CHAPTER III

RESULTS AND DISCUSSION

1. Evaluations of Core Pellets

1.1 Morphology

The core pellets were examined using scanning electron microscope at different magnifications. The shape and surface topography of core pellet are illustrated in Figure 10. The core pellet exhibited rough and spongy-like surface. The cross-section of uncoated pellet was also observed for the high porosity.

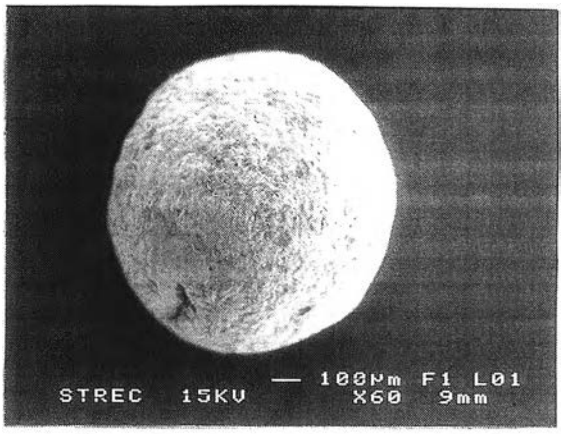
1.2 Drug content

The average drug content of propranolol hydrochloride pellets was 43.04% with a standard deviation of 0.599. This low value of standard deviation represented the uniformity of drug in the bulk pellets.

2. Preliminary Investigations for Coating Formulations and Coating Conditions

2.1 Coating formulations

Coating the pellets with the polymers can be performed with aqueous dispersions or from organic solutions. Eventhough the present trend in film coating is toward aqueous-based film coating, both aqueous and solvent-based film-coating systems are still employed in the pharmaceutical industry.



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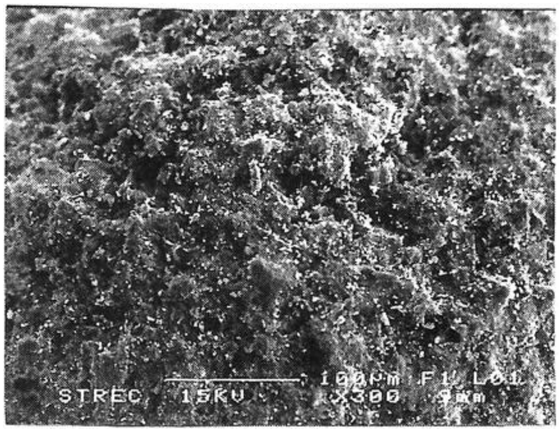

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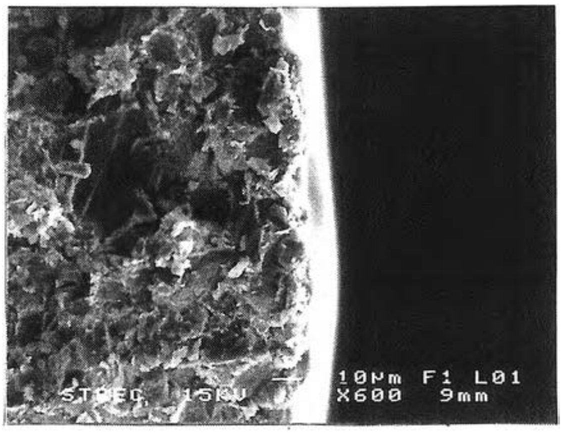


x 600 cross-section

Figure 10 Photomicrographs of core pellets at different magnifications

The main compositions of the coating formulation in organic system were ethylcellulose and Eudragit®RS100. Ethylcellulose is often used as water insoluble polymer due to the many advantages such as good film formability, excellent physicochemical stability, minimum toxicity, etc. As part of Eudragit®RS100, it is synthesized from acrylic and methacrylic acid esters which contains a low level of quaternary ammonium groups. These charged groups are considered only slightly permeable to water vapor. These two polymers could be blended together without any troubles (Coowanitwong, 1997).

For the aqueous dispersion system, two selected commercially available ethylcellulose aqueous dispersion, Aquacoat® and Surelease®, were investigated in the preliminary study to determine which one could be blended with Eudragit®RS30D and showed a good film characteristic. The blending between Aquacoat® and Eudragit®RS30D provided an initial viscous appearance. When the plasticizer (eg. dibutyl phthalate, tributyl citrate, triacetin) was added into this mixing dispersions, it appeared to form solid flakes even after mixing for 2 hours. Although the blending of Surelease® and Eudragit®RS30D also exhibited viscous appearance and the most viscous mixture between Surelease® and Eudragit®RS30D occurred at the ratio of 3:7. This appearance disappeared after further blending with plasticizers for 2 hours.

In preparation of Surelease®, the plasticizer is incorporated in the dispersion during the manufacturing process. A hot melt of the polymer, the plasticizer (dibutyl sebacate or fractionated coconut oil), and the stabilizer (oleic acid) is created to form a homogeneous mixture. The mixture is then diluted with an alkali solution and this dispersion can be directly applied on substrates. However, the studies by Arwidsson et al. (1991) indicated that a more ductile film was easily obtained by adding more quantity of dibutyl sebacate to Surelease®. This may be an advantage in specific applications where ductilily is more important than stress resistance. Consequently, Surelease® could be added with plasticizer to improve its properties.

Plasticizers cause changes in the physicomechanical properties of polymer, such as reduction in the glass transition temperature and in tensile strength and an increase in elongation and flexibility of the polymer film. The added plasticizers are generally classified as being water soluble or water insoluble. For the organic system, dibutyl phthalate was previously selected by Coowanitwong (1997) to facilitate coalescence of the coating and to improve the barrier properties of water insoluble film. It was known that a potential disadvantage of water soluble plasticizers could leach from the coating after contact with dissolution or physiological fluids (Bodmeier and Paeratakul, 1992, 1994a). This leaching property of water soluble plasticizer was chosen to compare with water insoluble plasticizer in order to modify the film properties. Triethyl citrate is one of the most popular water soluble plasticizer that was used in organic system (Phuapradit et al., 1995; Hyppola et al., 1996; Schultz et al., 1997).

The water soluble plasticizer, triethyl citrate would be an ideal plasticizer for Aquacoat® based on the minimum film temperature data. Another advantage of the water soluble plasticizers is that the distribution of plasticizer into a polymeric dispersion rapidly reaches equlibrium (Obara and McGinity, 1995). Nevertheless, the water insoluble plasticizers are often emulsified into the dispersion and the equilibration time can sometimes be quite lengthy. Schmidt and Niemann (1993) concluded that dibutyl phthalate should be used to plasticize Eudragit®RS30D rather than with triethyl citrate or polyethylene glycol 6000. The sustained release properties of the resulting films were independent of the application temperature. Hence, both water soluble plasticizer and water insoluble plasticizer could be mixed with Eudragit®RS30D (Schmidt and Niemann, 1993).

From the preliminary study, either dibutyl phthalate or tributyl citrate could not be blended with the mixed polymers of aqueous system while triacetin and triethyl citrate could be blended with the mixed polymers of this system. Therefore, triacetin and triethyl citrate were chosen to study their effects on polymeric films.

The influence of various levels of plasticizer was also studied in this present work. Dibutyl phthalate-plasticized films for organic system could not be applied at both 30% level and 20% level due to the sticking of pellets during coating though the feed rate was reduced to 4-6 ml/min. Hence, talcum and magnesium stearate were added as antiadhesive agent. Despite adding antiadhesive agent, the agglomeration of pellets was still observed at 30% level of plasticizer. Finally, the levels of plasticizers used in this study were 10% and 20%. At 20% concentration of triethyl citrate in Surelease®, the pellets stuck together and could not be operated eventhough antiadhesive agent was used. Then, the amount of plasticizers at 10% and 15% was used in the aqueous dispersion system.

2.2 Coating conditions

The coating of organic system formulations was performed using the same conditions as described by Coowanitwong (1997). Nevertheless, there were some changes in the conditions due to the different components of coating formulations. The suitable temperature was previously selected at 45 °C for the organic system with 10% plasticizer. In order to prevent the problem of tackiness, which was most likely to occur if the coated pellets with 20% plasticizer were exposed to the same temperature, the 10% level formulations, the coated pellets were operated at 40 °C.

For successful formulation of an aqueous latex film, the minimum film-forming temperature (MFT) must be concerned since this is the lowest temperature at which a polymer emulsion forms a continuous film. The application temperature should exceed the MFT by 10 to 20 °C, otherwise cracking will be observed on free films (Lehmann, 1989). Parikh et al.(1993a) studied the influence of various temperatures on film properties and concluded that the Surelease® films coalesced at or around 50 °C may be less susceptible to physical defects. Furthermore, the plasticizers added to the aqueous dispersion system could decrease the MFT of both Surelease® and Eudragit® RS30D so a continuous film in coating conditions could occur at 50 °C.

A suitable feed rate was set at 8-10 ml/min which was different from the former study. A feed rate at 20 ml/min was too high and resulted in agglomeration of pellets. To avoid this incident, the pellets in each coating formulation were coated with lower spray rate of 8-10 ml/min.

While the need for a curing step has been suggested in the case of dispersion-based coating system, there were many studies to collaborate the necessity of a curing process. Rekhi, Porter, and Jambhekar (1995) studied the effect of aging on release profile and concluded that curing of Surelease® coating was not always been deemed to be necessary. They stored the coated beads in sealed plastic containers at room temperature for 24 months. Surelease® coated beads showed no difference in release rates on aging. This conclusion was in accordance with the study of Shah et al. (1994). The Surelease® films were not affected by the curing process which was operated at 45 °C for 12, 24, 36, 48 and 72 hours.

The effect of post-coating drying on the release of theophylline from Eudragit®RS pseudolatex coated pellets was studied by Chang and Hsiao (1989). Theophylline release was not significantly altered by additional oven drying at 60 °C for 10 hours. Other groups, however, reported that curing for 24 hours at 38 ± 0.5 °C was necessary for homogeneous film coats of Eudragit®RS30D and hence stable drug release characteristics (Govender and Dangor, 1997).

Schmidt and Niemann (1993) presented that the permeability of Eudragit®RS30D films with 10% plasticizer was reduced by tempering the pellets at 50 °C for 24 hours and nearly reached those obtained from coatings with 20% plasticizer without heat treatment. Adverse effects occurred when films with high plasticizer concentrations were tempered at 50 °C. After 24 hours the pellets stuck together and could not be separated without damaging the coat. To observe a remarkable contrast between low and high level of plasticizers, the curing process with various conditions was excluded except for drying the coated pellets in the chamber for another 15 minutes at the coating temperature.

3. Evaluations of Propranolol Hydrochloride Coated Pellets and Mechanical Properties of Free Films

3.1 Drug content

The percent drug content of coated pellets in various formulations is illustrated in Table 9. The data represented that the drug content of coated pellets was less than uncoated pellets. It was due to the presence of coating solutions/dispersions in coated pellets. The low value of standard deviation indicated the uniformity of drug in the coated pellet products. It was implied that the coating was reproducibly performed. Nevertheless, repeated nozzle blockage which appeared with aqueous dispersion of Surelease®: Eudragit®RS30D in the ratio of 3:7 could not be overcome by any dilution of aqueous dispersion to 5 or 8%. The coated pellets with this ratio of blended polymer could not be accomplished.

3.2 Morphology of coated pellets

Scanning electron microscopy was used to characterize the surface morphology of the coated pellets. The cross sections of propranolol hydrochloride pellets coated with either ethylcellulose, Eudragit®RS 100 or the various ratios between ethylcellulose and Eudragit®RS 100 were also examined.

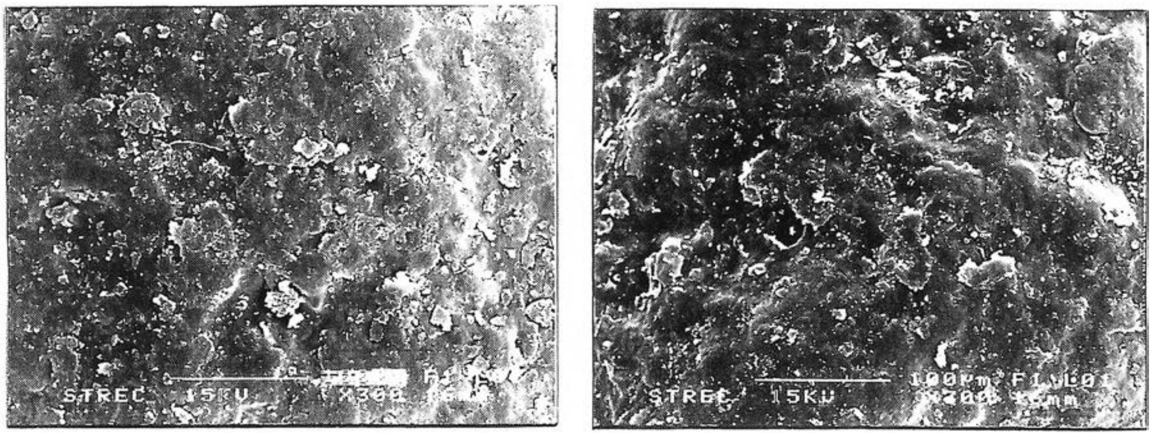
Table 9 The percentage of drug content in coated pellets (S.D. in parenthesis)

Formulation	% Experimental drug content	Formulation	% Experimental drug content	Formulation	% Experimental drug content	Formulation	% Experimental drug content
A1	36.36(1.662)	A11	34.71(0.797)	B1	37.22(0.348)	B11	37.72(0.350)
A2	35.00(0.534)	A12	35.17(0.312)	B2	37.77(0.575)	B12	37.18(0.370)
A3	35.83(0.365)	A13	35.97(0.455)	B3	37.74(0.595)	B13	37.24(1.129)
A4	35.21(0.480)	A14	36.51(0.080)	B4	36.91(0.946)	B14	35.83(0.641)
A5	36.22(0.510)	A15	36.16(0.759)	B5	36.66(0.773)	B15	37.04(0.253)
A6	35.61(0.416)	A16	34.19(0.416)	B6	36.77(0.949)	B16	36.54(0.597)
A7	36.75(0.146)	A17	36.57(0.451)	B7	-	B17	-
A8	37.28(0.970)	A18	34.84(0.433)	B8	-	B18	-
A9	35.91(0.233)	A19	35.43(1.091)	B9	37.05(0.256)	B19	37.18(0.444)
A10	35.63(0.290)	A20	34.66(0.180)	B10	36.03(0.587)	B20	36.96(0.126)

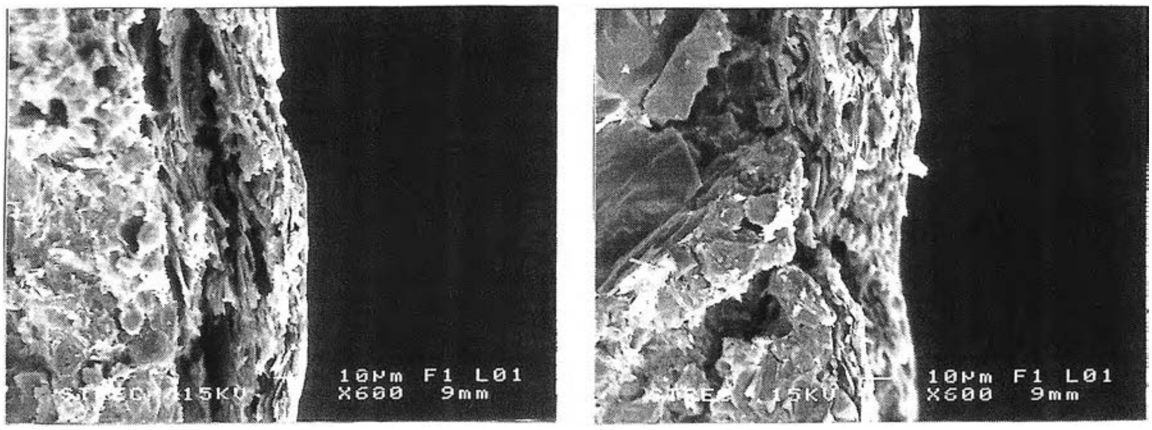
The organic system of formulations A1-A20 was first investigated. Figure 11 shows the quality and surface characteristics of pellets coated with ethylcellulose (EC) plasticized with 10% dibutyl phthalate (DBP) and 10% triethyl citrate (TEC). The pictures present rough surface filled with some flakes of polymer. The cross section of coated pellets at x600 magnification exhibited an obvious stratified film layers. There was no difference in surface topography of the pellets obtained by different types of plasticizers between dibutyl phthalate and triethyl citrate.

The photomicrographs of the coated pellets produced by ethylcellulose at 20% of dibutyl phthalate and triethyl citrate are shown in Figure 12. The microscopic view was similar to coated pellets with 10% plasticizer but the coated pellets with 20% of dibutyl phthalate presented the smoother surface than those with 10% of dibutyl phthalate. Dibutyl phthalate-plasticized film gave smoother surface than triethyl citrate-plasticized film. The cross section of coated pellets likewise displayed an obvious stratified film layers and had a porous structure.

A1 x 60 B1 x 60

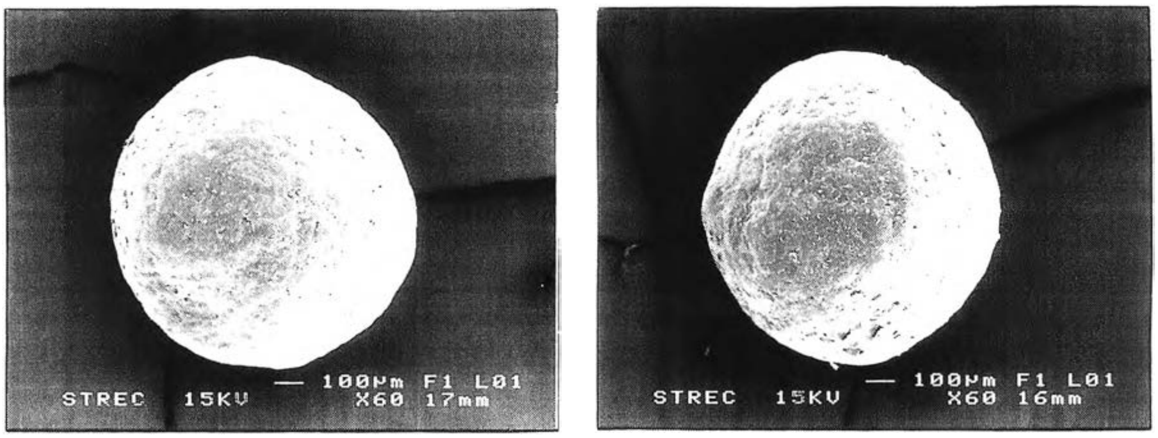


A2 x 300 B2 x 300



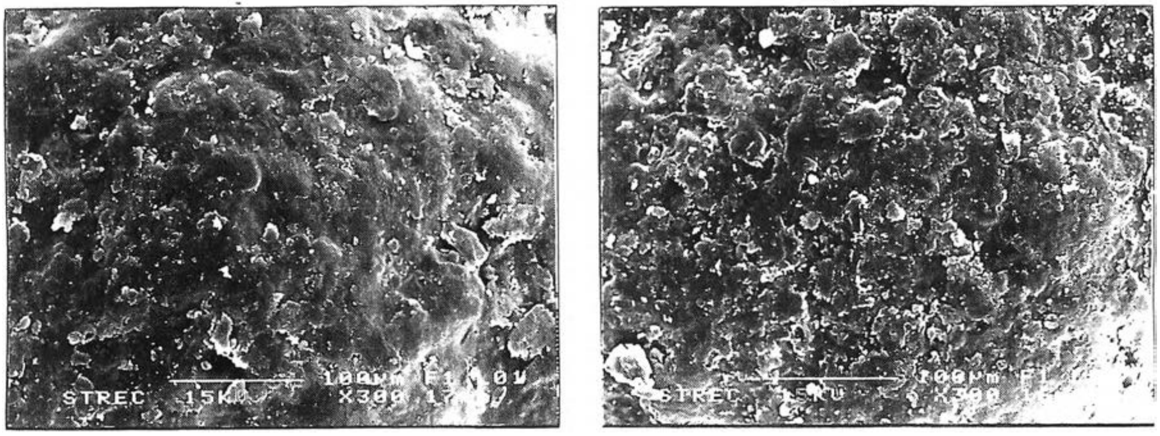
A3 x 600 cross-section B3 x 600 cross-section

Figure 11 Photomicrographs of coated pellets with ethylcellulose with 10% DBP and 10% TEC at different magnifications. (A1, A2, A3 are coated pellet with 10% DBP; B1, B2, B3 are coated pellet with 10% TEC)



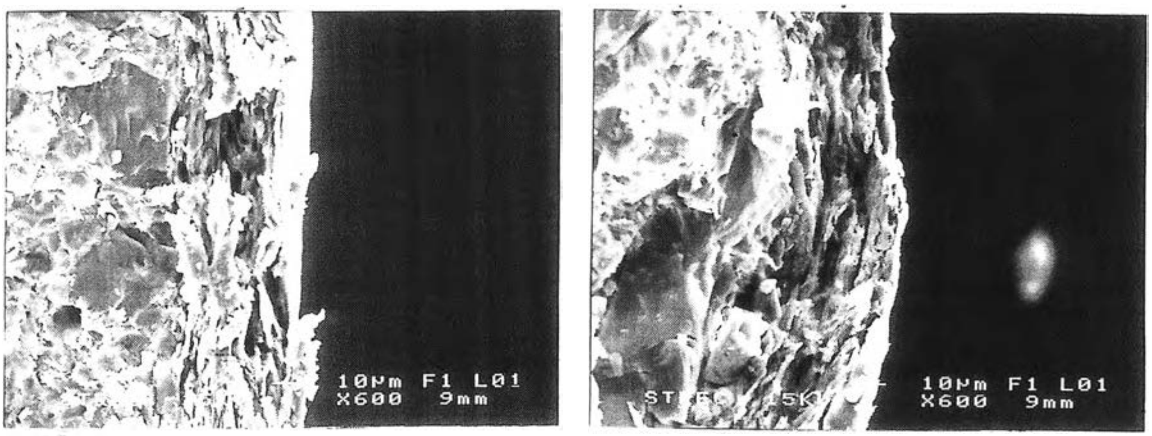
A1 x 60

B1 x 60



A2 x 300

B2 x 300



A3 x 600 cross-section

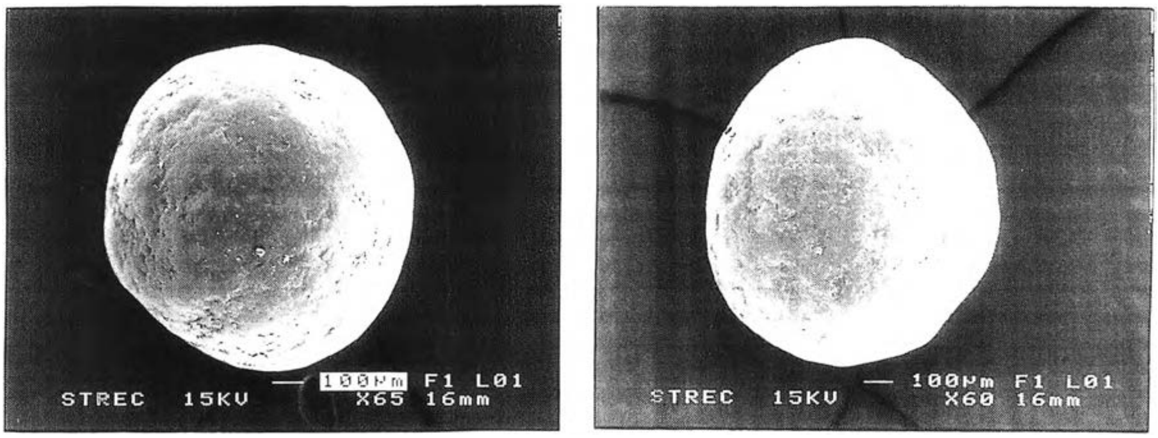
B3 x 600 cross-section

Figure 12 Photomicrographs of coated pellets with ethylcellulose with 20% DBP and 20% TEC at different magnifications. (A1, A2, A3 are coated pellet with 20% DBP; B1, B2, B3 are coated pellet with 20% TEC)

As illustrated in Figure 13, the Eudragit®RS100 coated pellets with 10% dibutyl phthalate and triethyl citrate showed the smooth and continuous surface feature. The coated pellets incorporated with 10% dibutyl phthalate illustrated smoother surface than those with 10% triethyl citrate. When compared to the photomicropraphs of Eudragit®RS100 coated pellets using 20% dibutyl phthalate and triethyl citrate that are shown in Figure 14. The higher amount of plasticizers, both dibutyl phthalate and triethyl citrate, resulted in the smoother, more homogeneous surface. Triethyl citrate apparently gave smoother surface of coated pellets than dibutyl phthalate. The cross section of the Eudragit®RS100 coated pellet with both 10% and 20% of plasticizers showed a clear interface between the core and the coating. The polymer layer displayed compact, smooth and uniform features. The similar feature was observed from tablets coated with Eudragit®RS100 and plasticized with dibutyl phthalate 20% (Rafiee-Tehrani and Sadegh-Shobeiri, 1995).

