CHAPTER III
RESULTS

1. Evaluation of Core Pellets

1.1 Physical properties of uncoated DTZ HCl pellets

In this study, DTZ HCl core pellets were prepared by extrusion and spheronization process. Avicel PH 101® was used as a filler because of its spheronization enhancing property. HPC-M® solution was used as a liquid binder.

Size and size distribution of the pellets were determined by sieve analysis and shown in Figure 12 and Table 10. It was found that each fraction showed a narrow particle size distribution and a good reproducibility, which approximately 60% of the pellets retained on sieve no.18. About 82.73% pellets were in the sieve size of 14-20 mesh cut, and can be used to fill capsule with uniform dosage unit. The average size of pellets (n = 300) was approximately 1089.05±20.47 mm.

Physical properties of uncoated DTZ HCl pellets were presented in Figure 13 and Table 11. Scanning electron micrographs of DTZ HCl pellets clearly showed that the pellets possess smooth surface and spherical shape which are ideal for coating. It was found that bulk density and tapped density were not different. The pellets had good flow property as indicated by percent Carr's compressibility (4.29±0.79%), high flow rate (264.73±3.35 g/min) and low value of angle of repose (23.88±0.14°). The percent friability was very low and the moisture content of core pellets was about 1.21±0.02%.

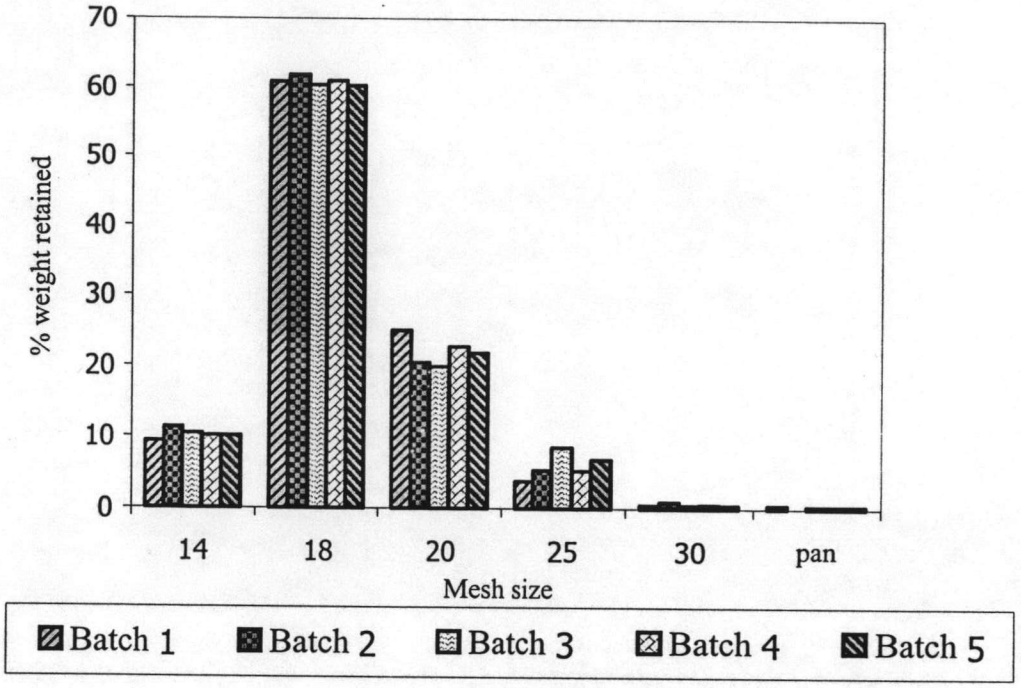
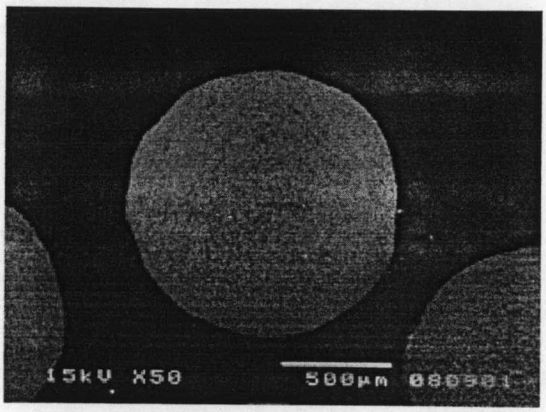


Figure 12 Size distribution histrogram of DTZ HCl pellets from five different batches

Table 10 Sieve analysis of DTZ HCl pellets

Sieve no.	% Weight retained					Average	±SD
	Batch no.						
	1	2	3	4	5		
14	9.36	11.32	10.45	10.11	10.16	10.28	0.71
18	60.70	61.77	60.24	60.87	60.14	60.74	0.65
20	25.05	20.45	19.87	22.74	21.84	21.99	2.05
14/20 mesh cut	85.75	82.22	80.11	83.61	81.98	82.73	2.10
25	3.87	5.44	8.55	5.35	6.92	6.03	1.78
30	0.53	1.00	0.47	0.56	0.54	0.62	0.22
pan	0.49	0.02	0.42	0.37	0.40	0.34	0.18
From 25-mesh	4.89	6.46	9.44	6.28	7.86	6.99	1.73
Total	100	100	100	100	100	100	0.00



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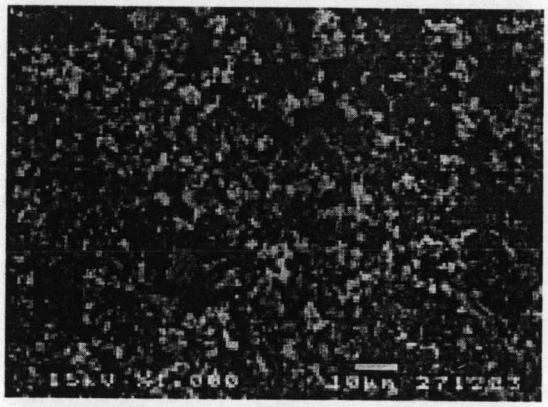

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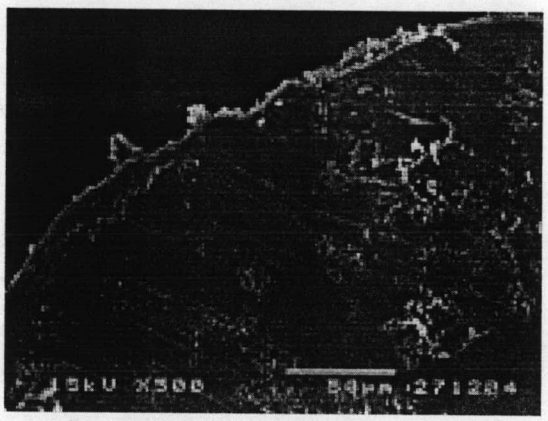


A3 × 500

Figure 13 Photomicrographs of DTZ HCl uncoated pellets.

Table 11 Physical properties of uncoated DTZ HCl pellets.

Physical Properties	
Sieve analysis	
Percentage weight retained on [a]	
Sieve # 14	10.28
Sieve # 18	60.74
Sieve # 20	21.99
Sieve # 25	6.03
Sieve # 30	0.62
pan	0.34
Persentage sieve fraction on 14/20 mesh cut pellets	82.73
Average size (μm, ±SD, n = 300)	1089.05(20.47)
Bulk density (g/ml, ±SD) [b]	0.66 (0.00)
Tapped density (g/ml, ±SD) [b]	0.69 (0.01)
Carr's compressibility (%)	4.29 (0.79)
Flow rate (g/min, ±SD) [b]	264.73 (3.35)
Angle of repose (° , ±SD) [b]	23.88 (0.14)
Percent friability (%)	0.05, 0.05
Moisture content (%)	1.21, 1.22

a = Averaged from five determinations

b = Averaged from three determinations

1.2 Dissolution profile of uncoated DTZ HCl pellets

The dissolution data of uncoated DTZ HCl pellets are shown in Table 1C (Appendix C). The release profile of uncoated DTZ HCl pellets plotted between the percentage amount of drug release as a function of time was presented in Figure 14. The uncoated DTZ HCl pellets were rapidly release about 96.16% in the first 15 minutes.

2. Preliminary Investigations for Coating Conditions and Coating Formulations

2.1 Coating conditions

The coating of DTZ HCl core pellets was performed using the same condition as described in Table 7. The suitable temperature was previously selected at 50 °C, in order to prevent tackiness which occurred if the temperature decreased to 40-45 °C. A suitable feed rate was set at 15 ml/min to avoid agglomeration of the pellets.

2.2 Coating formulations

Various kinds of wax such as carnauba wax, glyceryl monostearate (GMS), Compritol 888 ATO® and polymer (EC) were used as coating materials and organic solvent was used as medium. The pellets coated with GMS were melted and agglomerate during fluidizing process. Where as pellets coated by carnauba wax, Compritol 888 ATO® , and EC did not occurred. So, as part of the mixture of the coating solution, Compritol 888 ATO® was selected to mixed with EC and showed a good film characteristic. Because the mixture of Compritol 888 ATO® and EC provided a clear solution then various ratios of these two substances mixture were further studied.

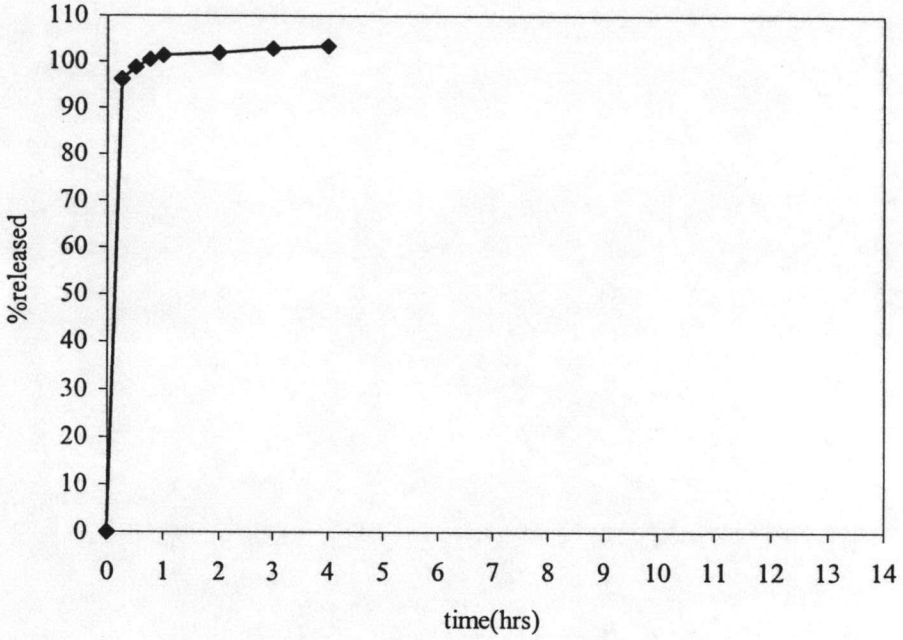


Figure 14 Dissolution profile of uncoated DTZ HCl pellets in deionized water as medium.

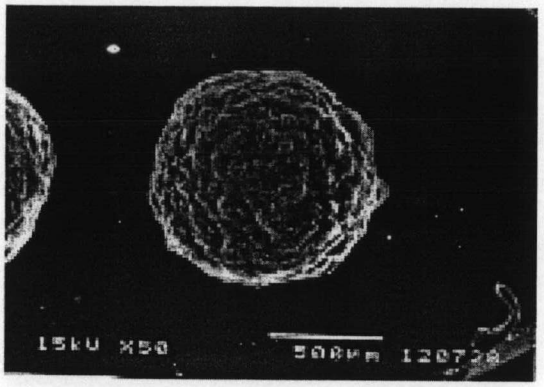
3. Evaluations of DTZ HCl Coated Pellets

3.1 Influence of various kinds of wax on morphology and release profiles of coated pellets

The morphological changes in the surface of the coated pellets before and after dissolution study were determined by scanning electron microscopy. The cross sections of DTZ HCl pellets coated with carnauba wax, GMS, and Compritol 888 ATO® were also examined

3.1.1 Carnauba wax

The results from Figures 15-17 shows the surface characteristics of pellets coated with carnauba wax 10%, 15% and 20% coating level, respectively. The surface of the coated pellets before dissolution test were irregular surface. The irregular texture of coated pellets increased when the amount of carnauba wax in the formulation increased up to 15%. However, at 20% coating level showed less surface roughness. After dissolution test, the surface of the pellets coated with 10% carnauba wax cracked and clearly shown pellet core structure. While both 15 and 20% of carnauba wax, increasing the smoother surface after dissolution test was done. This above phenomenon can be explained by slow and continuing erosion of surface wax lead to the exposure of new surfaces. The cross section of coated pellets with carnauba wax at 10, 15 and 20% of coating levels showed compact and stratified film layers.



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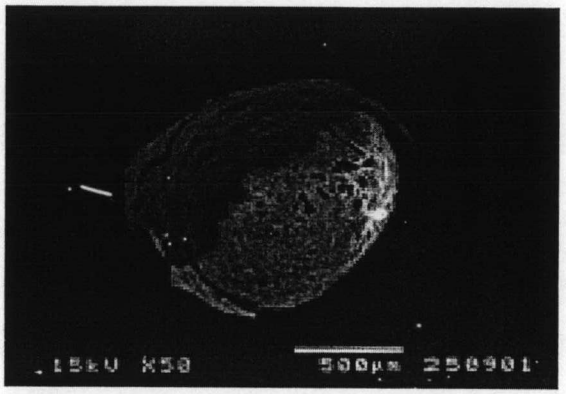

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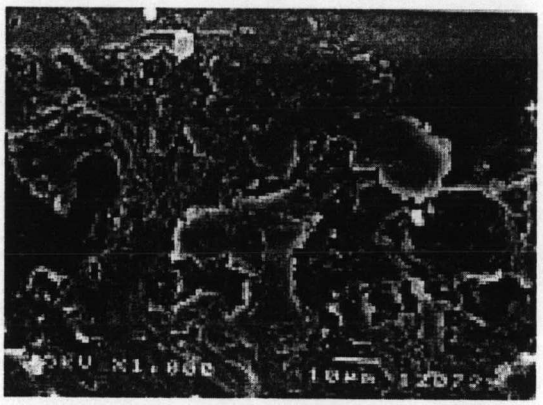

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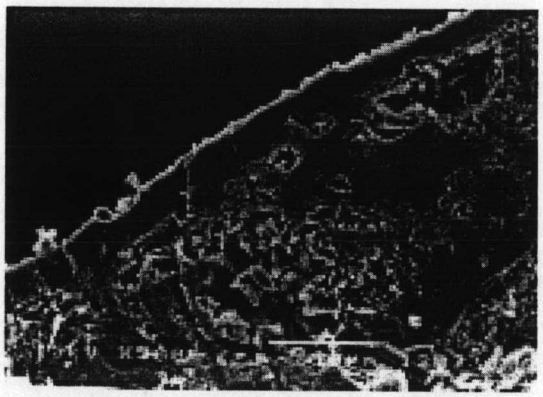
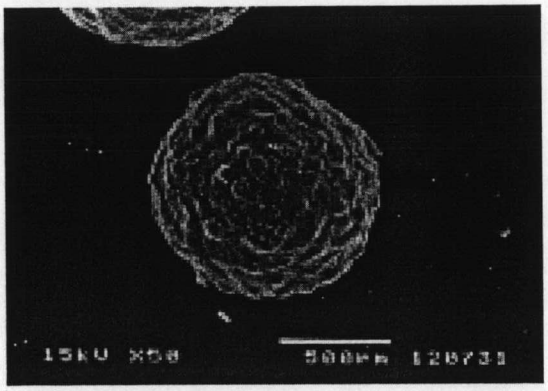


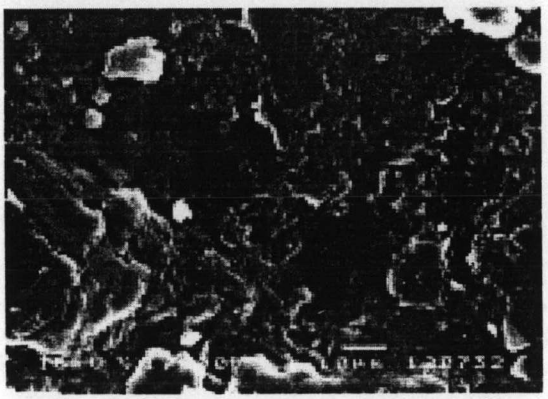
A3 × 500

Figure 15 Photomicrographs of DTZ HCl coated pellets with Carnauba wax 10% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1 is after dissolution test).



A1 × 50

B1 × 50



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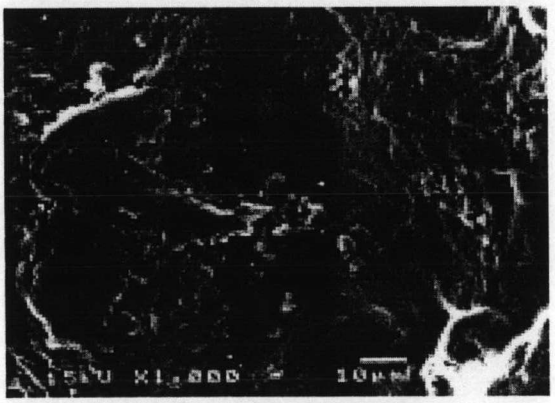

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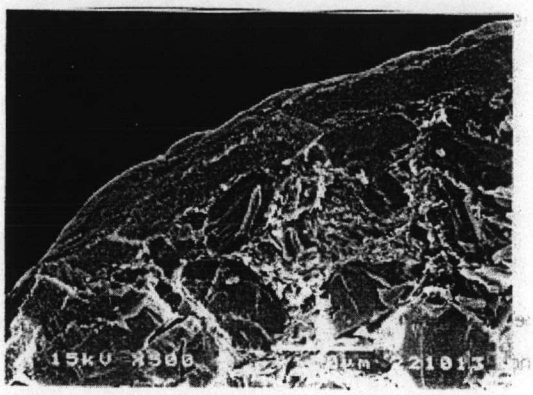

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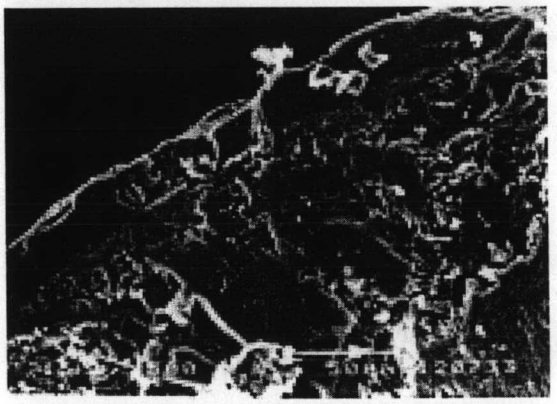
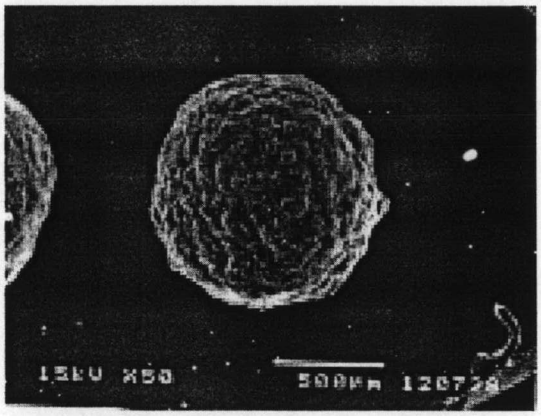


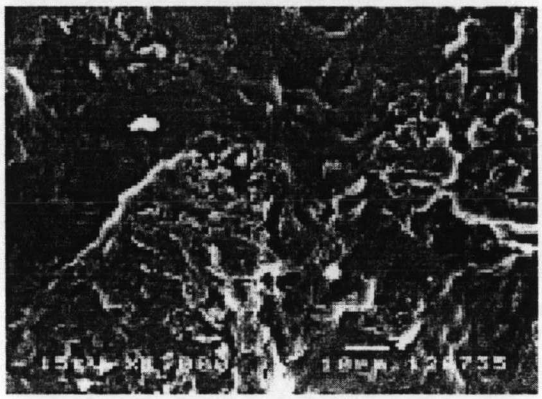
B3 × 500

Figure 16 Photomicrographs of DTZ HCl coated pellets with carnauba wax 15% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).



A1 × 50

B1 × 50



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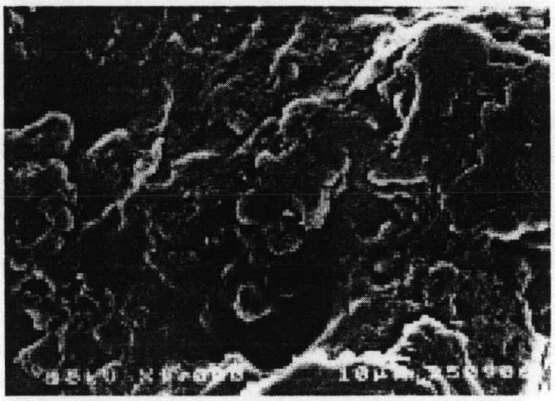

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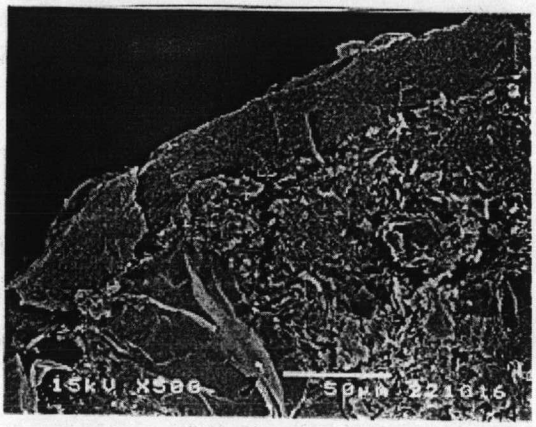

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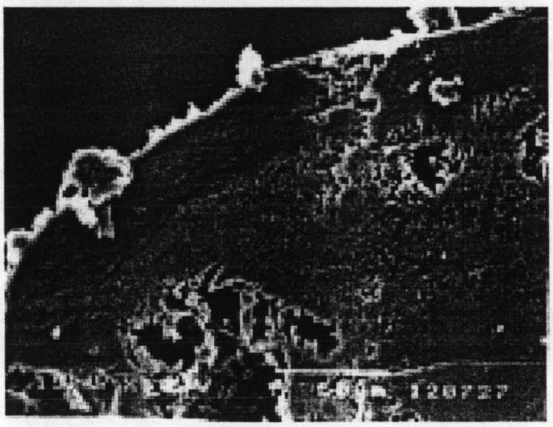


B3 × 500

Figure 17 Photomicrographs of DTZ HCl coated pellets with carnauba wax 20% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).

