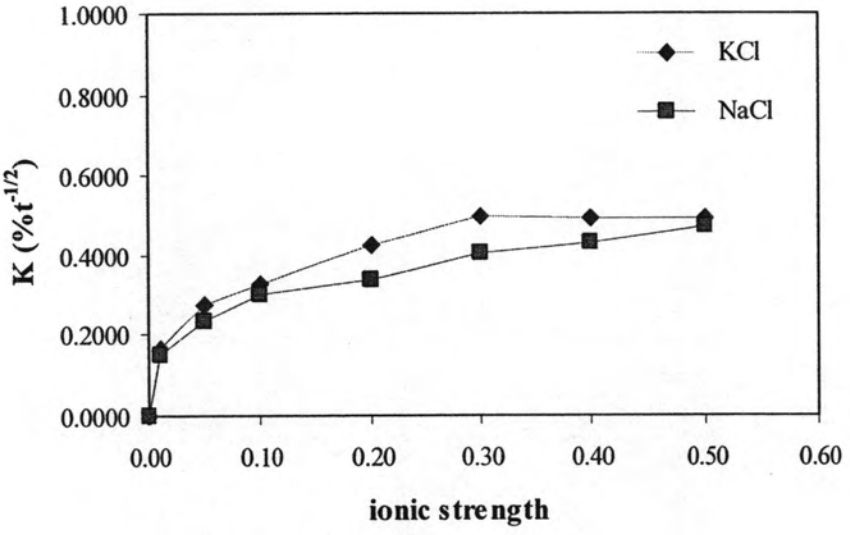


Figure 16 Effect of ionic strength on release rate.

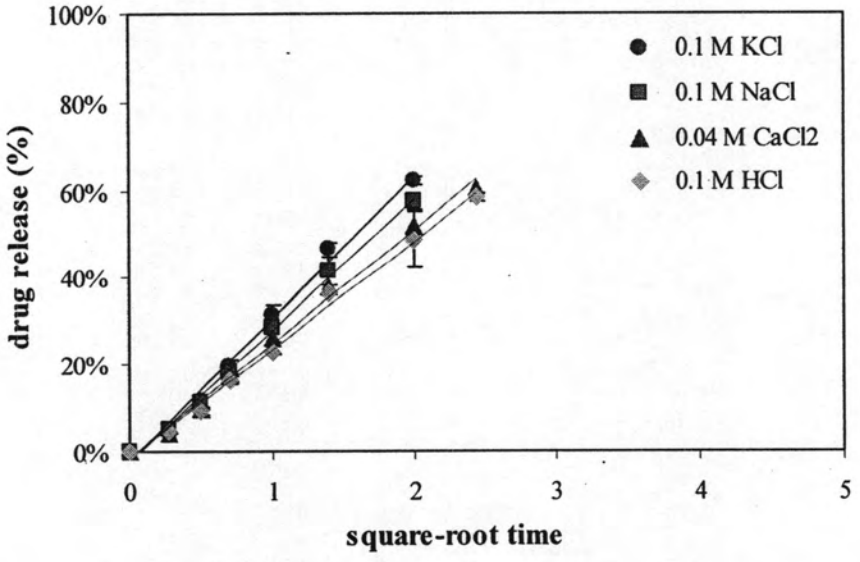


Figure 17 The Higuchi plot of diltiazem release from resinates in various counter ion types (ionic strength = 0.1).

4.2 Effect of pH of dissolution medium

The result of this study shows in Figure 18 and 19, the pH of dissolution medium slightly affected the release rate of the drug from resinates (Table 16). This might be indicated that their exchange capacity tended to be independent on pH. Deasy (1984) reported that the pH of dissolution medium affected the dissociation of the functional groups on resin. This parameter influenced interaction between functional group and ionized drug. Weak cation exchange resins such as carboxylic acid resin which had a pKa value of about 5.2 or greater tended to have rapid release in simulated gastric fluid while strong cation exchange resins which had a pKa value of about 1 were highly dissociated at all pH range in the gastrointestinal tract.

Table 16 The diltiazem released from resinates in various dissolution mediums

Dissolution medium	Ionic strength	pH	R^2	K ($\%t^{-1/2}$)	% drug release at 12 hr
Buffer pH 7.2	0.085	7.2	0.9947	0.2606	76.68% (0.79)
Buffer pH 7.2	0.1	7.2	0.9936	0.2769	77.14% (0.13)
Buffer pH 6.8	0.072	6.8	0.9910	0.2957	77.12% (0.89)
Buffer pH 6.8	0.1	6.8	0.9917	0.3090	79.17% (0.99)
0.1 M HCl	0.1	1.2	0.9951	0.2487	71.52% (0.45)

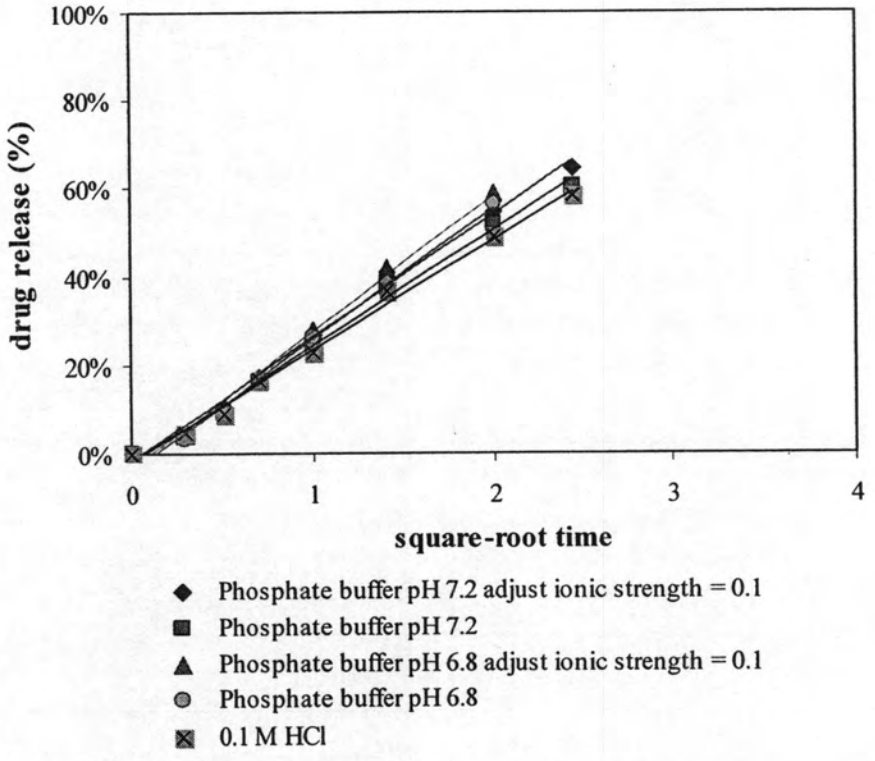


Figure 18 The Higuchi plot of diltiazem release from resinates in various dissolution mediums.

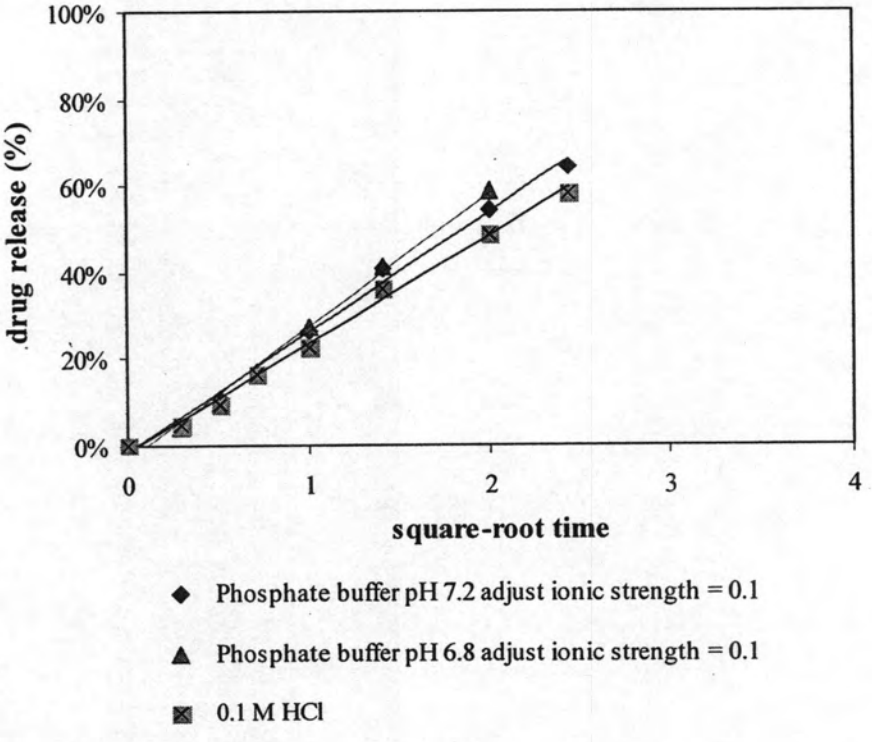


Figure 19 The Higuchi plot of diltiazem release from resinates in various dissolution mediums adjust ionic strength = 0.1.

Part II. Study of resinate coating

In previous study, polymers used in the film coating of multiple-unit dosage forms such as disintegrating tablets were in two broad groups, cellulose and acrylate polymers. The polymeric coating must be able to withstand the compression force, it can deform but it should not rapture. Most studies on the compaction of particles coated with ethylcellulose revealed damage to the coating with a loss of the extended release properties. Addition of different plasticizers was not enough for the film to deform and resist rupturing. The molecular structure of the polymer, which was based on acrylic esters, indicated the lack of strong interchain interaction (hydrogen bond) (Bodmeier, 1997). This explained that acrylate polymers were more softness and flexible character of the polymer film and therefore more suitable for the compression of coated particles (Bodmeier and Paeratakul, 1994).

1. Characteristic of coated resinates

In preliminary study, it was found that the agglomeration of resinates could occurred. To solve this problem, the spraying rate and the atomizing air pressure should be optimized. At atomizing air pressure 1.5 bar and spray rate 2.4 ml/min, it was found that all film coating formulations showed no agglomeration. However, addition of talcum which was the antiadherent in the film coating solution, reduced tackiness problem. The addition of 20 % triethyl citrate was used as plasticizer for the polymer.

The surface morphology of all coating formulations was not different. The Figure 20 and 21 show the particle shape and surface morphology of coated resinates. The moisture content of all formulations was between 4.22-5.83 %. The drug content of coated resinates was decreased when the coating level increased (Table 17).

