CHAPTER III

RESULTS

The results of the studies will be summarized in the following order:

1. Preformulation of Free Film Formulations
    - 1.1 Effect of Polymer Ratios on Thickness and Mechanical Properties of Free Film
    - 1.2 Effect of Plasticizers on Thickness and Mechanical Properties of Free Film

2. Formulation Development of DTZ HCl TDDS
    - 2.1 Determination of Drug Solubility in Various Solvent Systems
    - 2.2 Effect of Polymer Ratios on DTZ HCl Content
    - 2.3 Effect of Enhancers on DTZ HCl Content
    - 2.4 Effect of Polymer Ratios on Moisture Uptake
    - 2.5 Effect of Enhancers on Moisture Uptake
    - 2.6 Effect of Polymer Ratios on Transparency
    - 2.7 Effect of Enhancers on Transparency
    - 2.8 Effect of Polymer Ratios on Surface Topography
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3. An Evaluation of DTZ HCl TDDS
    - 3.1 *In vitro* Drug Release of DTZ HCl from Various Film Formulations
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    - 3.2 *In vitro* Skin Permeation of DTZ HCl Film
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        - 3.2.2 Effect of Enhancers on *In vitro* Skin Permeation

1. Preformulation of Free Film Formulations

In this section, prescreening the effects of polymer ratios and plasticizers on the physical characteristics of free film formulations such as thickness and mechanical properties, were investigated.

1.1 Effect of Polymer Ratios on Thickness and Mechanical Properties of Free Film

Formulations *F1*, *F2*, *F5*, *F8*, *F9*, and *F10* composed of various polymer ratios. Their thicknesses were not different, as illustrated in Figure 20. However, formulation *F5* with HPMC:EC 6:4 gave the higher thickness.

The effects of polymer ratios on mechanical properties of the above formulations are shown in Table 7. Figures 21 – 24 show the value of ultimate tensile strength (UTS), the percentage of elongation at break, Young's modulus, and toughness, respectively. Since the films from Formulation *F9* and *F10* stuck to the plate and were not strong enough, they were not tested for mechanical properties. Figures 20 and 22 show the decrease in UTS and Young's modulus when the EC ratios were increased from 0 to 40%. Conversely, the UTS and Young's modulus were increased with increasing the percentage of EC ratios from 40 to 60% of the total polymer concentration, respectively. Although, the percentage of elongations at break were increased with increasing of EC ratio from 20 to 60%, they were still much lower than the formulation without EC, as may be seen in Figure 21. Furthermore, Figure 23 shows an extreme decreasing of toughness of formulations with EC as compared to the formulation without EC.

Table 7 Mechanical properties of free film formulations at various ratios of HPMC and EC (n=6).

Formulations	Ingredients (ratio)			Thickness (mm)	UTS (MPa)	% Elongation at break (%)	Young's modulus (MPa)	Toughness (MPa)
	HPMC	EC	DBP					
F1	10	0	3	0.100 ± 0.008	76.7 ± 7.8	106.6 ± 30.9	516.9 ± 77.1	45.0 ± 4.5
F2	8	2	3	0.101 ± 0.018	19.9 ± 3.4	17.7 ± 3.2	137.9 ± 25.7	2.0 ± 0.9
F5	6	4	3	0.118 ± 0.006	6.9 ± 7.4	22.1 ± 2.4	98.9 ± 14.7	1.9 ± 0.3
F8	4	6	3	0.104 ± 0.010	24.8 ± 3.4	27.6 ± 2.6	351.8 ± 34.9	2.3 ± 0.5
F9	2	8	3	0.102 ± 0.016	n/a*	n/a*	n/a*	n/a*
F10	0	10	3	0.092 ± 0.007	n/a*	n/a*	n/a*	n/a*

* n/a (not available)

Table 8 Mechanical properties of free film formulations of HPMC and EC with various plasticizers (n=6).

Formulations	Ingredients (ratio by weight)					Thickness (mm)	UTS (MPa)	% Elongation at break (%)	Young's modulus (MPa)	Toughness (MPa)
	HPMC	EC	DBP	DEP	TEC					
F0	10	0	-	-	-	0.067 ± 0.004	74.8 ± 4.2	10.3 ± 0.9	899.8 ± 63.6	4.0 ± 0.6
F1	10	0	3	-	-	0.100 ± 0.008	76.7 ± 7.8	106.6 ± 30.9	516.9 ± 77.1	45.0 ± 4.5
F2	8	2	3	-	-	0.101 ± 0.018	19.9 ± 3.4	17.7 ± 3.2	137.9 ± 25.7	2.0 ± 0.9
F3	8	2	-	3	-	0.091 ± 0.024	19.2 ± 3.3	33.1 ± 15.0	126.1 ± 27.6	4.4 ± 2.7
F4	8	2	-	-	3	0.121 ± 0.026	5.7 ± 8.2	33.2 ± 7.8	99.9 ± 23.6	3.2 ± 1.0
F5	6	4	3	-	-	0.118 ± 0.006	6.9 ± 7.4	22.1 ± 2.4	98.9 ± 14.7	1.9 ± 0.3
F6	6	4	-	3	-	0.096 ± 0.017	8.1 ± 4.3	23.4 ± 7.2	87.7 ± 11.2	1.7 ± 1.0
F7	6	4	-	-	3	0.106 ± 0.012	0.4 ± 0.3	29.2 ± 4.2	104.6 ± 12.9	2.4 ± 0.7

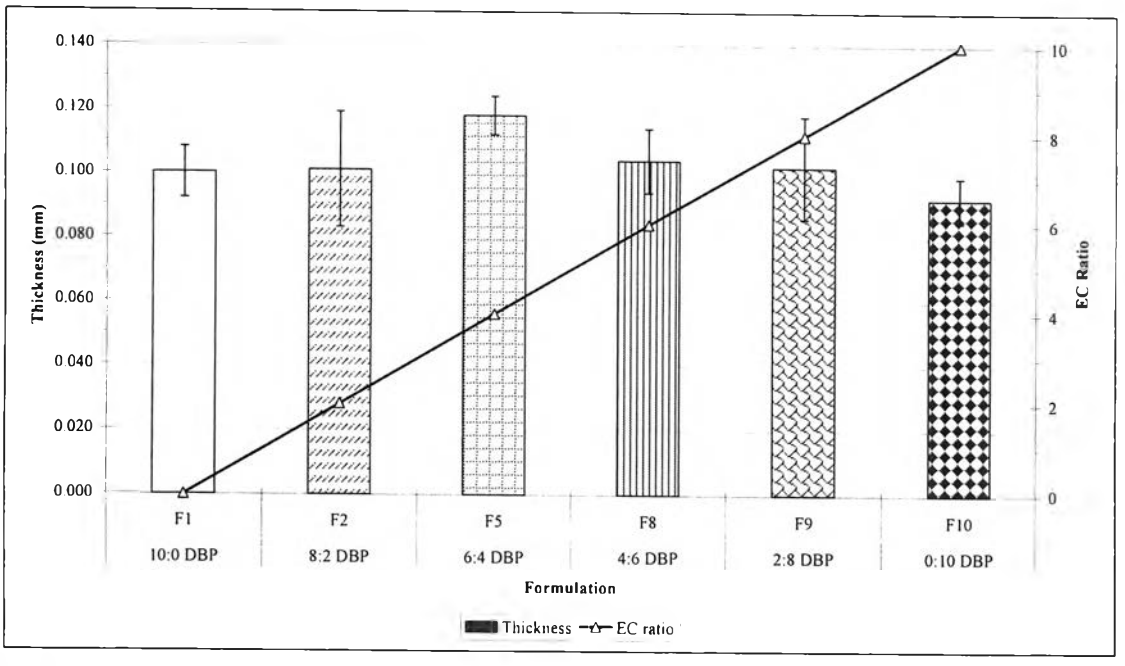

Figure 20 Effect of polymer ratios of HPMC:EC on thickness of the films in various formulation studied.

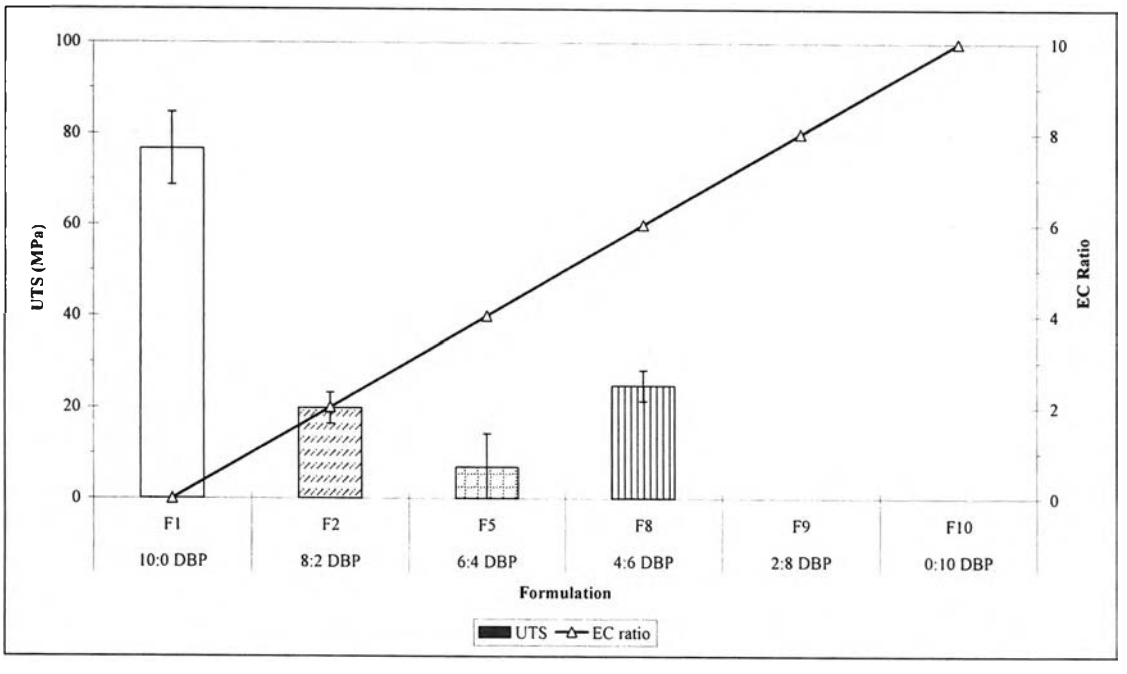

Figure 21 Effect of polymer ratios of HPMC:EC on ultimate tensile strength of the films in various formulations studied (Note: UTS results of formulation *F9* and *F10* are not available).

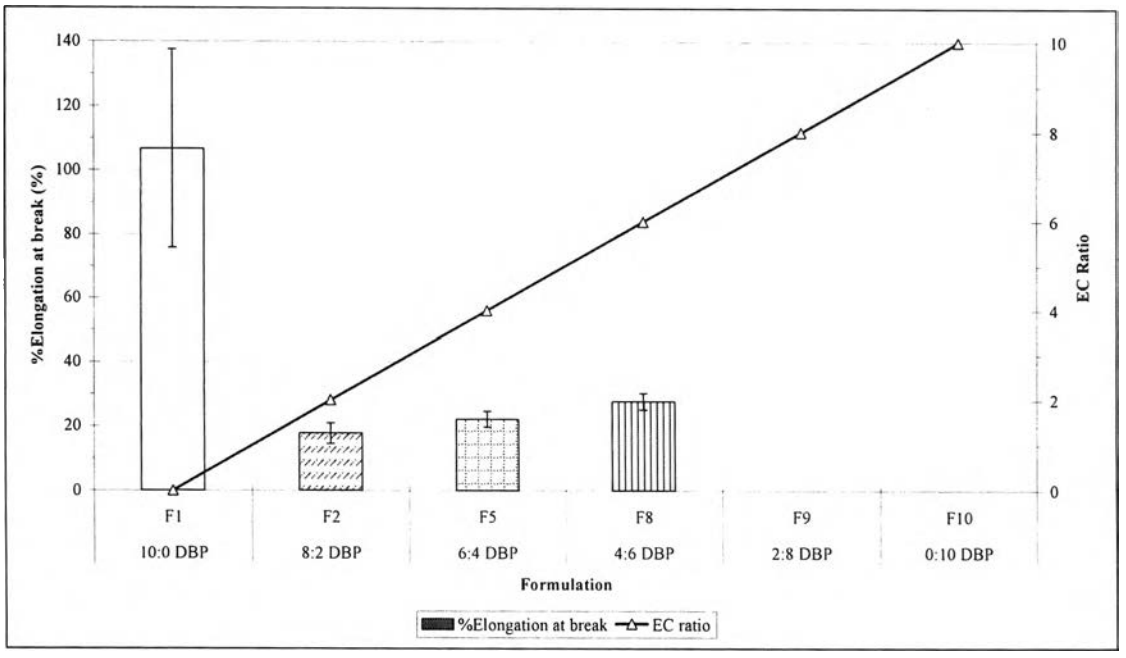

Figure 22 Effect of polymer ratios of HPMC:EC on percentage of elongation at break of the films in various formulations studied (Note: % elongation at breaks of formulation *F9* and *F10* are not available).

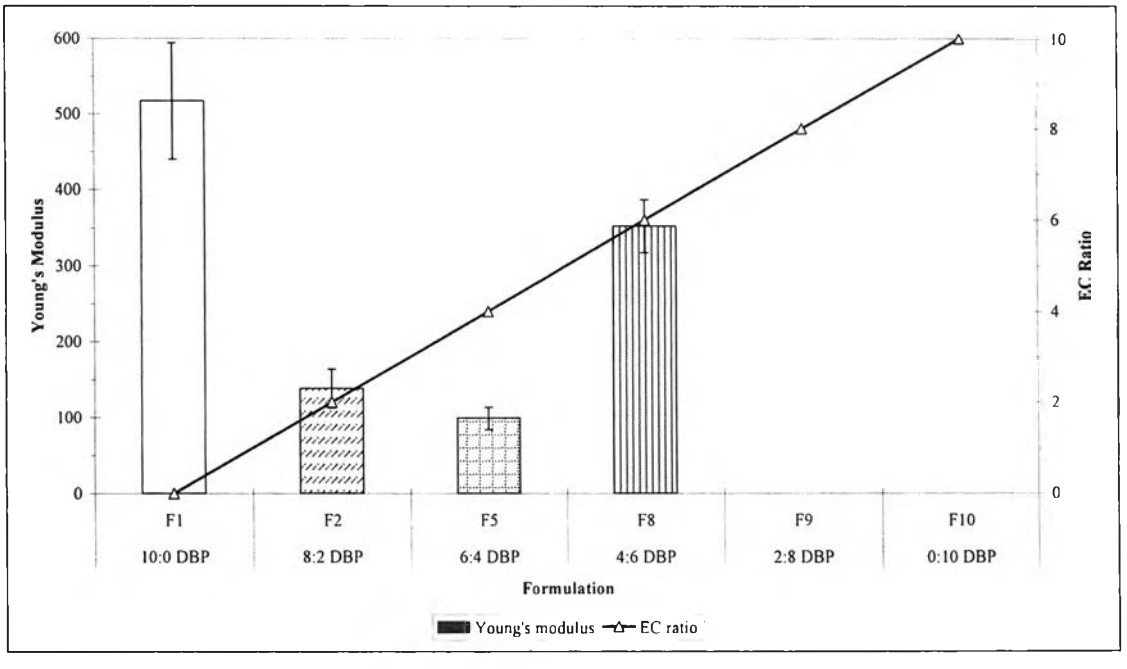

Figure 23 Effect of polymer ratios of HPMC:EC on Young's modulus of the films in various formulations studied (Note: Young's moduli of formulation *F9* and *F10* are not available).