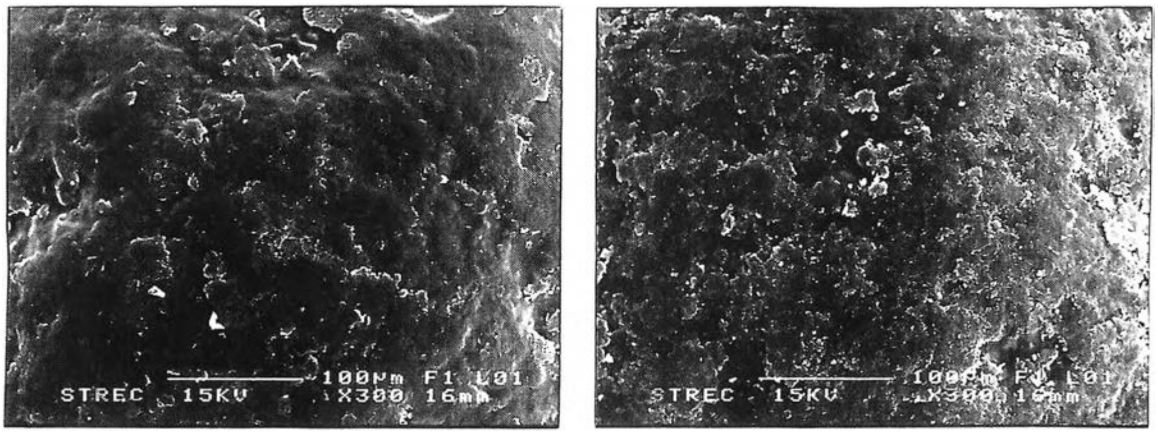
At the same magnification, the surface morphology of the Eudragit® RS100 coated pellets (Figures 13 and 14) was illustrated to be visibly different from that of ethylcellulose coated pellets which exhibited more orange peel like surface (Figures 11 and 12).

Figure 15 presents the photomicrographs of coated pellets obtained from the mixture of ethylcellulose and Eudragit®RS100 with the ratio of 5:5 and plasticized with 10% dibutyl phthalate and triethyl citrate. The coated pellets with these two plasticizers had rough surface with many spots of polymer, however the surface of coated pellets with triethyl citrate was much rougher than those with dibutyl phthalate. The cross section of the coated pellet plasticized with triethyl citrate displayed compact, smooth feature whereas the coated pellet plasticized with dibutyl phthalate showed stratified film layers formation.



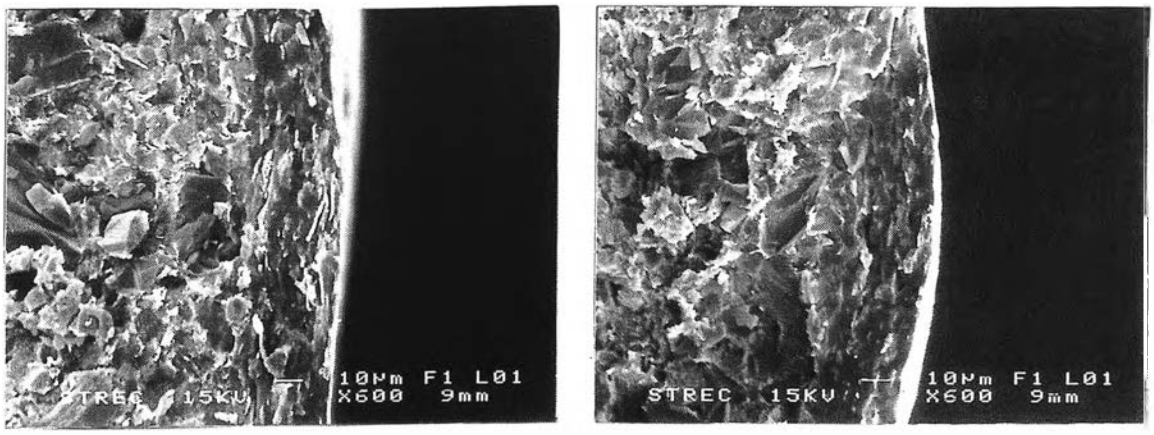
A1 x 60

B1 x 60



A2 x 300

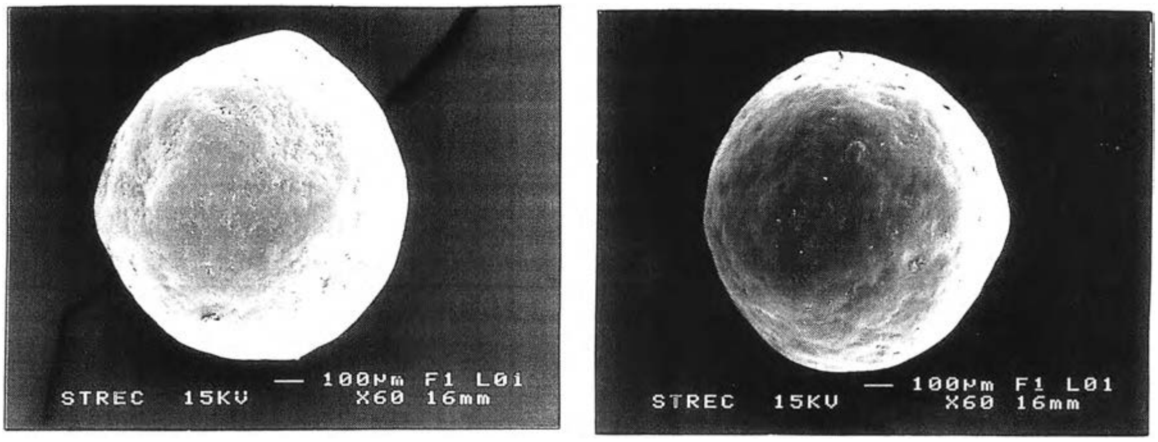
B2 x 300



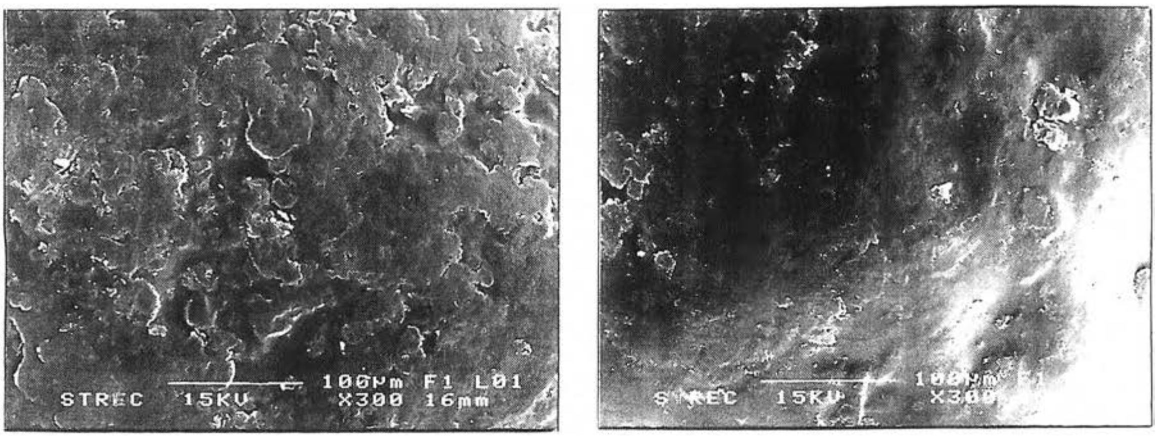
A3 x 600 cross-section

B3 x 600 cross-section

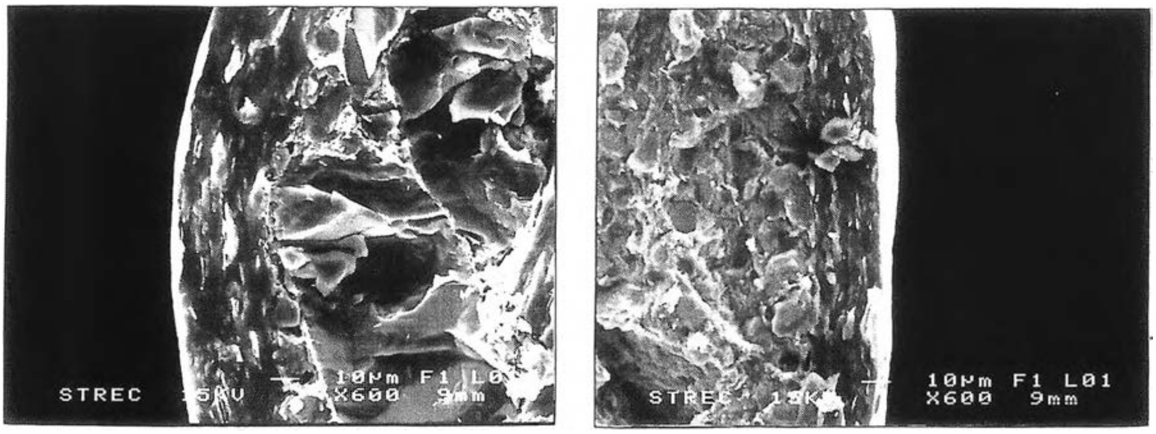
Figure 13 Photomicrographs of coated pellets with Eudragit®RS100 with 10% DBP and 10% TEC at different magnifications. (A1, A2, A3 are coated pellet with 10% DBP; B1, B2, B3 are coated pellet with 10% TEC)



A1 x 60 B1 x 60

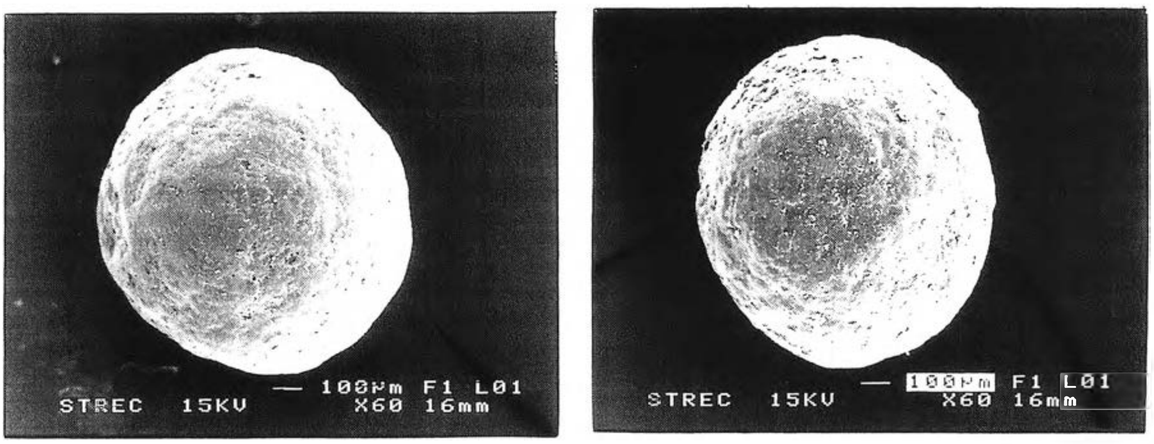


A2 x 300 B2 x 300

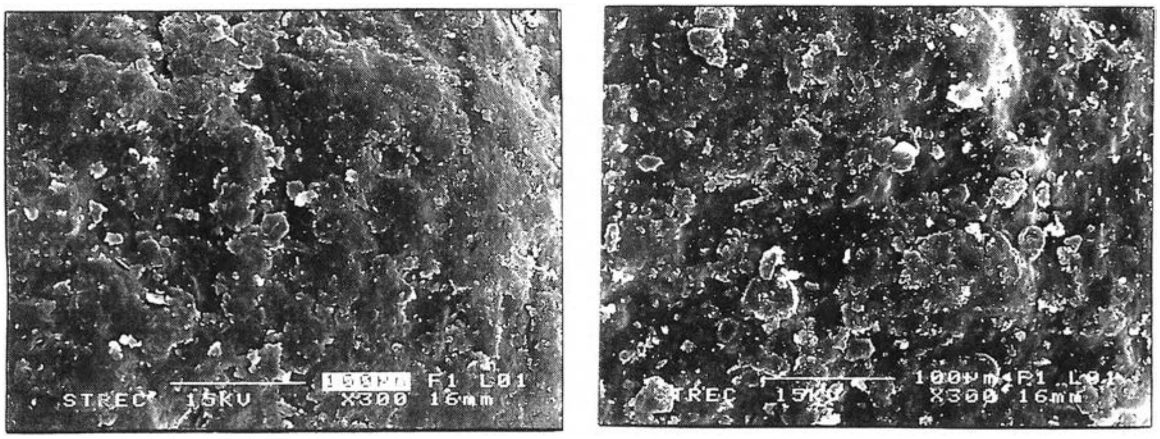


A3 x 600 cross-section B3 x 600 cross-section

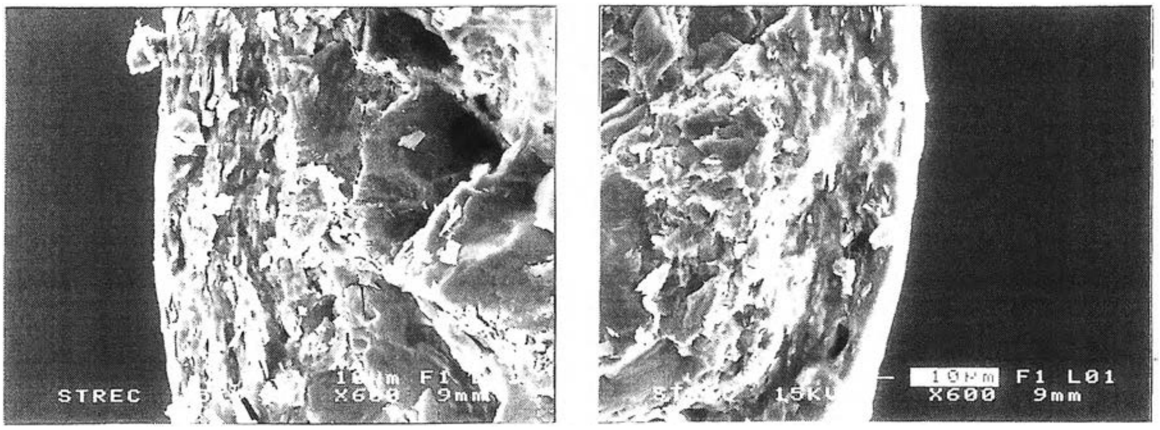
Figure 14 Photomicrographs of coated pellets with Eudragit®RS100 with 20% DBP and 20% TEC at different magnifications. (A1, A2, A3 are coated pellet with 20% DBP; B1, B2, B3 are coated pellet with 20% TEC)



A1 x 60 B1 x 60



A2 x 300 B2 x 300



A3 x 600 cross-section B3 x 600 cross-section

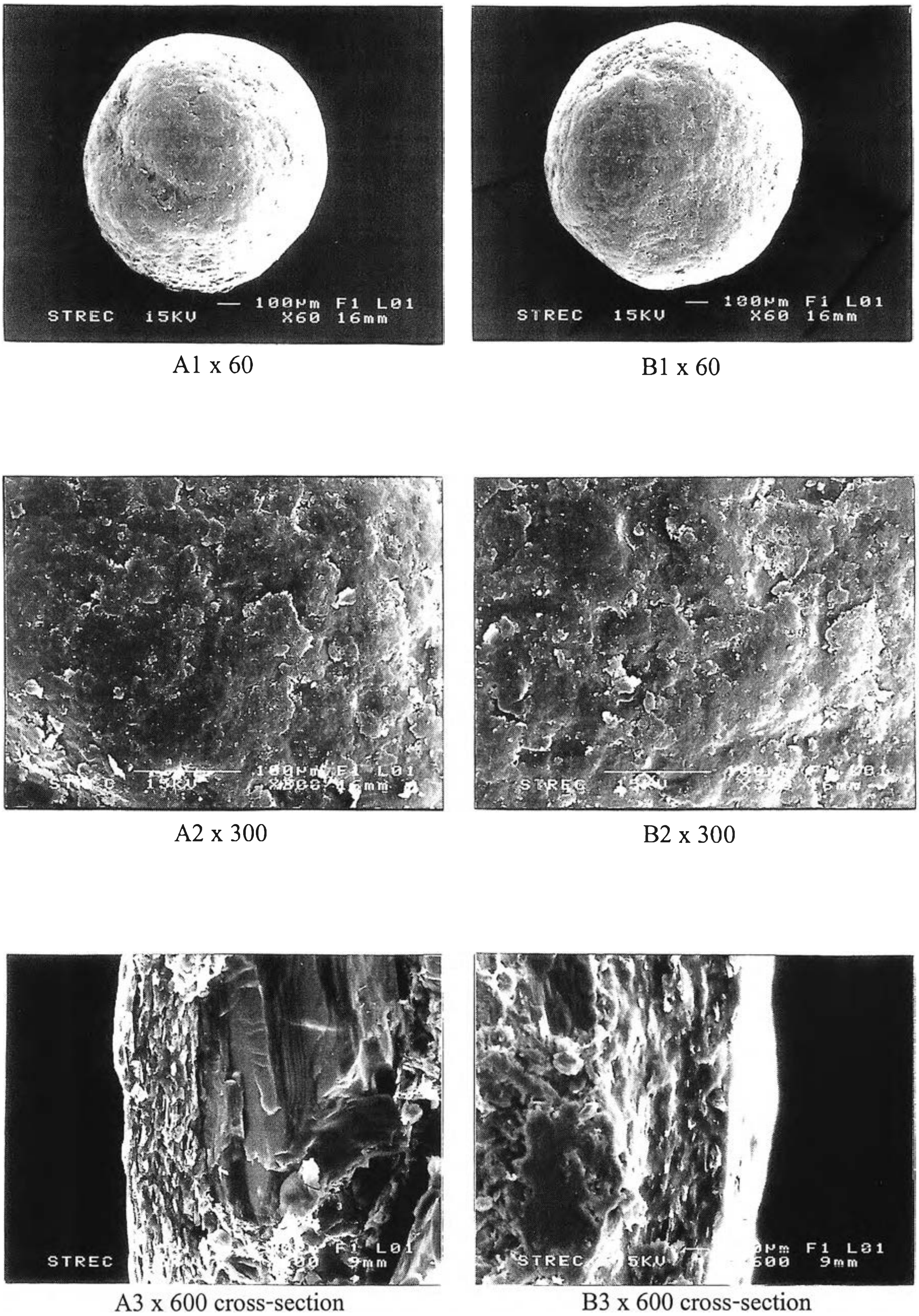
Figure 15 Photomicrographs of coated pellets with ethylcellulose:Eudragit®RS100 in the ratio of 5:5 with 10% DBP and 10% TEC at different magnifications. (A1, A2, A3 are coated pellet with 10% DBP; B1, B2, B3 are coated pellet with 10% TEC)

The higher quantity of plasticizer had an impact on surface topography. Figure 16 represents the microscopic appearance and the cross section of the pellets coated with ethylcellulose and Eudragit®RS100 in the ratio of 5:5 and plasticized with 20% dibutyl phthalate and triethyl citrate. The coated pellet using dibutyl phthalate had smoother surface than those using triethyl citrate while the film layers plasticized with triethyl citrate displayed more compact and smooth appearance than those plasticized with dibutyl phthalate. When compared with lower amount of plasticizer, the higher the amount of plasticizer used, the smoother surface of coated pellet was acheived.

Scanning electron microscopy studies on the mixtures of ethylcellulose and Eudragit®RS100 coated pellets with the ratio of 3:7 and plasticized by 10% dibutyl phthalate and triethyl citrate are illustrated in Figure 17. The smoother surface was obtained when this formulation was added with triethyl citrate. The formulations incorporated with dibutyl phthalate or triethyl citrate had the similar cross section view. They showed less stratified layers formation of film. Most of the film layers coalesced and caused compact film.

Figure 18 illustrates pellets coated with the same ratio of ethylcellulose and Eudragit®RS100 with 20% dibutyl phthalate or triethyl citrate. The surface morphology showed a smoother appearance than the formulations which contained lower amount of plasticizers. Triethyl citrate had more pronounced effect than dibutyl phthalate. The distinct layering of coating polymer was found with dense film layer.

