CHAPTER III

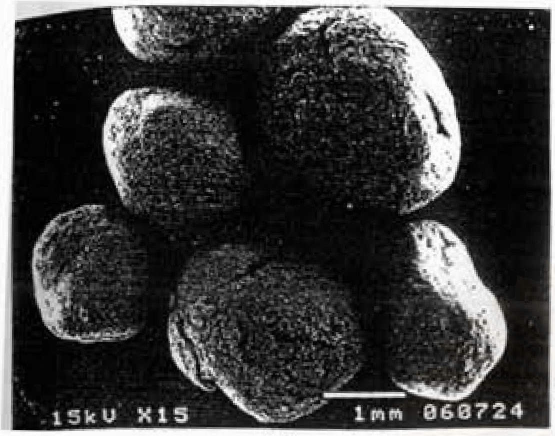
RESULTS

1. Development and Evaluation of Diltiazem HCl Core Pellets

1.1 Organoleptic Properties of Diltiazem HCl Pellets

The photomicrograph of DTZ HCl 90 mg pellets using HPC-M® 2% as a binder and at various amount of water contents range from 40 %(A1), 30 %(A2), 25 % (A3) and 20 %(A4) w/w on a dry basis respectively, are shown in the Figure 19. The pellets used high level of water (Figure 19A1) shows the large size with irregular shape. Figure 19A2 seem to be elliptical in shape and has the size approximately 1 mm. In the case of Figure 19A3 more spherical shape in the size about 1 mm obtained and 25 % moisture content was chosen for the further step of experiment. When water content decreased to 20 % as showed in Figure 19A4, the some dog bone shapes and irregular size pellets resulted. In this case, it is indicated that the water content level may be too low to form spherical pellets since it can be observed that some particles still have short rod shape. The rough surface was also observed on pellets that used low water content (25 % - 20 %). It may be due to the viscosity of binder solution make it unable to completely spread throughout the mass.

After the suitable amount of used water was obtained then various amount of HPC-M® concentrations from 1.5, 1.0, 0.5 and 0.0 % w/w in the formulation were evaluated, in order to achieve more sphere shaped pellets and the results are illustrated in the Figure 20. From the photomicrograph, it was found that the pellets containing a higher amount of HPC-M® showed larger in size as compare to the lower



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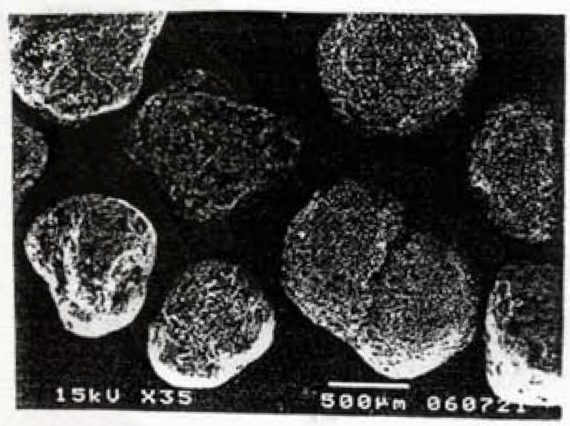

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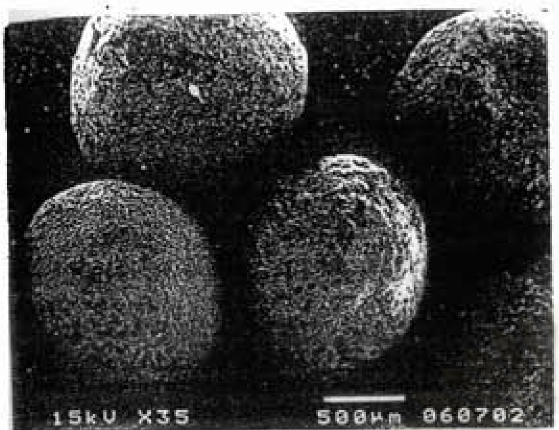
Figure 19. Photomicrographs of DTZ HCl 90 mg pellets using 2% HPC-M® at various amounts of water, and at a spheronization speed of 900±10 rpm for 15 minutes (A1, A2, A3 and A4 are 40%, 30%, 25% and 20% water base on a dry basis at x15 (A1) and x35 magnification)



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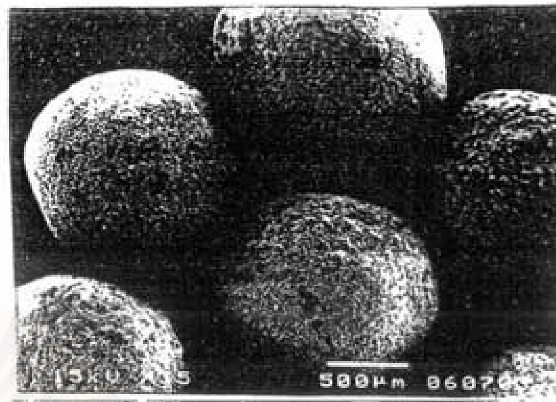

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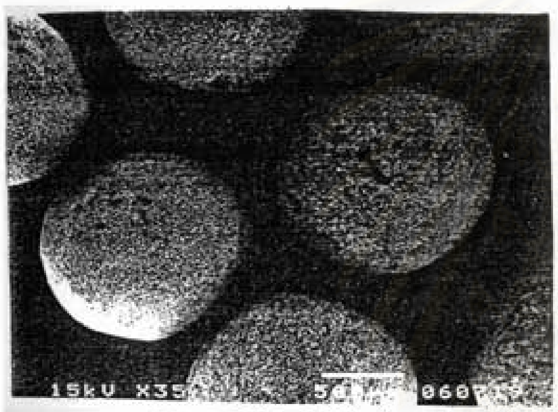

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Figure 20. Photomicrographs of DTZ HCl 90 mg pellets using various concentrations of HPC-M® at 25% water base on a dry basis, and at a spheronization speed of 900±10 rpm for 15 minutes (A1, A2, A3, A4and A5 are 2.0%, 1.5%, 1.0%, 0.5% and 0.0% at x35 magnification)

ones. In addition, a spherical shape with rather smooth surface obtained for all binder concentrations employed. It was noticed that pellets with 0.0 % HPC-M® (Figure 20A5) gave similar in size as pellets containing 0.5 % HPC-M®, however the roundness seem to be less. For the amount of binder studies, 0.5 % HPC-M® formulation (Figure 20A4) gave the most spherical shape pellets. This percentage of HPC-M® in the formula was used in order to formulate the other doses of DTZ HCl pellets (60, 45 and 30 mg) by varying the ratio of DTZ HCl and Avicel® PH 101. It can be seen that, when the amount of water increased the ratio of Avicel® PH 101: DTZ HCl also increased as demonstrated in Figure 21. Because of pellets obtained from this study appeared to be round shape. In term of micro adjustment, scientific confirmation of the sphericity of the pellets was established by using parameters calculated from image analyzer.

1.2 Sphericity of Pellets.

The four characteristics of core pellets i.e., perimeter, area, feretmin and feretmax were measured by optical microscopy and image analyzer. These measured parameters are given in the Table 9. The results of size parameters show that the size of pellets decreased when drug concentration is decreased from 90 mg to 30 mg/150 mg dose. Size data in Table 9 were calculated into six parameter models by using equations that have been referred to emphasis the spherical (circularity, roundness), oblongated (elongation, modelx), elliptical (pellips) or rectangular (rectang) shape of pellets (Hellen and Yliruusi, 1993). These values are presented in the Table 10. The raw data could be seen in the part of Appendices.

From Table 10 and Figure 22 the values of all shape parameter models of each formulations are given and plotted in order to clearly obtain the most spherical

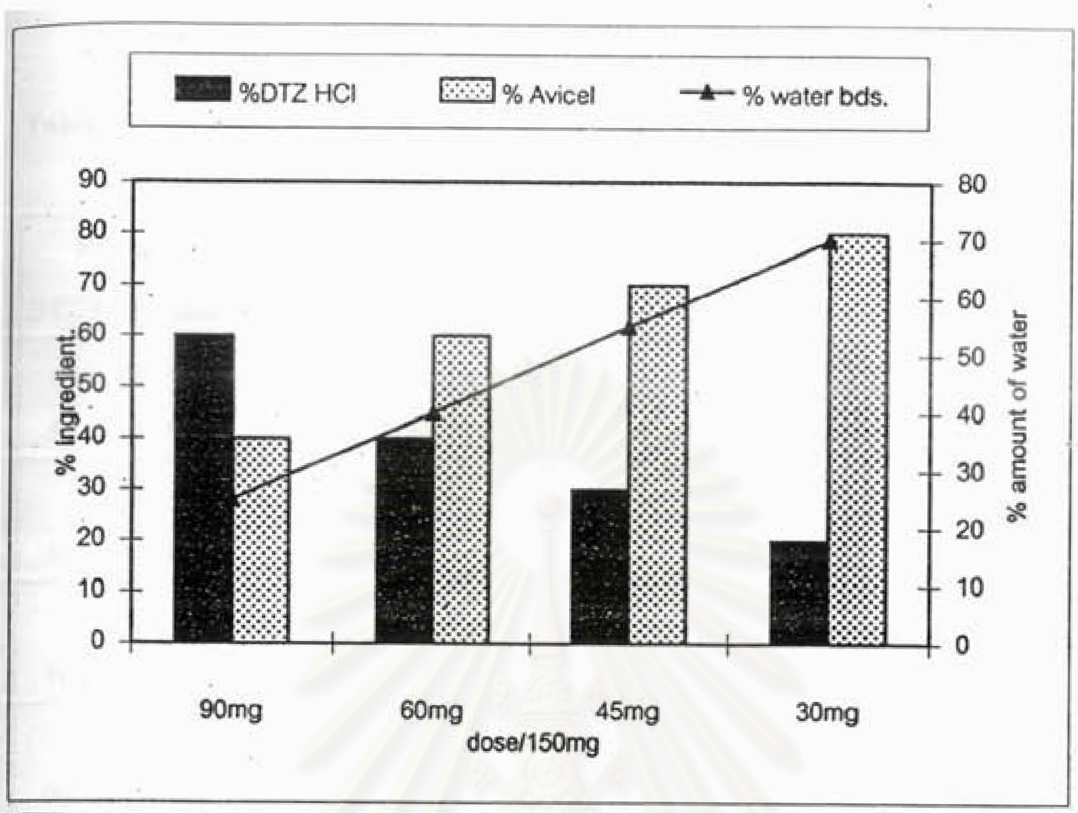


Figure 21. Schematic representation for the effect of varying the ratio of DTZ HC and Avicel PH 101 on the amount of water used.

Table 9. Size data from image analyzer.

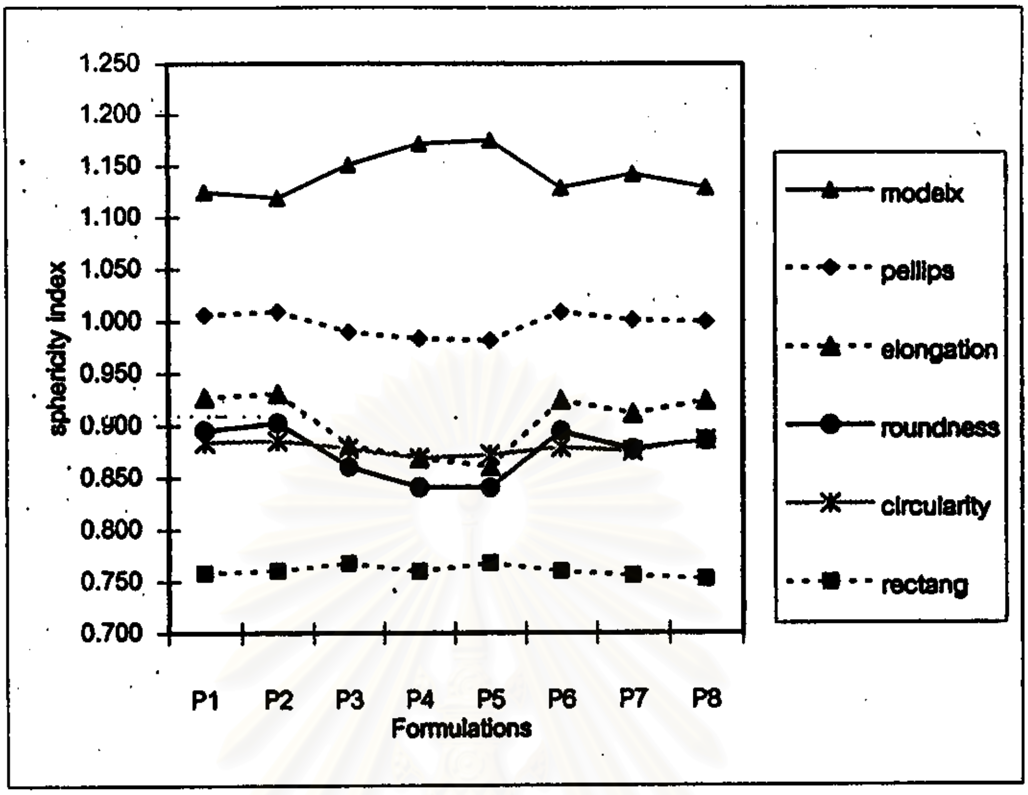
Formula DTZ HCl Pellets	Perimeter (mm) (±S.D.)	Area (mm^2) (±S.D.)	Feretmin (mm) (±S.D.)	Feretmax (mm) (±S.D.)
P1 90 mg 0.0%b.	3.036 (±0.193)	0.651 (±0.081)	0.890 (±0.056)	0.960 (±0.060)
P2 90 mg 0.5%b.	3.297 (±0.161)	0.768 (±0.076)	0.969 (±0.050)	1.040 (±0.051)
P3 90 mg 1.0%b.	3.403 (±0.256)	0.814 (±0.127)	0.964 (±0.087)	1.094 (±0.081)
P4 90 mg 1.5%b.	3.687 (±0.320)	0.947 (±0.166)	1.037 (±0.099)	1.194 (±0.104)
P5 90 mg 2.0%b.	3.548 (±0.486)	0.873 (±0.171)	0.983 (±0.061)	1.152 (±0.166)
P6 60 mg 0.5%b.	3.230 (±0.180)	0.732 (±0.082)	0.942 (±0.053)	1.020 (±0.059)
P7 45 mg 0.5%b.	2.653 (±0.166)	0.492 (±0.062)	0.769 (±0.054)	0.844 (±0.051)
P8 30 mg 0.5%b.	2.378 (±0.114)	0.400 (±0.038)	0.699 (±0.032)	0.757 (±0.038)

** determine from 100 determinations , b. represent for binder (HPC-M®)

Table 10. Comparing shape parameters of pellets with various amounts of binder and active drug.

Formula DTZ HCl Pellets	Sphericity parameter**					
	Circularity	Roundness	Elongation	Pellips	Rectang	Modelx
P1 90 mg 0.0%b.	0.884 (± 0.012)	0.895 (±0.023)	0.927 (±0.024)	1.006 (±0.013)	0.758 (±0.011)	1.125 (±0.018)
P2 90 mg 0.5%b.	0.885 (±0.010)	0.902 (±0.019)	0.931 (±0.020)	1.009 (±0.012)	0.761 (±0.009)	1.119 (±0.013)
P3 90 mg 1.0%b.	0.878 (±0.013)	0.861 (±0.043)	0.881 (±0.051)	0.990 (±0.022)	0.768 (±0.016)	1.151 (±0.035)
P4 90 mg 1.5%b.	0.869 (±0.014)	0.841 (±0.041)	0.869 (±0.044)	0.983 (±0.022)	0.760 (±0.015)	1.171 (±0.034)
P5 90 mg 2.0%b.	0.872 (±0.046)	0.841 (±0.057)	0.861 (±0.063)	0.982 (±0.017)	0.768 (±0.017)	1.175 (±0.121)
P6 60 mg 0.5%b.	0.879 (±0.013)	0.894 (±0.025)	0.925 (±0.029)	1.009 (±0.015)	0.760 (±0.011)	1.129 (±0.020)
P7 45 mg 0.5%b.	0.875 (±0.016)	0.877 (±0.028)	0.911 (±0.029)	1.001 (±0.018)	0.756 (±0.011)	1.142 (±0.022)
P8 30 mg 0.5%b.	0.886 (±0.014)	0.886 (±0.022)	0.924 (±0.021)	1.000 (±0.015)	0.752 (±0.012)	1.129 (±0.016)

** Averaged from 100 determinations, b. represent for binder (HPC-M®)



1 **Figure 22.** The comparing values of shape parameter of each formulation

shape pellets formulation. Along the same line the formulation that has the most spherical shape must offer the sphericity index close to 1 except for the rectang parameter model which exhibits the lowest value of approximately 0.760. In the case of modelx parameter, the obtained values usually greater than 1 but the value close to 1 indicated more spherical in shape. The results from Figure 22 indicate that P2 formulation gives the most spherical shape for DTZ HCl 90 mg/dose pellets and P6, P7 and P8 formulation give the suitable value in order to produce for DTZ HCl 60, 45 and 30 mg/dose pellets, respectively. In addition, Figure 22 also presented the sensitivity of each parameter model because the difference of sphericity value is higher when the shape is changed from the perfect sphere as seen in the modelx, elongation and roundness parameter model. These three shape parameter models are suitable for using in order to evaluate the spherical shape in this study.

1.3 Particle Size Distribution.

Particle size distribution of DTZ HCl pellets in various amounts of binder are presented in Table 11 and Figure 23. The formulations of P1-P6 mostly have the 18 mesh sized pellets. The selected size of pellet used in coating process was between 14/20 mesh cut. In the Figure 24 showed the percent weight retained of 14/20 mesh cut and the rest of pellets that have smaller size than 25 mesh cut in each formulation. It was noticed that P1-P6 have pellet size of 14/20 mesh cut more than 70 % weight retained but P7-P8 have 14/20 mesh size less than 50% weight retained. In addition, the percentage of sieve fraction on 14/20 mesh cut of the formulation can be range as follow: P1 < P2 < P3 < P4 < P5 as the amount of HPC-M® was increased from 0, 0.5, 1.0, 1.5 and 2.0 % w/w, respectively. The above results also showed that sieve fraction on 14/20

Table 11. Sieve analysis of DTZ HCl pellets with various amounts of binder and active drug.

Sieve no.	% weight retained*							
	DTZ90mg (0.0%b) P1	DTZ90mg (0.5%b) P2	DTZ90mg (1.0%b) P3	DTZ90mg (1.5%b) P4	DTZ90mg (2.0%b) P5	DTZ60mg (0.5%b) P6	DTZ45mg (0.5%b) P7	DTZ30mg (0.5%b) P8
14	1.01 (± 0.04)	2.98 (±0.36)	12.57 (±0.40)	29.40 (± 0.77)	32.54 (± 0.80)	0.36 (±0.01)	0.00 (±0.00)	0.00 (±0.00)
18	61.97 (±2.23)	65.39 (±4.80)	71.41 (±2.27)	58.37 (±1.54)	61.48 (±1.51)	58.04 (±1.31)	20.11 (±0.67)	13.52 (±0.38)
20	16.49 (±0.59)	15.25 (±0.78)	5.22 (±0.17)	5.94 (±0.16)	3.34 (±0.58)	19.92 (±0.45)	27.08 (±0.78)	20.64 (±0.57)
14/20Mesh cut	79.47	83.62	89.20	93.71	97.36	78.32	47.20	34.16
25	17.49 (±0.63)	14.85 (±2.29)	10.08 (±1.32)	5.37 (±1.14)	2.08 (±1.05)	19.60 (±3.44)	44.45 (±5.27)	52.18 (±7.45)
30	2.01 (±0.07)	1.12 (±0.96)	0.47 (±0.01)	0.38 (±0.01)	0.31 (±0.01)	1.48 (±0.03)	6.43 (±0.18)	10.35 (±0.29)
Pan	1.02 (±0.04)	0.41 (±0.08)	0.26 (±0.01)	0.55 (±0.01)	0.25 (±0.01)	0.61 (±0.01)	1.92 (±0.05)	3.31 (±0.09)
From25-mesh	20.53	16.38	10.80	6.29	2.65	21.68	52.80	65.84
Total	100	100	100	100	100	100	100	100

* Averaged from 2 determinations, b. represent for binder (HPC-M®)

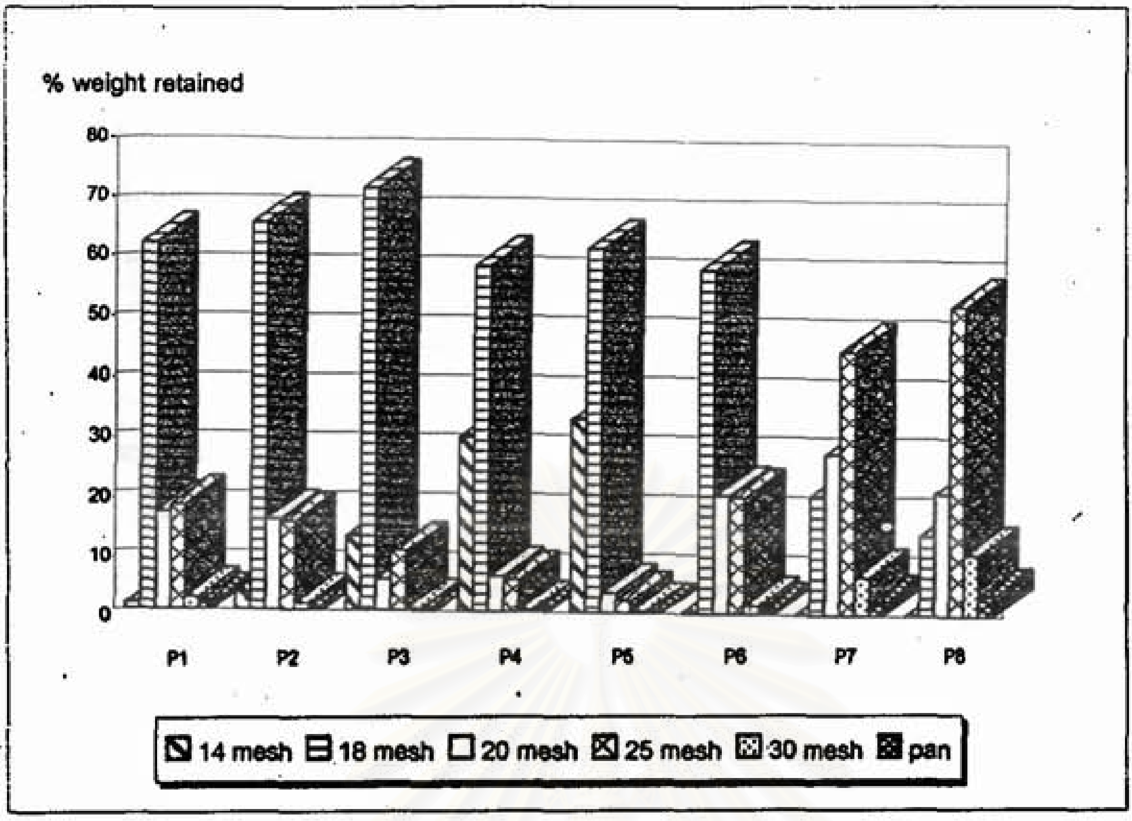


Figure 23. Percentage of sieve fraction on 14-30 mesh of various formulations.