The released data of DTZ HCl coated pellets with carnauba wax at various percentage of coating levels were listed in Tables 2C-4C (Appendix C) and released profile of these preparations in deionized water were illustrated in Figure 18. The release rate of these formulations decreased with the time when the percentage of carnauba wax was increased. At 10% of carnauba wax showed faster release rate than 15 and 20%. The percent drug release of coated pellets with 10, 15, and 20% carnauba wax at 12 hour were 95.65%, 39.28%, and 36.07%, respectively. So, the percent drug releases were decreased with increasing amount of the wax in the formulations.

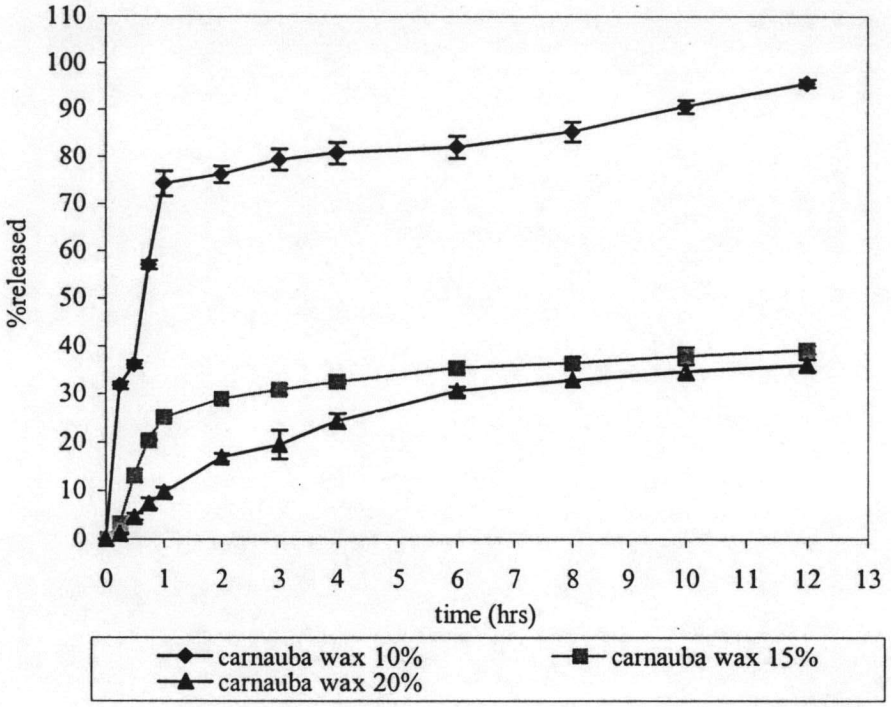
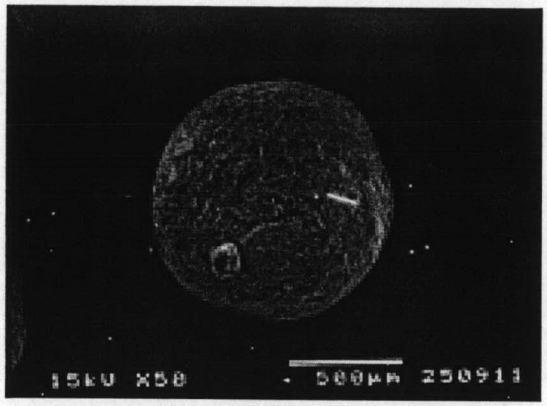


Figure 18 Effect of quantity of carnauba wax on dissolution profiles of DTZ HCl coated pellets

3.1.2 GMS

Figures 19-21 shows the microscopic image of pellets coated with GMS at 10, 20 and 30% of coating levels, respectively. The pellets showed smooth consistent surface but also had some flakes of waxes. When the higher amount of GMS was used (Figure 20), the pellets had smoother surface features than those of the lower. The cross section of coated pellets with GMS before dissolution test represented the stratified film layers. After dissolution test, the pellets coated with GMS at all coating levels left a few particles of wax adhered to the surface because the coating was removed from the coated pellets.

The release profile of pellets coated with GMS at 10-30% of coating level are shown in Figure 22 and Tables 5C-7C (Appendix C). The release rates of DTZ HCl from coated pellets containing various levels of GMS were faster than that of formulations containing carnauba wax and reached 100% drug release at the first hour.



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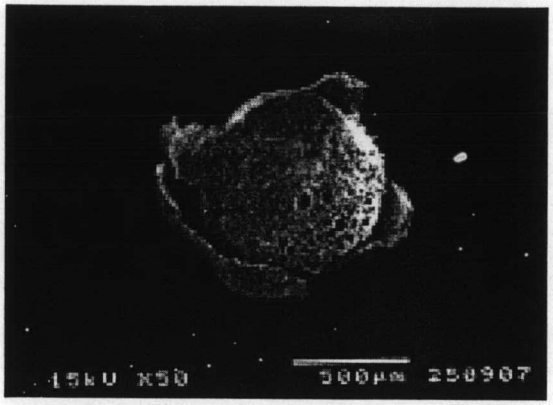
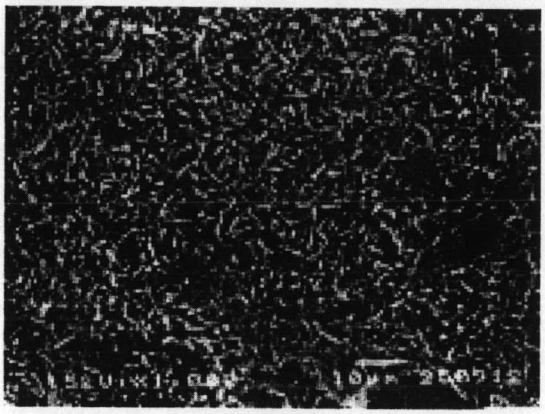


B1 × 50



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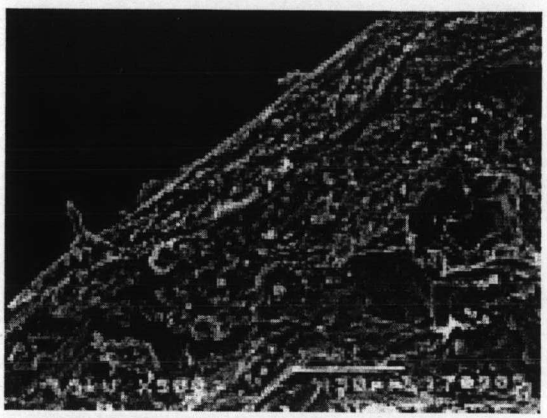
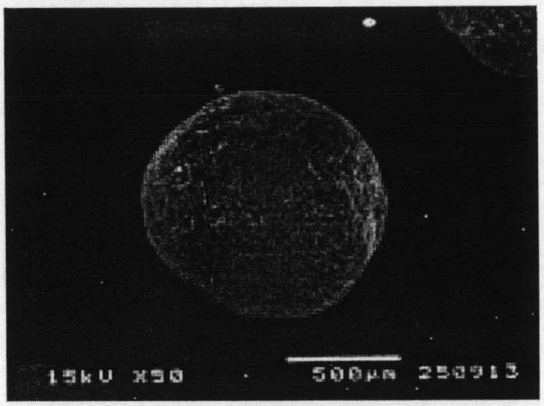
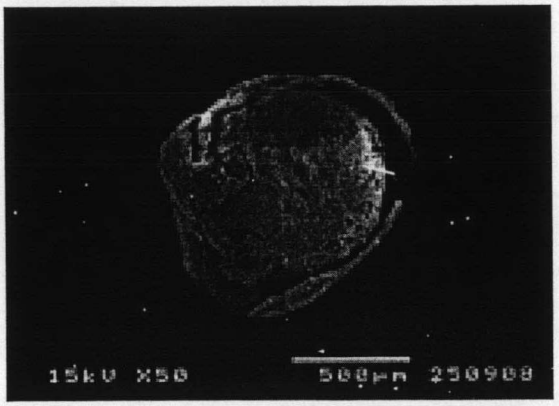


A3 × 500

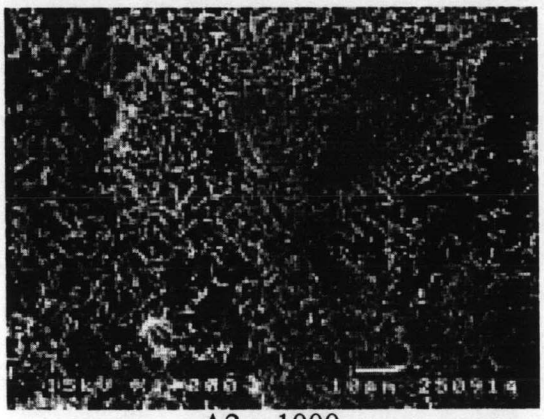
Figure 19 Photomicrographs of DTZ HCl coated pellets with glyceryl monostearate 10% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1 is after dissolution test).



A1 × 50



B1 × 50



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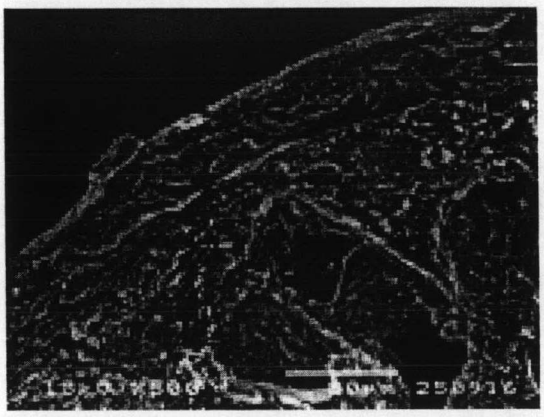
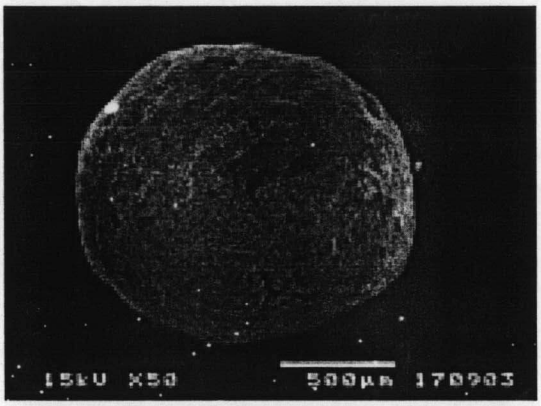
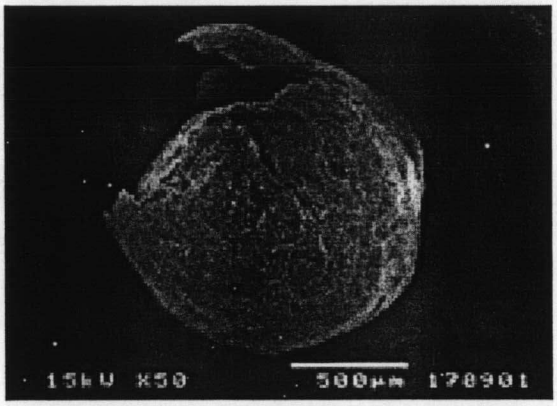


A3 × 500

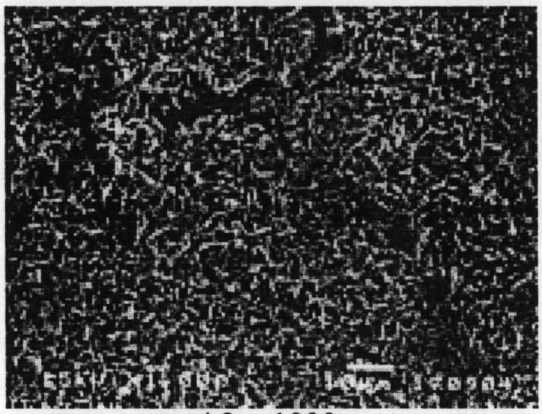
Figure 20 Photomicrographs of DTZ HCl coated pellets with glyceryl monostearate 20% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1 is after dissolution test).



A1 × 50



B1 × 50



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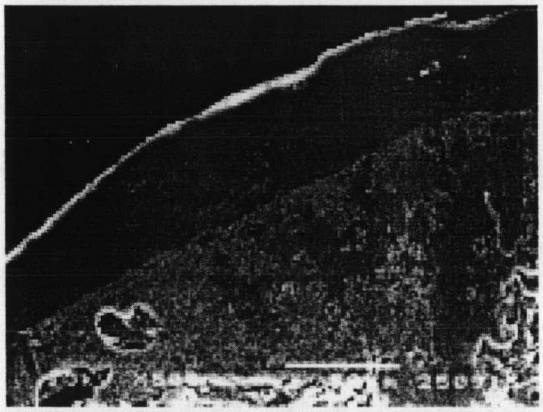


A3 × 500

Figure 21 Photomicrographs of DTZ HCl coated pellets with glyceryl monostearate 30% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1 is after dissolution test).

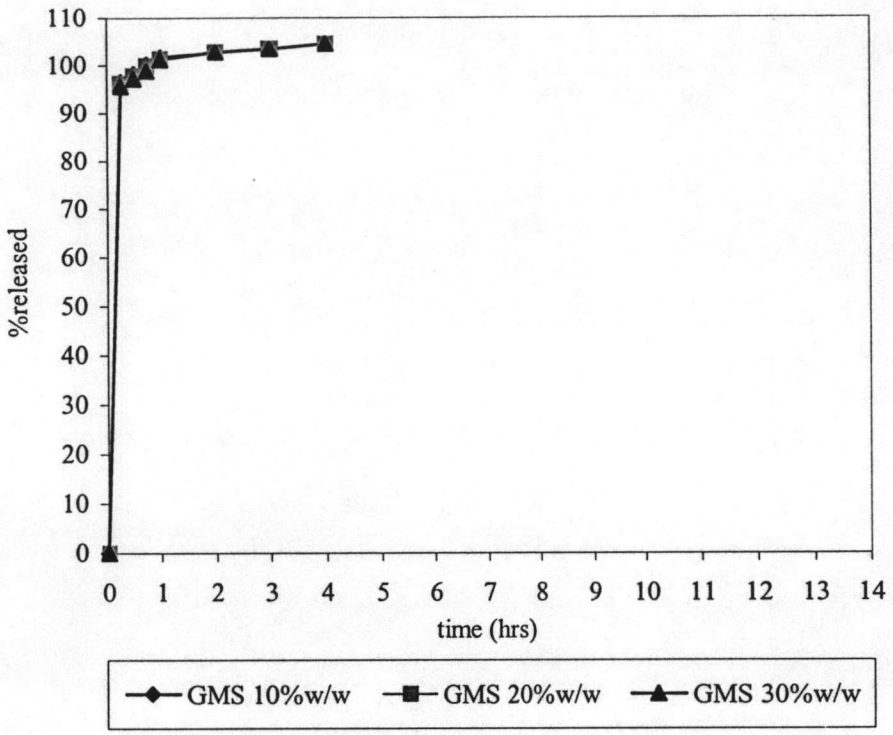
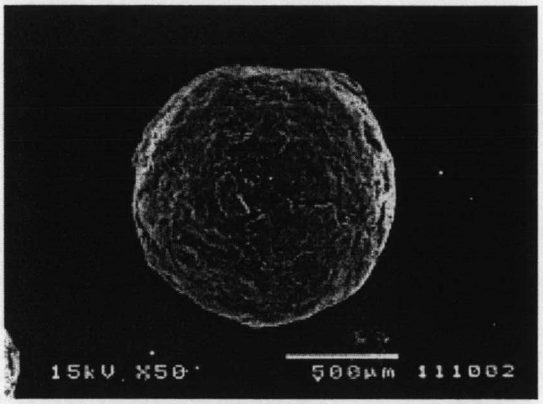


Figure 22 Effect of quantity of GMS on dissolution profiles of DTZ HCl coated pellets

3.1.3 Compritol 888 ATO®

The photomicrographs of the pellets coated with Compritol 888 ATO® at 10-60% of coating levels before and after dissolution test are shown in Figures 23-28. The coated pellets showed an uncontinuous film, and had irregular surface because the Compritol 888 ATO® had settled in stacking discontinuous film. The previous coating phenomenon depended on the amount of Compritol 888 ATO® deposited on the pellets. After dissolution test, the surface of pellets coated with Compritol 888 ATO® at 10 and 20% of coating levels were either cracked or ruptured. Higher level of Compritol 888 ATO® (30-50%w/w) had a smoother surface. At higher coating level of Compritol 888 ATO®, the surface of pellets were dense and did not show any cracks before and after dissolution test. The cross section view clearly showed that the thickness of coating film increase as function of coating material.

The release profile of pellets coated with Compritol 888 ATO® at 10-60% w/w are shown in Figure 29 and fast release rate was observed from the coated pellets with 10 and 20% of Compritol 888 ATO®. The release of these formulations were completed within one hour. At the higher coating levels of 30 to 50% of Compritol 888 ATO®, the profile showed an initial fast release and followed with constant slow release. For the formulation using Compritol 888 ATO®, the percentage release of the coated pellets with 30, 40, and 50% Compritol 888 ATO® at 12 hour were 82.43%, 72.39%, and 56.01%, respectively. The percent release of these formulations reached the plateau state within 7-8 hours. At 60% w/w of coating level, the drug dissolved from the pellets was lower than 5% within 12 hrs.



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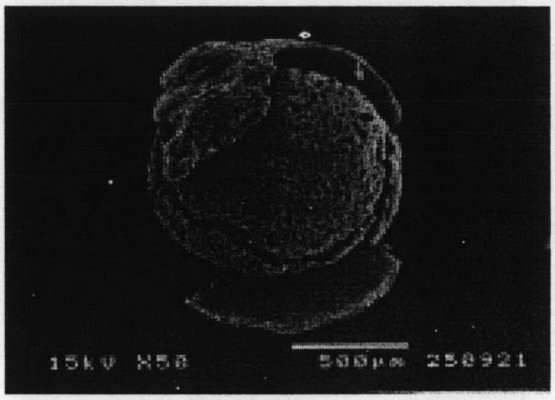
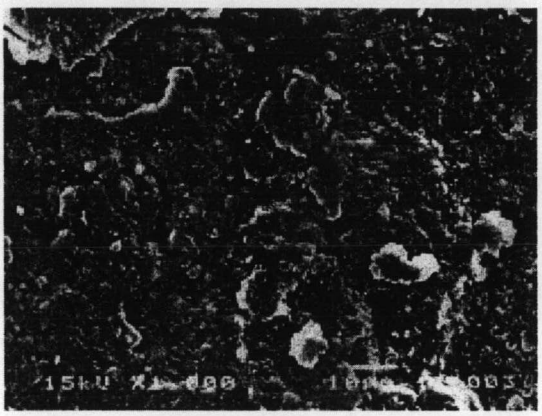


B1 × 50



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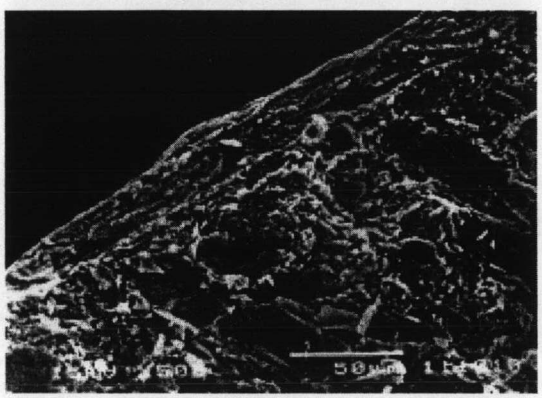
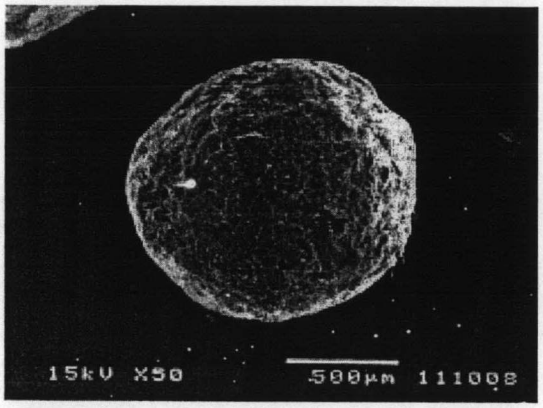
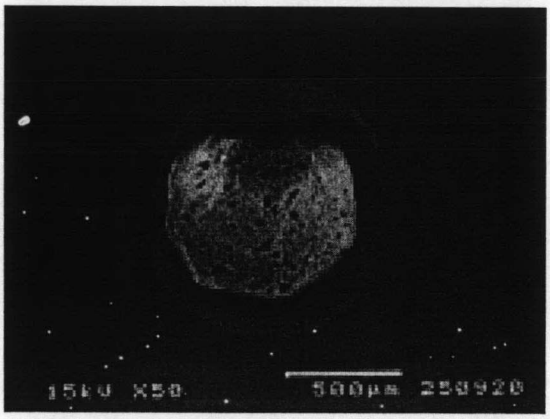


A3 × 500

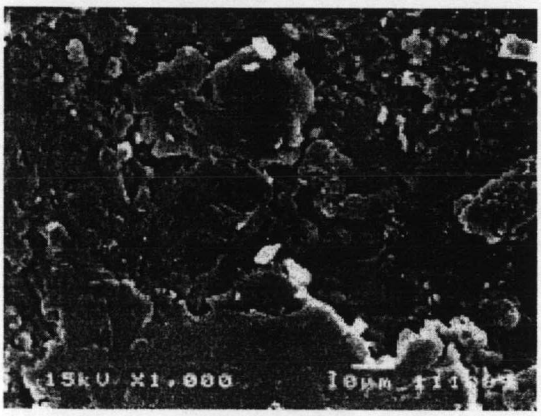
Figure 23 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO® 10% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1 is after dissolution test).



