CHAPTER 4

RESULTS AND DISCUSSION

4.1 Selection of Polymers for Pentoxifylline Tablets

Swelling of Polymers

The swelling of polymers were observed for 24 hours by reading the volume of cylinders. The swelling volume of polymer which has approximate the same viscosity was indicated by the position of the pin head. The results are shown in Table 4.1. The swelling of polymers as a function of time are shown in Figure 4.1 – 4.4 respectively.

The swelling of polymers was used to be an initial information for selection of polymer. HEC QP52000 and HEC M_v90000 completely swelled in 24 hours, while the water penetrated into almost all of HEC WP40. In the case of HEC M_v90000 the polymer was completely swelled and soluble therefore the viscosity shows much less than HEC WP40 and HEC QP52000. (Figure 4.11) The swelling of HEC WP40 is less than HEC QP52000 and HEC M_v90000. For HPMC E4M and F4M, after the water was pour onto the polymers in the cylinder the water penetrated into the surface of polymer bed and then the protective layer was formed. This made the water penetration into the inner polymer bed slow. The study found that the water did not completely penetrate into HPMC for a period of 24 hours. For this reason the HPMC would be more suitable polymer for sustained release preparation than HEC. In order to confirm the selection of proper polymer for pentoxifylline, the tablets were prepared with all of the above polymers.

Table 4.1 : Swelling Volume of Polymers in Water

Polymers	Volume (ml)		
	0 hour	18 hours	24 hours
HEC WP40	0.40 ± 0.00	0.97 ± 0.06	1.30 ± 0.06
HEC QP52000	0.35 ± 0.00	4.33 ± 0.21	4.43 ± 0.12
HEC M_v 90000	0.87 ± 0.03	1.93 ± 0.03	full
HPMC E4M	0.30 ± 0.00	1.02 ± 0.03	1.10 ± 0.00
HPMC F4M	0.60 ± 0.00	1.10 ± 0.10	1.23 ± 0.06

Note : hydroxy ethylcellulose WP40 (HEC WP40), hydroxy ethylcellulose QP52000 (HEC QP52000), hydroxy ethylcellulose M_v 90000 (HEC 90000), hydroxypropyl methylcellulose E4M (HPMC E4M) and hydroxypropyl methylcellulose F4M (HPMC F4M)

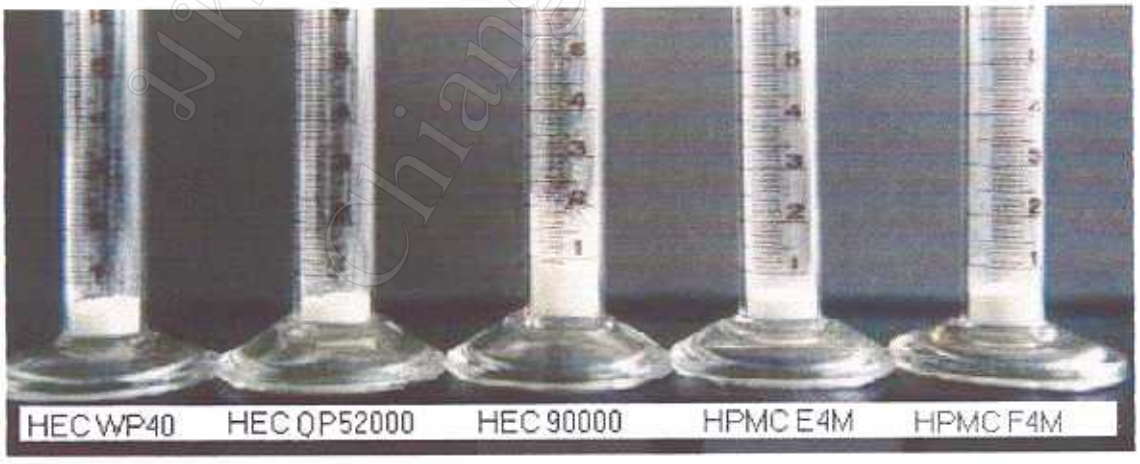

Figure 4.1 : The polymers before adding of distilled water (0 hour).

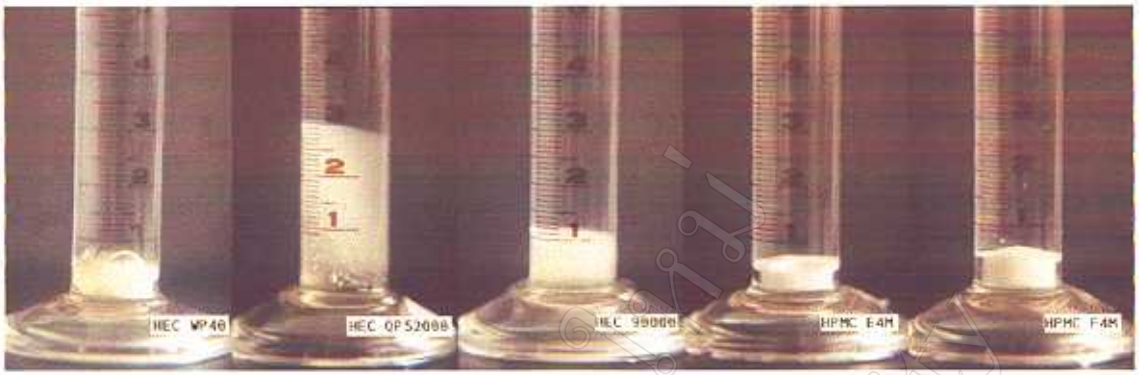

Figure 4.2 : The swelling of polymers at 1 hour after adding of distilled water.

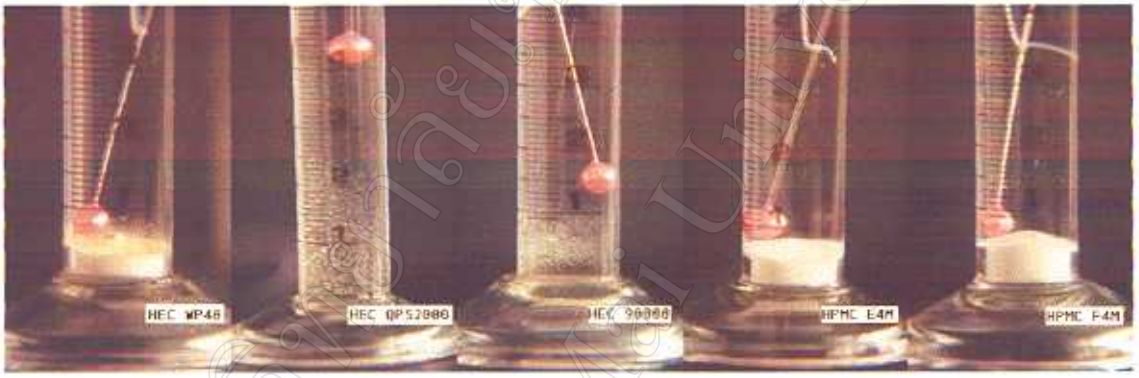

Figure 4.3 : The swelling of polymers at 3 hour after adding of distilled water.

Figure 4.4 : The swelling of polymers at 24 hour after adding of distilled water.

4.2 A Typical Physical Characteristic of Pentoxifylline Granules

The physicochemical properties of granules is useful in formulating and producing the suitable tablet. Final tablet characteristics such as dissolution rate, disintegration time, porosity, capping tendency, and hardness can be affected by granulation characteristics. In this study, the physical characteristic of 3 batches of granules formulation D7 were investigated for the typical demonstration. (Table 4.2 and Appendix 5)

Table 4.2 : The Physical Characteristic of Granules Formulation D7

Properties	D7 lot1	D7 lot2	D7 lot3
Bulk Density (g/ml)	0.52 ± 0.00	0.56 ± 0.00	0.51 ± 0.00
Tapped Density (g/ml)	0.62 ± 0.00	0.67 ± 0.00	0.60 ± 0.00
Compressibility Ratio (%)	15.83 ± 0.28	15.71 ± 0.19	15.16 ± 0.01
Repose Angle α (degree)	43.24 ± 0.60	43.40 ± 0.08	43.51 ± 0.68
Flow ability	Good	Good	Good
Moisture Content of granules before compressing (% w/w)	1.65 ± 0.11	1.23 ± 0.08	1.62 ± 0.15
Median Size (μ)	367.37	343.77	371.48

The repose angle can refer to the flow property of the granules. For most pharmaceutical powders and granules, the values range from 25° to 45°, with lower values indicating better flow characteristic. If the repose angle value is more than 45°, the flow ability is not good. (52) The compressibility ratio is the ability of granules to form a compact under pressure. The previous study showed that the small granules has poor flow rate but gave the high compressibility, so the less value of compressibility ratio indicated the good flow ability. (45,53) The repose angle and the compressibility ratio of the granules obtained in this study revealed a good flow ability. There are an acceptable range of moisture contents in the granules. The size distribution of the granules determined by

sieving method are shown in Figure 4.5. The median of the granule size of the three batches are very close as shown in Table 4.2.

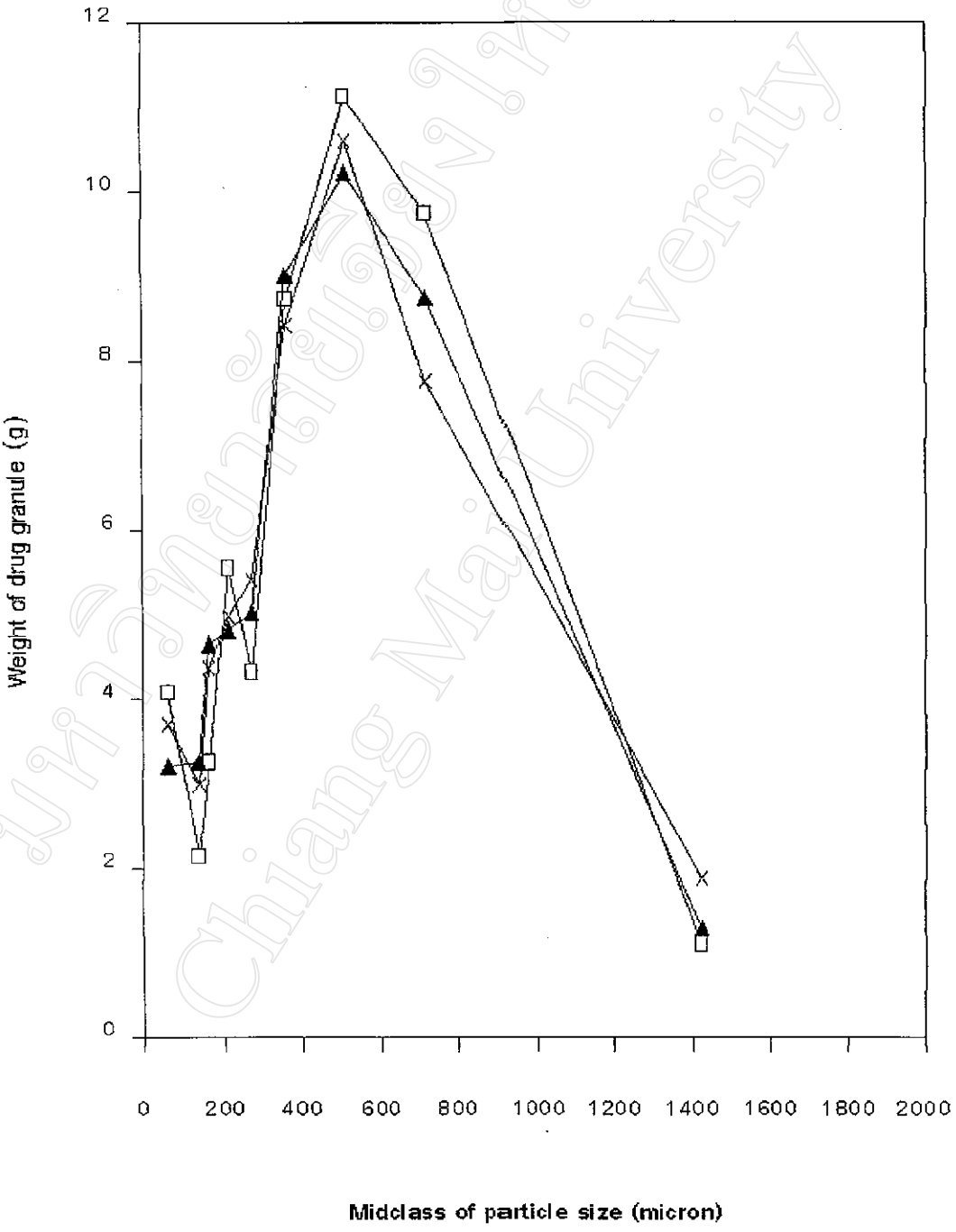

Figure 4.5 : Size distribution of pentoxifylline granules for tableting. Keys: (-▲-) D7 lot1, (-□-) D7 lot2 and (-✳-) D7 lot3

4.3 Physical Characteristic of Pentoxifylline Tablets

The pentoxifylline matrix tablet prepared with hydroxyethyl cellulose WP40, hydroxyethyl cellulose QP52000, hydroxypropyl methylcellulose E4M and hydroxypropyl methylcellulose F4M as polymers can be easily compressed into tablets. On the contrary, the pentoxifylline-HEC M_v90000 mixture was unable to obtain a good tablet due to capping, easy to split. Figure 4.6 shows the characteristic of pentoxifylline sustained release tablets.