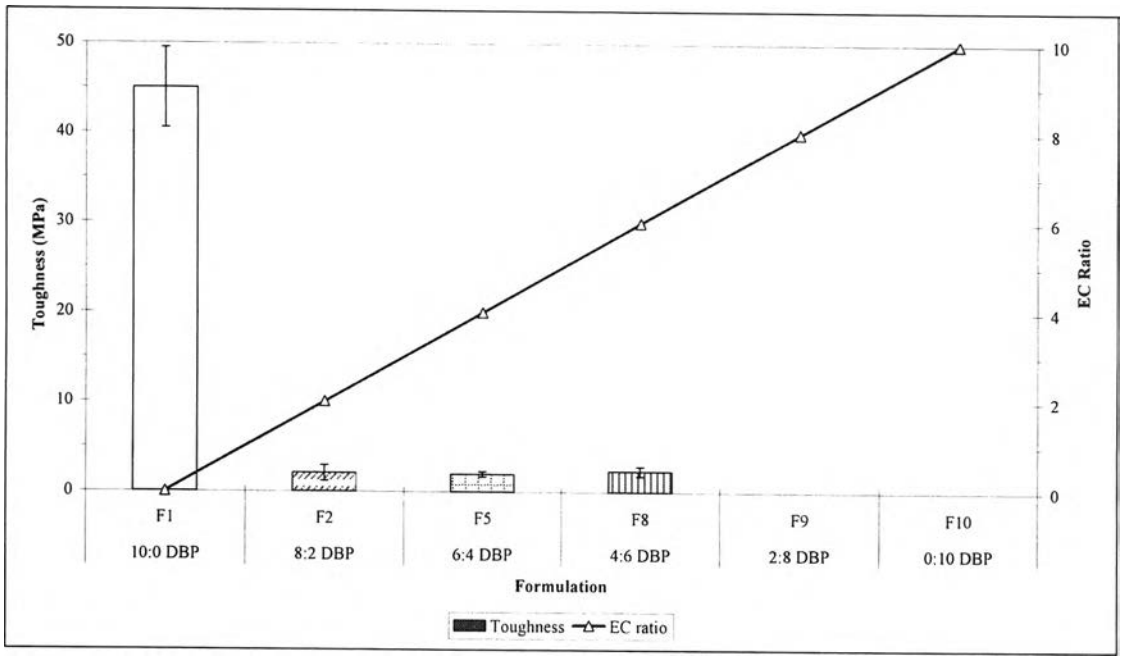

Figure 24 Effect of polymer ratios of HPMC:EC on toughness of the films in various formulations studied (Note: Toughness results of formulation *F9* and *F10* are not available).

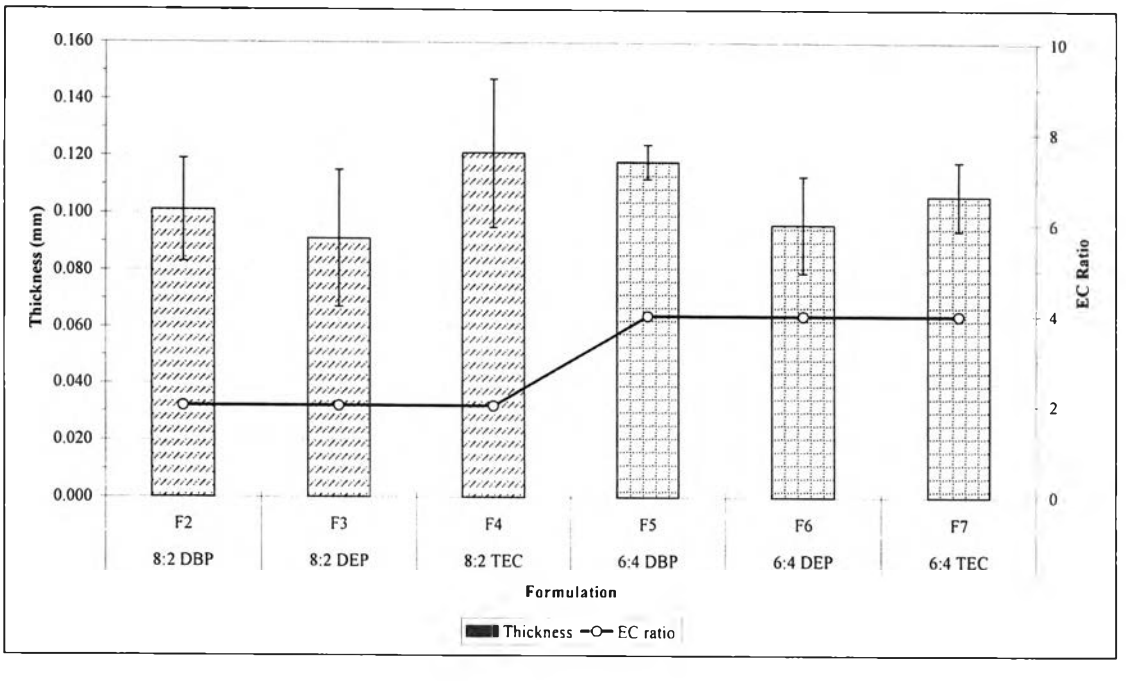

Figure 25 Effect of plasticizers on thickness of the films in various formulations studied.

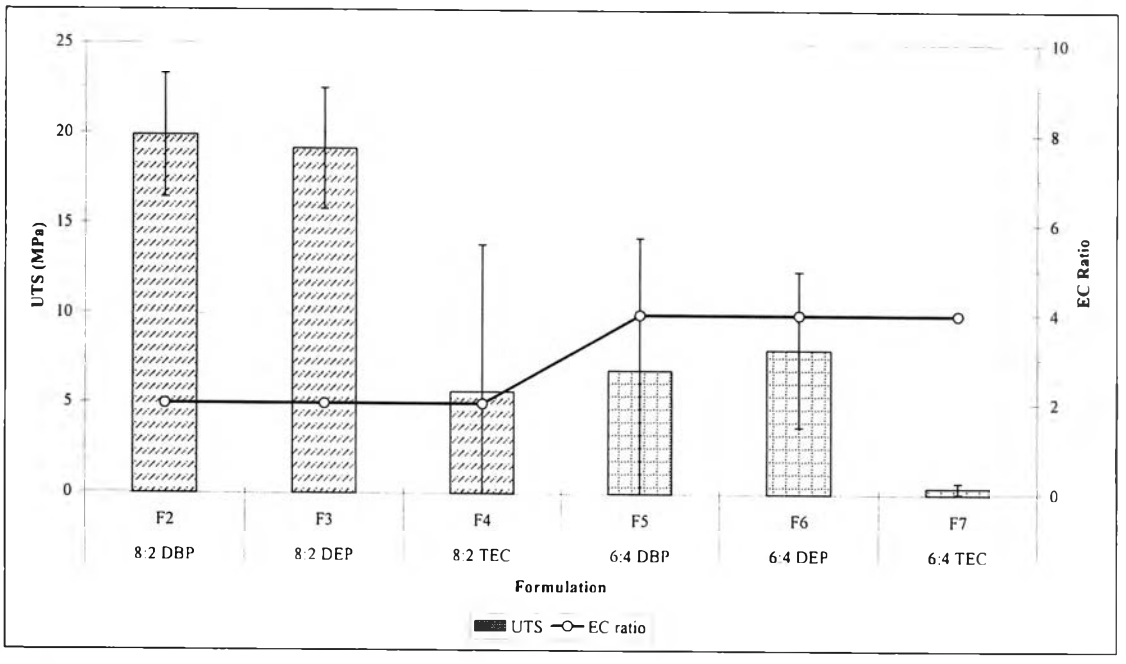

Figure 26 Effect of plasticizers on ultimate tensile strength of the films in various formulations studied.

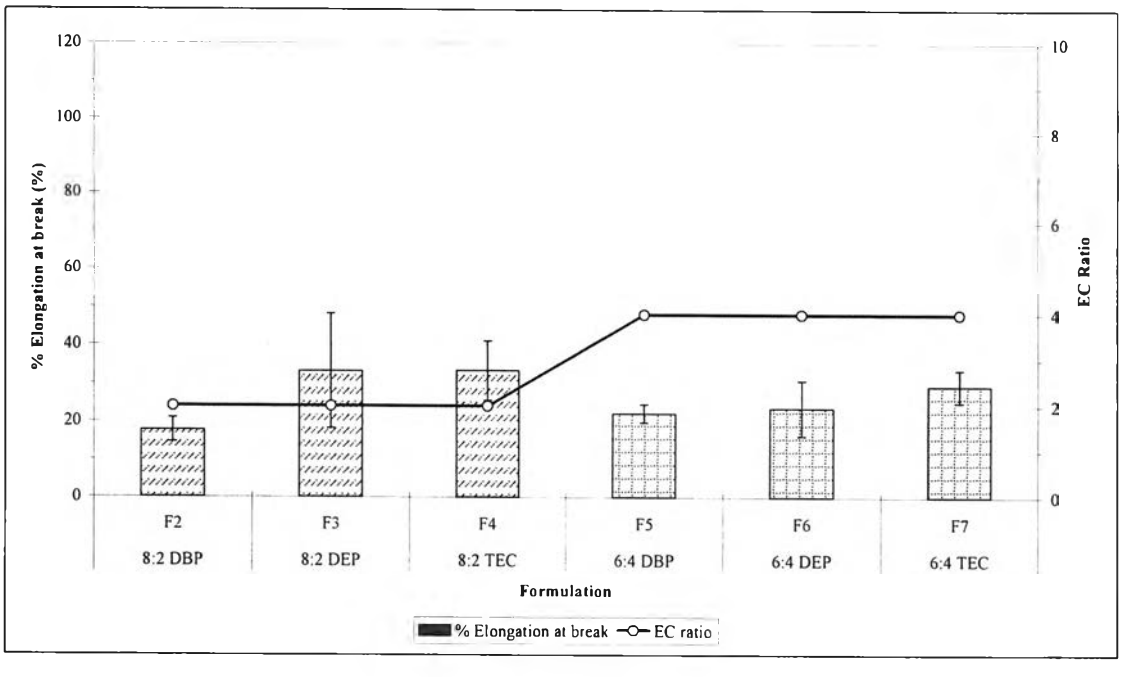

Figure 27 Effect of plasticizers on percentage of elongation at break of the films in various formulations studied.

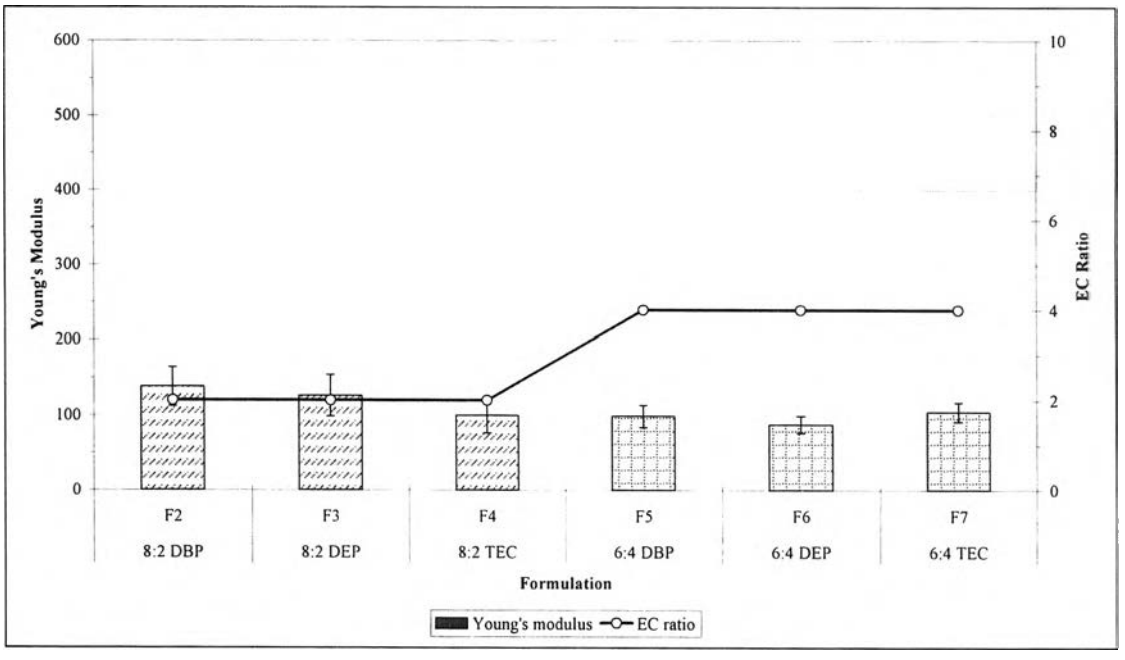

Figure 28 Effect of plasticizers on Young's modulus of the films in various formulations studied.