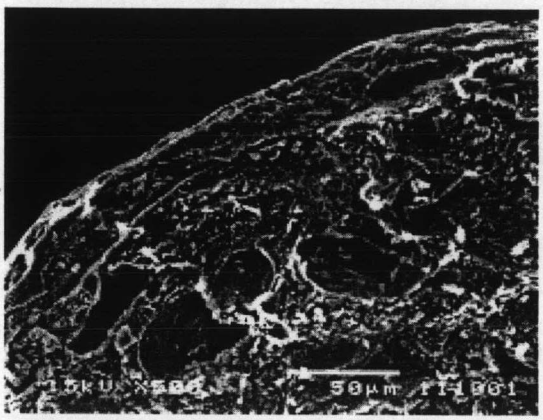
A1 × 50



B1 × 50

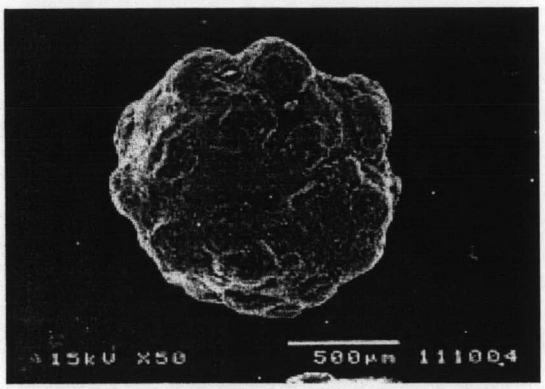


A2 × 1000



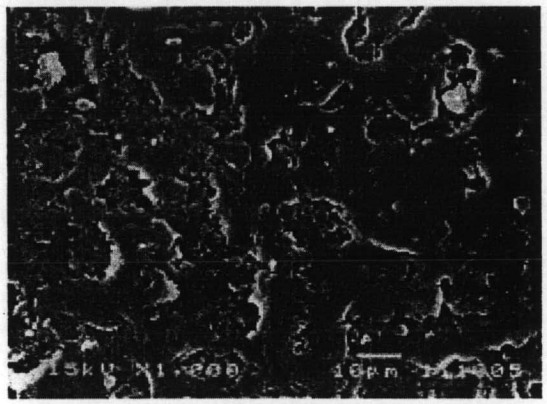
A3 × 500

Figure 24 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO® 20% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1 isafter dissolution test).

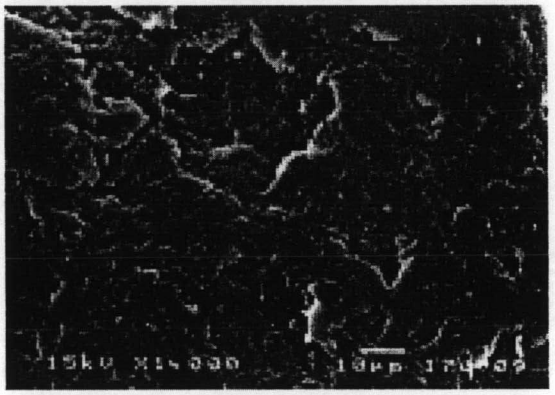


A1 × 50

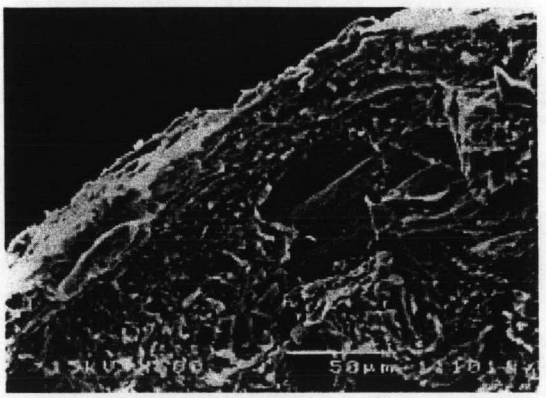
B1 × 50



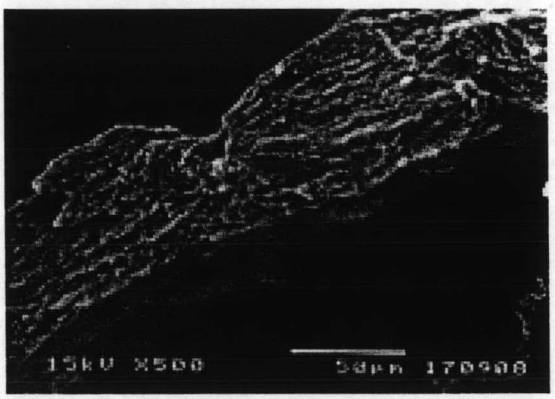
A2 × 100



B2 × 1000

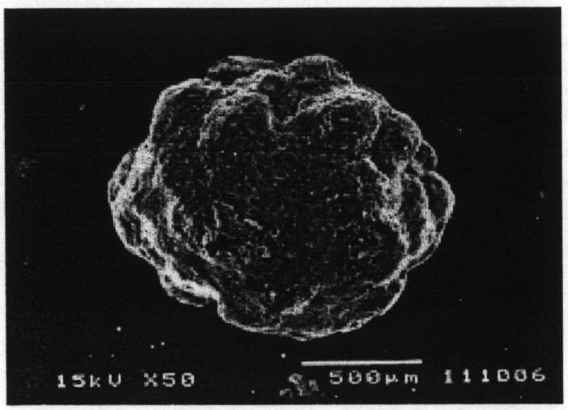


A3 × 500

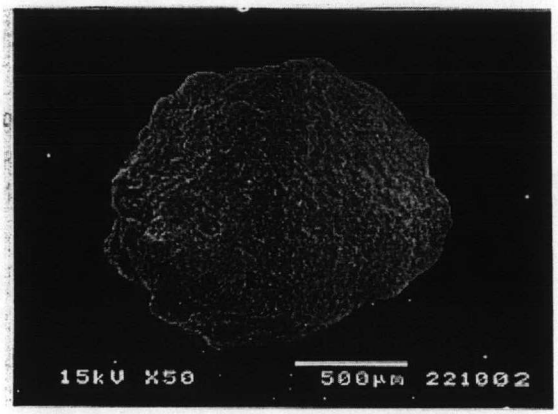


B3 × 500

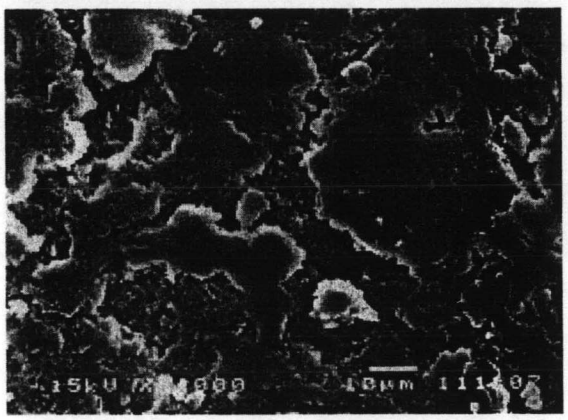
Figure 25 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO® 30% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).



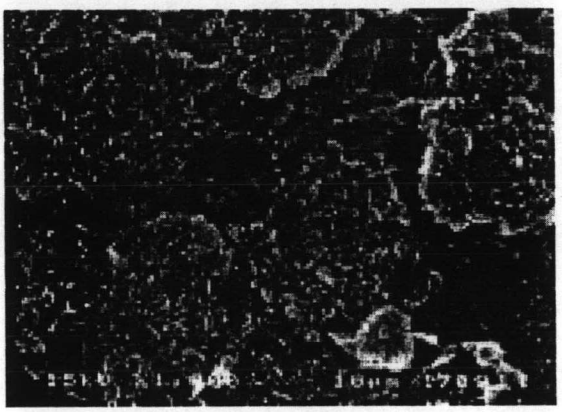
A1 × 50



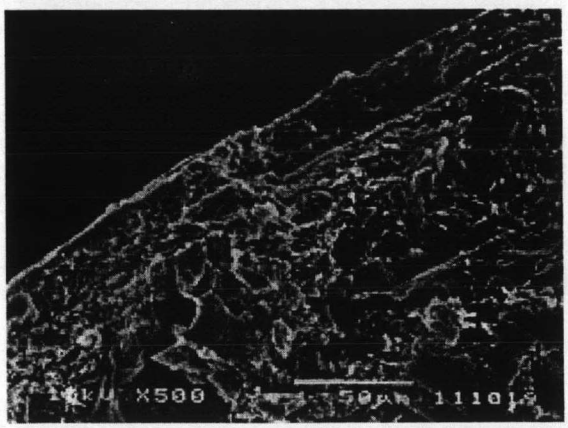
B1 × 50



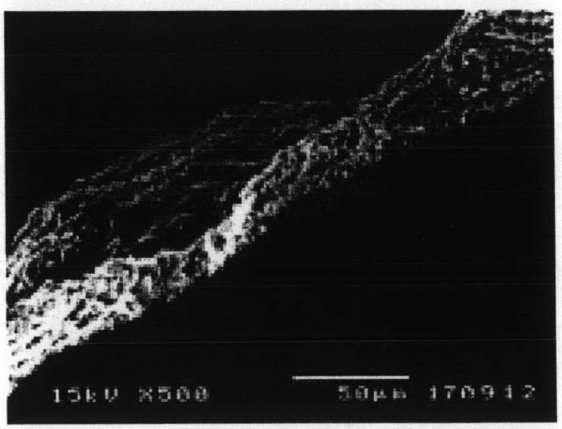
A2 × 1000



B2 × 1000

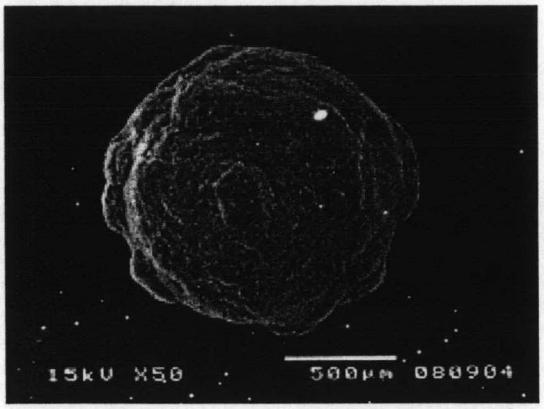


A3 × 500

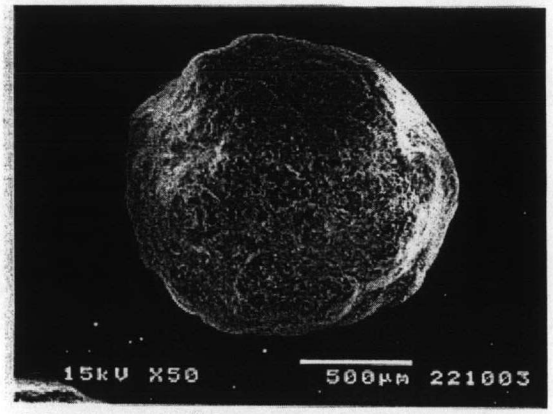


B3 × 500

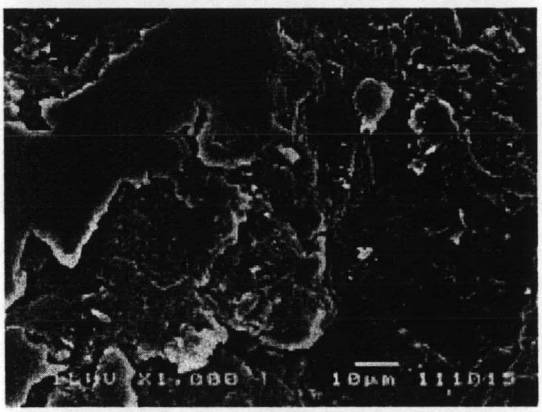
Figure 26 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO® 40% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).



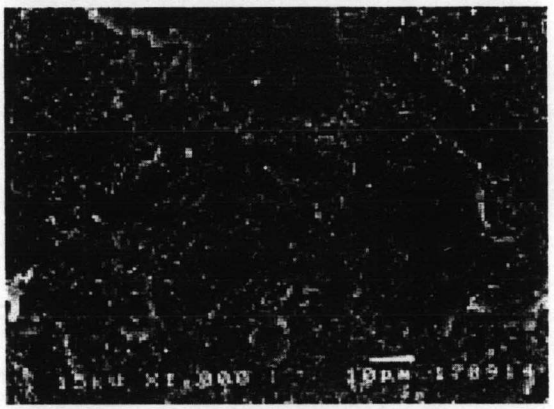
A1 × 50



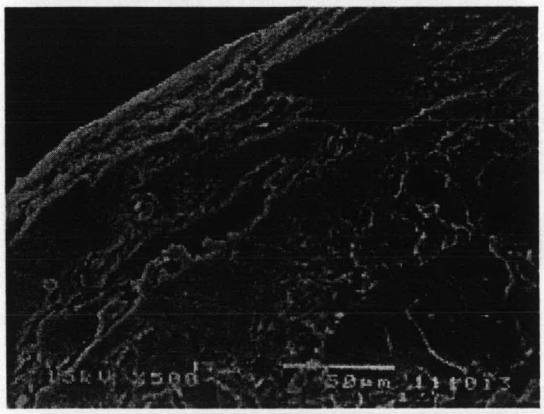
B1 × 50



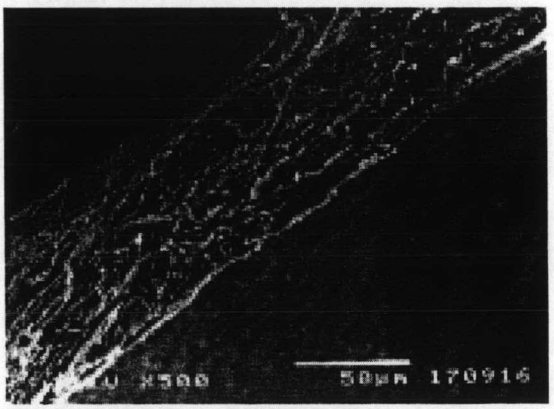
A2 × 1000



B2 × 1000

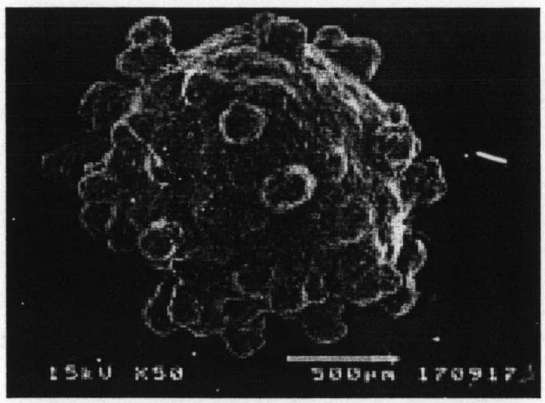


A3 × 500

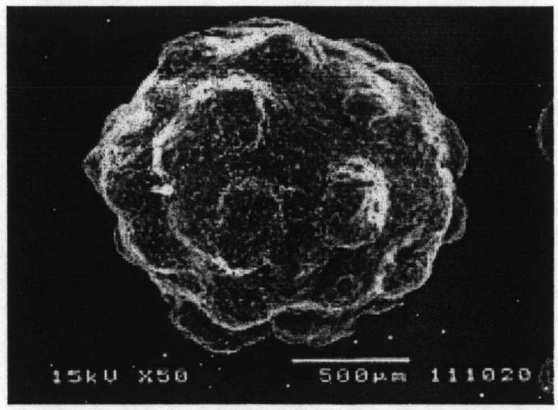


B3 × 500

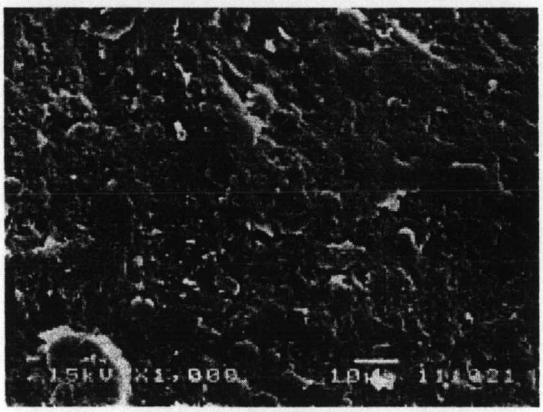
Figure 27 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®50% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).



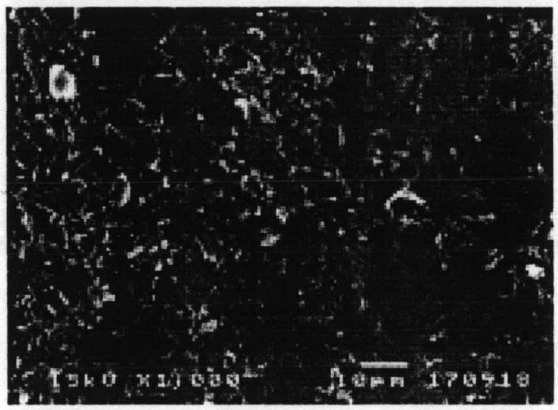
A1 × 50



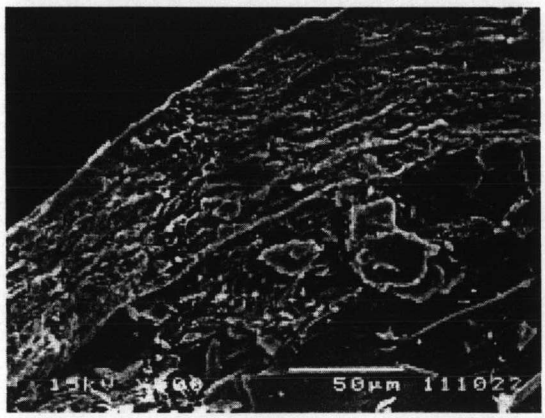
B1 × 50



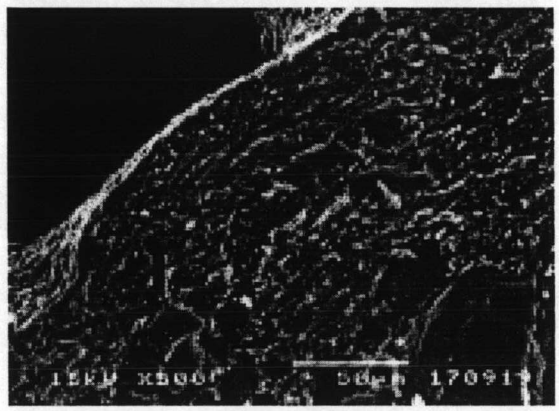
A2 × 1000



B2 × 1000



A3 × 500



B3 × 500

Figure 28 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®60% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).

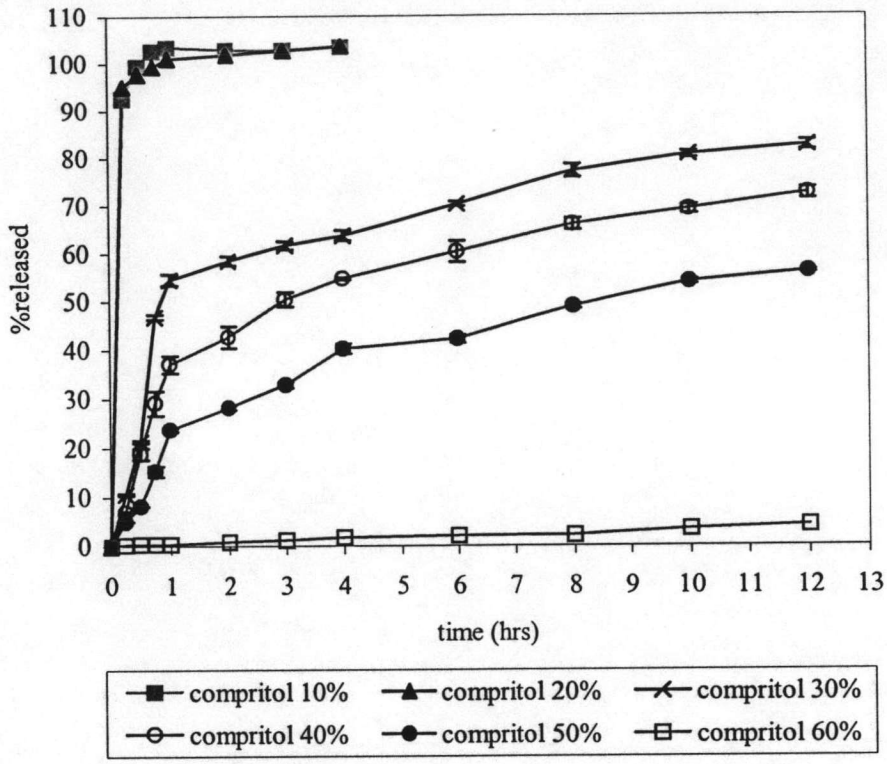
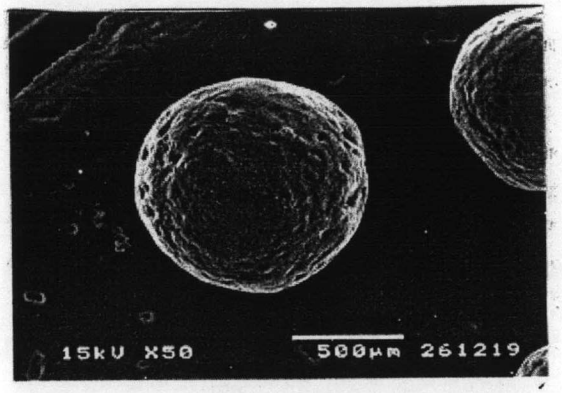


Figure 29 Effect of quantity of Compritol 888 ATO® on dissolution profiles of DTZ HCl coated pellets.

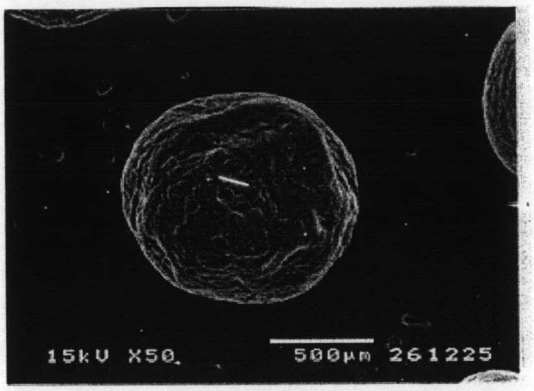
3.2 Influence of EC on morphology and release profile of coated pellets

The photomicrographs of coated pellets with EC film at 5, 7, 9 and 11% on dry polymer weight are presented in the Figures 30-33. It indicated that each coating formulation used can totally encapsulate the core pellets, and the surface of all coated pellets did not show any cracks or wicking points. After dissolution test, the cross-section of all pellets showed that the coating layers did not adhere to the surface core. The release profile of coated pellets with different percentages of EC, plasticized with 30% triethyl citrate (TEC) are shown in Figure 34 and EC film could retard the percentage release of coated pellets, especially when employed at different coating levels. When the amount of EC was increased, the release of DTZ HCl was decreased. The faster release rate was observed from the coated pellets was with 5% of EC.