Table 4.3 : Physical Characteristic of Pentoxifylline Tablet of Formulation A1, A2, B1, B2, D1, D2, E1, E2, F1 and F2.

Formulation	Type of Polymers	Average Weight (mg)	SD.	Average Hardness (N)	SD.
A1	HEC WP40 (Ethanol)	0.6010	0.0019	49.6	1.4
A2	HEC WP40 (Water)	0.6038	0.0019	65.7	2.2
B1	HEC QP52000 (Ethanol)	0.6017	0.0009	51.1	1.6
B2	HEC QP520000 (Water)	0.6019	0.0008	44.7	4.3
C1	HEC M_v90000(Ethanol)	Unable to compress into tablets			
C2	HEC M_v90000(Water)	Unable to compress into tablets			
D1	HPMC E4M (Ethanol)	0.5840	0.0013	66.3	8.3
D2	HPMC E4M (Water)	0.5958	0.0009	69.8	4.2
E1	HPMC F4M (Ethanol)	0.5924	0.0015	51.7	4.5
E2	HPMC F4M (Water)	0.5965	0.0019	46.9	2.7
F1	Lactose (Ethanol)	0.5898	0.0008	47.7	4.6
F2	Lactose (Water)	0.5959	0.0014	56.1	4.7

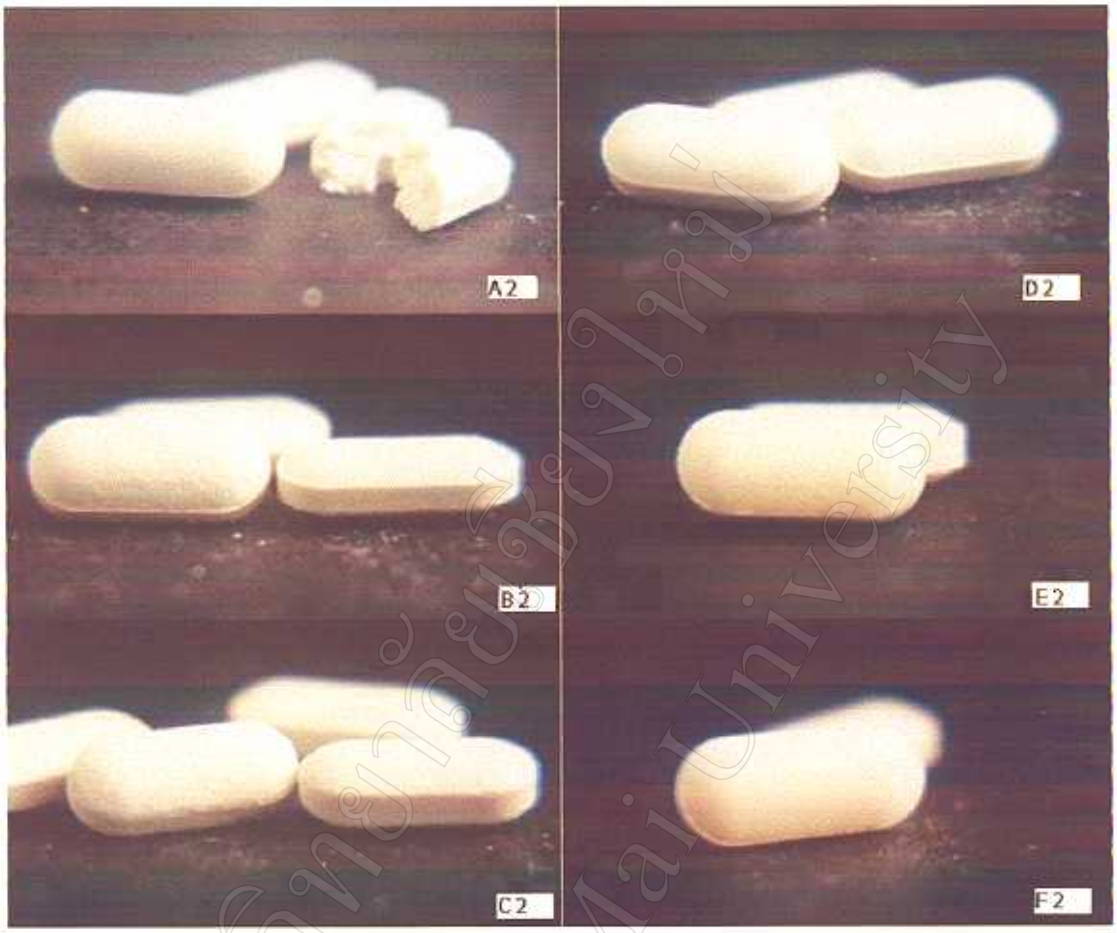

Figure 4.6 : Characteristic of pentoxifylline sustained release tablets in formulation A2, B2, C2, D2, E2 and F2

A tablet is designed to contain a specific amount of drug in a specific amount of tablet formula. To check that a tablet contains the proper amount of drug, the weight of the tablet being made is measured. Besides, a tablet require a certain amount of hardness to withstand mechanical shocks of handling in its manufacture, packing and shipping. Adequate tablet hardness is necessary requisites for consumer acceptance. Therefore the hardness an weight variation of the tablets were tested. The results in Table 4.3 shows that the weight variation of the drug has uniformity range and the hardness is in the 40-70 N range. However the hardness was not effected on the release of drug from the swelling polymer, this result was also observed by the others. (19, 20)

4.4 Pentoxifylline contents

In general, tablets with a good weight variation dose not ensure good content uniformity, but a large weight variation precludes good content uniformity. It is obvious that the pentoxifylline contents must be determined. Pentoxifylline assay was carried out by spectrophotometer. The maximum absorbance wavelength (λ_{max}) of pentoxifylline in SGF, SIF and distilled water are at 208 and 273 nm, but in dichloromethane shows only a peak of 273 nm. This result is conformed with the data reported by Alan W and Stephen P.C. (2) In these studies all absorbances of pentoxifylline were measured at 273 nm. In order to determine the concentration of pentoxifylline in the above solutions, the standard curves were prepared and the regression equations are shown in Table 4.4, Appendix 1 and Appendix 2

Table 4.4 : Equation for Determination of Pentoxifylline Concentration in SGF, SIF, Dichloromethane, Distilled Water and Phosphate Buffer

Solution	Equation	R
SGF	$A = 34.21C + (6.34 \times 10^{-4})$	0.9999
SIF	$A = 35.71C + (2.93 \times 10^{-3})$	0.9998
Dichloromethane	$A = 31.63C + (2.34 \times 10^{-3})$	0.9996
Distilled Water	$A = 35.63C + (2.36 \times 10^{-3})$	0.9999
Phosphate Buffer pH 5.8	$A = 35.43C + (5.98 \times 10^{-3})$	0.9998
Phosphate Buffer pH 7.0	$A = 35.39C + (2.04 \times 10^{-3})$	0.9999
Phosphate Buffer pH 8.0	$A = 35.82C + (3.73 \times 10^{-3})$	0.9999

Note : A is absorbance and C is concentration of pentoxifylline

Selection of Solvent

The solvent for pentoxifylline assay was selected base on the solubility of the drug in each solution of phosphate buffer pH 5.8, 7.0, 8.0, distilled water, SGF, SIF and

dichloromethane. Dichloromethane is a suitable solvent for dissolving pentoxifylline because of its solubility which is higher than distilled water, phosphate buffer pH 8.0, 5.8, 7.0 and SIF. The results of the solubility of pentoxifylline are shown in Table 4.5.

Table 4.5 : Solubility of Pentoxifylline in Various Solvent at 37 °C.

Solvent	Solubility (mg/ml)	SD
Phosphate Buffer pH 5.8	99.56	0.77
Phosphate Buffer pH 7.0	98.42	1.15
Phosphate Buffer pH 8.0	97.66	0.55
Distilled Water	100.75	0.60
Simulated Intestinal Fluid	97.47	0.91
Dichloromethane	103.95	1.30

Determination of Pentoxifylline Content

After tabletting, the tablets was undergone the content analysis. The solvent used in analysis of pentoxifylline in tablet was selected depend on the solubility. It was found that solubility of pentoxifylline in dichloromethane is highest among the solvents tested as shown in Table 4.5. Therefore, dichloromethane was used as a solvent for pentoxifylline assay. The method used in this study was validated for analysis of pentoxifylline in the tablet. Table 4.6 shows the pentoxifylline content in tablet of each formulation of sustained release tablet.

Table 4.6 : Pentoxifylline Content in Tablets of Each Formulation.

Formulation	Pentoxifylline Content (mg)	
	Average	SD
A1	404.4	1.3
A2	399.6	4.1
B1	402.4	1.3
B2	401.7	4.4
D1	395.1	1.3
D2	400.9	3.1
E1	400.0	4.9
E2	401.0	2.9
F1	400.7	2.2
F2	403.4	0.6
D3	408.3	2.3
D4	406.0	1.7
D5	404.3	2.8
D6	407.1	2.3
D7	402.8	0.1

Note: Average quantity was corrected by % recovery of pentoxifylline (% recovery = 100.72, SD = 1.26, %CV = 1.25)

4.5 Release Studies

Since a drug must normally be in solution before absorption can take place. Often, the rate drug absorption is determined by the rate of drug release from the tablet. It is therefore important to evaluate whether a tablet release its drug contents when placed into the environment similar to the gastrointestinal tract. Release Profiles of pentoxifylline

tablet prepared with water or ethanol as granulating solution, in SGF and SIF are shown in Figure 4.7-4.11. There are no differences on the release profiles of pentoxifylline from the same formulation when tested in simulated gastric fluid and simulated intestinal fluid (Figure 4.7-4.11). Furthermore, The results observed from Figure 4.7-4.11 show that the release profiles of pentoxifylline in formulation which use ethanol or distilled water give the same profiles. Therefore, both ethanol and water can be used as granulating liquid for polymers in wet granulation process. Ethanol obtained the better wet mass for easy granulating in wet granulation process because it stuck on sieve much less than the wet mass that used distilled water as granulating liquid. Either ethanol or distilled water gave the same characteristic tablets. (Table 4.6 and Figure 4.6) However distilled water was chosen for further experiment due to economical reason.

A comparison of drug release from tablets prepared with different hydrophilic polymers and lactose which water was added as granulating solution in SGF and SIF are shown in Figure 4.12 and 4.13, respectively. Pentoxifylline in tablet prepared with lactose was rapidly released while SGF was used as a dissolution media. Similar results were observed in SIF. To delay the release of the drug, different polymers were used as a matrix former in tablet formulation. All the polymers in this study can delay drug release from matrix tablets. In the same concentration of polymers in tablet formulation, HPMC E4M and HPMC F4M were more effective in retarding the release of pentoxifylline than HEC QP52000 and HEC WP40 as shown in Figure 4.12-4.13. HPMC E4M is a suitable polymer to use as polymer-drug matrix tablet because of its hydration is better than HPMC F4M. It can be described that when the HPMC E4M-pentoxifylline tablet contact with water, the water will be penetrate into the tablet and form a protective layer better than HPMC F4M-pentoxifylline (1, 7, 11, 16, 51).