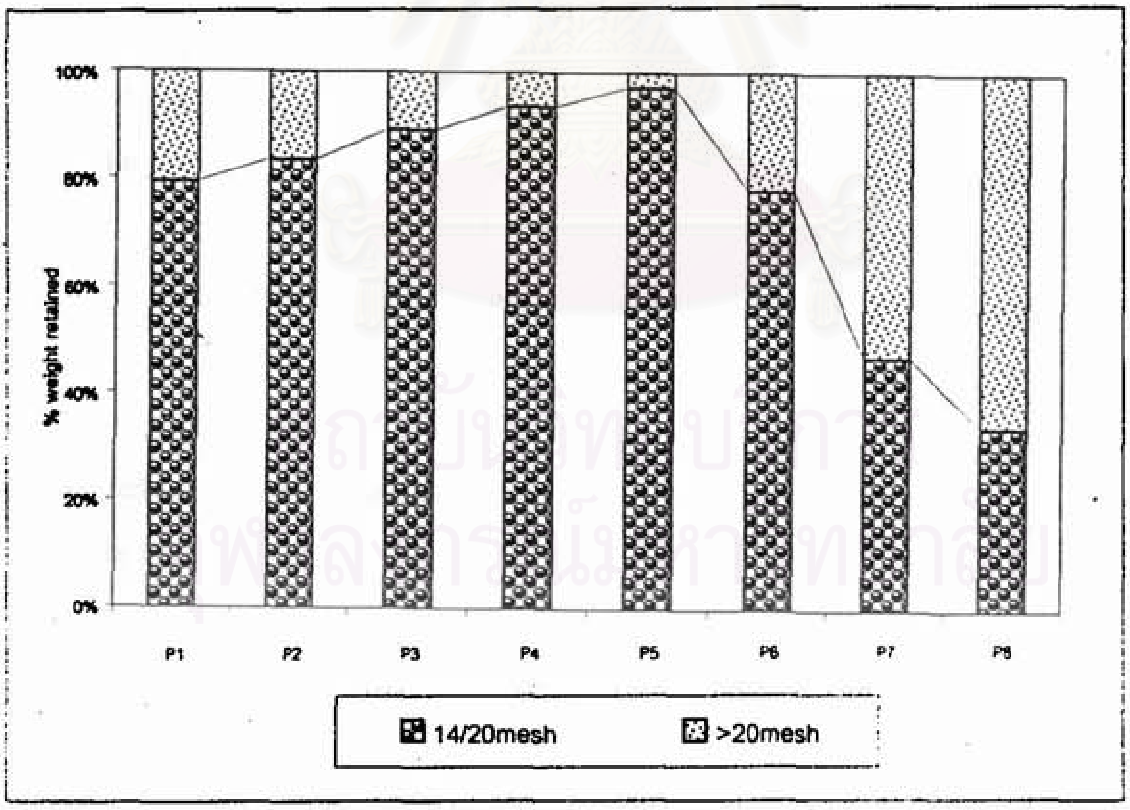


Figure 24. The ratio of percentage of sieve fraction on 14/20 mesh cut and >20 mesh cut of various formulations.

mesh cut related to drug concentration, when the amounts of drug decreased from 60 %, 40 %, 30 % and 20% which are equivalent to DTZ HCl 90(P2), 60(P6), 45(P7) and 30 (P8) mg, respectively.

1.4 Bulk Density, Tapped Density and Carr's Compressibility Determination.

Bulk volume and tapped volume of DTZ HCl pellets in any formulations were recorded from the experiments. In the case of bulk density, tapped density and % Carr's compressibility were calculated from the data obtained. The results are showed in Table 12. Bulk volume and tapped volume of formulation P1 had the highest value and P5 had the lowest one. On the other hand bulk density and tapped density compared for 5 formulations of DTZ HCl 90 mg pellets, the results are given as follows: P1 $<$ P2 $\approx$ P3 $\approx$ P4 $<$ P5, respectively. Bulk density and tapped density when compared P2 with P6, P7 and P8. The results are presented in the following orders: P2 $\approx$ P7 $<$ P6 $<$ P8. In the case of, Carr's index of 8 formulations had the range from 4.23 – 7.50.

1.5 Flow rate and Angle of repose determination.

Angles of repose is the best known as flow property of dry substance was studied and can be represented in each formulation. The results are presented in the Table 13.

When the angles of repose and flow rates of DTZ HCl 90 mg pellets (P1-P5) were compared, found that P2 had the highest flow rate of 309.2 g/min and the lowest angle of repose of 20.82 degree. For angle of repose the order are: P4 $>$ P3 $>$

Table 12. Bulk volumes/densities, tapped volumes/densities and Carr's compressibility of prepared pellets.

Formula DTZ HCl Pellets	Bulk vol. (cm^3)*	Tapped vol. (cm^3)*	Bulk d. (g/cm^3)*	Tapped d. (g/cm^3)*	% Carr's * Compressibility
P1 90 mg.(0.0%binder.)	62.67 (±0.58)	58.33 (±0.00)	0.64 (±0.01)	0.69 (±0.01)	6.85 (±1.67)
P2 90 mg.(0.5%binder)	60.00 (±0.00)	57.00 (±0.58)	0.67 (±0.00)	0.70 (±0.01)	4.35 (±1.37)
P3 90 mg.(1.0%binder)	60.00 (±0.00)	57.00 (±0.00)	0.67 (±0.00)	0.70 (±0.00)	4.29 (±0.00)
P4 90 mg.(1.5%binder)	61.00 (±0.00)	57.67 (±1.00)	0.66 (±0.00)	0.69 (±0.01)	4.29 (±0.79)
P5 90 mg.(2.0% binder)	58.67 (±0.58)	55.00 (±0.58)	0.68 (±0.01)	0.73 (±0.00)	7.25 (±0.79)
P6 60 mg.(0.5%binder.)	59.00 (±0.00)	56.67 (±0.58)	0.68 (±0.00)	0.71 (±0.01)	4.23 (±0.79)
P7 45 mg.(0.5%binder.)	55.33 (±0.58)	52.00 (±0.00)	0.72 (±0.01)	0.77 (±0.00)	6.49 (±1.50)
P8 30 mg.(0.5%binder.)	54.00 (±0.00)	50.00 (±0.00)	0.74 (±0.00)	0.80 (±0.00)	7.50 (±0.00)

* Averaged from 3 determinations, binder is HPC-M®

Table 13. Flow rate and angle of repose of prepared pellets.

No. DTZ HCl Pellets	Angle of repose (degrees)** (±S.D.)	Flow rate(g/min)** (±S.D.)
P1 90 mg.(0.0%binder.)	20.92 (±0.26)	295.12 (±4.22)
P2 90 mg.(0.5%binder)	20.82 (±0.12)	309.02 (±2.31)
P3 90 mg.(1.0%binder)	23.88 (±0.14)	264.73 (±3.35)
P4 90 mg.(1.5%binder)	24.11 (±0.55)	263.8 (±2.90)
P5 90 mg.(2.0% binder)	20.93 (±0.05)	300.00 (±0.00)
P6 60 mg.(0.5%binder.)	20.91 (±0.07)	281.26 (±1.90)
P7 45 mg.(0.5%binder.)	19.68 (±0.41)	305.13 (±4.44)
P8 30 mg.(0.5%binder.)	18.38 (±0.38)	421.14 (±7.39)

** Averaged from 3 determinations, binder is HPC-M®.

$P5 \approx P1 > P2$. In the case of flow rate, $P4 < P3 < P5 < P1 < P2$. Comparing angle of repose between drug concentration which equivalent to DTZ HCl 30(P8), 45(P7), 60(P6) and 90(P2) mg pellets, respectively. The results indicate that $P6 \approx P2 > P7 > P8$, for flow rate, $P6 < P7 < P2 < P8$.

1.6 Percent Friability.

Friability test was implied to determine the strength of pellets that was able to tolerate the stress from following processes such as coating process. The result is shown in the Table 14. The friability of all formulations showed very low values which range from 0.016 to 0.067 % and standard deviation between two parallel measurements are 0.001-0.021, respectively.

1. 7 *Moisture content.*

The moisture content of each formulation is also shown in the Table 14. The results of moisture content of prepared pellets from this Table shows that moisture content of $P8 > P7 > P6 > P1 \approx P2 \approx P3 \approx P4 \approx P5$, respectively. It was noticed that the moisture content left in the core was high or low depending on the amount of water employed in preparing process because the drying period was set as constant (6 hours).

Table 14. Percent friability and moisture content of prepared pellets.

Formula DTZ HCl Pellets	% Friability**		Moisture content**	
	Average	S.D.	Average	S.D.
P1) 90 mg.0.0% HPC-M®	0.0670	0.0212	1.14	0.026
P2) 90 mg.0.5% HPC-M®	0.0475	0.0064	1.21	0.015
P3) 90 mg.1.0% HPC-M®	0.0270	0.0085	1.18	0.038
P4) 90 mg.1.5% HPC-M®	0.0640	0.0042	0.99	0.022
P5) 90 mg.2.0% HPC-M®	0.0205	0.0007	1.25	0.02
P6) 60 mg.0.5% HPC-M®	0.0260	0.0028	1.42	0.017
P7) 45 mg.0.5% HPC-M®	0.0160	0.0071	1.75	0.025
P8) 30 mg.0.5% HPC-M®	0.0485	0.0021	1.95	0.032

** Averaged from 2 determinations

2. Physical Properties of Selected DTZ HCl Core Pellets Formulation

Physical properties of uncoated DTZ HCl pellets are presented in Table 15. Figures 25-27 show the physical appearance of selected core pellets. All of DTZ HCl concentration between 30-90 mg used in this study can prepare the sphericle pellets. However, low drug concentration pellets seem to have smaller size than higher drug concentration as shown in Figure 25. The narrow size distribution was observed from 90 and 60 mg/150 mg dose pellets which ranged from 14/20 mesh cut was 83.62 % and 78.32 %, respectively. For 45 and 30 mg/150 mg dose pellets, size distribution fell into 18/25 mesh cut, the amount was 91.65 % and 86.34 %, respectively. However, The desired size of 14/20 mesh cut was 47.20 % and 34.16 %, respectively. These indicated that the mean particle size of low dose DTZ HCl pellets was lower than high dose. The pellets obtained show good flow properties of greater than 263.8 mg/min and also indicated by low angle of repose. In addition, the percent friability was very low.

3. Evaluation of Film Casting

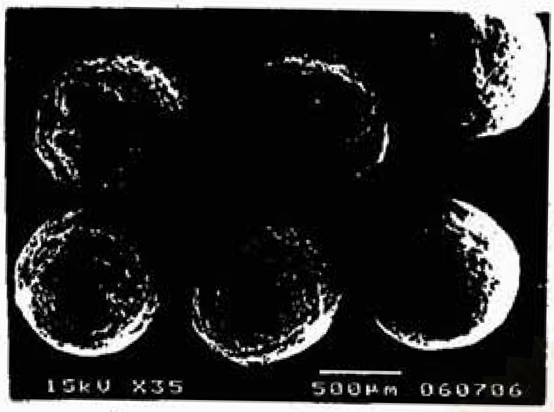
Free film of EC formulations were pre-evaluated by pour plate method and found that after drying in hot air oven all prepared films were colorless transparent, except for Formula 2. It appeared to be white, turbid and took several minutes of film to peel off the plate by itself. This formula wasn't selected for tensile strength measurement because of its unsatisfied characteristic.

The thickness of each casting film was ranged from 0.048-0.077 mm. In film casting solution with single solvent, anhydrous ethyl alcohol or methylene chloride gave the lowest and the highest thickness respectively. However, for mixed solvent, anhydrous ethyl alcohol with methylene chloride 50:50 v/v, gave the short range of

Table 15. Physical properties of uncoated DTZ HCl pellets.

Physical Properties	Equivalent dose per 150 mg pellets			
	90 mg	60mg	45mg	30mg
1.sphericity (a)				
1.1 Circularity	0.885±0.01	0.879±0.013	0.875±0.016	0.886±0.014
1.2 Roundness	0.902±0.019	0.894±0.025	0.877±0.028	0.886±0.022
1.3 Elongation	0.931±0.020	0.925±0.029	0.911±0.029	0.924±0.021
1.4 Pellips	1.009±0.012	1.009±0.015	1.001±0.018	1.000±0.015
1.5 Rectang	0.761±0.009	0.760±0.011	0.756±0.011	0.752±0.012
1.6 Modelx	1.119±0.013	1.129±0.020	1.142±0.022	1.129±0.016
2. % weight retained on (b)				
sieve no. 14	2.98	0.36	0.00	0.00
18	65.39	58.04	20.11	13.52
20	15.25	19.92	27.08	20.64
25	14.85	19.60	44.45	52.18
30	1.12	1.48	6.43	10.35
pan	0.41	0.61	1.92	3.31
% sieve fraction on 14/20 mesh cut pellets	83.62	78.32	47.20	34.16
3. Bulk density (c)	0.67	0.68	0.72	0.74
4. Tapped density (c)	0.70	0.71	0.77	0.80
5. Carr's index (c)	4.35	4.23	6.49	7.50
6. Angle of repose (c)	20.82±0.12	20.91±0.07	19.68±0.41	18.38±0.38
7. Flow rate (c)	309.02±2.31	281.26±1.90	305.13±4.44	421.14±7.39
8. % Friability (b)	0.0475±0.0212	0.0260±0.0028	0.0160±0.0071	0.0485±0.0021
9. % Moisture content (b)	1.210±0.015	1.512±0.017	1.82±0.025	2.16±0.032

(a) average from 100 determinations, (b) average from 2 determinations, (c) average from 3 determinations.



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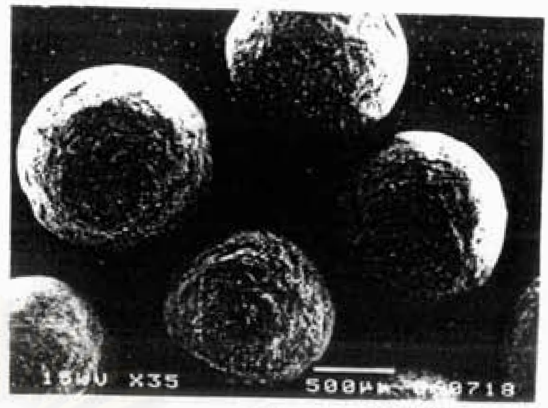

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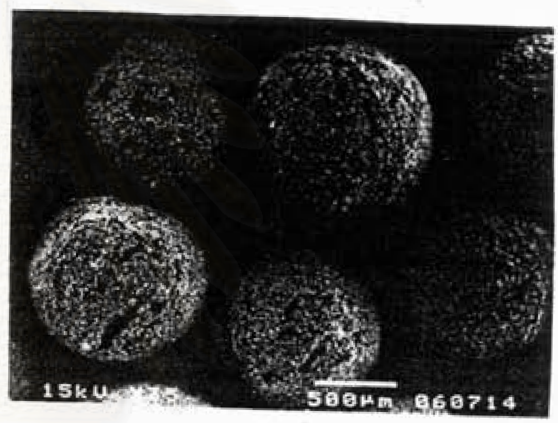

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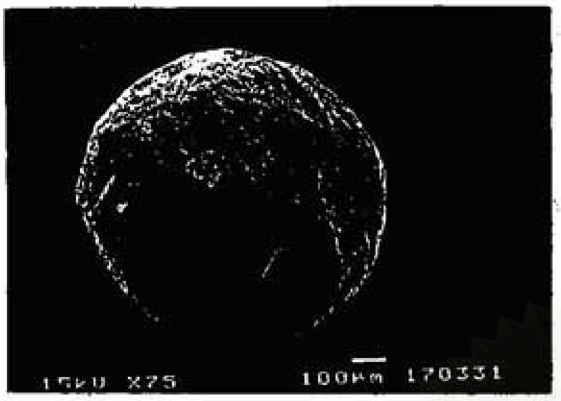
Figure 25. Photomicrographs of various DTZ HCl concentrations pellets at 0.5% HPC-M®, and amount of water are 25, 40, 55 and 70 % at a spheronization speed of 900±10 rpm for 15 minutes (A1, A2, A3 and A4 are 30 mg, 45 mg, 60 mg and 90 mg at x35 magnification)



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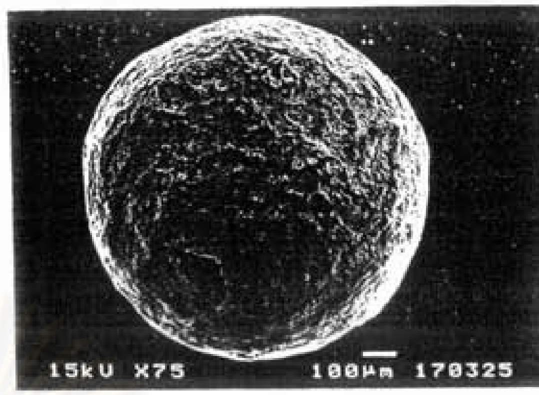

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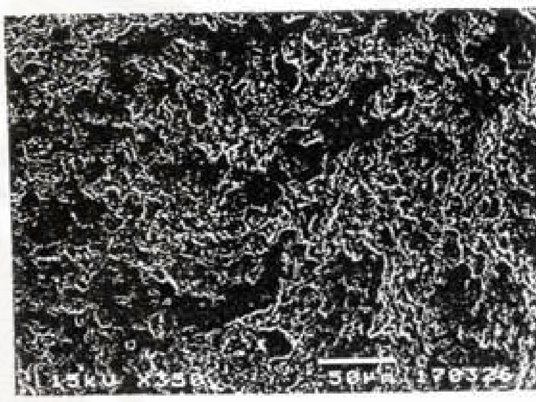

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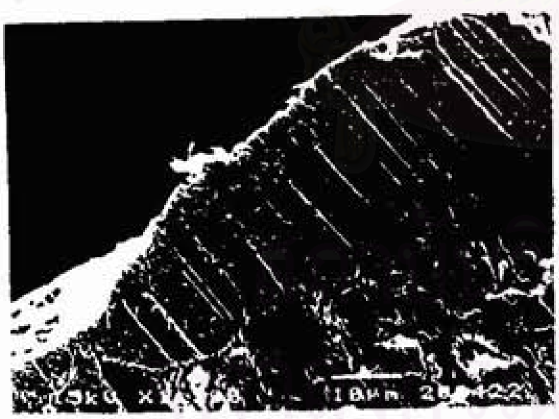
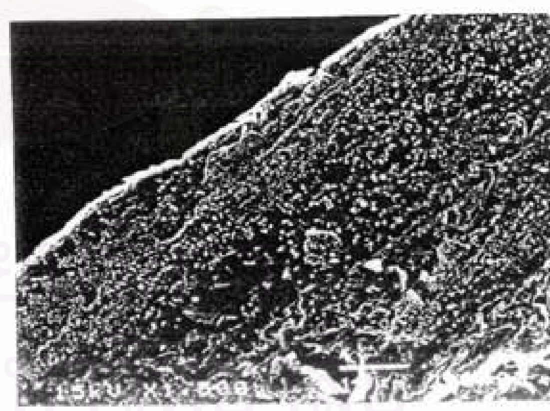
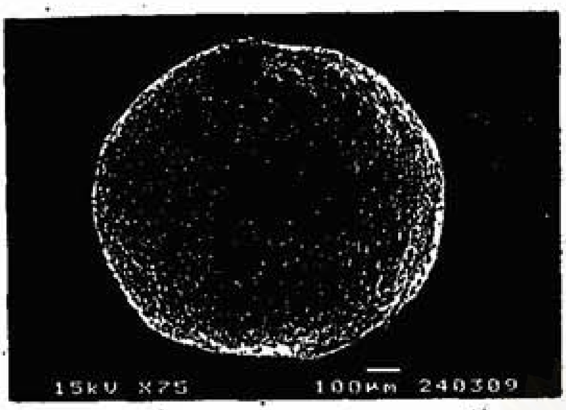


A3

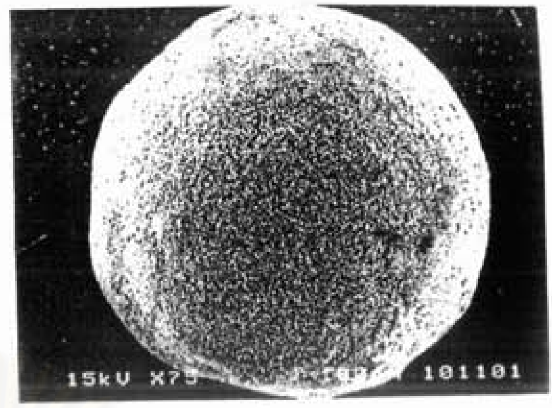


B3

Figure 26. Photomicrographs of uncoated DTZ HCl pellets (A1, A2, A3 are DTZ HCl 30 mg pellets at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are DTZ HCl 45mg pellets at x75, x350, x1500 (cross-section) magnification).

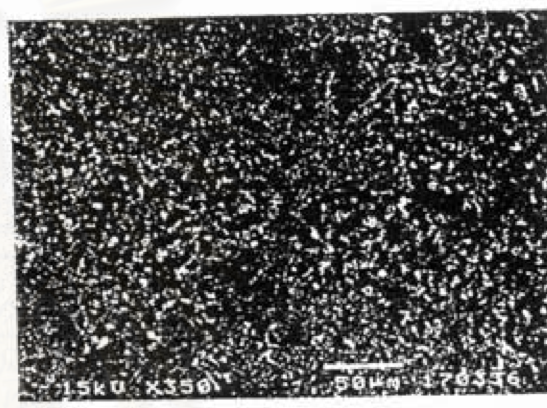


A1

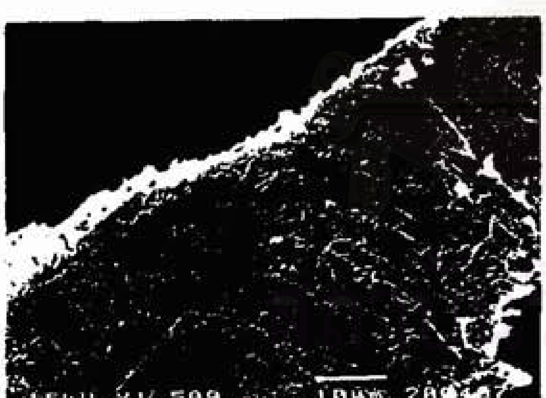


B1

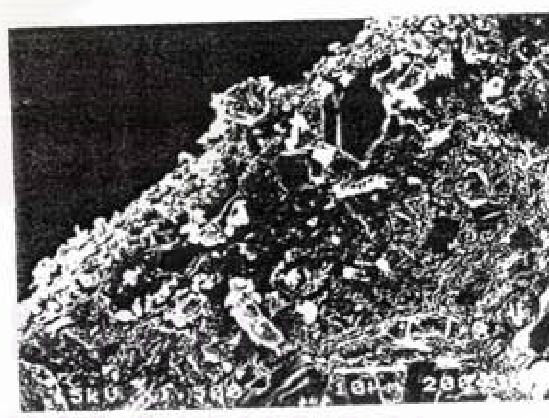
A2



B2



A3



B3

Figure 27. Photomicrographs of uncoated DTZ HCl pellets (A1, A2, A3 are DTZ HCl 60 mg pellets at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are DTZ HCl 90mg pellets at x75, x350, x1500 (cross-section) magnification).

thickness around 0.05-0.06 mm except for the film plasticized by castor oil had 0.069 – 0.073 mm. The mechanical properties of free film are shown in the Table 16. Figures 28-31 present the ultimate tensile strength, % elongation to break, Young's modulus of elasticity and toughness. The above results are compared between each formulation studied. The effect of types and amounts of plasticizer used on mechanical properties of free film are shown in the Figures 32-35. The results of varying amount of plasticizer showed that when increase the amount of the same type of plasticizer used in the film, the ultimate tensile strength and Young's modulus of elasticity were decreased, whereas % elongation at break was increased. However toughness values of film seem to be varied. The results of varying type of plasticizer used in the film showed that TEC affect the ultimate tensile strength and Young's modulus of elasticity more than CO and DEP, respectively. However % elongation at break was affected by CO > TEC > DEP, respectively. Toughness values of film seem to be affected by following: CO > TEC ≈ DEP. Stress-strain curve of tested free film formulation can be available in the part of Appendices. The amount of plasticizer at 20 % level on dry polymer's weight indicated, the ultimate tensile strength and Young's modulus of elasticity found to be DEP > CO ≈ TEC. In the case of % elongation at break and toughness of free film the order are: CO > TEC > DEP, respectively.

The effect of type of plasticizer on mechanical properties of EC free film was evaluated accompanied with release studying and the results are given in Figure 36. DTZ HCl 90 mg pellets was coated with EC film that plasticized with 20% of CO, DEP and TEC, respectively at 5 % w/w coating level. The release profile showed that CO suppress the releasing of DTZ HCl more than other plasticizers follow by DEP and TEC, respectively.

Table 16. Mechanical properties of free film.