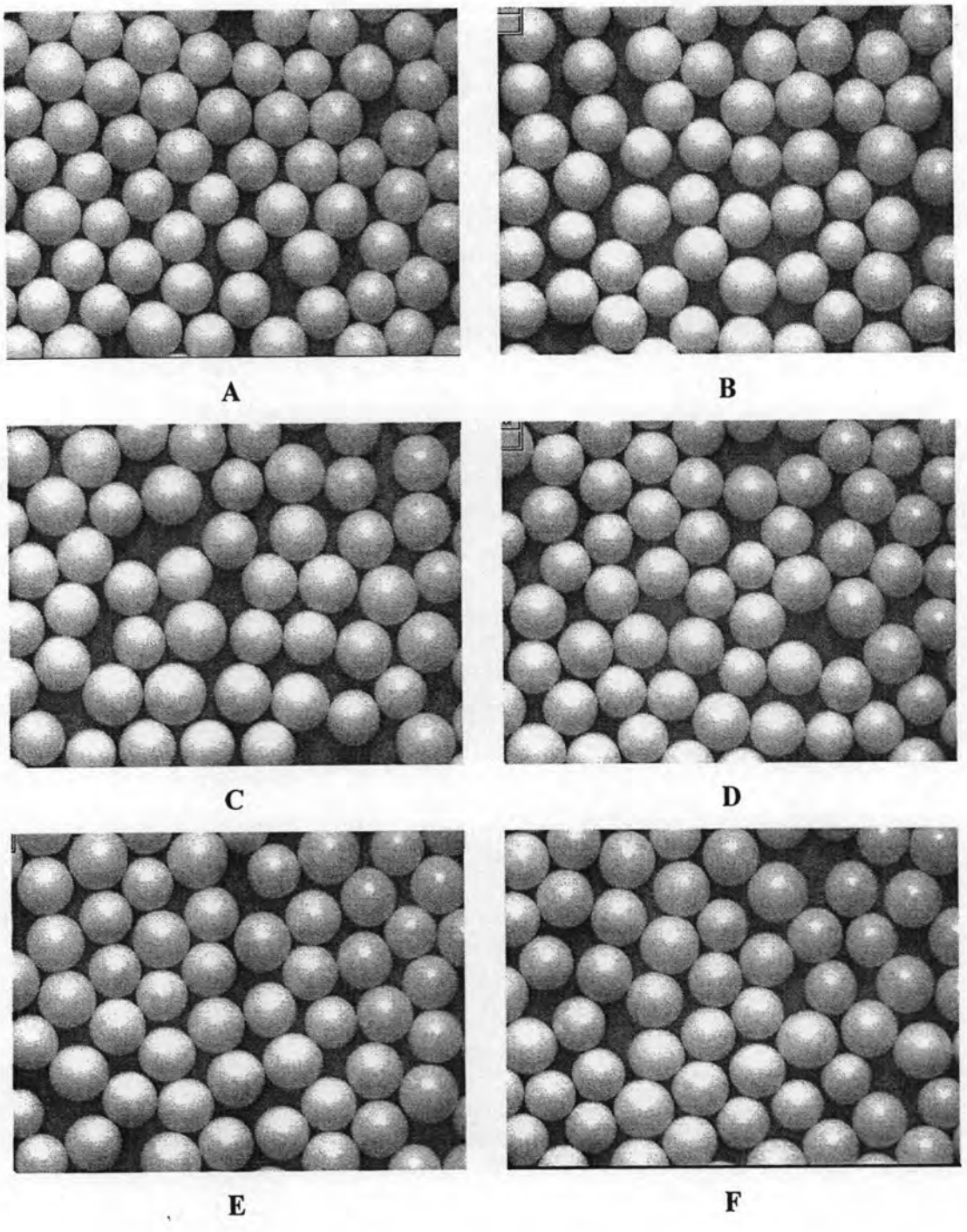
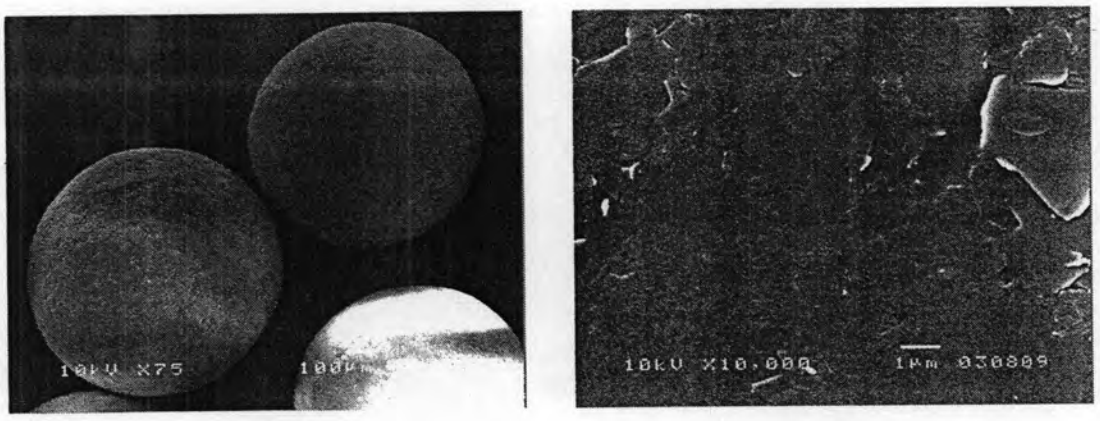


Figure 20 The microscopic morphology (Stereomicroscope x10) of coated resinate
(A) formulation C1 (7.5% coating level of Eudragit®RL),
(B) formulation C2 (10% coating level of Eudragit®RL),
(C) formulation C3 (15% coating level of Eudragit®RL),
(D) formulation C4 (15% coating level of Eudragit®RL:RS 80:20),
(E) formulation C5 (15% coating level of Eudragit®RL:RS 60:40) and
(F) formulation C6 (15% coating level of Eudragit®RL:RS 50:50).



A B

Figure 21 The photomicrograph (SEM) of the coated resinate formulation C3 (A) x75 and (B) x10,000.

Table 17 The physical properties of coated resinates (mean (SD), n=3)

Formulation	%Coating level	Eudragit® RL:RS	Moisture content (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility (%)	Diltiazem content (%)
C1	7.5%	100:0	5.20% (0.04)	0.658 (0.005)	0.680 (0.004)	3.22 (0.002)	24.49% (0.23)
C2	10.0%	100:0	5.30% (0.08)	0.653 (0.002)	0.686 (0.004)	4.79 (0.004)	23.37% (0.32)
C3	15.0%	100:0	5.83% (0.05)	0.667 (0.001)	0.681 (0.002)	2.00 (0.002)	22.44% (0.14)
C4	15.0%	80:20	4.30% (0.05)	0.671 (0.003)	0.696 (0.005)	3.58 (0.004)	22.34% (0.25)
C5	15.0%	60:40	4.22% (0.04)	0.671 (0.011)	0.696 (0.004)	3.57 (0.011)	21.96% (0.38)
C6	15.0%	50:50	5.29% (0.05)	0.676 (0.005)	0.698 (0.000)	3.15 (0.008)	22.43% (0.06)

2. Study of drug release

The drug release from coated resinates was also best described by the Higuchi model. All formulations of acrylate polymer coating solution, Eudragit®RL and Eudragit®RS, would retard drug release rate of the resinates (Table 18). Coating with only Eudragit®RL polymer (formulation C1-C3) presented the percentage of drug release higher than 50 % at 12 hours. Increasing the coating level of Eudragit®RL presented the decreasing of release rate (Figure 22 and 24). Addition of Eudragit®RS in formulations gave slower drug release rate (Figure 23).

In agreement with Arthur (2000) which reported that the ammonio methacrylate copolymer type A (Eudragit®RL) and type B (Eudragit®RS) composed of trimethyl ammonioethyl methacrylate chloride, ethylacrylate and methylmethacrylate. These polymers were quarternary ammonium groups which increased the permeability of methacrylate film due to their hydrophilic nature. Type A had a ratio between ammonium group and neutral methacrylates of 1:20, and type B 1:40 which made differently permeability. Type A could was more permeable than type B.

Table 18 The diltiazem released from resinates coated with Eudragit® in 0.1 M potassium chloride solution

Formulation	Coating level (%wt gained)	Eudragit® RL : RS	R^2	K ($\%t^{-1/2}$)	% drug release at 12 hr
Uncoated resinates	-	-	0.9918	0.3289	84.20% (0.30)
C1	7.5%	100:0	0.9973	0.2232	66.71% (0.55)
C2	10%	100:0	0.9967	0.2177	63.93% (0.18)
C3	15%	100:0	0.9961	0.1980	59.03% (0.42)
C4	15%	80:20	0.9944	0.1682	49.90% (0.21)
C5	15%	60:40	0.9894	0.1307	38.80% (0.47)
C6	15%	50:50	0.9831	0.1126	33.27% (0.32)

The microscopic morphology (SEM) of uncoated and coated resinates after dissolution test in 0.1 M potassium chloride (Figure 25) presented no different in surface morphology when compared with the uncoated and coated resinates before

dissolution test. This indicated that after dissolution test, the film coating layer was still appeared. It could support the hydrophobic property of Eudragit®.

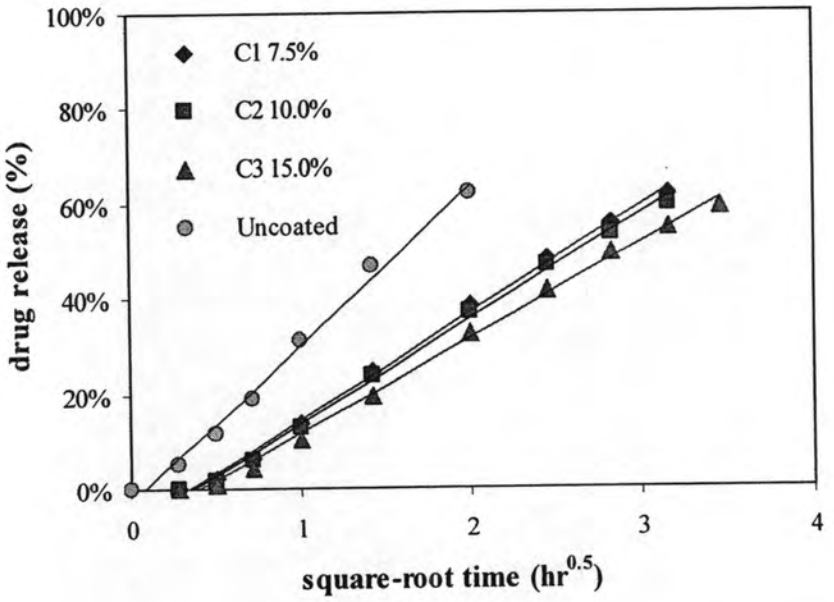


Figure 22 The Higuchi plot of diltiazem release from resinates coated with various coating levels of Eudragit®RL in 0.1 M potassium chloride solution.

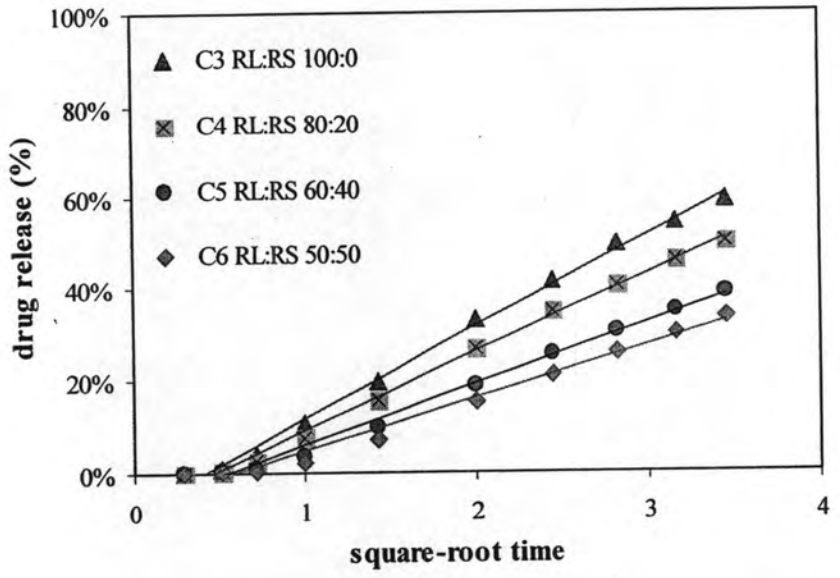


Figure 23 The Higuchi plot of diltiazem release from resinates coated with Eudragit®RL and Eudragit®RS in 0.1 M potassium chloride solution.