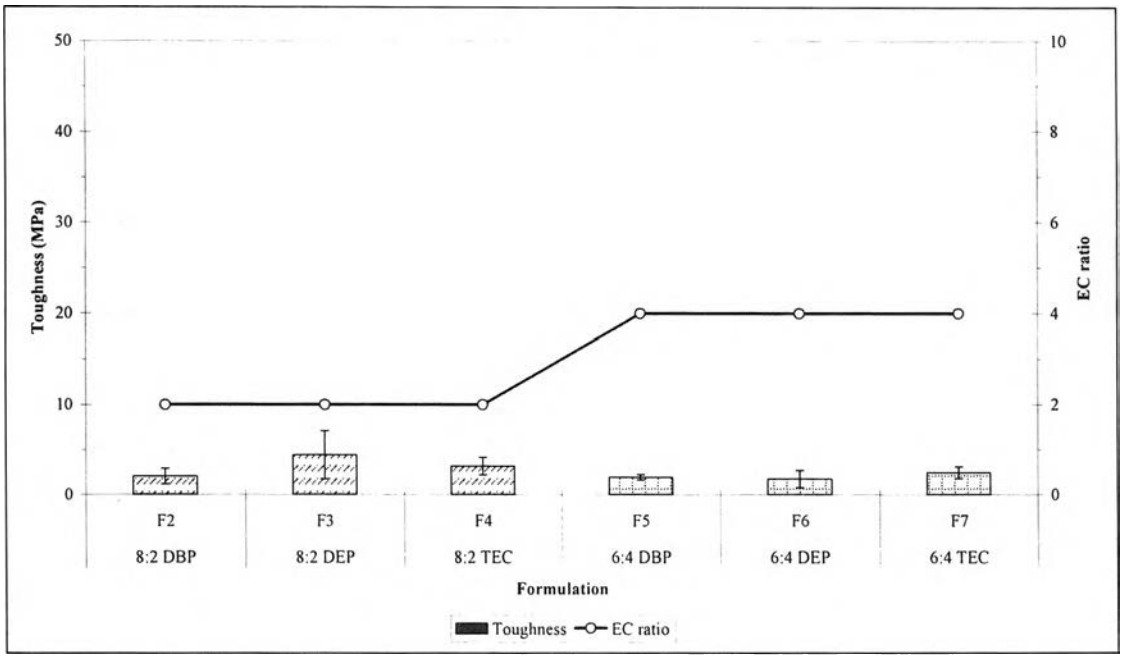

Figure 29 Effect of plasticizers on toughness of the films in various formulations studied.

1.2 Effect of Plasticizers on Thickness and Mechanical Properties of Free Film

The effects of plasticizer type on mechanical properties of free film formulations are shown in Table 8. Formulations *F2*, *F3*, and *F4* composed of HPMC:EC 8:2 with DBP, DEP, and TEC, respectively, as plasticizer. It was found that thickness of these formulations, as seen in Figure 25, are in the order of TEC > DBP > DEP, respectively. From Figure 26 and Figure 28, UTS and Young's modulus of these formulations are in the same order of DBP > DEP > TEC, respectively. However, the percentage of elongation at break of these formulations in Figure 27 are in the difference order of DEP ~ TEC > DBP, respectively.

Formulations *F5*, *F6*, and *F7* composed of HPMC:EC 6:4 with DBP, DEP, and TEC, as plasticizer, respectively. The results showed that the thickness of films were in the order of DBP > TEC > DEP, respectively. But UTS of these films were in different order of DEP > DBP > TEC, respectively. Furthermore, % elongation at break were in order of TEC > DEP > DBP, respectively. Finally, Young's modulus and toughness of these films were the same order of TEC > DBP > DEP, respectively.

2. Formulation Development of DTZ HCl TDDS

2.1 Determination of Drug Solubility in Various Solvent Systems

The equilibrium solubilities of DTZ HCl in different solvents at 32 ± 1°C are listed in Table 9. The rank order of solubilities of DTZ HCl in various solvent systems is: DI Water (486.4) > PBS (461.9) > PG (86.0) > Ethyl alcohol (52.0) > PEG (20.5) > IPP (19.0) > IPM (14.3), respectively.

Table 9 Solubility of diltiazem hydrochloride at 32 ± 1°C (n = 3).

Solvents	Solubilities (mg/ml)	Dielectric constant (ε)
Phosphate buffer saline, pH 7.4	461.9	n/a [d]
DI Water	486.4	80.4 [a]
Ethyl alcohol	52.0	24.3 [a]
Propylene glycol (PG)	86.0	32.0 [a]
Isopropyl myristate (IPM)	14.3	3.3 [b]
Isopropyl palmitate (IPP)	19.0	n/a [d]
Polyethylene glycol 400 (PEG)	20.5	12.4 [c]

[a] Pharmaceutical Codex 12[ed] (1994); [b] Harada (2000),
[c] U.S. National Bureau of Standard Circular 514, [d] n/a (not available)

2.2 Effect of Polymer Ratios on DTZ HCl Content

Determination of DTZ HCl content was calculated from equation in Appendix B. The results of DTZ HCl content in various formulations are shown in Table 10. The DTZ HCl contents in various formulations are ranged from 138.9 – 169.3 mg/g. From Figure 30, it was found that the rank order of drug content in films with various polymer ratios was A4 (8:2) ~ A8 (4:6) > A1 (10:0) > A5 (6:4) > A9 (2:8), respectively.

2.3 Effect of Enhancers on DTZ HCl Content

The results of DTZ HCl content of each formulation from Table 10 are ranged from 135.1 – 154.2 mg/g. The rank order of drug content in the films with various types of enhancers as illustrated in Figure 31 is A45 (PEG) > A41 (IPM) ~ A46 (PG) > A43 (NMP) ~ A47 (Tw) > A42 (IPP) ~ A44 (OA), respectively.

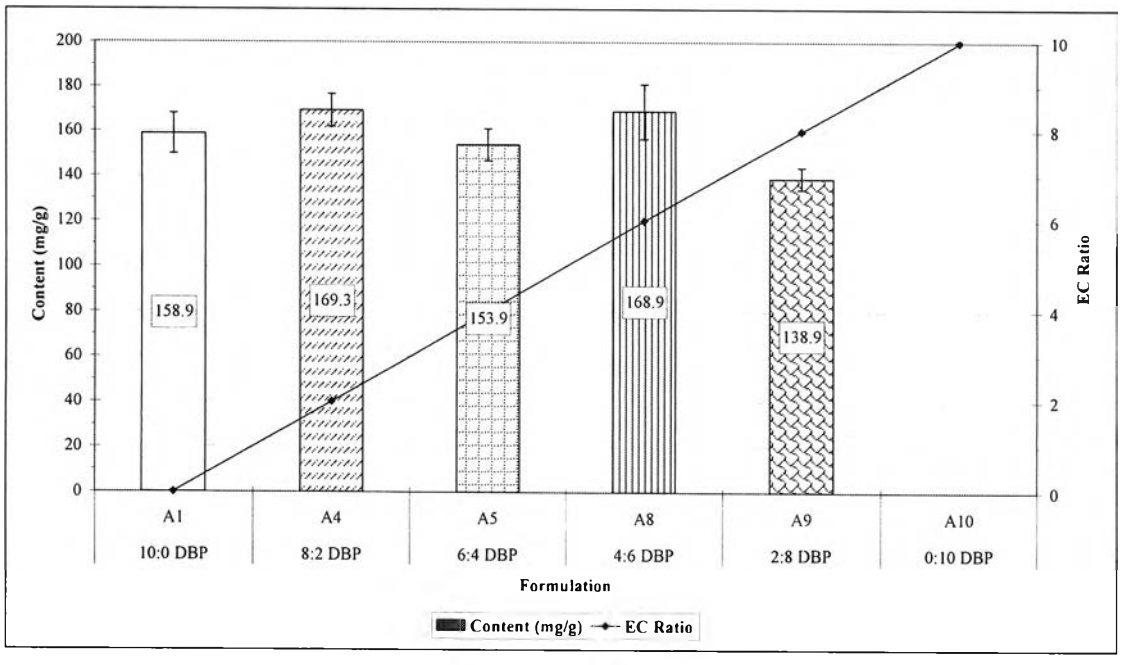

Figure 30 Effect of polymer ratios of HPMC:EC on diltiazem hydrochloride content of the films in various formulations studied (Note: drug content of formulation A10 is not available).

Table 10 Diltiazem hydrochloride content in various film formulations (n=6).

Formulations	Content (mg/g)
A1 (10:0)	158.9 ± 9.0
A4 (8:2)	169.3 ± 7.4
A5 (6:4)	153.9 ± 7.2
A8 (4:6)	168.9 ± 12.3
A9 (2:8)	138.9 ± 4.9
A10 (0:10)	n/a*
A41 (IPM)	148.6 ± 8.7
A42 (IPP)	135.1 ± 6.0
A43 (NMP)	142.3 ± 3.0
A44 (OA)	136.0 ± 3.1
A45 (PEG)	154.2 ± 2.5
A46 (PG)	148.2 ± 1.5
A47 (Tw)	142.3 ± 2.2

*n/a (not available)

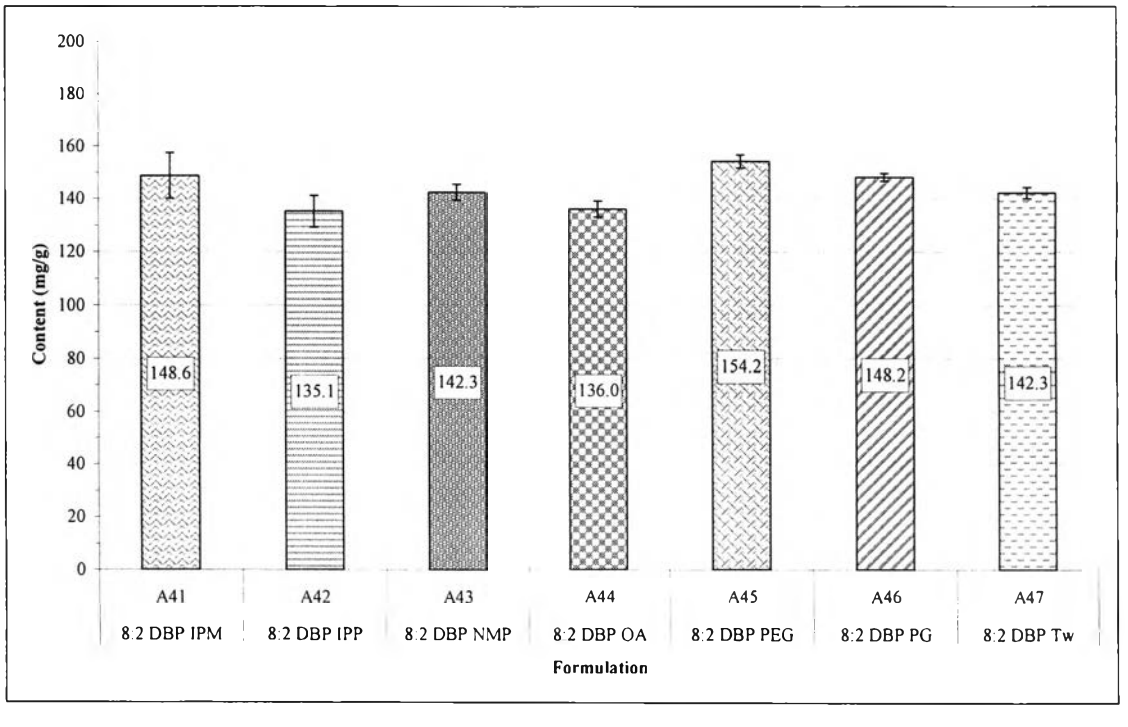

Figure 31 Effect of enhancers on diltiazem hydrochloride content of the films in various formulations studied.

2.4 Effect of Polymer Ratios on Moisture Uptake

The moisture uptake of DTZ HCl films containing various ratios of HPMC:EC were evaluated. The percentage of moisture uptake of the films is presented in Table 11. It can be found that the percentage of moisture uptake of films are in the order of A1 (10:0) > A4 (8:2) > A5 (6:4) > A8 (4:6) > A9 (2:8) > A10 (0:10), respectively. As depicted in Figure 32, the increasing of EC ratios affected to the decreasing of moisture uptake.

Table 11 Percent moisture uptake of films containing diltiazem hydrochloride and various ratios of HPMC and EC (n=6).

Formulations	% Moisture Uptake ± SD
A1 (10:0)	48.1 ± 4.6
A4 (8:2)	29.5 ± 3.6
A5 (6:4)	18.3 ± 4.4
A8 (4:6)	15.0 ± 3.6
A9 (2:8)	11.6 ± 3.0
A10 (0:10)	2.8 ± 1.6

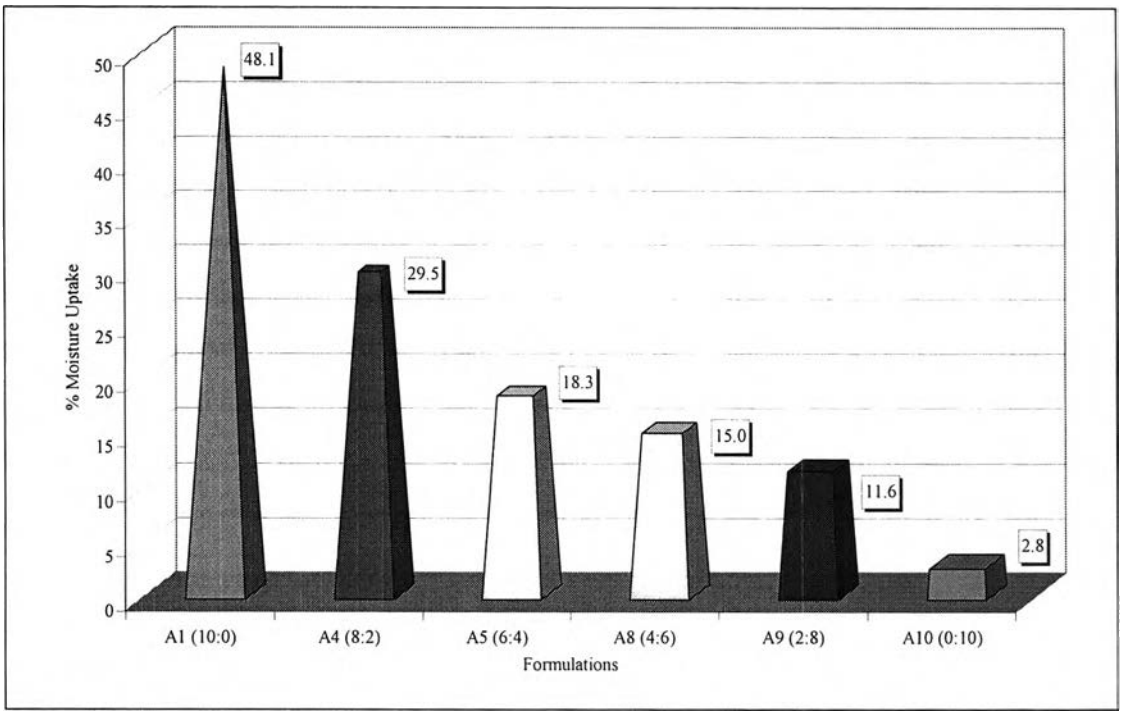

Figure 32 Effect of polymer ratios on percent moisture uptake of films containing diltiazem hydrochloride (n=6).