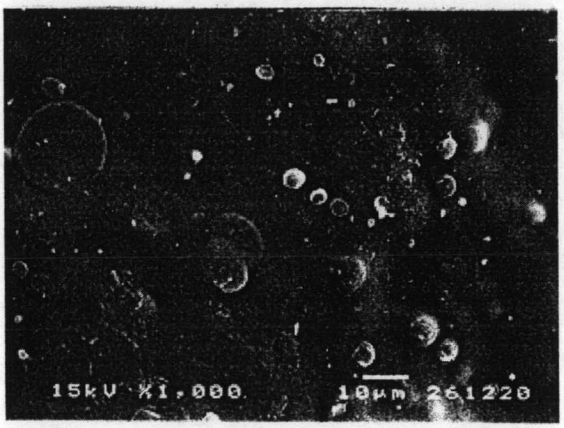
The percentage of drug release of coated pellets with 5, 7, 9, and11% of EC at 12 hour were 95.62%, 86.78%, 76.72% and 69.52%, respectively. As expected, the percent drug release decreased with increasing amount of the polymer in the formulations.



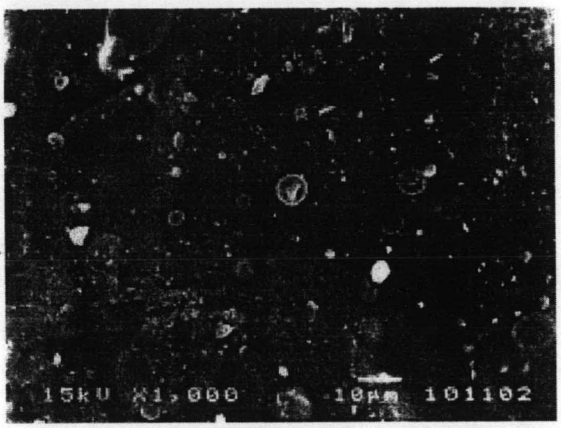
A1 × 50



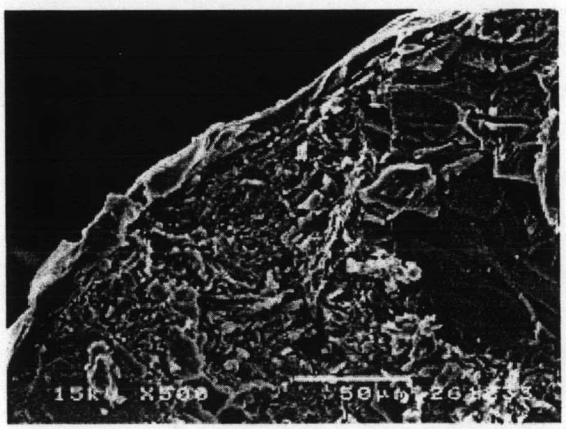
B1 × 50



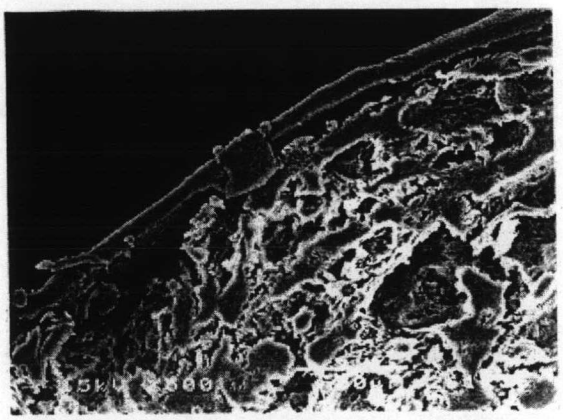
A2 × 1000



B2 × 1000

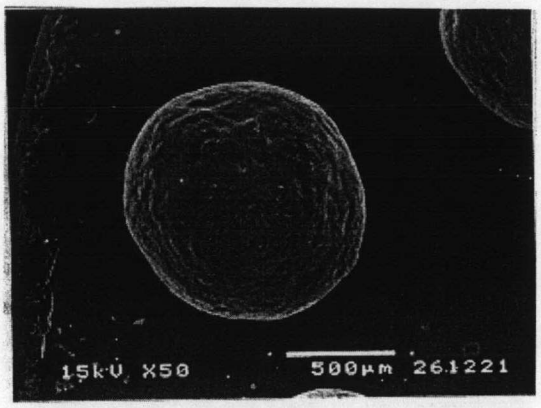


A3 × 500

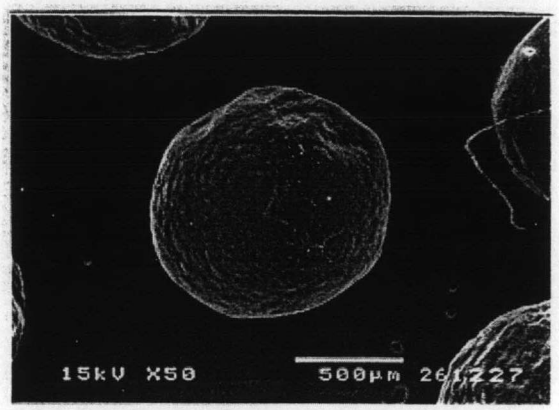


B3 × 500

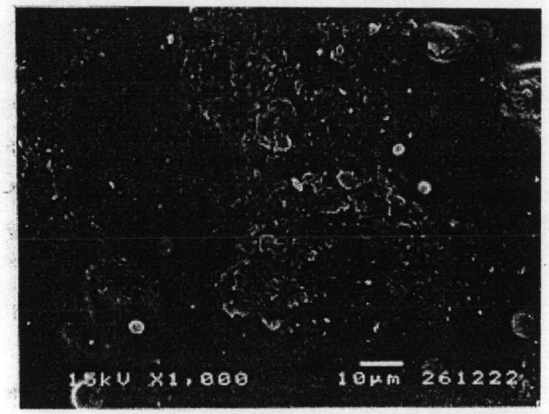
Figure 30 Photomicrographs of DTZ HCl coated pellets with EC 5% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2, B3are after dissolution test).



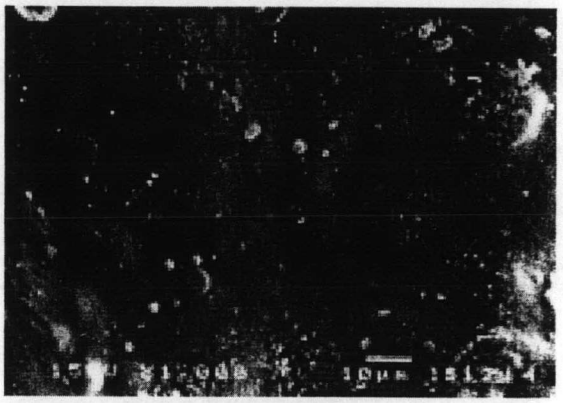
A1 × 50



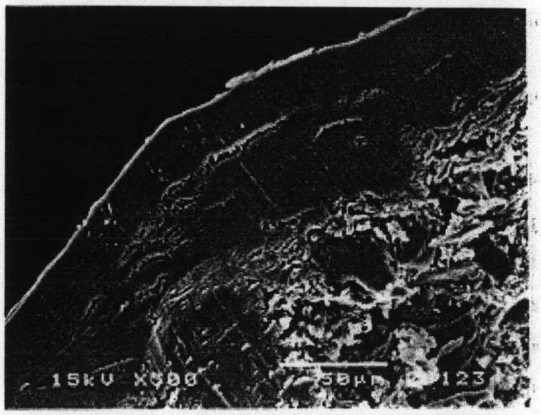
B1 × 50



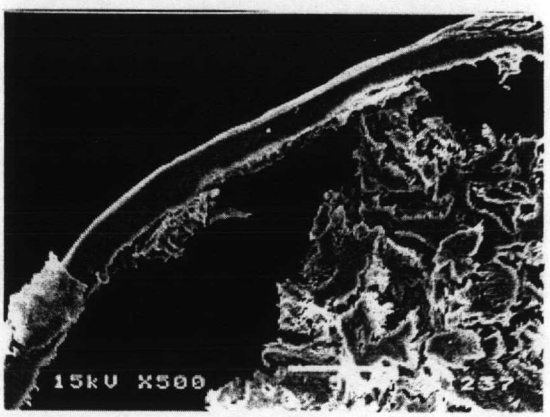
A2 × 1000



B2 × 1000

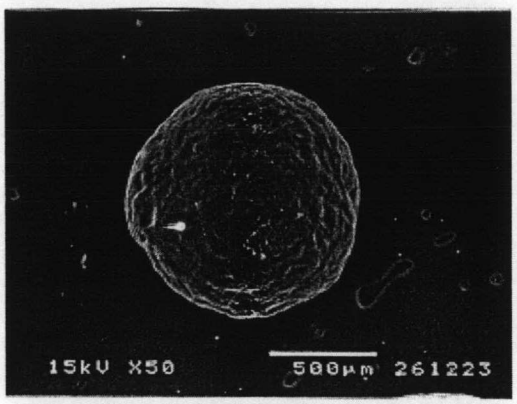


A3 × 500

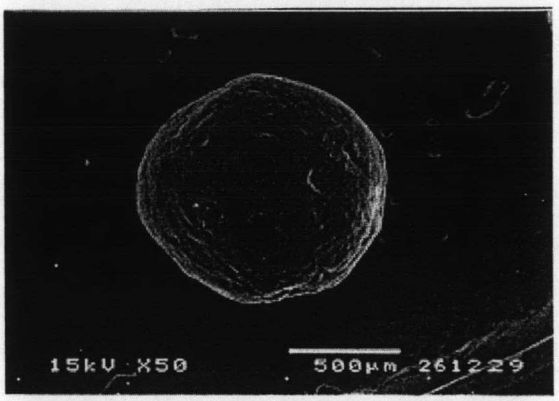


B3 × 500

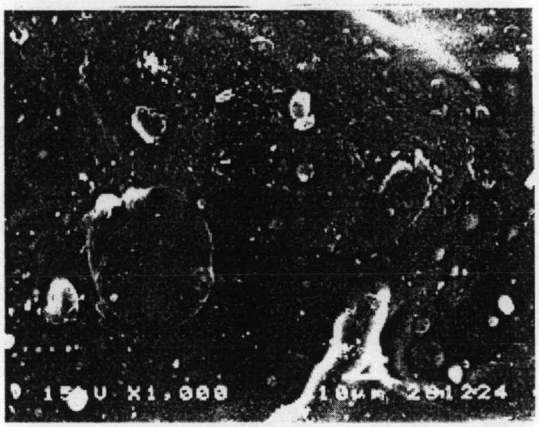
Figure 31 Photomicrographs of DTZ HCl coated pellets with EC 7% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2, B3 are after dissolution test).



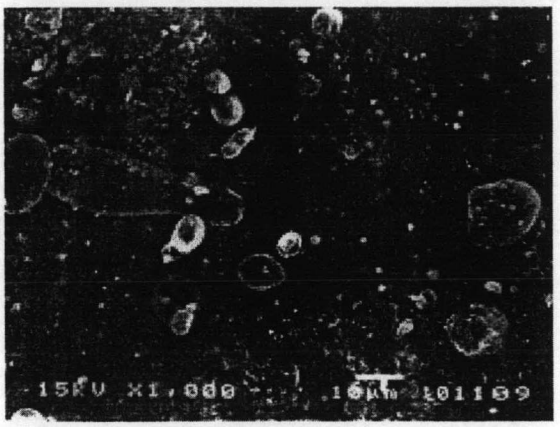
A1 × 50



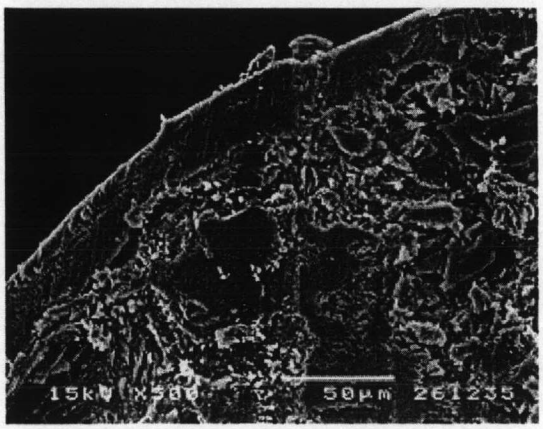
B1 × 50



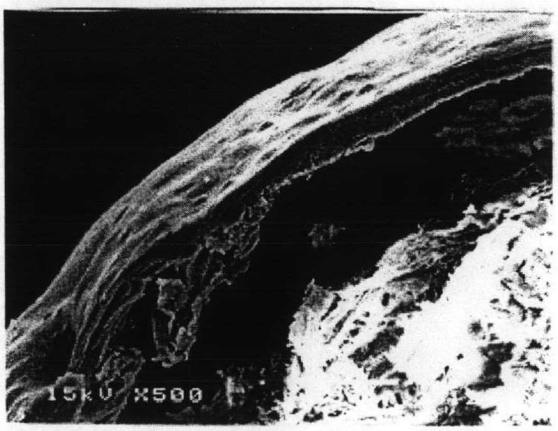
A2 × 1000



B2 × 1000

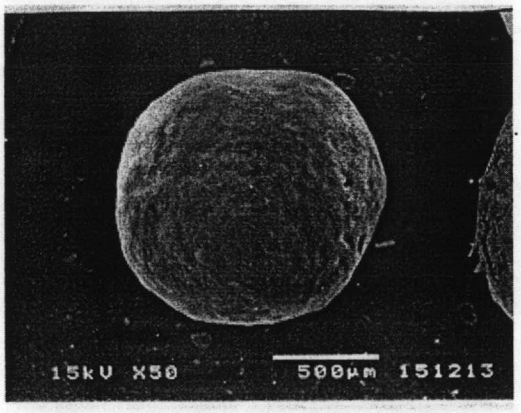


A3 × 500

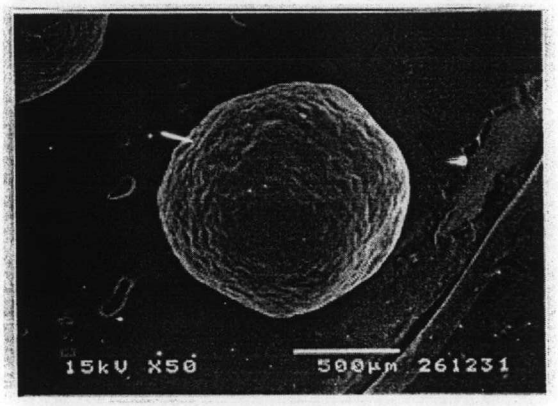


B3 × 500

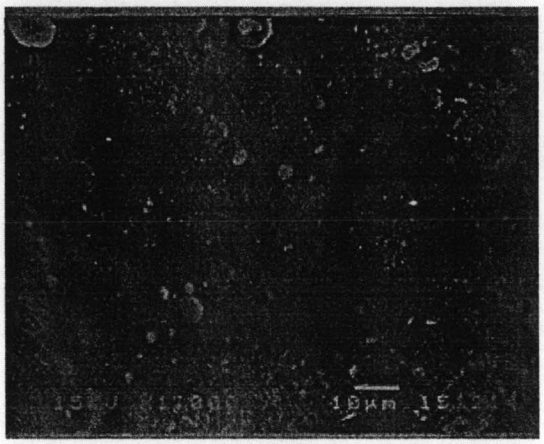
Figure 32 Photomicrographs of DTZ HCl coated pellets with EC 9% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2, B3 are after dissolution test).



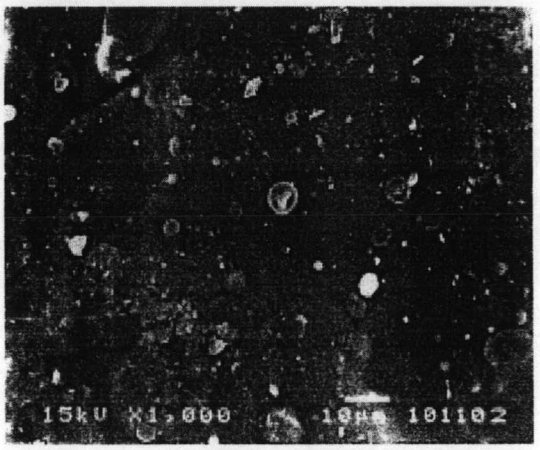
A1 × 50



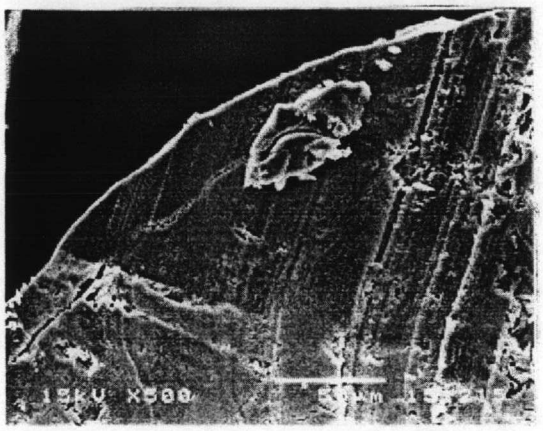
B1 × 50



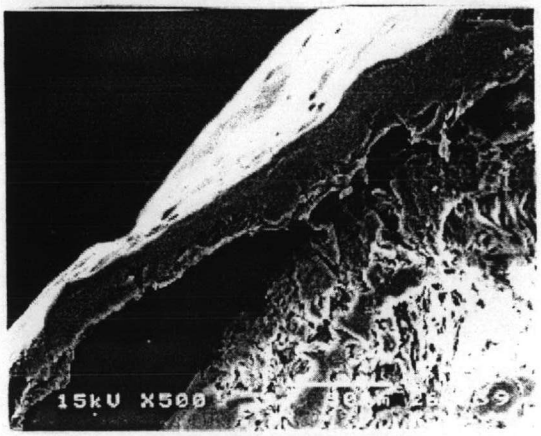
A2 × 1000



B2 × 10000



A3 × 500



B3 × 500

Figure 33 Photomicrographs of DTZ HCl coated pellets with EC 11% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2, B3 are after dissolution test).

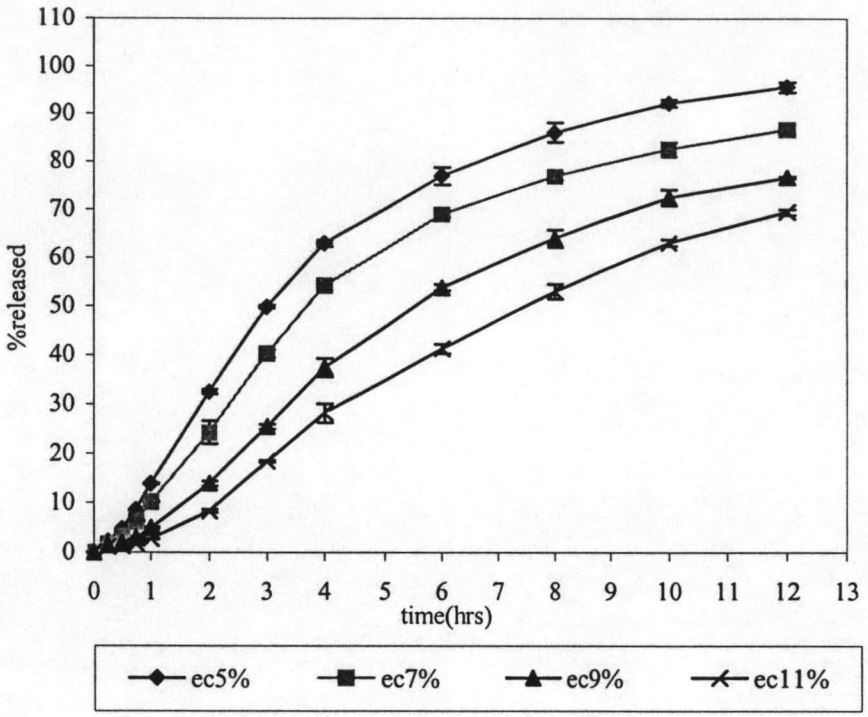


Figure 34 Effect of quantity of EC on dissolution profiles of DTZ HCl coated pellets.

3.3 Influence of the combination of Compritol 888 ATO®and EC on morphology of coated pellets

From preliminary studies, Compritol 888 ATO® was better than carnauba wax and GMS. However, Compritol 888 ATO® alone could not modify the release of DTZ HCl to meet the requirement of USP 24. Combination between Compritol 888 ATO® and EC was selected coat at various proportions.

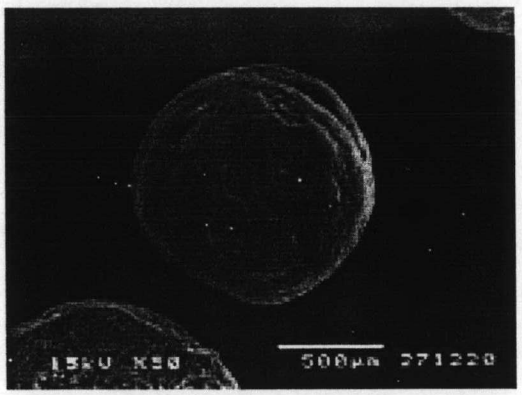
Figures 35-37 presents the photomicrographs of coated pellets obtained from the mixture of Compritol 888 ATO® and EC in the ratio of 1:1 at 10, 15 and 20% coating level. The coating of pellet with these three different percentage of coating levels gave rough and small waxy flakes on the surface, however the surface of coated pellet with 20% of coating level was smoother than those of the other levels.