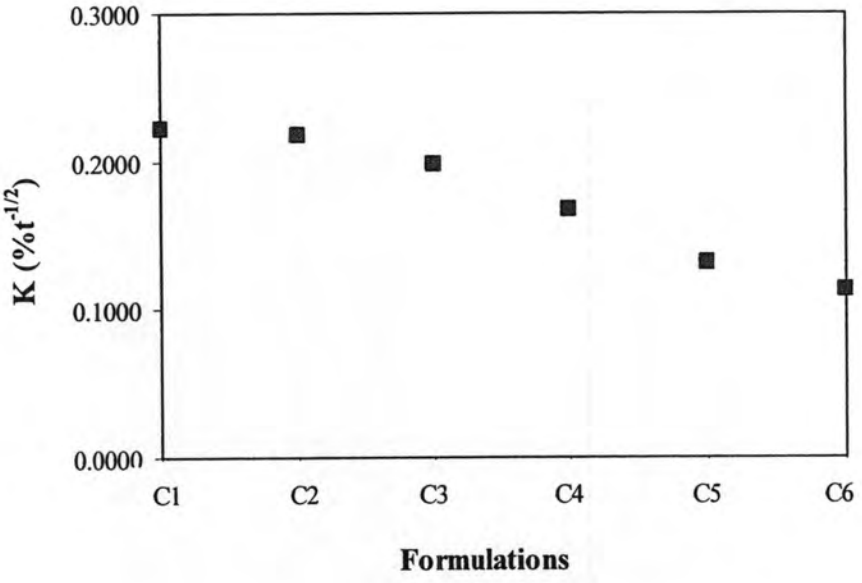


Figure 24 Effect of polymer type and effect of coating level on release rate.

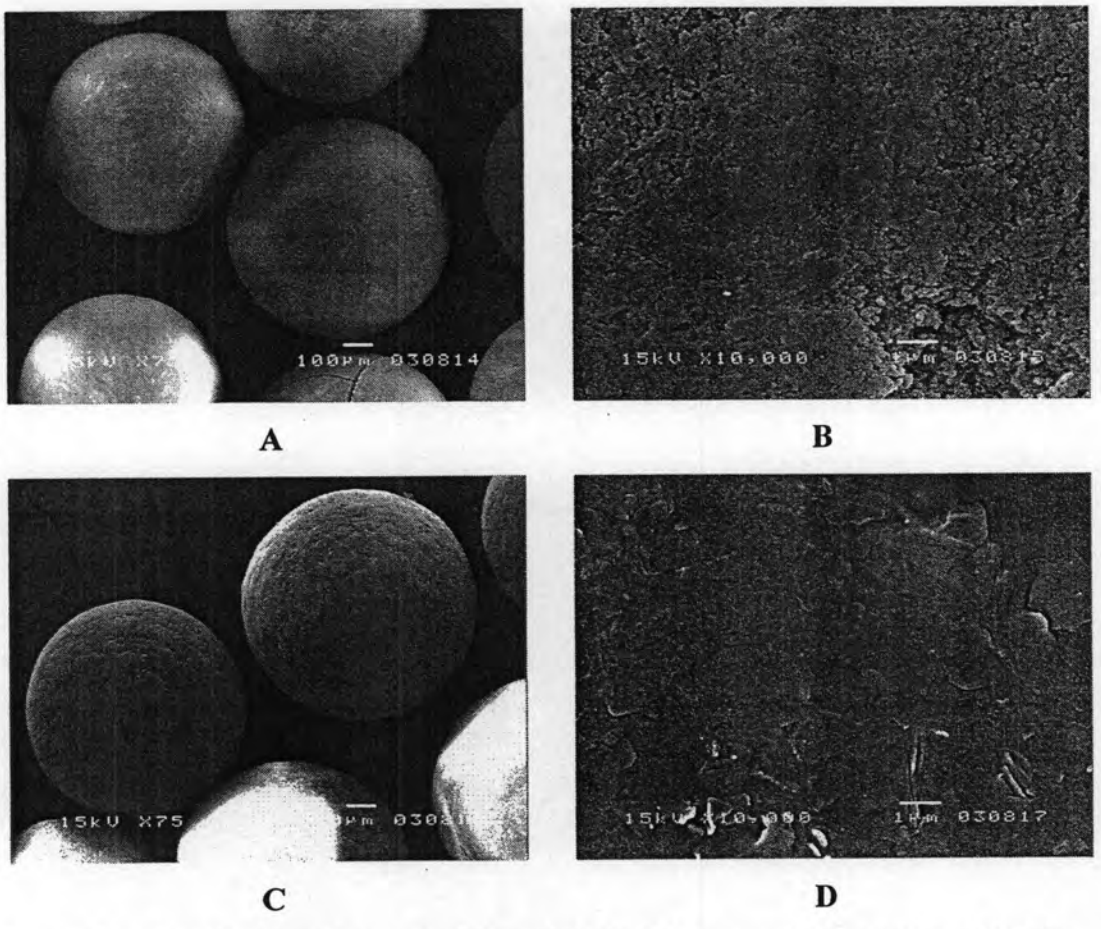
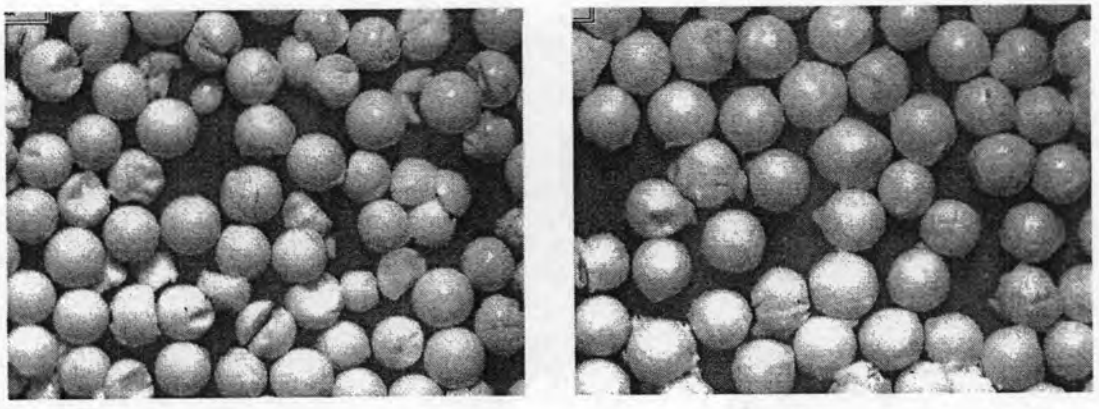


Figure 25 The microscopic morphology (SEM) of (A) uncoated resinate (x75), (B) uncoated resinate (x10,000), (C) coated resinate formulation C3 (x75) and (D) coated resinate formulation C3 (x10,000) after dissolution test in 0.1 M potassium chloride.

3. Study on the effect of compression pressure on uncoated and coated resinates

Compression of uncoated resinates without any excipients at compression pressure 3,000 psi presented no different in diltiazem release profile when compared with the resinates before compressed, while the compression of coated resinates formulation C3 presented increasing in drug release. Figure 26 shows the characteristic of uncoated and coated resinates when subjected to compression force at 3,000 psi. The coated resinates appeared to break up in less degree than uncoated resinates. It was observed that release rate of uncoated resinates remained unchanged (f_2=77.77) after compression (Table 19 and Figure 27). This result could be explained by the release mechanism of uncoated resinates. It was due to drug release from the resinates by exchanging with ions in a surrounding medium, followed by drug diffusion through the polymer matrix of the resinates (Pongjanyakul et al., 2005). Although the resin matrix was broken by compression pressure, it still had ion exchange mechanism to controlled drug release. The drug release from coated resinates was increased (f_2=58.23) after compression because of the film rupture (Table 20).



A B

Figure 26 The microscopic morphology of (A) uncoated resinate and (B) coated resinate formulation C3 after compression (Stereomicroscope x10).

Table 19 The diltiazem release from uncoated and coated resinates C3 after compression in 0.1 M potassium chloride (mean (SD), n=3)

Formulation	% drug release at 12 hr
Uncoated resinate	84.20% (0.30)
Uncoated resinate after compressed at 3,000 psi	83.52% (0.92)
Coated resinate C3	59.03% (0.42)
Coated resinate C3 after compressed at 3,000 psi	66.04% (0.16)

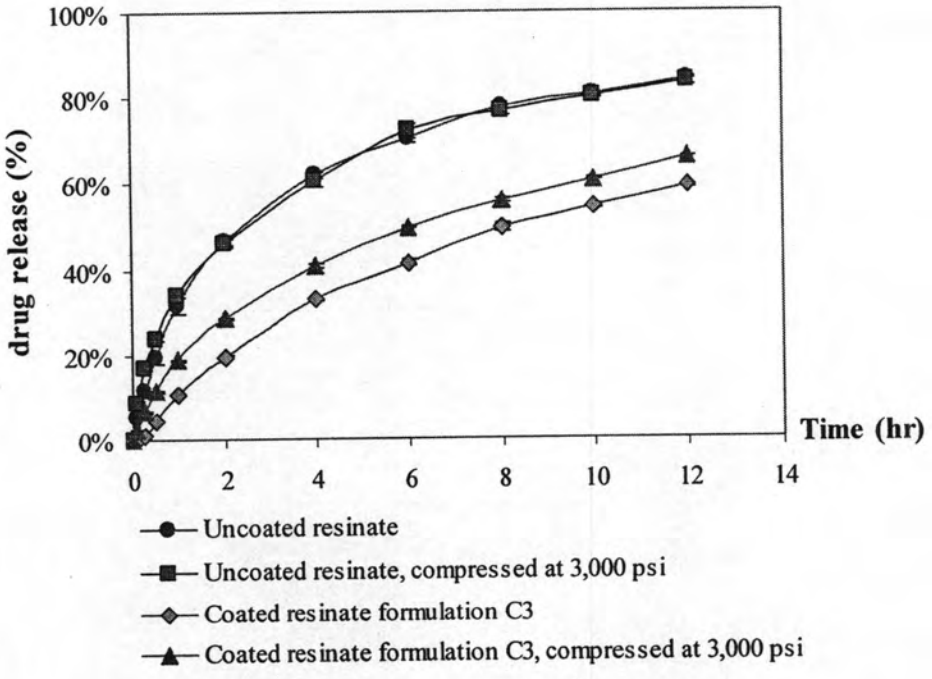


Figure 27 The diltiazem release from uncoated and coated resinates after compression in 0.1 M potassium chloride.

Table 20 The comparison of dissolution profile

Formulation in comparison	Similarity factor (f_2)
Uncoated resinate VS Uncoated resinate after compressed at 3,000 psi	77.77
Coated resinate C3 VS Coated resinate C3 after compressed at 3,000 psi	58.23

Part III. Development of multiple-unit sustained release tablets

From the study of resinates coating (Part II), the resinates coated with coating formulation C1-C3 were selected as they exhibited the diltiazem release more than 50 % in 12 hours, which was suitable for formulating into disintegrating tablets.

1. Study on the effect of amount of resinates

Table 21 shows the physical properties of microcrystalline cellulose (MCC) granules. The moisture content of MCC granules was between 1.21-1.41 %. The bulk density and tapped density of granule formulation F7, F8, F9 were higher than of granule formulation F4, F5, F6 and F1, F2, F3. The particle which has high density tends to present free-flowing characteristic. Thus, the granule formulation F7, F8, F9 had better flow property than of other formulations. The Carr's compressibility was between 14.11-17.84 % which indicated that the granules showed good flowing property (Davies, 2001). The particle size distributions of all granule formulations appeared indifference (Figure 28).

All formulations gave poor physical properties of tablets. The tablet formulation F1, F2, F4, F5, F7 and F8 which contained 30-50 % coated resinates could not be compressed to tablet form. They were too soft to handle (Table 22). The tablets which produced from the formulation F3, F6 and F9 which contained 20 % coated resinates presented high % friability. It caused by the low binding property of granules. The optimal quantity of resinates in tablets compressed with microcrystalline cellulose granules seem to be about 20 % and needed some excipients to improve cohesion force within the tablets such as polyethylene glycol. Figure 29 shows the photograph of tablet formulation F3. The spots of resinate appeared on the surface of tablets.