2.5 Effect of Enhancers on Moisture Uptake

The moisture uptakes of DTZ HCl films containing various types of enhancer were also conducted. The percent moisture uptake of films is presented in Table 12. It can be found that the percentage of moisture uptake of films are in the order of A47 (Tw) > A41 (IPM) > A45 (PEG) > A44 (OA) > A43 (NMP) > A46 (PG) > A42 (IPP), respectively. It can be seen from Figure 33 that the two highest formulations were composed of Tw and IPM. However, the formulation A42 which composed of IPP gave the lowest moisture uptake. There was only formulation A42 gave the lower moisture uptake than formulation A4.

2.6 Effect of Polymer Ratios on Transparency

The influences of polymer ratios on the DTZ HCl film transparency were carried out. The results are presented in Appendix B. The average absorbance values of films are given in Table 13. The rank order of absorbance values is A10 (0:10) > A1 (10:0) > A4 (2:8) > A5 (4:6) > A8 (6:4) > A9 (8:2), respectively. Figure 34 presents the effects of increasing EC ratio on transparency of DTZ HCl films. It was found that the increasing of EC ratio with HPMC resulting in the increasing of transparency. However, the EC film alone was less transparent.

2.7 Effect of Enhancers on Transparency

The absorbance values of the DTZ HCl films containing various types of enhancer are shown in Table 14. The rank order of absorbance values is A47 (Tw) > A46 (PG) > A41 (IPM) > A42 (IPP) > A44 (OA) > A43 (NMP) > A45 (PEG) > A4 (no enhancer), respectively. The effects of various enhancer types are illustrated in Figure 35. It can be seen that the adding of all enhancers affected to the decreasing of transparency. The highest effect came from adding Tw.

Table 12 Percent moisture uptake of 8:2 HPMC:EC films containing diltiazem hydrochloride and various types of enhancers (n=6).

Formulations	% Moisture Uptake ± SD
A4	29.5 ± 3.6
A41 (IPM)	35.9 ± 2.2
A42 (IPP)	23.8 ± 2.1
A43 (NMP)	30.9 ± 3.6
A44 (OA)	33.2 ± 2.5
A45 (PEG)	34.9 ± 4.5
A46 (PG)	29.6 ± 1.8
A47 (Tw)	37.8 ± 2.3

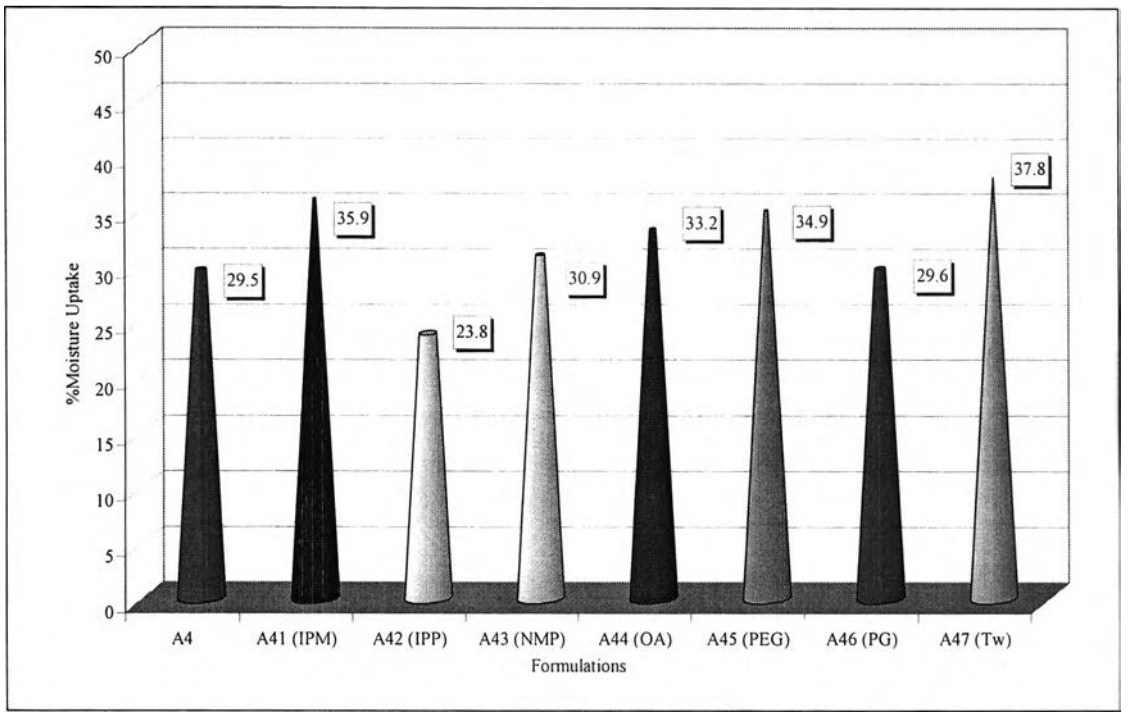

Figure 33 Effect of enhancer types on percent moisture uptake of films containing diltiazem hydrochloride (n=6).

Table 13 Absorbance of films containing diltiazem hydrochloride and various ratios of HPMC and EC (n=6).

Formulations	Absorbance ± SD
A1 (10:0)	0.0626 ± 0.0014
A4 (8:2)	0.0614 ± 0.0014
*A5** (6:4)	0.0609 ± 0.0008
A8 (4:6)	0.0603 ± 0.0006
A9 (2:8)	0.0597 ± 0.0020
A10 (0:10)	0.0653 ± 0.0041

*n=5

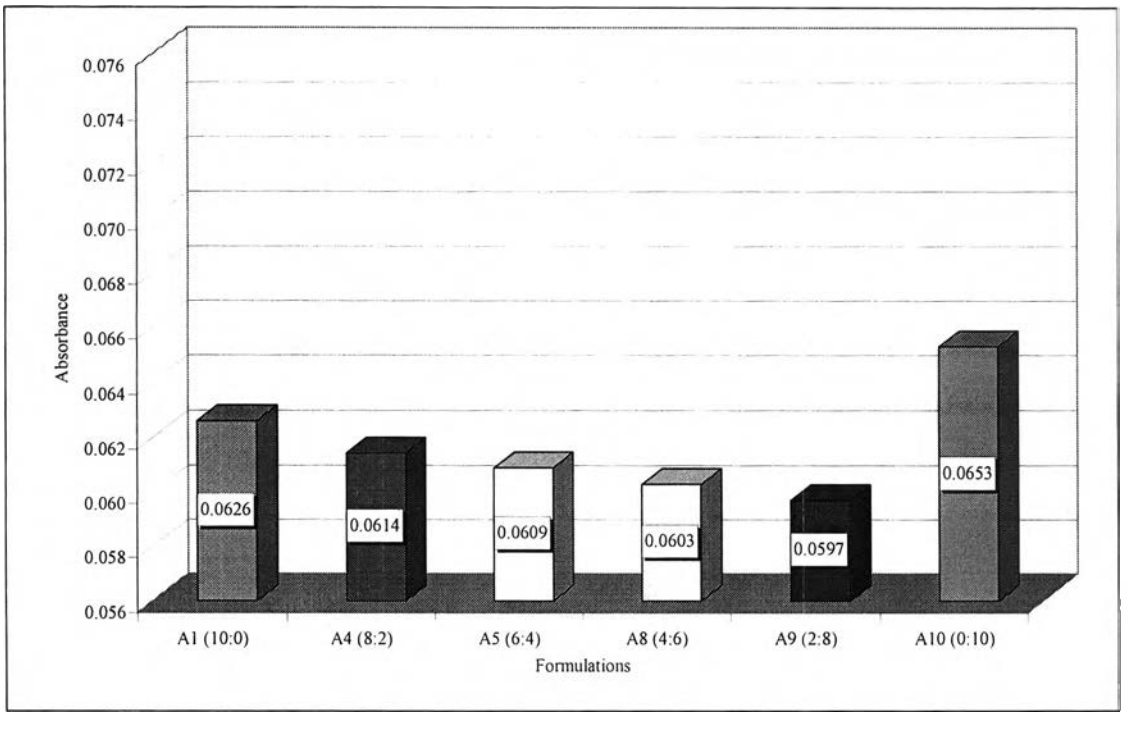

Figure 34 Effects of polymer ratios on transparency of films formulation containing diltiazem hydrochloride.

Table 14. Absorbance of 8:2 HPMC:EC films containing diltiazem hydrochloride and various types of enhancers (n=6).

Formulations	Absorbance ± SD
A4	0.0614 ± 0.0014
A41 (IPM)	0.0670 ± 0.0023
A42 (IPP)	0.0662 ± 0.0031
A43 (NMP)	0.0640 ± 0.0027
A44 (OA)	0.0651 ± 0.0036
A45 (PEG)	0.0636 ± 0.0011
A46 (PG)	0.0694 ± 0.0023
A47 (Tw)	0.0756 ± 0.0036

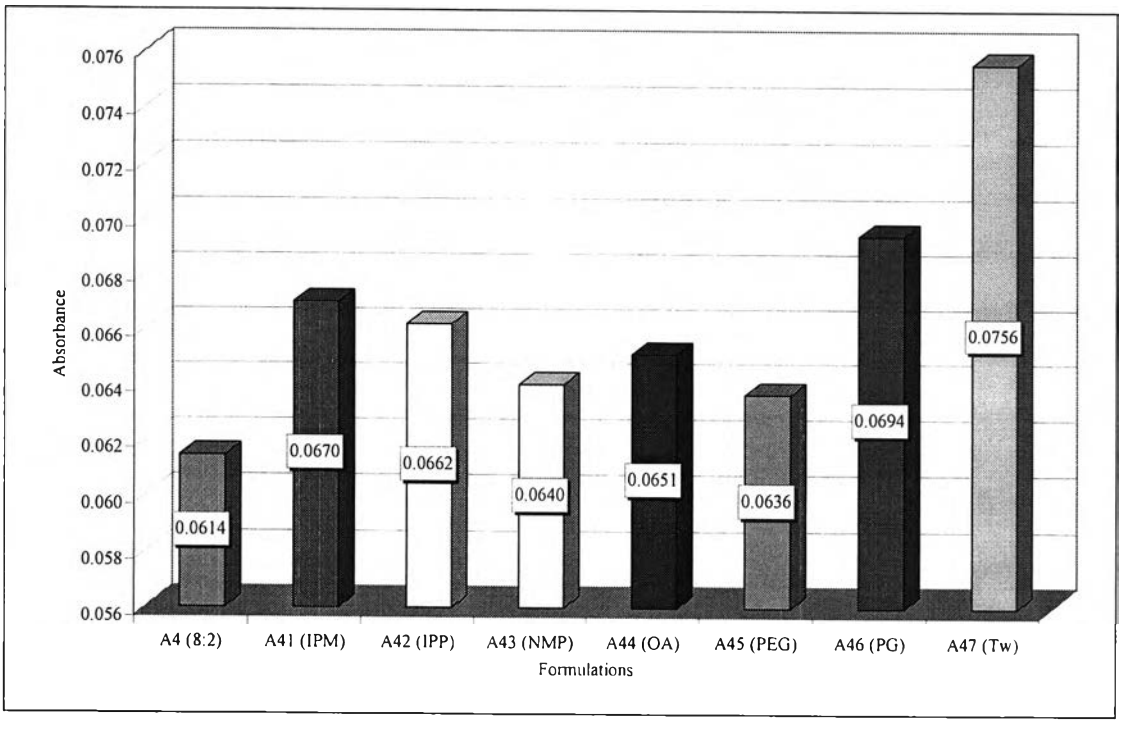

Figure 35 Effect of enhancer types on transparency of films containing diltiazem hydrochloride (n=6).

2.8 Effect of Polymer Ratios on Surface Topography

The surface topography of the HPMC:EC free films at various ratios are illustrated in Figures 36 (10:0), 37 (8:2), 38 (4:6), and 39 (6:4). Figure 36 shows the porosity of film before increasing EC ratio. After increasing EC ratio, it can be found that the porosity of film disappeared both in Figures 37 and 38. However, the increasing of EC ratio to 6 parts affected to the separating of EC part as seen in Figure 39. Furthermore, the effects of DTZ HCl on the surface topography of various ratios HPMC:EC films is shown in Figure 40 (10:0), 41 (8:2), 42 (4:6), and 43 (6:4). No effect on the surface topography of these films was investigated. However, there are many DTZ HCl crystals stuck on the film surface.

2.9 Effect of Enhancers on Surface Topography

The surface topography of the 8:2 HPMC:EC film containing various types of enhancers are illustrated in Figures 44 (IPM), 45 (IPP), 46 (NMP), 47 (OA), 48 (PEG), 49 (PG), and 50 (Tw). It was found that the addition of IPM and IPP results in the traces of oil drop on the film surface (Figures 44 and 45, respectively). Especially, Figure 44 shows many pores on the surface like HPMC film containing DTZ HCl (Figure 40). However, the surface topographies of films in Figures 46 – 49 (contained NMP, OA, PEG and PG, respectively) seem to be the same as films without enhancers. Finally, Figure 50 shows a lot of DTZ HCl crystal covered almost the film surface. Thus, the changing in surface topography can not be found.