When augmented the amount of ethylcellulose in the coating formulation, the use of triethyl citrate had a better effect than the use of dibutyl phthalate. Figure 19 presents the photomicropraphs of coated pellets with the mixtures of ethylcellulose and Eudragit®RS100 in the ratio of 7:3 plasticized with 10% dibutyl phthalate and triethyl citrate. As described above, the smoother surface was observed when using triethyl citrate. The cross section of coated pellets plasticized with dibutyl



A1 x 60

B1 x 60

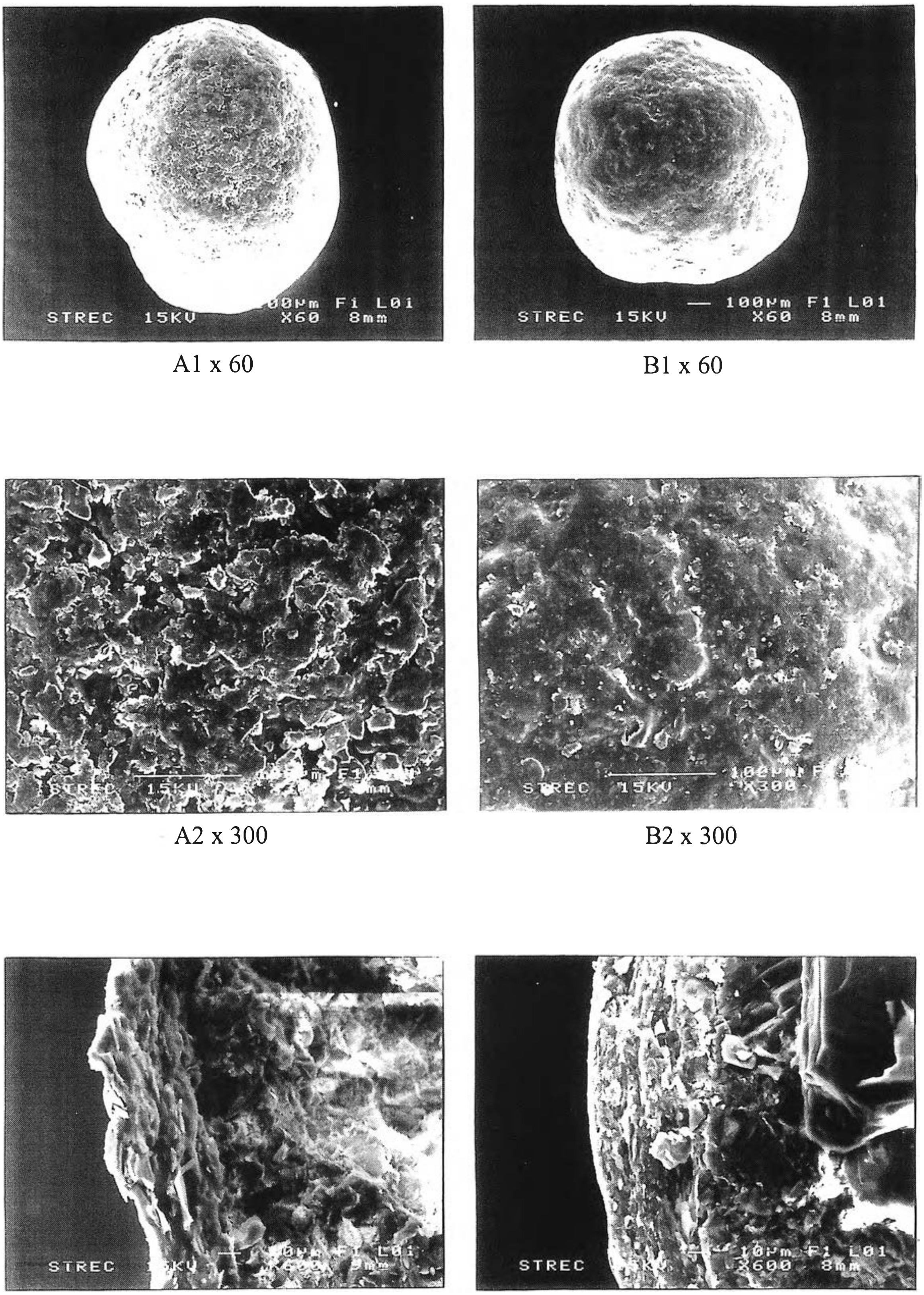
A2 x 300

B2 x 300

A3 x 600 cross-section

B3 x 600 cross-section

Figure 16 Photomicrographs of coated pellets with ethylcellulose:Eudragit®RS100 in the ratio of 5:5 with 20% DBP and 20% TEC at different magnifications. (A1, A2, A3 are coated pellet with 20% DBP; B1, B2, B3 are coated pellet with 20% TEC)



A1 x 60

B1 x 60

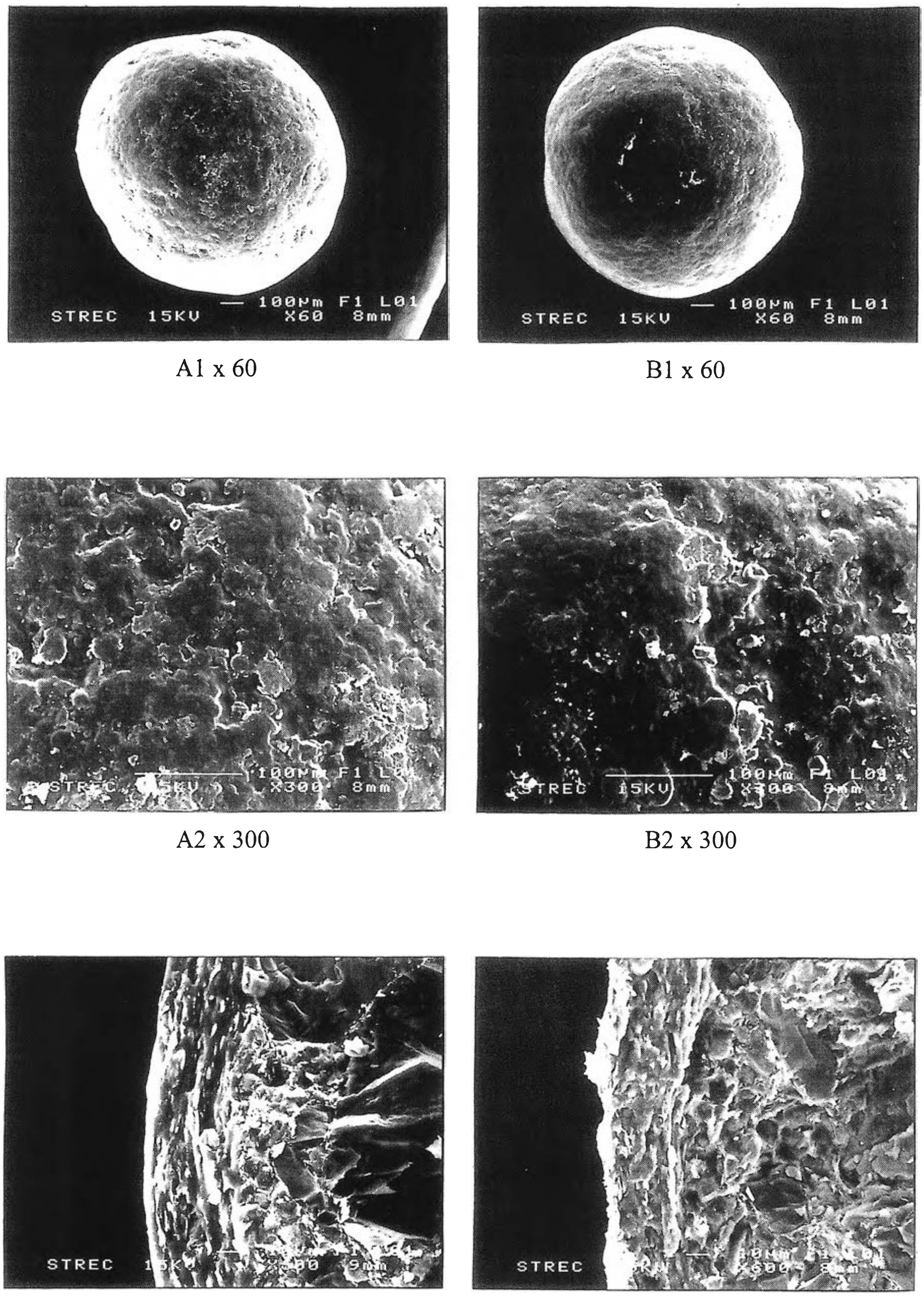
A2 x 300

B2 x 300

A3 x 600 cross-section

B3 x 600 cross-section

Figure 17 Photomicrographs of coated pellets with ethylcellulose:Eudragit®RS100 in the ratio of 3:7 with 10% DBP and 10% TEC at different magnifications. (A1, A2, A3 are coated pellet with 10% DBP; B1, B2, B3 are coated pellet with 10% TEC)



A1 x 60

B1 x 60

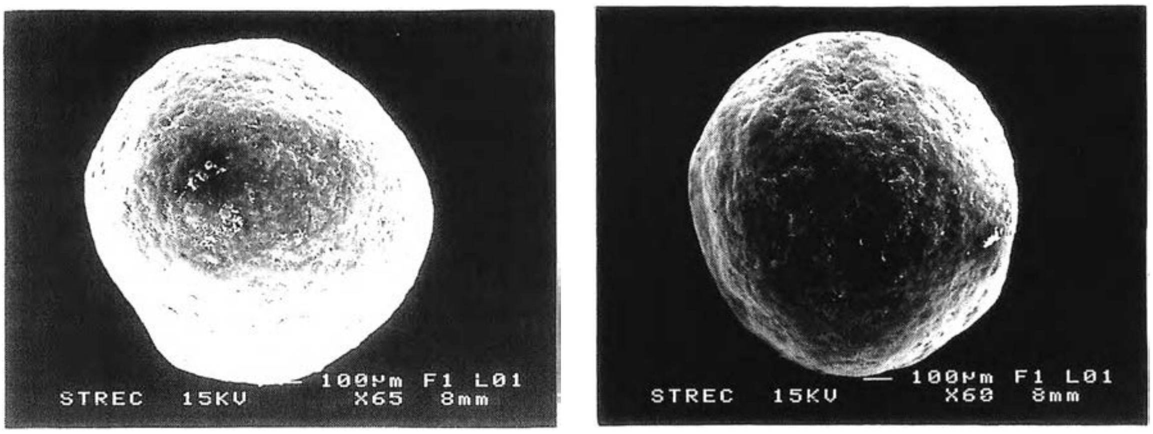
A2 x 300

B2 x 300

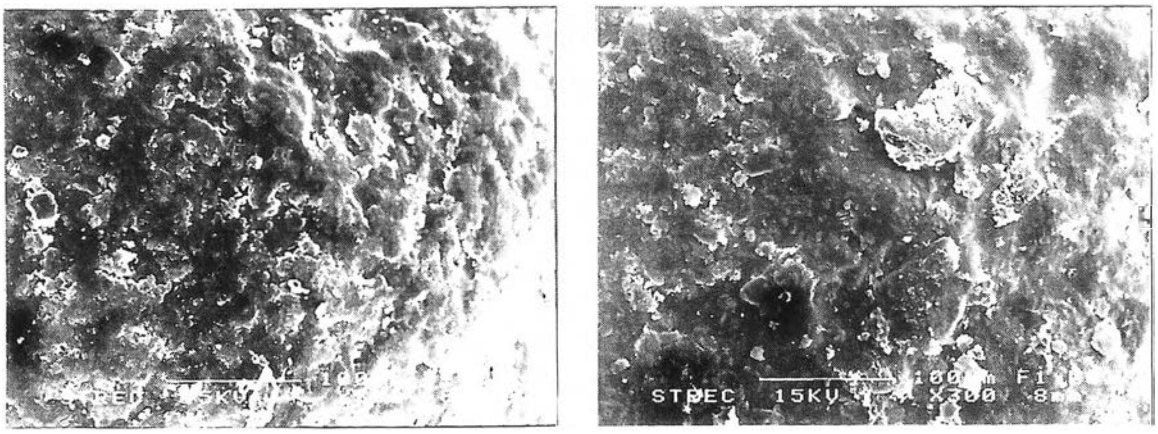
A3 x 600 cross-section

B3 x 600 cross-section

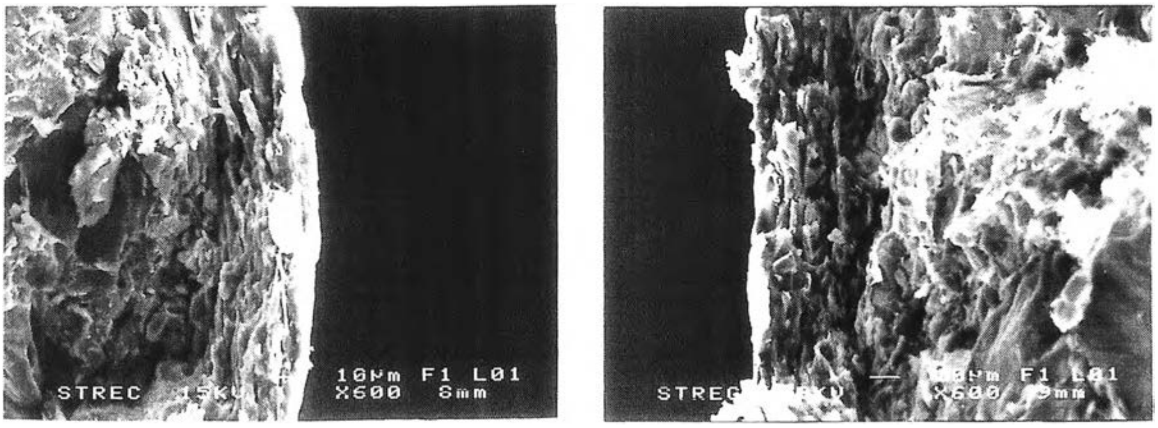
Figure 18 Photomicrographs of coated pellets with ethylcellulose:Eudragit®RS100 in the ratio of 3:7 with 20% DBP and 20% TEC at different magnifications. (A1, A2, A3 are coated pellet with 20% DBP; B1, B2, B3 are coated pellet with 20% TEC)



A1 x 60 B1 x 60



A2 x 300 B2 x 300



A3 x 600 cross-section B3 x 600 cross-section

Figure 19 Photomicrographs of coated pellets with ethylcellulose:Eudragit®RS100 in the ratio of 7:3 with 10% DBP and 10% TEC at different magnifications. (A1, A2, A3 are coated pellet with 10% DBP; B1, B2, B3 are coated pellet with 10% TEC)

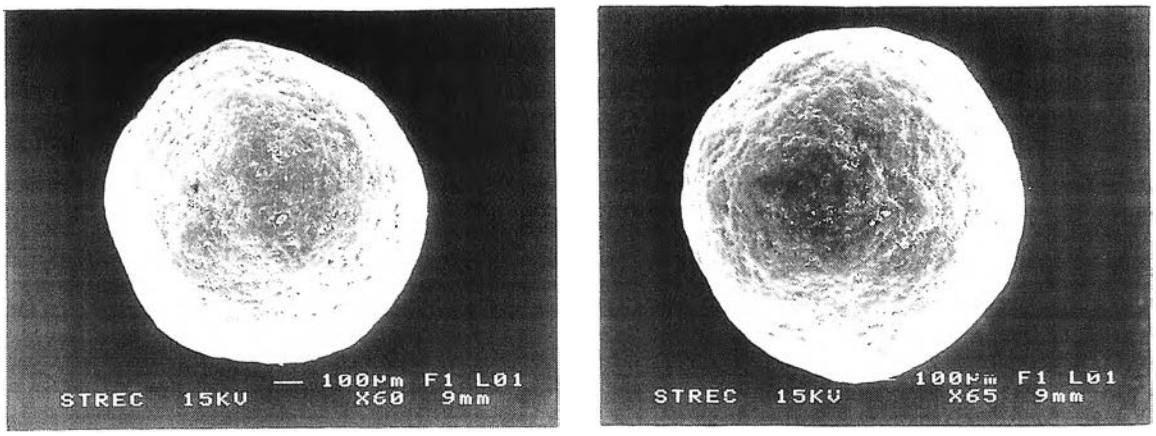
phthalate represented the stratified film layers more obviously than those plasticized with triethyl citrate.

The photomicrographs of the coated pellets obtained from the same ratio of ethylcellulose and Eudragit®RS100 with 20% dibutyl phthalate and triethyl citrate are exhibited in Figure 20. Triethyl citrate containing film likewise had a smoother surface than dibutyl phthalate containing film. Higher level of plasticizer led to the surface characteristic effects represented by an increase in smoothness and denser of film. The coated pellets plasticized with dibutyl phthalate or triethyl citrate showed stratified film layers.

Scanning electron microscopy studies were also performed on the aqueous system of formulations B1-B20. When viewed at the similar magnification (Figure 21), the surface morphology of Surelease® coated pellets plasticized with 10% triethyl citrate and triacetin was smooth but also had some flakes of polymer. When the higher amount of plasticizers was used (Figure 22), the surface features were smoother. This effect was more outstanding when triethyl citrate was employed than triacetin. The cross section of coated pellets in both Figure 21 and Figure 22 appeared compact films with stratified film layers.

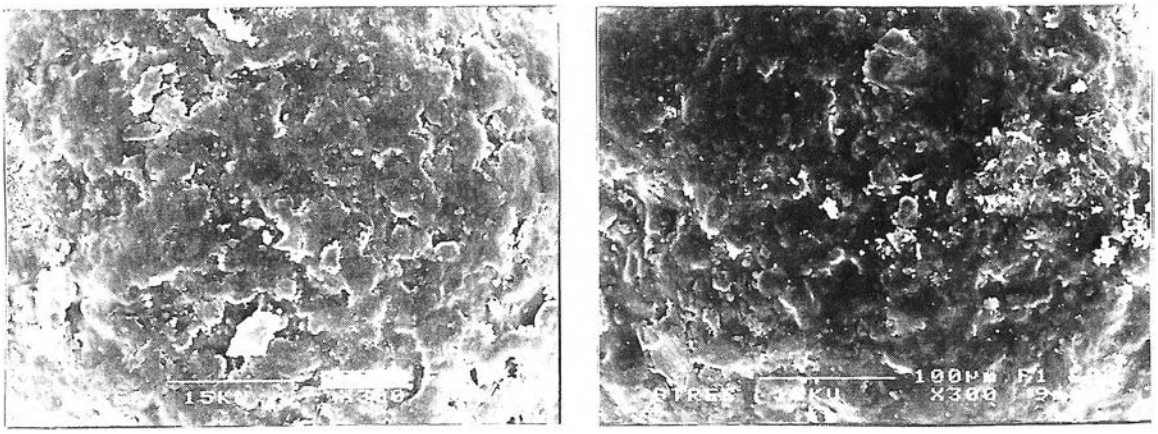
Figure 23 displays the microscopic images of pellets coated with Eudragit®RS30D and plasticized with 10% triethyl citrate and triacetin. The pellets showed a continuous and orange peel like surface. When viewed at x300 magnification. There was no marked difference in surface topography between the use of triethyl citrate and the use of triacetin. Continuous dense film layers were clearly observed at the cross section of Eudragit®RS30D coated pellets with 10% triethyl citrate and triacetin.

When the quantity of plasticizer was increased to 15% as in Figure 24. The smoother surfaces were not clearly observed when compared with 10% level.



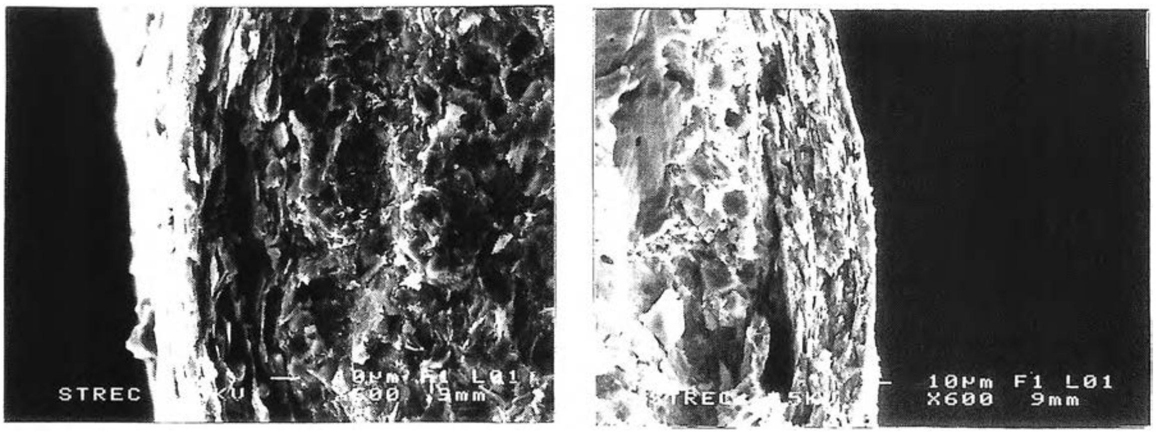
A1 x 60

B1 x 60



A2 x 300

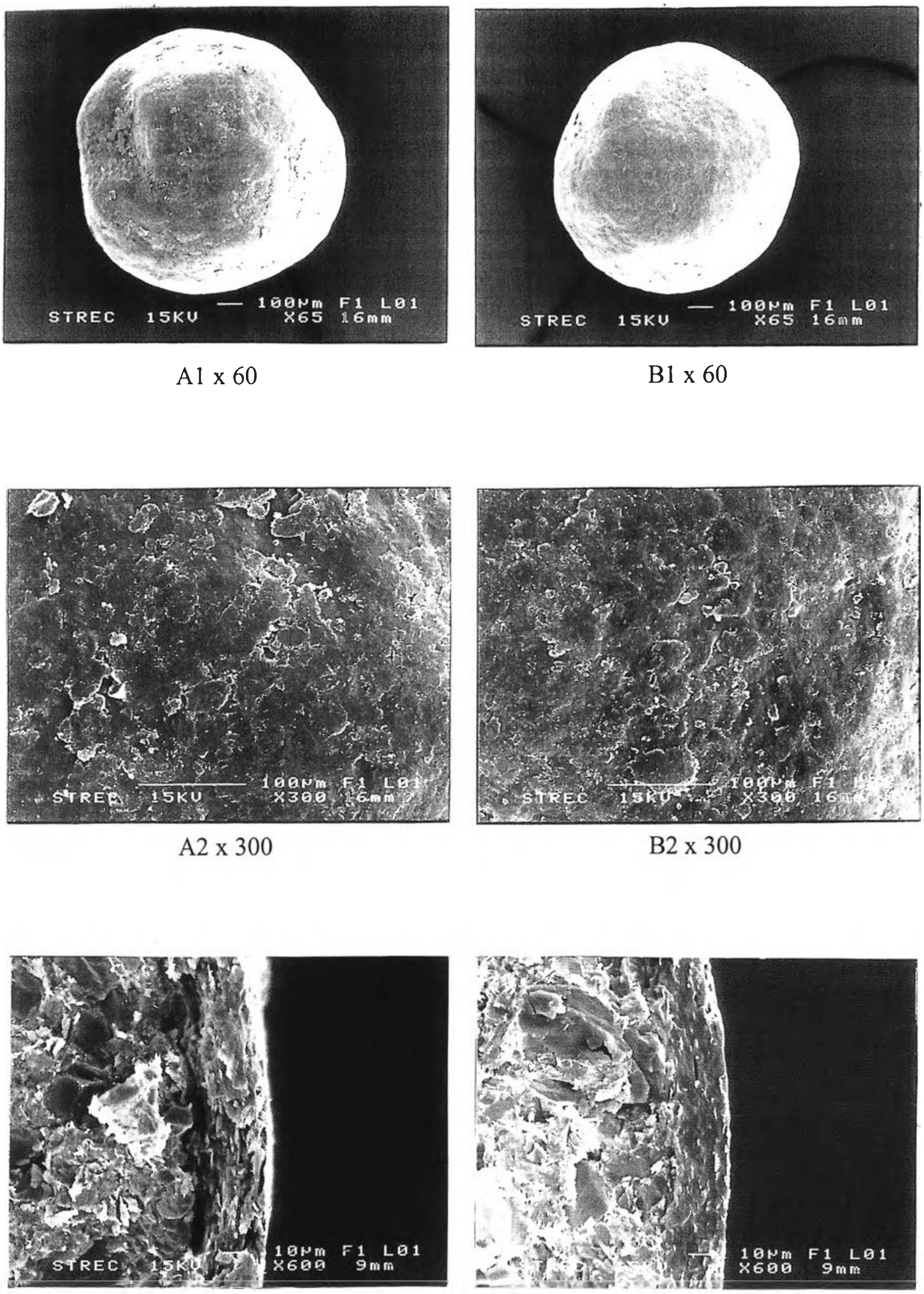
B2 x 300



A3 x 600 cross-section

B3 x 600 cross-section

Figure 20 Photomicrographs of coated pellets with ethylcellulose:Eudragit®RS100 in the ratio of 7:3 with 20% DBP and 20% TEC at different magnifications. (A1, A2, A3 are coated pellet with 20% DBP; B1, B2, B3 are coated pellet with 20% TEC)



A1 x 60

B1 x 60

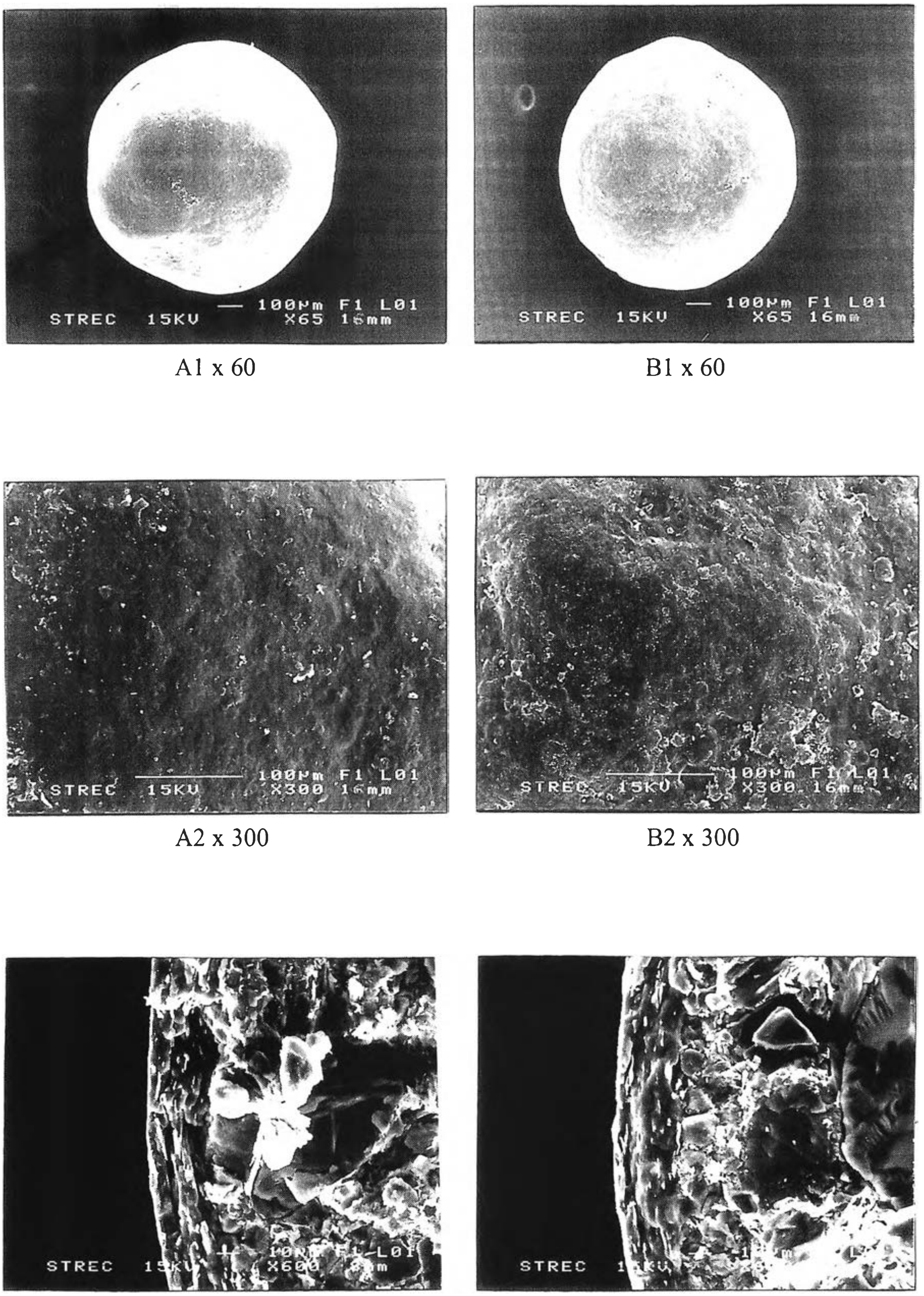
A2 x 300

B2 x 300

A3 x 600 cross-section

B3 x 600 cross-section

Figure 21 Photomicrographs of coated pellets with Surelease® with 10% TEC and 10% TRC at different magnifications. (A1, A2, A3 are coated pellet with 10% TEC; B1, B2, B3 are coated pellet with 10% TRC)