Table 21 The physical properties of microcrystalline cellulose granules (mean (SD), n=3)

Formulation	Moisture content (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility (%)
F1,F2,F3 (PVP K30 5%)	1.23 (0.064)	0.330 (0.001)	0.401 (0.004)	17.84% (0.006)
F4,F5,F6 (PVP K30 10%)	1.21 (0.142)	0.342 (0.001)	0.404 (0.003)	15.24% (0.008)
F7,F8,F9 (PVP K90 5%)	1.41 (0.070)	0.385 (0.001)	0.448 (0.001)	14.11 (0.002)

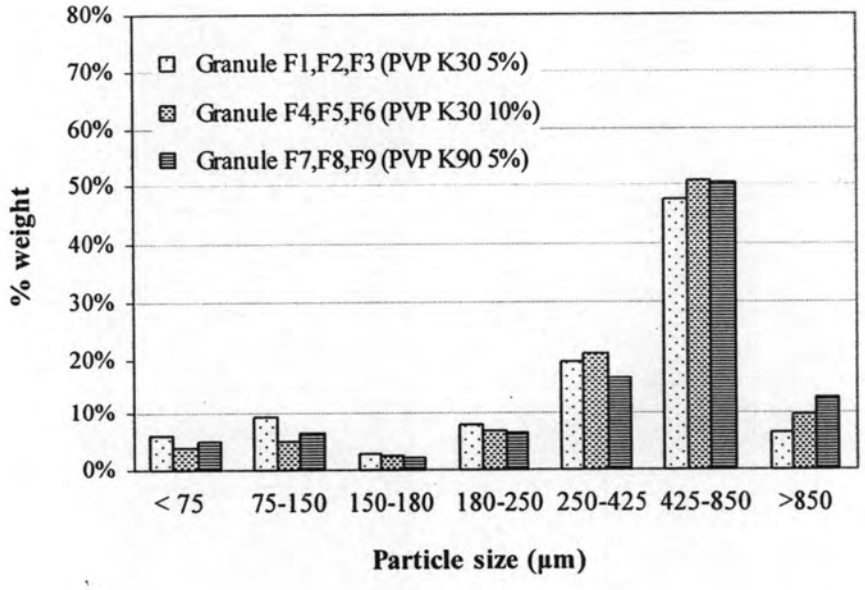


Figure 28 Particle size distributions of microcrystalline cellulose granules evaluated by sieve analysis.

Table 22 The physical properties of disintegrating tablets

Formulation	Binder	Quantity of coated resinates	Appearance
F1	PVP K30 5%	50%	could not handle
F2		30%	could not handle
F3		20%	capping during friability test
F4	PVP K30 10%	50%	could not handle
F5		30%	could not handle
F6		20%	capping during friability test
F7	PVP K90 5%	50%	could not handle
F8		30%	could not handle
F9		20%	capping during friability test

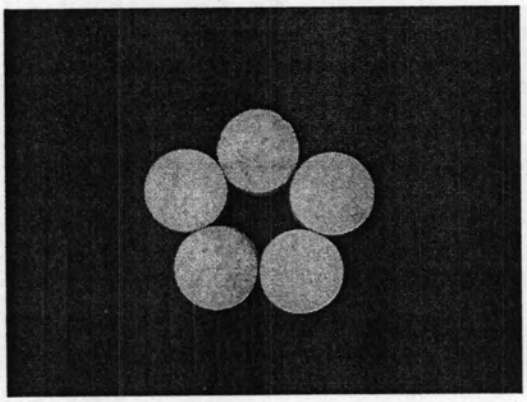


Figure 29 The photograph of tablet formulation F3.

2. Study on the effect of soft material

In the previous reports, the resinates (100-200 microns) could be compressed with only microcrystalline cellulose and had an acceptable physical properties and the least deterioration in the release profile (Prapaitrakul and Whitworth, 1990; Pongjanyakul et al., 2005), but in this study, the use of microcrystalline cellulose to prepare tablets of resinates was not successful. This might be caused by the bigger size of resins (700-800 microns) used in this experimental.

Larhrib and Wells (1997) investigated the compaction property of mixtures of a plastic and soft material, polyethylene glycol (PEG) and fragmenting material, dicalcium phosphate. The mixture materials produced tablets with higher tensile strength than tablets from the pure material alone. PEG was a series of water soluble synthetic polymers. In solid dosage formulations, it was used as a flow improvement agent, lubricant, dry binder, wet granulating agent and plasticizer. Their mechanical property varies according to molecular weight. The higher molecular weight PEG could enhance the effectiveness of tablet binder and impart plasticity to granules. However, they had only limited binding action when used alone, and can prolong disintegration if present in concentration greater than 5 % w/w. In practice, two or more compression aids were blended together because tablet appearance and their hardness were often better than the individual excipient. PEG exhibited good compressibility and produced tablets with high tensile strength. A small amount of PEG was introduced into a formula to improve rheological property, as a lubricant or to improve cohesion within the tablets. Therefore, in this study PEG was selected to improve binding property within the tablets and to protect resinates from compression force.

2.1 The physical properties of granules and disintegrating tablets

Table 23 shows the physical properties of MCC and PEG granules. The moisture content of granules was between 1.26-1.51 %. The Carr's compressibility of granule formulation F10 was 18.37 % which indicated that the granules showed fair flowing property. The Carr's compressibility of granule formulation F11, F12, F13

were 13.25-14.22 % which indicated that the granules showed good flowing property. This result might be caused by increasing of PEG which was a lubricating agent improved flowability of granules. The wet mass of granule formulation F13 which had 20 % PEG 6000 was very sticky. It was very difficult to screen. The amount of PEG 6000 in granule formulation should not more than 10 %. The particle size of granules increased when the molecular weight and amount of PEG was increased (Figure 30).

Addition of PEG produced the tablets with high hardness property but caused long disintegration time. To solve this problem, the addition of 8 % Explotab® was used as disintegrating agent in tablets. Physical properties of tablets of various formulations are presented in Table 24. Tablet formulation F10 was too friable with friability of 1.13 %. Tablet formulation F12 and F13 showed too long disintegration time as 56 and 70 min respectively, though their friability were less than 1.0 %. The tablet formulation F11, F14, F15 and F16 (PEG 4000 20 %) exhibited the satisfactory physical properties, these formulations were more suitable for in vitro release study. The photograph of tablet formulation F11 was shown in Figure 31 and the microscopic morphology of surface and cross section of tablet formulation F11 was shown in Figure 32-34. Whereas the microscopic morphology of surface and cross section of tablet formulation F14 were shown in Figure 35-37.

Table 23 The physical properties of MCC and PEG granules (mean (SD), n=3)

Formulation	Moisture content (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility (%)
F10	1.26% (0.095)	0.391 (0.002)	0.479 (0.003)	18.37% (0.002)
F11,F14,F15,F16	1.26% (0.064)	0.385 (0.000)	0.444 (0.010)	13.25% (0.020)
F12	1.30% (0.091)	0.405 (0.001)	0.471 (0.000)	14.09% (0.002)
F13	1.51% (0.110)	0.391 (0.003)	0.456 (0.001)	14.22% (0.005)

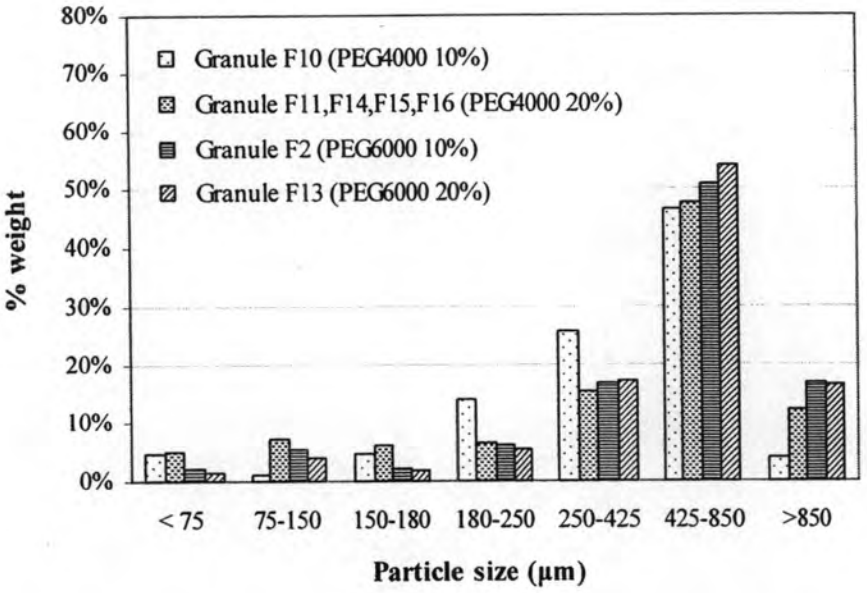


Figure 30 Particle size distributions of MCC and PEG granules evaluated by sieve analysis.

Table 24 The physical properties of tablets (mean (SD))

Formulation	Weight variation (gm)	Hardness (kp)	Thickness (mm)	Friability (%)	Disintegration time (min)	Diltiazem content (%)	% drug release at 12 hr
F10	1.5002 (0.015)	12.7 (0.23)	0.760 (0.002)	1.13%	19	102.76% (0.81)	55.96% (2.81)
F11	1.5086 (0.015)	11.5 (0.17)	0.756 (0.002)	0.67%	23	101.44% (1.06)	53.36% (3.75)
F12	1.5170 (0.020)	15.0 (0.20)	0.762 (0.003)	0.41%	56	101.94% (0.50)	45.23% (2.33)
F13	1.5116 (0.017)	16.0 (0.20)	0.744 (0.003)	0.36%	70	103.20% (1.24)	N/A
F14	1.5050 (0.012)	12.3 (0.23)	0.760 (0.002)	0.71%	13	103.61% (1.19)	68.34% (4.74)
F15	1.5008 (0.014)	11.8 (0.16)	0.758 (0.003)	0.55%	21	101.98% (1.20)	58.31% (0.15)
F16	1.5011 (0.014)	14.8 (0.31)	0.760 (0.002)	0.60%	23	103.06% (0.64)	56.56% (1.03)

N/A = *Did not perform because this formulation presented too long disintegration time.*

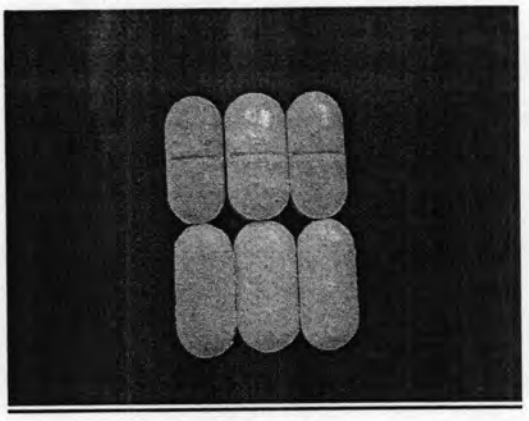


Figure 31 The photograph of tablet formulation F11.