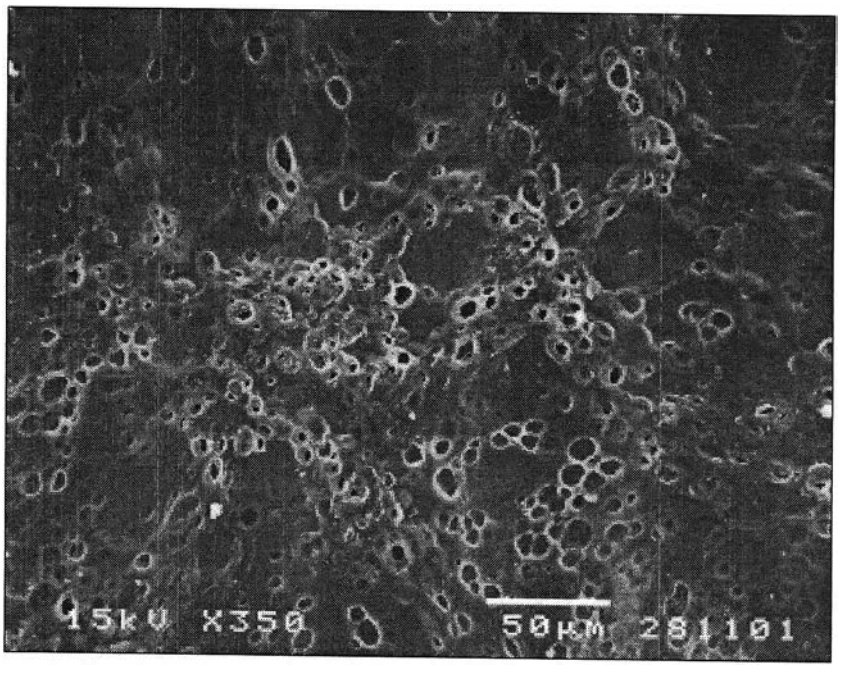

Figure 36 Surface topography of the HPMC free film.

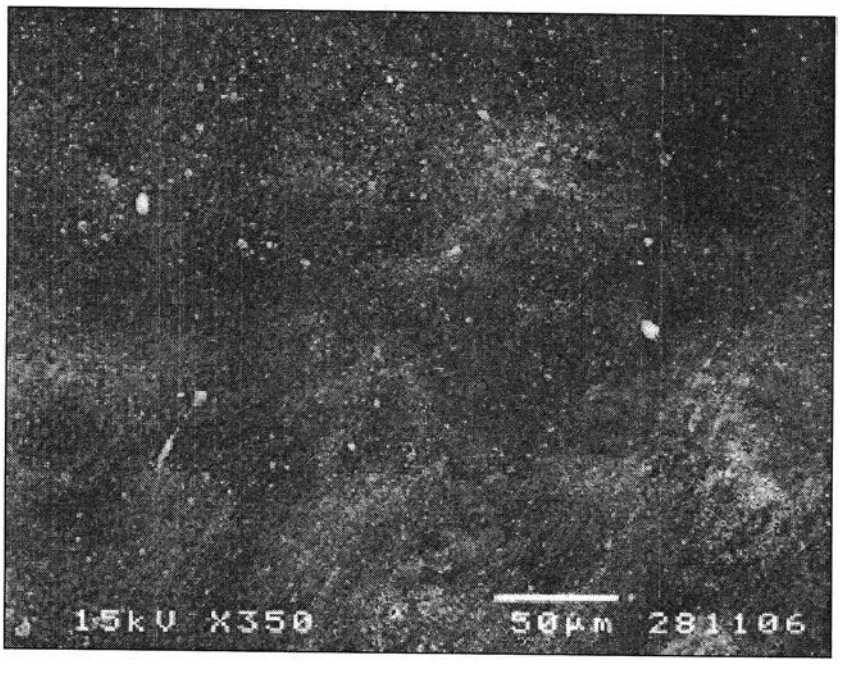

Figure 37 Surface topography of the HPMC:EC free film at the ratio of 8:2.

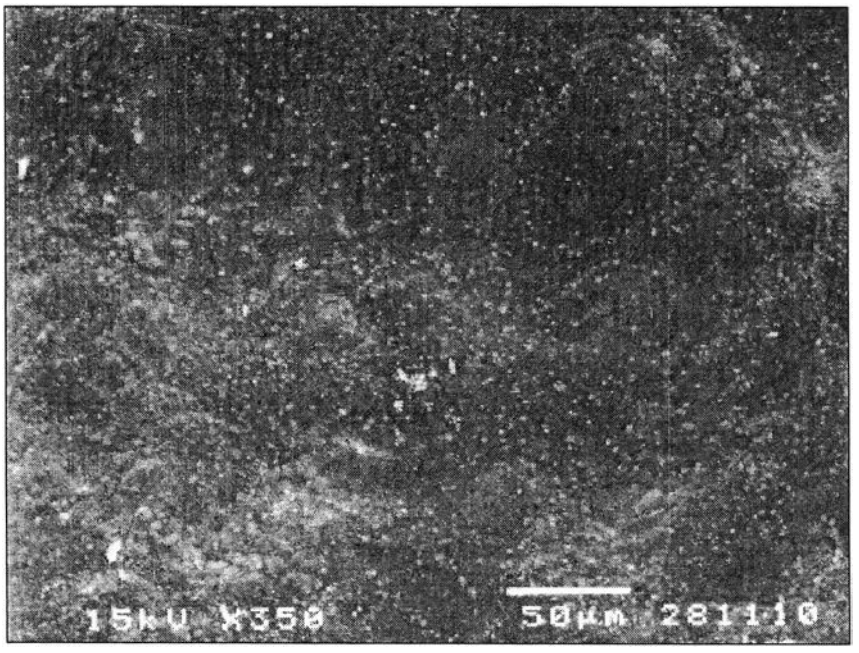

Figure 38 Surface topography of the HPMC:EC free film at the ratio of 6:4.

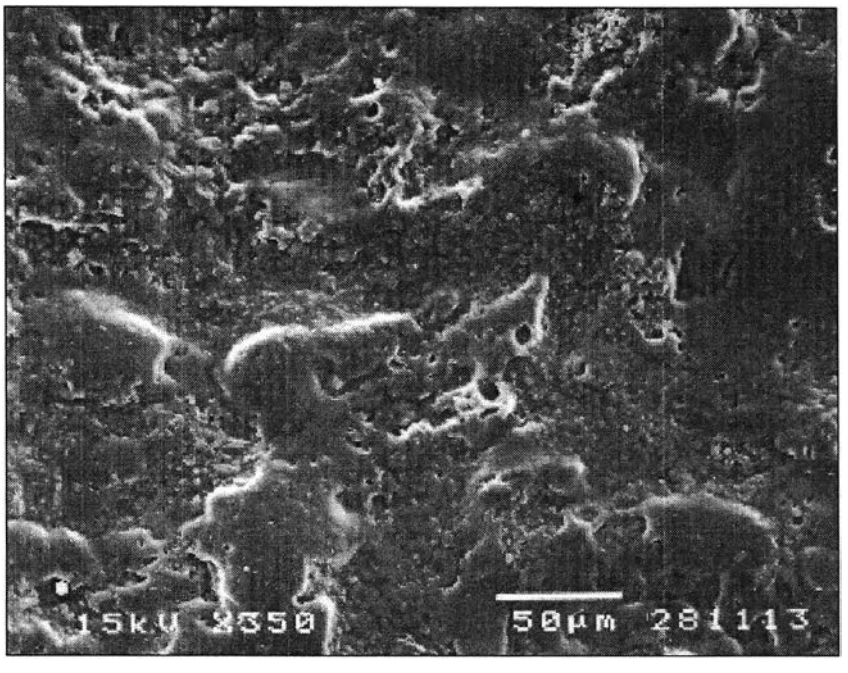

Figure 39 Surface topography of the HPMC:EC free film at the ratio of 4:6.

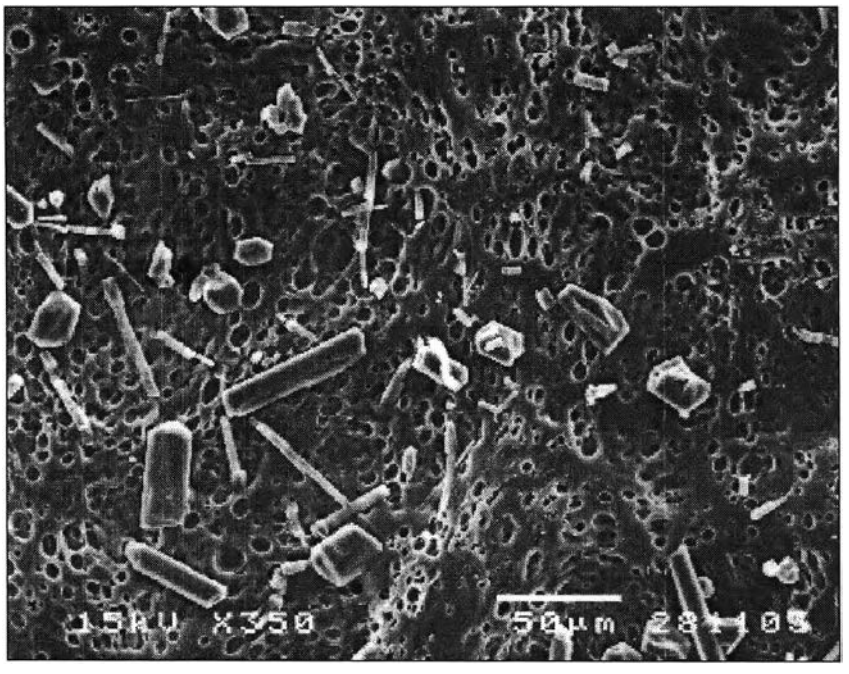

Figure 40 Surface topography of the HPMC film containing diltiazem hydrochloride.

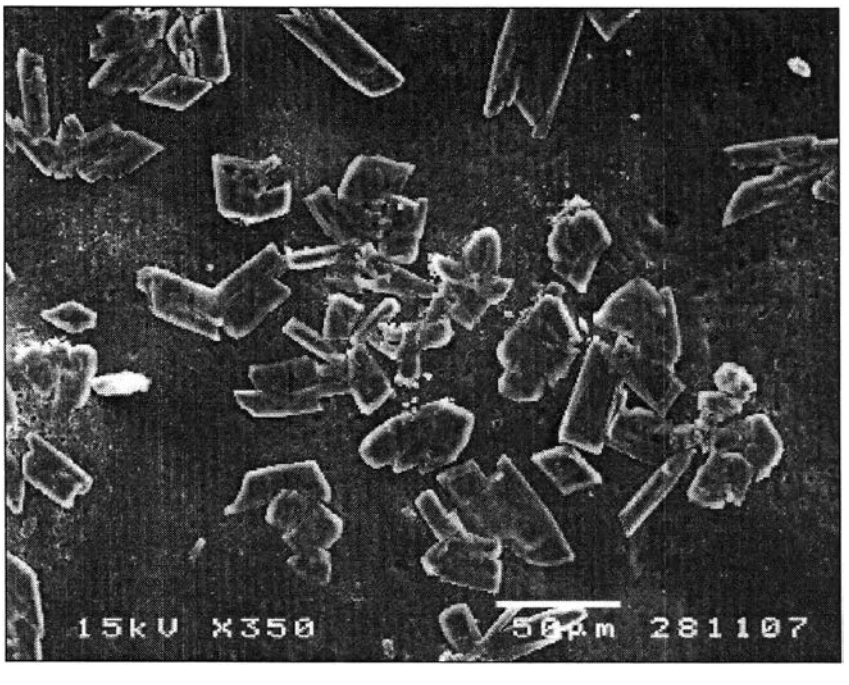

Figure 41 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride.

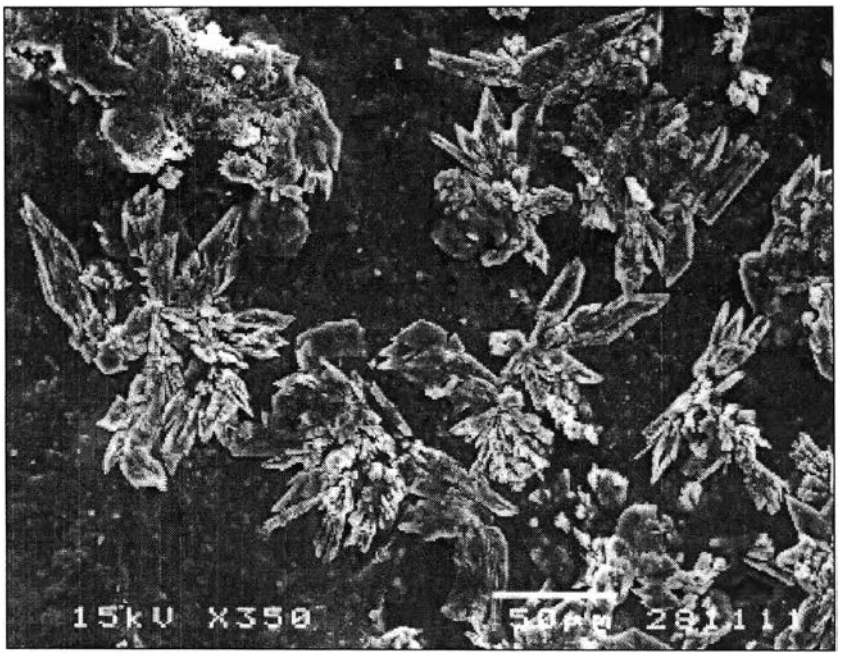

Figure 42 Surface topography of the HPMC:EC film at the ratio of 6:4, containing diltiazem hydrochloride.

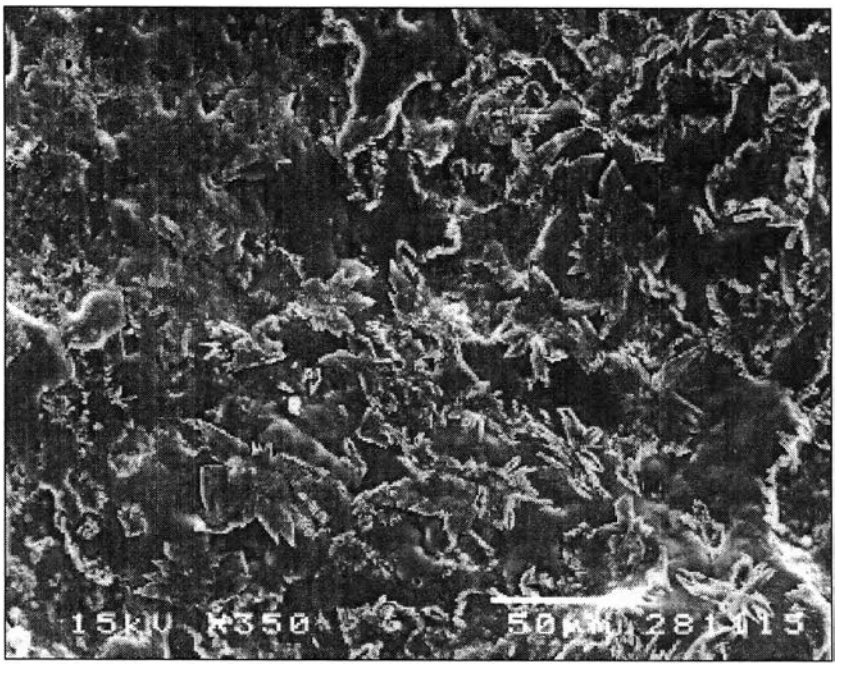

Figure 43 Surface topography of the HPMC:EC film at the ratio of 4:6, containing diltiazem hydrochloride.