At the same magnification, the surface morphology of the pellet coated with Compritol 888 ATO® and EC with the ratio of 2:1, 3:1 and 4:1 at 10, 15 and 20% of coating level (Figures 38-46) are illustrated to be visibly different from that of the pellets coated with Compritol 888 ATO® and EC with the ratio of 1:1 which exhibited many spots of wax. The Compritol 888 ATO® and EC coated pellets in the ratio of 2:1 at 10, 15 and 20% of coating level are presented in Figures 38-40. The higher percentage of coating level is smoother and showed more homogeneous surface than the lower percentage.

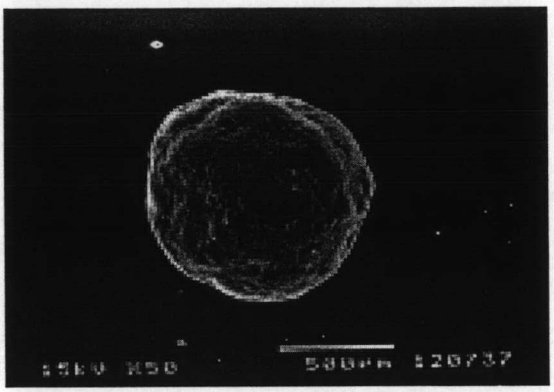
Similarly, for the film mixture of Compritol 888 ATO® and EC in the ratio of 3:1 and 4:1, the smoother films were obtained when higher percentage of coating level (Figures 41-46).

The cross section of the coated pellets of all ratio of Compritol 888 ATO® and EC at 10, 15 and 20% of coating level showed a clear interface between the core and the coating. The film layer displayed compact, smooth and uniform features.

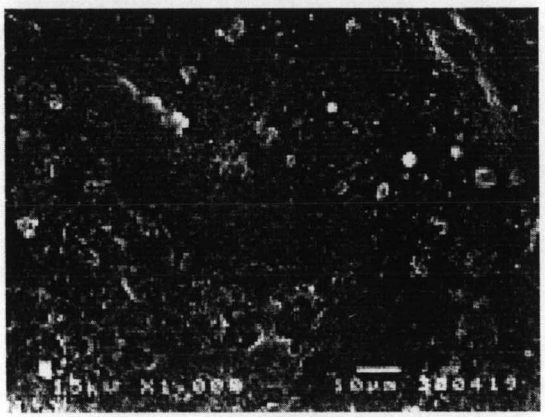
After dissolution test, the cross section of the pellets coated with Compritol 888 ATO® and EC with the ratio of 1:1, 2:1, 3:1 and 4:1 at 10 and 15 % of coating level showed that the coating layers did not adhere to the surface core. The film of 20% coating level was more smooth and dense than that of the lower coating level.



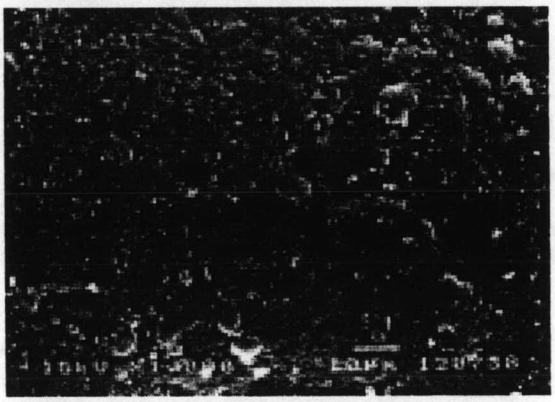
A1 × 50



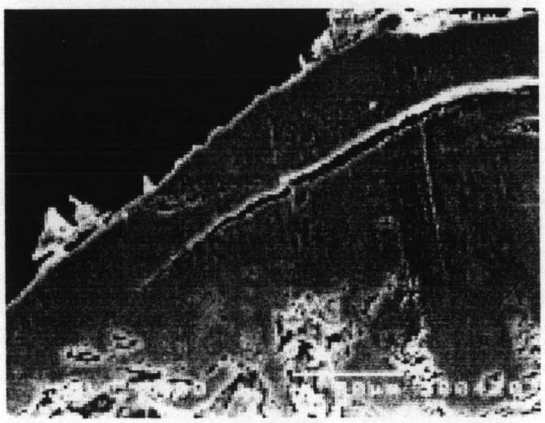
B1 × 50



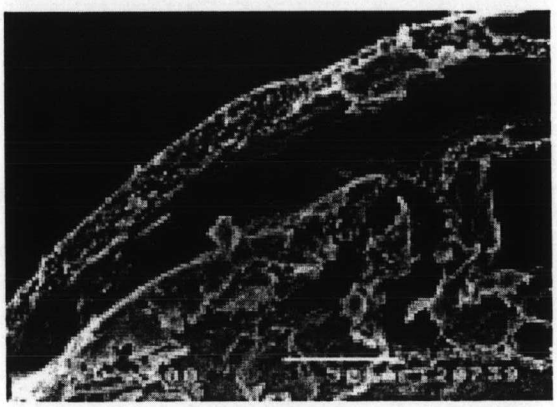
A2 × 1000



B2 × 1000



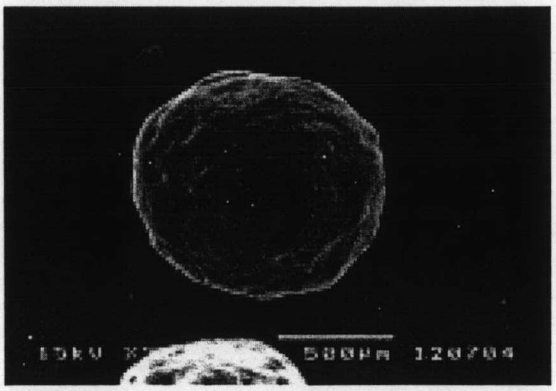
A3 × 500



B3 × 500

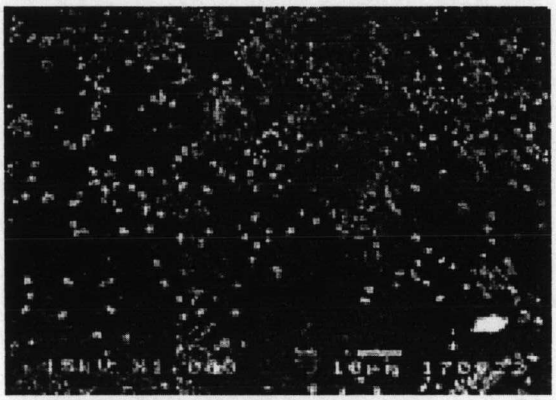
Figure 35 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (1:1) 10% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).

A1 × 50

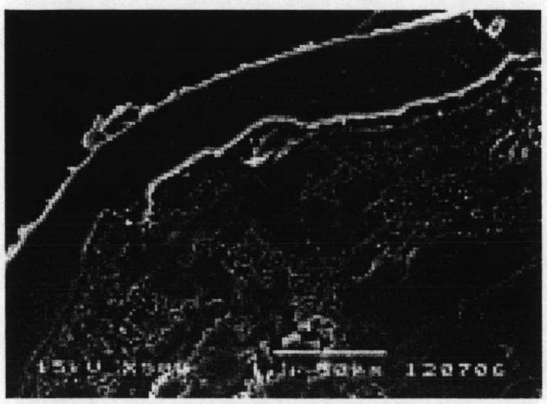


B1 × 50

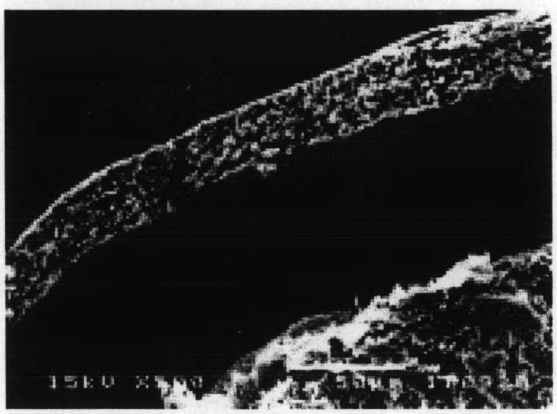
A2 × 1000



B2 × 1000

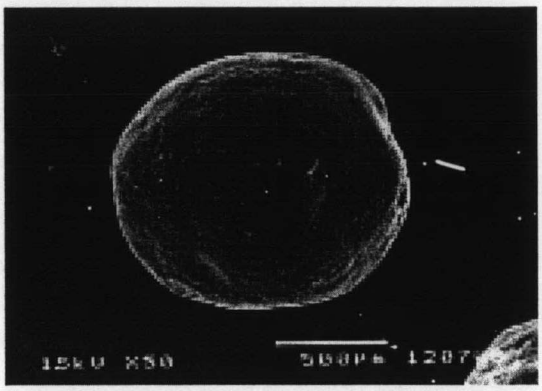


A3 × 500

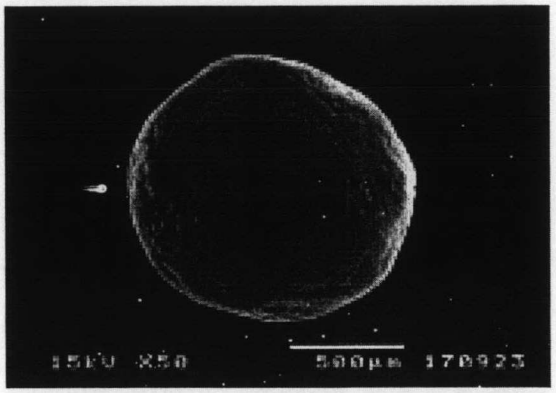


B3 × 500

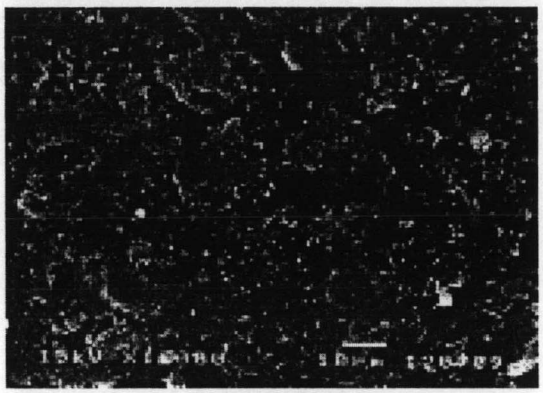
Figure 36 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (1:1) 15% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



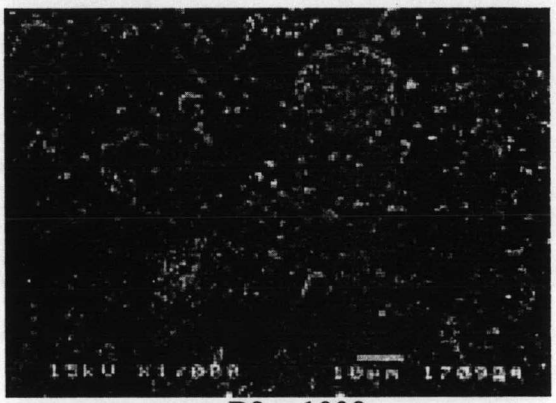
A1 × 50



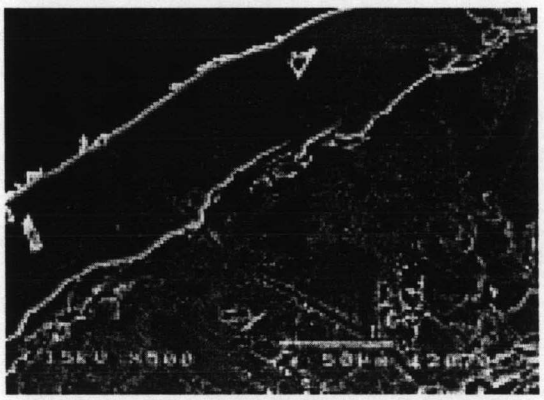
B1 × 50



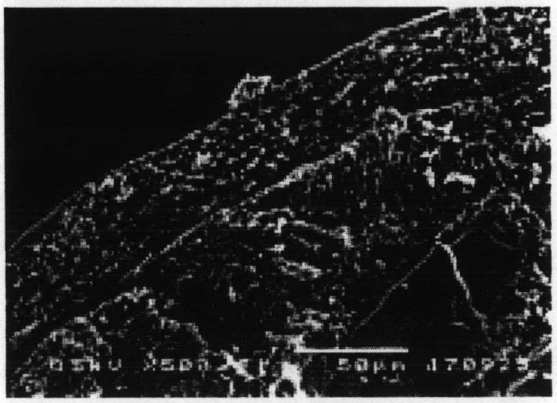
A2 × 1000



B2 × 1000

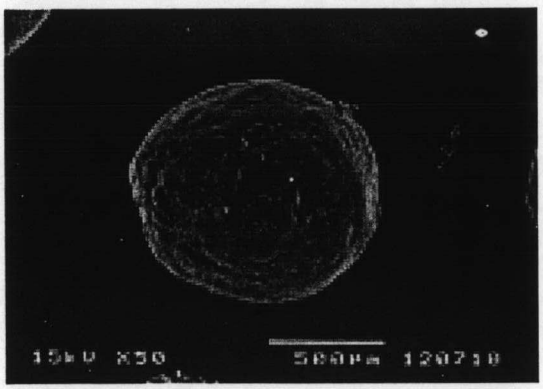


A3 × 500

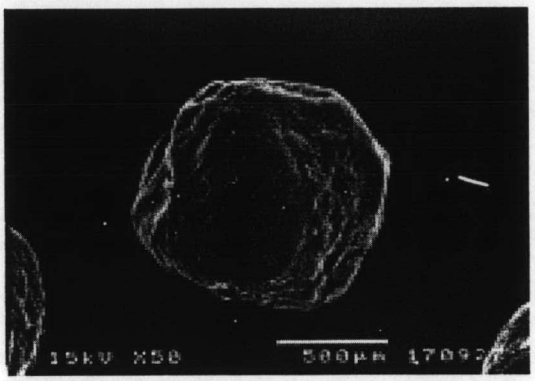


B3 × 500

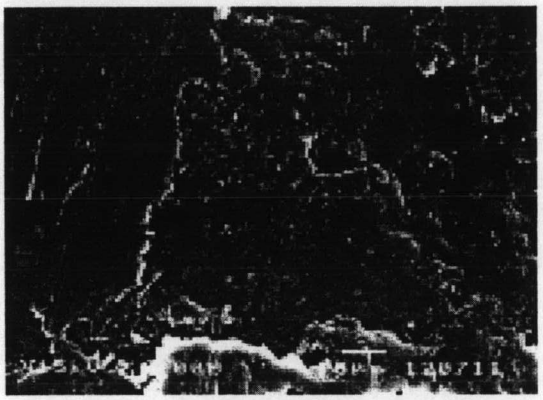
Figure 37 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (1:1) 20% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



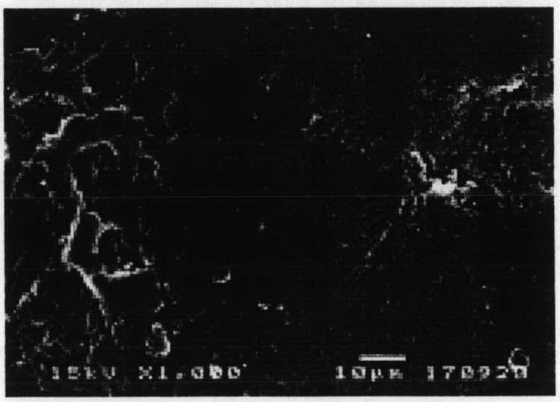
A1 × 50



B1 × 50



A2 × 1000

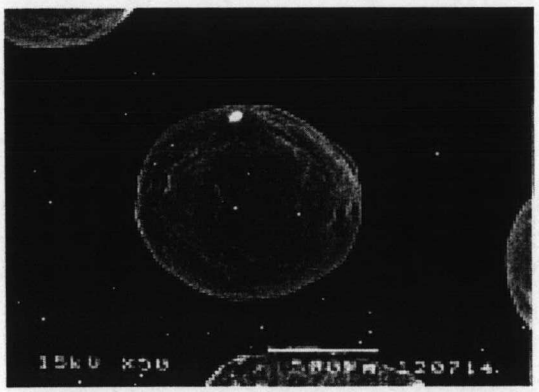


B2 × 1000

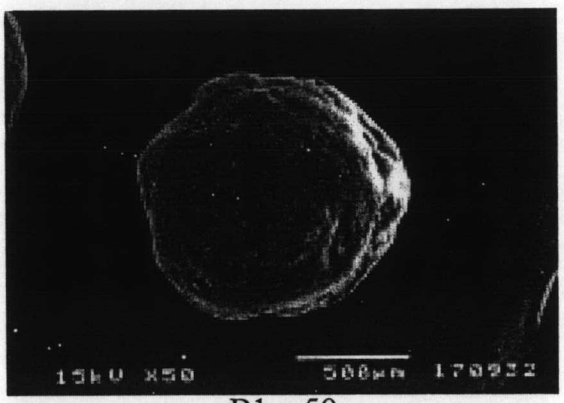
A3 × 500

B3 × 500

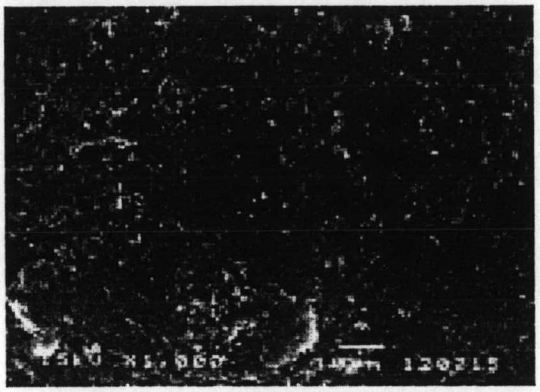
Figure 38 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (2:1) 10% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



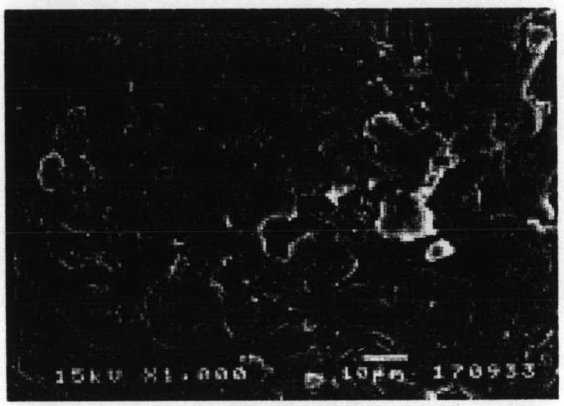
A1 × 50



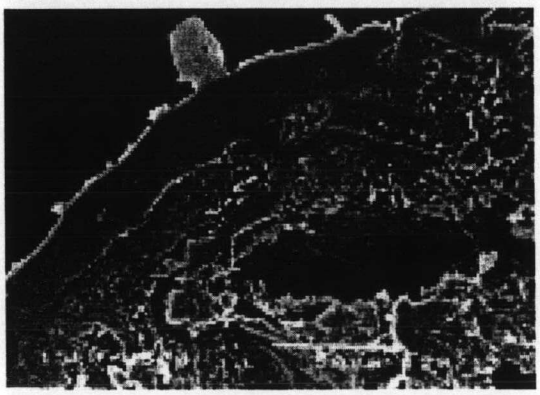
B1 × 50



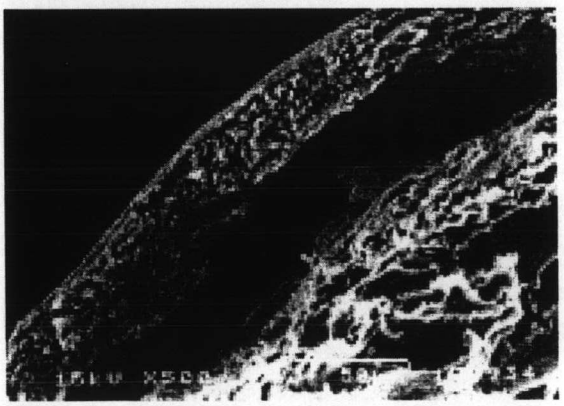
A2 × 1000



B2 × 1000

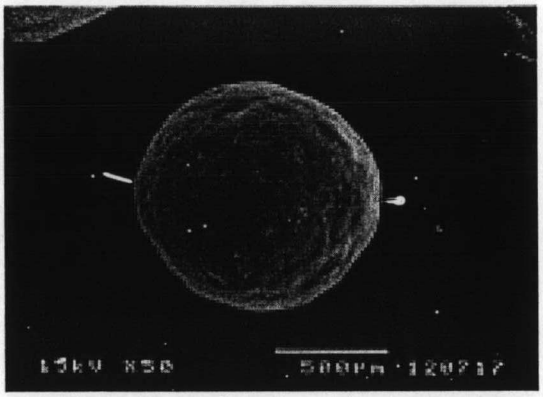


A3 × 500

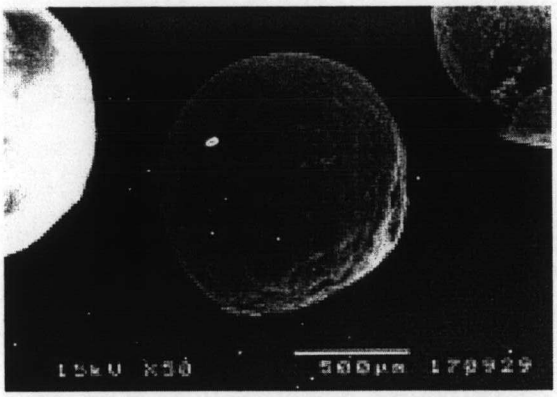


B3 × 500

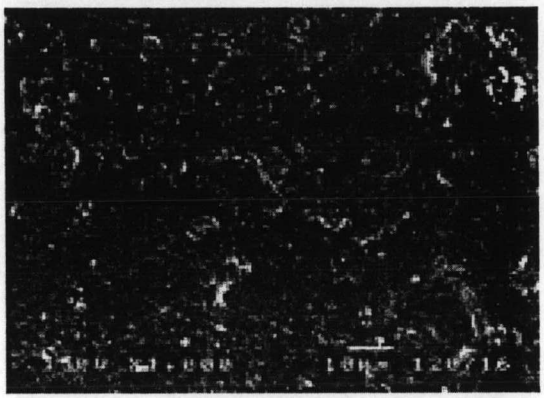
Figure 39 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (2:1) 15% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