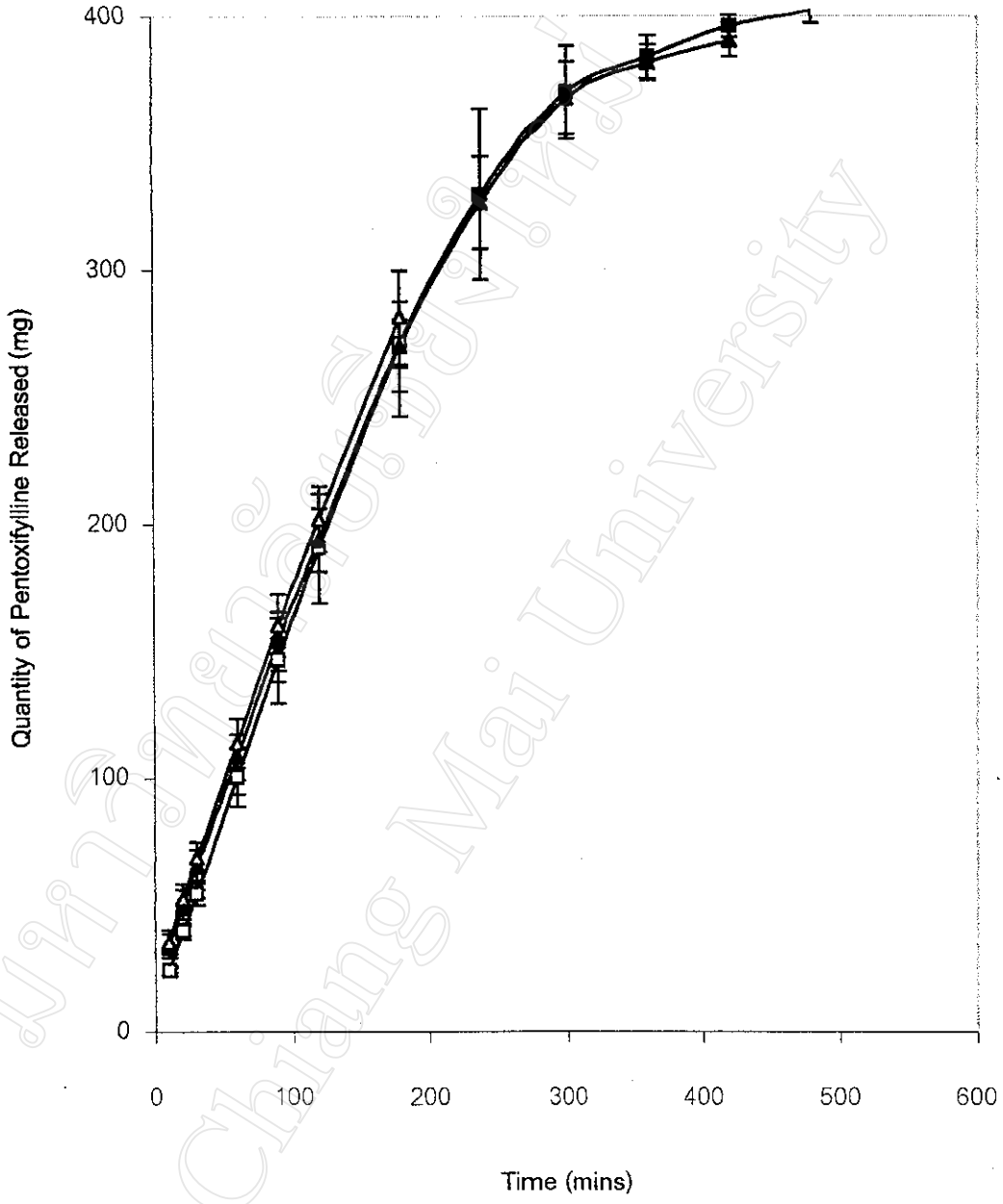

Figure 4.7 : Release profiles of pentoxifylline matrix tablets formulation A1 (pentoxifylline in HEC QP52000, ethanol was used as granulating liquid) and A2 (pentoxifylline in HEC QP52000, water was used as granulating liquid) in SGF and SIF. Error bars are standard diviation of the means. Keys: (-▲-) A1 in SGF, (-▲-) A1 in SIF, (-□-) A2 in SGF and (-▮-) B2 in SIF.

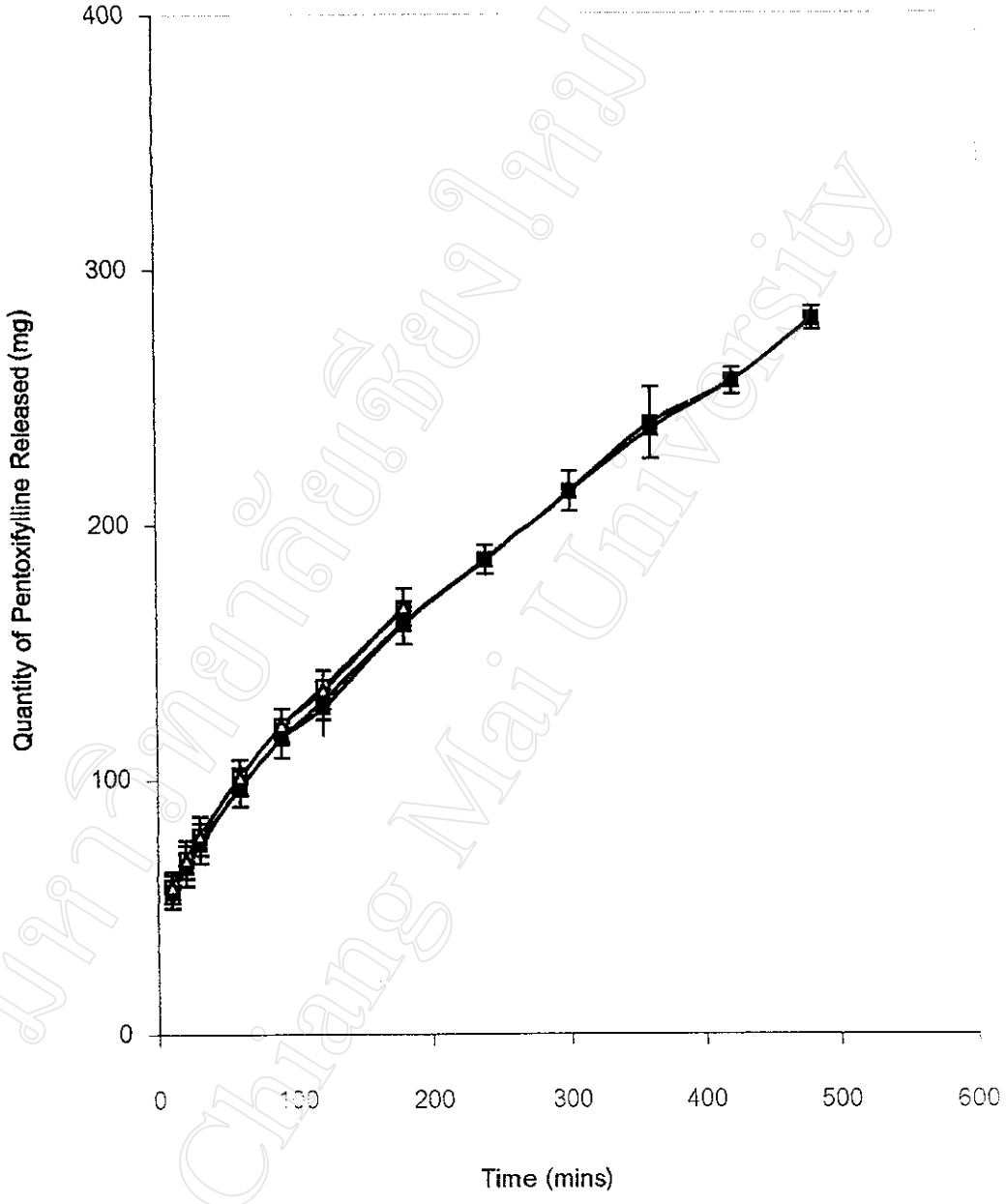

Figure 4.8 : Release profiles of pentoxifylline matrix tablets formulation B1 (pentoxifylline in HEC QP52000, ethanol was used as granulating liquid) and B2 (pentoxifylline in HEC QP52000, water was used as granulating liquid) in SGF and SIF. Error bars are standard diviation of the means. Keys: (-▲-) B1 in SGF, (-▲-) B1 in SIF, (-□-) B2 in SGF and (-■-) B2 in SIF.

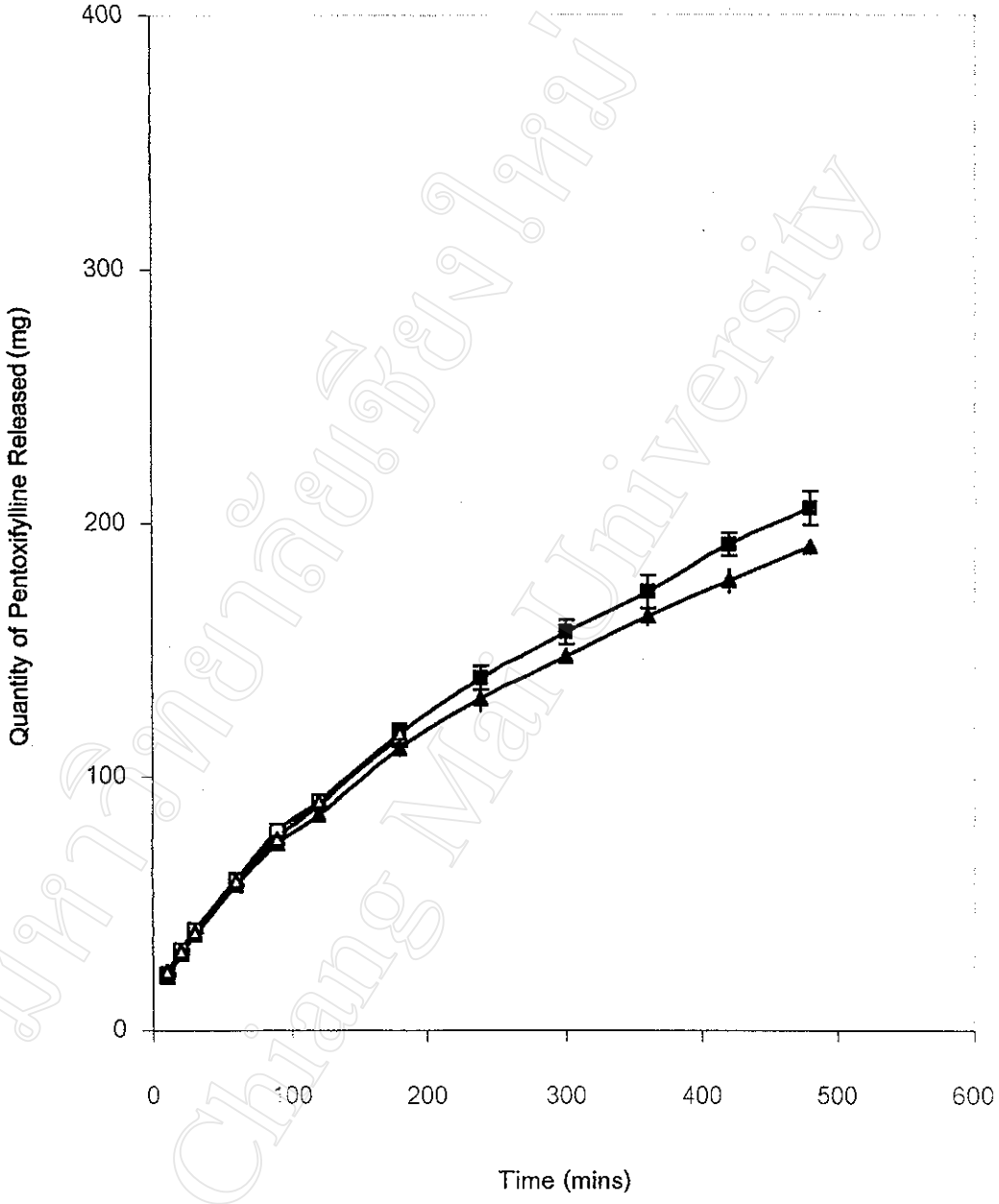

Figure 4.9 : Release profiles of pentoxifylline matrix tablets formulation D1 (pentoxifylline in HEC QP52000, ethanol was used as granulating liquid) and D2 (pentoxifylline in HEC QP52000, water was used as granulating liquid) in SGF and SIF. Error bars are standard diviation of the means. Keys: (-△-) D1 in SGF, (-▲-) D1 in SIF, (-□-) D2 in SGF and (-■-) D2 in SIF.