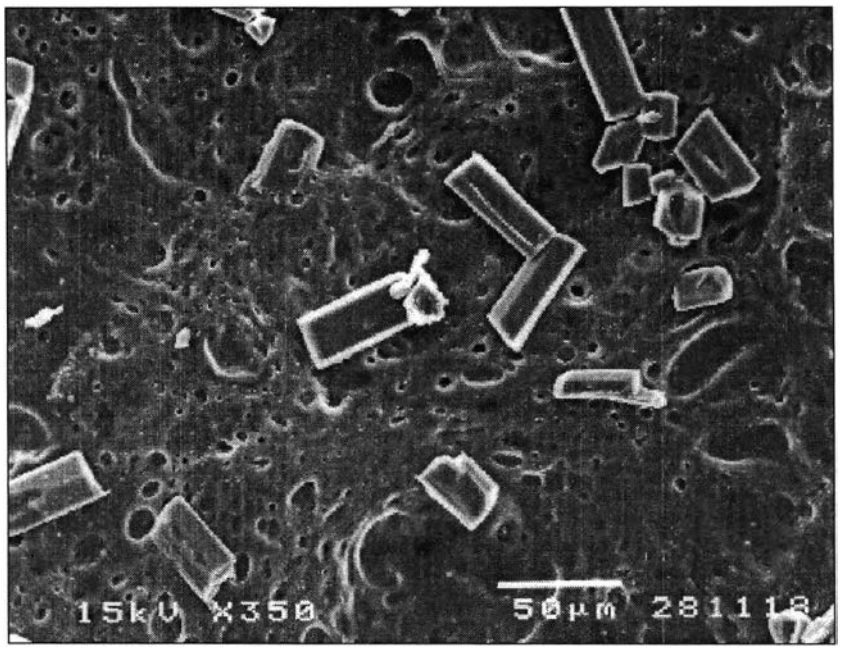

Figure 44 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and isopropyl myristate.

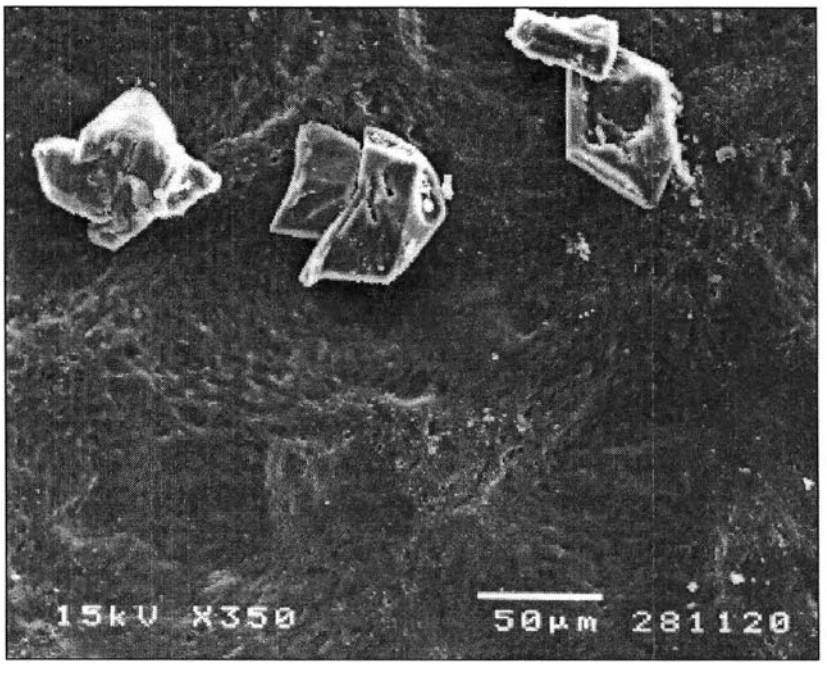

Figure 45 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and isopropyl palmitate.

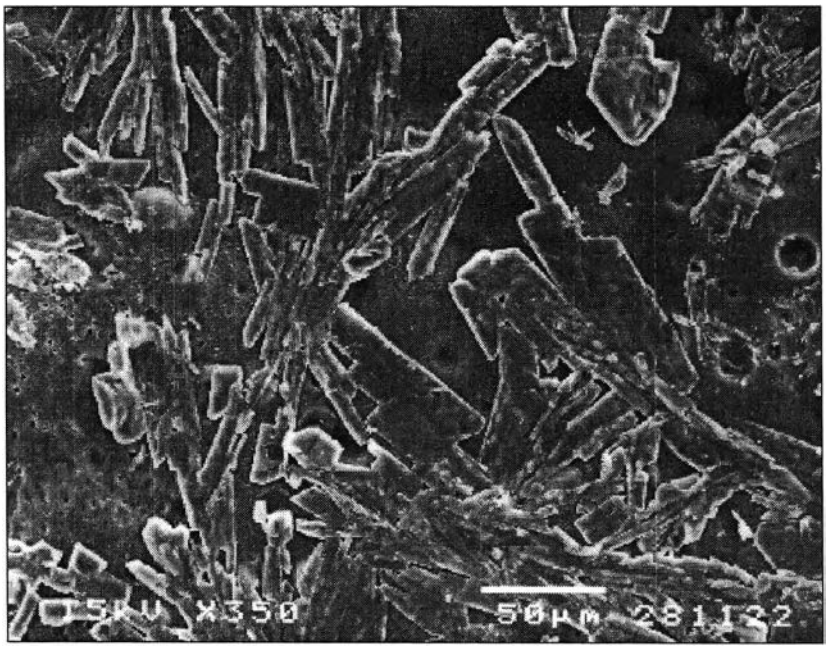

Figure 46 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and N-methyl-2-pyrrolidone.

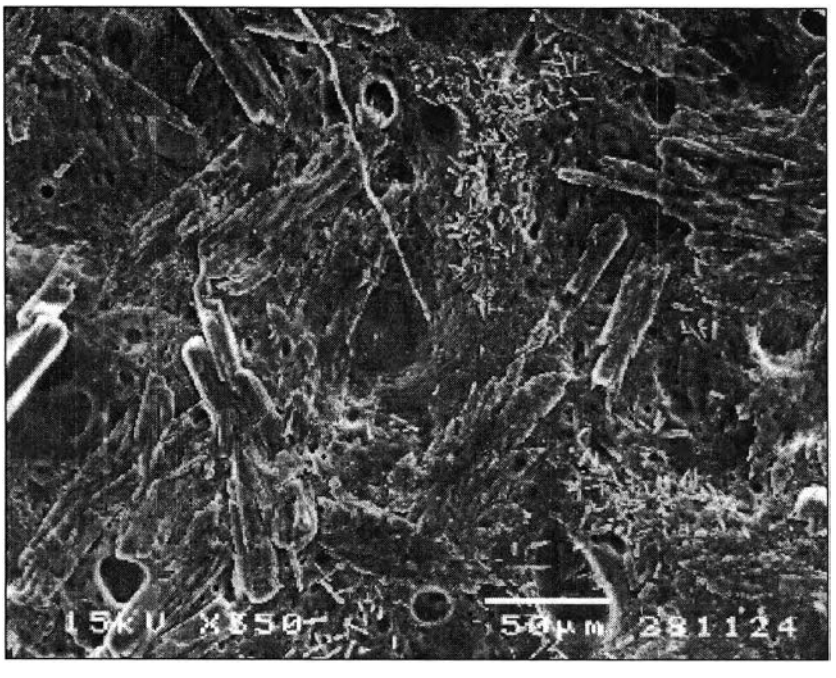

Figure 47 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and oleic acid.

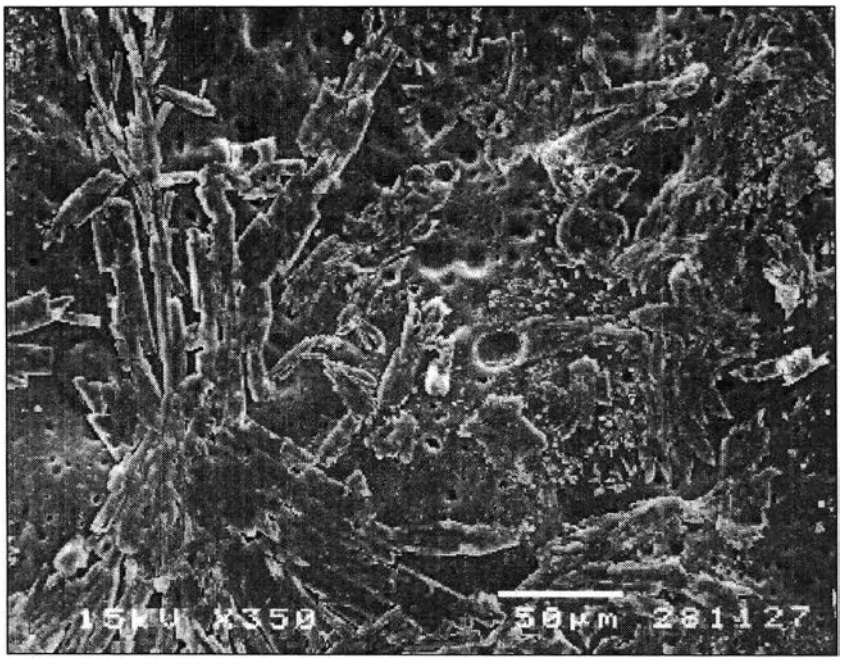

Figure 48 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and propylene glycol.

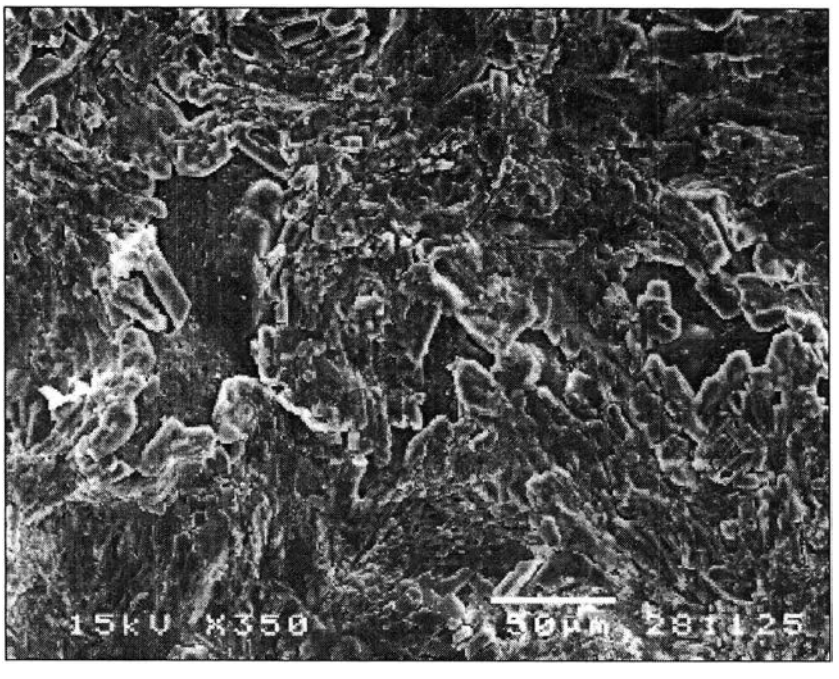

Figure 49 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and polyethylene glycol 400.

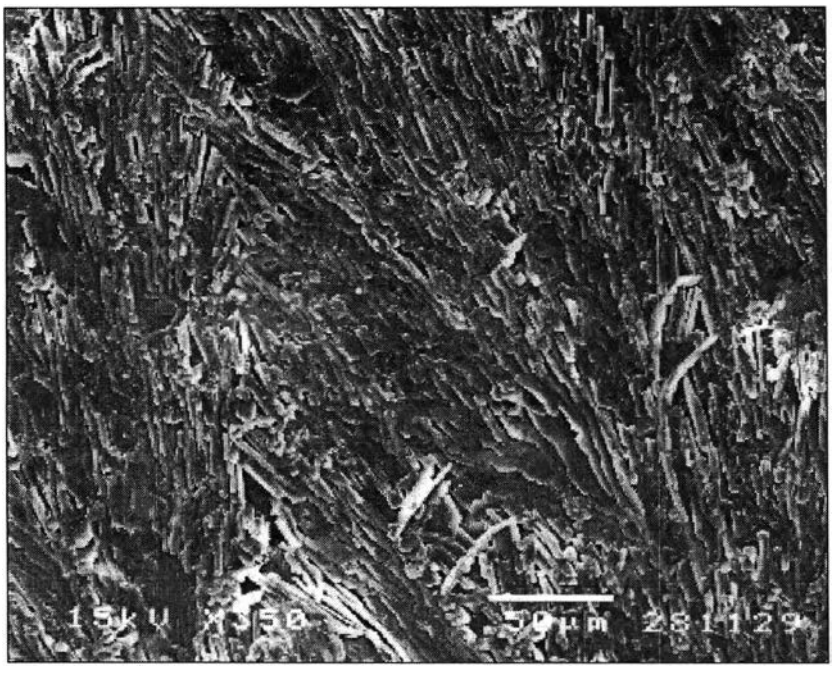

Figure 50 Surface topography of the HPMC:EC film at the ratio of 8:2, containing diltiazem hydrochloride and Tween 80.

3. An Evaluation of DTZ HCl TDDS Formulation

3.1 *In vitro* Drug Release of DTZ HCl from Various Film Formulations

The *in vitro* release studies of DTZ HCl from the films were carried out. The results of drug release are presented in Appendix C. The average cumulative percent of drug release are given in Tables 15 - 17. The typical release-time profiles are shown in Figures 51 - 53. The release-time profiles in Figures 51 - 53 are similar; they can be separated into 2 parts. The first part showed the faster release of drug, with higher slope, and in the second part of after 1-2 hours, showed the slower release of drug from the films.