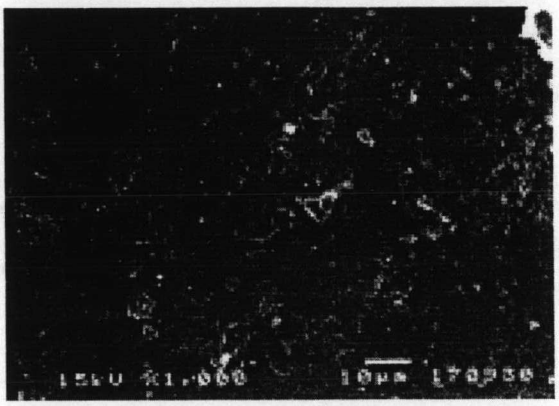
A1 × 50



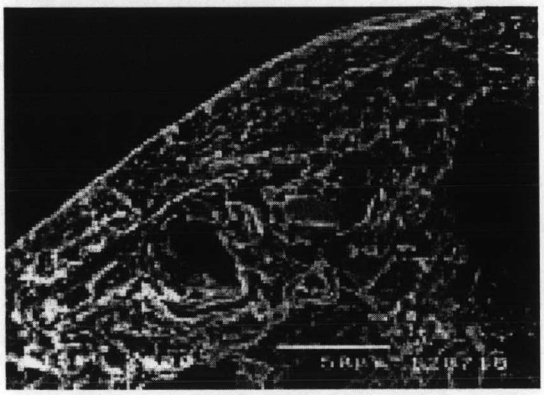
B1 × 50



A2 × 1000



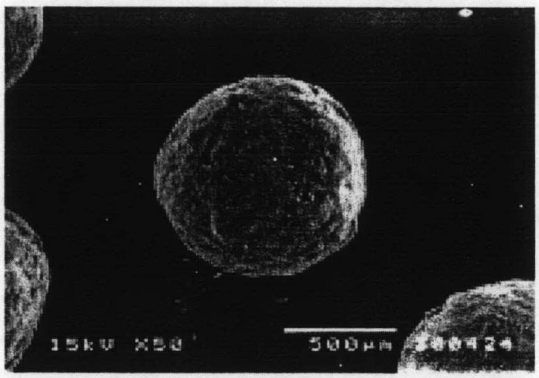
B2 × 1000



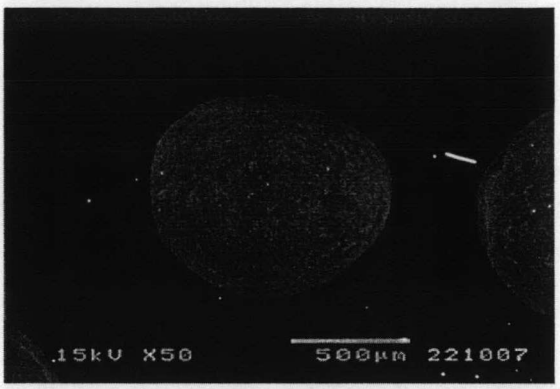
A3 × 500

B3 × 500

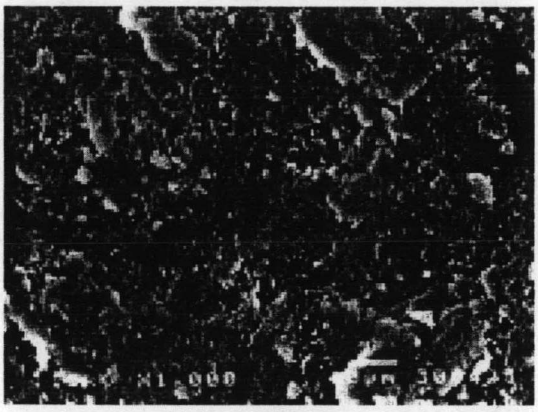
Figure 40 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (2:1) 20% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



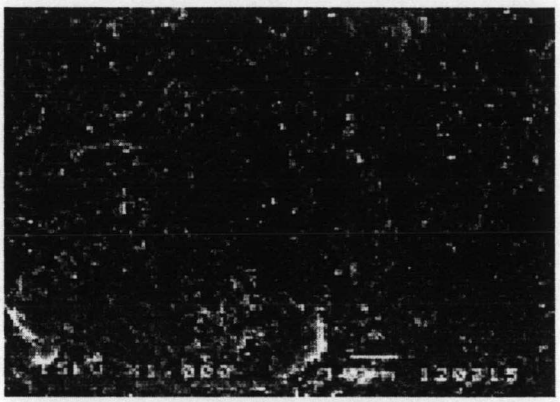
A1 × 50



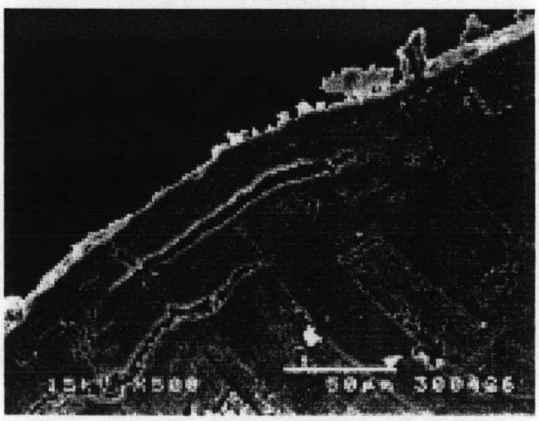
B1 × 50



A2 × 1000



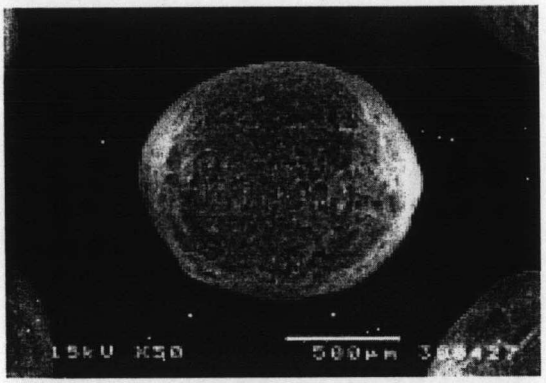
B2 × 1000



A3 × 500

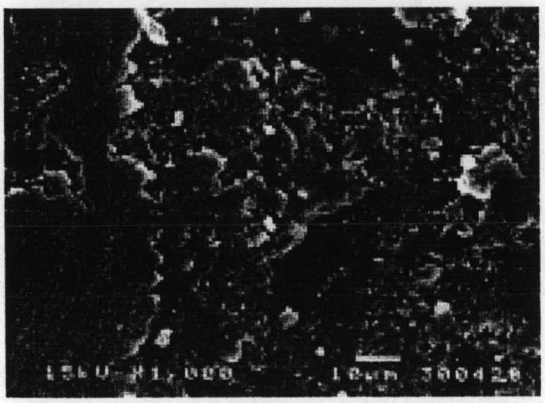
B3 × 500

Figure 41 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (3:1) 10% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).

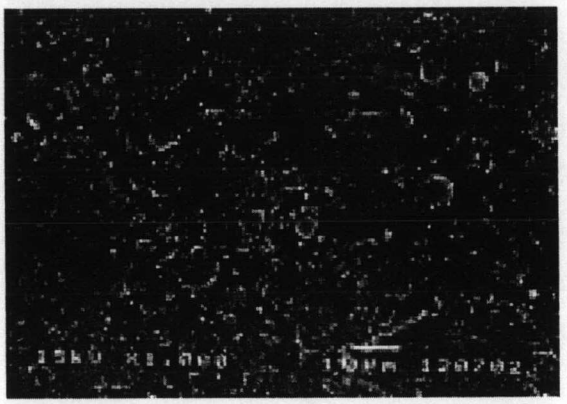


A1 × 50

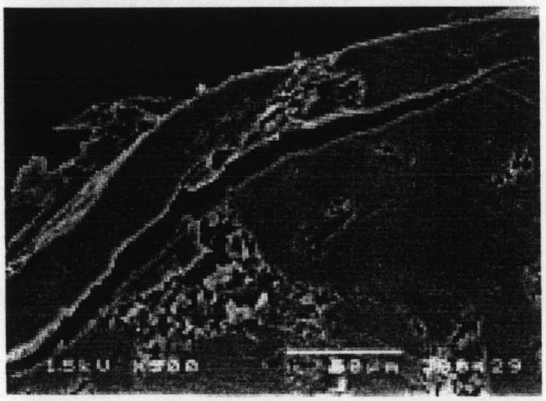
B1 × 50



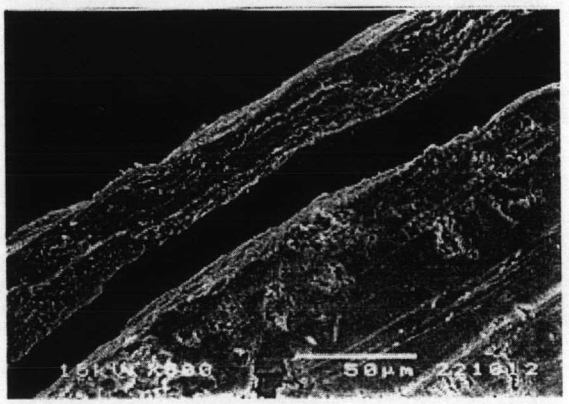
A2 × 1000



B2 × 1000

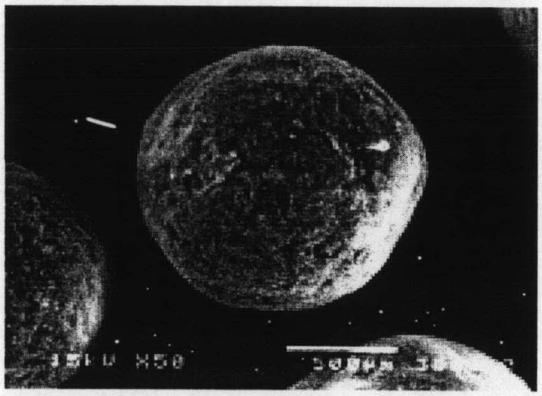


A3 × 500



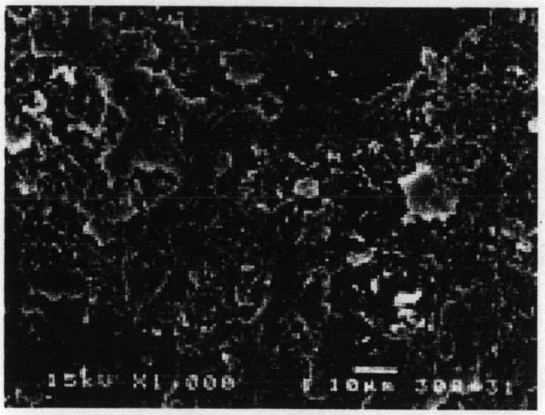
B3 × 500

Figure 42 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (3:1) 15% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).

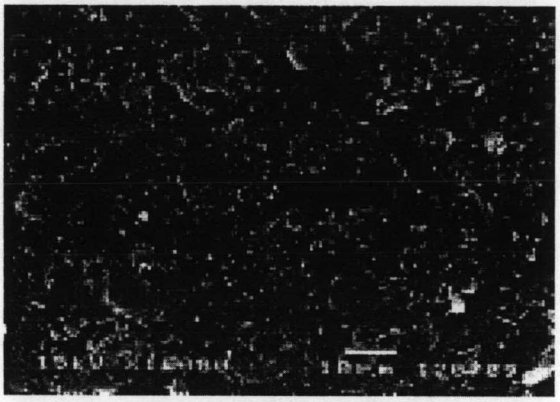


A1 × 50

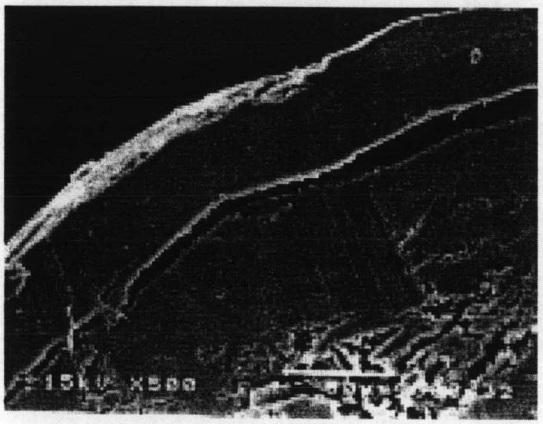
B1 × 50



A2 × 1000



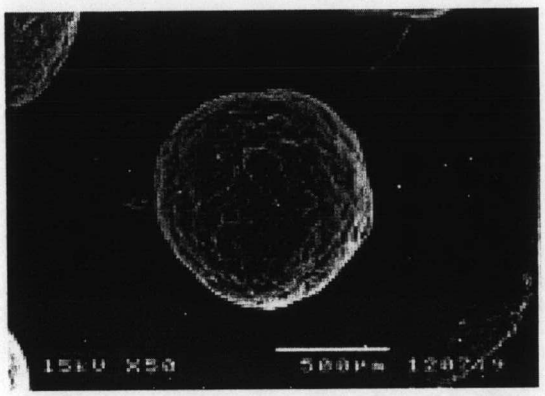
B2 × 1000



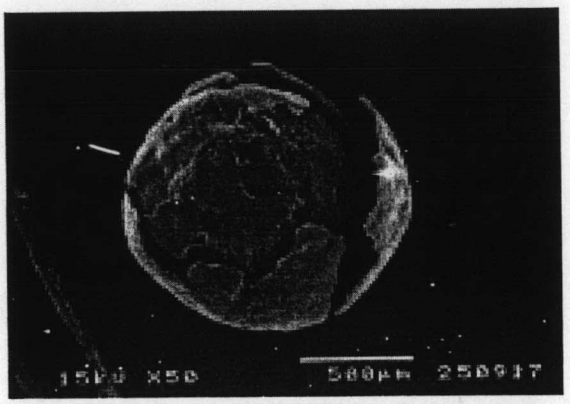
A3 × 500

B3 × 500

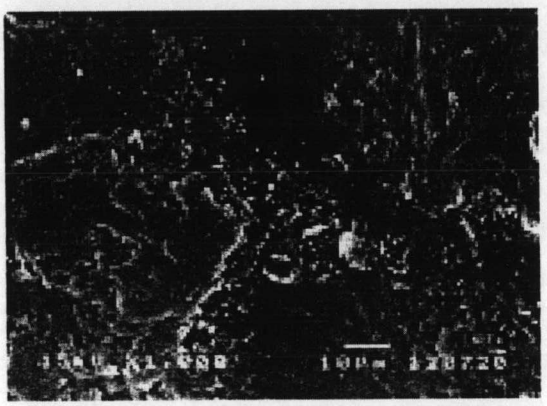
Figure 43 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (3:1) 20% w/w before and after dissolution test (A1, A2, A3 are before dissolution test, B1, B2, B3 are after dissolution test).



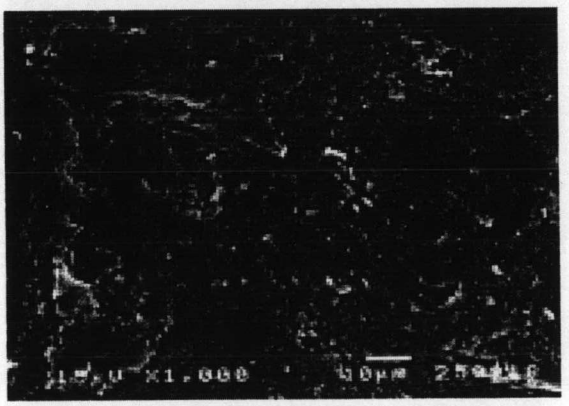
A1 × 50



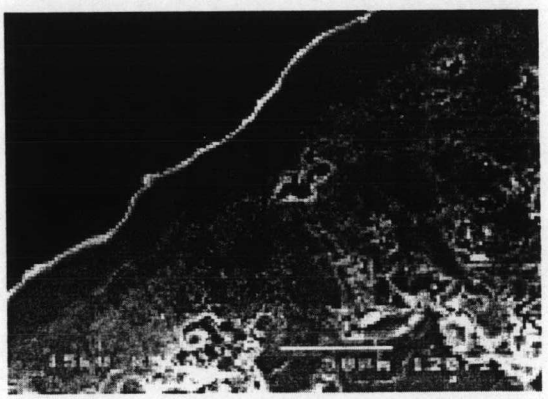
B1 × 50



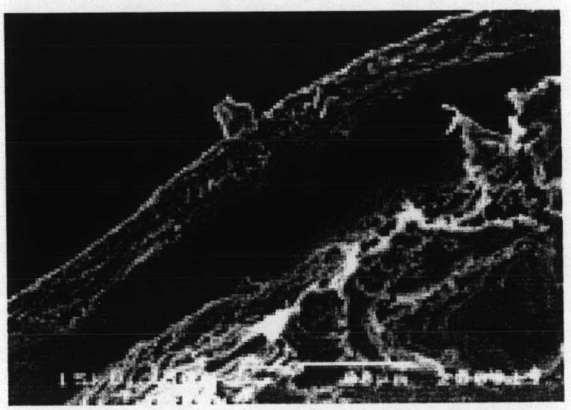
A2 × 1000



B2 × 1000

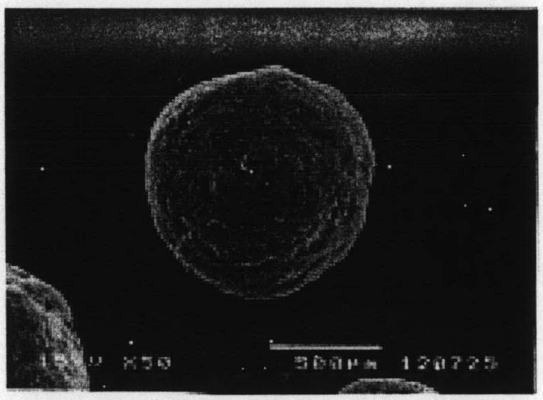


A3 × 500

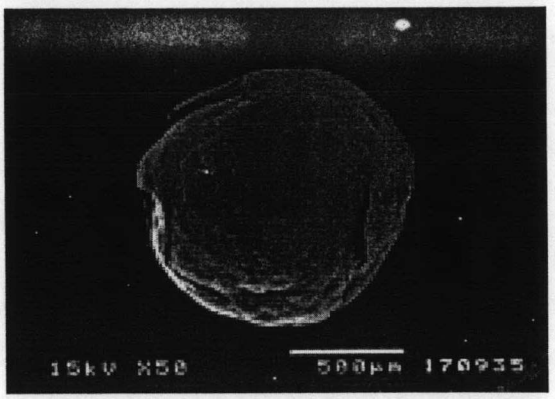


B3 × 500

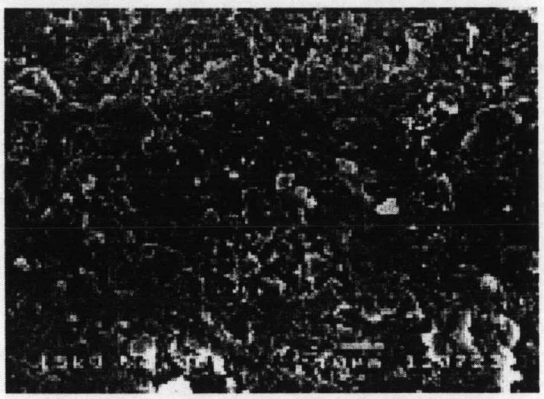
Figure 44 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (4:1) 10% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



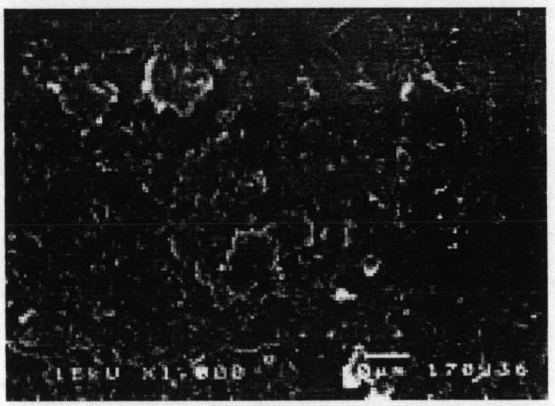
A1 × 50



B1 × 50

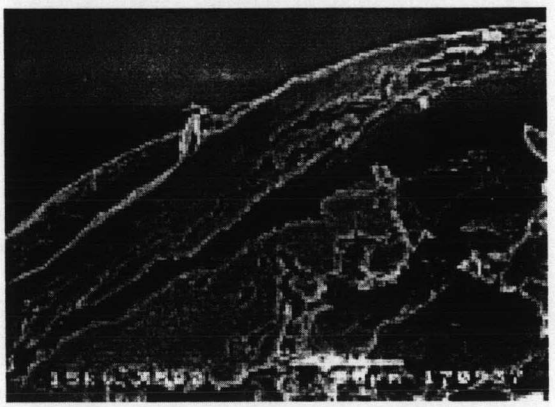


A2 × 1000



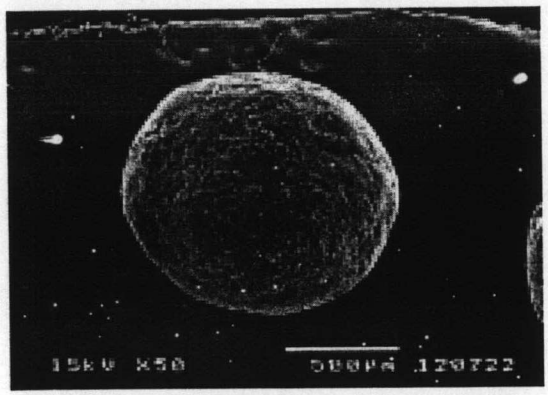
B2 × 1000

A3 × 500

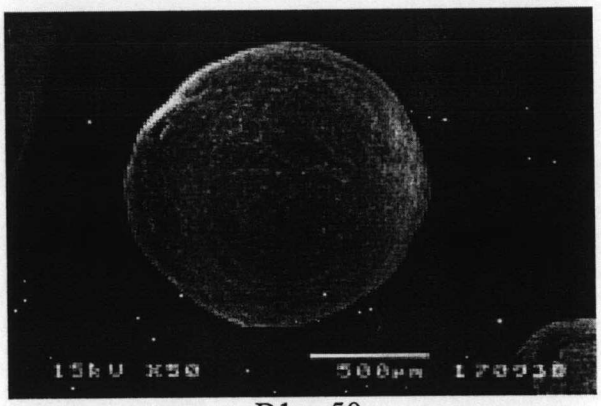


B3 × 500

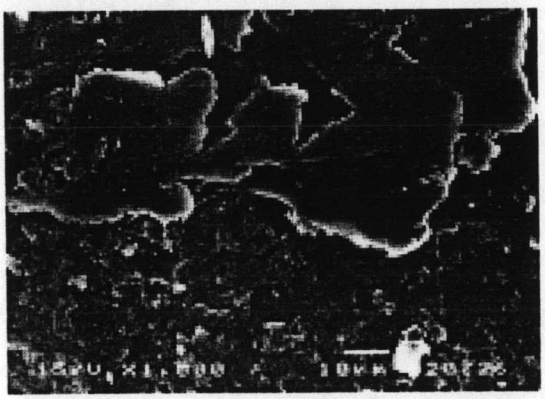
Figure 45 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (4:1) 15% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).