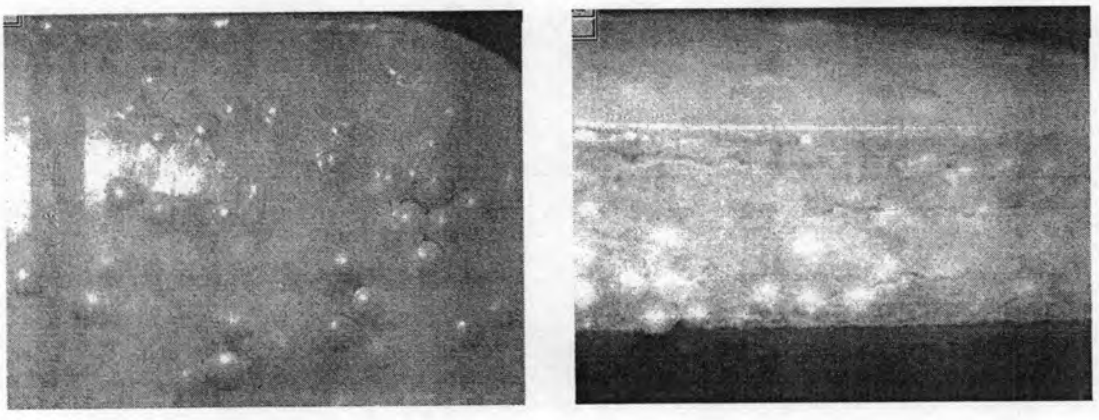


Figure 32 The microscopic morphology of surface of tablet formulation F11 (prepared from coated resinate C3) when observed by stereomicroscope (x7).

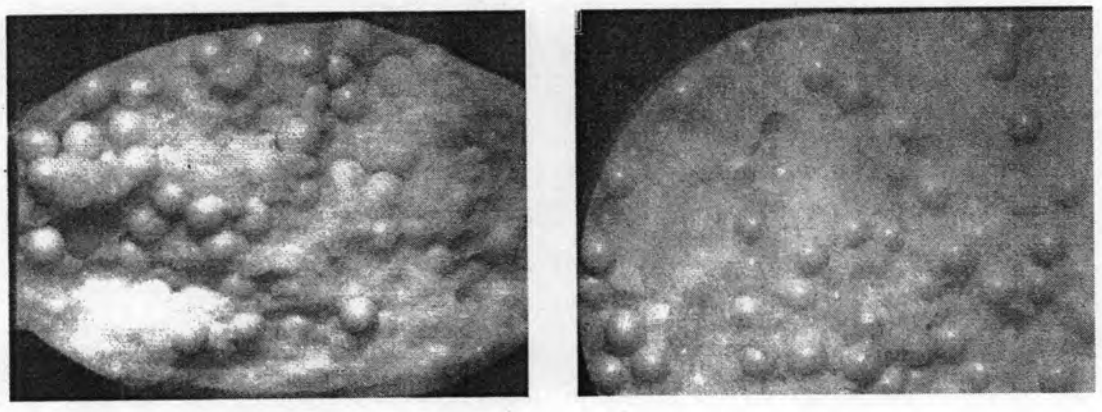
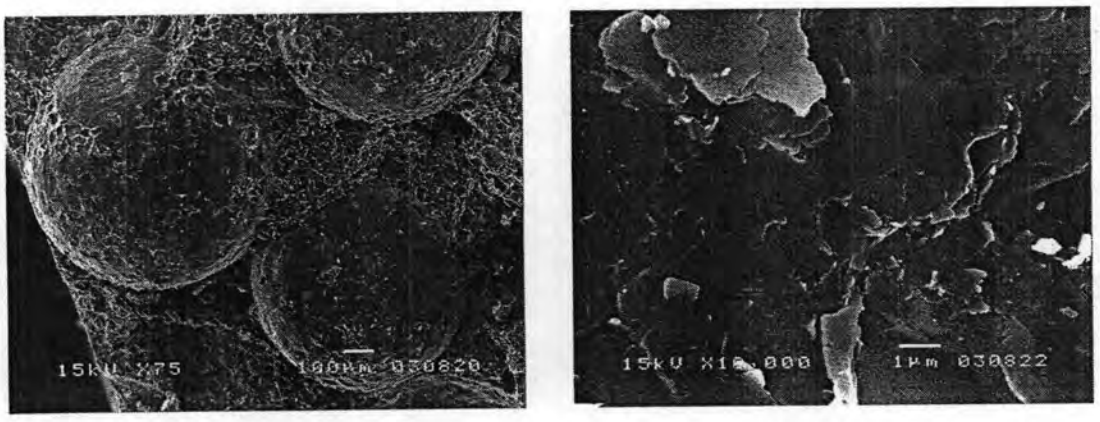


Figure 33 The microscopic morphology of cross section of tablet formulation F11 (prepared from coated resinate C3) when observed by stereomicroscope (x7).



A B

Figure 34 The photomicrograph (SEM) of tablet formulation F11 (prepared from coated resinate C3) (A) x75 and (B) x10,000.

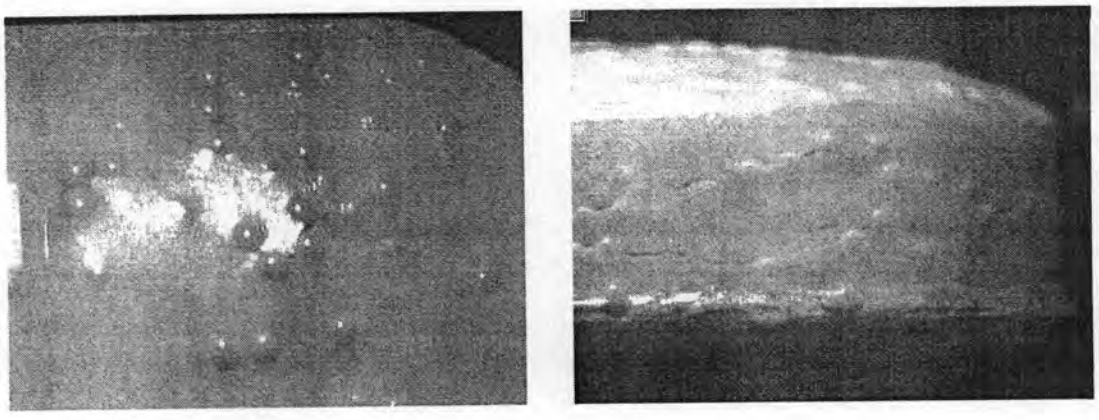


Figure 35 The microscopic morphology of surface of tablet formulation F14 (prepared from uncoated resinate) when observed by stereomicroscope (x7).

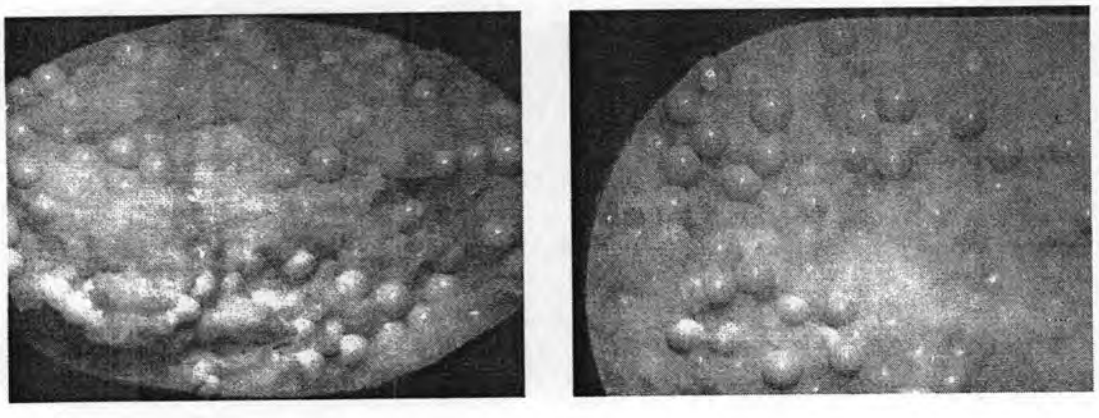
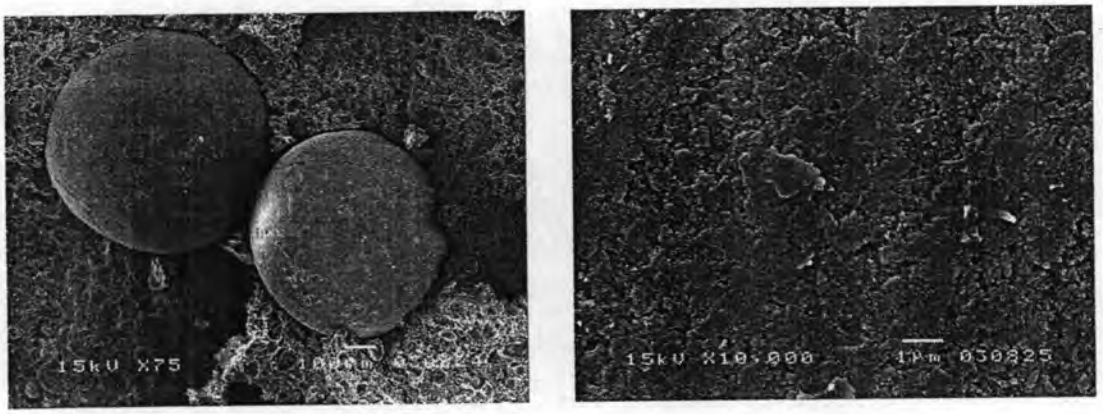


Figure 36 The microscopic morphology of cross section of tablet formulation F14 (prepared from uncoated resinate) when observed by stereomicroscope (x7).



A B

Figure 37 The photomicrograph (SEM) of tablet formulation F14 (prepared from uncoated resinate) (A) x75 and (B) x10,000.

2.2 Study of drug release

The diltiazem release from tablet formulation F12, which formulated from 10 % PEG 6000 was slowest when compared with the tablet formulated from PEG 4000 (Figure 38). The tablet formulation F10 which formulated from 10 % PEG 4000 presented the most similar dissolution profile when compared with coated resinate formulation C3 before compressing into tablets (f_2=69.94) but it was too friable with friability of 1.13 % (Table 25). Then, the tablet formulation F11 (20 % PEG 4000) was suitable for the further studies, because it presented acceptable characteristic tablets and dissolution profile. The similarity factor (f_2) of tablet formulation F11 was 65.71 when compared with the dissolution profile of coated resinate formulation C3 before compressing into tablets.

Figure 39 shows the decreasing of drug release from tablets when increased the coating level of resinates. When compared the dissolution profile of tablets with the resinates which had the same coating level, the tablet formulation F11 (15 % coating level) exhibited the most similar dissolution profile (f_2=65.71) (Table 26).

Table 25 The comparison of dissolution profile

Formulation in comparison	Similarity factor (f_2)
Coated resinate C3 VS Tablet F10	69.94
Coated resinate C3 VS Tablet F11	65.71
Coated resinate C3 VS Tablet F12	47.96

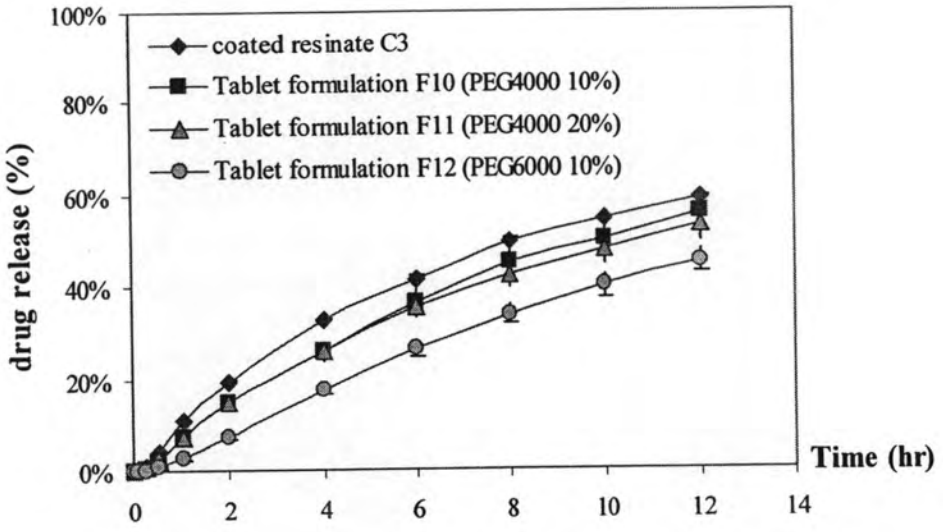


Figure 38 The diltiazem release in 0.1 M potassium chloride.