A1 x 60

B1 x 60

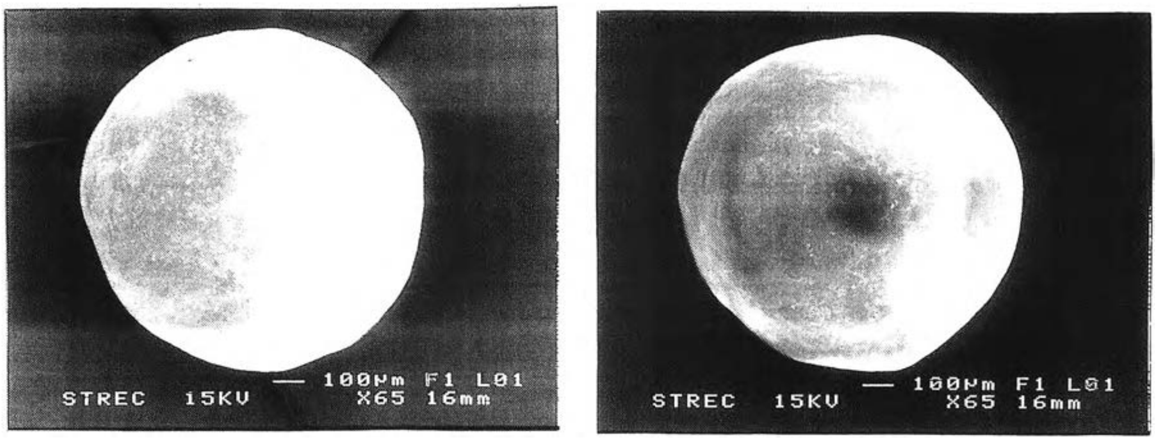
A2 x 300

B2 x 300

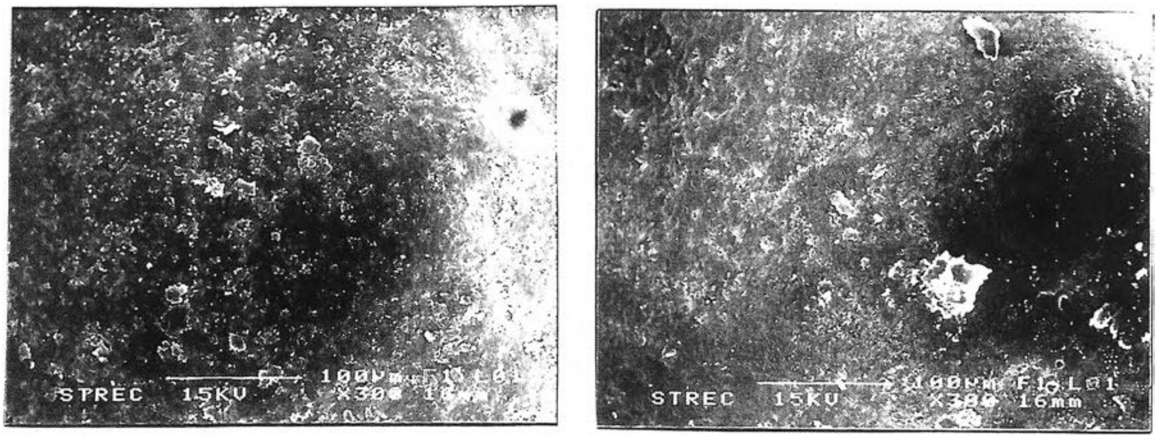
A3 x 600 cross-section

B3 x 600 cross-section

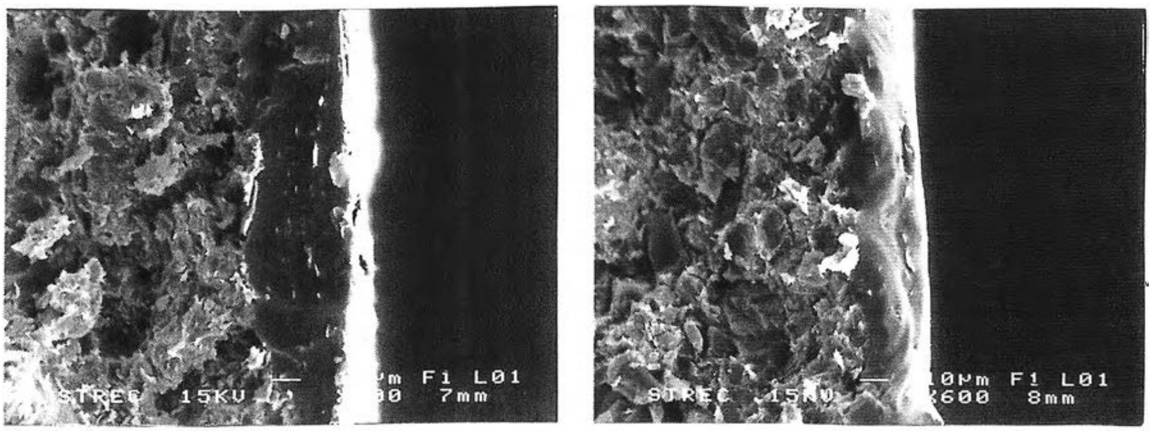
Figure 22 Photomicrographs of coated pellets with Surelease® with 15% TEC and 15% TRC at different magnifications. (A1, A2, A3 are coated pellet with 15% TEC; B1, B2, B3 are coated pellet with 15% TRC)



A1 x 60 B1 x 60

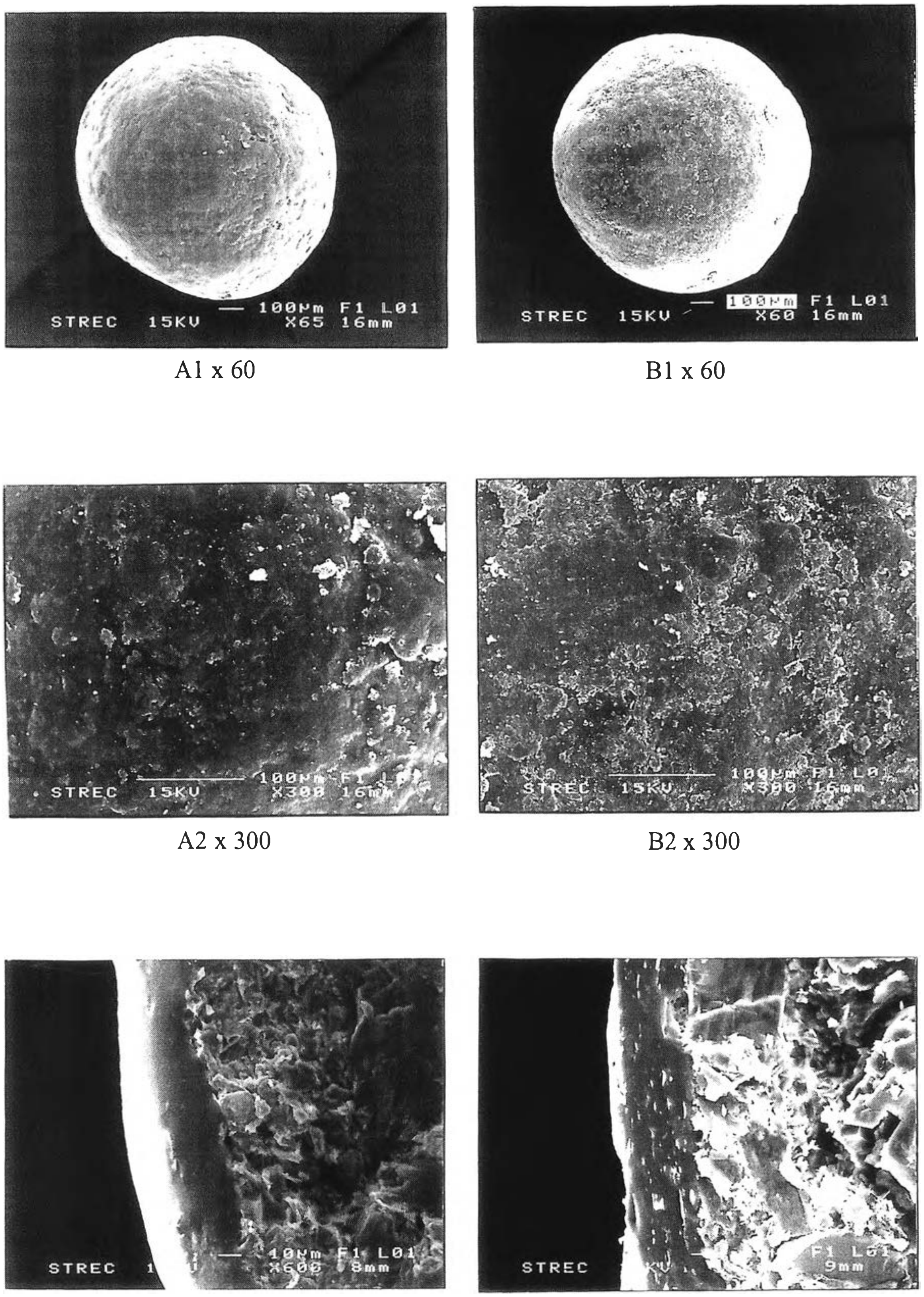


A2 x 300 B2 x 300



A3 x 600 cross-section B3 x 600 cross-section

Figure 23 Photomicrographs of coated pellets with Eudragit® RS30D with 10% TEC and 10% TRC at different magnifications. (A1, A2, A3 are coated pellet with 10% TEC; B1, B2, B3 are coated pellet with 10% TRC)



A1 x 60

B1 x 60

A2 x 300

B2 x 300

A3 x 600 cross-section

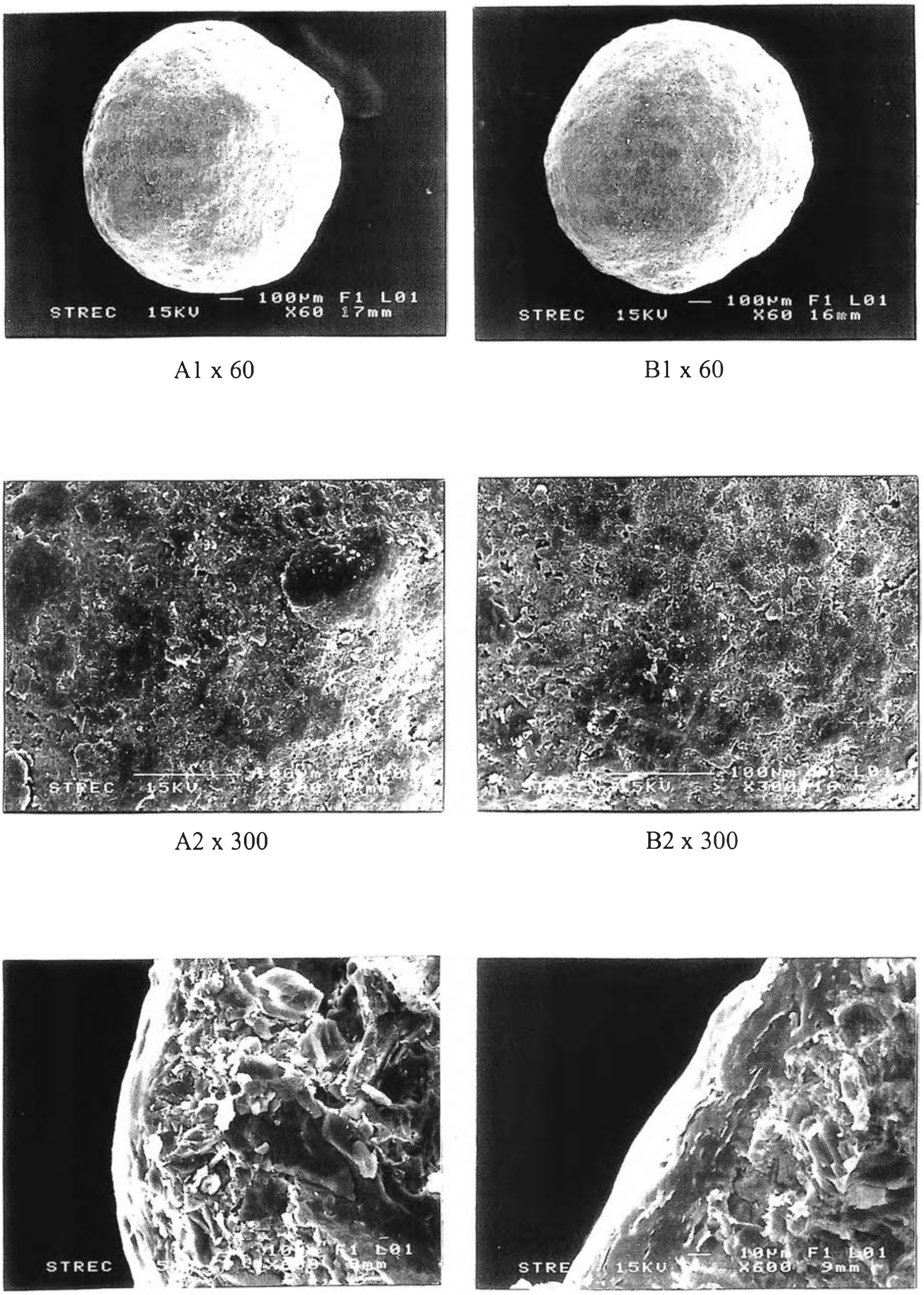
B3 x 600 cross-section

Figure 24 Photomicrographs of coated pellets with Eudragit®RS30D with 15% TEC and 15% TRC at different magnifications. (A1, A2, A3 are coated pellet with 15% TEC; B1, B2, B3 are coated pellet with 15% TRC)

Nevertheless, the using of triethyl citrate resulted in better appearance than the using of triacetin. Figure 24, which also illustrates the cross section of coated pellets, shows obvious separation between the film layer and surface of the pellet. These distinct polymer layers appeared continuous dense film and very smooth film, however the formulation with triacetin illustrated some stratified layers of film. The microscopic appearance of coated pellet containing 15% triethyl citrate was in agreement with results of Govender, Dangor, and Chetty (1997). They explained that the plasticizer quantity (triethyl citrate 12.5% w/w based on polymer content) incorporated into the formulation was adequate to promote deformation and coalescence of Eudragit®RS30D polymeric spheres. Hence, the smooth, uninterrupted film coats of the pellets should add the quantity of plasticizer more than 12.5% w/w.

The microscopic views of pellets coated with the mixed film between Surelease® and Eudragit®RS30D at the ratio of 5:5 and plasticized with 10% or 15% triethyl citrate and triacetin are presented in Figures 25 and 26, respectively. No apparent difference was seen by changing either the types of plasticizers or the amounts of plasticizers. All coated pellets in this proportion exhibited rough surface and were accompanied by the appearance of a number of pits. The cross sections of these formulations appeared compact and smooth film except the coated pellet with 10% triethyl citrate in Figure 25. This polymer layer could not be clearly observed from this picture.

As shown in Figure 27, the pellets coated with Surelease®and Eudragit®RS30D in the ratio of 7:3 with 10% triethyl citrate and triacetin exhibited smooth and uniform surface characteristics. The obvious polymer layers showed compact and smooth film. Triacetin-plasticized formulation produced smoother surface than triethyl citrate-plasticized formulation.



A1 x 60

B1 x 60

A2 x 300

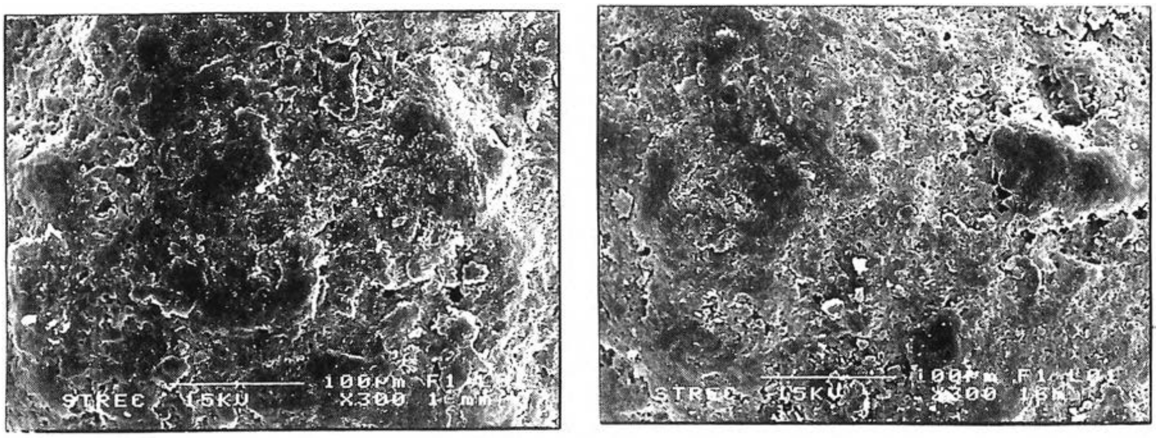
B2 x 300

A3 x 600 cross-section

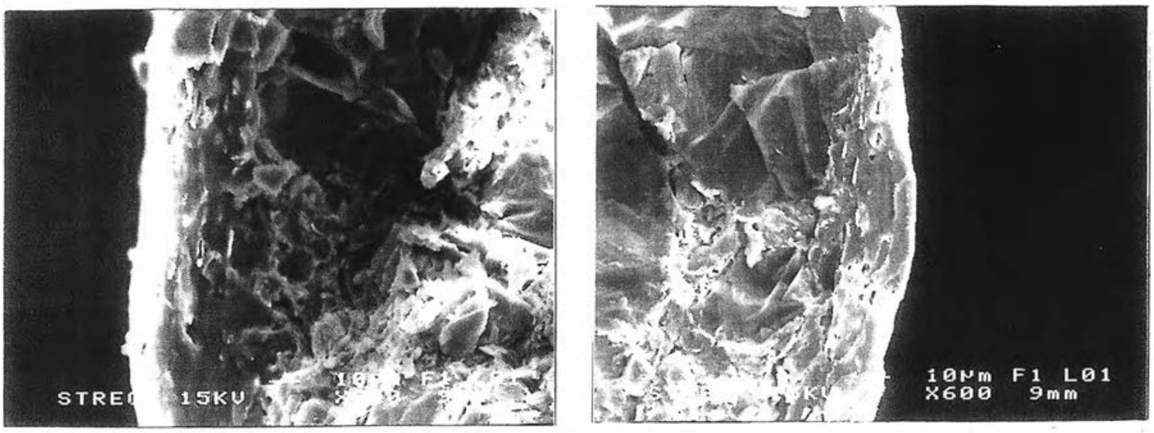
B3 x 600 cross-section

Figure 25 Photomicrographs of coated pellets with Surelease®:Eudragit®RS30D in the ratio of 5:5 with 10% TEC and 10% TRC at different magnifications. (A1, A2, A3 are coated pellet with 10% TEC; B1, B2, B3 are coated pellet with 10% TRC)

A1 x 60 B1 x 60

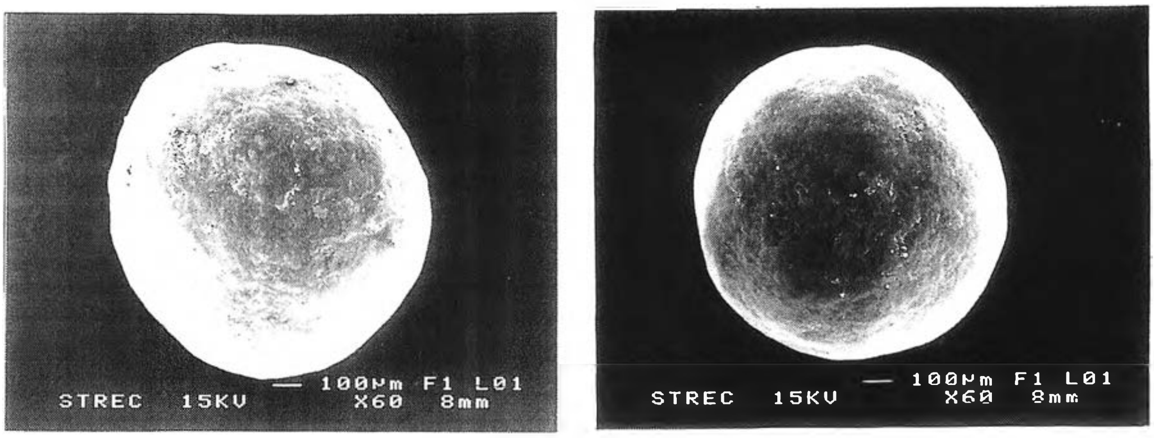


A2 x 300 B2 x 300

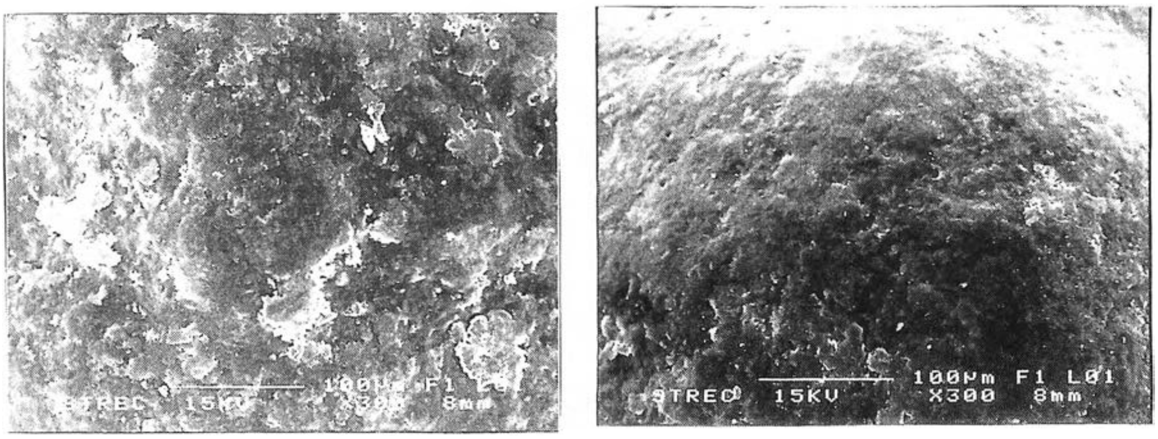


A3 x 600 cross-section B3 x 600 cross-section

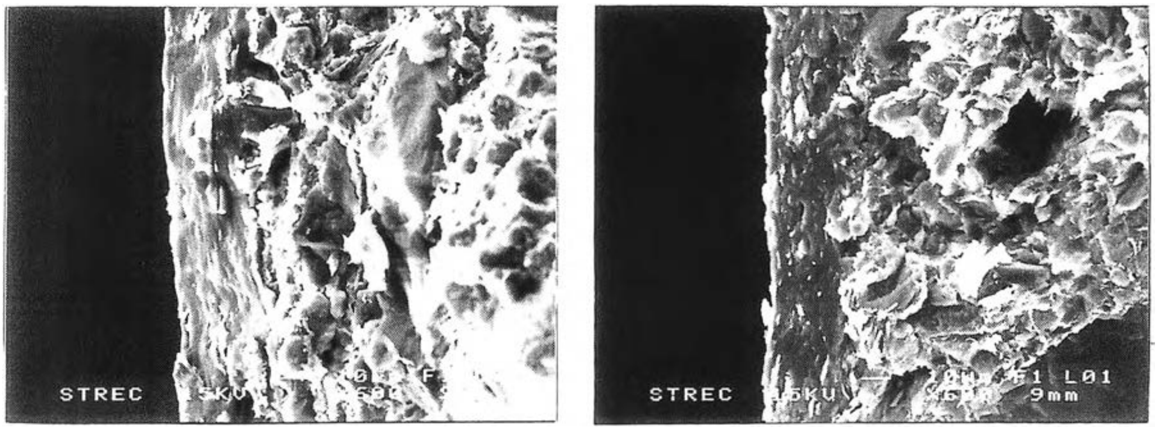
Figure 26 Photomicrographs of coated pellets with Surelease®:Eudragit®RS30D in the ratio of 5:5 with 15% TEC and 15% TRC at different magnifications. (A1, A2, A3 are coated pellet with 15% TEC; B1, B2, B3 are coated pellet with 15% TRC)