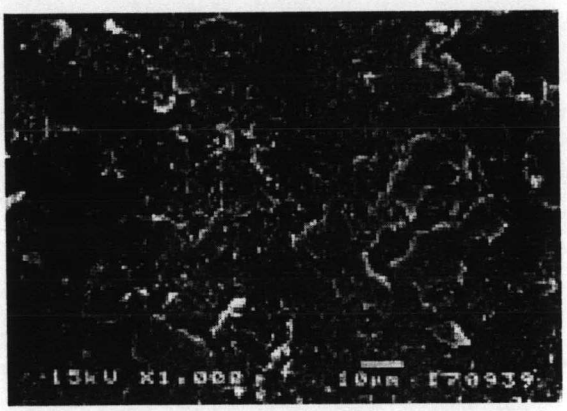
A1 × 50



B1 × 50

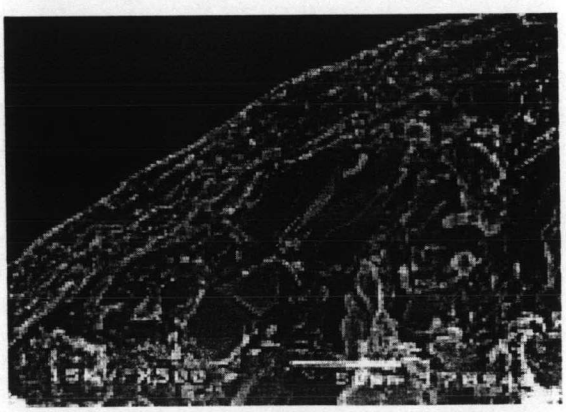


A2 × 1000



B2 × 1000

A3 × 500



B3 × 500

Figure 46 Photomicrographs of DTZ HCl coated pellets with Compritol 888 ATO®: EC (4:1) 20% w/w before and after dissolution test (A1 , A2 , A3 are before dissolution test , B1 , B2 , B3 are after dissolution test).

3.4 Evaluation of physicochemical properties of casted films of Compritol 888 ATO®in combination with EC

The blending of Compritol 888 ATO® and EC were evaluated and observed for chemical interaction. The various methods were used such as X-rays, IR and DSC.

3.4.1 The powder X-ray diffraction analysis

The powder X-ray diffraction method was used for detection of the interaction between Compritol 888 ATO® and EC , in order to observed the change in the crystal nature of these two polymers. Basically every crystalline material has its own characteristic powder pattern. That means powder X-ray diffraction pattern of crystalline materials will contain numereous sharp peaks, whereas powder X-ray diffraction patterns of amorphous materials such as a most polymers will show an amorphous halo baseline. Figure 47 shows the X-ray diffraction pattern of Compritol 888 ATO® , EC, and the mixture between Compritol 888 ATO® and EC in the ratio of 1:1, 2:1, 3:1, and 4:1, respectively.

The crystallinity of Compritol 888 ATO® was clearly demonstrated by their unique X-ray diffraction patterns. The EC polymer is amorphous in nature due to the absence of complete steroregularity and the presence of bulky side groups (Jenquin and McGinity, 1994). The diffraction pattern of the mixture of Compritol 888 ATO® and EC at all ratio contained sharp diffraction peaks indicating no chemical interaction, corresponding to the crystalline form of Compritol 888 ATO® which was present in the mixture. From these results, it could be deduced that at various ratios of mixed Compritol 888 ATO® and EC had no effect on changing the X-ray diffraction patterns.

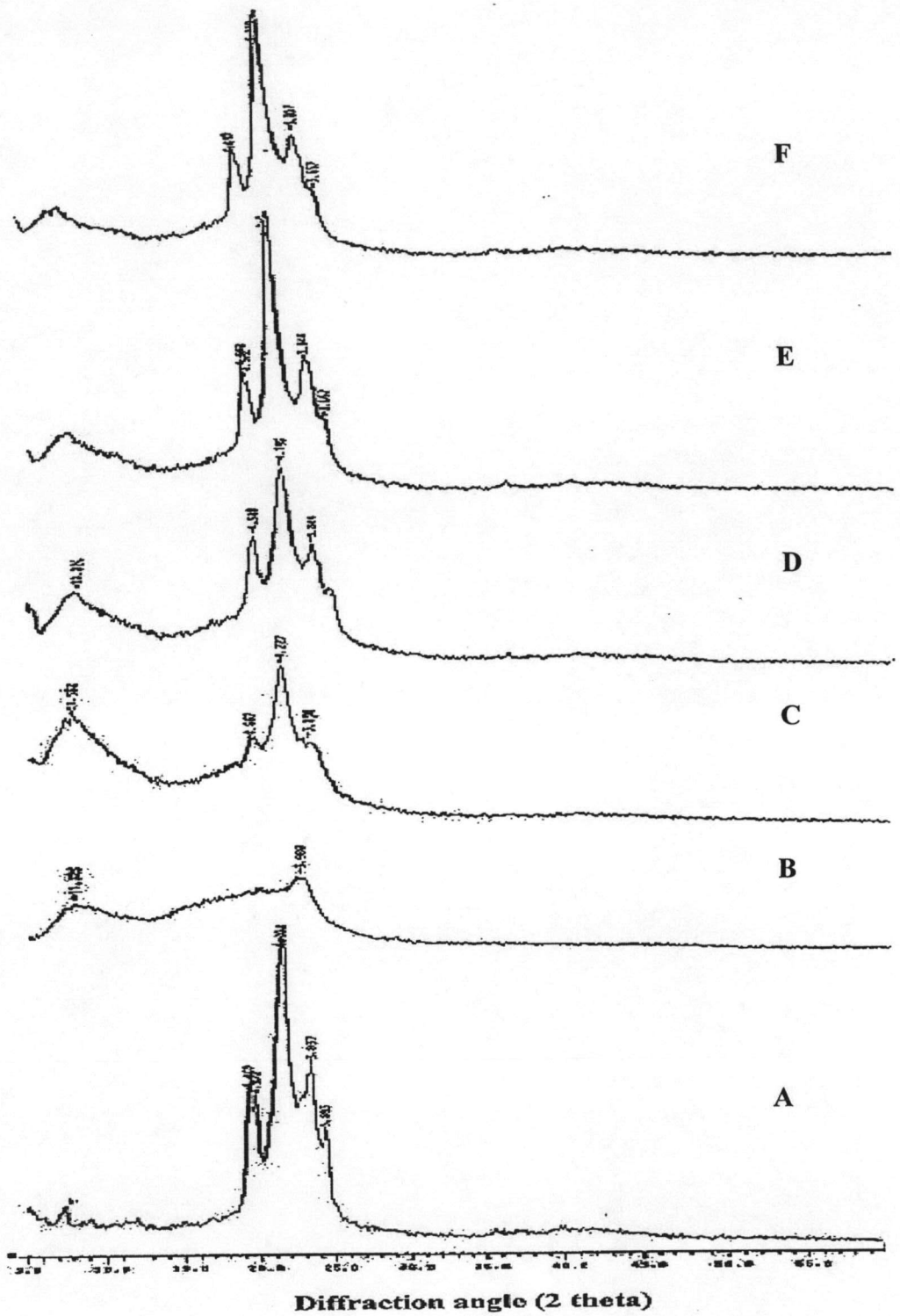


Figure 47 X-ray diffractograms of (A) Compritol 888 ATO®; (B) EC; (C) Compritol 888 ATO® : EC (1:1); (D) Compritol 888 ATO® : EC (2:1); (E) Compritol 888 ATO® : EC (3:1); (F) Compritol 888 ATO® : EC (4:1).

3.4.2 The infrared spectroscopy

IR spectroscopy was used for determination of the chemical moieties of the sample. Every molecules due to the functional groups shows characteristic frequencies of vibrations and thus a characteristical absorption pattern which forms the IR spectrum. The change of an environment of a molecule will lead to shift in the absorption pattern. This can be used for the analysis of interaction in our coating system. The shifting of any peaks in the IR spectrum should be considered and found out of which chemical bonds they are in order to make a decision whether interactions have happened or not. The IR spectra of Compritol 888 ATO® , EC, and the mixture between Compritol 888 ATO® and EC with various ratios are depicted in Figure 48. The principle peaks of Compritol 888 ATO® were observed at the wavenumbers of 1178, 1471, 1739, 2851, and 2919 cm^{-1}. The C-O stretching peak is represented at 1178 cm^{-1} . The aliphatic CH_2 bending is represented at 1471 cm^{-1} . The C=O stretching is represented at 1739 cm^{-1} . The IR peaks at 2851 and 2919 cm^{-1} are resulted from aliphatic CH stretching. The peaks of EC are observed at the wavenumbers of 1745, 2975, and 3466 cm^{-1} . The peak at 1745 cm^{-1} is resulted from C=O stretching. The C-H stretching is observed at 2979 cm^{-1} and the broad absorption band at 3466 cm^{-1} is observed due to O-H stretching. The IR spectra of mixed between Compritol 888 ATO® and EC in various ratios showed the combination of Compritol 888 ATO® peaks and EC peaks. No additional band was observed with any ratios of the mixed films. It could be concluded that there was no evidence of intermolecular chemical interaction between Compritol 888 ATO® and EC.

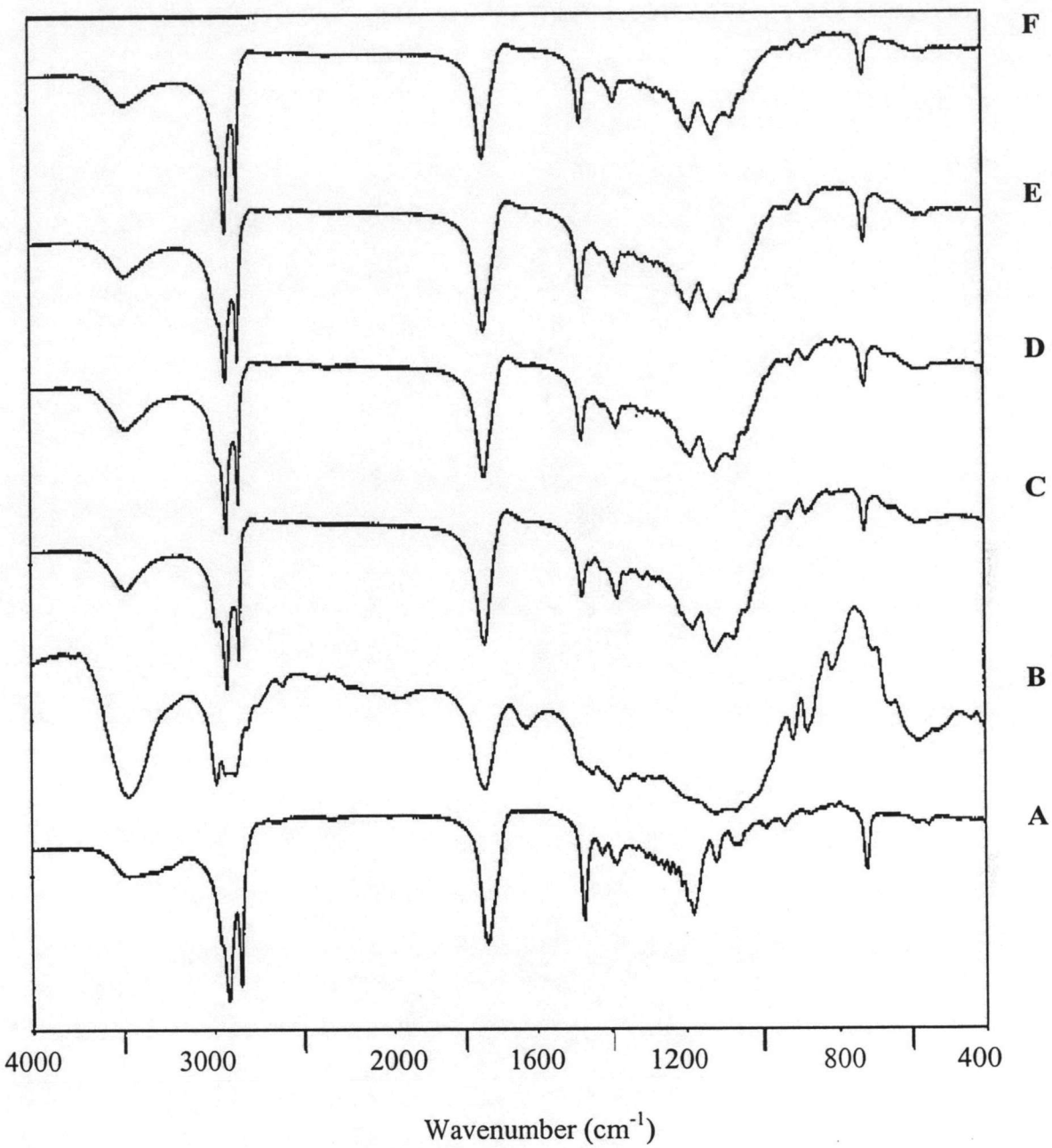


Figure 48 IR spectra of (A) Compritol 888 ATO®; (B) EC; (C) Compritol 888 ATO® : EC (1:1); (D) Compritol 888 ATO® : EC (2:1); (E) Compritol 888 ATO® : EC (3:1); (F) Compritol 888 ATO® : EC (4:1).

3.4.3 The differential scanning calorimetry

Differential scanning calorimetry or DSC is used to detect the thermal behavior of a drug or a polymer which is a characteristic behavior for each substance. Moreover this technique can measure a glass transition temperature of the polymeric material. DSC thermograms of Compritol 888 ATO® , EC, and the mixture between Compritol 888 ATO® and EC with various ratios are depicted in Figure 49. The melting points are 71.6 °C for Compritol 888 ATO ® alone , 69.9°C , 72.7 °C , 69.5 °C and 70.2 °C for Compritol 888 ATO ® mixed with EC at the ratio of 1:1 , 2:1 , 3:1 and 4:1, respectively. It seemed that the melting point of the Compritol 888 ATO® in the mixture with EC was closed to that of Compritol 888 ATO® alone. No change was observed in thermal analytical profiles, indicating absence of interaction between Compritol 888 ATO® and EC.

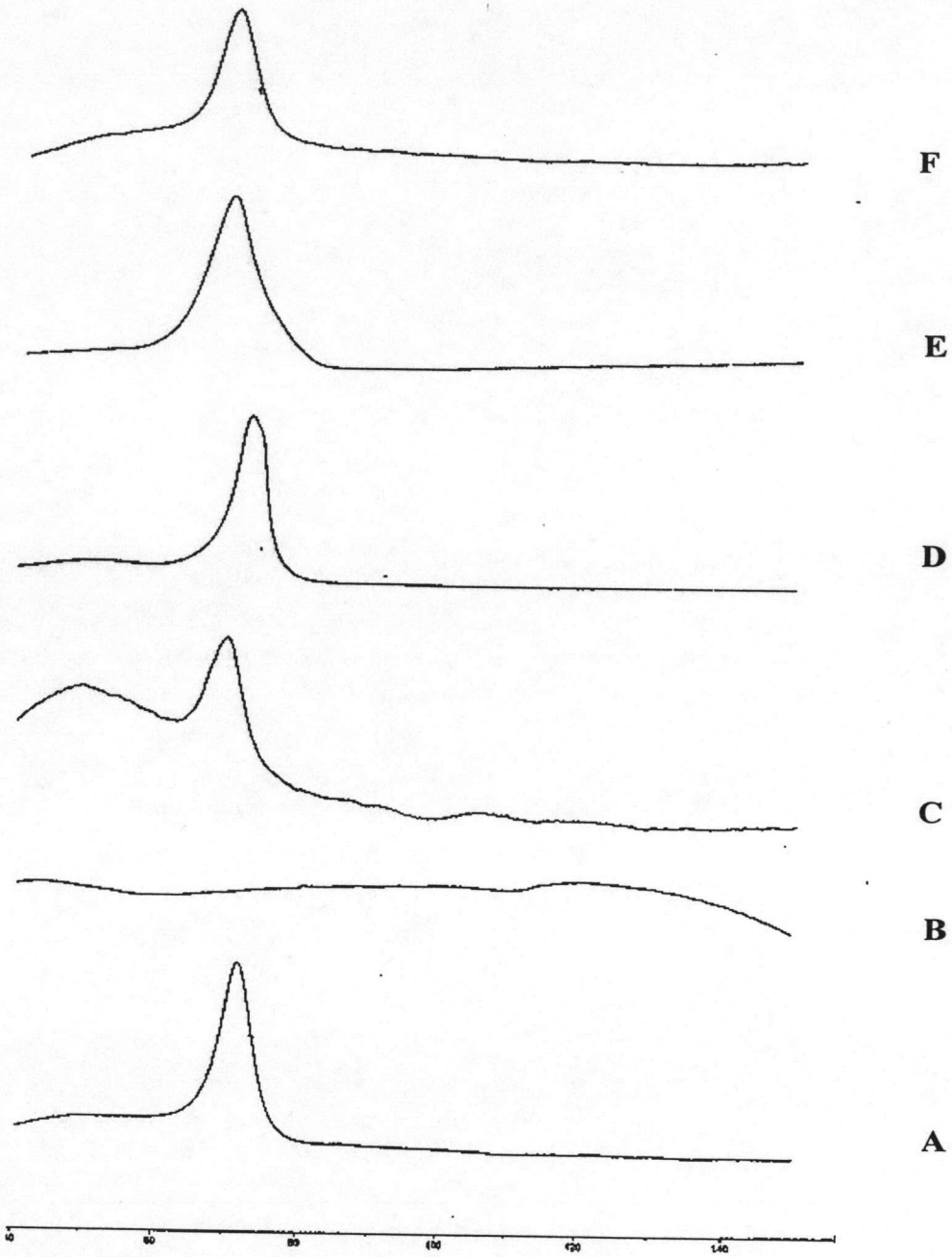


Figure 49 DSC thermograms of (A) Compritol 888 ATO®; (B) EC; (C) Compritol 888 ATO® : EC (1:1); (D) Compritol 888 ATO® : EC (2:1); (E) Compritol 888 ATO® : EC (3:1); (F) Compritol 888 ATO® : EC (4:1).

3.5 Effect of the combination of Compritol 888 ATO®and EC on the release profile and permeability coefficient

The effect of mixing Compritol 888 ATO® with EC on the drug release profiles are exhibited in Figures 50-52 and Tables 18C-29C (Appendix C). The release was dramatically decreased with the incorporation of EC in the coating formulation. Figure 50 show the effect of different ratios of Compritol 888 ATO® and EC at 10% coating level on the release characteristics of DTZ HCl pellets. Increasing the proportion of Compritol 888 ATO® resulted in an increasing the percent drug release. The pellets coated with the mixture of Compritol 888 ATO® and EC at ratio 4:1>3:1>2:1 yield faster rate of release than coated with ratio 1:1. As expected, the presence of Compritol 888 ATO® in the coating enhances the access of the dissolution medium to the pellets core. It is clear that as the level of coating solution increase from 10% to 20%, the release rates decrease, and no crack of the coating layer was observed with all formulations studied.

For mechanistic point of view, the permeability coefficients (P) of DTZ HCl coated pellets in this study can be calculated by Fick 's first law as follows:

$$J = \frac{dQ/dt}{A} = P \times C_s / h \qquad (11)$$

Flux (J) or release rate (dQ/dt), film thickness (h), surface area (A), and solubility of drug (C_s) can be obtained. Then permeability coefficients of each dissolution profile was calculated and present in Tables 12-13

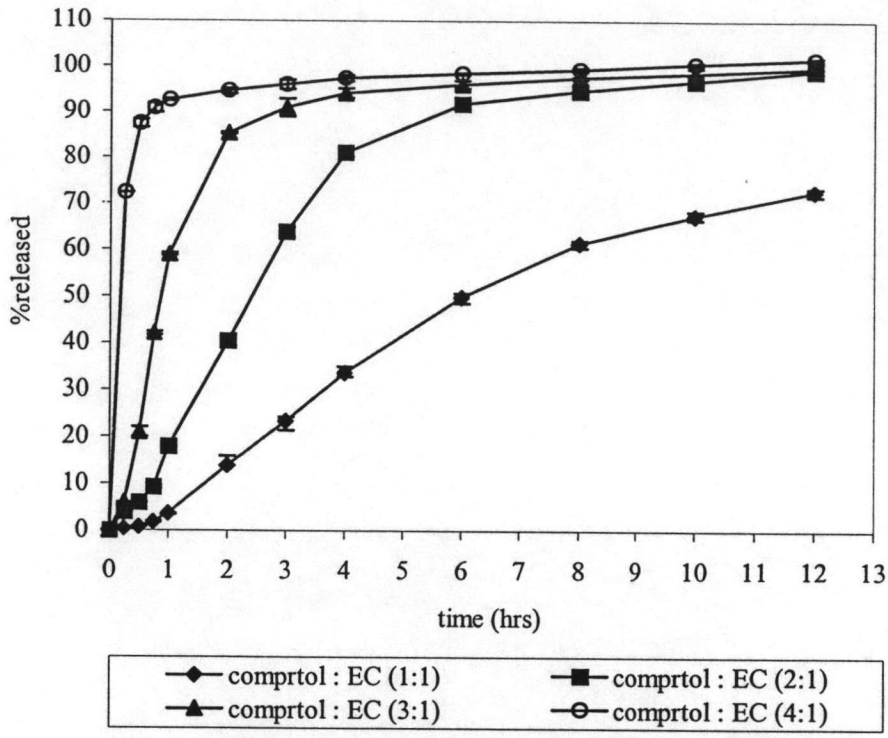


Figure 50 Effect of different ratios of Compritol 888 ATO® and EC at 10% coating level on dissolution profiles of DTZ HCl coated pellets.