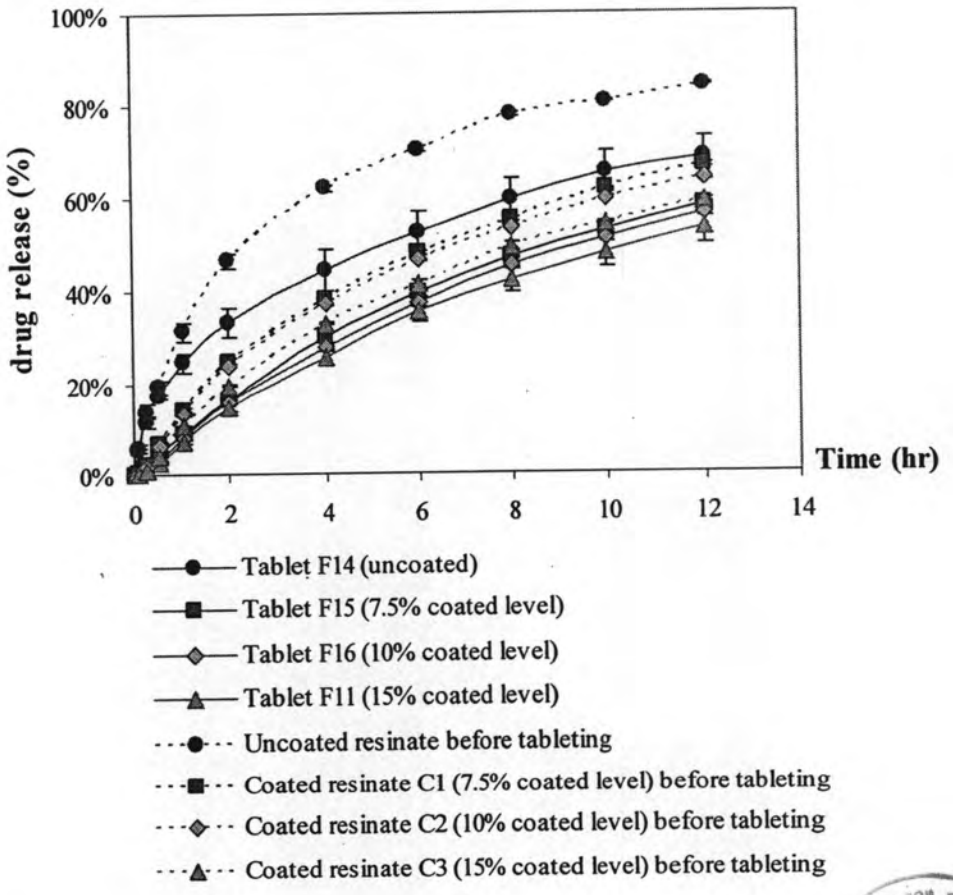


Figure 39 The diltiazem release in 0.1 M potassium chloride.

Table 26 The comparison of dissolution profile

Formulation in comparison	Similarity factor (f_2)
Uncoated resinate VS Tablet F14	45.38
Coated resinate C1 VS Tablet F15 (C1)	59.24
Coated resinate C2 VS Tablet F16 (C2)	59.19
Coated resinate C3 VS Tablet F11 (C3)	65.71

In order to study the effect of PEG 4000 in the tablet formulation, the tablet formulation F17 which had no PEG 4000 (control formulation) was produced to comparing the dissolution profile with the tablets produced from PEG 4000 granules. Table 27 shows the physical properties of the tablet formulation F17, the friability could not be measured because of the capping of tablets during friability test. The microscopic morphology of surface and cross section of tablet formulation F17 was shown in Figure 40-42.

The dissolution profile exhibited the similarity factor (f_2) was 88.13 when compared with the tablet formulation F11 (Table 28). This indicated that the dissolution profile of the tablets with and without PEG 4000 appeared indifference (Figure 43), but the PEG 4000 was still important in the formulation because it improved binding property of tablets.

Table 27 The physical properties of tablets (mean (SD))

Formulation	Weight variation (gm)	Hardness (kp)	Thickness (mm)	Friability (%)	Disintegration time (min)	Diltiazem content (%)	% drug release at 12 hr
Tablet F17 (without PEG 4000)	1.5013 (0.020)	9.5 (0.10)	0.760 (0.001)	capping	8	102.05% (1.00)	52.47% (2.32)

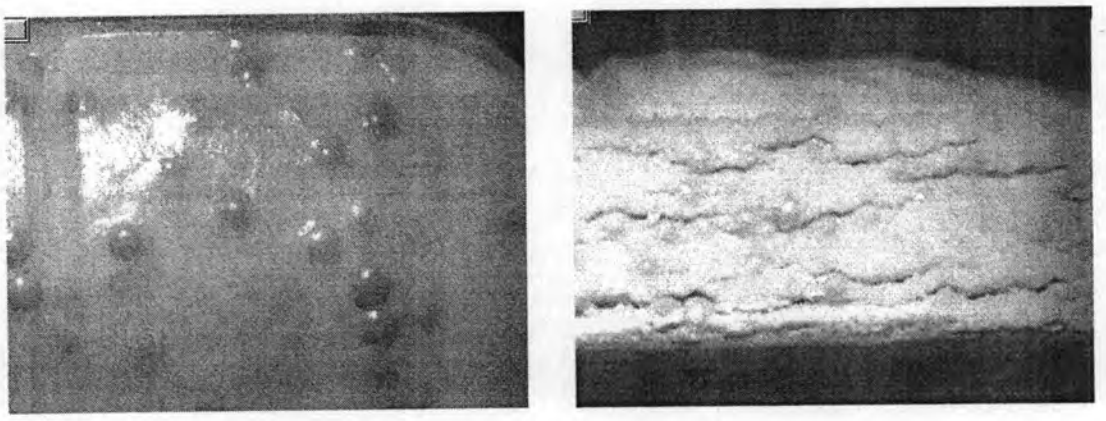


Figure 40 The microscopic morphology of surface of tablet formulation F17 (prepared without PEG 4000) when observed by stereomicroscope (x7).

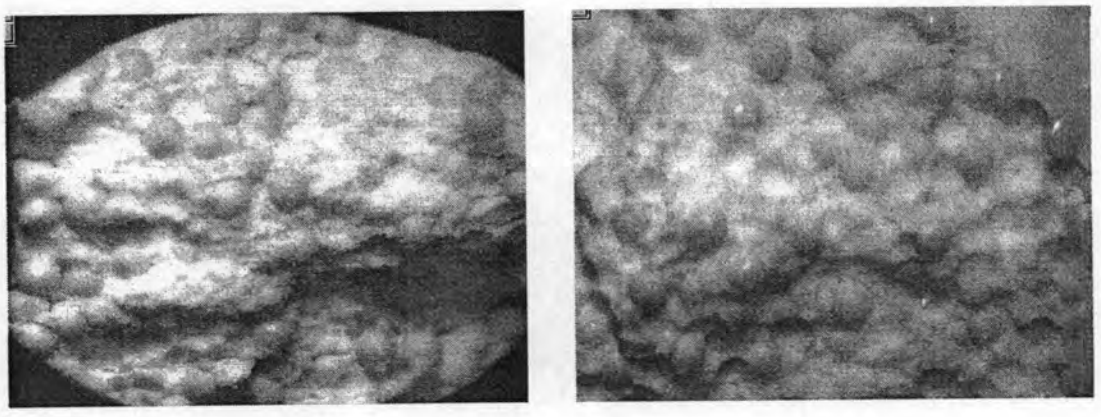
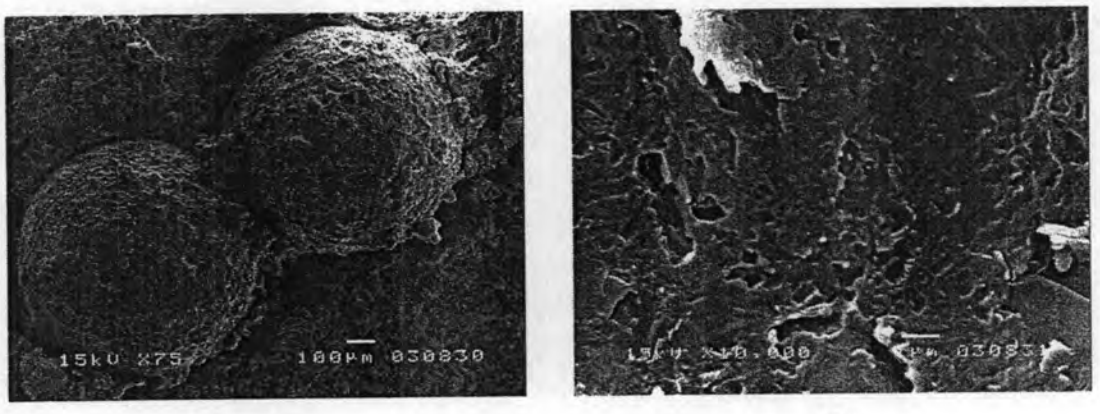


Figure 41 The microscopic morphology of cross section of tablet formulation F17 (prepared without PEG 4000) when observed by stereomicroscope (x7).



A B

Figure 42 The photomicrograph (SEM) of tablet formulation F17 (prepared without PEG 4000) (A) x75 and (B) x10,000.

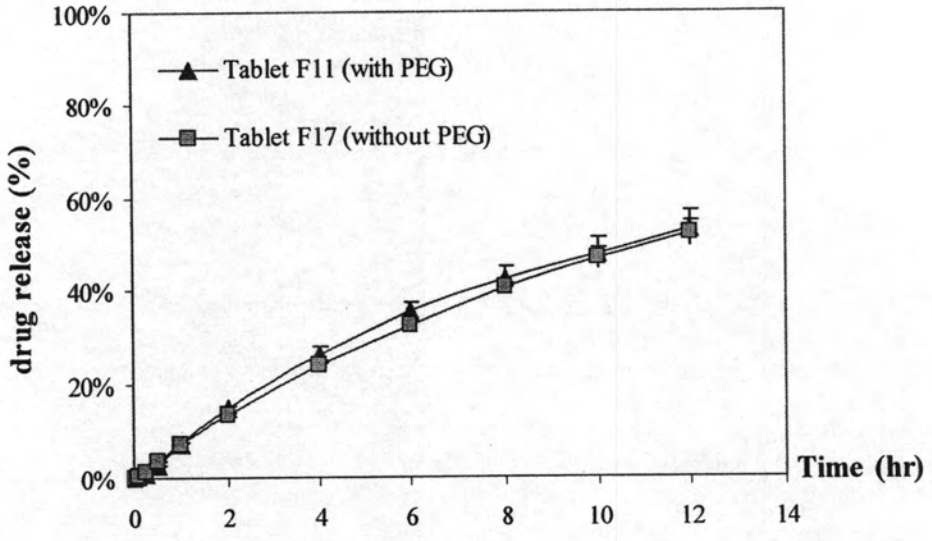


Figure 43 The diltiazem release in 0.1 M potassium chloride.