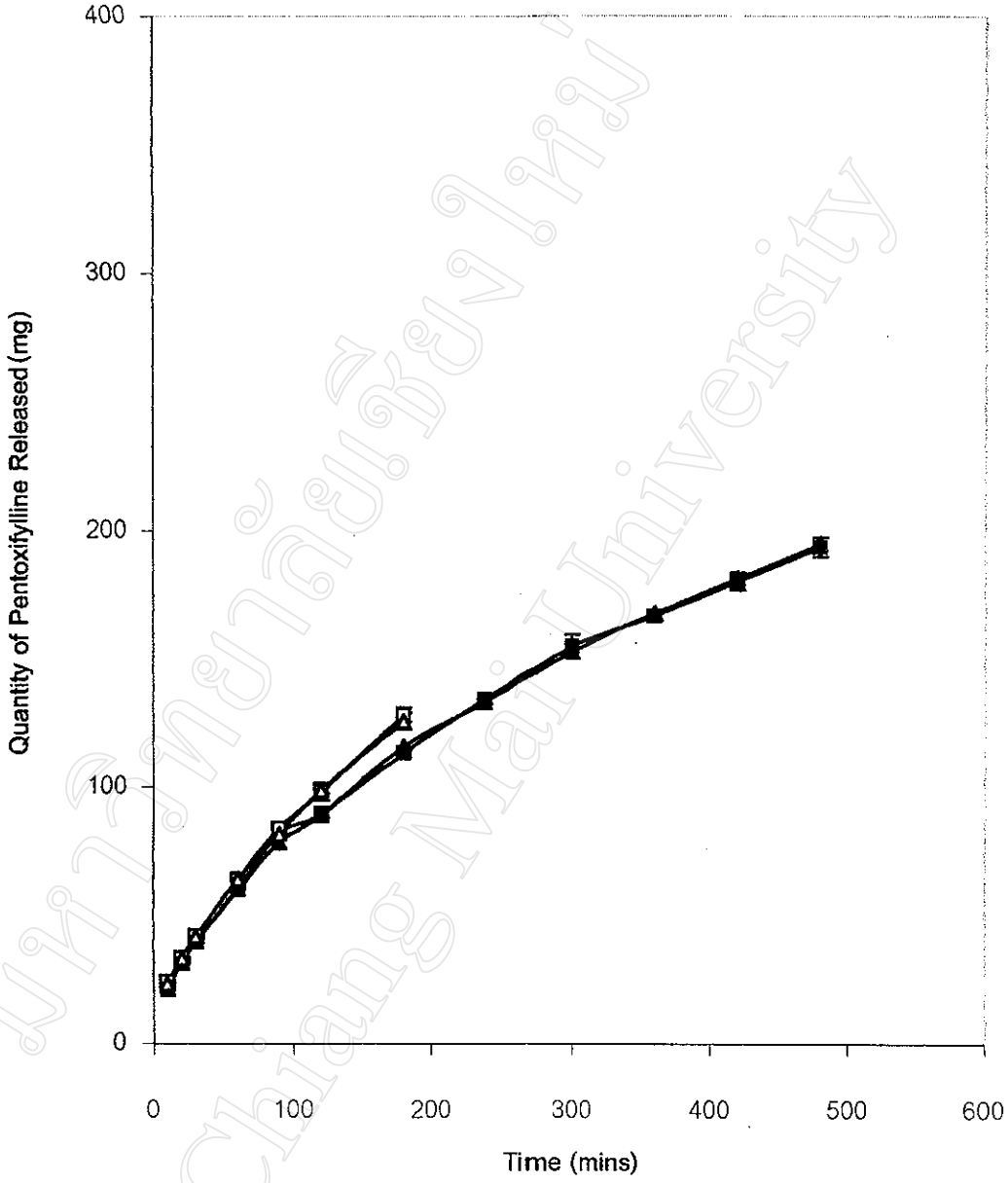

Figure 4.10 : Release profiles of pentoxifylline matrix tablets formulation E1 (pentoxifylline in HEC QP52000, ethanol was used as granulating liquid) and E2 (pentoxifylline in HEC QP52000, water was used as granulating liquid) in SGF and SIF. Error bars are standard diviation of the means. Keys: (-▲-) E1 in SGF, (-▲-) E1 in SIF, (-□-) E2 in SGF and (-■-) E2 in SIF.

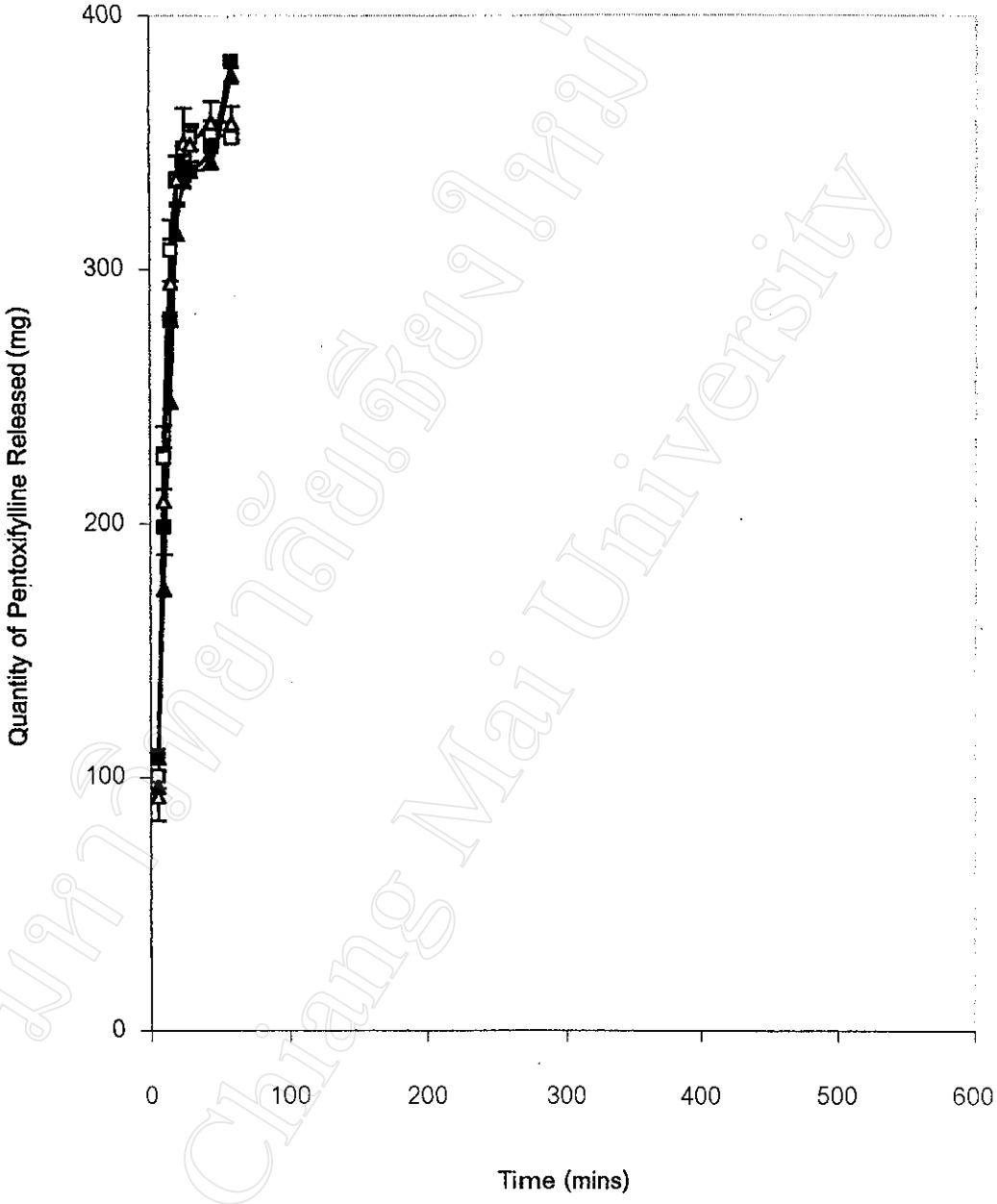

Figure 4.11 : Release profiles of pentoxifylline matrix tablets formulation F1 (pentoxifylline in HEC QP52000, ethanol was used as granulating liquid) and F2 (pentoxifylline in HEC QP52000, water was used as granulating liquid) in SGF and SIF. Error bars are standard diviation of the means. Keys: (-△-) F1 in SGF, (-▲-) F1 in SIF, (-□-) F2 in SGF and (-■-) F2 in SIF.

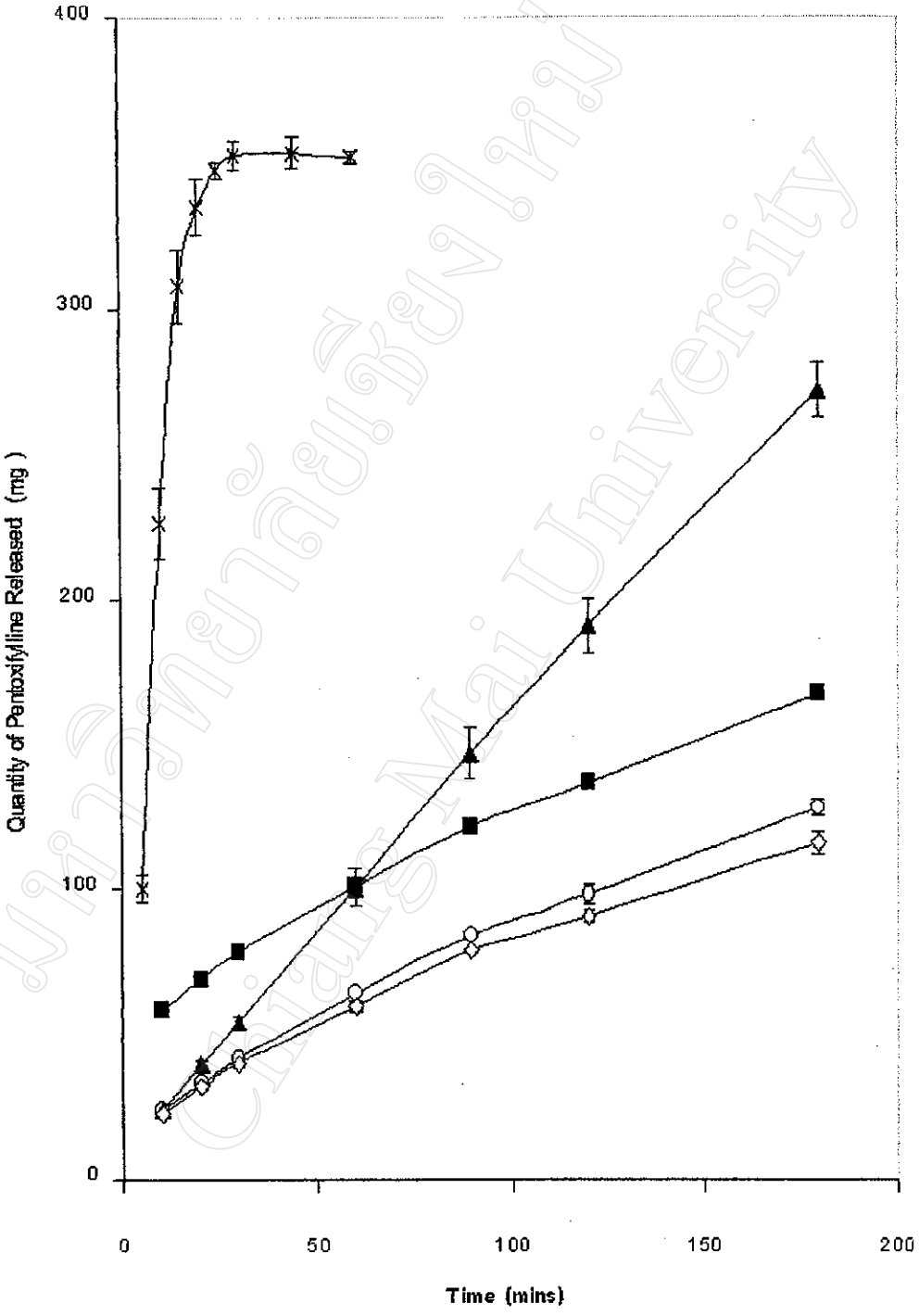

Figure 4.12 : Release profiles of pentoxifylline matrix tablets formulation A2, B2, D2, E2 and F2 in SGF. Error bars are standard diviation of the means. Keys: (-▲-) A2, (-╋-)B2, (-◊-) D2, (-○-) E2 and (-✱-) F2.