Formulas	Thickness* (mm)	Ultimate Tensile Strength* (MPa)	%elongation at break*	Young's modulus* (MPa)	Toughness* (MPa)
1	0.053 (±0.005)	8.800 (±0.256)	0.911 (±0.055)	993.723 (±53.415)	0.042 (±0.004)
2**	N/A	N/A	N/A	N/A	N/A
3	0.06 (±0.003)	20.134 (±0.884)	3.815 (±0.388)	730.257 (±53.156)	0.485 (±0.095)
4	0.055 (±0.003)	14.689 (±1.037)	5.696 (±0.299)	564.461 (±53.786)	0.631 (±0.076)
5	0.057 (±0.003)	5.386 (±0.947)	8.965 (±0.770)	205.580 (±20.636)	0.421 (±0.050)
6	0.052 (±0.004)	19.997 (±1.258)	2.925 (±0.246)	802.741 (±29.022)	0.328 (±0.053)
7	0.050 (±0.003)	17.680 (±0.793)	3.851 (±0.216)	682.246 (±44.234)	0.435 (±0.036)
8	0.052 (±0.004)	16.880 (±1.878)	5.436 (±0.574)	589.723 (±72.906)	0.669 (±0.131)
9	0.069 (±0.005)	23.428 (±1.742)	6.558 (±0.544)	784.557 (±77.056)	1.155 (±0.132)
10	0.072 (±0.003)	15.704 (±0.550)	6.075 (±0.684)	576.774 (±48.454)	0.716 (±0.087)
11	0.073 (±0.005)	9.814 (±0.642)	16.344 (±1.164)	312.605 (±18.966)	1.524 (±0.134)

* Averaged from 6 determinations, **N/A (not available)

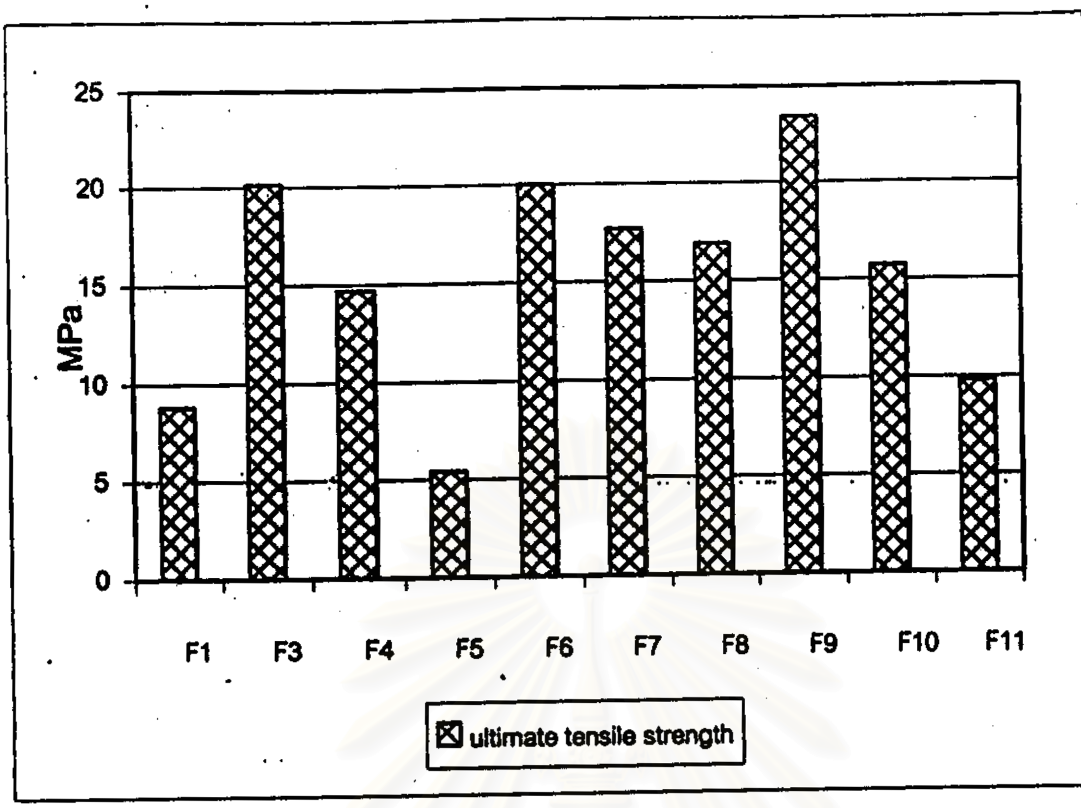


Figure 28. Ultimate tensile strength of films in each formulation.

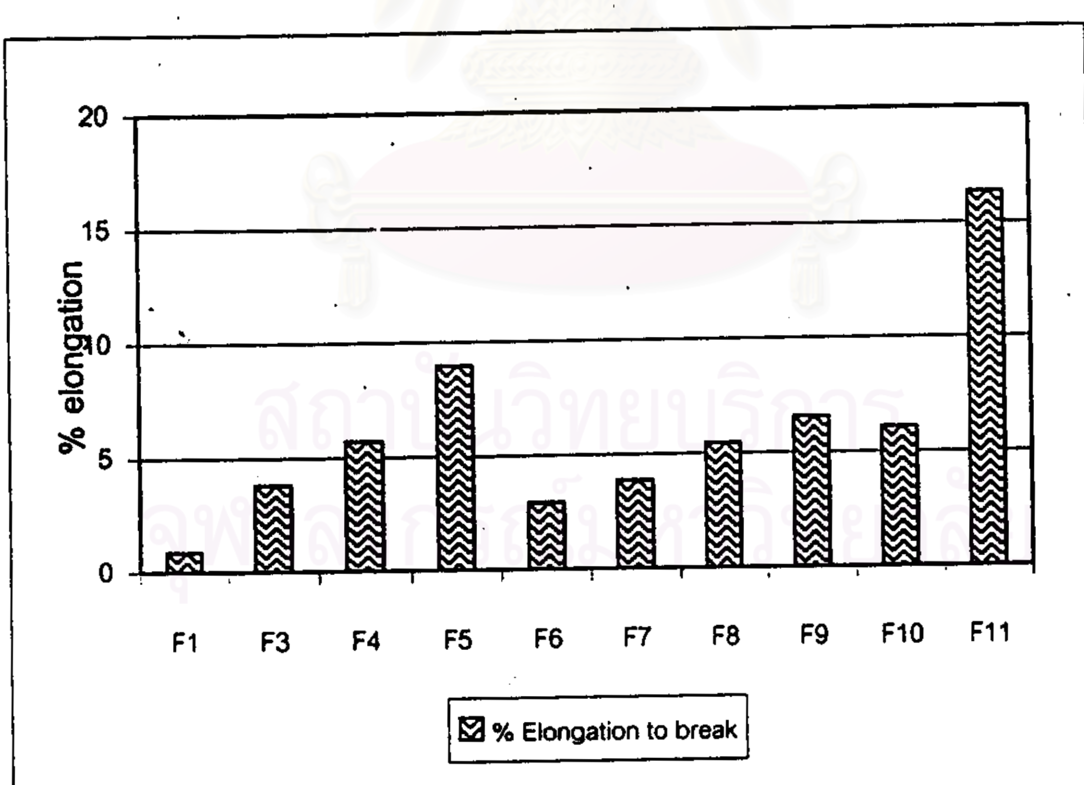


Figure 29. Percent elongation of films before breaking in each formulation.

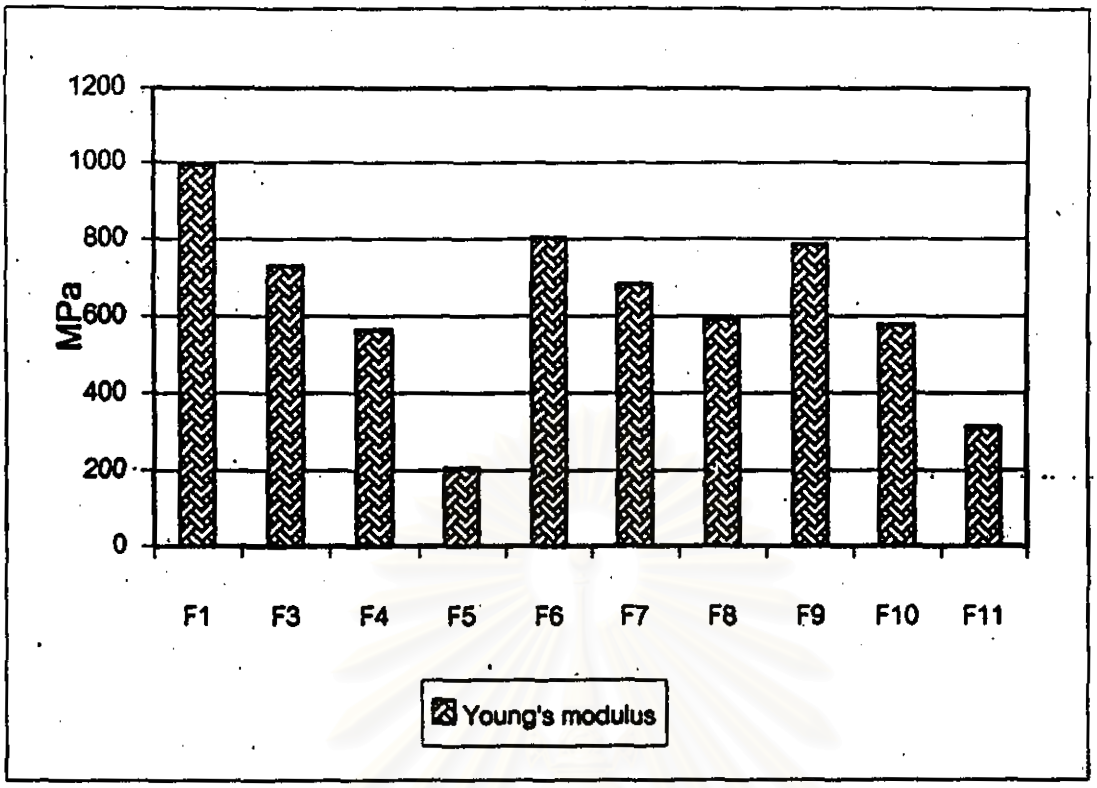


Figure 30. Young's modulus of films in each formulation.

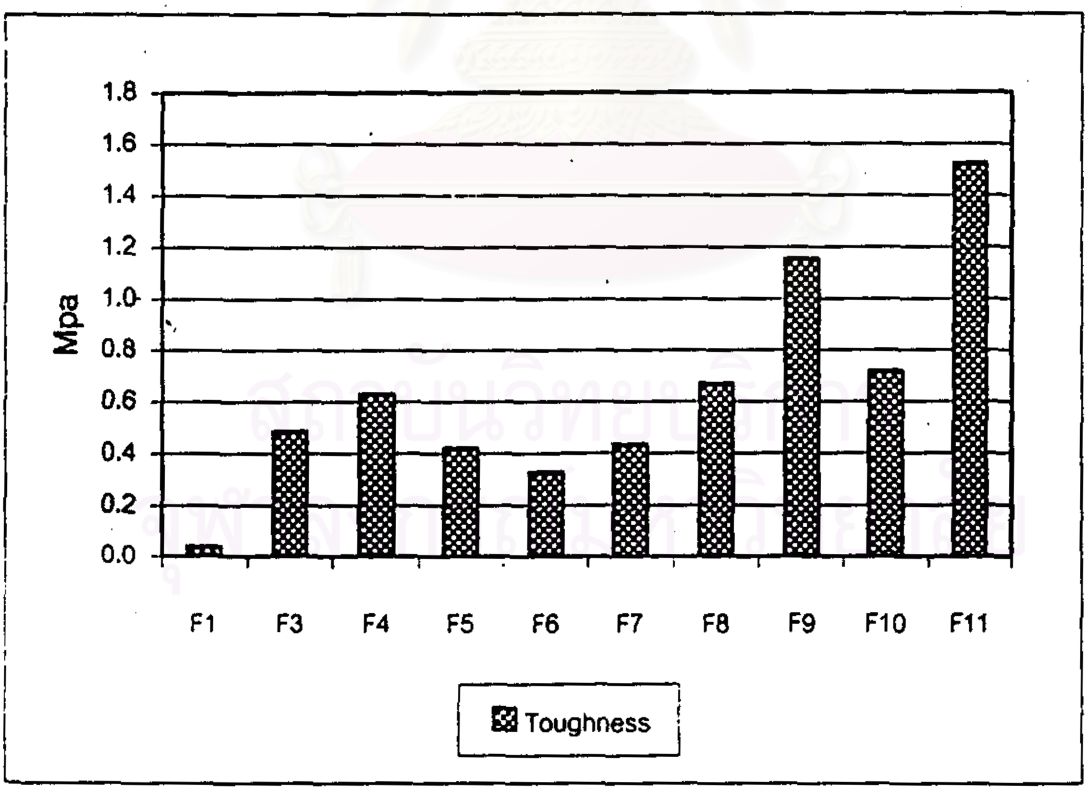


Figure 31. Toughness of films in each formulation.

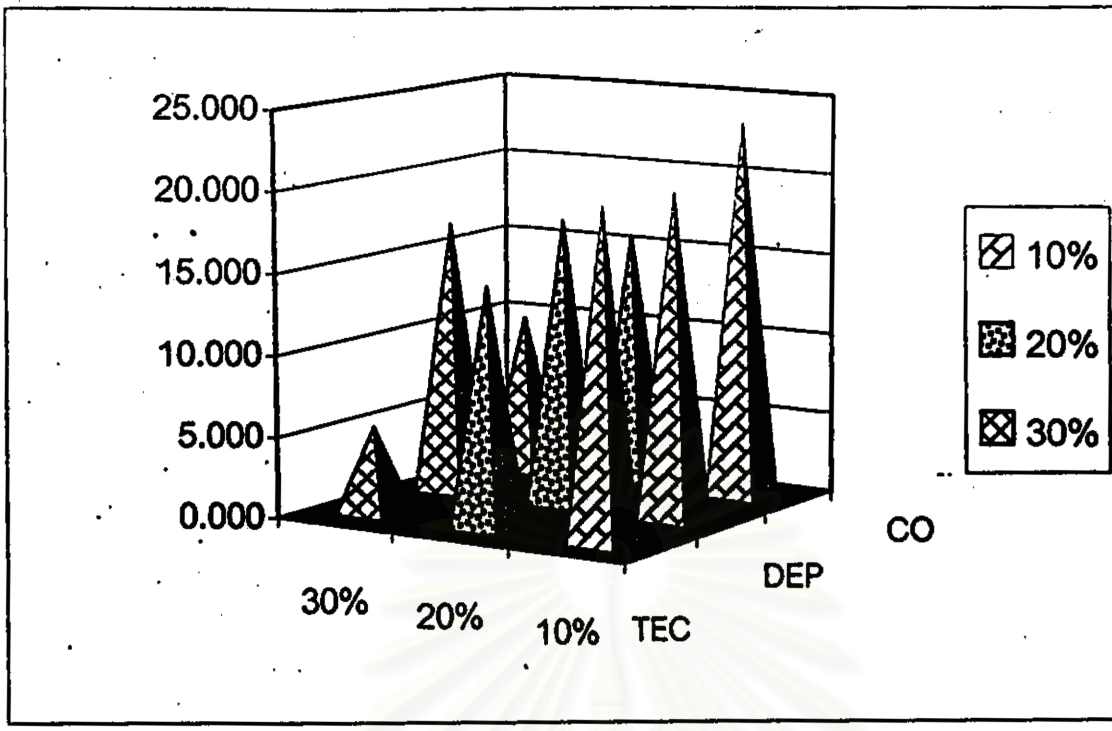


Figure 32. Ultimate tensile strength of EC film at various amounts and types of platicizer.

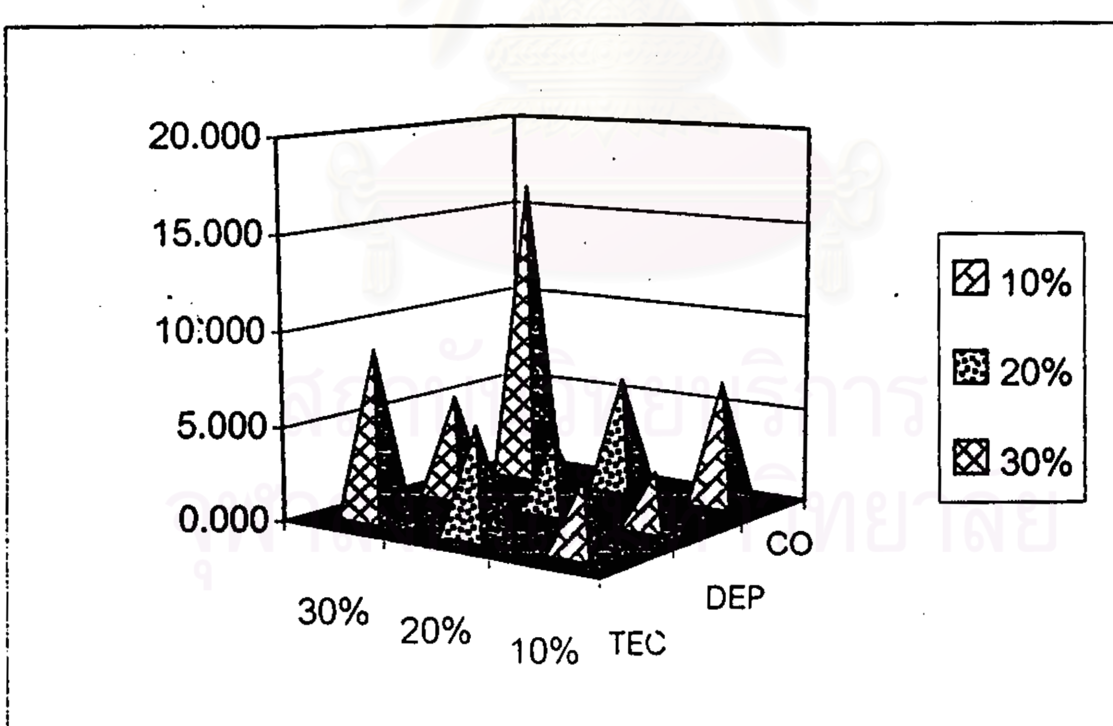


Figure 33. Percent elongation of breaking EC film at various amounts and types of platicizer.

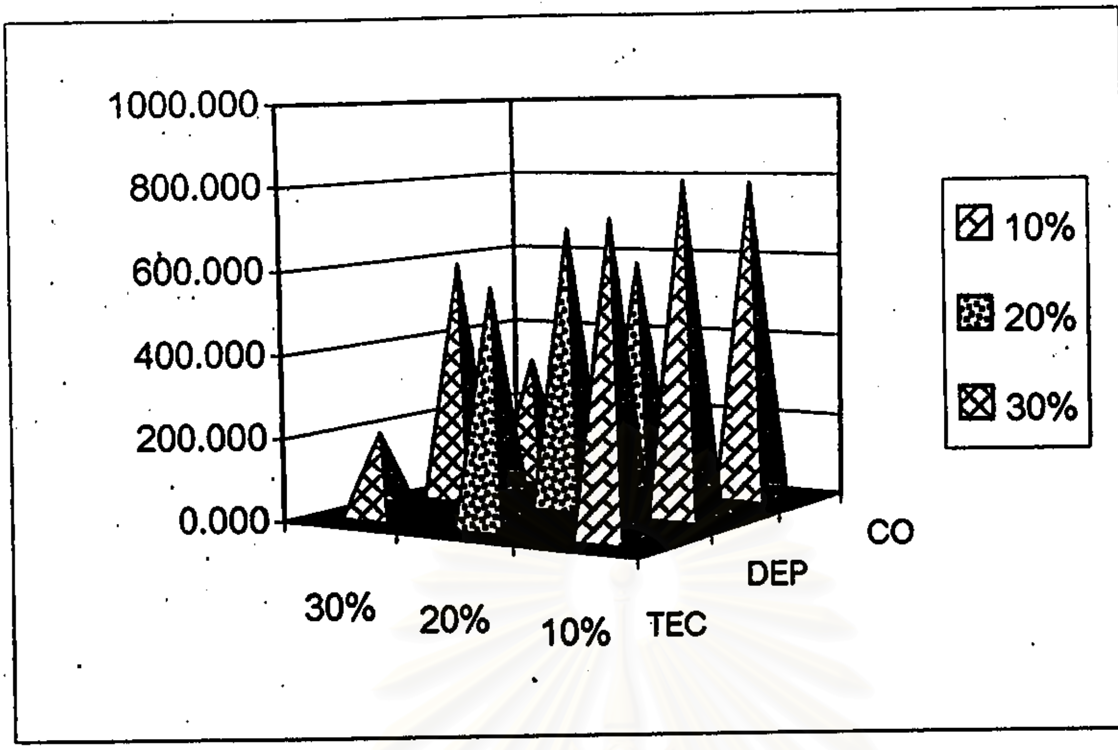


Figure 34. Young's modulus of EC film at various amounts and types of platicizer.

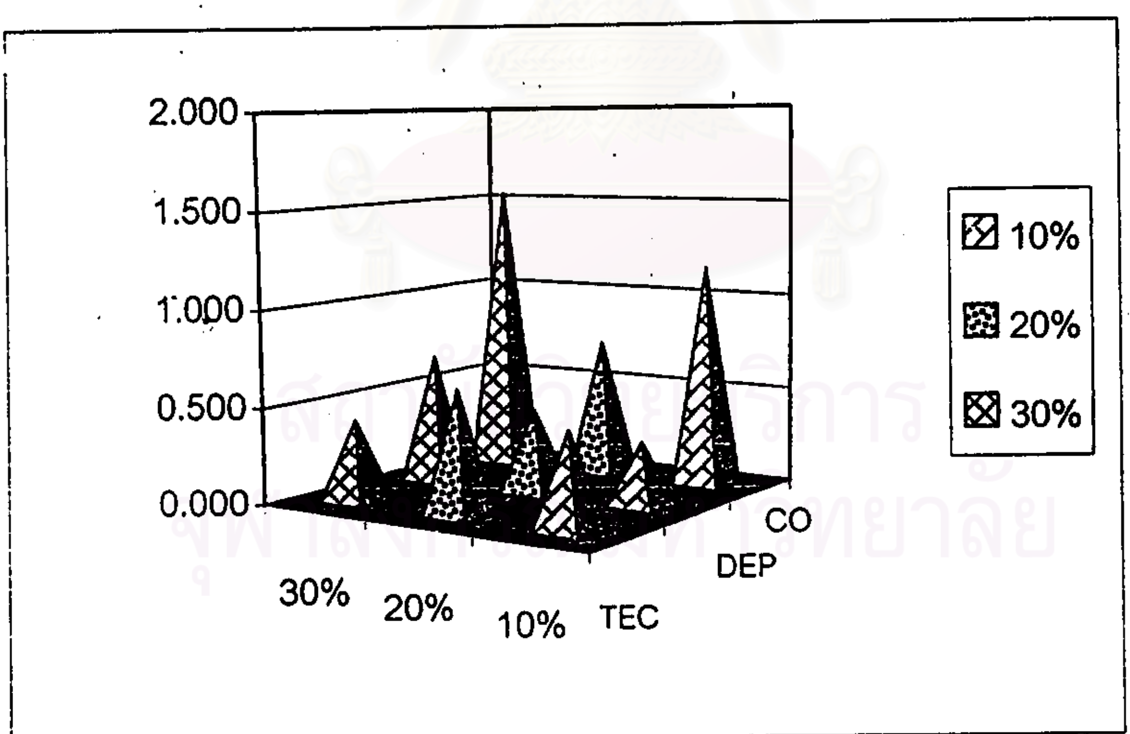


Figure 35. Toughness of EC film at various amounts and types of platicizer.