3.1.1 Effect of Polymer Ratios on *In vitro* Drug Release

Table 15 and Figure 51 show the effects of polymer ratios on the average cumulative percent release and average release-time profiles of DTZ HCl from the film formulations, respectively. The slopes of 0-1 hour represented the release rate of drug, they can be ranked in the order of A1 (10:0) > A4 (8:2) > A5 (6:4) > A8 (4:6) > A9 (2:8) > A10 (0:10), respectively. Moreover, the average cumulative percent of drug release at 12 hours are in the order of A1 ~ A4 > A5 > A8 > A9 > A10, respectively. It seems to be that the increasing of EC ratio affected to the decreasing of percentage of drug release.

3.1.2 Effect of Plasticizers on *In vitro* Drug Release

Table 16 and Figure 52 show the effects of plasticizer types on the average cumulative percent release and average release-time profiles of DTZ HCl from HPMC films. The rank order of the slopes (0-1 hour) is A1 (DBP) > A3 (TEC) > A2 (DEP), respectively. However, at 12 hours, the average cumulative percent of drug release are in the order of A1 > A2 > A3, respectively. It can to be found that various type of plasticizers in HPMC films only affected on to the initial release rate of drug.

Table 17 and Figure 53 show the effects of plasticizer types on the average cumulative percent release and average release-time profiles of DTZ HCl from 6:4, HPMC:EC films. The slopes of 0-1 hour and the average cumulative percent of drug release at 12 hours can be ranked in the same order of A5 (DBP) ~ A7 (TEC) > A6 (DEP), respectively. It was found that various type of plasticizers types of HPMC films affected to both the initial release rate and average cumulative percent release.

The initial release rate and the average cumulative percent of drug at 12 hours from formulations A4 (8:2) and A5 (6:4) are higher than those from formulations A8 (4:6) and A9 (2:8). Moreover, the initial release rates of the film formulations with DBP illustrated the highest slope. Therefore, HPMC:EC ratios at 8:2 and 6:4 (as film

Table 15 Average cumulative percent release of diltiazem hydrochloride from the films containing various ratios of HPMC and EC with 30% DBP (n=6).

Time (hours)	%Drug Release					
	A1 (10:0)	**A4 (8:2)**	**A5 (6:4)**	**A8 (4:6)**	**A9 (2:8)**	**A10 (0:10)**
0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	50.6 ± 12.5	43.1 ± 7.4	31.5 ± 4.6	22.7 ± 3.4	5.6 ± 0.7	0.4 ± 0.1
1	67.0 ± 12.3	64.7 ± 5.1	49.1 ± 7.3	38.5 ± 5.3	12.5 ± 1.5	0.6 ± 0.1
2	79.5 ± 9.0	79.4 ± 1.7	69.1 ± 5.5	61.6 ± 7.1	26.0 ± 3.3	0.9 ± 0.1
3	84.5 ± 7.4	81.9 ± 1.6	76.4 ± 3.3	71.8 ± 7.1	37.3 ± 4.3	1.2 ± 0.1
4	88.7 ± 6.8	85.2 ± 1.1	79.7 ± 2.6	77.0 ± 6.7	45.4 ± 4.2	1.3 ± 0.1
6	93.2 ± 6.9	92.6 ± 4.2	87.6 ± 4.0	81.8 ± 5.7	58.4 ± 3.5	1.6 ± 0.1
8	95.1 ± 7.2	93.8 ± 2.9	90.3 ± 4.2	84.7 ± 5.4	69.0 ± 2.2	1.8 ± 0.1
12	99.8 ± 7.0	100.0 ± 5.0	92.4 ± 3.6	88.0 ± 4.8	85.8 ± 4.7	2.4 ± 0.2
r^2*	0.920	0.965	0.974	0.989	0.996	0.974
Slope*	67.0	64.7	49.1	38.5	12.5	0.6
X-Intercept*	-0.04	-0.04	-0.03	-0.02	0.02	-0.03

* r^2 calculated from time range of 0-1 hour.

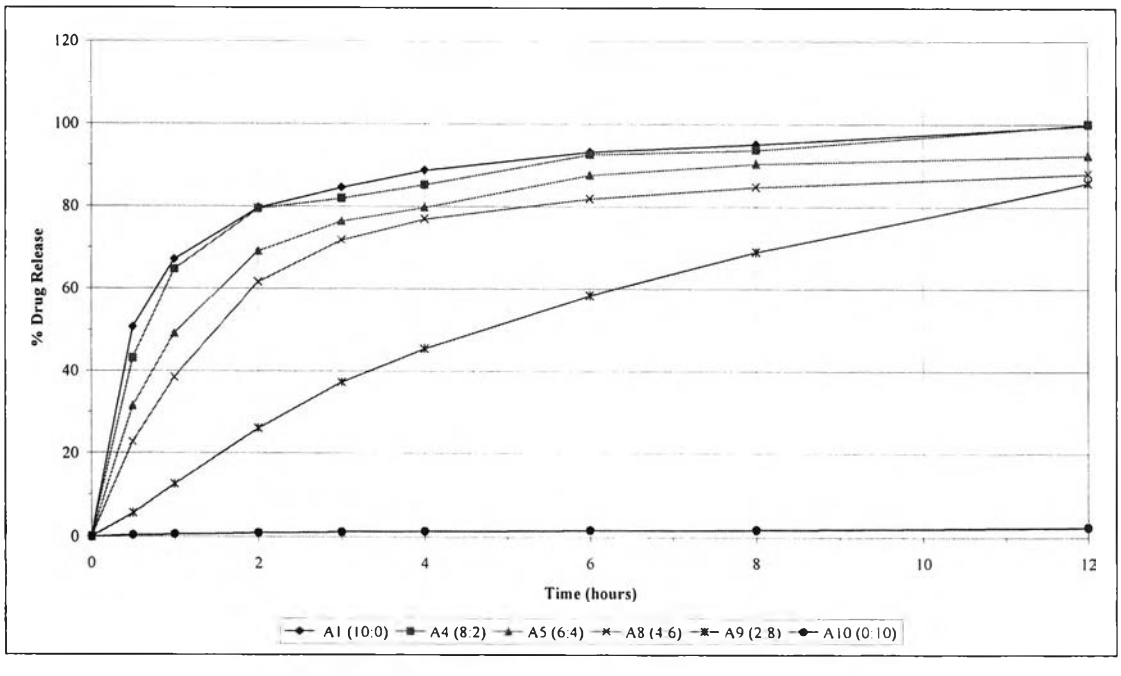

Figure 51 Effect of polymer ratios on average release time profile of diltiazem hydrochloride from HPMC and EC films with 30% DBP (n=6).

Table 16 Average cumulative percent release of diltiazem hydrochloride from the films of HPMC containing various types of plasticizers (n=6).

Time (hours)	% Drug release ± SD		
	A1 (DBP)	A2 (DEP)	A3 (TEC)
0	0	0	0
0.5	50.6 ± 12.5	23.8 ± 4.6	30.5 ± 13.9
1	67.0 ± 12.3	33.8 ± 5.8	42.9 ± 15.1
2	79.5 ± 9.0	48.1 ± 7.2	60.5 ± 13.0
3	84.5 ± 7.4	56.7 ± 7.0	70.7 ± 12.4
4	88.7 ± 6.8	64.3 ± 6.7	78.2 ± 12.9
6	93.2 ± 6.9	74.1 ± 6.8	84.9 ± 12.9
8	95.1 ± 7.2	82.7 ± 6.7	89.1 ± 12.2
12	99.8 ± 7.0	95.3 ± 4.6	92.4 ± 12.5
r^2*	0.920	0.948	0.944
Slope*	67.0	33.8	42.9
X-Intercept*	-0.04	-0.04	-0.04

* calculated from time range of 0-1 hour.

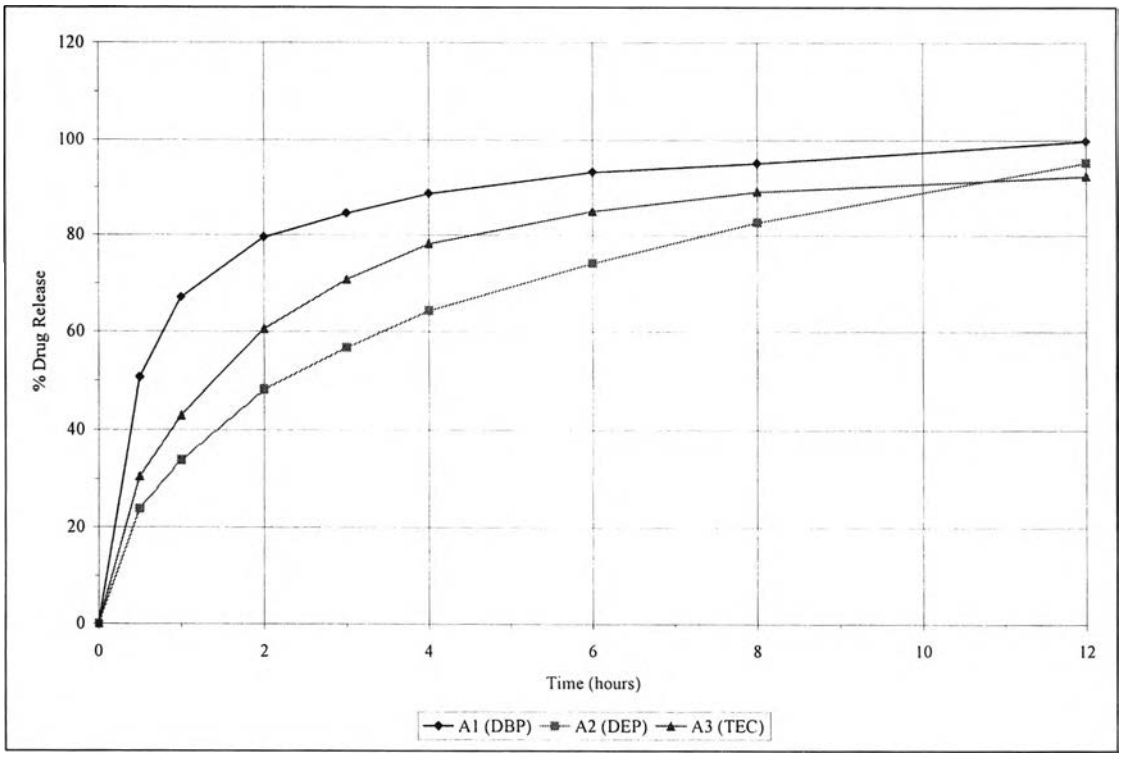

Figure 52 Effect of plasticizer types on average release time profile of diltiazem hydrochloride from HPMC films (n=6).

Table 17 Average cumulative percent release of diltiazem hydrochloride from the films of 6:4, HPMC:EC containing various type of plasticizers (n=6).

Time (hours)	% Drug release ± SD		
	A5 (DBP)	A6 (DEP)	A7 (TEC)
0	0	0	0
0.5	31.5 ± 4.6	15.4 ± 4.3	30.6 ± 8.8
1	49.1 ± 7.3	25.4 ± 3.3	47.0 ± 13.2
2	69.1 ± 5.5	39.8 ± 4.6	68.4 ± 14.6
3	76.4 ± 3.3	49.4 ± 4.7	76.5 ± 12.9
4	79.7 ± 2.6	55.7 ± 5.4	80.0 ± 11.3
6	87.6 ± 4.0	65.5 ± 5.6	83.4 ± 9.0
8	90.3 ± 4.2	72.7 ± 5.1	85.6 ± 8.5
12	92.4 ± 3.6	85.8 ± 7.4	89.6 ± 8.1
r^2*	0.974	0.985	0.970
Slope*	49.1	25.4	47.0
X-Intercept*	-0.03	-0.03	-0.03

* calculated from time range of 0-1 hour.

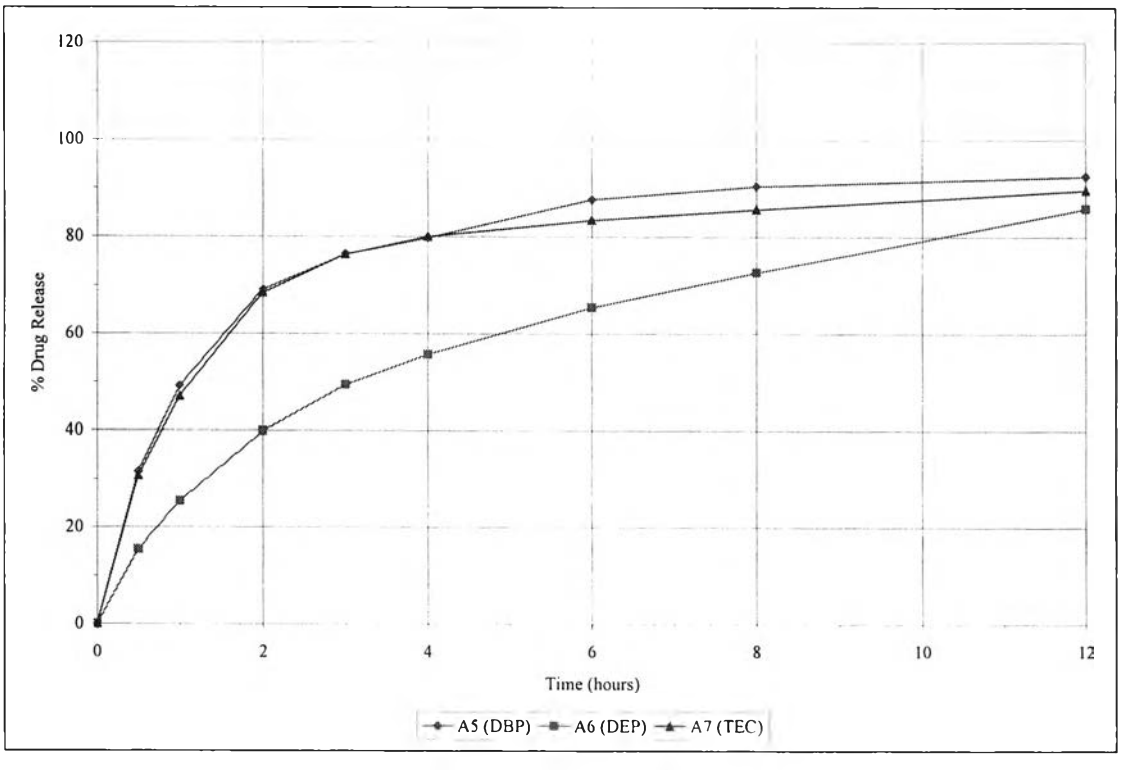

Figure 53 Effect of plasticizer types on average release time profile of diltiazem hydrochloride from 6:4, HPMC:EC films (n=6).

formers) and DBP (as plasticizer) were used through the *in vitro* skin permeation studies of DTZ HCl from the film formulations.