Table 28 The comparison of dissolution profile

Formulation in comparison	Similarity factor (f_2)
Tablet F11 (with PEG) VS Tablet F17 (without PEG)	88.13

3. Study on the effect of disintegrating time of tablets on drug release

The previous study in Part III (2), using of polyethylene glycol in the tablet formulation might caused the prolong disintegration time. In order to study this effect, the total resinates were manually separated from tablet formulation F11 and F14 from study Part III (2). The drug release profiles from separated coated resinates and separated uncoated resinates were studied comparing with the same tablet formulation and compression pressure. Table 29 shows the drug release from the separated coated resinates and separated uncoated resinates from tablet formulation F11 and F14 in 12 hour which was 54.61 % and 77.41 %. Figure 44 shows dissolution profile of the separated coated resinates from tablets in comparing with disintegrating tablet formulation F11. Drug release from separated coated resinates from tablet formulation F11 was not different from the tablet formulation F11 (f_2=85.54) (Table 30). This was indicated that disintegration time did not affect drug release. The drug release mechanism of disintegrating tablets was due to only the diffusion through the resin matrix and film coating membrane. While drug release from separated uncoated resinates from tablet formulation F14 was increased when compared with tablet formulation F14 (f_2=61.47) (Figure 45). It showed that disintegration time had slightly influent to drug release from tablets prepared from uncoated resinates.

Table 29 The drug release from the uncoated and coated resinates from tablets (mean (SD), n=3)

Formulation	% drug release at 12 hr
Separated coated resinates from Tablet F11	54.61% (2.64)
Separated uncoated resinates from Tablet F14	77.41% (3.42)

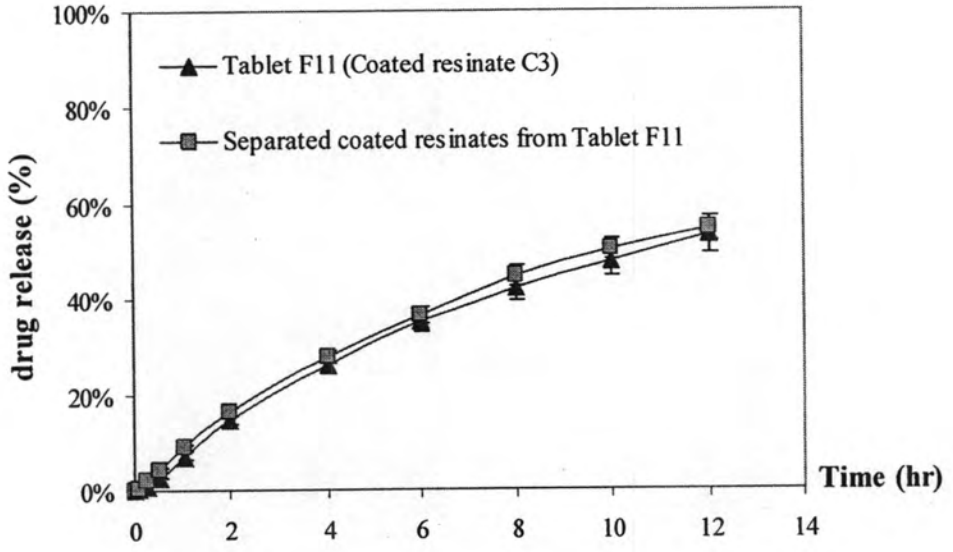


Figure 44 The diltiazem release in 0.1 M potassium chloride.

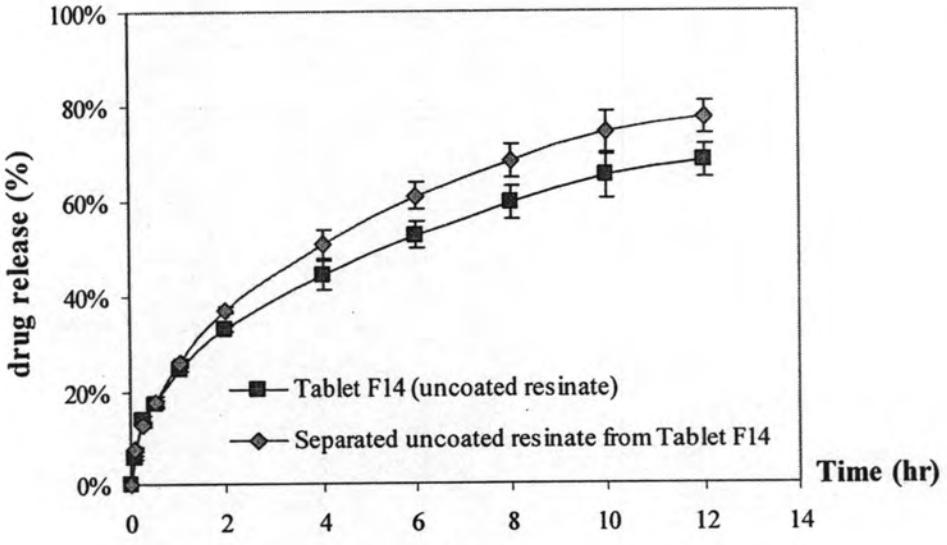


Figure 45 The diltiazem release in 0.1 M potassium chloride.

Table 30 The comparison of dissolution profile

Formulation in comparison	Similarity factor (f_2)
Tablet F11 VS Separated coated resinates from Tablet F11	85.54
Tablet F14 VS Separated uncoated resinates from Tablet F14	61.47

4. Study on the effect of compression force

To study the effect of compression force during tableting process, the granules of the formulation F11 (using coated resinate formulation C3) and F14 (using uncoated resinates) from study Part III (2) was compressed at three compression pressures of 1,500 psi (340 pound), 3,000 psi (681 pound) and 4,500 psi (1,022 pound) by the hydraulic press. The relationships of compression force and the drug release behaviors were evaluated. Table 31 shows the physical properties of disintegrating tablets. The hardness of all formulations was between 8.5-12.3 kp and friability was 0.44-0.71 %. Increasing in compression pressure presented the higher hardness property. Disintegration time of tablet formulation F14 was less than tablet formulation F11, because uncoated resinates could swell when exposed to water and acting as disintegrating agent (Hughes, 2005).

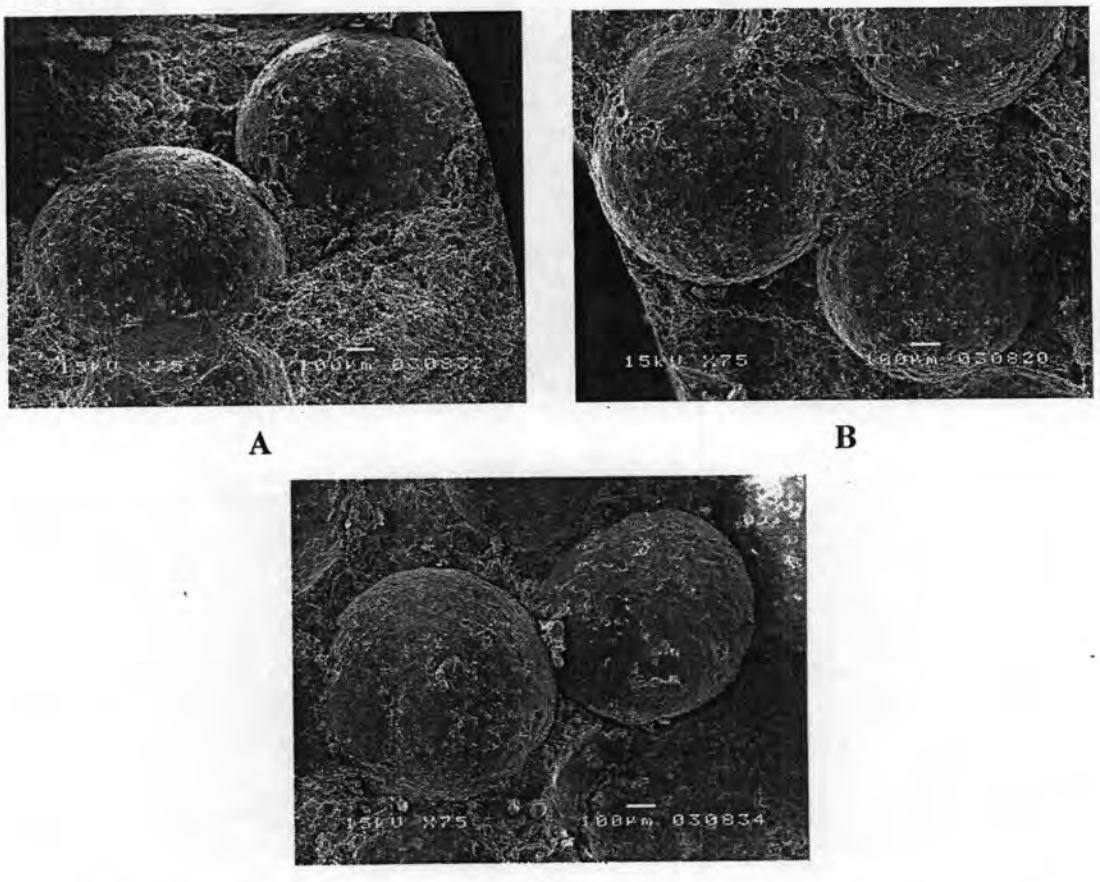
Table 31 The physical properties of tablets compressed at various compression pressures (mean (SD))

Formulation	Weight variation (gm)	Hardness (kp)	Thickness (mm)	Friability (%)	Disintegration time (min)	Diltiazem content (%)	% drug release at 12 hr
F11 (1,500 psi)	1.5106 (0.011)	9.4 (0.30)	0.761 (0.001)	0.60%	20	101.15% (2.10)	55.68% (1.83)
F11 (3,000 psi)	1.5086 (0.015)	11.5 (0.17)	0.756 (0.002)	0.67%	23	101.44% (1.06)	53.36% (3.75)
F11 (4,500 psi)	1.5044 (0.010)	11.7 (0.11)	0.760 (0.001)	0.54%	28	102.50% (1.40)	51.03% (2.62)
F14 (1,500 psi)	1.5083 (0.034)	8.5 (0.10)	0.767 (0.002)	0.63%	10	102.44% (1.00)	79.00% (0.18)
F14 (3,000 psi)	1.5050 (0.012)	12.3 (0.23)	0.760 (0.002)	0.71%	13	103.61% (1.19)	68.34% (4.74)
F14 (4,500 psi)	1.5170 (0.012)	12.0 (0.26)	0.755 (0.002)	0.44%	13	103.10% (2.00)	67.05% (3.76)

Coating resinates with acrylate polymer was important to protect resinates from compression pressure. Uncoated resinates exhibited some broken resinates when

applied pressure during compression process (Figure 47), while coated resinates were not occurred (Figure 46). In case of tablet formulation F11 which prepared from coated resinate formulation C3 was indifferent in dissolution profile between various compression pressures (Figure 48) which was indicated by the similarity factor (f_2=72.88-91.06) in Table 32. This result showed that the compression pressure between 340-1,022 pound (1,500-4,500 psi) did not affect to the drug release profile of tablets formulated from coated resinates.

While the drug release of tablet formulation F14 which prepared from uncoated resinates was decreased when the compression pressure increased (Figure 49). The similarity factor was 59.90-65.29 (Table 32). This result might be caused by the effect of compression pressure to the adhesion force of PEG on the surface of uncoated resinates which caused decreasing of surface area for release and it inhibited swelling of resinates.



A B C

Figure 46 The photomicrograph of the coated resinates in tablet formulation F11 compressed with various compression pressures (A) 1,500, (B) 3,000 and (B) 4,500 psi (SEM x75).