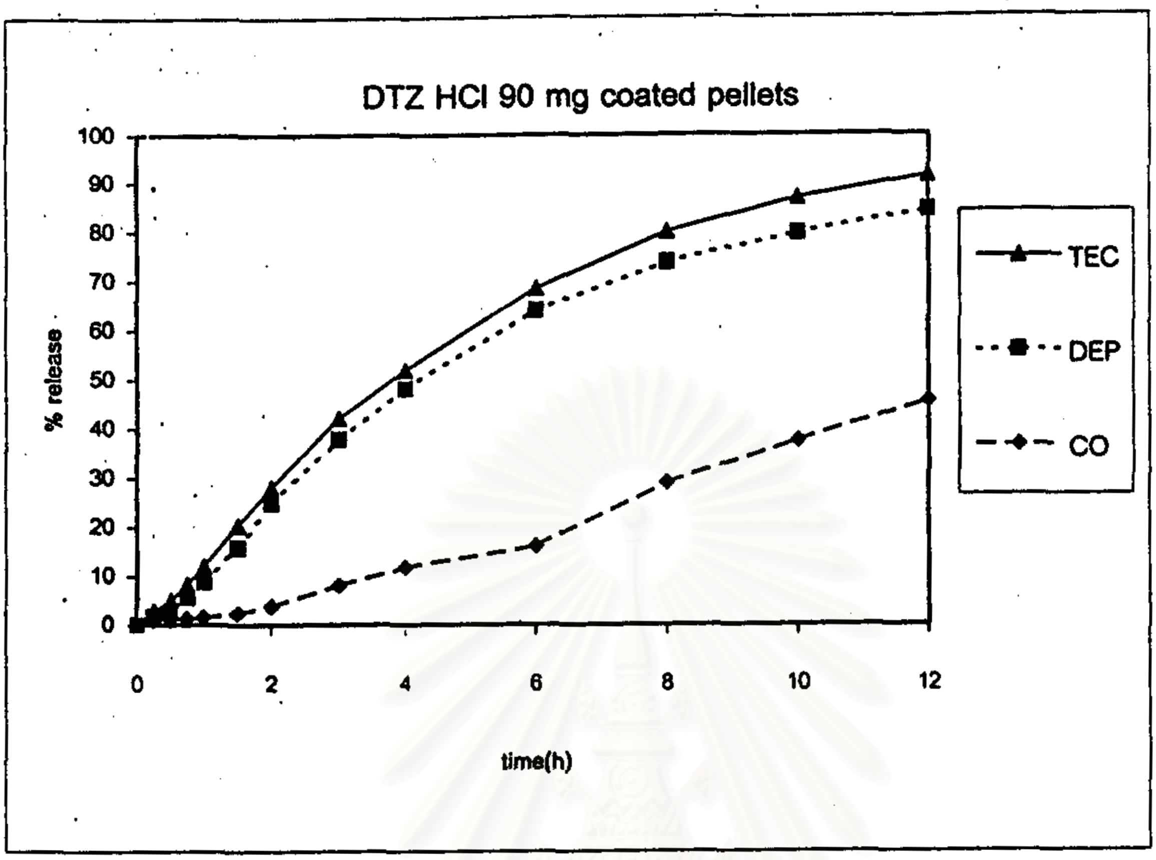


Figure 36. Dissolution profiles of DTZ HCl from pellets coated with EC film plasticized with 20 % of vaious types of plasticizer and at 5 % coating level.

From overall results of studied, TEC seem to be the best which gave the suitable film strength, Young's modulus of elasticity, toughness and process convenient during application when compared to the others.

4. Development of Controlled release DTZ HCl Pellets

4.1 Dissolution Profiles of Uncoated DTZ HCl Pellets

The content of all uncoated and coated pellet formulations were assayed before dissolution test and the results are shown in the Tables d1-d2. Each pellets weight used in dissolution study was calculated from the results of the content assay.

The dissolution profile of uncoated DTZ HCl pellets for low dose (30 mg) and high dose (90 mg) are shown in Figures 37 and 38, respectively. The released profile of both uncoated DTZ HCl pellets exhibited that all of them were rapidly release of active drug, approximately 90 % of DTZ HCl was released at the first 15 minutes. The dissolution data of both uncoated pellets are shown in Tables a2 and a3, respectively.

4.2 Dissolution Profiles of DTZ HCl from 90 mg Pellets as Compared to Herbesser® 90 SR

The release profiles of DTZ HCl from EC coated pellets plasticized with 20 % TEC at 2.5, 5.0 and 7.5 % coating levels as compare to Herbesser® 90 SR are shown in Figure 39. The results indicated that when increase the coating level the release profile was suppressed. In addition, The release profile of DTZ HCl at 7.5% coating level seem to be lower parallel to the profile of Herbesser® 90 SR. In this case,

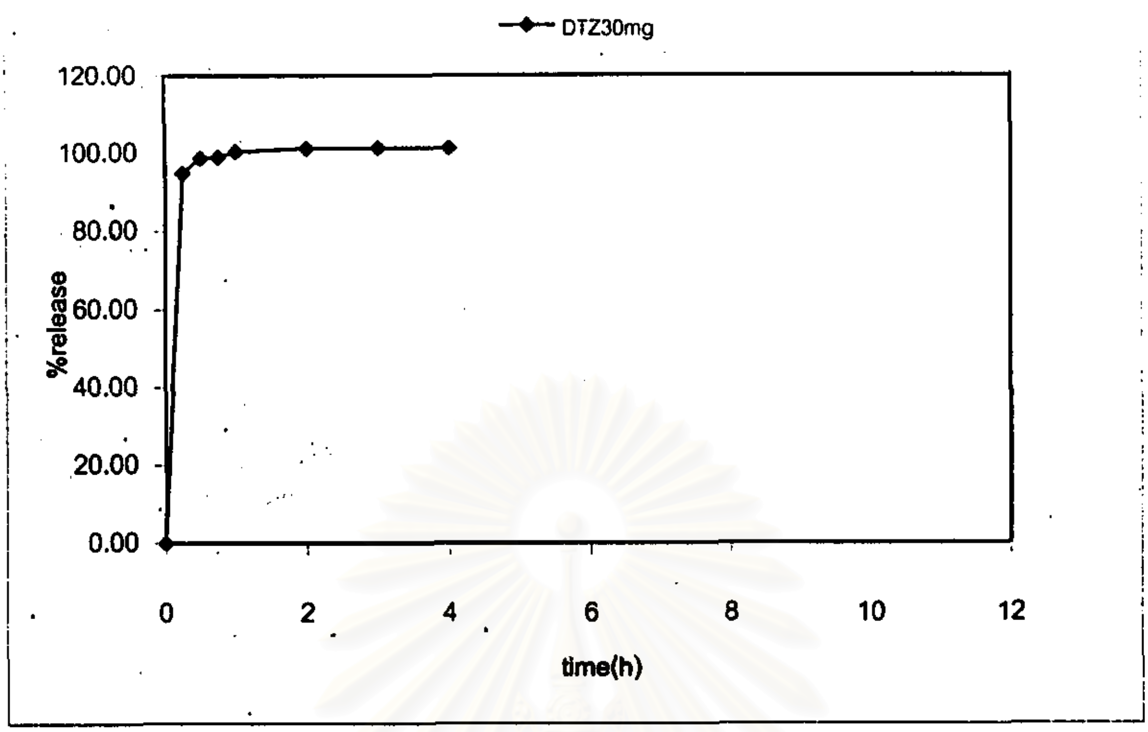


Figure 37. **Dissolution profile of uncoated DTZ HCl 30mg/150 mg pellets in D.I. water as medium.**

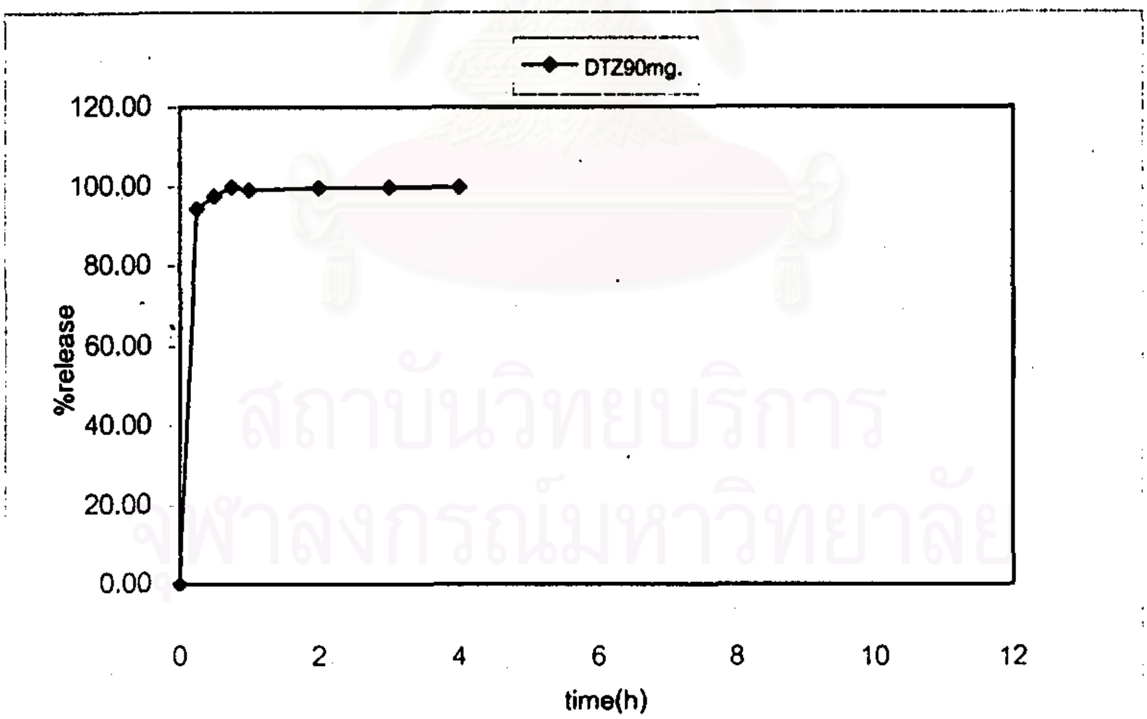


Figure 38. Dissolution profile of uncoated DTZ HCl 90 mg/150 mg pellets in D.I. water as medium.

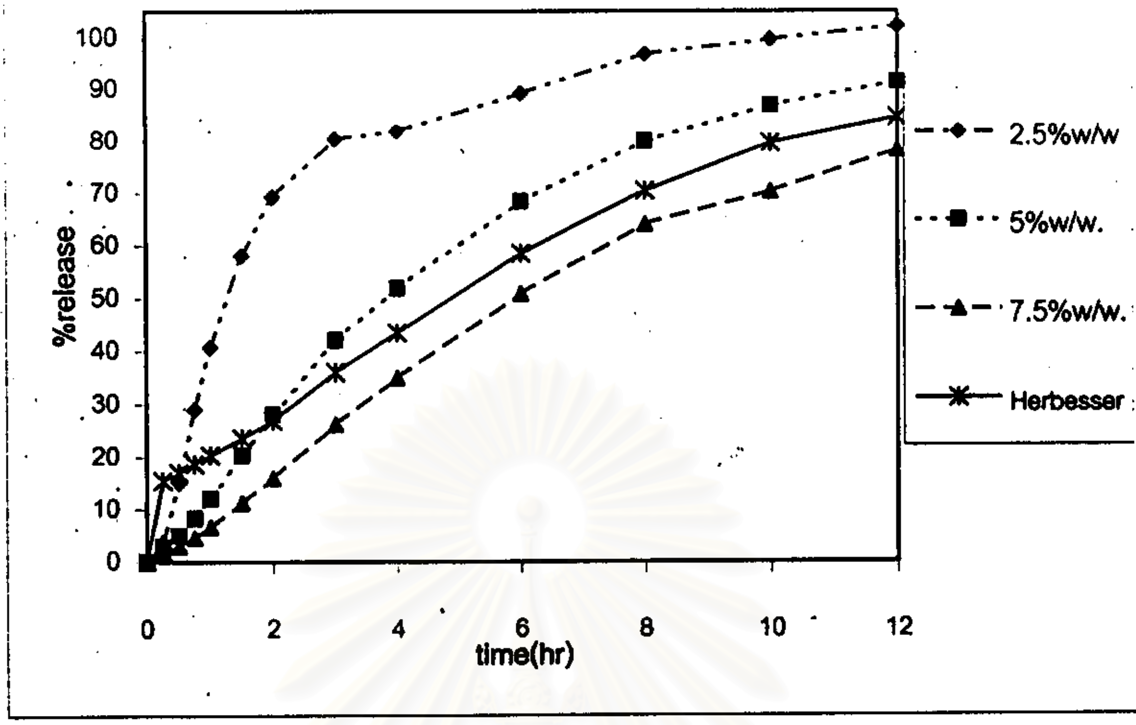


Figure 39. Dissolution profiles of DTZ HCl from coated pellets at various coating levels as compared to Herbesser 90 SR in D.I. water medium.

the use of proper amount of loading dose in combination of coating the DTZ HCl core pellets with 20 % TEC and 7.5 % EC are important for release adjusting, in order to obtain similar release profile. So, the mixture of uncoated pellets in proper ratio with coated pellets to achieve the satisfactory profiles was established.

The effect of loading dose of the mixture between film coated DTZ HCl pellets and uncoated DTZ HCl pellets in the ratio of 4:1 w/w on released profile of drug was found that percent cumulative release of DTZ HCl was increased in the first sampling time interval during dissolution test. Dissolution profiles of this selected formulation compared to commercial product (Herbesser® 90 SR) were determined in both D.I. water medium and pH changed mediums as shown in the Figures 40 and 41 respectively. The results exhibited that the profile of selected formulation and Herbesser® 90 SR gave an insignificantly different release profile in both mediums ($P< 0.05$ and 0.1, respectively). The results were treated by t-test for testing the different between means of percentage of releasing of prepared pellets and Herbesser® 90 SR at 2, 8, 10 and 12 hours of sampling time interval, respectively. Null hypothesis (H_0) is the average percentage of releasing of DTZ HCl from prepared pellets(μ_1) and Herbesser® 90 SR (μ_2) in water and in pH changed medium are not different at any determination of time. Alternative hypothesis(H_1) is the percentage of releasing of DTZ HCl from prepared pellets pellets(μ_1) are different from Herbesser® 90 SR(μ_2) in both water and in pH changed medium.

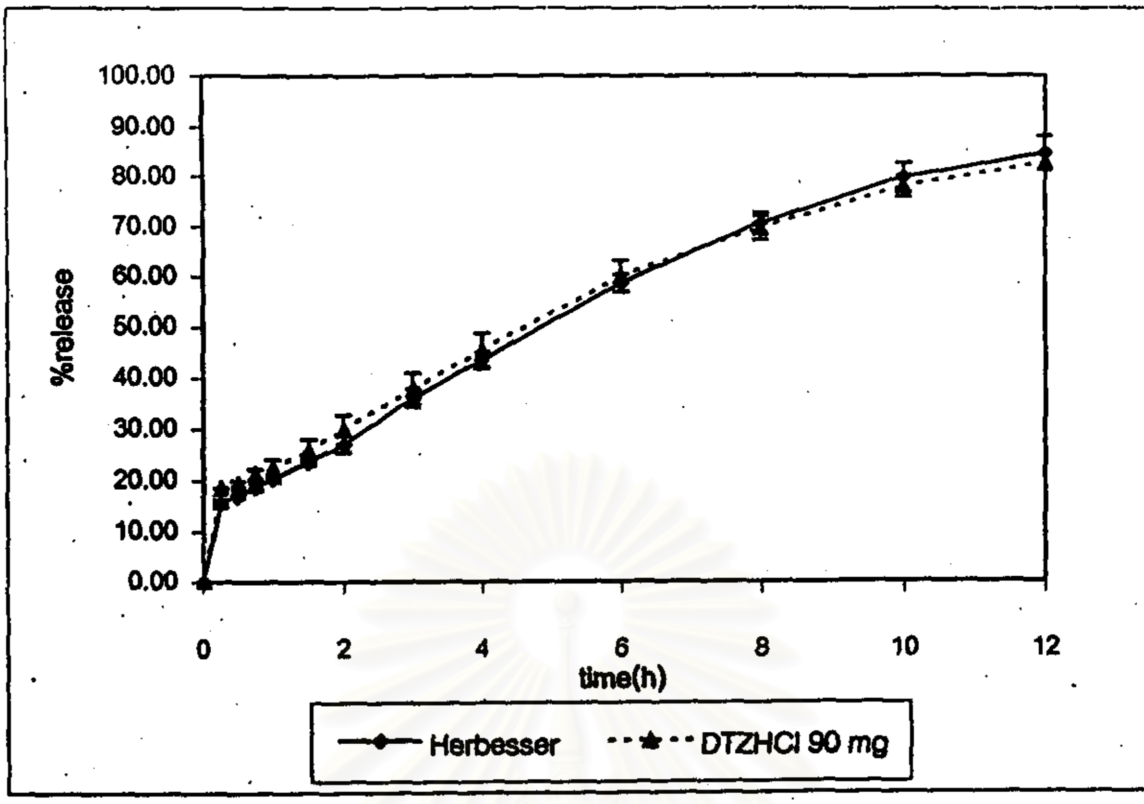


Figure 40. Dissolution profiles of DTZ HCl from mixed coated pellets and uncoate pellets at ratio 4:1 compared to Herbesser 90 SR in D.I. water as medium

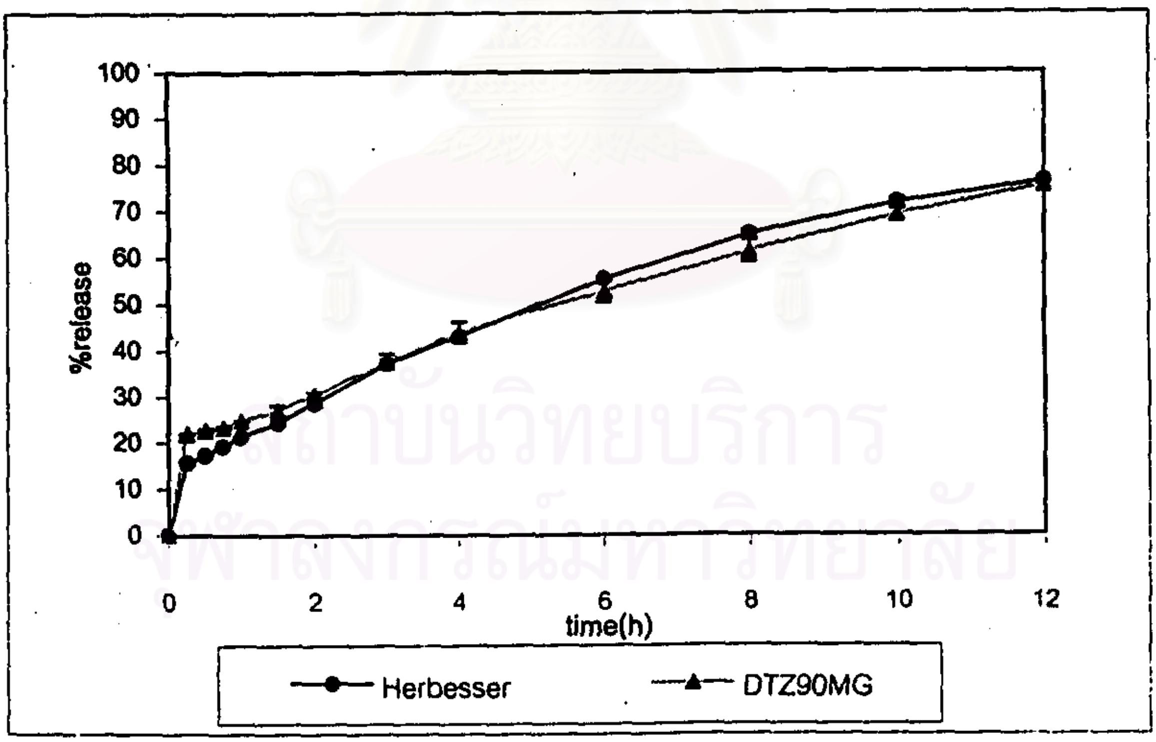


Figure 41. Dissolution profiles of DTZ HCl from mixed coated pellets and uncoated pellets at ratio 4:1 as compared to Herbesser 90 SR in pH changed mediu from 1.2 at first 2 hours to 6.8.

5. Evaluation of Release Mechanism

5.1 The Effect of EC Coating Level on the Released Characteristic of Film Coated DTZ HCl Pellets.

The dissolution data of each formulation are shown in Tables e2-e18. The release profiles of each formulation were plotted between the cumulative percentage amount of drug released as a function of time. These are presented in Figure 42 for DTZ HCl 30 mg/150 mg dose pellets (low dose) and Figure 43 for DTZ HCl 90 mg/150 mg dose pellets (high dose). The results indicated that release profile of drug decreased with increasing amount of EC from 3.0, 7.5 and 12.0 % w/w in both drug concentrations, respectively. However, at 7.5 and 12.0 % coating level of high dose DTZ HCl pellets (90 mg/150 mg dose), it can be observed that the released profile appeared to be linear line after lag time period up to 12 hours, whereas low dose DTZ HCl pellets (30 mg/150 mg dose) can be observed only at 12 % coating level (Figures 42-43).

The microscopic appearance of cross-section coated pellets both before and after dissolution test are given in Figures 44 and 45 for DTZ HCl 30 mg pellets and DTZ HCl 90 mg pellets, respectively. These showed uniform film thickness for both formulas, which indicated reliable of using Wurster type coating. In addition, the thickness of EC coating membrane increased by increasing the coating level. In term of the release rate (mg/h) of DTZ HCl from prepared pellets coated with each coating level was plotted with the reverse of thickness. The results showed the release rate has directly proportional to the reverse of thickness at coefficient of determinations of 0.982 and 0.9584 as exhibit in the Figures 46 and 47 for 30 and 90 mg/ 150 mg dose of DTZ HCl pellets, respectively. These indicated that the film may control the release process.

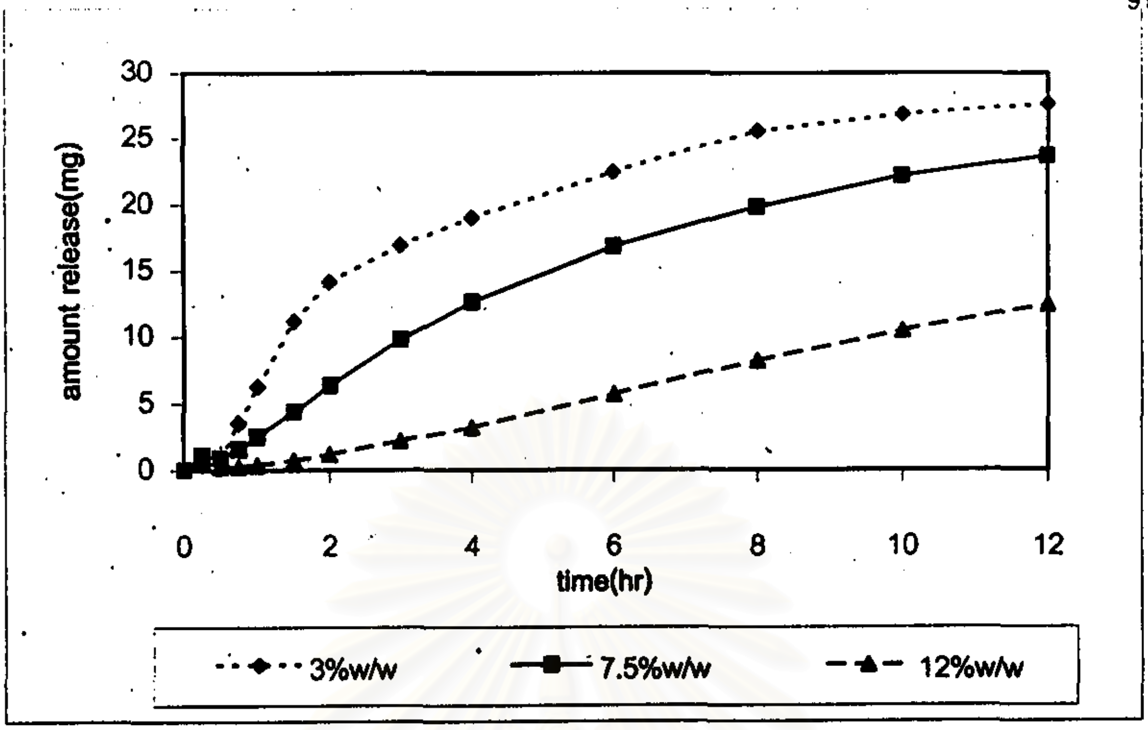


Figure 42. Amount release of DTZ HCl from 30 mg/150 mg dose pellets coated with EC at 20%TEC and at various coating levels in pH 6.8 buffer medium.