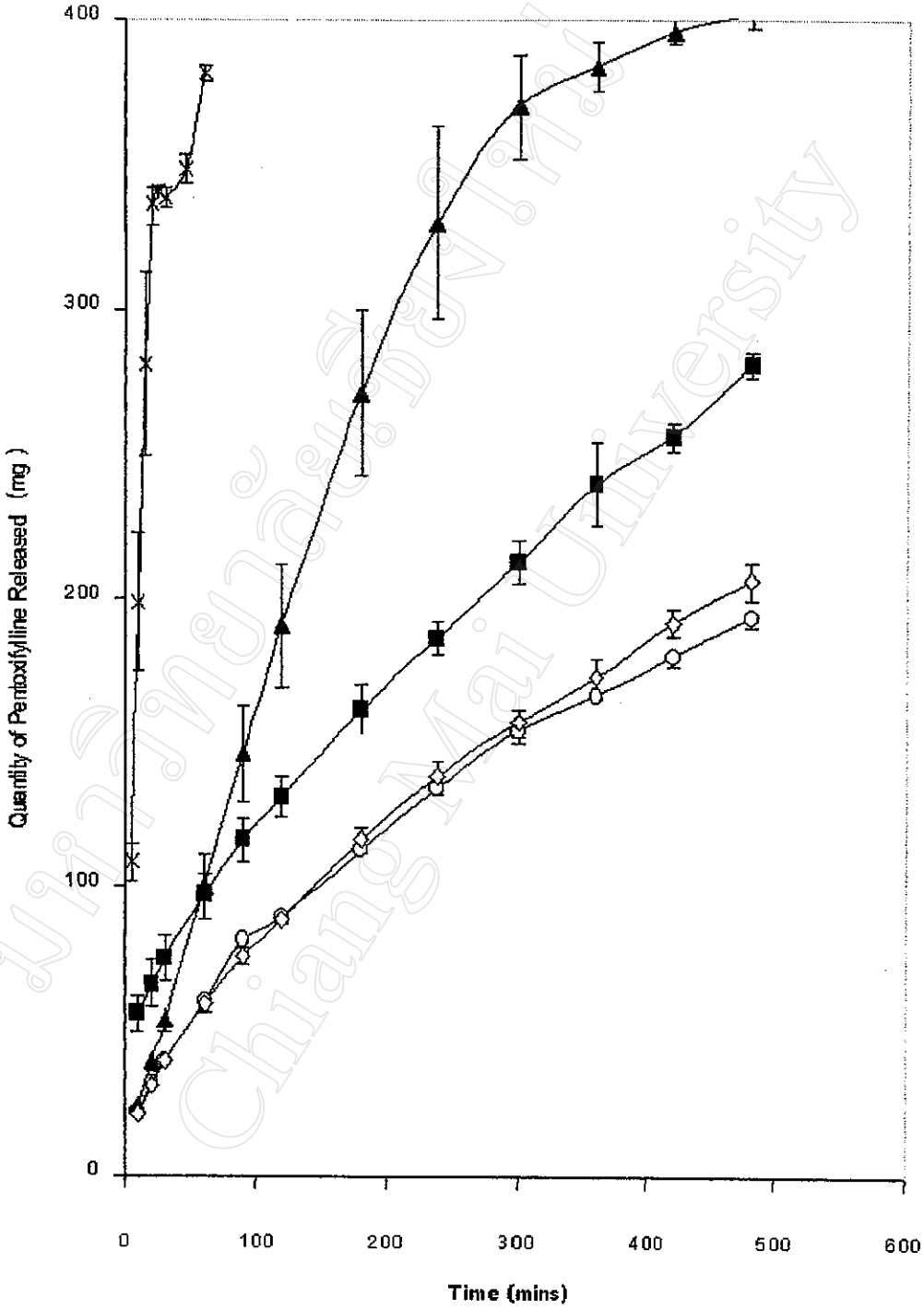

Figure 4.13 : Release profiles of pentoxifylline matrix tablets formulation A2, B2, D2, E2 and F2 in SIF. Error bars are standard diviation of the means. Keys: (-▲-) A2, (-■-)B2, (-◇-) D2, (-○-) E2 and (-✳-) F2.

4.6 Effect of Some Additives on Release Profiles of Pentoxifylline

Hydroxypropyl methylcellulose E4M (HPMC E4M) was chosen as a polymers base for preparing pentoxifylline matrix tablets. Polyvinyl pyrrolidone (PVP) K15, K25, K30 and lactose at the concentration of 10% were added in order to increase the release of pentoxifylline. The results are shown in figure 4.14 - 4.15 and appendix 4. The concentration of drug released was ploted as a function of square root time as shows in Figure 4.16 - 4.17.

Lactose and three types of polyvinyl pyrrolidone (PVP) are the hydrophilic substances used to modify the release of pentoxifylline. Formulation D2 that use HPMC E4M as swelling polymer base was selected to modified the release of the drug. PVP K15, PVP K25 and PVP K30, which have different molecular weight about 50000, 30000 and 80000 respectively, was added into the formulation. Lactose was also added into the formulation like PVP. The result shows that all types of PVP and lactose in the study can increase the release rate of pentoxifylline. The result can be supported by the previous study of matrix additives. (11, 17, 51) Lactose and other hydrophilic additives increased the release rate of drug from the cellulose matrix. As the hydrophilic additives dissolved, it diffused outward and decreased the tortuosity of the diffusion path of the drug through the water. (1, 17, 19, 20) However, in this result there is no difference between the release rate of the drug from tablet has PVP K25 and PVP K30 as additives.

The different quantity of PVP K25 that affect on the dissolution profiles and release rate of pentoxifylline matrix tablets are shown in Figure 4.18 - 4.21 and Appendix 4. When the quantity of PVP K25 varied from 5% to 10%. The pentoxifylline release was not changed with the increase in concentration of PVP K25. The results are similar in both SGF and SIF.

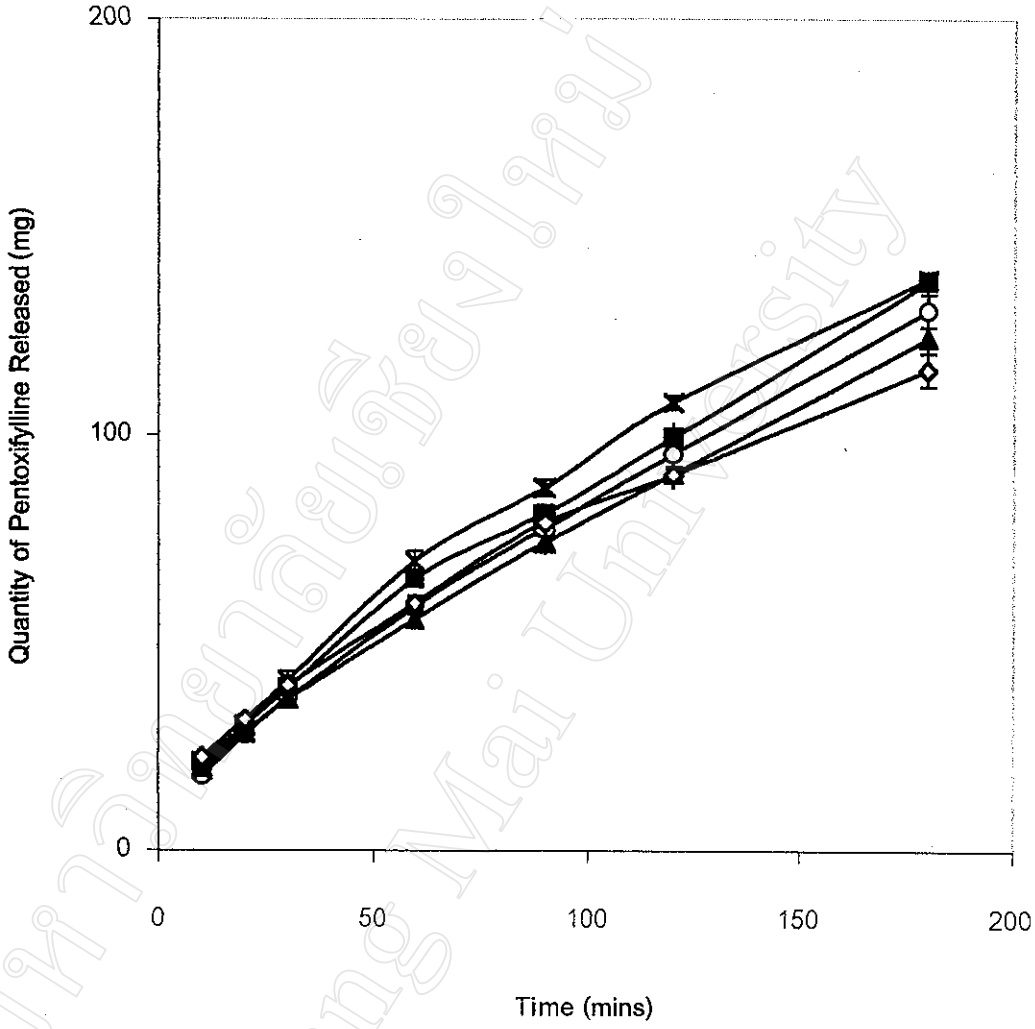

Figure 4.14 : Effect of additives on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SGF. Error bars are standard diviation of the means. Keys: (-◊-) no additives , (-▲-)PVP K15, (-✚-)PVP K25, (-◊-)PVP K30 and (-✳-)lactose.