A1 x 60 B1 x 60



A2 x 300 B2 x 300



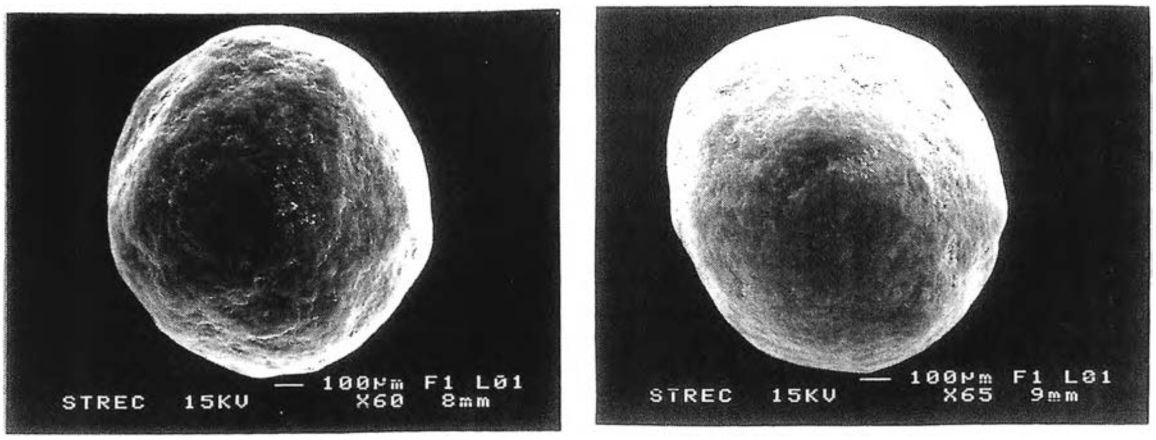
A3 x 600 cross-section B3 x 600 cross-section

Figure 27 Photomicrographs of coated pellets with Surelease®:Eudragit®RS30D in the ratio of 7:3 with 10% TEC and 10% TRC at different magnifications. (A1, A2, A3 are coated pellet with 10% TEC; B1, B2, B3 are coated pellet with 10% TRC)

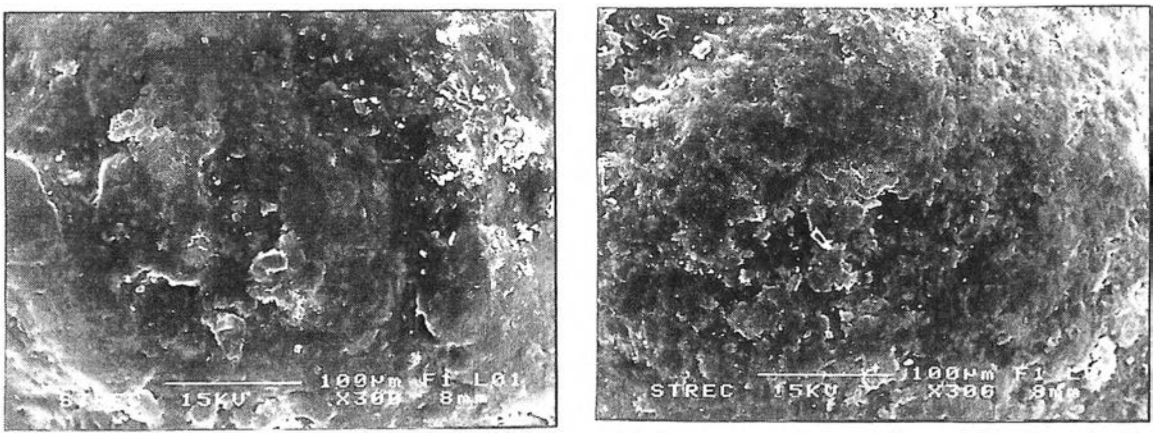
The photomicropraphs of Figure 28 that used the similar proportion of polymers with higher amount of triethyl citrate and triacetin were compared. The higher the quantity of plasticizer the smoother the surface features. Triethyl citrate improved the surface properties of these formulations more than triacetin did. The characteristics of film layers in this figure were quite similar to the characteristics of film layers in Figure 27 except they showed denser layers than those with lower amount of plasticizers.

The microscopic characteristics were dependent on not only the types and amounts of plasticizers but also the various ratios of two polymers. In this study, as illustrated in Table 10, dibutyl phthalate (the water insoluble plasticizer) was the efficient plasticizer for ethylcellulose in organic system coating. Films incorporated with dibutyl phthalate illustrated the smoother and uniform surface. The similar effect was studied by Hyppola et al. (1996) by employing various types of plasticizers. They concluded that dibutyl sebacate and Myvacet® as the water insoluble plasticizer were the two most efficient plasticizers for ethylcellulose films whereas triethyl citrate provided more pronounced improvement of Eudragit®RS100 film properties than did dibutyl phthalate.

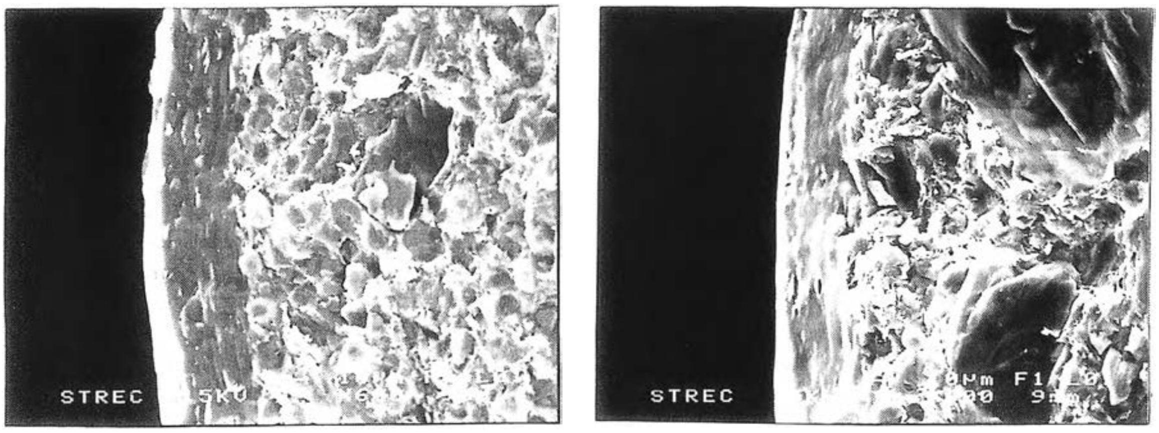
However, for the film mixtures of ethylcellulose and Eudragit®RS100 in the ratio of 3:7 and 7:3, the smoother films were obtained when triethyl citrate was used. On the other hand, dibutyl phthalate was more efficient than triethyl citrate for improving surface topography of polymer blends between ethylcellulose and Eudragit® RS100 in the ratio of 5:5. The smoothness of the combined polymer in the ratio of 3:7 that was achieved by using 10% triethyl citrate was not in agreement with the types of plasticizers that could affect the surface characteristics. When the proportion of ethylcellulose was augmented, dibutyl phthalate should provide a better surface characteristic of films. Furthermore, almost of the films plasticized with higher amount of triethyl citrate at 20% level presented smoother and denser film formation than those plasticized with the same level of dibutyl phthalate. These results indicated that triethyl



A1 x 60 B1 x 60



A2 x 300 B2 x 300



A3 x 600 cross-section B3 x 600 cross-section

Figure 28 Photomicrographs of coated pellets with Surelease®:Eudragit®RS30D in the ratio of 7:3 with 15% TEC and 15% TRC at different magnifications. (A1, A2, A3 are coated pellet with 15% TEC; B1, B2, B3 are coated pellet with 15% TRC)

Table 10 The type and amount of plasticizer that could improve more smoothness of surface characteristics of the single films and the blended films when compared to another plasticizer in both organic and aqueous systems

The ratio of EC:EuRS100	Type of plasticizer		The ratio of SR:EuRS30D	Type of plasticizer	
	10% level	20% level		10% level	20% level
10:0	No difference between DBP and TEC	DBP better than TEC	10:0	No difference between TEC and TRC	TEC better than TRC
7:3	TEC better than DBP	TEC better than DBP	7:3	TRC better than TEC	TEC better than TRC
5:5	DBP better than TEC	DBP better than TEC	5:5	No difference between TEC and TRC	No difference between TEC and TRC
3:7	TEC better than DBP	TEC better than DBP	3:7	–	--
0:10	DBP better than TEC	TEC better than DBP	0:10	No difference between TEC and TRC	TEC better than TRC

citrate at high level had more tendency to improve surface characteristics of films than did dibutyl phthalate.

The studies about aqueous dispersion system of two polymers exhibited that almost all of aqueous dispersion formulations containing triethyl citrate had smoother surface features. However, neither triethyl citrate nor triacetin had improved surface characteristics of the pellets coated with Surelease®: Eudragit®RS30D in the ratio of 5:5.

The surfaces of coated pellets displayed an improvement in the smoothness and continuity of the polymer film when the higher quantity of plasticizers was used. As demonstrated by Arwidsson et al. (1991), the structure of the Aquacoat® films with 12% triethyl citrate showed the granular structure due to incompletely coalesced polymer particles. A structure without visible uncoalesced particles was obtained at 22% triethyl citrate. The same phenomenon was presented by Govender et al. (1995). Their results illustrated that increasing the plasticizer concentration from 8%

to 12.5% enhanced the deformation and coalescence of the Eudragit®RS30D which resulted in smoother surface appearances.

When considered the different ratios of polymers, the changed proportion of two polymers had an important effect on the surface features. The smoother and denser film was observed when the higher proportion of Eudragit®RS100 was used in organic system. This characteristic was noticeable with higher amount of plasticizers. The blending between Surelease®and Eudragit®RS30D with two ratios did not improve surface features. Although, the blended film of Surelease®: Eudragit® RS30D in the ratio of 7:3 had the smooth and uniform surface characteristic, the pure films of either Surelease®or Eudragit®RS30D had the smoother surface. Hence, the blended film between Surelease®and Eudragit®RS30D could not improve film formation.

The comparison of the coating film using organic system and the aqueous system showed that the pellets coated with ethylcellulose had rougher surface than those coated with Surelease®. In comparison with Eudragit®RS30D coated pellets, the smoother surface of Eudragit®RS100 coated pellets was obtained. The formulation with ethylcellulose and Eudragit®RS100 in the ratio of 5:5 appeared smoother features when compared to films from aqueous system in the corresponding ratio. However the films prepared from Surelease® and Eudragit®RS30D in the ratio of 7:3 exhibited better features than those prepared from ethylcellulose and Eudragit®RS100 in the same ratio. These surface features were due to the property of ethylcellulose in aqueous dispersion system (Surelease®) that had better film characteristic than those of ethylcellulose in organic system. Consequently, the film mixture of Surelease® and Eudragit®RS30D produced smoother surface than the film mixture of ethylcellulose and Eudragit®RS100 at the ratio of 7:3.

3.3 Mechanical evaluation of the free films

Film coating system which produces tough films with high mechanical strength and elongation are best suited for tablet coating. Alternatively, softer films with lower modulus and higher elongation are recommended for use in transdermal system (Hutchings et al., 1994).

However, the formation of free films during casting might be different from the formation of the film during the real coating process of the pellets, for example sedimentation of talcum or magnesium stearate or migration of the additive in coating formulation occurred differently. So the results from the mechanical testing of the free film did not absolutely foretell the properties of the film on the coated pellets.

3.3.1 Effect of plasticizer amount

The addition of the plasticizers had a significant effect on the mechanical properties of all film samples. The results in Tables 11-14 and Figures 29-44 show the influence of two different levels of the plasticizer on the percent strain at break, stress at break, Young's modulus and toughness.

% Strain at break or elongation which is defined as the distance at break related to original distance of free film, represents the ductility of the membrane. The % strain at break of free films in both organic and aqueous systems was found to increase with a corresponding increase in plasticizer concentration except the formulation with ethylcellulose: Eudragit®RS100 in the ratio of 10:0 that plasticized with dibutyl phthalate (Figure 29). Tensile strength can be used to indicate the strength of the membrane. As expected, the addition of plasticizers resulted in a reduction of the stress at break of almost all of film samples with the exception of Surelease®: Eudragit®

Table 11 Mechanical properties of blended films in organic system plasticized with dibutyl phthalate at two different levels (S.D. in parenthesis)

Mechanical properties	Composition of EC:EuRS100									
	10:0		7:3		5:5		3:7		0:10	
	10%(1)	20%(2)	10%	20%	10%	20%	10%	20%	10%	20%
% Strain at break	1.352 (0.073	1.261 (0.061)	1.032 (0.055)	1.161 (0.056)	0.950 (0.041)	1.310 (0.118)	0.539 (0.063)	1.646 (0.052)	1.439 (0.148)	9.657 (1.232)
Stress at break (MPa)	11.750 (0.409)	9.737 (0.177)	9.749 (0.477	7.663 (0.210)	8.796 (0.210)	6.837 (0.394)	3.213 (0.220)	3.462 (0.123)	7.515 (0.680)	2.484 (0.604)
Young's modulus (MPa)	1131.27 (52.291)	991.97 (50.053)	1137.25 (36.858)	872.48 (26.312)	1120.62 (36.135)	757.21 (43.714)	642.33 (37.177)	381.53 (22.449)	853.38 (111.23)	220.38 (51.390)
Toughness (MPa)	0.092 (0.007)	0.071 (0.004)	0.057 (0.006)	0.052 (0.004)	0.047 (0.003)	0.055 (0.009)	0.009 (0.002)	0.038 (0.003)	0.069 (0.013)	0.223 (0.021)

(1) and (2) = percentage amount of plasticizer used in the formulation

Table 12 Mechanical properties of blended films in organic system plasticized with triethyl citrate at two different levels (S.D. in parenthesis)

Mechanical properties	Composition of EC:EuRS100									
	10:0		7:3		5:5		3:7		0:10	
	10%(1)	20%(2)	10%	20%	10%	20%	10%	20%	10%	20%
% Strain at break	1.177 (0.094)	1.383 (0.081)	0.878 (0.032)	1.198 (0.077)	0.889 (0.065)	1.767 (0.088)	0.727 (0.044)	1.992 (0.098)	1.768 (0.227)	16.133 (1.689)
Stress at break (MPa)	11.522 (0.412)	10.153 (0.483)	8.451 (0.363)	6.634 (0.353)	8.283 (0.455)	4.611 (0.274)	5.426 (0.592)	2.600 (0.126)	7.675 (0.479)	1.865 (0.703)
Young's modulus (MPa)	1200.70 (51.366)	980.12 (26.230)	1125.17 (71.582)	744.29 (39.918)	1062.49 (98.001)	442.77 (20.662)	847.08 (75.256)	269.52 (13.928)	794.23 (83.500)	262.23 (8.764)
Toughness (MPa)	0.077 (0.009)	0.083 (0.010)	0,041 (0.003)	0.047 (0.006)	0.040 (0.004)	0.053 (0.006)	0.022 (0.004)	0.036 (0.003)	0.089 (0.014)	0.425 (0.058)

(1) and (2) = percentage amount of plasticizer used in the formulation

Table 13 Mechanical properties of blended films in aqueous dispersion system plasticized with triethyl citrate at two different levels (S.D. in parenthesis)

Mechanical properties	Composition of SR:EuRS30D									
	10:0		7:3		5:5		3:7		0:10	
	10%(1)	15%(2)	10%	15%	10%	15%	10%	15%	10%	15%
% Strain at break	5.535 (0.404)	10.531 (1.302)	4.156 (0.233)	4.475 (0.338)	5.742 (0.541)	5.984 (1.395)	1.288 (0.080)	5.606 (0.609)	1.763 (0.217)	23.702 (6.303)
Stress at break (MPa)	2.126 (0.375)	1.192 (0.145)	2.985 (0.180)	1.691 (0.671)	2.260 (0.391)	1.002 (0.411)	3.822 (0.180)	2.207 (0.562)	6.251 (0.749)	1.775 (0.313)
Young's modulus (MPa)	97.516 (8.215)	45.198 (7.165)	168.473 (8.344)	100.800 (15.907)	154.269 (23.789)	93.910 (4.566)	461.459 (23.911)	205.310 (31.376)	691.942 (29.132)	431.399 (30.657)
Toughness (MPa)	0.090 (0.010)	0.101 (0.009)	0.091 (0.018)	0.064 (0.014)	0.107 (0.020)	0.073 (0.029)	0.031 (0.003)	0.117 (0.015)	0.074 (0.016)	0.634 (0.172)

(1) and (2) = percentage amount of plasticizer used in the formulation

Table 14 Mechanical properties of blended films in aqueous dispersion system plasticized with triacetin at two different levels (S.D. in parenthesis)

Mechanical properties	Composition of SR:EuRS30D									
	10:0		7:3		5:5		3:7		0:10	
	10%(1)	15%(2)	10%	15%	10%	15%	10%	15%	10%	15%
% Strain at break	4.814 (0.465)	5.851 (0.690)	3.858 (0.559)	5.025 (0.280)	2.683 (0.675)	5.268 (1.989)	1.007 (0.050)	4.137 (0.747)	2.411 (0.133)	7.987 (1.527)
Stress at break (MPa)	4.168 (0.315)	3.182 (0.600)	2.402 (0.335)	3.278 (0.198)	2.923 (0.441)	1.298 (0.885)	4.294 (0.227)	3.608 (0.243)	5.771 (1.114)	2.686 (1.148)
Young's modulus (MPa)	203.039 (9.918)	170.195 (13.499)	137.309 (14.150)	169.197 (10.438)	255.258 (28.338)	188.139 (78.775)	557.847 (21.114)	347.011 (27.488)	809.784 (64.162)	607.700 (54.450)
Toughness (MPa)	0.153 (0.025)	0.160 (0.023)	0.066 (0.012)	0.126 (0.014)	0.056 (0.019)	0.076 (0.031)	0.025 (0.003)	0.124 (0.027)	0.119 (0.011)	0.309 (0.073)

(1) and (2) = percentage amount of plasticizer used in the formulation

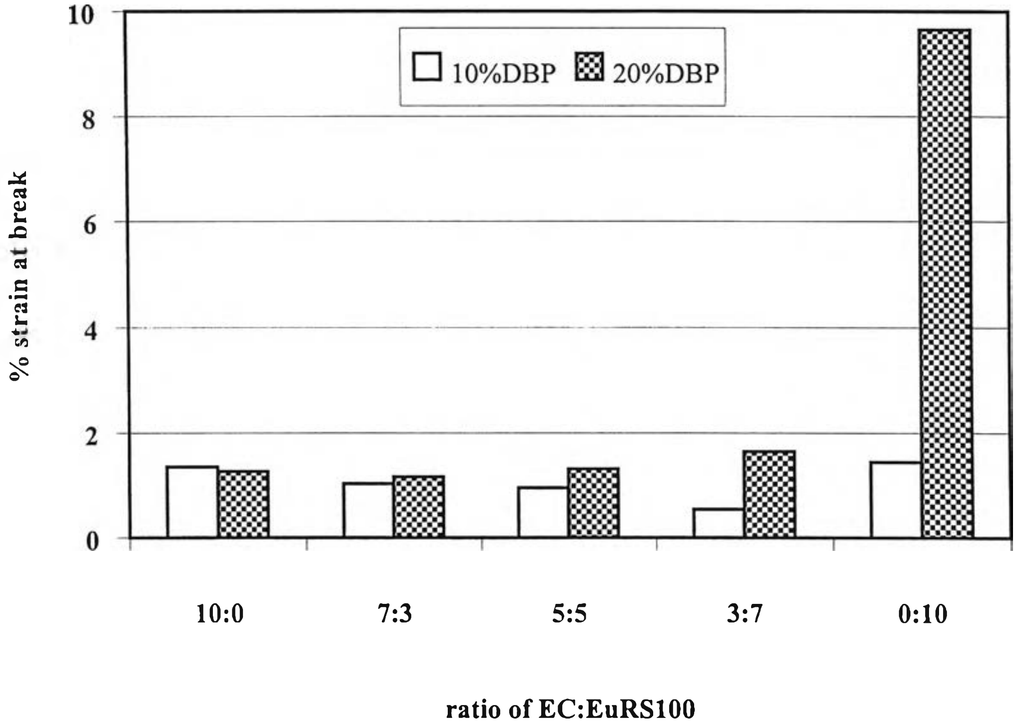


Figure 29 % Strain at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% DBP in organic system

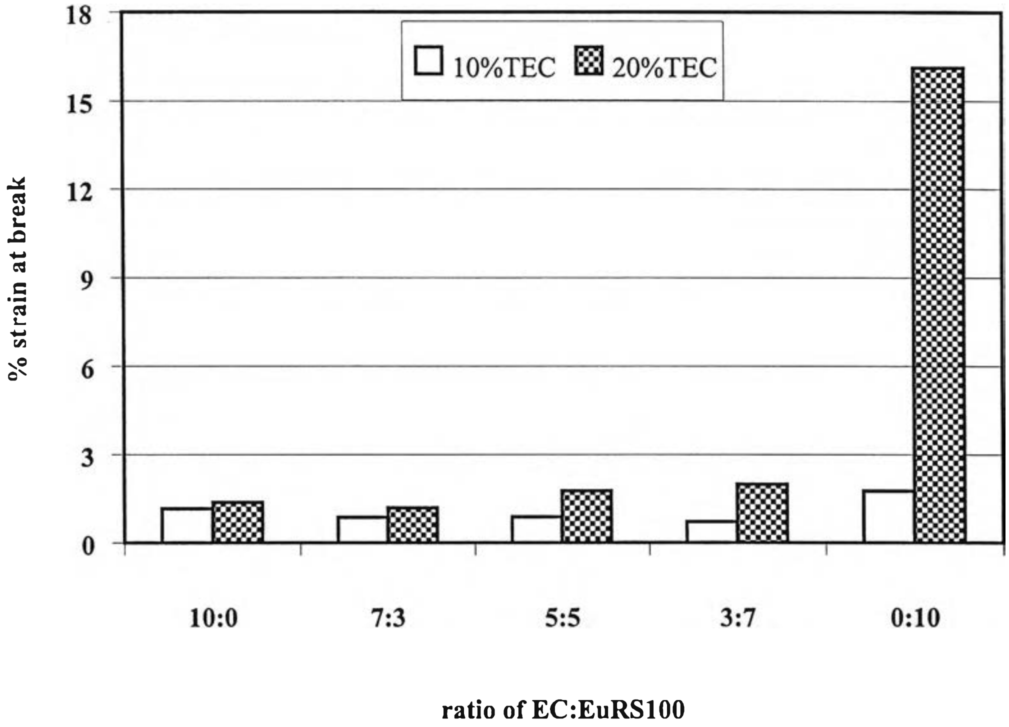


Figure 30 % Strain at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% TEC in organic system