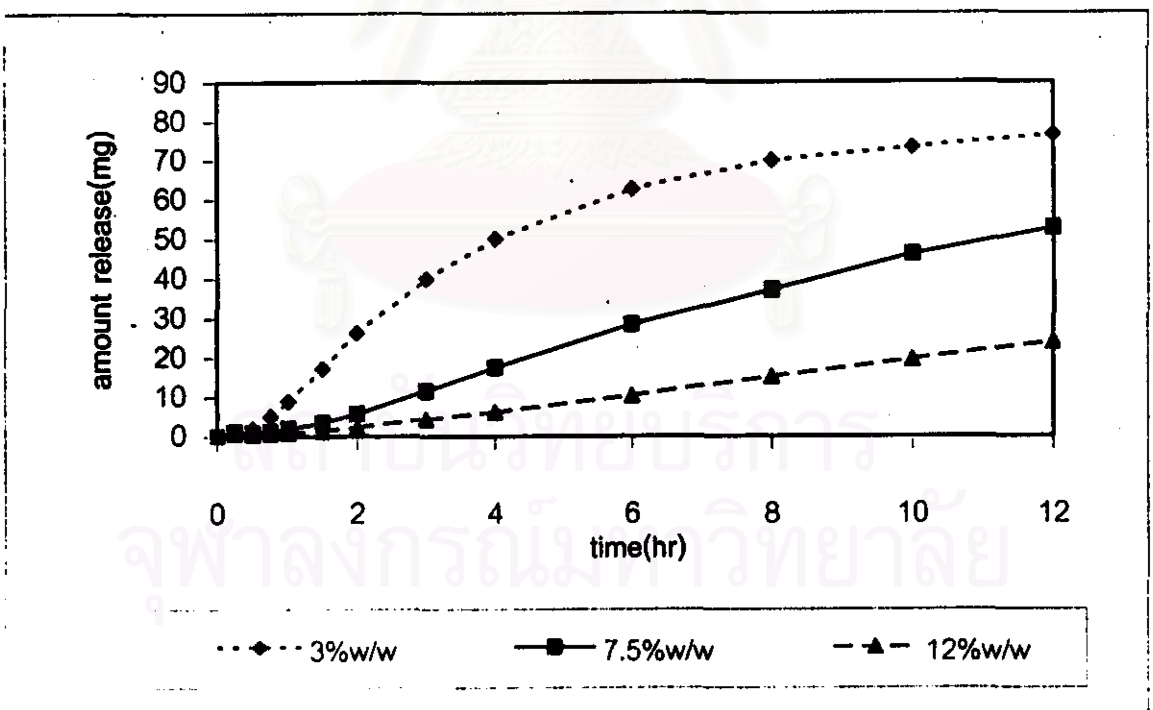
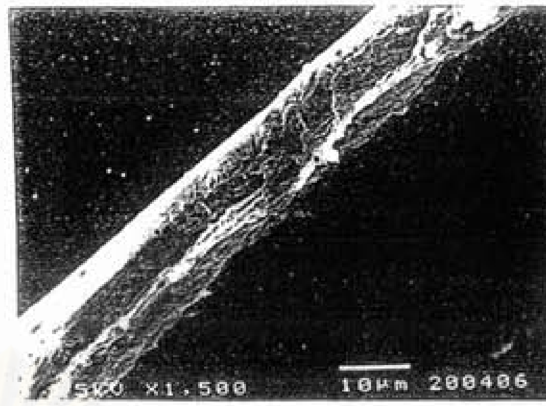
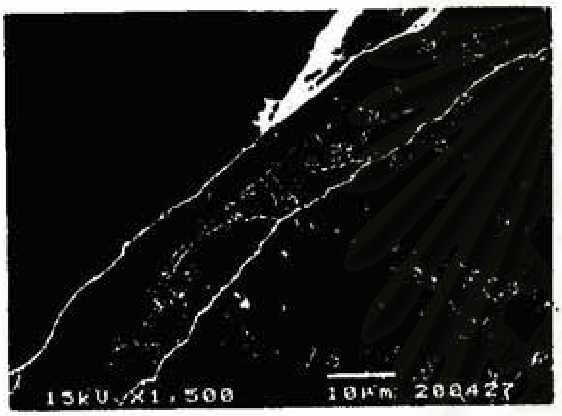


Figure 43. Amount release of DTZ HCl from 90 mg/150 mg dose pellets coated with EC at 20%TEC and at various coating levels in pH6.8 buffer medium.

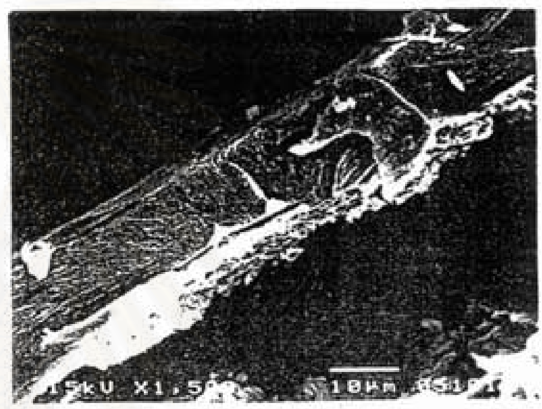
A1



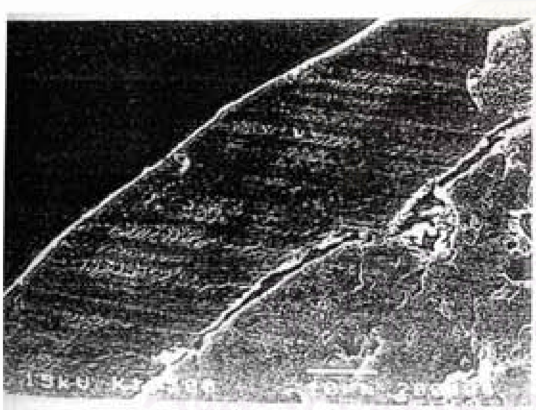
B1



A2



B2



A3

B3

Figure 44. Photomicrographs of cross-section DTZ HCl 30 mg/150 mg dose pellets at various coating levels before and after dissolution test (A1, A2, A3 are 3%, 7.5% and 12% w/w before dissolution test at x1500 magnification; B1, B2, B3 are after dissolution test at x1500 magnification).

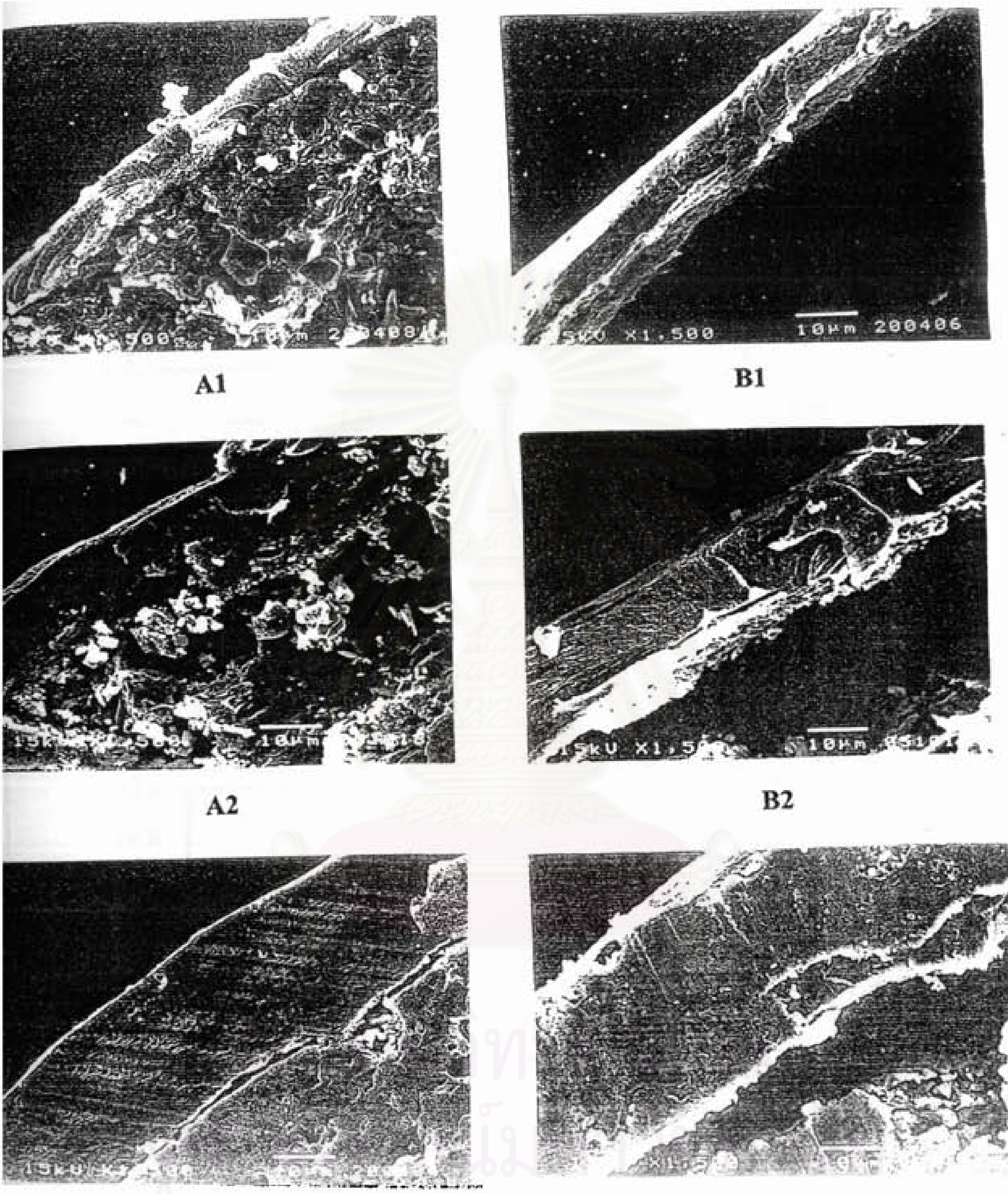


Figure 45. Photomicrographs of cross-section DTZ HCl 90 mg/150 mg dose pellets at various coating levels before and after dissolution test (A1, A2, A3 are 3%, 7.5 % and 12% w/w before test for dissolution at x1500 magnification; B1, B2, B3 are after dissolution test at x1500 magnification).

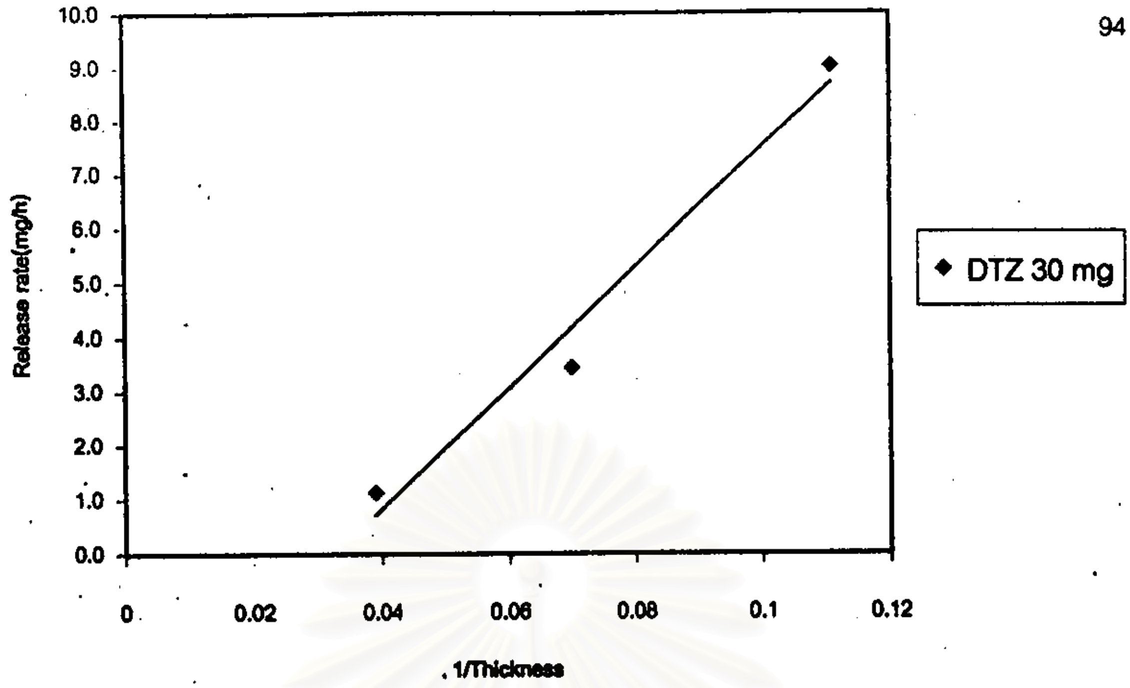


Figure 46. Effect of film thickness on DTZ HCl release rate from 30mg/dose coated pellets (r^2 = 0.9759),(y = 110.95x-3.602)

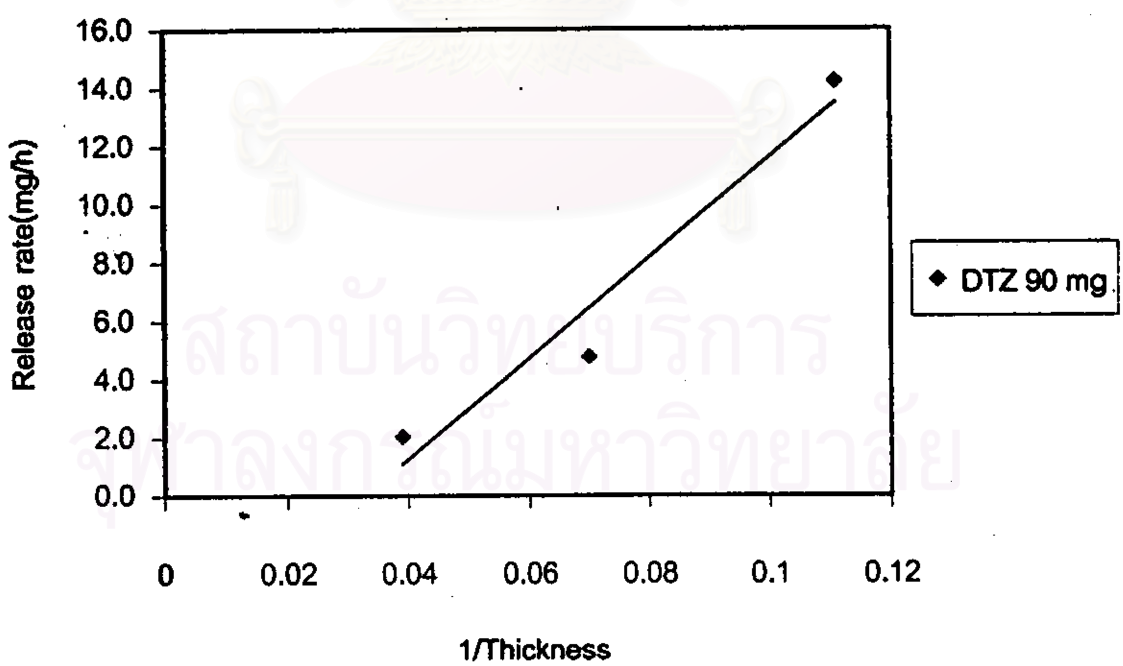


Figure 47. Effect of film thickness on DTZ HCl release rate from 90mg/dose coated pellets (r^2 = 0.9484),(y = 171.99x-5.6001)

5.2 The Effect of Ratio of TEC and EC on the Released Profiles of Film Coated DTZ HCl Pellets.

The dissolution data of DTZ HCl 30, 45, 60 and 90 mg/150 mg dose pellet coated with EC film at various percentage of TEC as plasticizer from 10, 20 and 30 % on dry polymer weight are shown in Tables e2-e16. And the release profiles of each formulation were plotted between the cumulative amount of drug released as a function of time, are presented in Figures 48-51. The release profiles of DTZ HCl exhibit that the ratio of TEC on EC polymer had no effect on the release profile of film coated DTZ HCl pellets in the range of percentage used in this study. This observation is also found in all 30, 45, 60 and 90 mg/150 mg dose of DTZ HCl concentrations. The photomicrographs of pellets before and after dissolution test are presented in the Figures 52-63. All of these Figures are indicated that each coating formulations used can totally encapsulate the core pellets and not necessary to adjust the applied conditions. The surface of all coated pellets does not show any cracks or wicking points. After dissolution test, the cross-section of all pellets show that the coating layers were not adhere to the surface core anymore.

5.3 The Effect of Drug Concentrations on the Released Profiles of Film Coated DTZ HCl Pellets.

The same percentage of coating level and the amount of TEC used was kept at 7.5 % w/w and 20 % on weight of dry polymer, respectively, for studying the effect of drug concentrations on the amount released profile of film coated DTZ HCl pellets. The results are shown in the Figure 64. The amount released of DTZ HCl was increased by increasing drug concentration in the pellet cores. In addition, when considered the release profile of DTZ HCl 30 and 45 mg/150 mg dose pellets could find

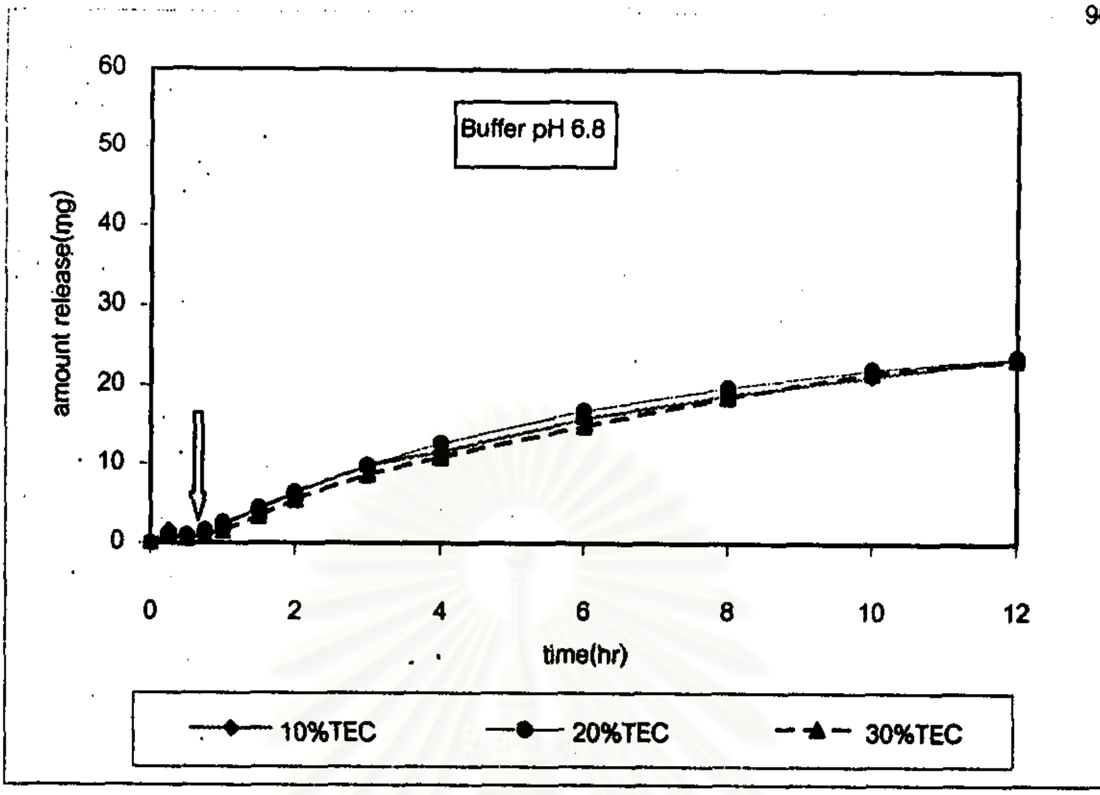


Figure 48. Release profiles of DTZ HCl from 30 mg/dose pellets coated with EC plasticized by various percentages of TEC at 7.5 % w/w coating level.

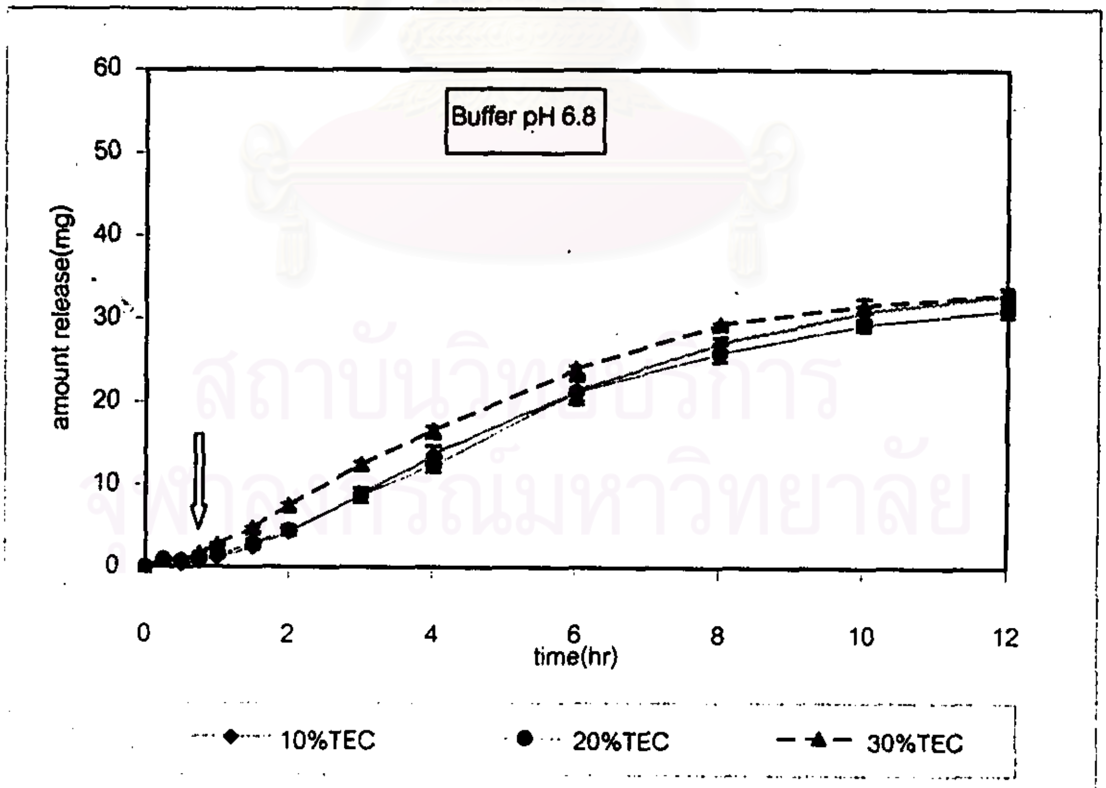


Figure 49. Release profiles of DTZ HCl from 45 mg/dose pellets coated with EC plasticized by various percentages of TEC at 7.5 % w/w coating level.