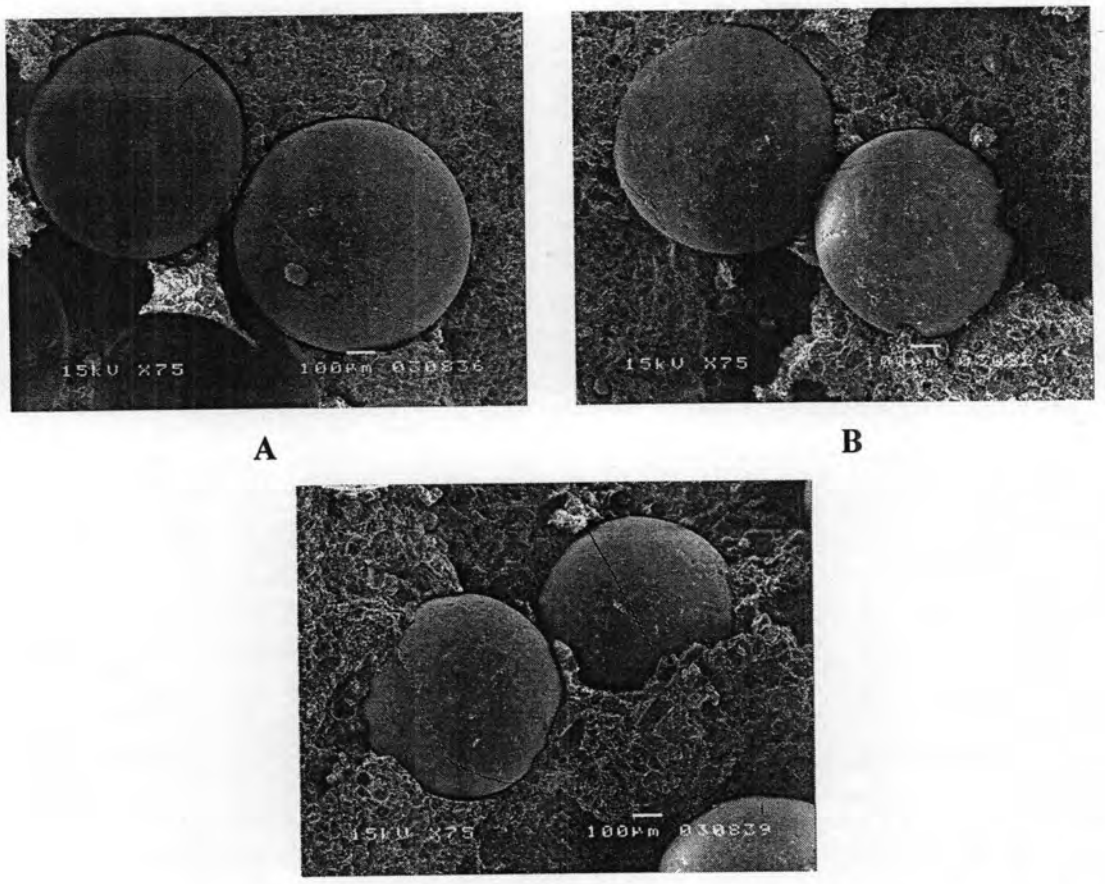


Figure 47 The photomicrograph of the uncoated resinates in tablet formulation F14 compressed with various compression pressures (A) 1,500, (B) 3,000 and (B) 4,500 psi (SEM x75).

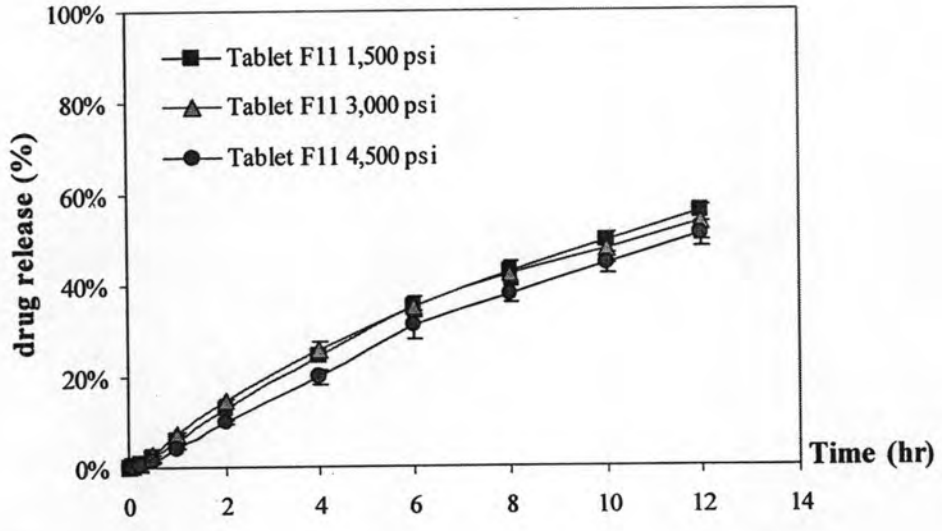


Figure 48 The diltiazem release of tablet formulation F11 prepared using different compression pressures in 0.1 M potassium chloride.

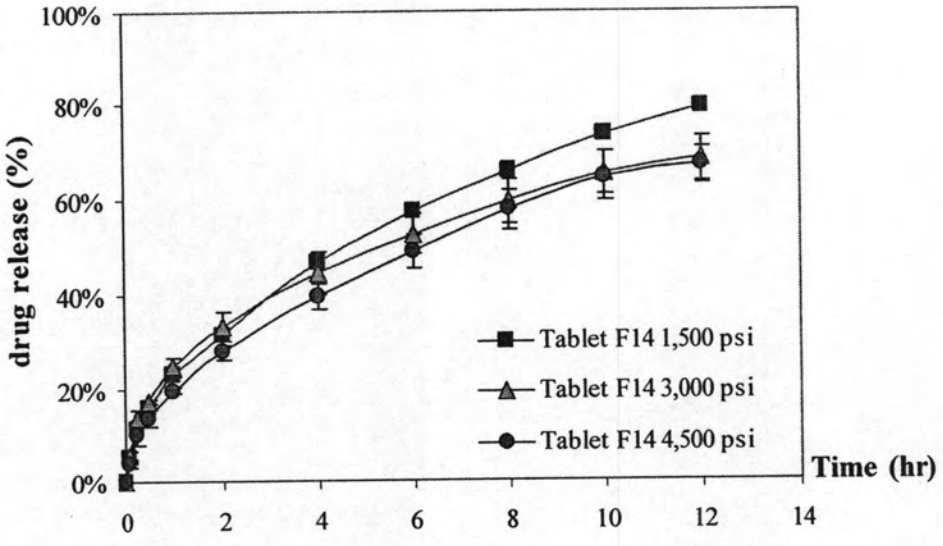


Figure 49 The diltiazem release of tablet formulation F14 prepared using different compression pressures in 0.1 M potassium chloride.

Table 32 The comparison of dissolution profile

Formulation in comparison	Similarity factor (f_2)
Tablet F11 (1,500 psi) VS Tablet F11 (3,000 psi)	91.06
Tablet F11 (1,500 psi) VS Tablet F11 (4,500 psi)	72.88
Tablet F14 (1,500 psi)VS Tablet F14 (3,000 psi)	65.29
Tablet F14 (1,500 psi)VS Tablet F14 (4,500 psi)	59.90

5. Study on the effect of compression machine

This experiment aimed to study the factor of compression machine between the hydraulic press tableting machine and the single punch tableting machine. The same size of punch and die, concaved oblong 10.3x21.9 mm, was used. The tablet formulation F11 which was prepared by using single punch tableting machine showed the acceptable characteristic tablets (Table 33). The comparison of dissolution profile between formulations prepared from different machines was shown in Figure 50. This result presented indifference in drug release profile, which was indicated by the similarity factor (f_2) which was 78.48 in Table 34. The release kinetic of tablets was also best described by the Higuchi model. Table 35 and Figure 51 show the release rate and the Higuchi plot of diltiazem release from tablet formulation F11 in 0.1 M potassium chloride.

Table 33 The physical properties of tablets compressed by single punch tableting machine (mean (SD))

Formulation	Weight variation (gm)	Hardness (kp)	Thickness (mm)	Friability (%)	Disintegration time (min)	Diltiazem content (%)	% drug release at 12 hr
F11	1.5108 (0.018)	10.4 (0.10)	0.758 (0.001)	0.77%	20	102.10% (1.05)	50.13% (0.50)

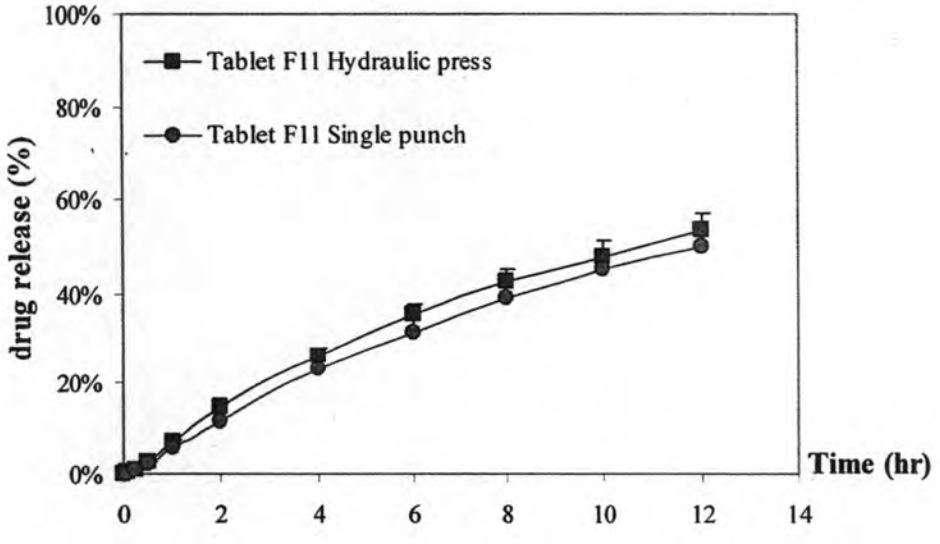


Figure 50 The diltiazem release in 0.1 M potassium chloride.

Table 34 The comparison of dissolution profile of tablet formulation F11

Machine in comparison	Similarity factor (f_2)
Hydraulic press VS Single punch machine	78.48

Table 35 The diltiazem released from tablet formulation F11 prepared from different compression machines in 0.1 M potassium chloride fitted to Higuchi model

Machine	R^2	K ($\%t^{-1/2}$)
Hydraulic press	0.9934	0.1772
Single punch	0.9882	0.1658

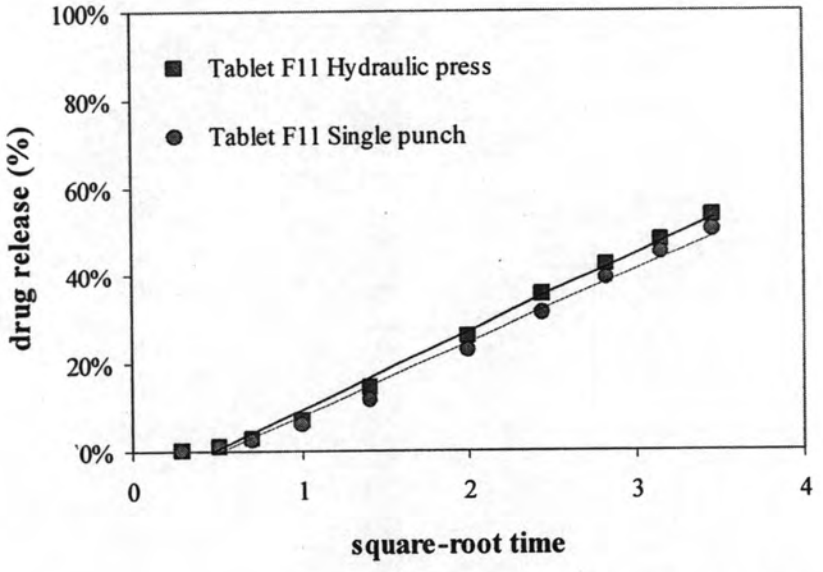


Figure 51 The Higuchi plot of diltiazem release from tablet formulation F11 prepared from different compression machines in 0.1 M potassium chloride.