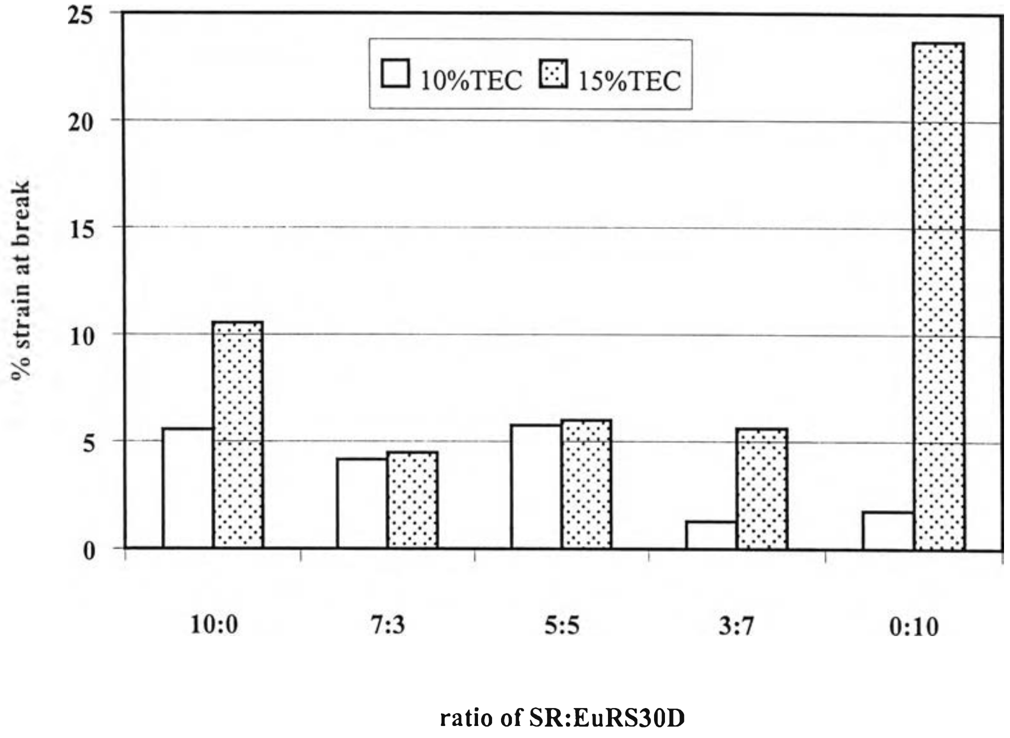


Figure 31 % Strain at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TEC in aqueous system

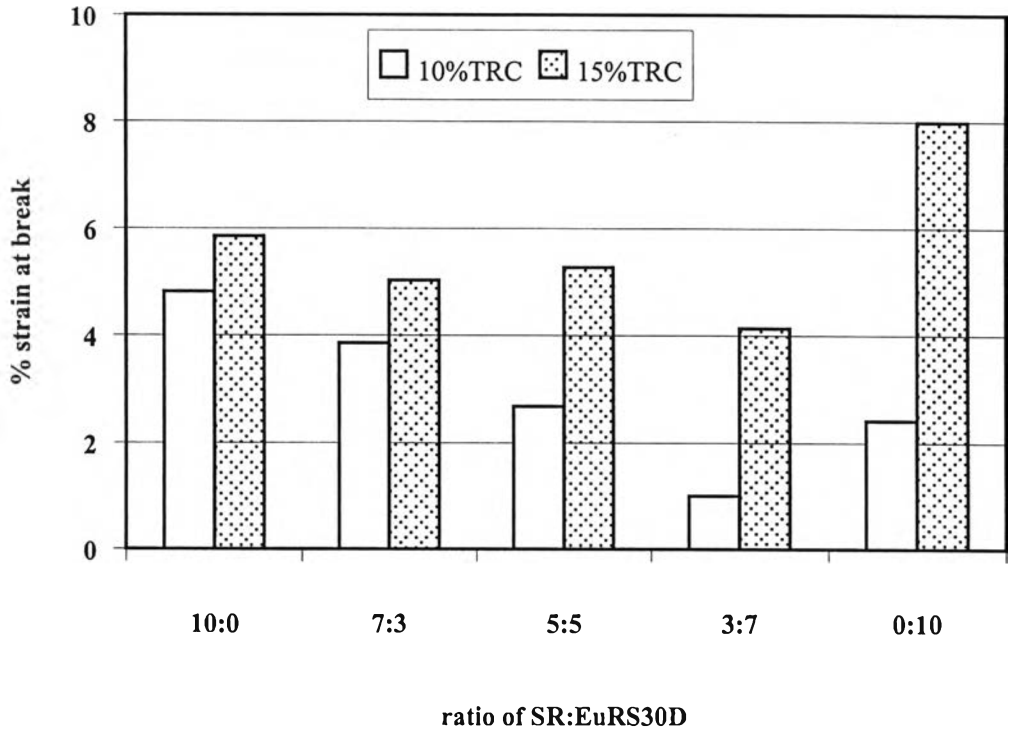


Figure 32 % Strain at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TRC in aqueous system

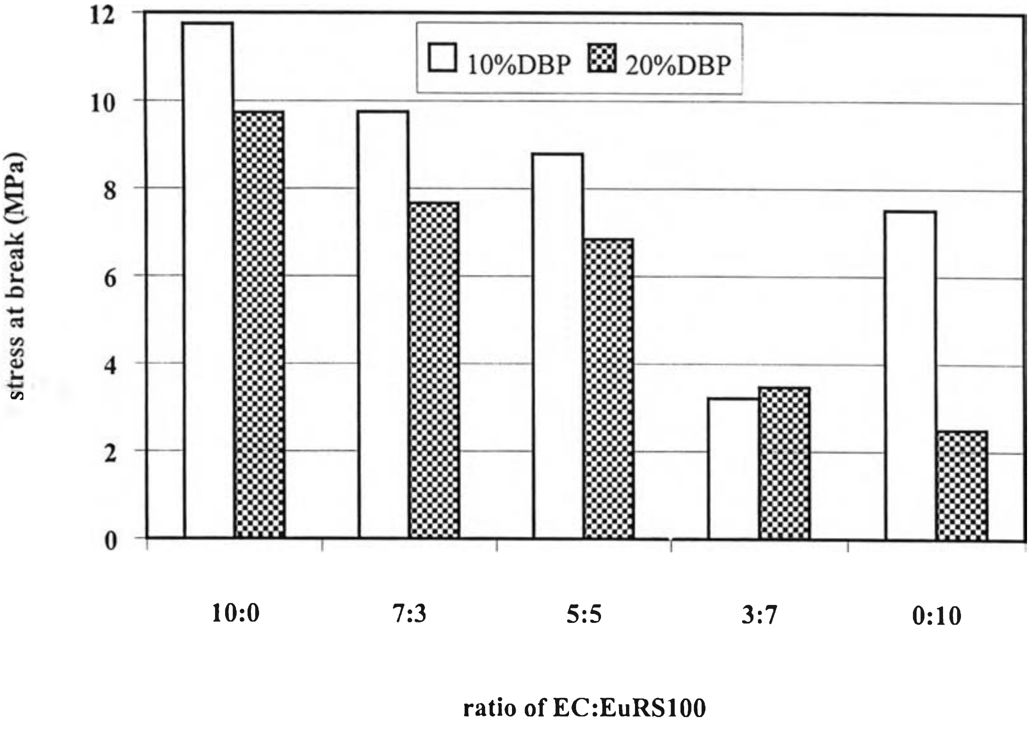


Figure 33 Stress at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% DBP in organic system

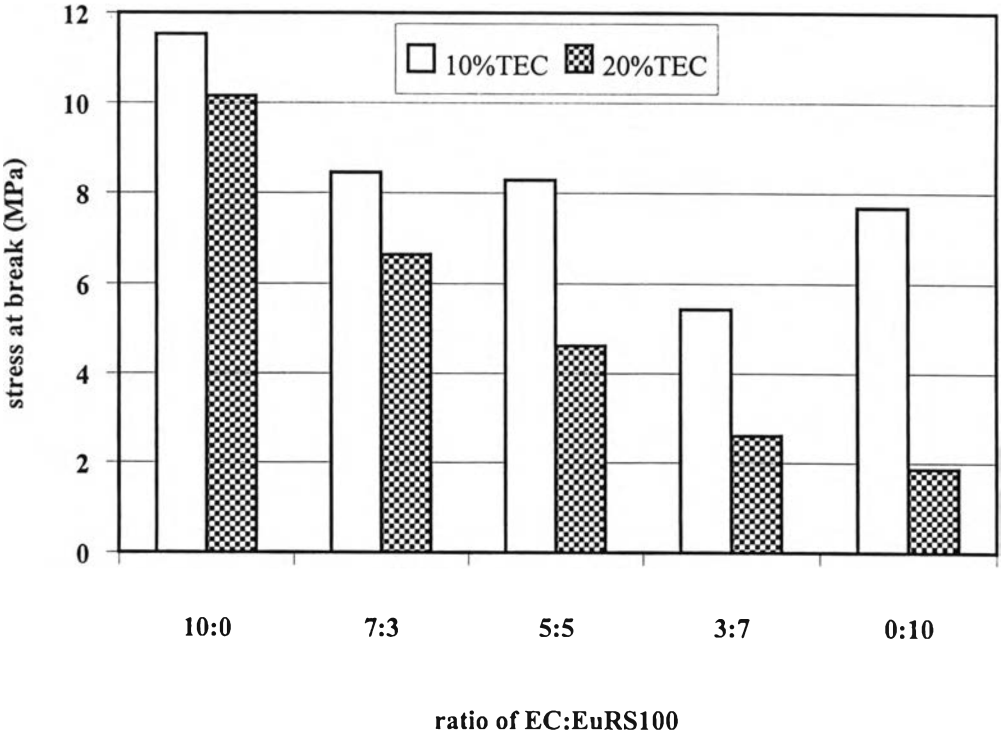


Figure 34 Stress at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% TEC in organic system

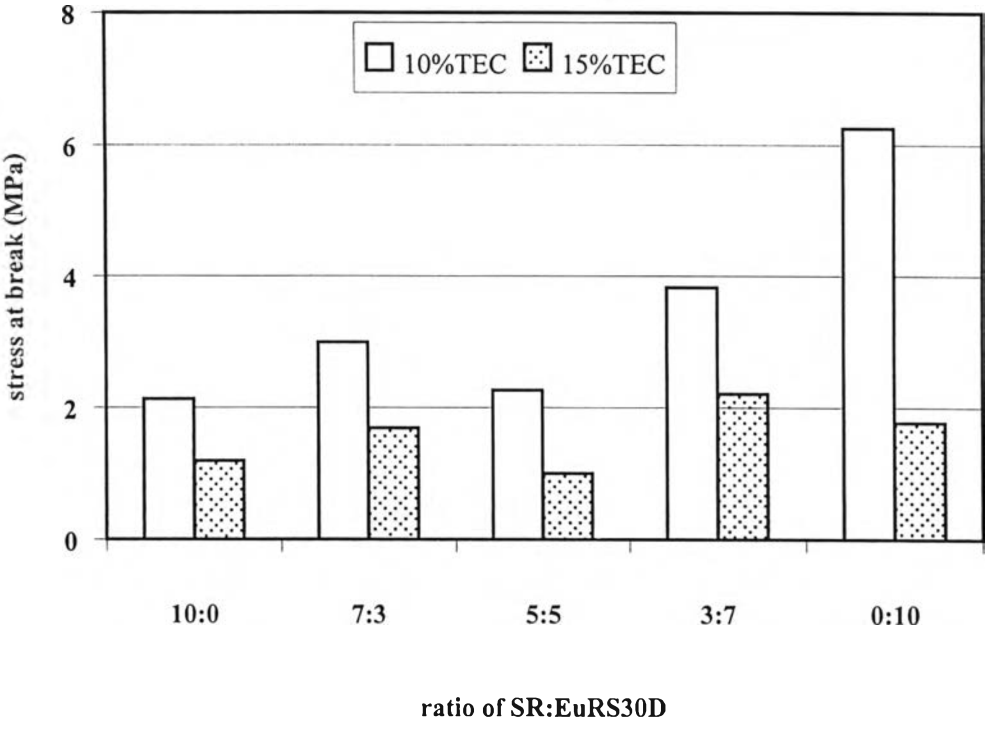


Figure 35 Stress at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TEC in aqueous system

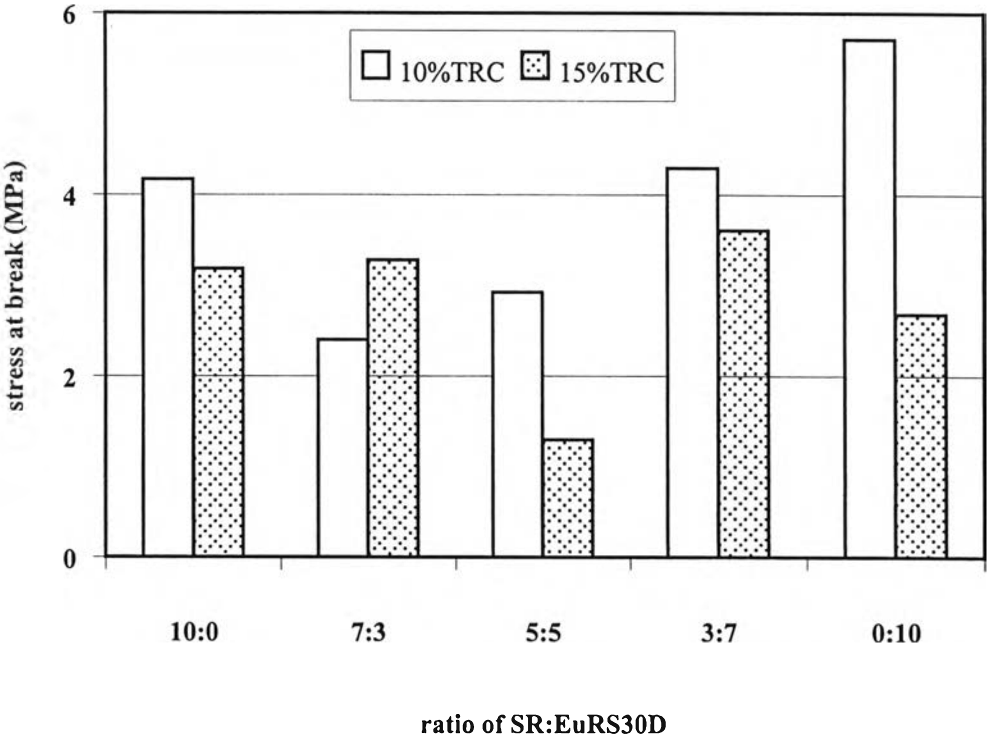


Figure 36 Stress at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TRC in aqueous system

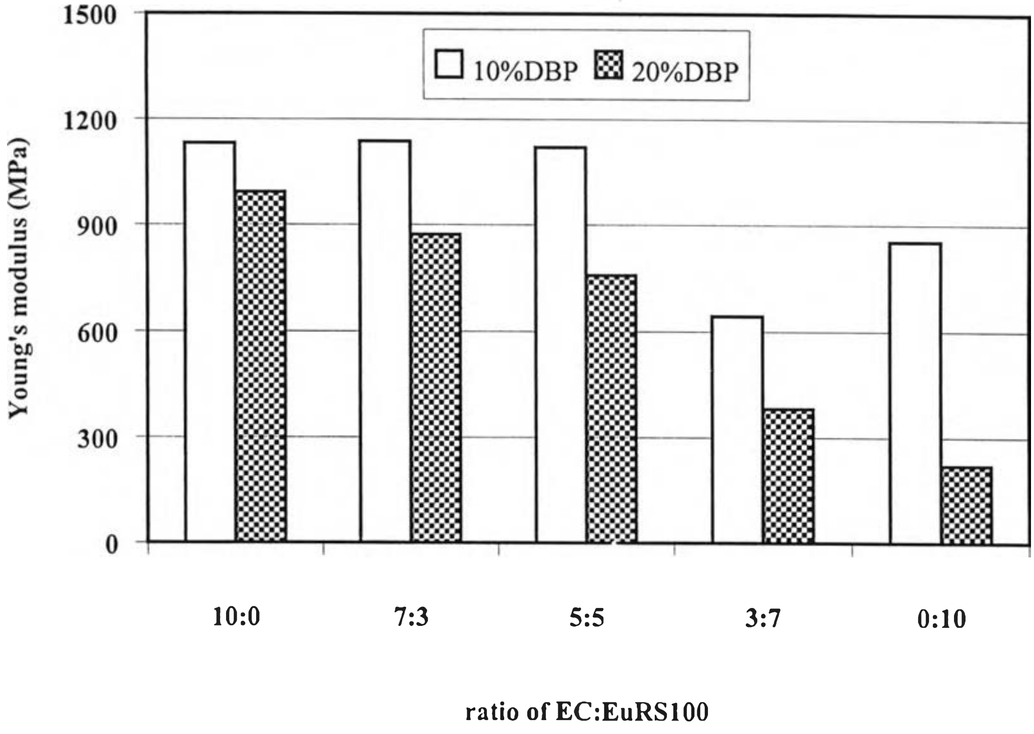


Figure 37 Young's modulus of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% DBP in organic system

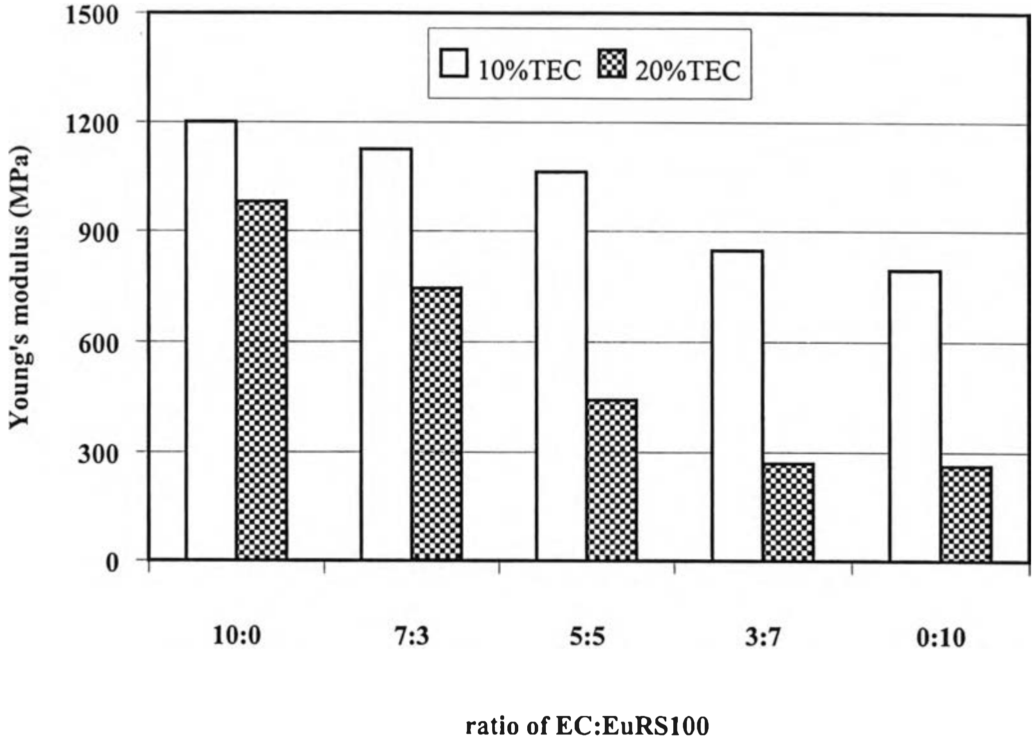


Figure 38 Young's modulus of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% TEC in organic system

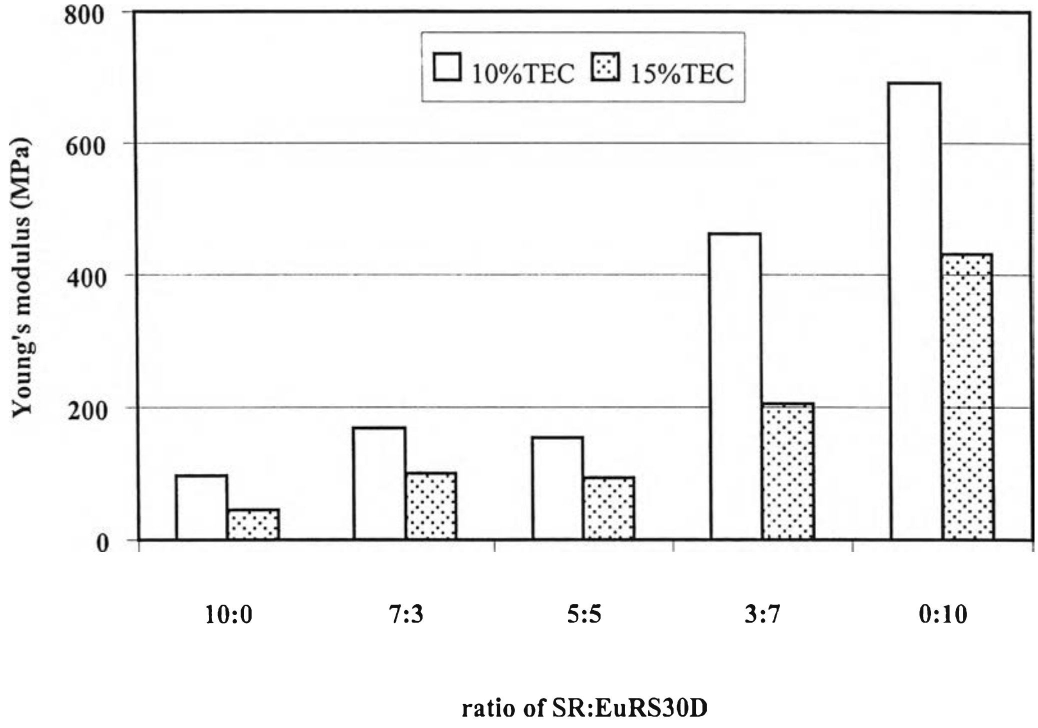


Figure 39 Young's modulus of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TEC in aqueous system

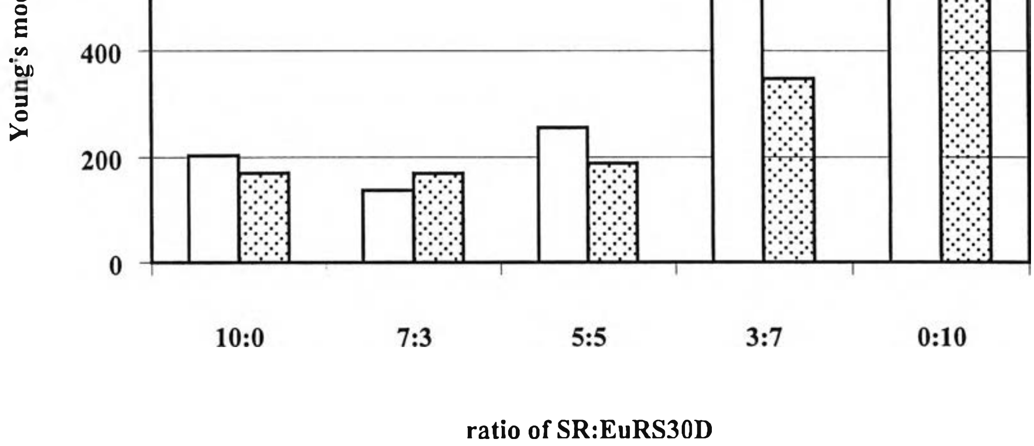


Figure 40 Young's modulus of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TRC in aqueous system