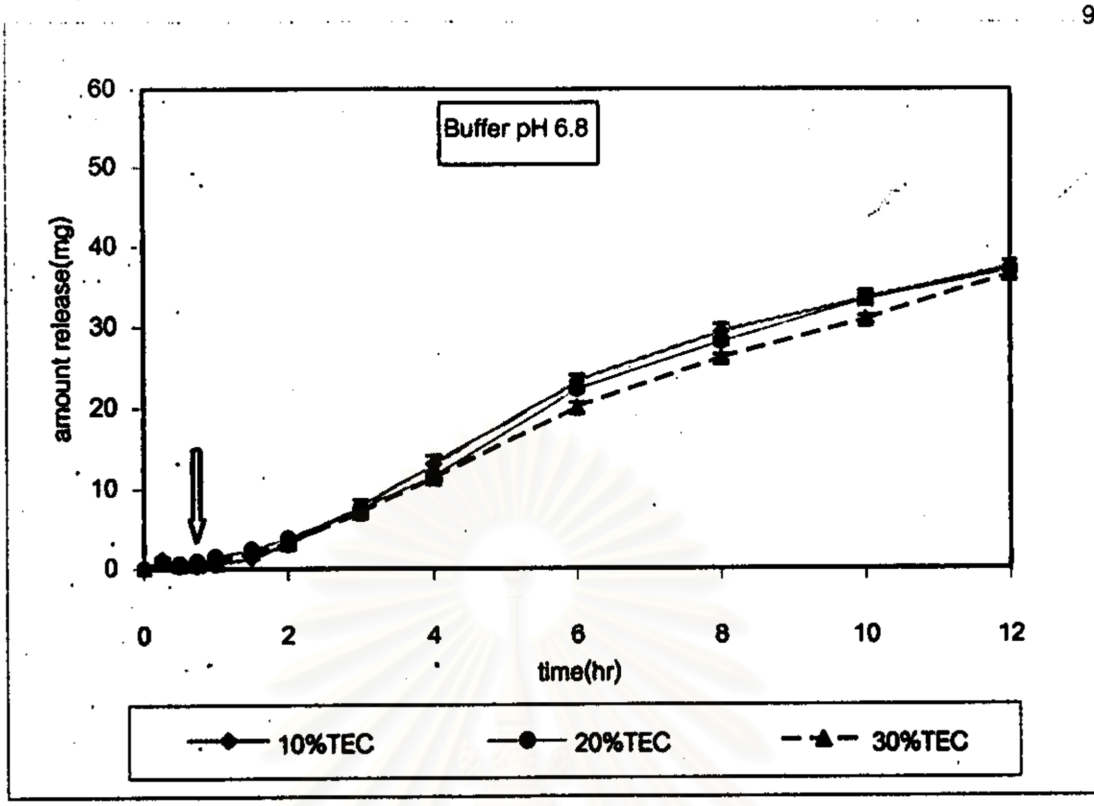


Figure 50. Release profiles of DTZ HCl from 60 mg/dose pellets coated with EC plasticized by various percentages of TEC at 7.5 % w/w coating level.

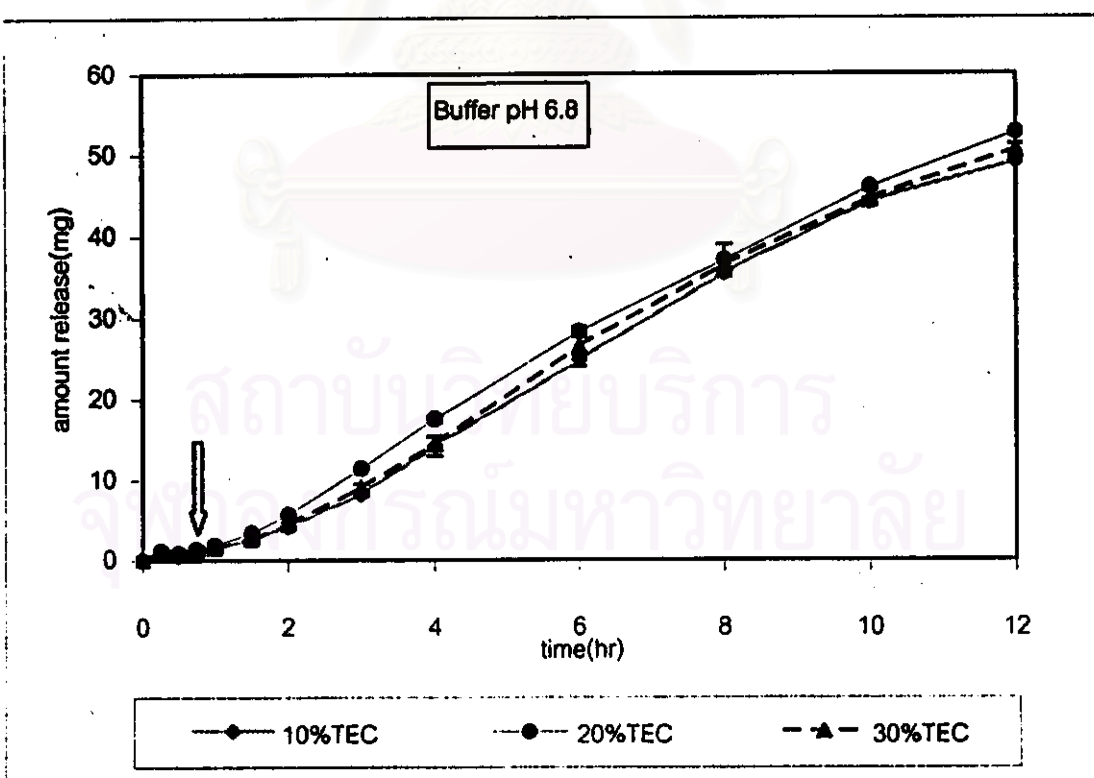
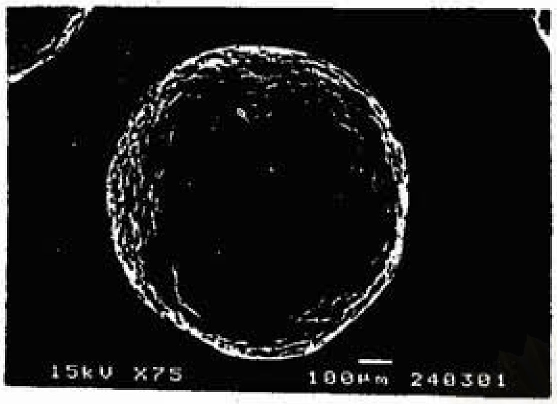
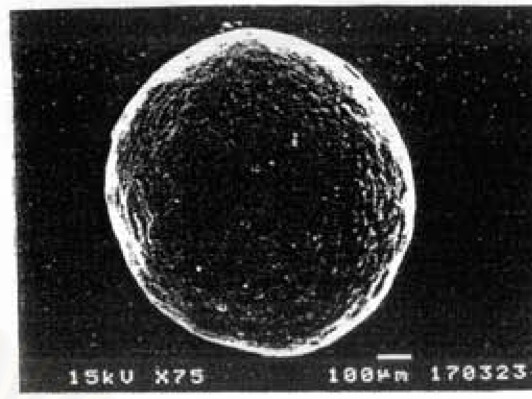


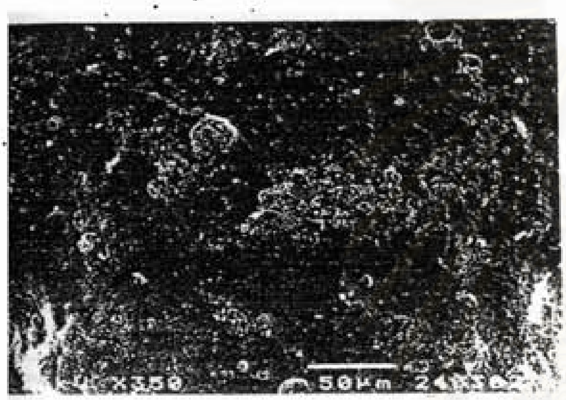
Figure 51. Release profiles of DTZ HCl from 90mg/dose pellets coated with EC plasticized by various percentages of TEC at 7.5 % w/w coating level.



A1

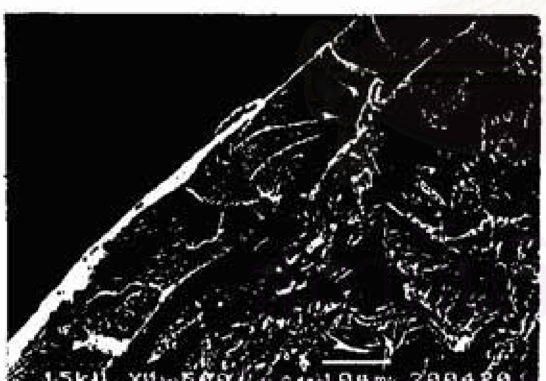


B1



A2

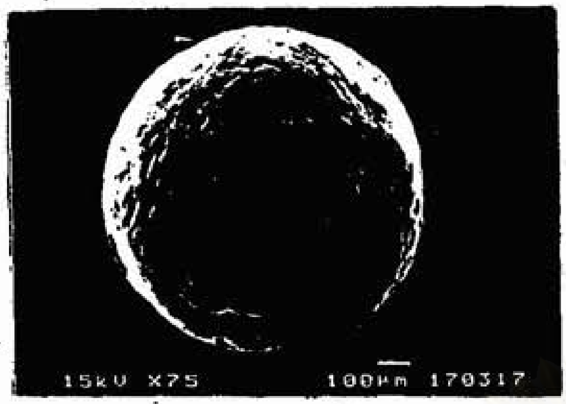
B2



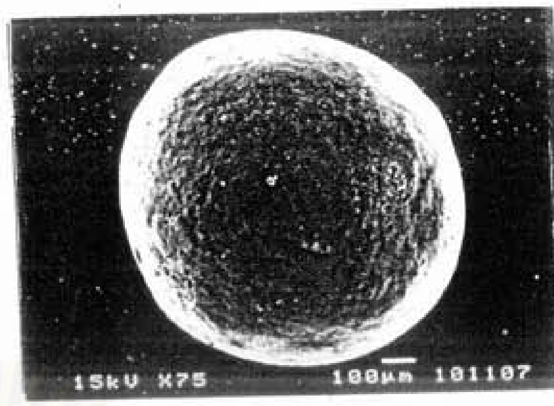
A3

B3

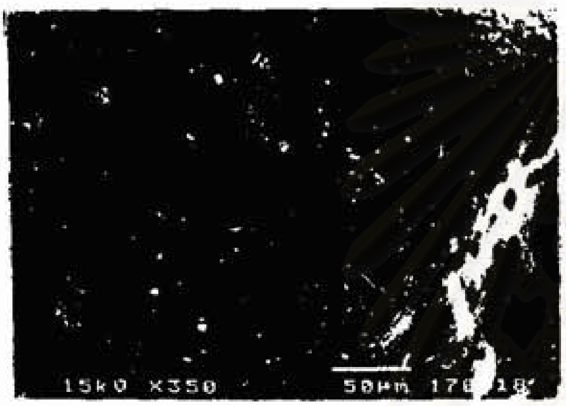
Figure 52. Photomicrographs of DTZ HCl 30 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 10% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).



A1



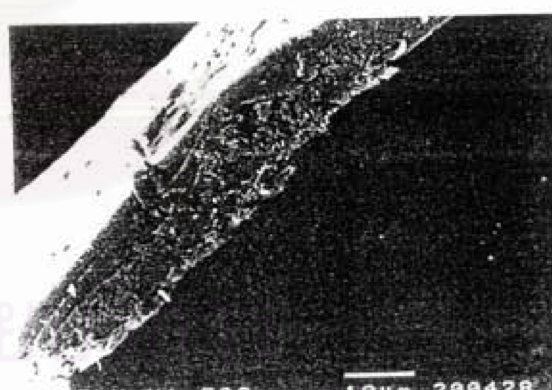
B1



A2

B2

A3



B3

Figure 53. Photomicrographs of DTZ HCl 30 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 20% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

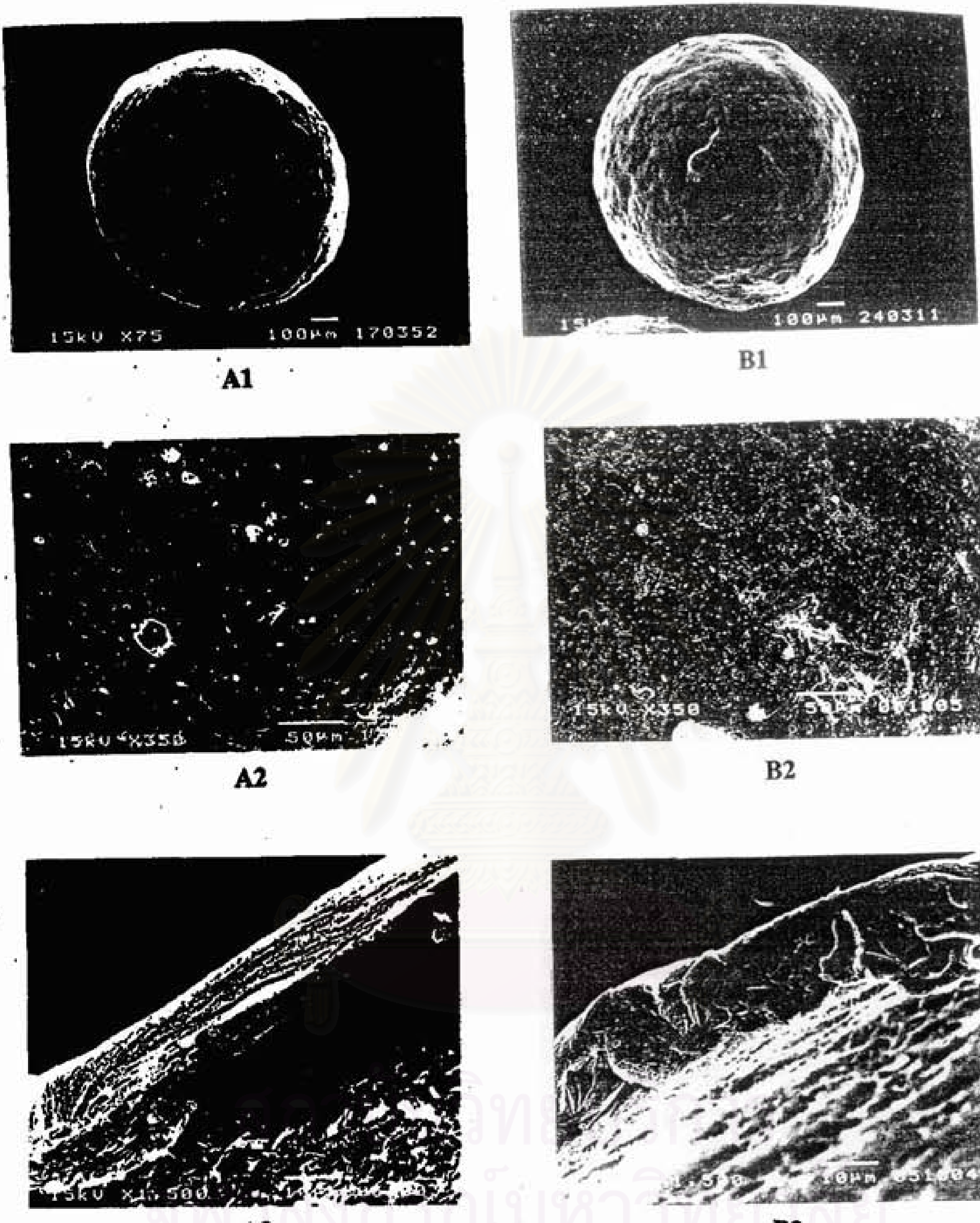


Figure 54. Photomicrographs of DTZ HCl 30 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 30% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

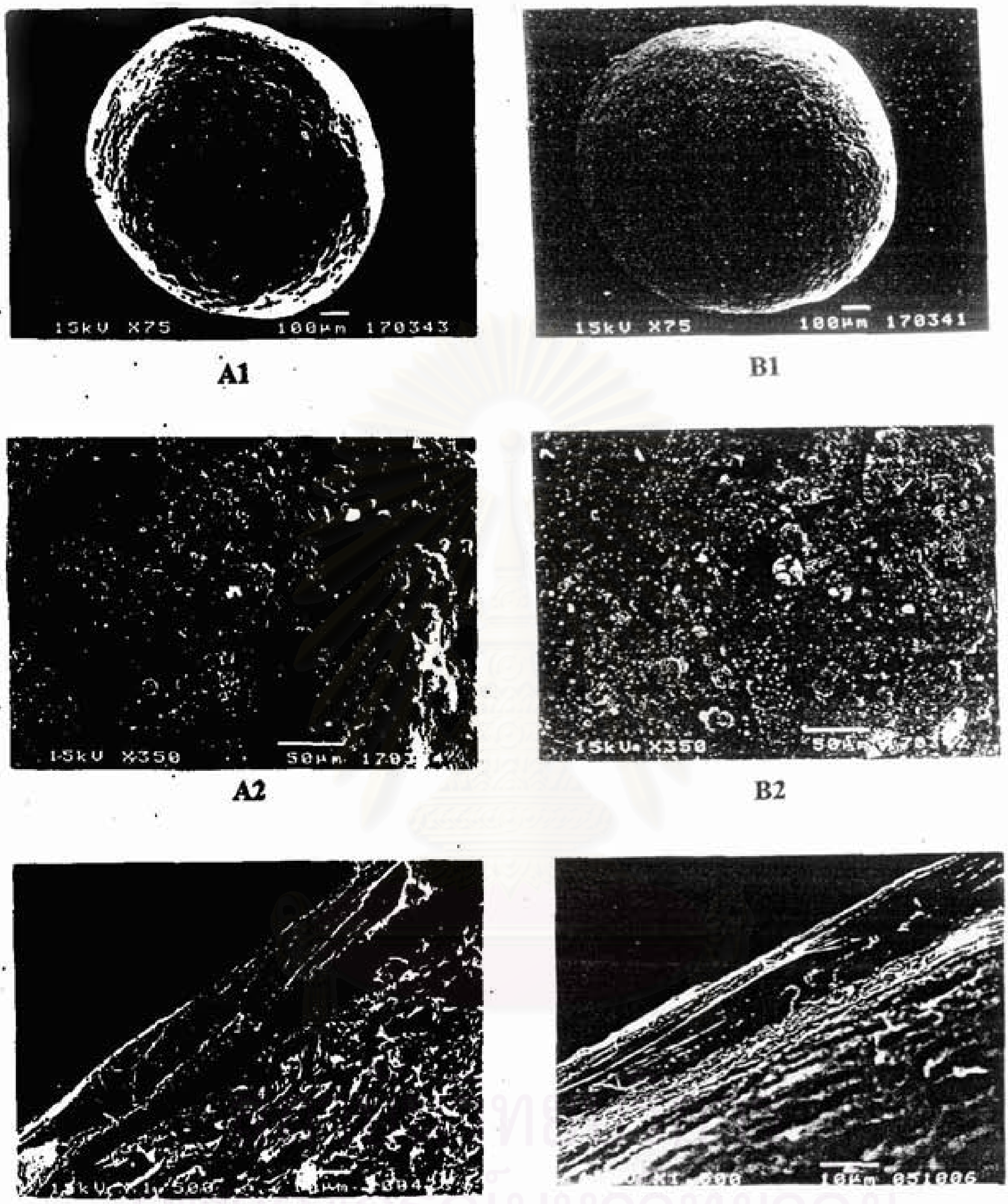
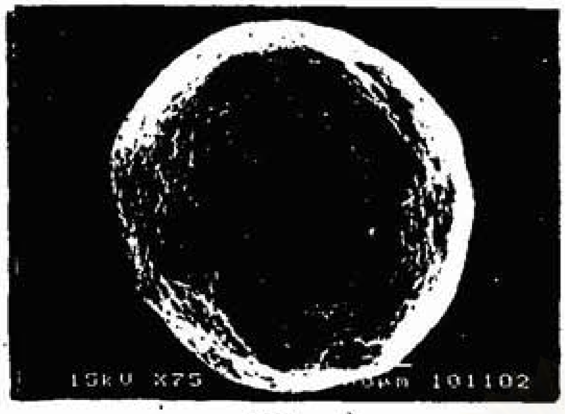
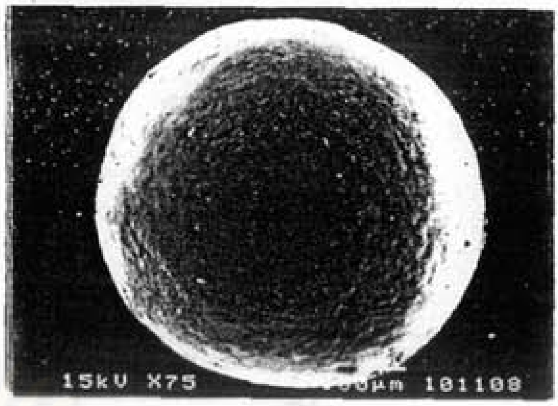


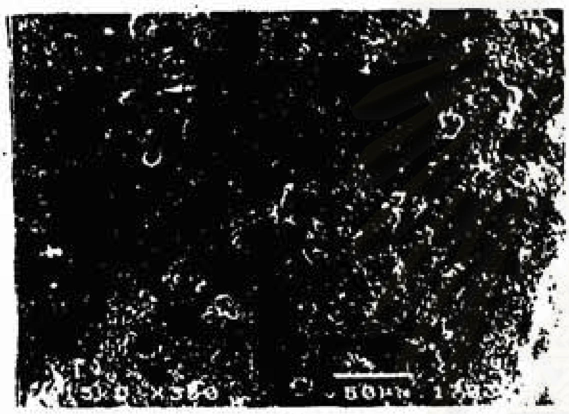
Figure 55. Photomicrographs of DTZ HCl 45 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 10% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).



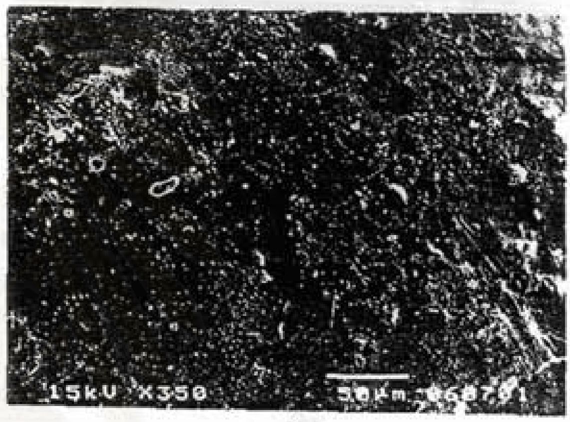
A1



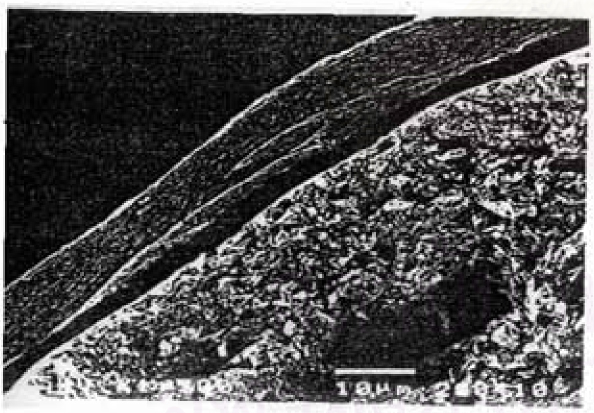
B1



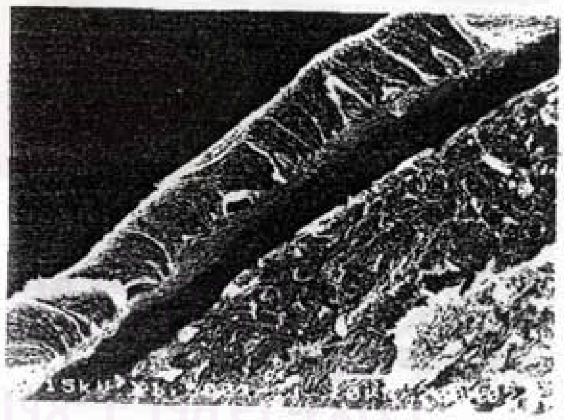
A2



B2

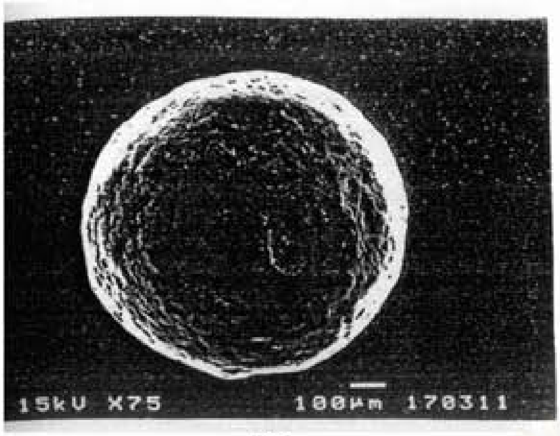


A3

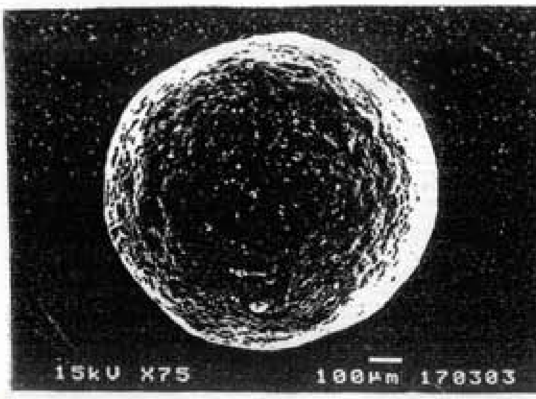


B3

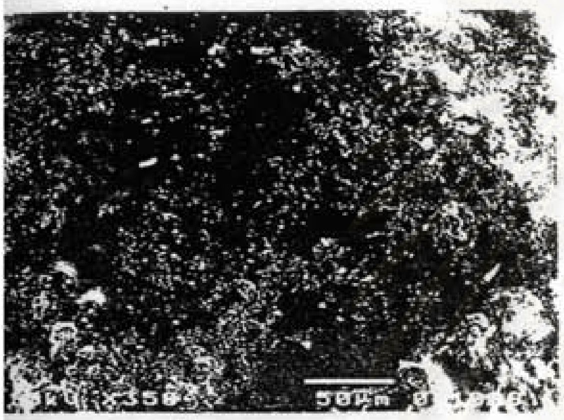
Figure 56. Photomicrographs of DTZ HCl 45 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 20% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).