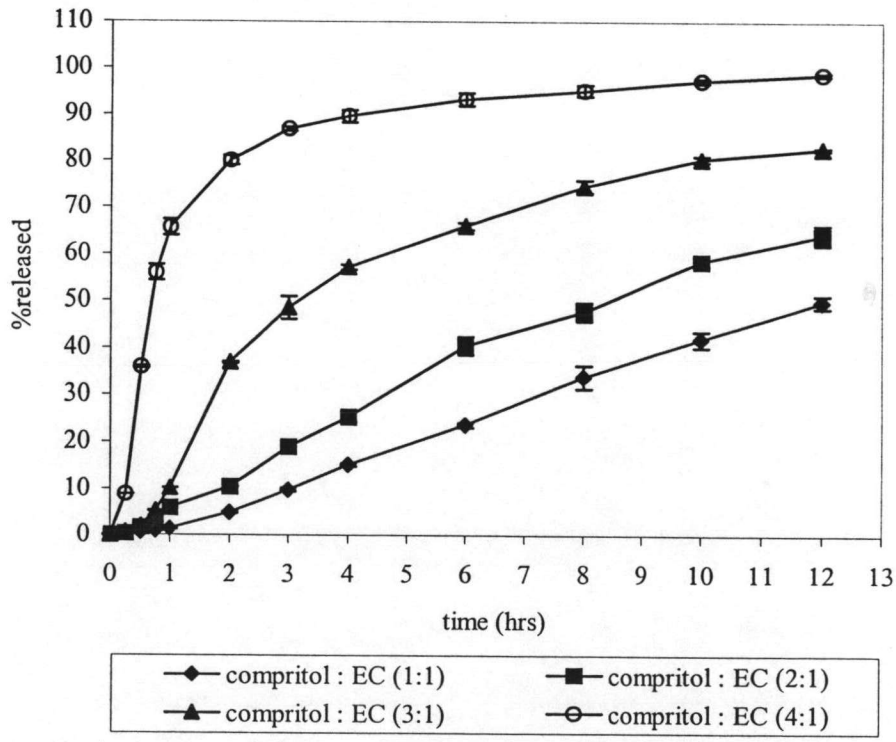


Figure 51 Effect of different ratios of Compritol 888 ATO® and EC at 15% coating level on dissolution profiles of DTZ HCl coated pellets.

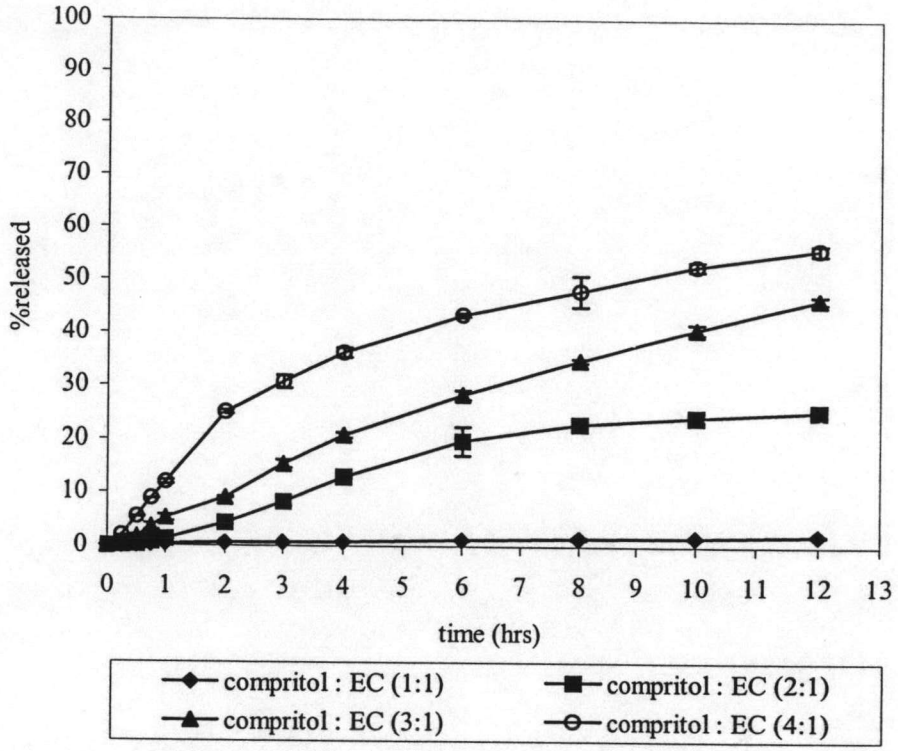


Figure 52 Effect of different ratios of Compritol 888 ATO® and EC at 20% coating level on dissolution profiles of DTZ HCl coated pellets.

The rate during the constant release phase were determined by linear regression of the cumulative release rate vs time describing the membrane diffusion process as suggested by Benita et al. (1986); Fites et al. (1970); Donbrow and Friedman (1974). The influence of membrane-coated formulations on the constant release rate in the present study is shown in Table 12.

The permeability coefficients (*P*) values were plotted against the thickness of the coated layer and show in Figures 53. Increasing in film thickness resulted in decreasing of the permeability coefficient because of an increased tortuosity of pore, and the film was also controlling the release process. Therefore, part of the drug solution had to partition into the film and then diffuse through the polymeric membrane down a concentration gradient across the membrane and eventually desorp from the down stream interface into the surrounding medium. The coating membrane barrier requires a period to establish the concentration gradient within the membrane prior to achieving a constant release rate as indicated by the presented lag time. The permeability coefficients (*P*) were plotted against the percentage of coating at four different ratio of Compritol 888 ATO® and EC as 1:1, 2:1, 3:1, and 4:1, respectively (Figure 54), we found that as the ratio of mixture between Compritol 888 ATO® and EC change, it would effect the value of *P*. At the ratio 4:1 of Compritol 888 ATO® and EC, the values of P at every percentage of coating levels were higher than the lower mixing ratio (3:1> 2:1> 1:1). It might be due to the increasing of aqueous pores and its property of Compritol 888 ATO® which was easily eroded. Moreover, the film that had a high amount of Compritol 888 ATO® reduced the total strength of the film. On the other hand, the low amount of Compritol 888 ATO® film mixture would give a desired drug release pattern.

Table 12 Regression analysis and correlation coefficient for dissolution rate of different formulations.

Ratio of Compritol 888ATO®and EC	Equation	*K* *(mg/hr)*	Time range	r^2
10% of coating level				
1:1	Y= 8.2995x-2.2676	8.2995	1-8 h	0.9917
2:1	Y= 22.099x-5.0279	22.099	1-4 h	0.9959
3:1	Y= 61.663x-5.1892	61.633	0-1 h	0.9699
4:1	Y= 174.75x+9.5611	174.75	0-0.5 h	0.8744
15% of coating level				
1:1	Y= 4.3346x-1.9542	4.3346	1-12 h	0.9961
2:1	Y= 6.8521x-1.5738	6.8521	1-6 h	0.9952
3:1	Y= 15.241x+0.0795	15.241	1-4 h	0.9291
4:1	Y= 71.391x-2.4343	71.391	0-1 h	0.9722
20% of coating level				
1:1	Y= 0.1663x+0.1441	0.1663	1-12 h	0.9764
2:1	Y= 3.4343x-1.3501	3.4343	1-6 h	0.9864
3:1	Y= 4.0085x+1.3943	4.0085	1-12 h	0.9857
4:1	Y= 12.814x-0.7229	12.814	0-2 h	0.9977

K: constant rate release

Table 13 Comparison of permeability coefficient (P) for DTZ HCl release in different ratios of Compritol 888 ATO® and EC coated pellets.

Ratio of Compritol 888ATO® and EC	h[a] ($10^2\mu m$)	$T50$ (h)	P ($10^8 cm^2 s^{-1}$)
10% of coating level			
1:1	0.1899	6.02	0.179
2:1	0.2216	2.41	0.464
3:1	0.2095	0.87	1.30
4:1	0.2073	0.17	3.690
15% of coating level			
1:1	0.2961	N/A[b]	0.132
2:1	0.3037	8.35	0.214
3:1	0.3029	3.25	0.469
4:1	0.3028	0.67	2.20
20% of coating level			
1:1	0.3843	N/A[b]	0.006
2:1	0.3759	N/A[b]	0.13
3:1	0.3819	N/A[b]	0.148
4:1	0.3900	9.04	0.492

h: Film thickness; $T50$: Time for 50% of drug release; P is defined by Eq.11;
N/A : not available.
a: Calculated from 300 particles
b: Slow release after dissolution test

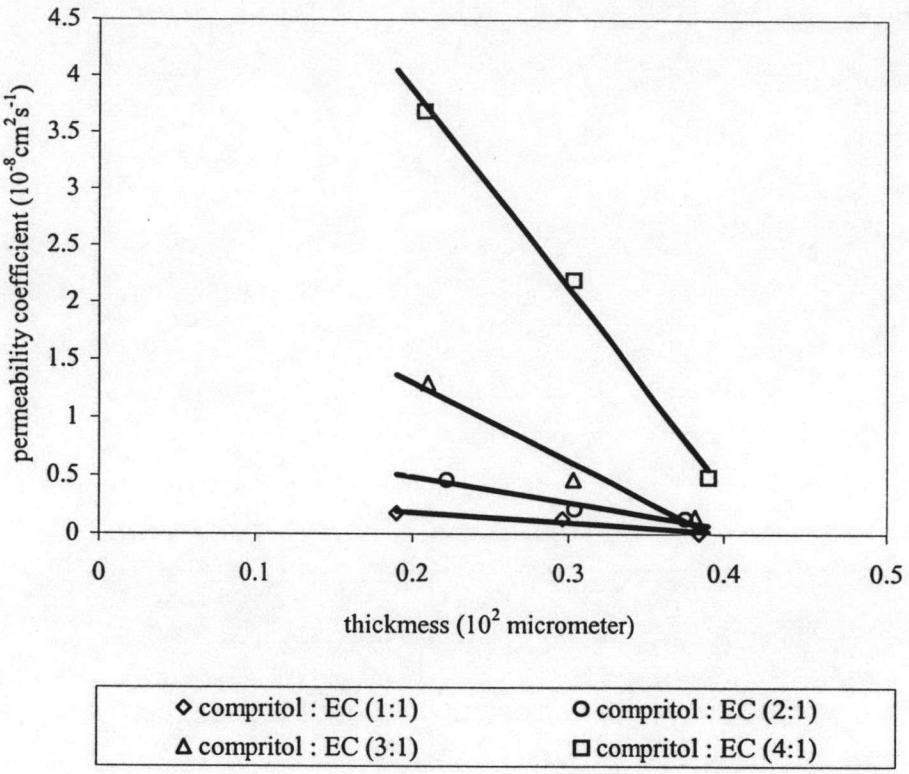


Figure 53 Effect of thickness of coated pellets on permeability coefficient of DTZ HCl from pellets coated with various combinations of Compritol 888 ATO® and EC (r^2 = 0.9062, 0.9424, 0.9597, and 0.9957, respectively) (y = -0.8749x+0.3595, y = -2.1846x+0.9256, y = -6.7488x+2.6508, y = -17.474x+7.3701, respectively).

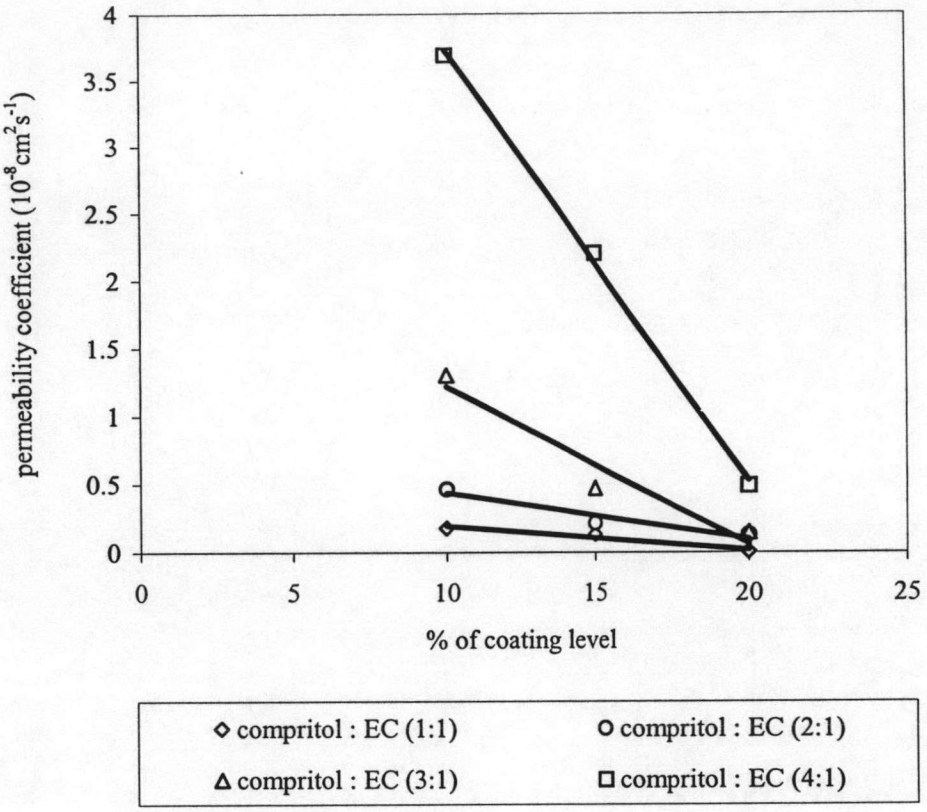


Figure 54 Effect of coating levels on permeability coefficient of DTZ HCl from pellets coated with various combinations of Compritol 888ATO® and EC
(r^2 = 0.935, 0.9239, 0.9387, and 0.9985, respectively)
(y = -0.0173x+0.3652, y = -0.0334x+0.7703, y = -0.1152x+2.367, and y = -0.3198x+6.9243, respectively).

3.6 Effect of physical stress caused by polystyrene beads on drug release

As reported earlier, after dissolution test, various formulas of pellets coated with waxes or combination of waxes and polymer had peeled off. In addition, the film coated pellets are also subject to various in-vivo mechanical stresses during their passage through the GI tract, such as internal osmotic pressure or external mechanical impact due to GI movement, etc. In order to examine the mechanical resistibility of the actual dosage form coated with the mixture of Compritol 888 ATO® and EC with ratio 1:1 at 10% of coating level. We generate mechanical destruction or frictional force by using polystyrene beads incorporated with DTZ HCl pellets during dissolution studies. This technique is done in the same manner of Narisawa et al (1994).

Figure 55 show the DTZ HCl release profiles in the modified dissolution test with polystyrene beads compared with a common dissolution test. It was found that there was no significant difference on the drug release rate from the coated pellets ($p > 0.05$, t-test). These results demonstrated that the mixture of Compritol 888 ATO® and EC with ratio 1:1 at 10% coating level can resistant against mechanical destruction or friction force.

3.7 Release with a pH change method

During passage through the gastrointestinal system, peroral controlled-release dosage forms are exposed to pH levels ranging from acidic to alkaline. The DTZ HCl coated pellets with the mixture of Compritol 888 ATO® and EC with ratio 1:1 at 10% coating level that pass the criterion following diltiazem hydrochloride extended-release capsule USP 24 supplement 5 (for products labeled for dosing every 12 hours, Test 1) was investigated on the pH change effect. Dissolution profiles of this selected formulation was

determined in pH change mediums as shown in Figures 56 and 57. The results exhibited that the drug release profile of selected formulation gave significantly different release profile in later period of dissolution (pH 6.8) ($p < 0.05$, t-test), but on the initial staged of dissolution experiment, it provided the same release characteristics in acidic phase (pH 1.2) of pH change study and also when deionized water was used in the typical dissolution test.

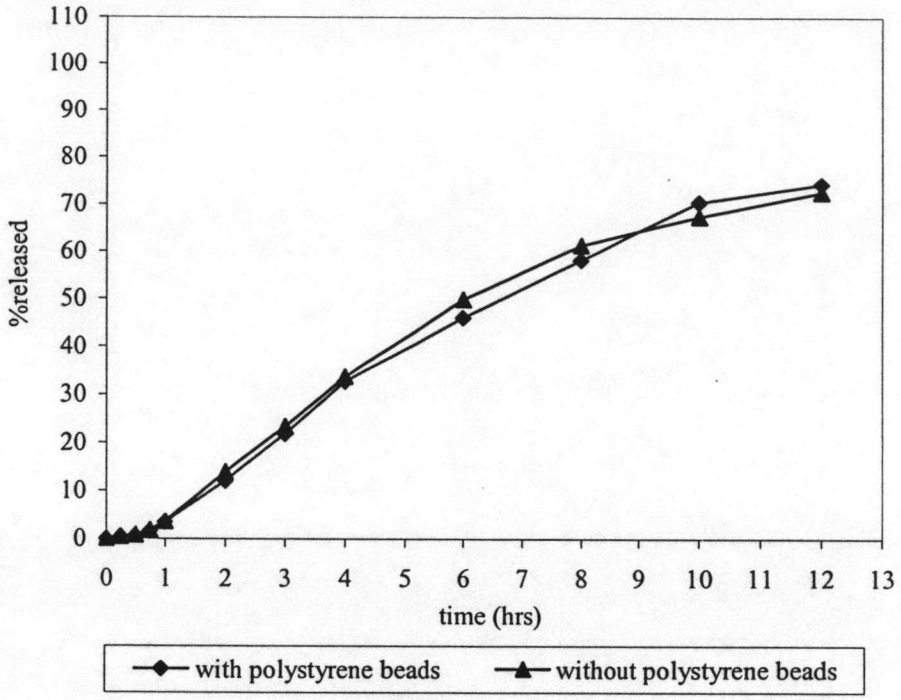


Figure 55 Effect of physical stress caused by polystyrene beads on DTZ HCl release pellets coated with with Compritol 888 ATO® and EC (1:1) at 10% of coating level in D.I. water.

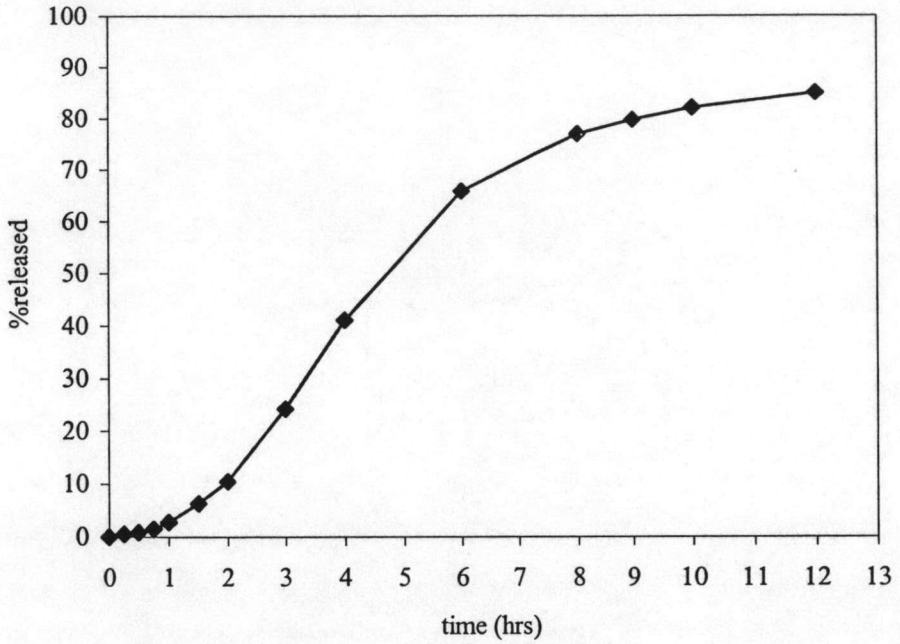


Figure 56 Dissolution profile of DTZ HCl from pellets coated with Compritol 888 ATO® and EC (1:1) at 10% of coating level pH changed medium from pH 1.2 at first 2 hours to pH 6.8.

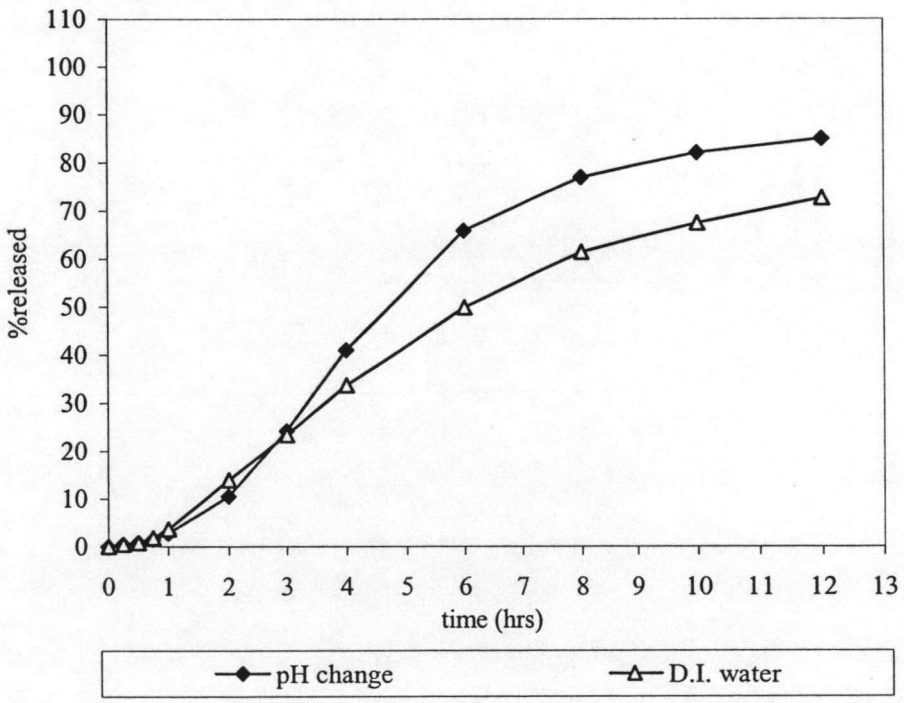


Figure 57 Dissolution profile of DTZ HCl from pellets coated with Compritol 888 ATO® and EC (1:1) at 10% coating level in D.I. water and pH changed medium from pH1.2 at first 2 hours to pH 6.8.