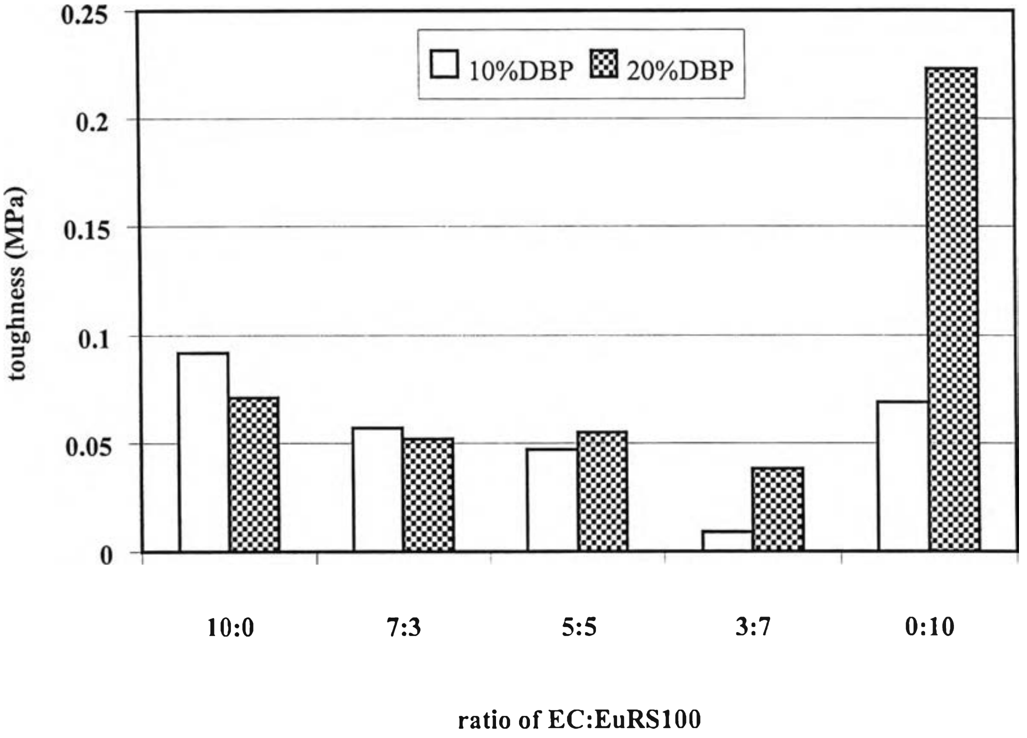


Figure 41 Toughness of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 0:10 with 10% and 20% DBP in organic system

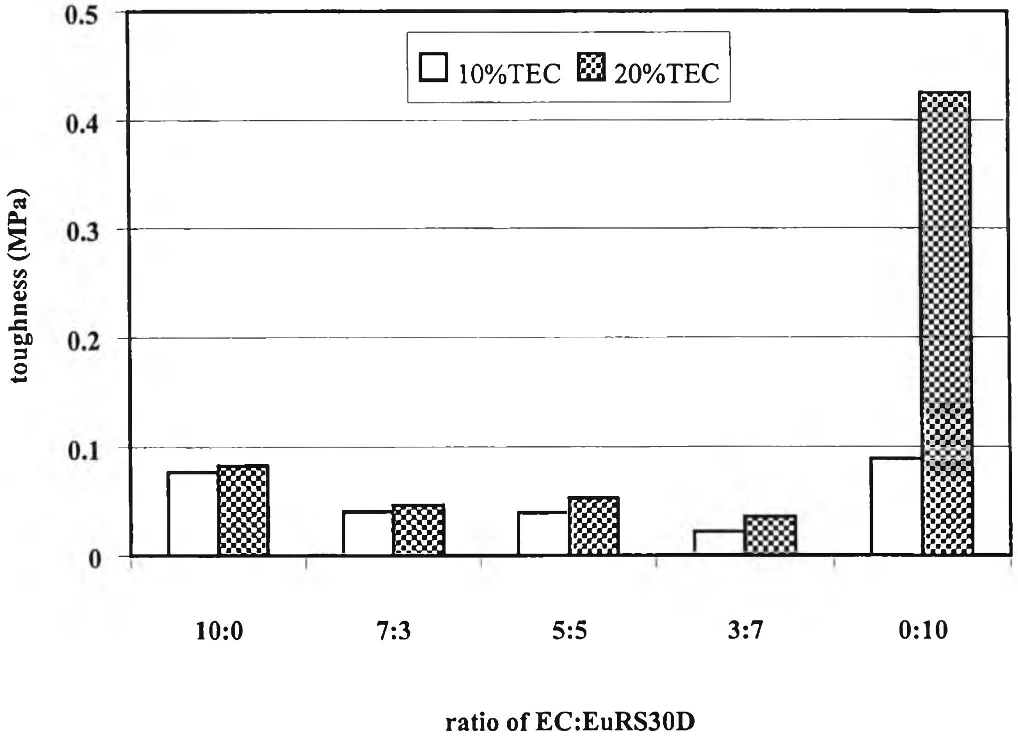


Figure 42 Toughness of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 20% TEC in organic system

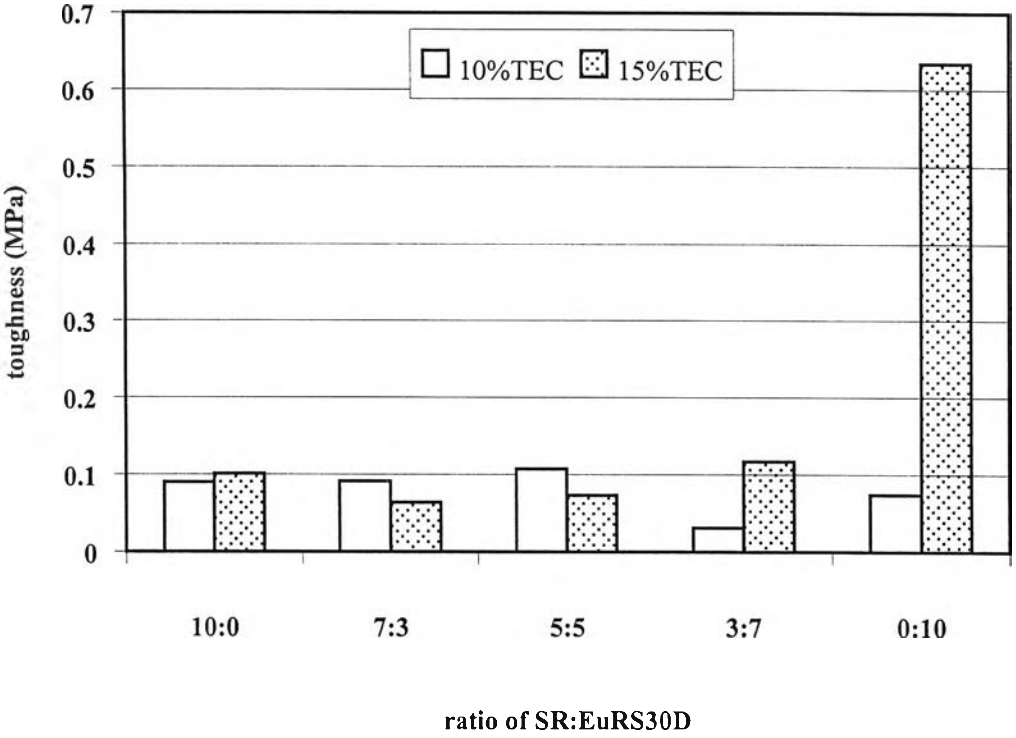


Figure 43 Toughness of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TEC in aqueous system

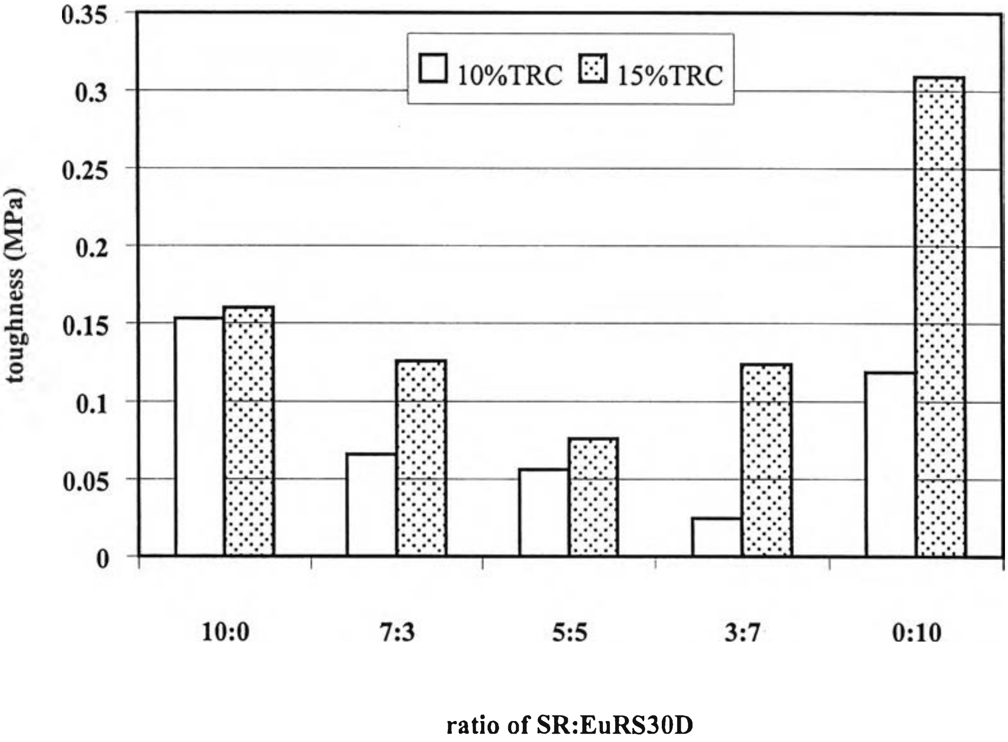


Figure 44 Toughness of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% and 15% TRC in aqueous system

RS30D in the ratio of 7:3 that was plasticized with triacetin (Figure 36). Young's modulus represented hardness or stiffness of a polymer showed an inclination for this value as the level of plasticizer increase. Toughness should be increased when higher amount of plasticizer was used. However the marked results were obtained only from Eudragit®RS films. Higher level of plasticizer could provide higher toughness.

Increasing amount of plasticizer led to an increase in the ductility and toughness of films, whereas films with higher quantity of plasticizer had less strength and less stiffness than films with lower quantity of plasticizer. This result was correlated with Hutchings et al. (1994). An increasing amount of dibutyl sebacate led to decreased tensile strength and an increase in the strain at rupture values of Aquacoat® film. Additionally, the area under the stress-strain curve increased, indicating that these films become tougher. In agreement with the result reported by Bodmeier and Paeratakul (1993), the puncture strength of Eudragit®RS30D-dry films plasticized with triethyl citrate decreased and the elongation increased with increasing triethyl citrate concentration. The increasing amount of plasticizer resulted in softer and more flexible films. Possibly, the presence of plasticizer reduced the number of active centers available for binding sites and polymer-polymer contacts, decreasing the rigidity of the polymer structure (Lin et al., 1991). In addition, the microscopic studies correlated very well with the results from the mechanical tests, as the photomicrograph properties of the polymer were improved by the higher level of plasticizers.

3.3.2 Effect of plasticizer type

The mechanical properties of the films in organic system were strongly affected by the type of plasticizer. From Figures 45-48, adding 10% dibutyl phthalate into the films of ethylcellulose: Eudragit®RS 100 in the ratio of 10:0, 7:3 and 5:5 resulted in hard and tough film with high values of % strain at break, stress at break and toughness whereas incorporation of triethyl citrate in the films with higher amount

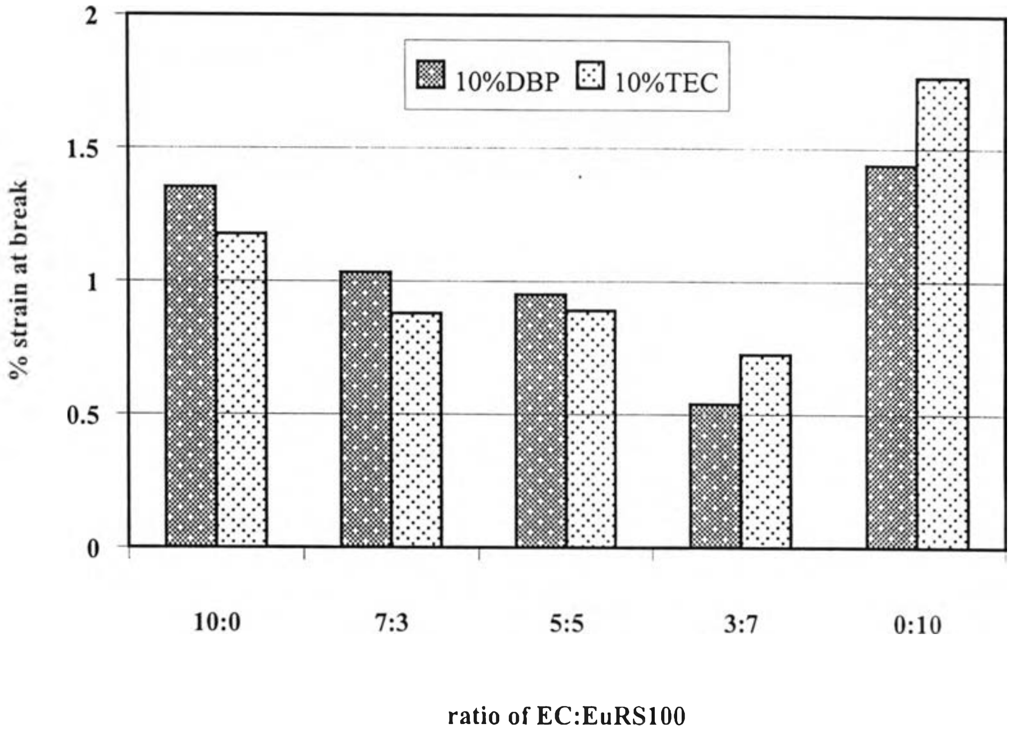


Figure 45 % Strain at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% DBP and 10% TEC in organic system

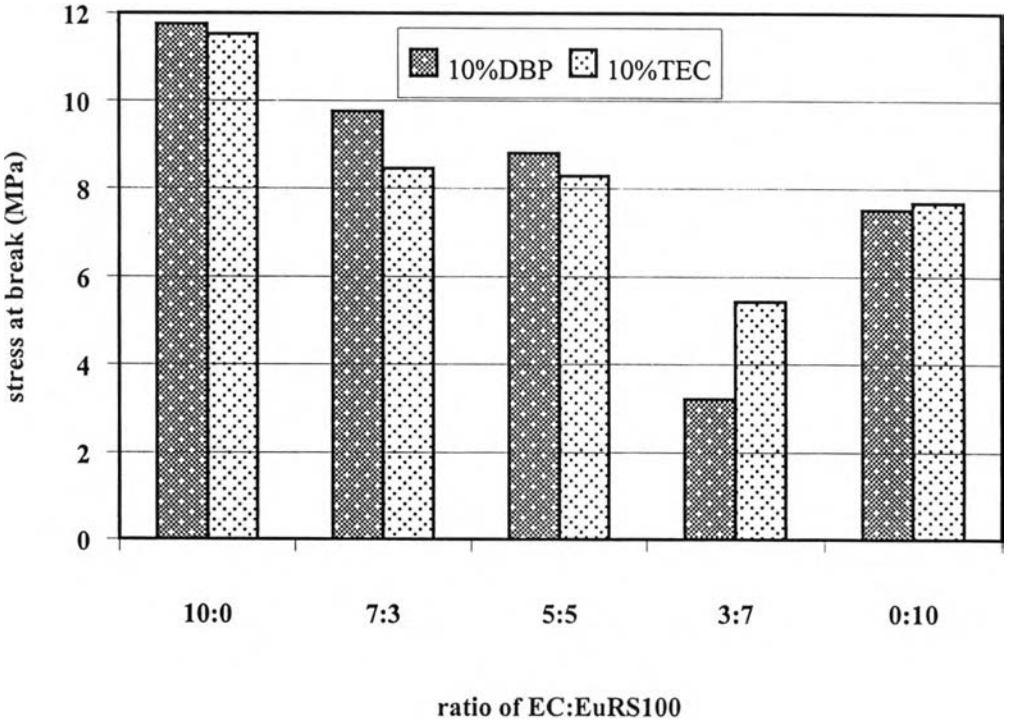


Figure 46 Stress at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% DBP and 10% TEC in organic system

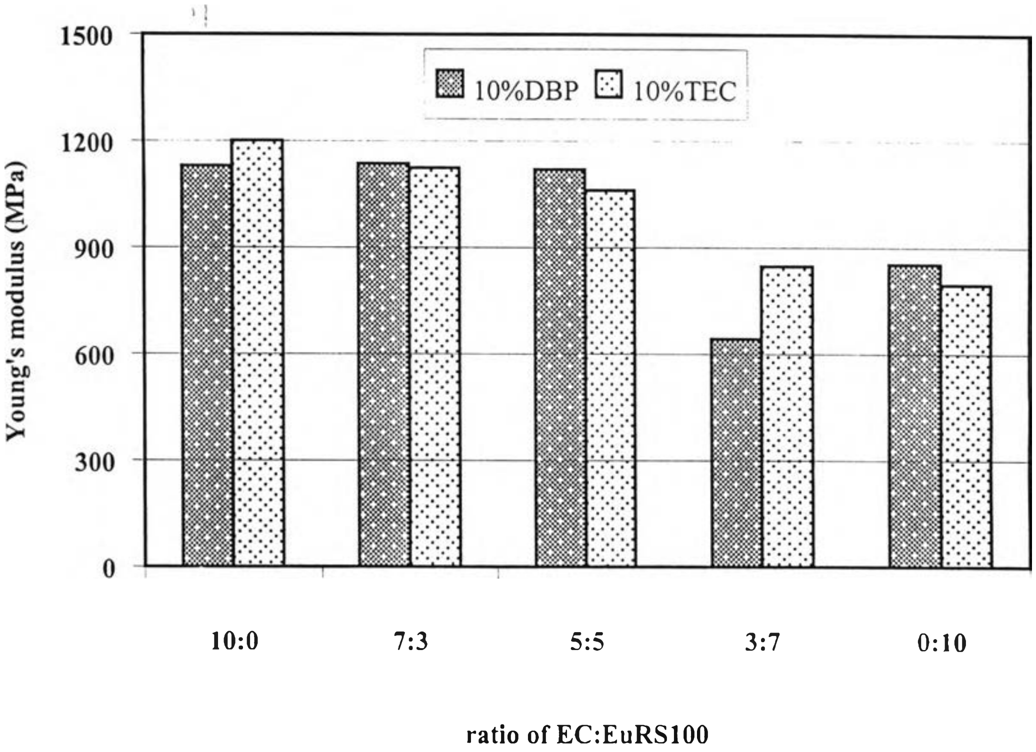


Figure 47 Young's modulus of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% DBP and 10% TEC in organic system

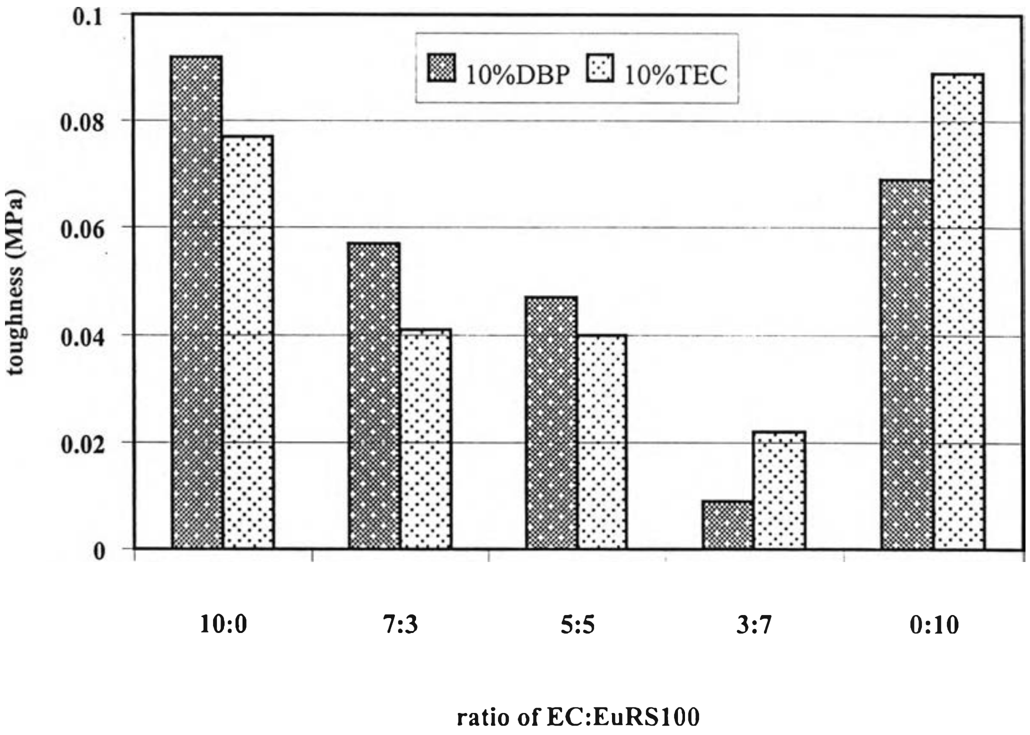


Figure 48 Toughness of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% DBP and 10% TEC in organic system

of Eudragit®RS 100 more than 50% caused an increase in % strain at break, stress at break and toughness. The effect of plasticizer type did not show marked difference of Young's modulus values. These results indicated that triethyl citrate, a water soluble plasticizer, was the competent plasticizer for the films with higher proportion of Eudragit®RS 100, while dibutyl phthalate, a water insoluble plasticizer, could be efficient for the films with higher proportion of ethylcellulose.

The solubility parameters permit assessment of plasticizer compatibility. They are defined as the square root of the cohesive energy density. Additionally, they can be calculated from the structured formula. This method also can estimate the solubility parameters. The mixtures with similar solubility parameters have a small enthalpy of mixing, which is indicative of good compatibility. The solubility parameter (δ) values from the literature of ethylcellulose and dibutyl phthalate are 19.4-21.1 $(\text{cal/ml})^{1/2}$ and 19.2-20.3 $(\text{cal/ml})^{1/2}$ respectively (Bauer et al., 1998). Dibutyl phthalate exhibited δ value near that of ethylcellulose, and this very small difference in the solubility parameters correlated with the results from mechanical properties. Hence, dibutyl phthalate appeared to be compatible with ethylcellulose. The same result was observed when dibutyl sebacate was used to compare with triethyl citrate or triacetin in ethylcellulose films produced by casting from acetone: absolute alcohol (9:1). Dibutyl sebacate as a water insoluble plasticizer had a greater potential for partitioning into the ethylcellulose polymer than did triethyl citrate or triacetin (Phuapradit et al., 1995).

Eudragit®RS 100 contains ester groups that are shown in Figure 2 and chemical structures of dibutyl phthalate and triethyl citrate are depicted in Figures 3 and 4, respectively. The ester groups were capable of interacting with other molecules by hydrogen bonding, as well as electrostatic and dispersion forces. Triethyl citrate had the ability to break up the polymer-polymer interaction, due to the accessibility of its free hydroxyl group to interact through hydrogen bonding with the ester groups of the copolymer. Although hindered by the presence of the side chains, they still had the ability to hydrogen bond with the copolymer (Gutierrez-Rocca and McGinity, 1994). As compared to dibutyl phthalate molecules, it could interact with this polymer by other forces. Thus, triethyl citrate had ability to interact with the active groups in the Eudragit®RS 100 more than dibutyl phthalate.

The resulting mechanical properties of films with 20% plasticizer are presented in Figures 49-52 and in Tables 11-14. The % strain and toughness of film with 20% plasticizer level were almost independent of type of plasticizer with the exception of Eudragit®RS 100. The Eudragit®RS100 films plasticized with higher level of triethyl citrate also displayed soft and tough film than those plasticized with dibutyl phthalate. Figures 53-54 and Table 15 show the percentage change of the various mechanical properties of films when the concentration of adding plasticizer was changed from 10 to 20% level. The minus symbol indicates percent reduction of these properties. The addition of dibutyl phthalate, a water insoluble plasticizer, at the 20% level resulted in percent increase in the elongation and toughness less than the addition of triethyl citrate. The films plasticized with triethyl citrate demonstrated higher percent reduction of stress at break and Young's modulus than the films plasticized with dibutyl phthalate at the 20% level plasticizer. The percent change of film properties was affected to a larger extent by water soluble plasticizer (triethyl citrate) than water insoluble plasticizer (dibutyl phthalate) at higher plasticizer level. From these results, only the films plasticized with higher amount of triethyl citrate were slightly soft and tough as indicated by lower Young's modulus and higher % strain at break when compared to those plasticized with corresponding dibutyl phthalate level.