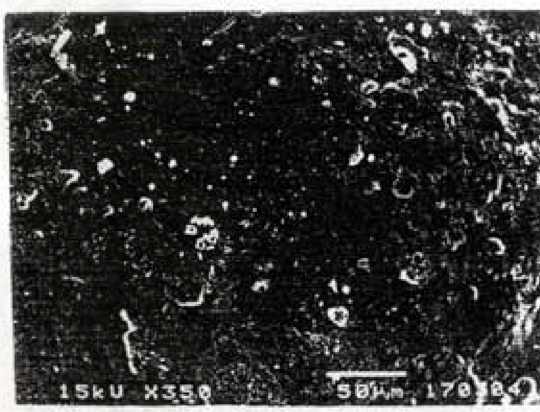
A1



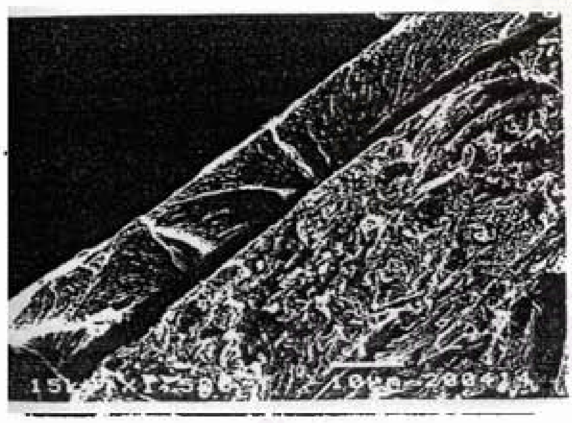
B1



A2



B2



A3

B3

Figure 57. Photomicrographs of DTZ HCl 45 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 30% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

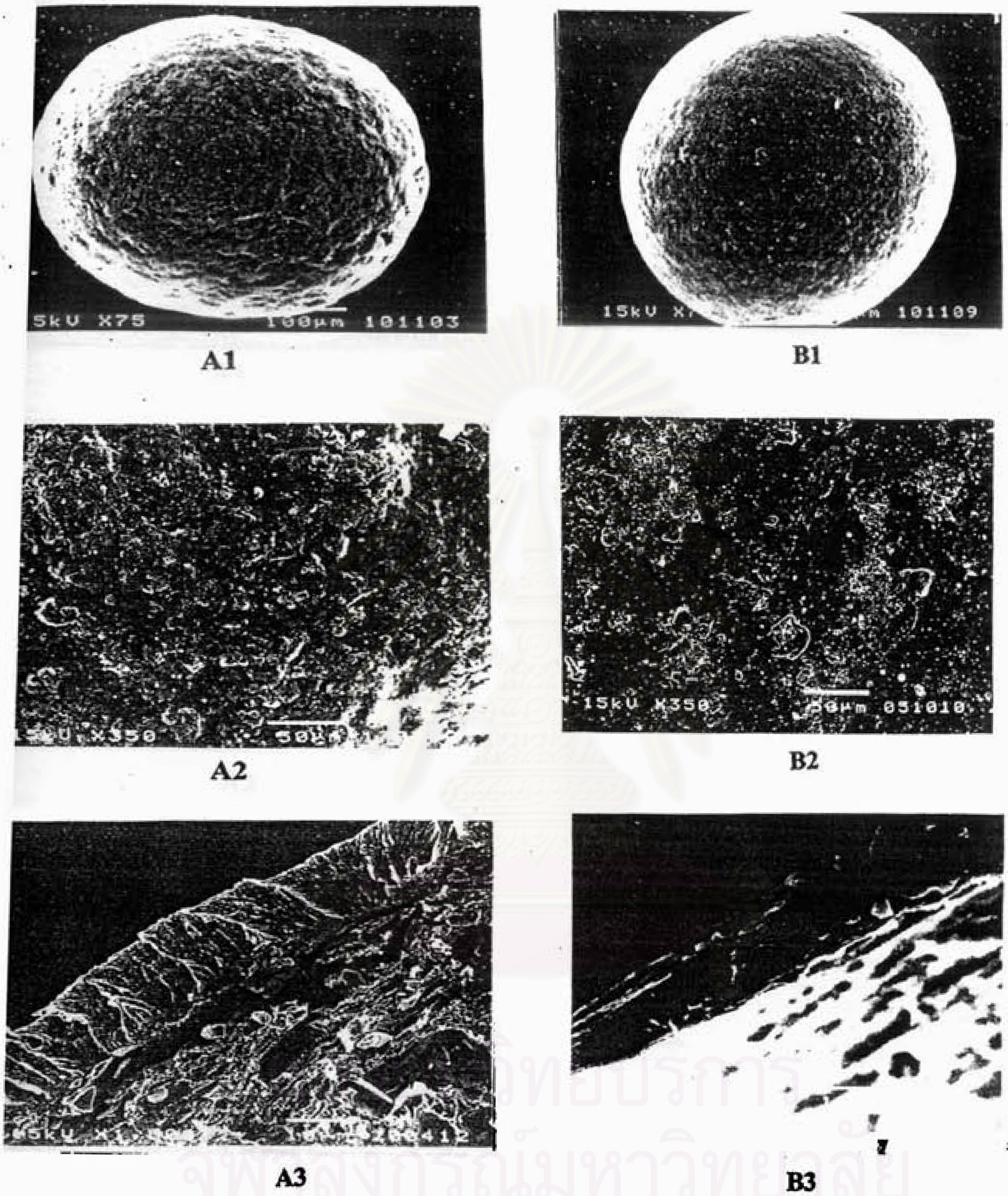


Figure 58. Photomicrographs of DTZ HCl 60 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 10% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

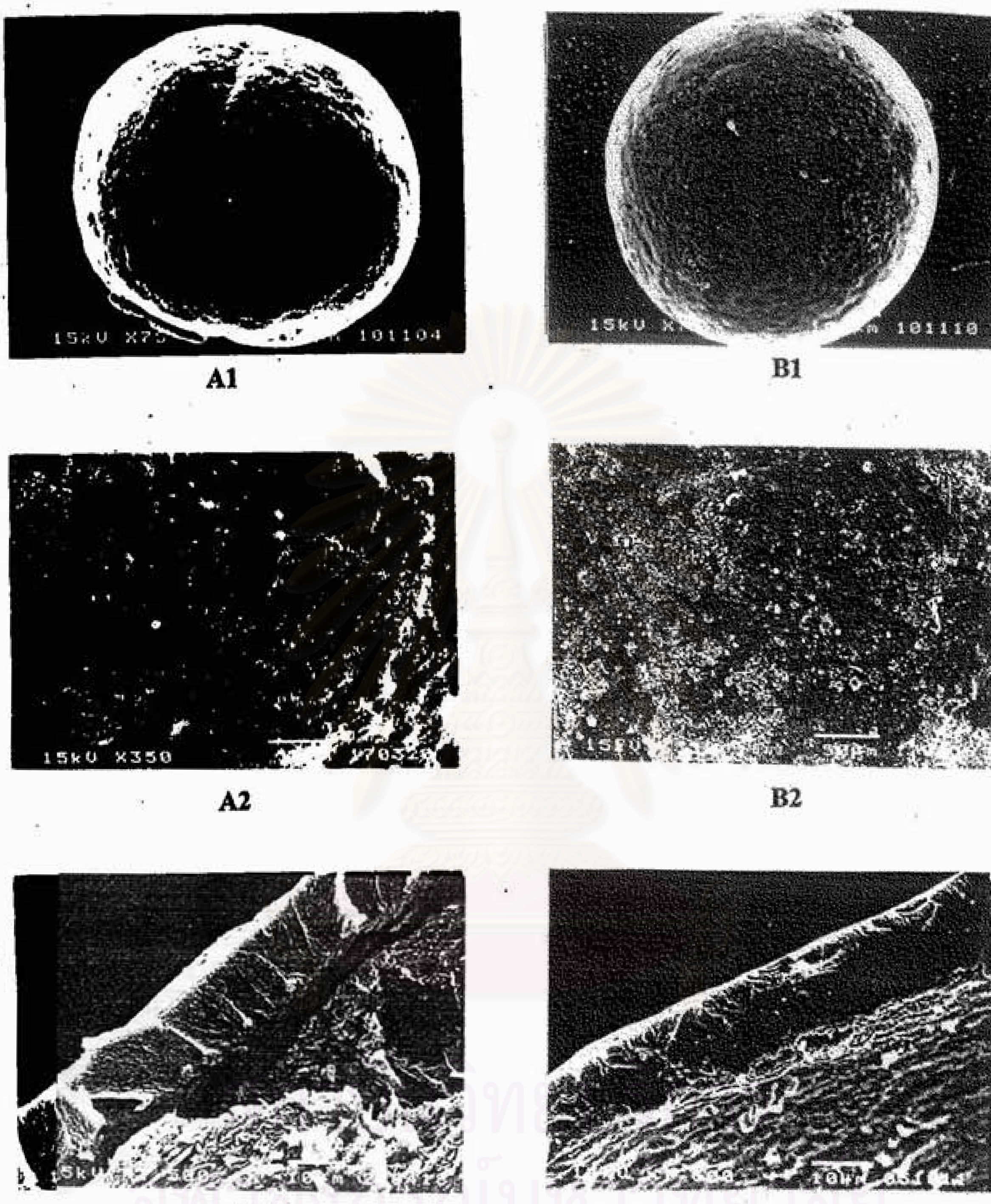
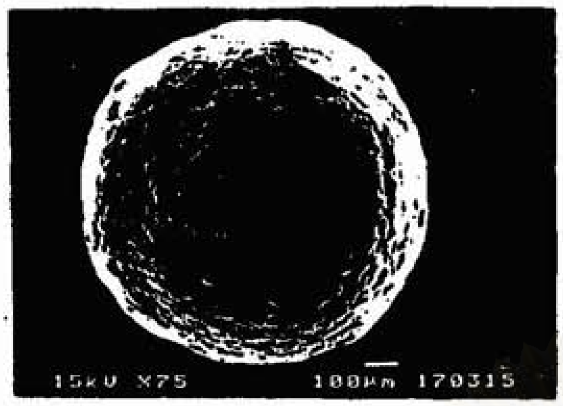
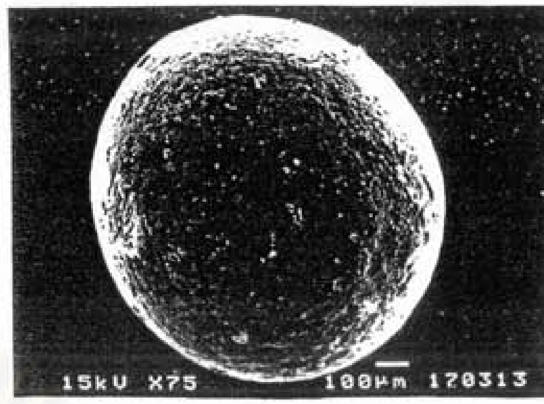


Figure 59. Photomicrographs of DTZ HCl 60 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 20% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

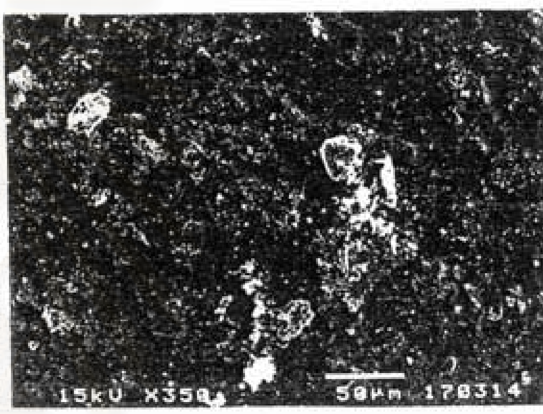


A1



B1

A2

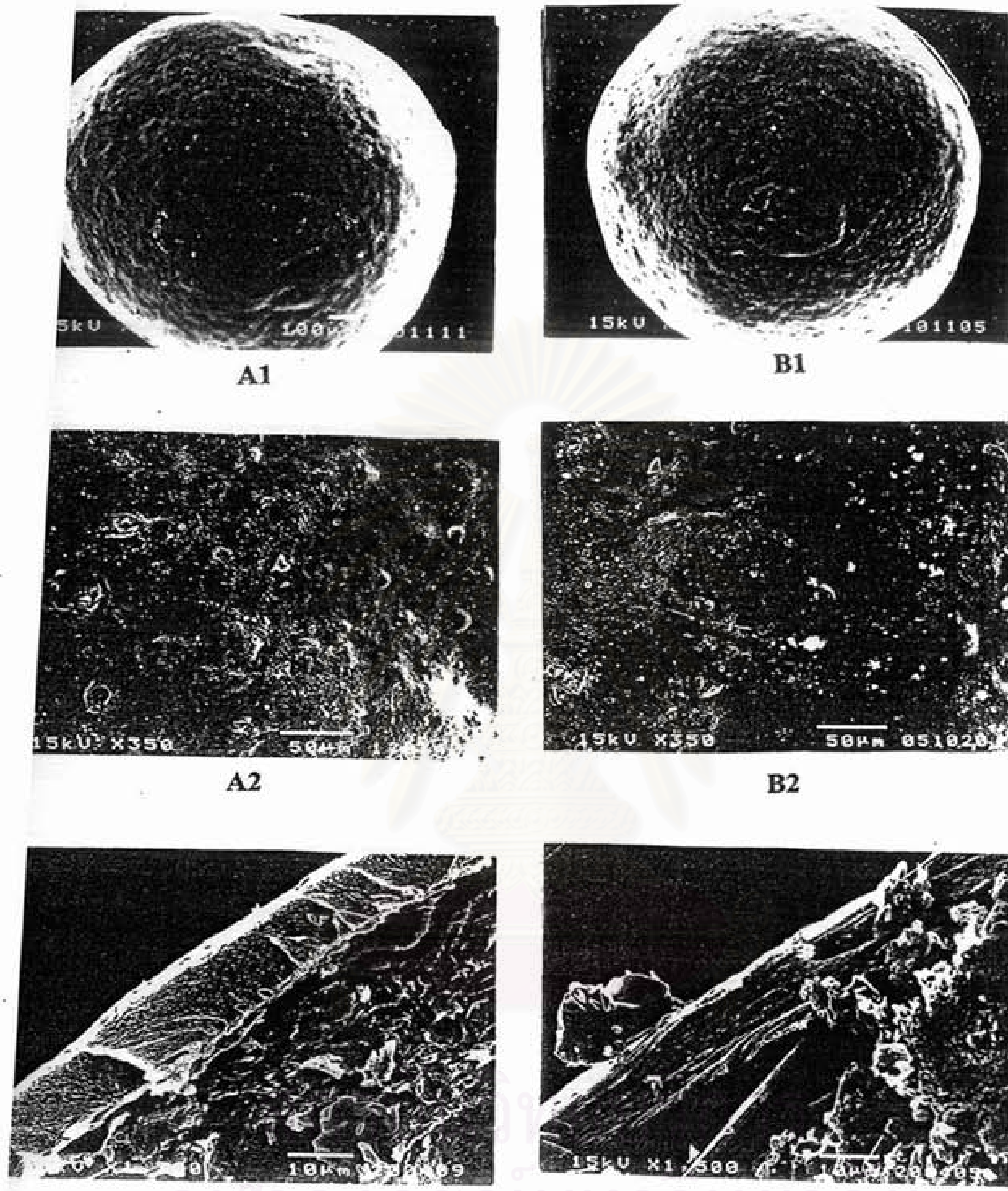


B2

A3

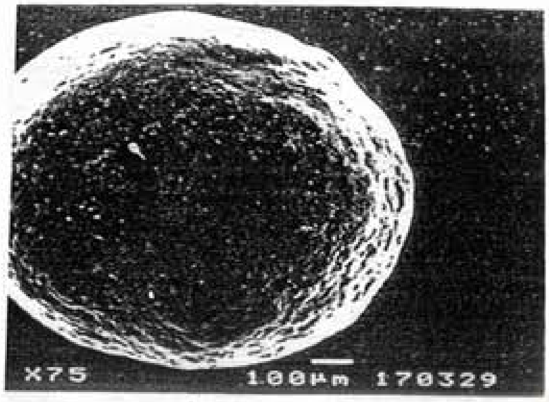
B3

Figure 60. Photomicrographs of DTZ HCl 60 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 30% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

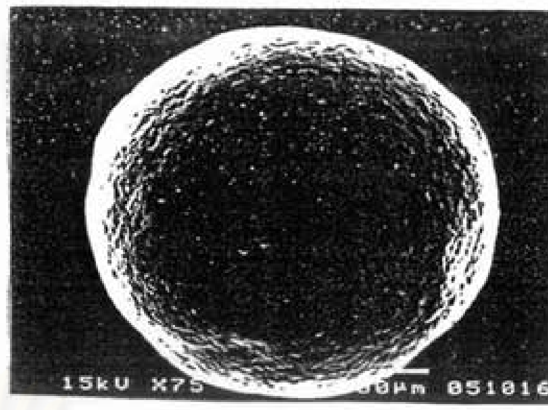


A1 B1 A2 B2 A3 B3

Figure 61. Photomicrographs of DTZ HCl 90 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 10% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).



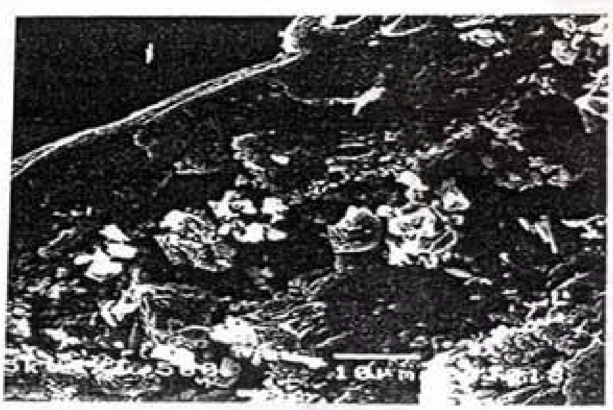
A1



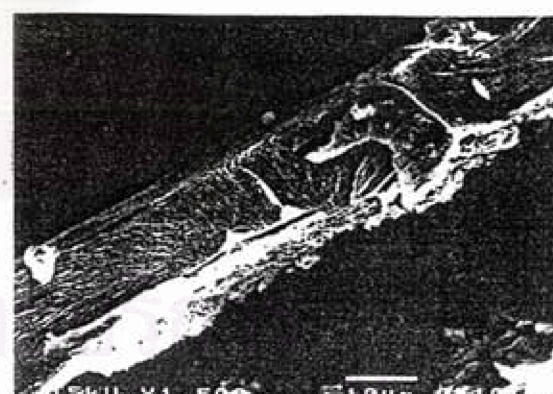
B1

A2

B2



A3



B3

Figure 62. Photomicrographs of DTZ HCl 90 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 20% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

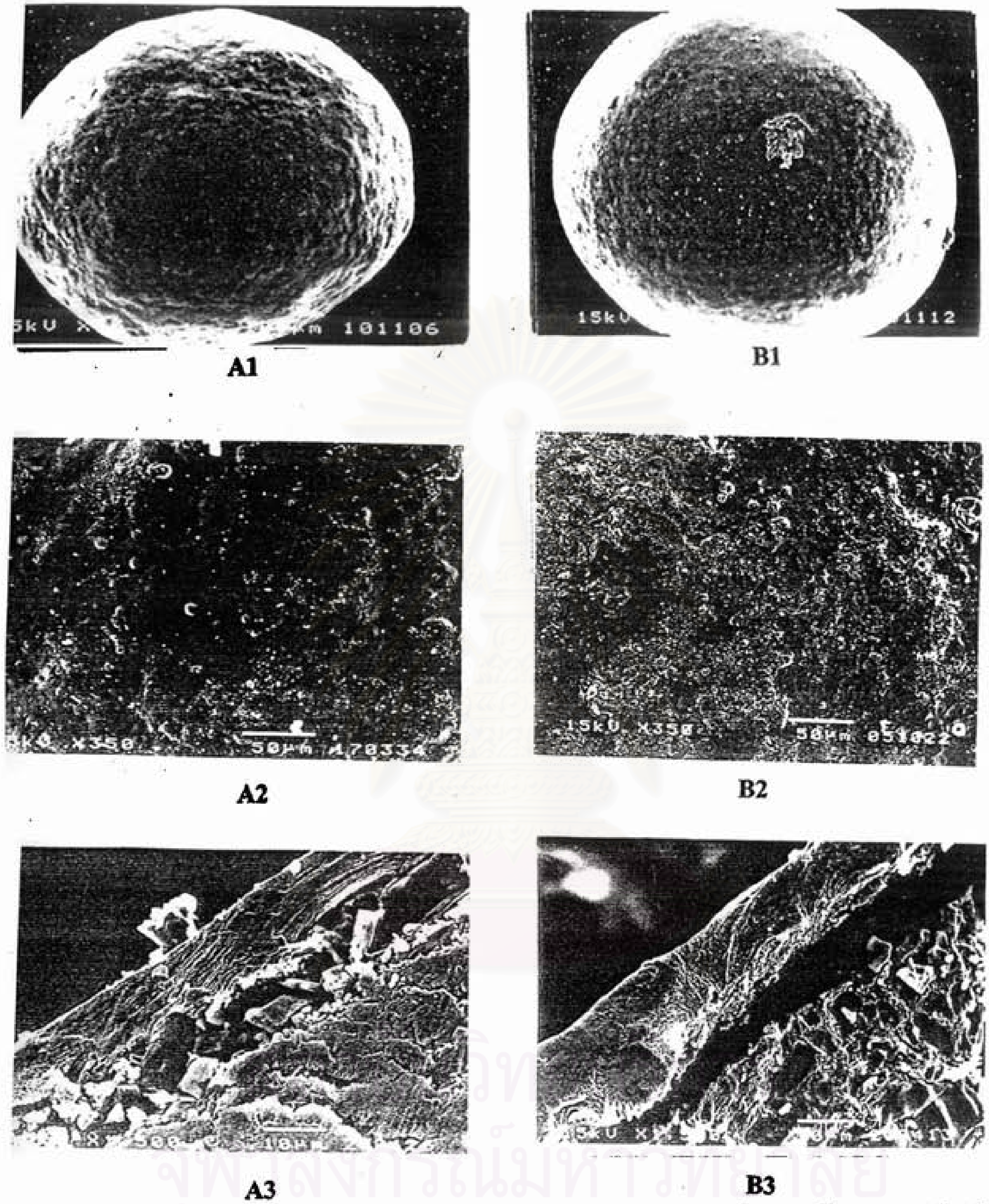


Figure 63. Photomicrographs of DTZ HCl 90 mg/150 mg dose pellets coated with 7.5% w/w EC film containing 30% TEC at before and after dissolution test (A1, A2, A3 are before dissolution test at x75, x350, x1500 (cross-section) magnification; B1, B2, B3 are after dissolution test at x75, x350, x1500 (cross-section)magnification).