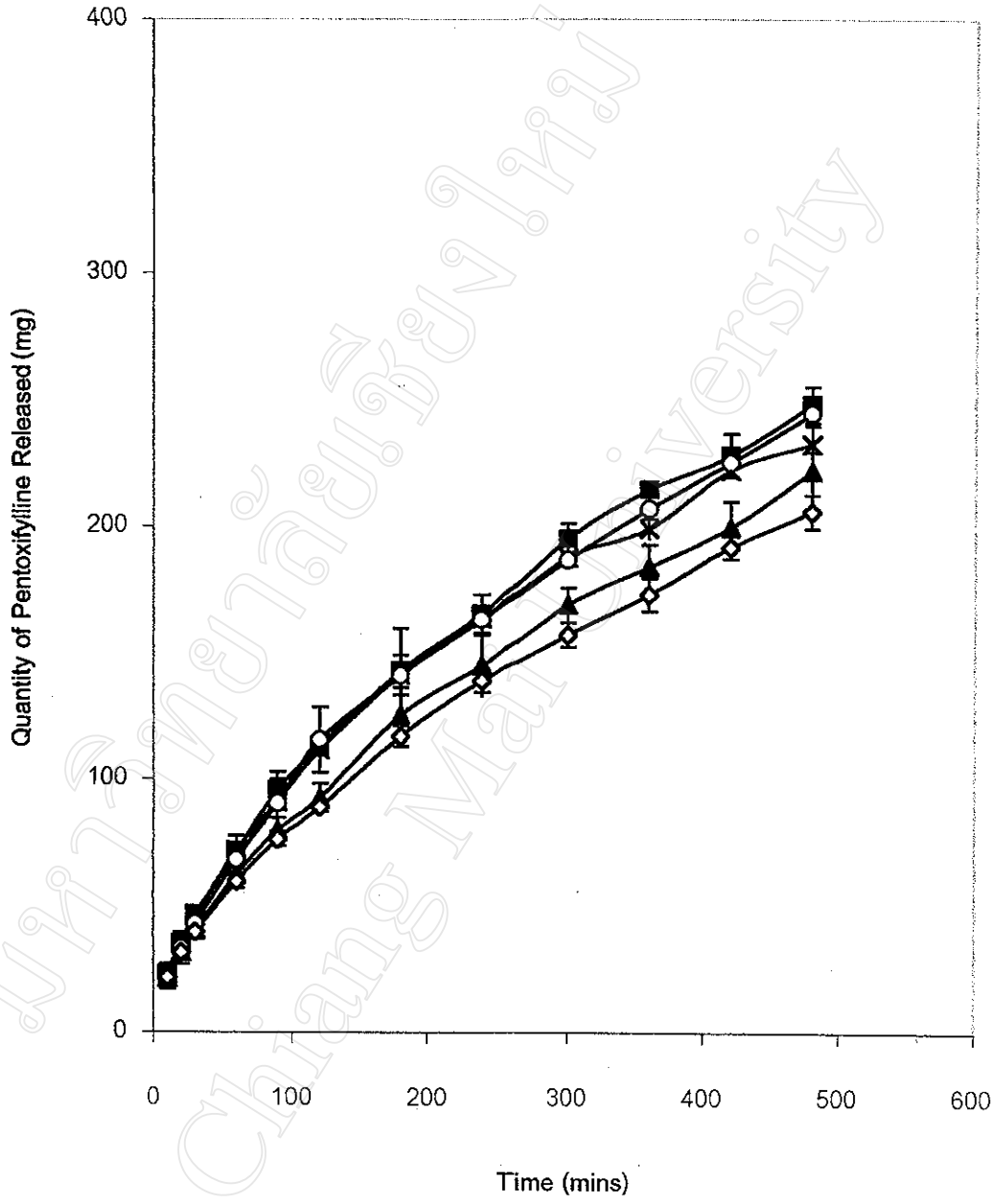

Figure 4.15 : Effect of additives on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SIF. Error bars are standard diviation of the means. Keys: (-◊-) no additives , (-▲-)PVP K15, (-■-)PVP K25, (-○-)PVP K30 and (-✳-)lactose.

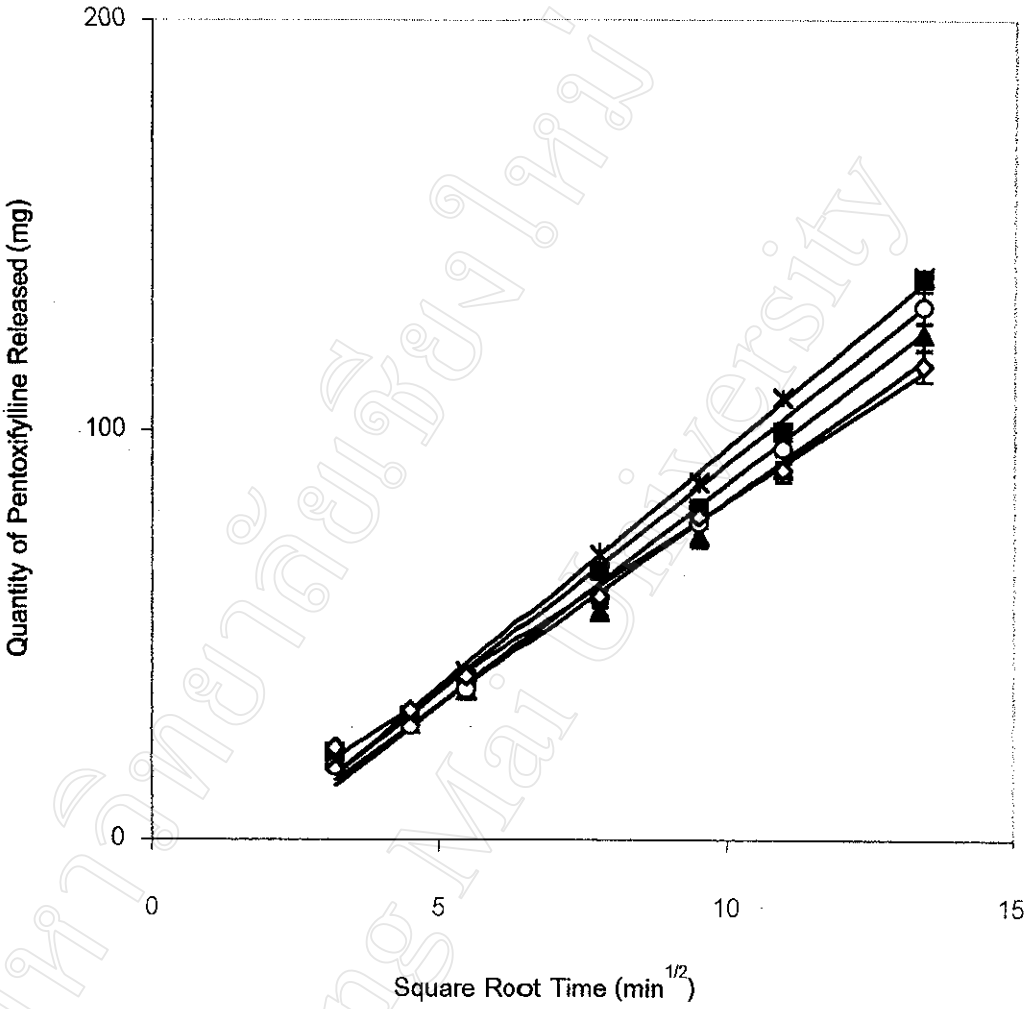

Figure 4.16 : Effect of additives on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SGF plotted as a function of square root time. Error bars are standard diviation of the means. Keys: (-◊-) no additives , (-▲-)PVP K15, (-▮-)PVP K25, (-○-)PVP K30 and (-✳-)lactose.

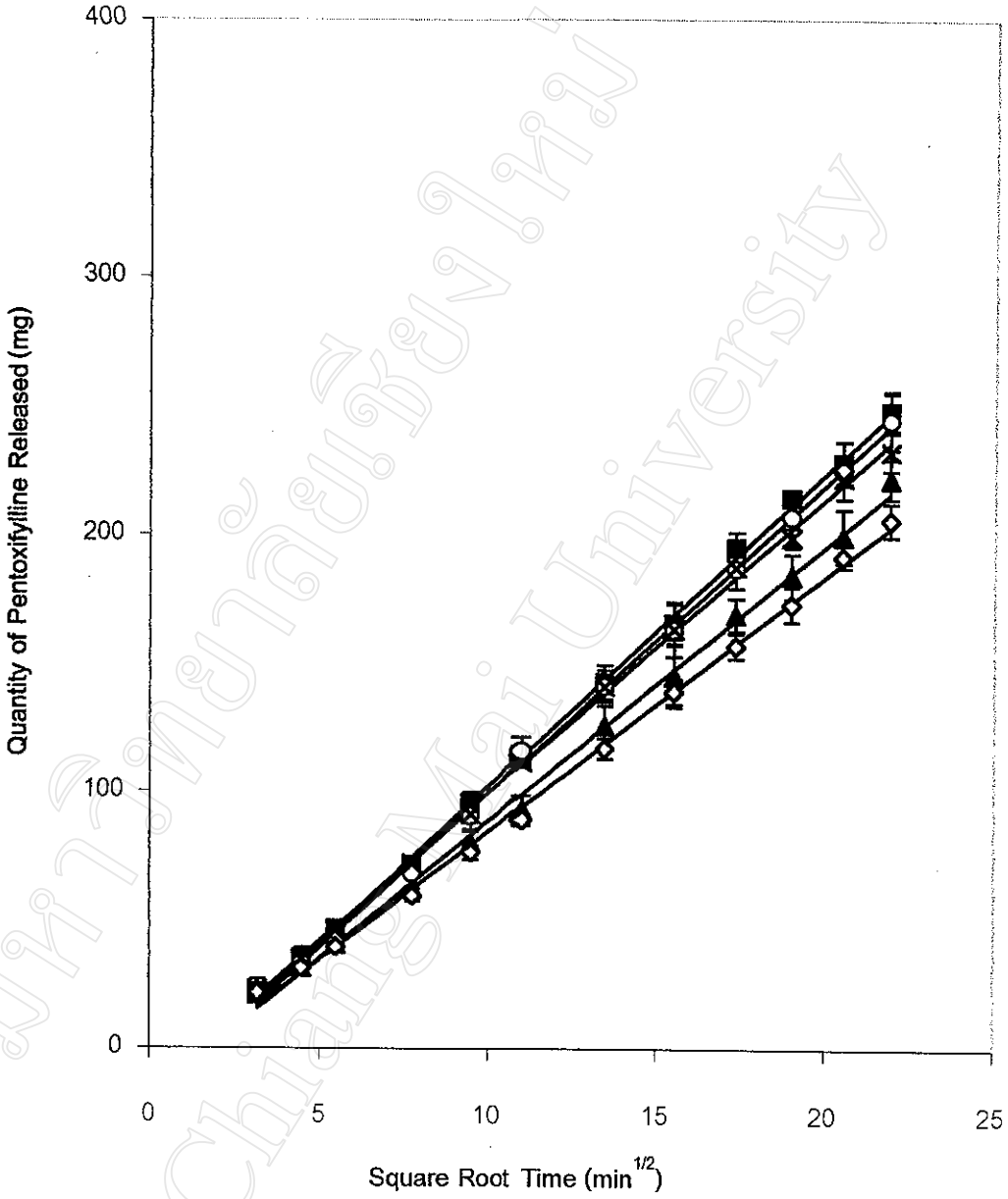

Figure 4.17 : Effect of additives on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SIF plotted as a function of square root time. Error bars are standard diviation of the means. Keys: (-◇-) no additives , (-▲-)PVP K15, (-■-)PVP K25, (-○-)PVP K30 and (-✳-)lactose.

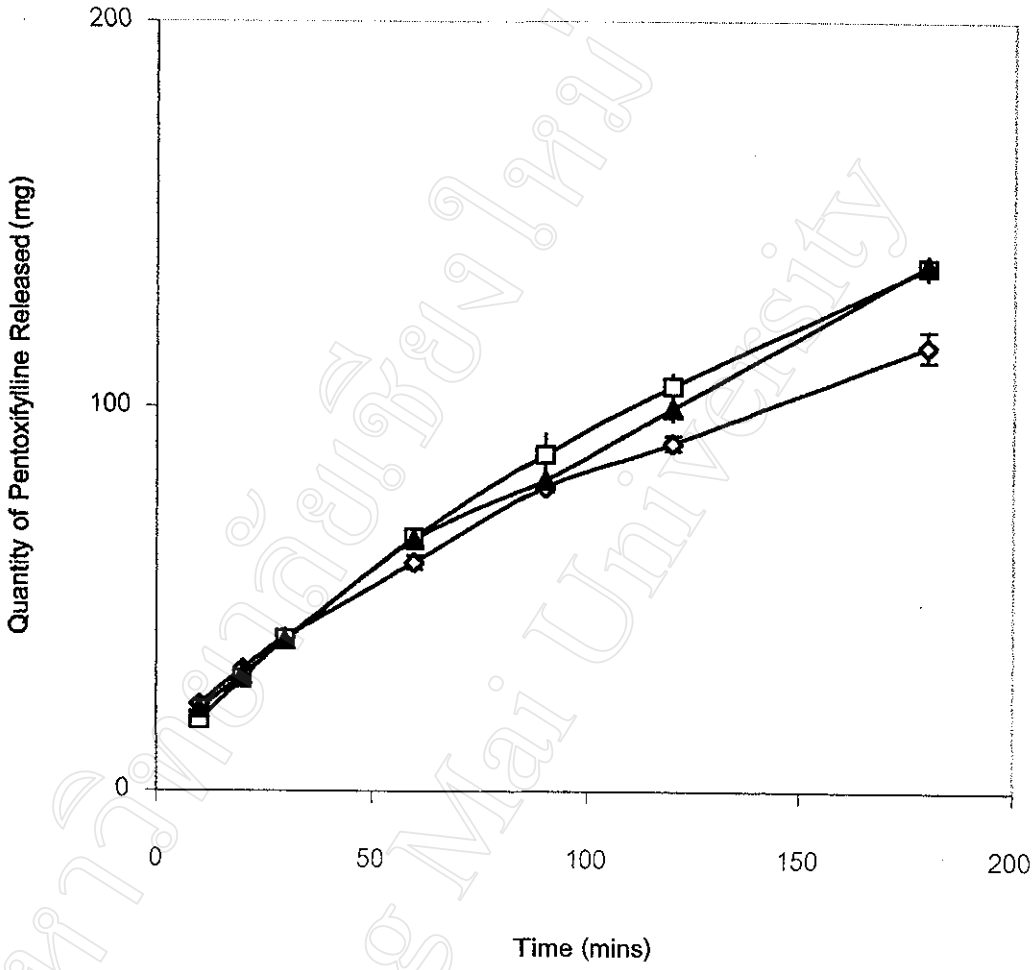

Figure 4.18 : Effect of PVP K25 concentration on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SGF. Error bars are standard diviation of the means. Keys: (-◊-) no PVP , (-▲-) 10 % PVP K25 and (-□-) 5 % PVP K25.