3.2 *In vitro* Skin Permeation of DTZ HCl Film

The *in vitro* skin permeation studies of DTZ HCl from the films were carried out. The drug permeation results are presented in Appendix C. The average cumulative amounts of drug permeation are shown in Tables 18 - 19. The typical permeation-time profiles are shown in Figures 54 - 56.

3.2.1 Effect of Polymer Ratios on *In vitro* Skin Permeation

It was found that the rank order of fluxes from Table 18 are in the order of A1 (10:0) ~ A4 (8:2) >A5 (6:4). However, the lag times are in the order of A1 ~ A4 < A5. Figure 54 shows almost the same permeation-time profiles of formulations A1 and A4. The average cumulative permeation amount of DTZ HCl at 12 hours from formulations A1 and A4 are higher than that of A5. The coefficient of correlations (r^2) of formulations A1 and A4 calculated from Higuchi's plot are higher than that from zero order plot. Thus, the skin permeation from formulations A1 and A4 seemed to follow the Higuchi's model. Furthermore, formulation A4 was chosen to study the effects of enhancer types in the next part of this studies.

3.2.2 Effect of Enhancer on *In vitro* Skin Permeation

The influences of enhancer types on the skin permeation of DTZ HCl were studied. The average cumulative amounts of drug permeation are shown in Table 19. It was found that the fluxes are in the order of A42 (IPP) > A41 (IPM) > A47 (Tw) > A45 (PEG) > A43 (NMP) > A44 (OA) ~ A 46 (PG), respectively. Moreover, the lag times are in the order of A43 ~ A44 > A46 > A45 > A41 > A42 > A47, respectively. There are 5 formulations (A41, A42, A43, A45 and A47) gave higher fluxes than formulation A4. The average permeation-time profiles of formulation A43, A44, A45, and A46 are not higher than that of formulation A4 (Figure 55), meanwhile, the

average permeation-time profiles of formulation A41, A42 and A47 are higher than formulation A4 as depicted in Figure 56. Thus, there are 3 interesting formulations including A41 (IPM), A42 (IPP) and A47 (Tw) to calculate for the permeation parameters and test for the significant differences. However, there was only one formulation (A47) gave lower lag time than formulation A4.

Table 18 Average cumulative permeation of diltiazem hydrochloride per surface area (mg/cm^2) from the films containing various ratios of HPMC and EC via pig ear skin (n=8).

Time (hours)		Cumulative skin permeation ± SD (mg/cm^2)		
		A1 (10:0)	A4 (8:2)	A5* (6:4)
0		0	0	0
1		0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
2		0.08 ± 0.04	0.08 ± 0.04	0.03 ± 0.01
3		0.18 ± 0.07	0.18 ± 0.08	0.05 ± 0.01
4		0.30 ± 0.10	0.31 ± 0.11	0.06 ± 0.01
6		0.55 ± 0.15	0.54 ± 0.16	0.09 ± 0.03
8		0.77 ± 0.19	0.76 ± 0.15	0.17 ± 0.05
12		1.05 ± 0.29	1.05 ± 0.13	0.35 ± 0.04
Zero order	**r^2****	0.980	0.985	0.960
	Flux (μg/cm^2.hr)**	97	97	34
	Lag time (hours)**	0.75	0.73	2.31
Higuchi's plot	**r^2****	0.997	0.999	0.913

*n=5, ** calculated from time range of 3-12 hours.

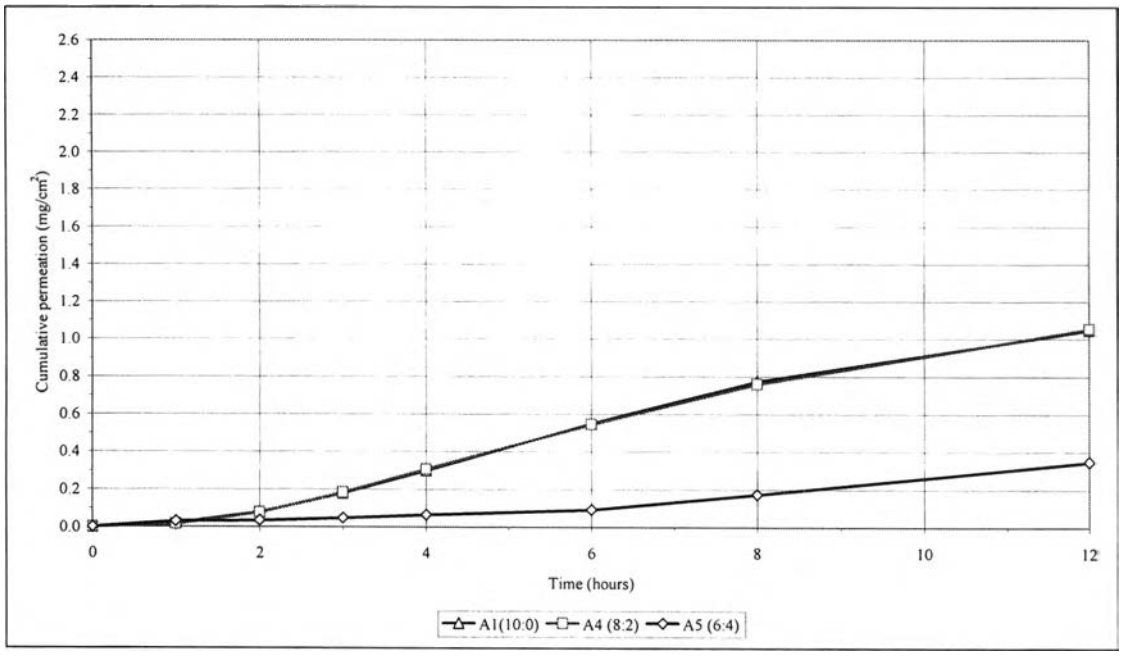

Figure 54 Effect of polymer ratios on average permeation time profiles of diltiazem hydrochloride from the HPMC and EC films.

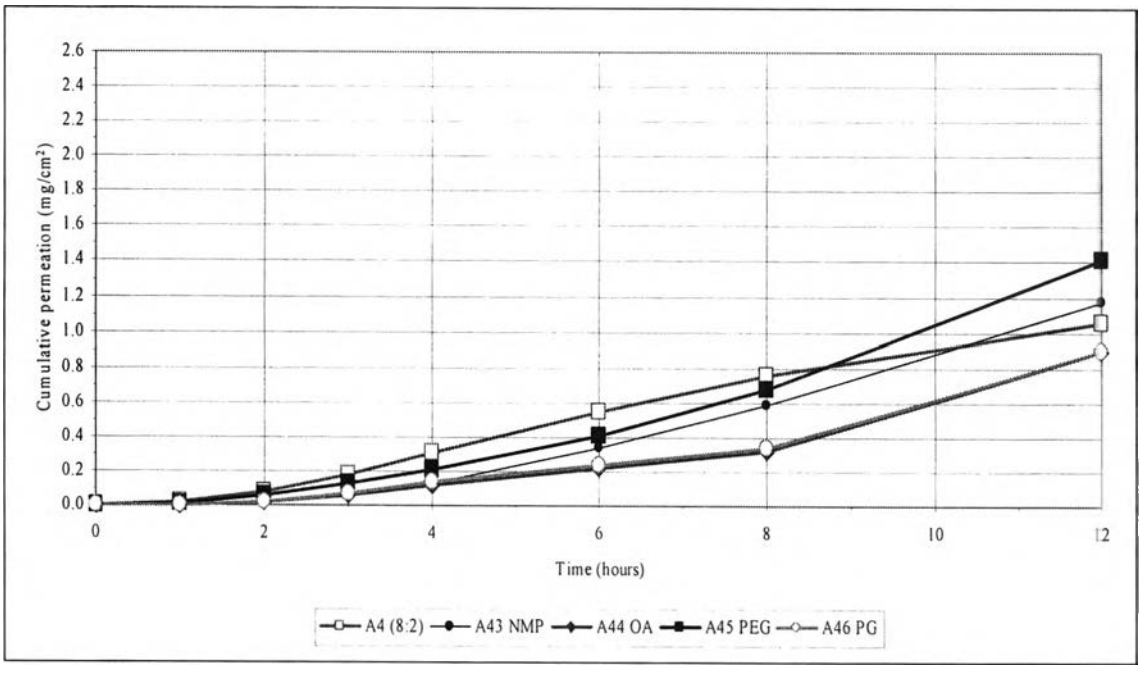

Figure 55 Effect of enhancers (NMP, OA, PEG, and PG) on average permeation-time profiles of diltiazem hydrochloride from the HPMC:EC films at the ratio of 8:2.

Table 19 Average cumulative permeation of diltiazem hydrochloride per surface area (mg/cm^2) from the films containing various ratios of HPMC and EC via pig ear skin (n=4).

Time (hours)		Cumulative skin permeation ± SD (mg/cm^2)						
		A41 IPM	**A42 IPP**	**A43 NMP**	**A44* OA**	**A45 PEG**	**A46* PG**	**A47 Tw**
0		0	0	0	0	0	0	0
1		0.01 ± 0.01	0.01 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.02 ± 0.01
2		0.08 ± 0.04	0.13 ± 0.12	0.02 ± 0.01	0.02 ± 0.01	0.06 ± 0.04	0.02 ± 0.01	0.18 ± 0.05
3		0.29 ± 0.09	0.36 ± 0.27	0.06 ± 0.03	0.06 ± 0.02	0.13 ± 0.08	0.07 ± 0.03	0.39 ± 0.12
4		0.51 ± 0.14	0.60 ± 0.43	0.13 ± 0.04	0.12 ± 0.03	0.21 ± 0.13	0.14 ± 0.05	0.67 ± 0.20
6		1.00 ± 0.20	1.12 ± 0.73	0.33 ± 0.08	0.22 ± 0.06	0.41 ± 0.25	0.24 ± 0.07	1.11 ± 0.27
8		1.51 ± 0.21	1.62 ± 0.93	0.59 ± 0.11	0.32 ± 0.11	0.68 ± 0.38	0.34 ± 0.09	1.46 ± 0.28
12		2.32 ± 0.22	2.48 ± 1.26	1.17 ± 0.13	0.89 ± 0.15	1.42 ± 0.59	0.90 ± 0.19	1.93 ± 0.28
Zero order	**r^2****	0.998	0.998	0.989	0.931	0.978	0.939	0.971
	Flux ($\mu g/cm^2.h$)**	228	238	125	90	144	89	169
	Intercept (hours)**	1.67	1.39	2.93	3.02	2.63	2.82	0.03
Higuchi's plot	**r^2****	0.995	0.996	0.959	0.877	0.940	0.889	0.995

*n=5, **calculated from time range of 3-12 hours.

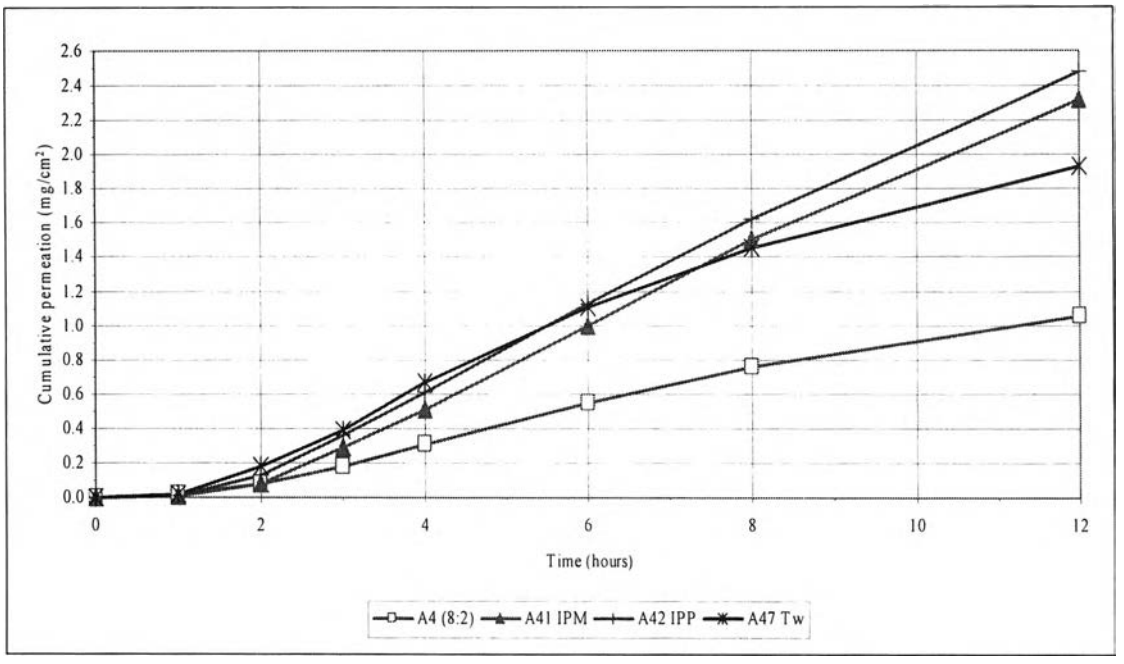

Figure 56 Effect of enhancers (IPM, IPP, and Tw) on average permeation-time profiles of diltiazem hydrochloride from the HPMC:EC films at the ratio of 8:2.

The corresponding permeation parameters of DTZ HCl from the film formulations were calculated and summarized in Table 20 such as steady state flux (J_{ss}) lag time (T_{lag}), apparent diffusivity (D_{ss}), steady state $Q/t^{1/2}$, drug loading dose (L_d), drug solubility in the polymer matrix (C_p), and drug diffusivity in the polymer matrix (D_p).

Table 20 Permeation parameters calculated from permeation time profiles of the film formulations with the selected enhancers including isopropyl myristate, isopropyl palmitate, and Tween 80.

Formulation	J_{ss} ($\mu g/cm^2.hr$)	T_{lag} (hr)	D_{ss} (cm^2/hr)	$Q/t^{1/2}$ ($\mu g/cm^2.hr^{1/2}$)	L_d (mg)	C_p (mg/ml)	D_p (cm^2/hr)
A4	97	0.73	0.009	510	7.6	0.17	0.101
A41 (IPM)	228	1.67	0.004	1,190	15.9	0.38	0.117
A42 (IPP)	238	1.39	0.005	1,240	15.0	0.41	0.128
A43 (Tw)	169	0.03	0.229	890	12.2	0.31	0.108