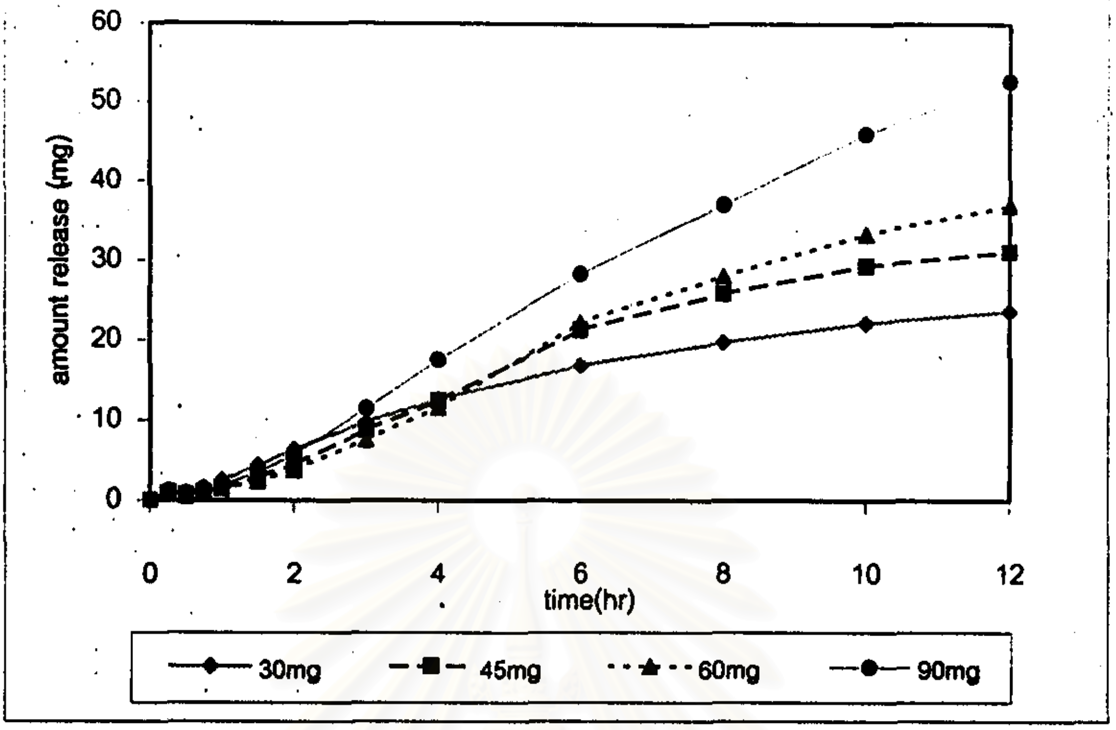


Figure 64. Amount release profiles of DTZ HCl pellets from various drug concentrations coated with EC at 20 % TEC, and at 7.5 % w/w coating level in D.I. water medium.

that after lag- time period the release profile of both drug concentration have rather constant release for approximately 6 hours, and declining release were observed after that as showed in the Figure 65. Whereas DTZ HCl 60 and 90 mg/150 mg dose pellets have constant released for approximately 12 hours after lag - time as showed in the Figure 66. The coefficient of determination for zero-ordered releasing in 30, 45, 60 and 90 mg DTZ HCl pellets are 0.9830, 0.9943, 0.9861 and 0.9955, respectively.

5.4 Effect of Osmotic Pressures of Dissolution Medium on Released Profiles of DTZ HCl pellets.

DTZ HCl is a highly water soluble drug which theoretically can produce osmotic pressure. This can be proved by the Table 17 and Figure 67, which presented the osmolality of DTZ HCl solution (osmol/kg) as a function of drug's concentration. It was indicated that DTZ HCl can act as osmotically inducing agent and the osmolality of DTZ HCl solution increased by increasing the drug's concentration. Then 0.8, 1.0 and 1.2 osmol/kg of sodium chloride were used and incorporated into dissolution medium in order to study the effect of various osmotic pressure values of medium on released profile of DTZ HCl from coated pellets. The results are showed in Figure 68, it can be found that the released profile of DTZ HCl from coated pellets was suppressed and the release rate (slope of released profile) was decreased by increasing the osmolal concentration of medium. For excluding the common ion effect of sodium chloride (NaCl) on DTZ HCl, Sodium sulphate was chosen to replace sodium chloride and the same result was obtained as showed in the Figure 69. However, the release rate is higher than in sodium chloride medium when compare within the same osmolal concentration. The solubility data of DTZ HCl in sodium chloride and sodium sulphate at 0.8, 1.0 and 1.2 osmol/kg concentrations are presented in Table 18 and the profiles are shown in Figure 70. The results indicated that solubility of DTZ HCl was decreased by increasing

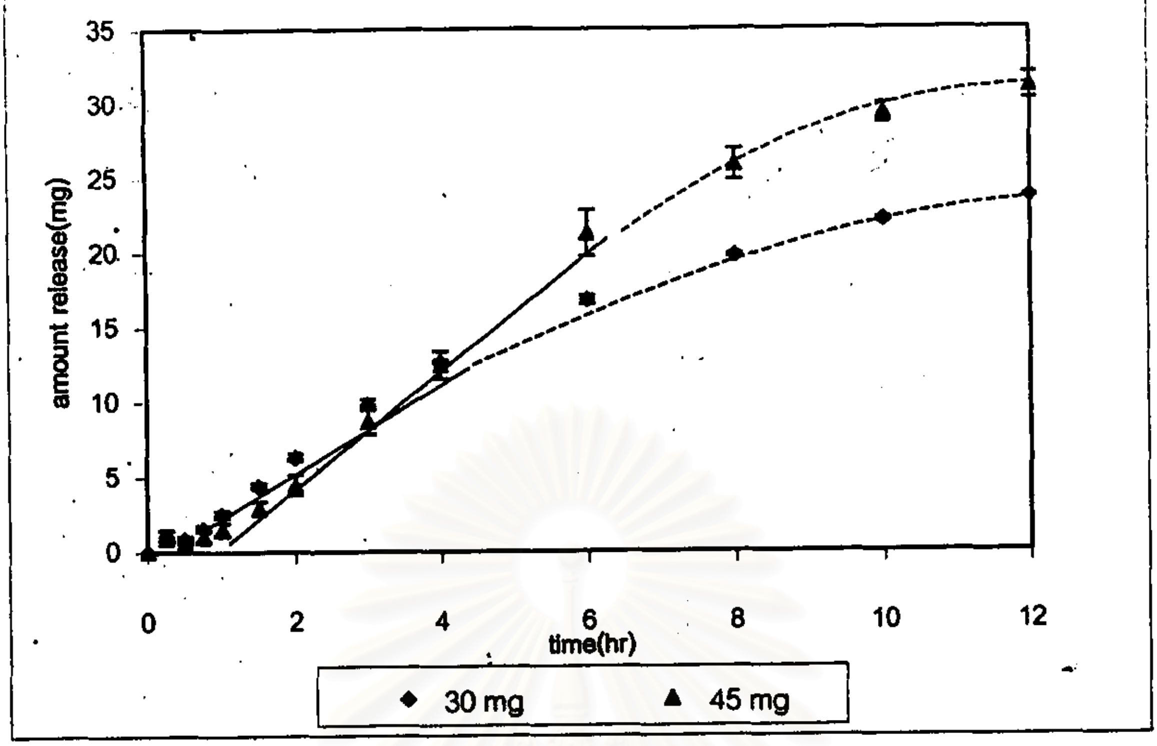


Figure 65. Zero order release of DTZ HCl 30 and 45 mg pellets in pH6.8 buffer mediur

(r^2 = 0.9966 and 0.9943, respectively)

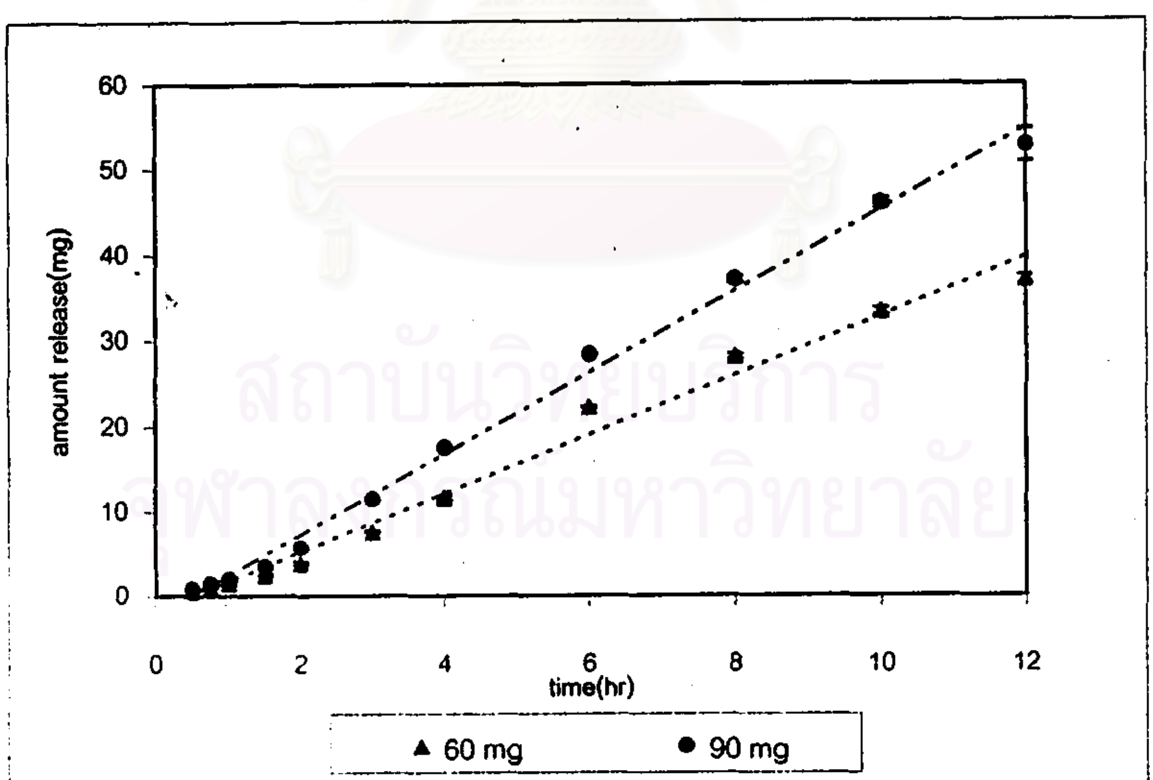


Figure 66. Zero order release of DTZ HCl 60 and 90 mg pelletsin pH6.8 buffer mediurr

(r^2 = 0.9901 and 0.9955, respectively)

Table 17. Osmolality of DTZ HCl solution.

concentrations	osmol/kg						av.	s.d.
0	0	0	0	0	0	0	0	0
2	0.068	0.068	0.068	0.067	0.067	0.068	0.068	0.001
4	0.106	0.107	0.106	0.107	0.108	0.106	0.107	0.001
6	0.136	0.136	0.137	0.137	0.139	0.138	0.137	0.001
8	0.161	0.162	0.161	0.161	0.161	0.161	0.161	0.000
10	0.195	0.195	0.194	0.195	0.193	0.193	0.194	0.001

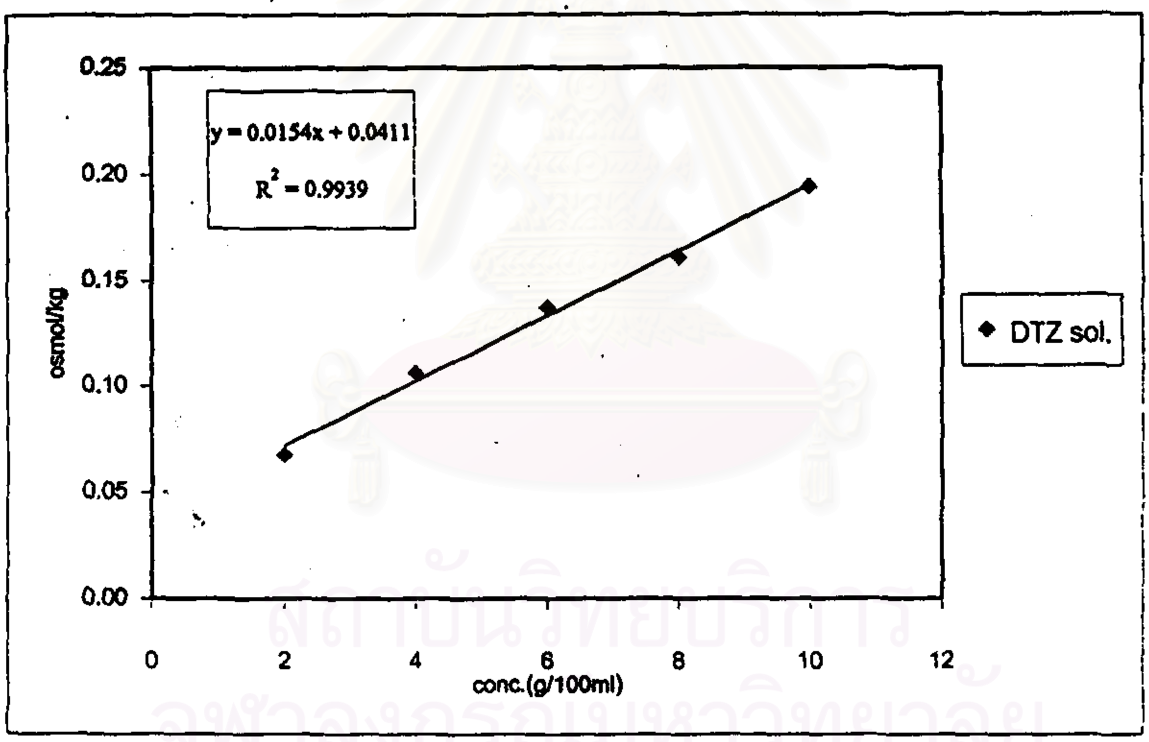


Figure 67. Standard curve of osmolality of DTZ HCl solution as a function of concentration.

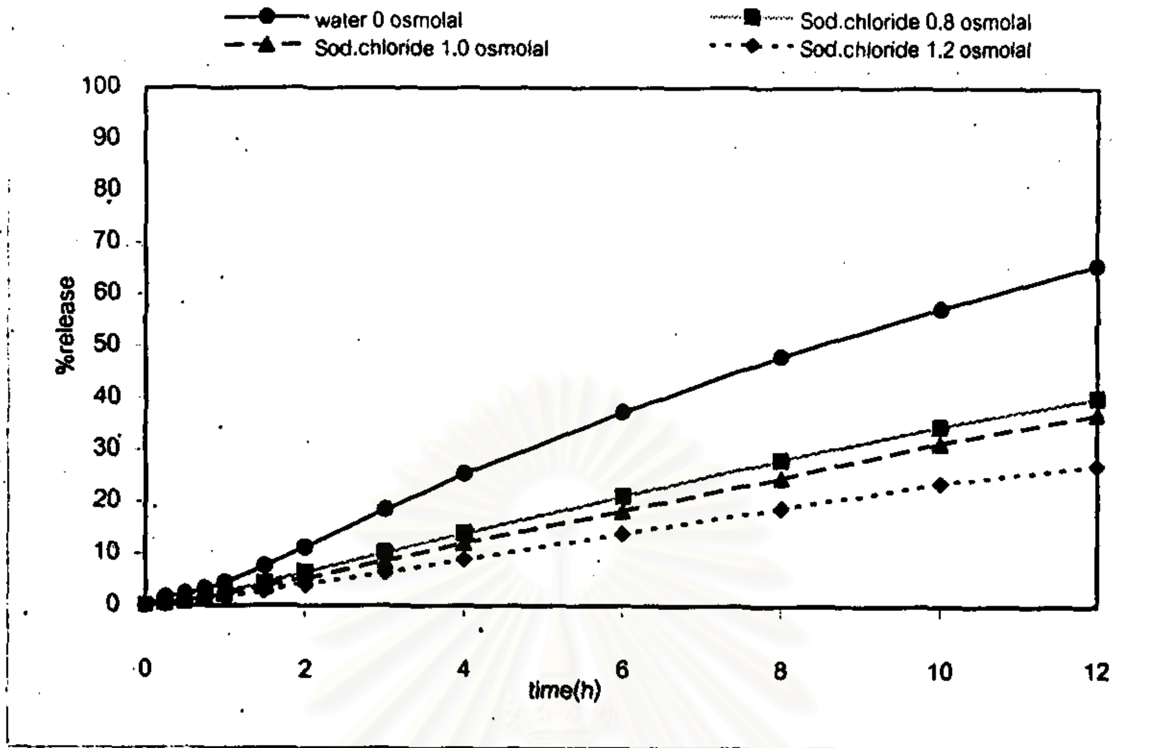


Figure 68. Dissolution profiles of DTZ HCl in various osmolality levels of sodium chloride containing in dissolution medium.

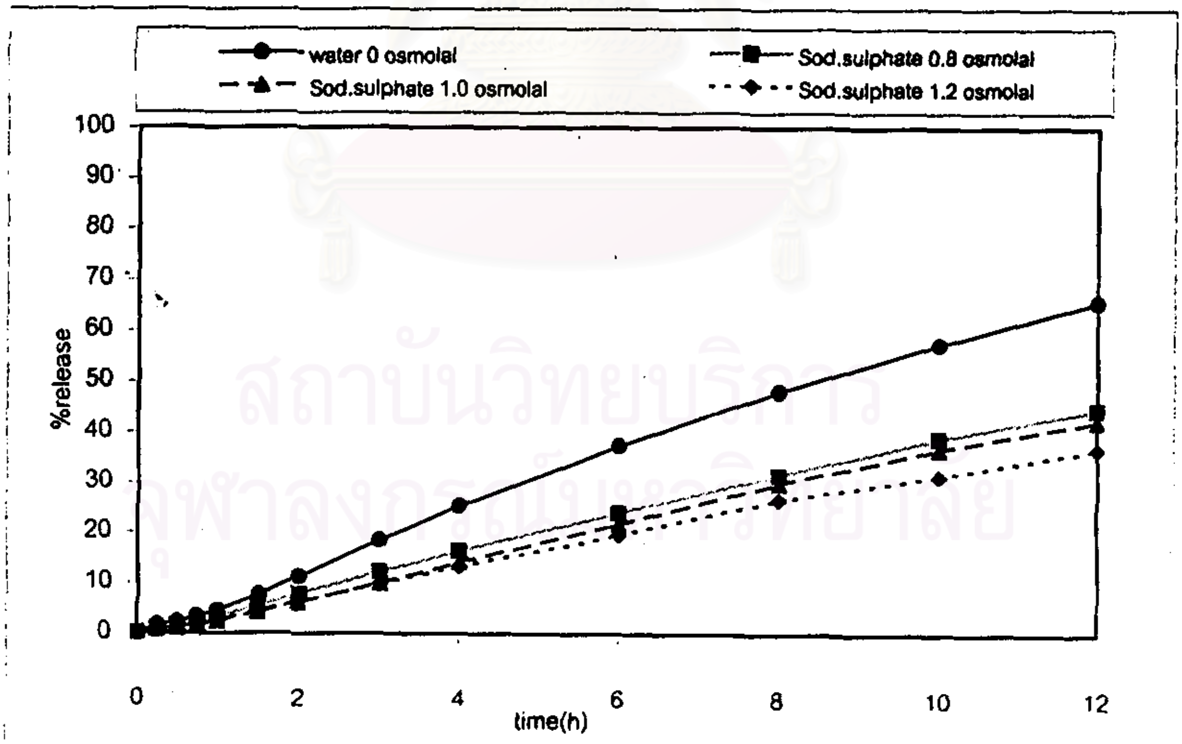


Figure 69. Dissolution profiles of DTZ HCl in various osmolality levels of sodium sulphate containing in dissolution medium.

Table 18. Solubility of DTZ HCl in various osmolal concentration medium at 37 °C

	concentration (g/ml)						
	water	NaCl			Na_2SO_4		
	0.0 osmolal	0.8 osmolal	1.0 osmolal	1.2 osmolal	0.8 osmolal	1.0 osmolal	1.2 osmolal
1	0.581	0.470	0.450	0.392	0.488	0.473	0.483
2	0.586	0.466	0.442	0.390	0.486	0.482	0.481
3	0.567	0.466	0.434	0.394	0.483	0.476	0.475
av.	0.578	0.467	0.442	0.392	0.486	0.477	0.480
s.d.	0.0098	0.0023	0.0077	0.0020	0.0025	0.0046	0.0042
%cv	1.70	0.49	1.75	0.51	0.52	0.96	0.87

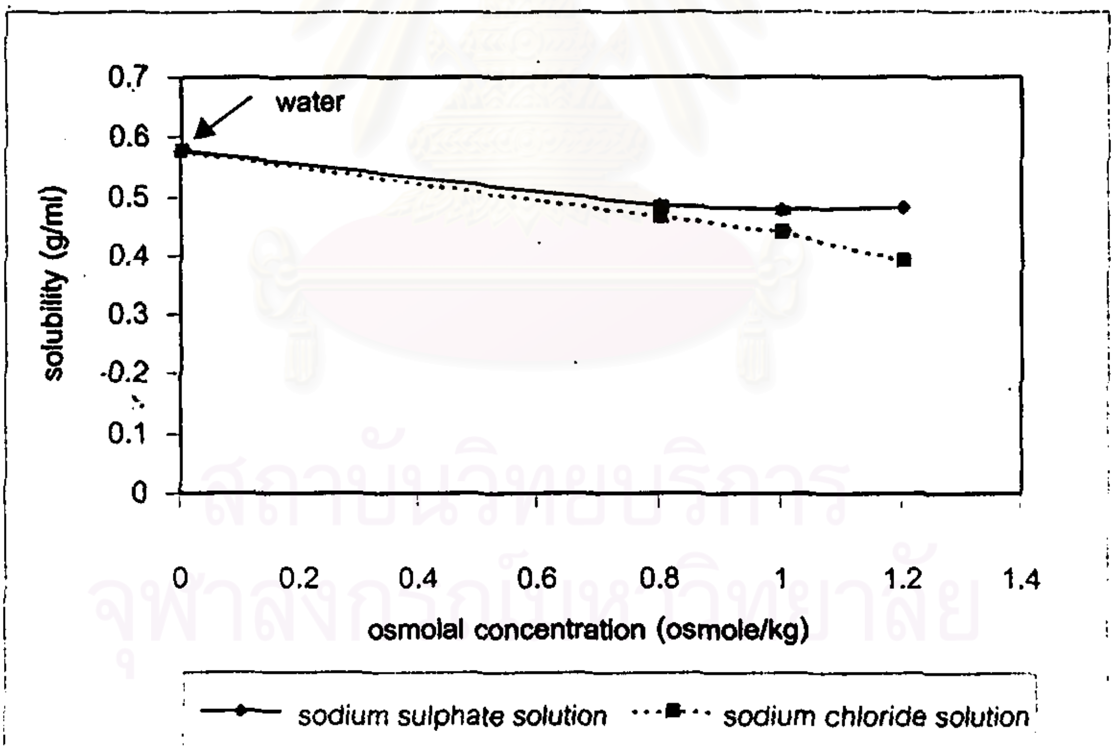


Figure 70. Solubility profile of DTZ HCl in various osmolal concentration medium.

concentration of sodium chloride in the medium. This may be due to common ion effect presented. However, this result was not observed in sodium sulphate medium. In this case, concentrations of sodium sulphate seem to have little effect on solubility of DTZ HCl.

5.5 Swelling Characteristics of Avicel PH 101® and HPC-M®

Avicel PH 101® and HPC-M® in the formulation of core pellets can swell in water as shows in Table 19.

Table 19. Swelling property in water of Avicel PH 101® and HPC-M® employed in the formulation of core pellets.

Day(s)	Volume(cc)			Average	%Swelling
	Sample1	Sample2	Sample3		
0	30	31	29.5	30.17	
1	37	37	36	36.67	21.544
2	36.5	36.5	36	36.33	20.42
3	36.5	37	36	36.5	20.99