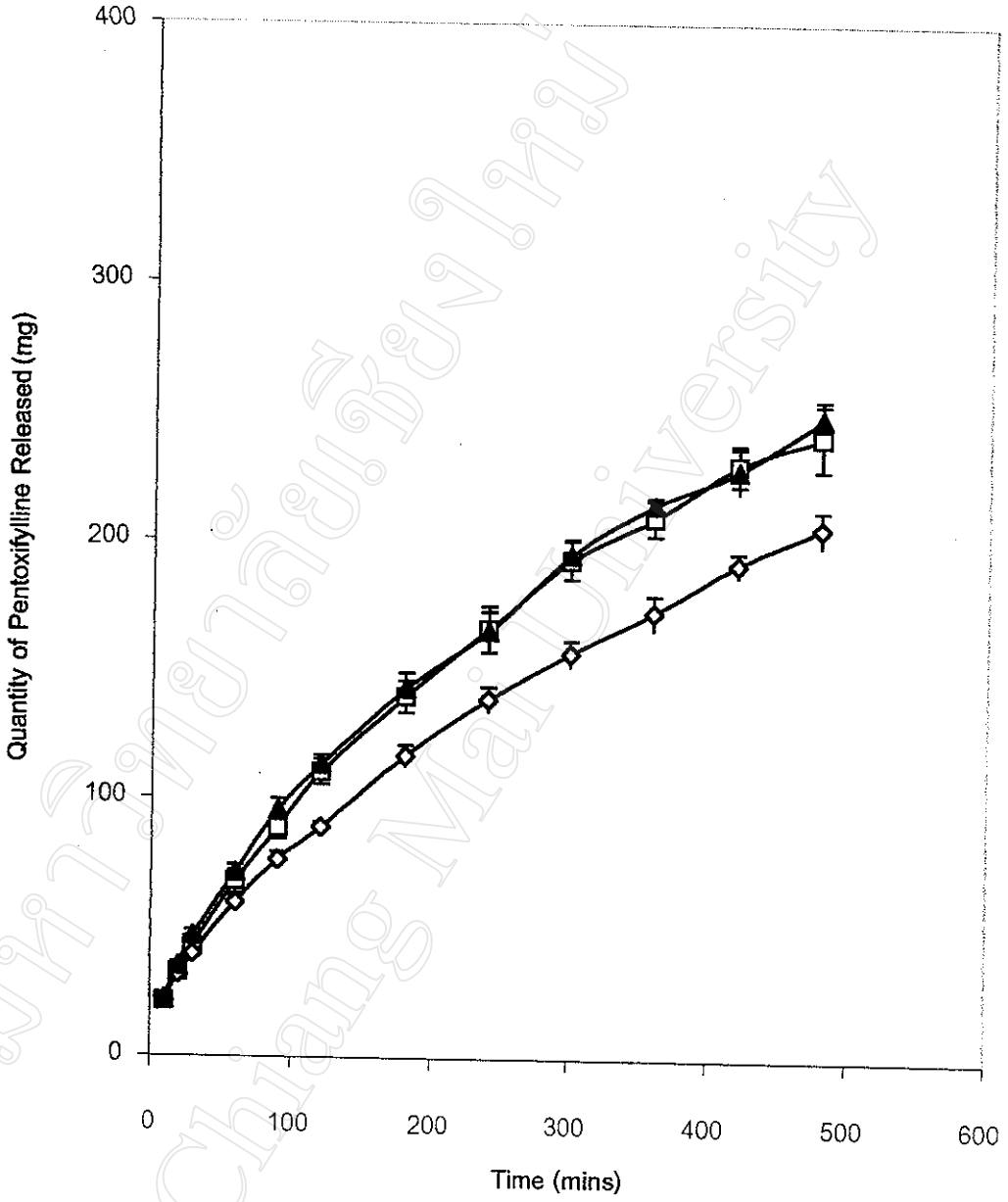

Figure 4.19 : Effect of PVP K25 concentration on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SIF. Error bars are standard diviation of the means. Keys: (-◇-) no PVP , (-▲-) 10 % PVP K25 and (-□-) 5 % PVP K25.

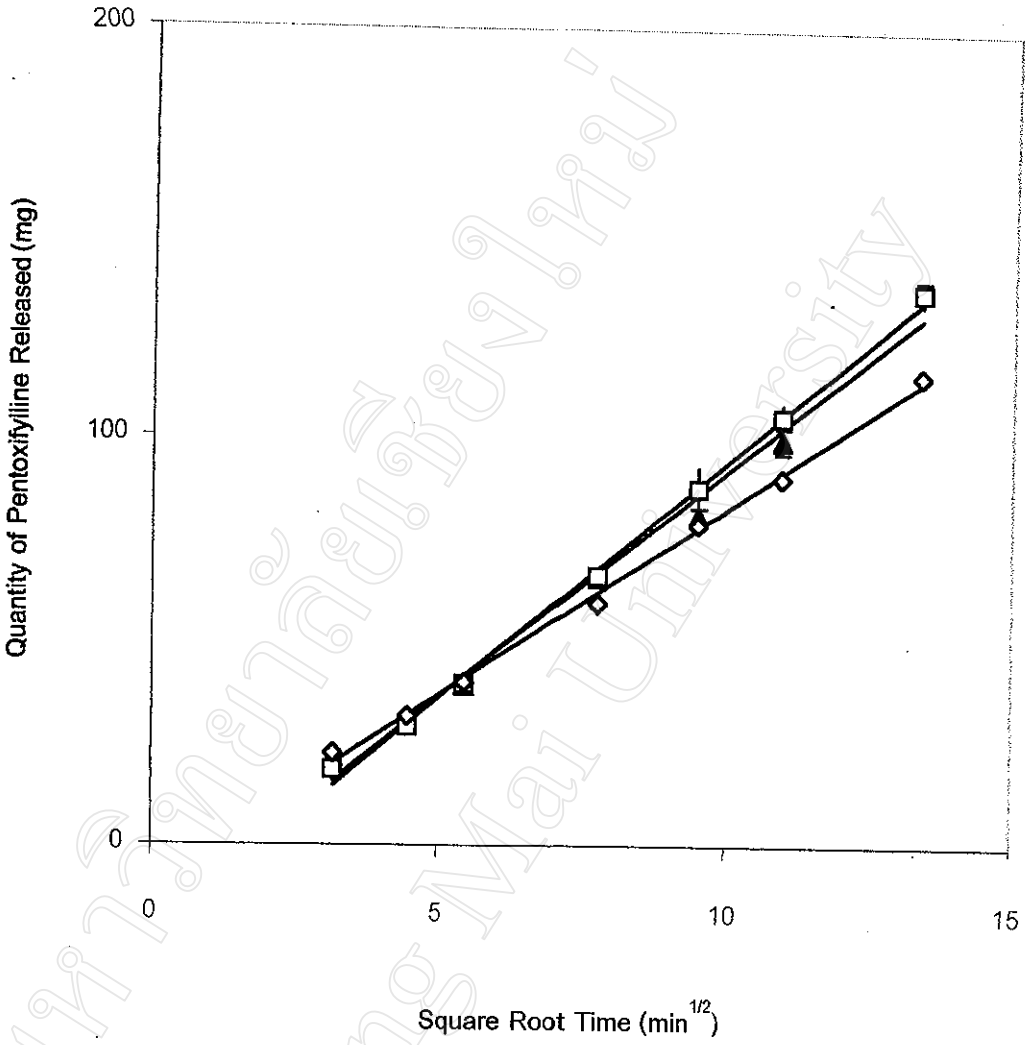

Figure 4.20 : Effect of PVP K25 concentration on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SGF plotted as a function of square root time. Error bars are standard diviation of the means. Keys: (-◇-) no PVP , (-▲-) 10 % PVP K25 and (-□-) 5 % PVP K25.

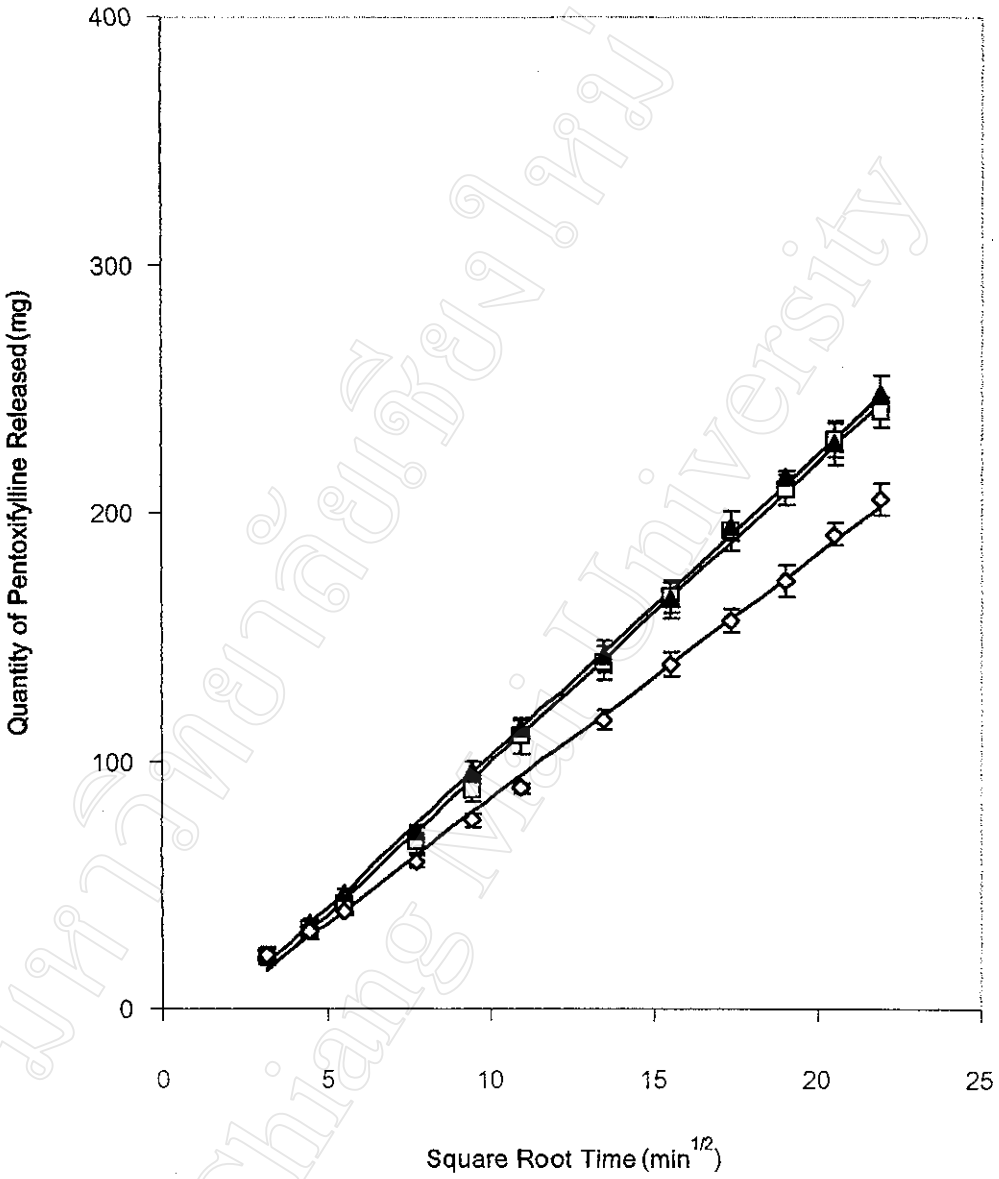

Figure 4.21 : Effect of PVP K25 concentration on release profiles of pentoxifylline matrix tablets prepared with HPMC E4M in SIF plotted as a function of square root time. Error bars are standard diviation of the means. Keys: (-◆-) no PVP , (-▲-) 10 % PVP K25 and (-□-) 5 % PVP K25.

In all cases, the release of the drug follows the Higuchi square root time kinetic which can be calculated from the equation as follow (12,24) :

$$Q = K_H t^{1/2}$$

When Q is the amount of drug released after time t per unit exposed area and K_H is the Higuchi release rate constant. The result shown in Table 4.7 and 4.8. The weight variation and hardness of pentoxifylline tablets prepared with HPMC E4M containing additive are shown in Table 4.9.

Table 4.7 : Effect of Different Types of PVP and Lactose on the Release Rate of Pentoxifylline in SGF and SIF

Media	Formulation	Additives	Higuchi Kinetic	
			K_H (mg/ml.min$^{1/2}$)	R^2
SGF	D2	No Additives	9.1724	0.9973
	D3	PVP K15	9.9791	0.9868
	D4	PVP K25	11.1396	0.9883
	D5	PVP K30	10.8065	0.9901
	D6	Lactose	11.6901	0.9976
SIF	D2	No Additives	9.9481	0.9980
	D3	PVP K15	10.6958	0.9990
	D4	PVP K25	12.1974	0.9974
	D5	PVP K30	12.0153	0.9988
	D6	Lactose	11.4763	0.9988

Table 4.8 : Effect of PVP K25 Concentration on the Release Rate of Pentoxifylline in SGF and SIF

Mediam	Formulation	PVP K25 Concentration	Higuchi Kinetic	
			K_H (mg/ml.min$^{1/2}$)	R^2
SGF	D2	0 %	9.1724	0.9973
	D4	10 %	11.1396	0.9883
	D7	5%	11.6503	0.9975
SIF	D2	0 %	9.9481	0.9980
	D4	10 %	12.1974	0.9974
	D7	5%	12.1947	0.9984

Table 4.9 : Weight and Hardness of Pentoxifylline Tablets Prepared with HPMC E4M.

Formulation	Additives	Average Weight (mg)	SD.	Average Hardness (N)	SD.
D2	0% PVP K25	0.5958	0.0009	69.8	4.2
D3	10% PVP K15	0.6086	0.0081	56.1	2.9
D4	10% PVP K25	0.6019	0.0101	68.2	8.5
D5	10% PVP K30	0.6034	0.0676	54.9	4.8
D6	10% Lactose	0.6030	0.0157	58.4	5.6
D7	5% PVP K25	0.5967	0.0055	48.3	7.3

4.7 Reproducibility Studies

The reproducibility of the pentoxifylline matrix tablet was studied. Table 4.10 and 4.11 show a good reproducibility of fabricating pentoxifylline sustained release tablets. All three batches of tablets prepared have a narrow variation in tablet weight, hardness and release rate. Figure 4.22-4.23 show the release profiles of three batches of pentoxifylline sustained tablets in SGF and SIF which have a good reproducibility.

Table 4.10 : Inter-batch Variation in Weight and Hardness of Pentoxifylline Tablet .

Formulation	**Average Weight (mg)**	**SD.**	**Average Hardness (N)**	**SD.**
D7 Lot1	0.5976	0.0046	55.9	8.3
D7 Lot2	0.6054	0.0027	46.1	2.8
D7 Lot3	0.6066	0.0029	50.4	4.9

Table 4.11 : Inter-batch Variation in Release Rate of Pentoxifylline Tablet .

Mediam	**Formulation**	**Higuchi Kinetic**	
		Rate ($mg/ml/min^{1/2}$)	$\mathbf{R^2}$
SGF	D7 Lot1	9.1724	0.9973
	D7 Lot2	11.1396	0.9883
	D7 Lot3	11.6503	0.9975
SIF	D7 Lot1	9.9481	0.9980
	D7 Lot2	12.1974	0.9974
	D7 Lot3	12.1947	0.9984

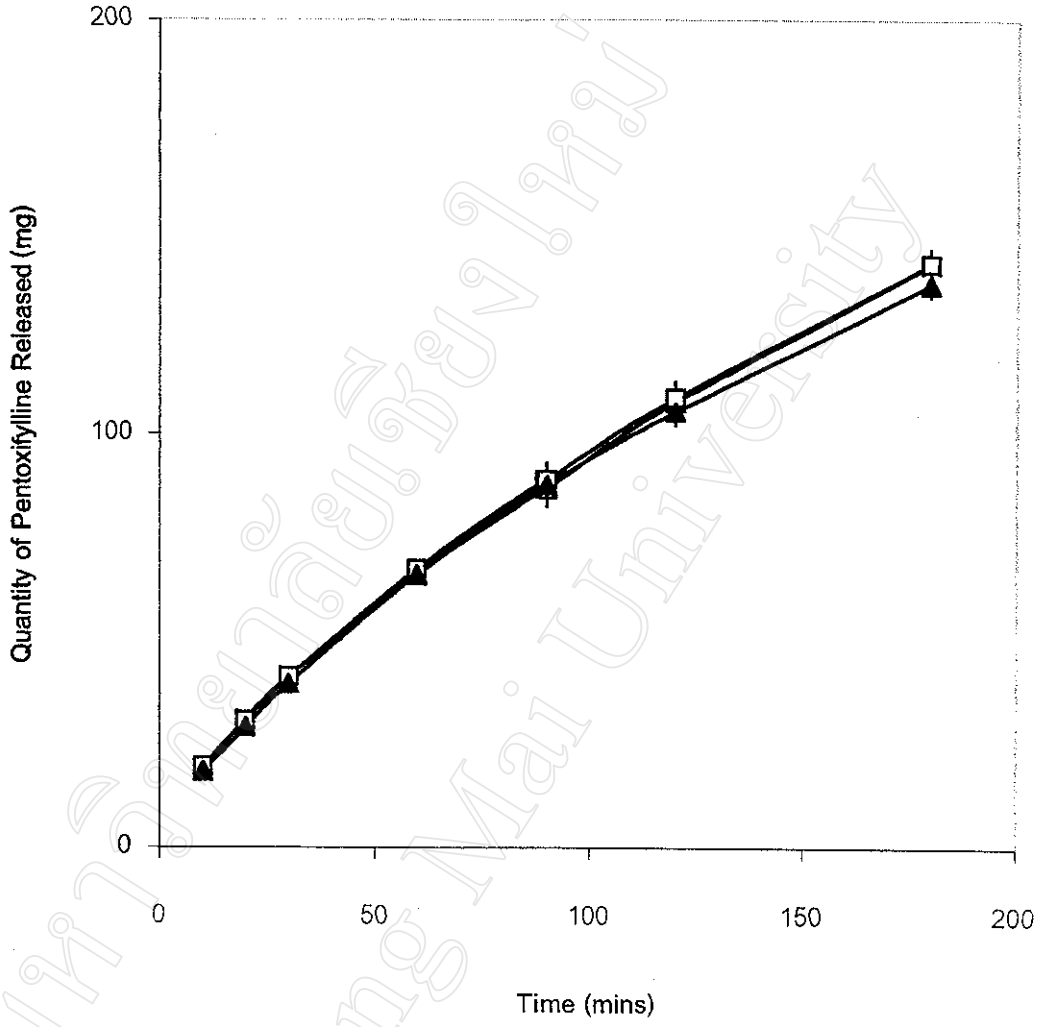

Figure 4.22 : Comparison Release profiles of pentoxifylline matrix tablets formulation D7 three batch in SGF. Error bars are standard diviation of the means. Keys: (-▲-) D7 lot1, (-□-) D7 lot2 and (-✳-) D7 lot3.

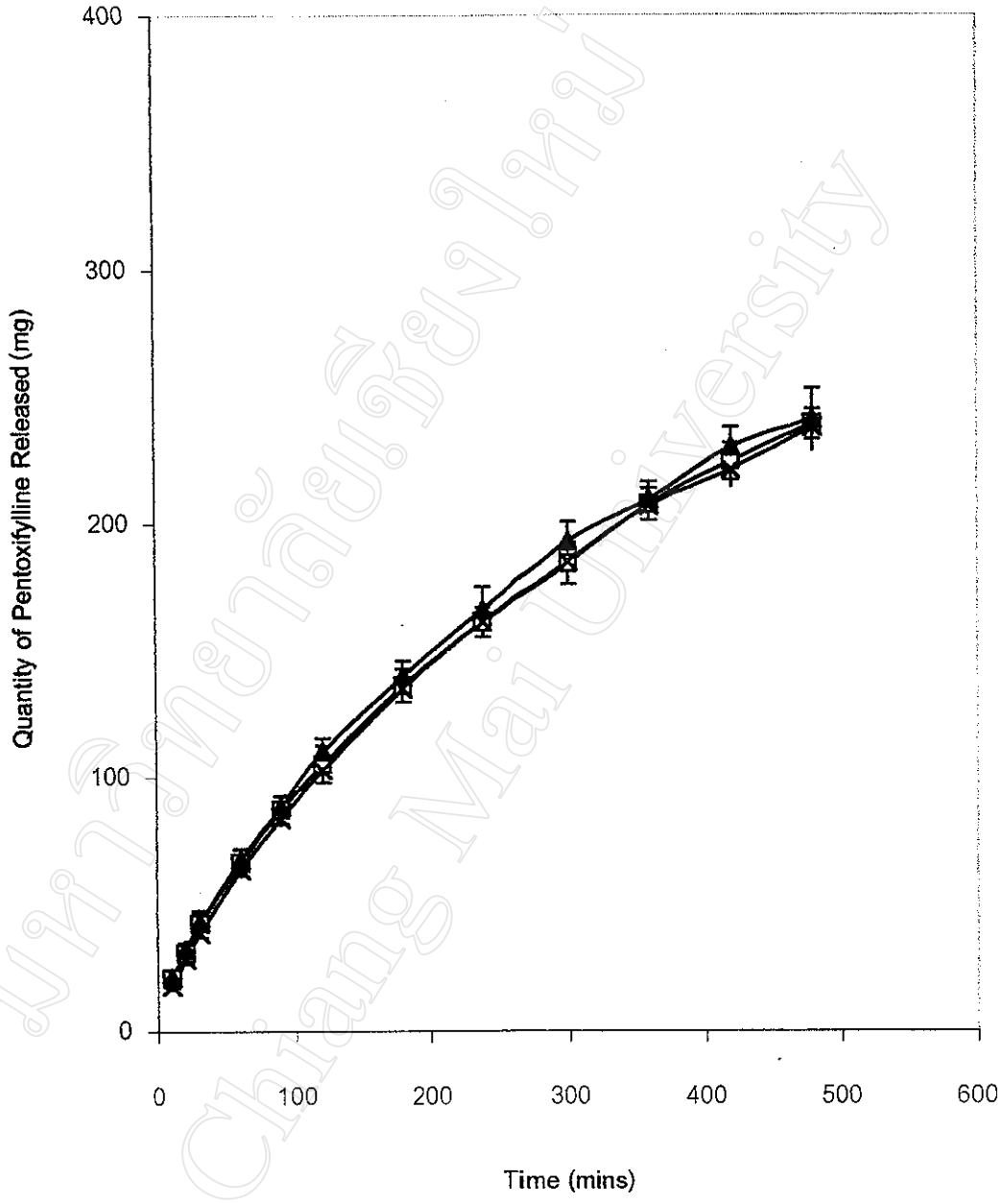

Figure 4.23 : Comparison Release profiles of pentoxifylline matrix tablets formulation D7 three batches in SIF. Error bars are standard diviation of the means. Keys: (-▲-) D7 lot1, (-□-) D7 lot2 and (-✳-) D7 lot3.