It was also apparent that films prepared from pure Eudragit®RS 100 with 20% triethyl citrate appeared more soft and tough than those with 20% dibutyl phthalate because triethyl citrate was the efficient plasticizer for Eudragit®RS 100 and its high affinity to interact with the polymer.

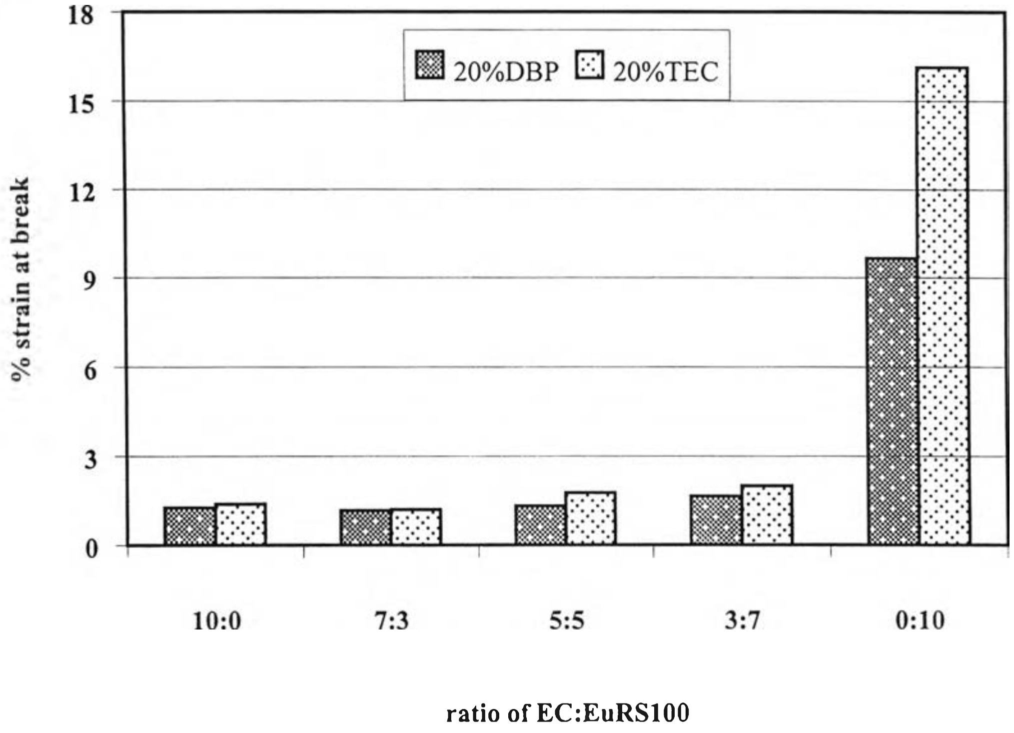


Figure 49 % Strain at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% DBP and 20% TEC in organic system

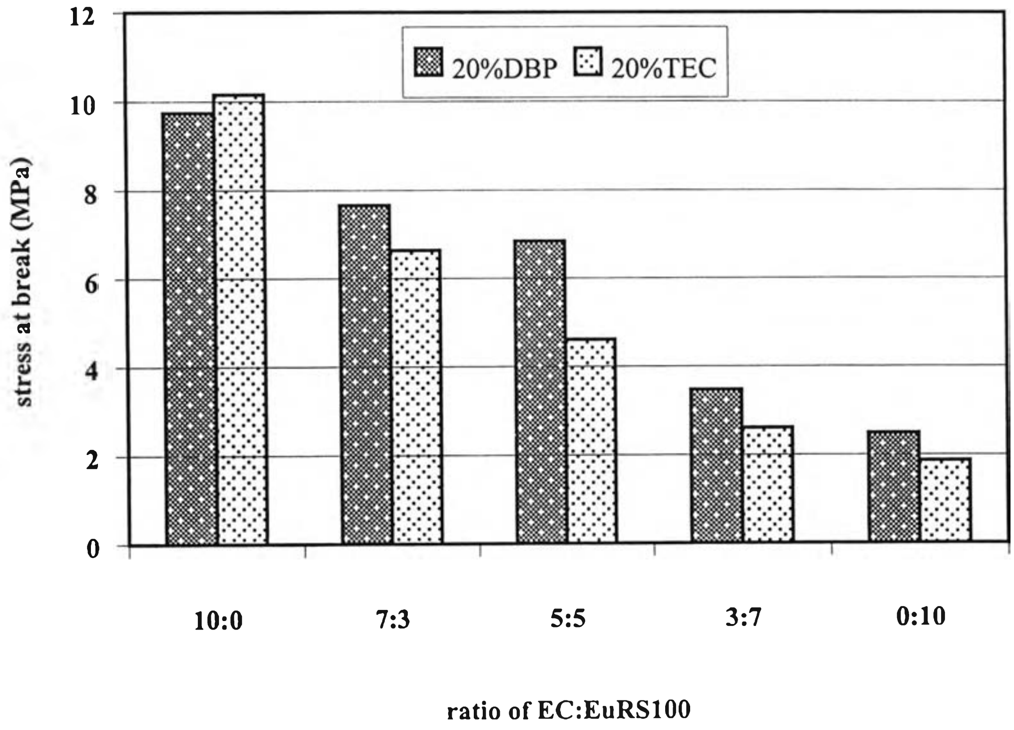


Figure 50 Stress at break of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% DBP and 20% TEC in organic system

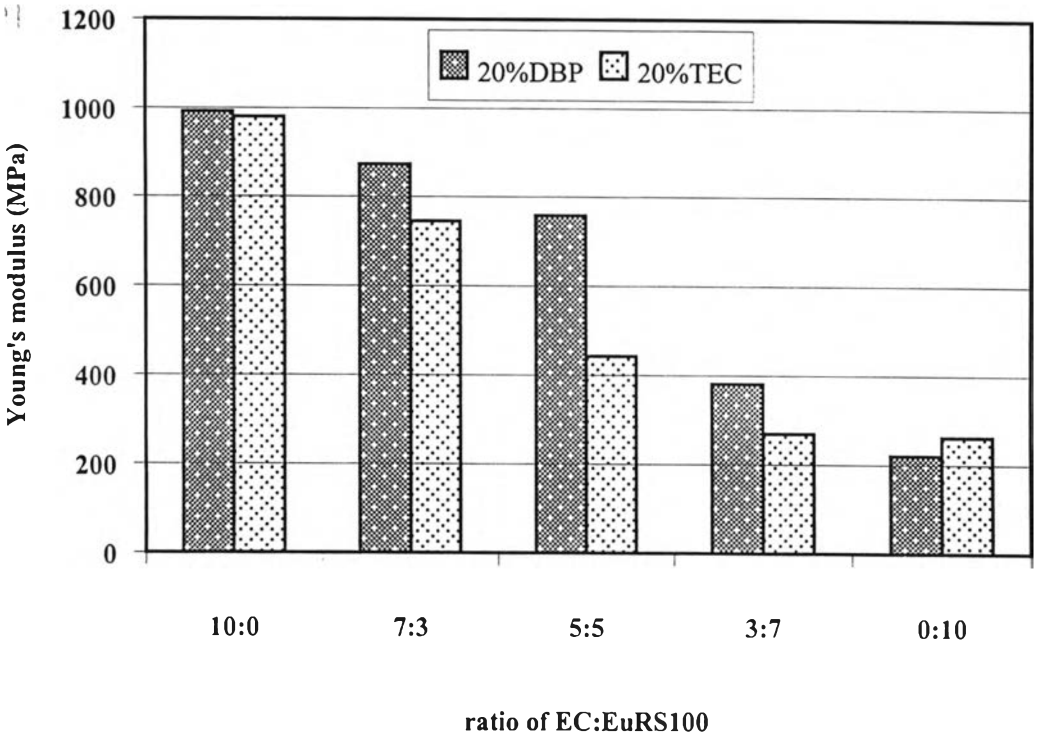


Figure 51 Young's modulus of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% DBP and 20% TEC in organic system

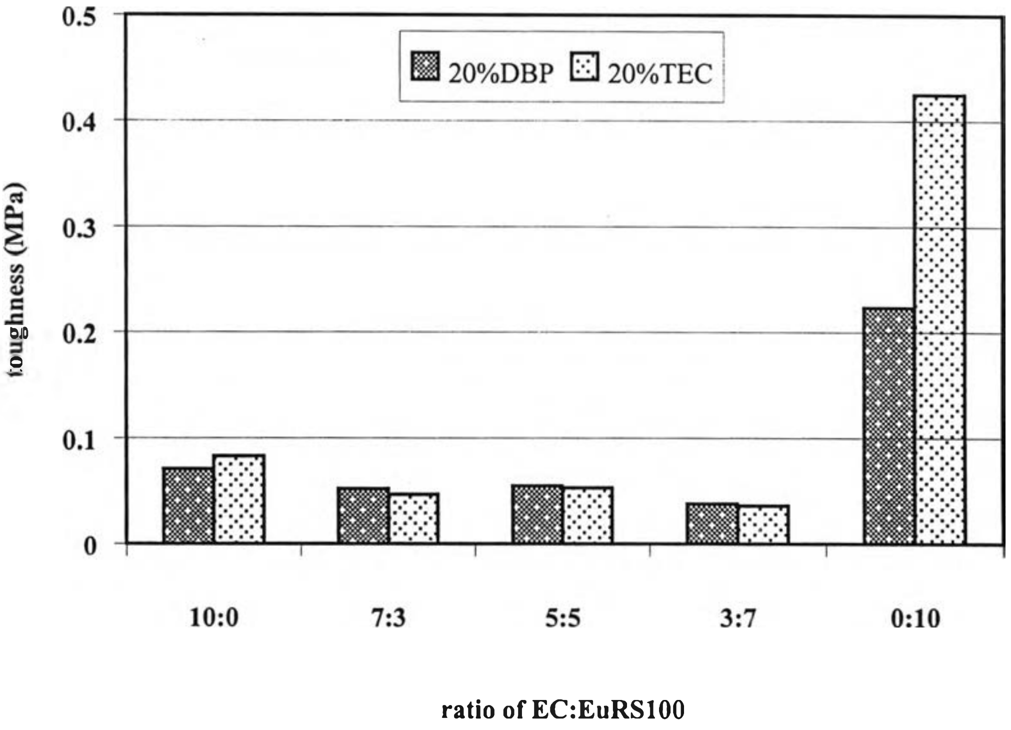


Figure 52 Toughness of films between EC:EuRS100 at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% DBP and 20% TEC in organic system

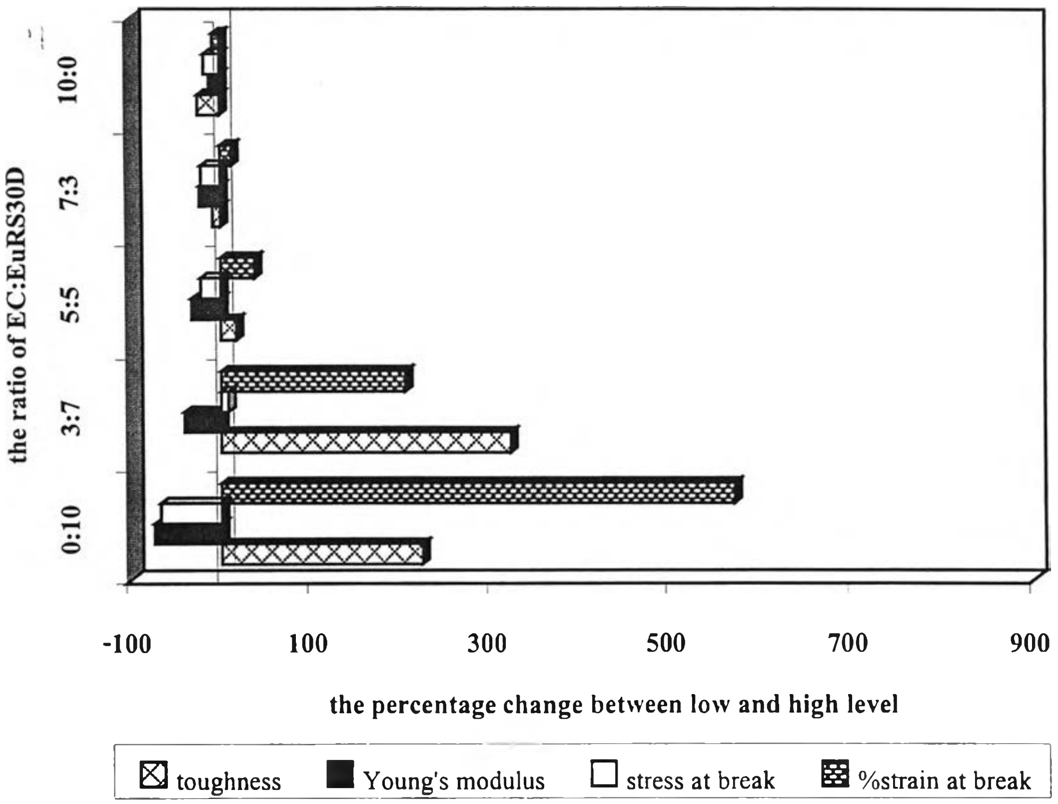


Figure 53 The percentage change in various mechanical properties when dibutyl phthalate content is increased from 10 to 20%

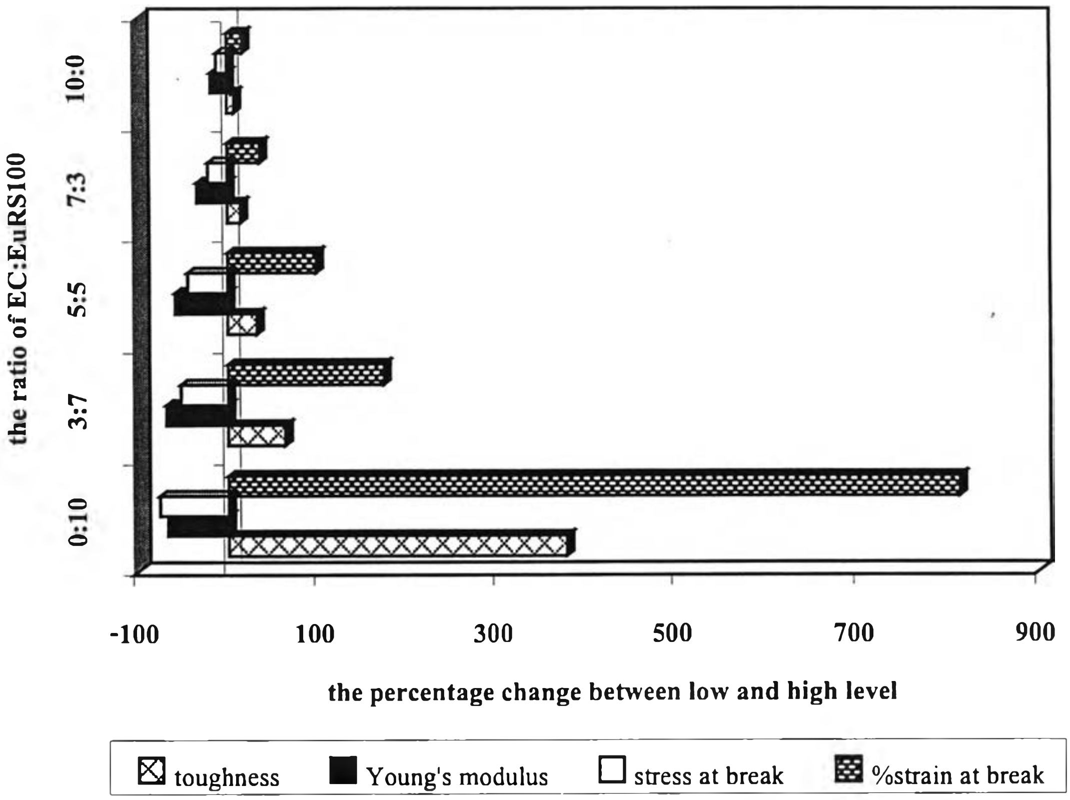


Figure 54 The percentage change in various mechanical properties when triethyl citrate content is increased from 10 to 20%

Table 15 The percent change of the various mechanical properties of films plasticized with 20% level as compared to the films at the 10% plasticizer content level.

Mechanical propertie	**Plasticizer type**	**Percent change of EC:EuRS100 with ratio**				
		10:0	**7:3**	**5:5**	**3:7**	**0:10**
% Strain at break	DBP	-7.82	12.50	37.89	205.38	571.09
	TEC	17.5	36.45	98.76	174.00	812.50
Stress at break	DBP	-17.68	-21.40	-22.27	7.75	-66.95
	TEC	-11.88	-21.50	-44.33	-52.08	-75.70
Young's modulus	DBP	-12.05	-23.28	-32.43	-40.60	-74.18
	TEC	-18.37	-33.85	-58.33	-68.18	-66.98
Toughness	DBP	-24.47	-8.77	17.02	322.22	223.19
	TEC	7.79	14.63	32.50	63.64	377.53

The resembling results from the physical-mechanical studies with the Eudragit®L polymer demonstrated that the addition of the water soluble plasticizers (triethyl citrate, triacetin, acetyl triethyl citrate) resulted in a continuous decrease in the elastic modulus as the level of plasticizer added to the Eudragit®L100-55 was increased. However, the reduction of the elastic modulus with the water insoluble plasticizers (tributyl citrate, acetyl tributyl citrate) resulted in no statistically changes when higher than 10% level was added. These results were due to the high affinity of the water soluble plasticizer. It could diffuse into and interact with the polymer molecules, thereby increasing the polymer's mobility, whereas there was no further reduction in the elastic modulus at higher concentrations due to the limited miscibility of the hydrophobic plasticizer with the Eudragit®L100-55. Therefore, dibutyl phthalate did not disrupt the polymer chains to the same extent as triethyl citrate (Gutierrez-Rocca and McGinity, 1994).

The comparisons of the various mechanical properties for the aqueous system films containing different levels of different plasticizer types are shown in Tables 11-14 and Figures 55-58. Almost all of films containing 10% triethyl citrate had higher % strain at break and toughness values when compared to films containing triacetin. Young's modulus was inversely related to % strain at break while stress at break was slightly correlated with Young's modulus. The more pronounced effect of triethyl citrate was displayed in the films with higher level of plasticizer (Figures 59-62).

From data displayed in Figures 63-64 and Table 16, the percentage change between low and high level in % strain at break and toughness of both Surelease® and Eudragit®RS30D with triethyl citrate was higher than those with triacetin. The percentage decrease in stress at break and Young's modulus when the plasticizer content was increased from 10% to 15% was corresponded with the higher value of the percentage change in % strain at break and toughness. The blended polymers of Surelease®: Eudragit®RS30D in the ratio of 7:3 and 5:5 showed the different relationship. The percent increase of % strain at break and toughness of blended polymer in these two ratios was affected by triacetin more than triethyl citrate. However triethyl citrate containing films resulted in lower stress at break values and Young's modulus values when compared to triacetin. All properties of blended polymer in these two ratios displayed less stiffness of films with triethyl citrate 15%.

The effectiveness of triethyl citrate beyond triacetin could be explained by the association coefficient reflecting the affinity of the plasticizer for the polymer of the colloidal polymer dispersion. The association coefficient was calculated as the ratio of the concentration of the plasticizer in the polymer phase to the concentration in the aqueous phase. With water insoluble plasticizers, the plasticizer concentration in the aqueous phase included the dissolved and emulsified portion. A large value indicated extensive partitioning into the colloidal particles, while a small value was indicative of a poor plasiticizer compatibility or affinity for the polymer. The

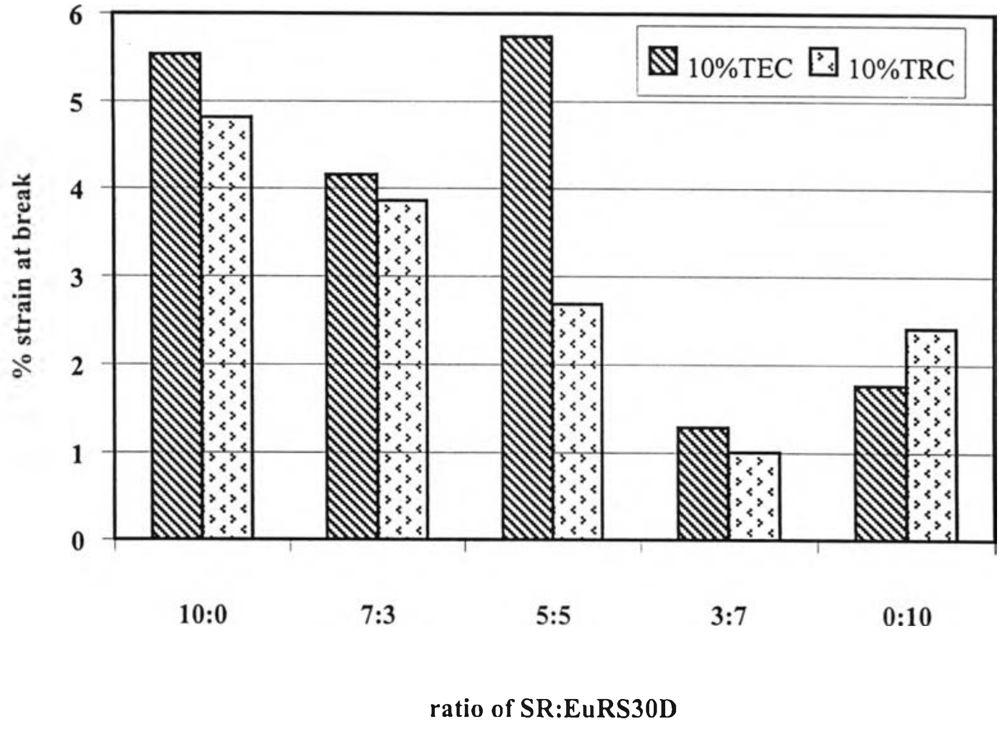


Figure 55 % Strain at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10%TEC and 10%TRC in aqueous system

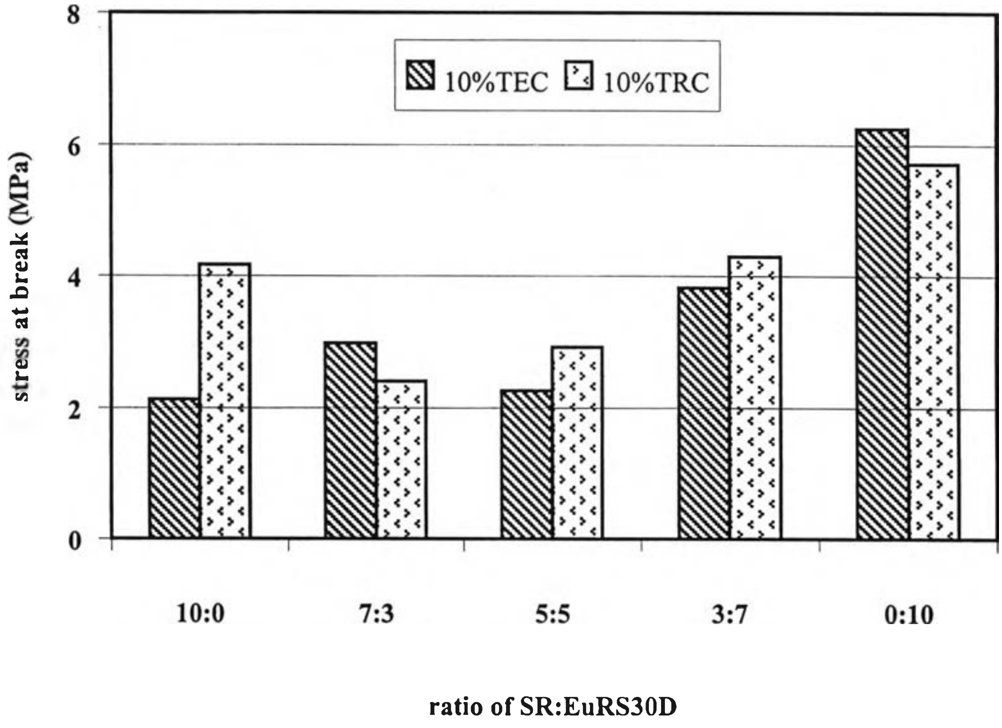


Figure 56 Stress at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10%TEC and 10%TRC in aqueous system

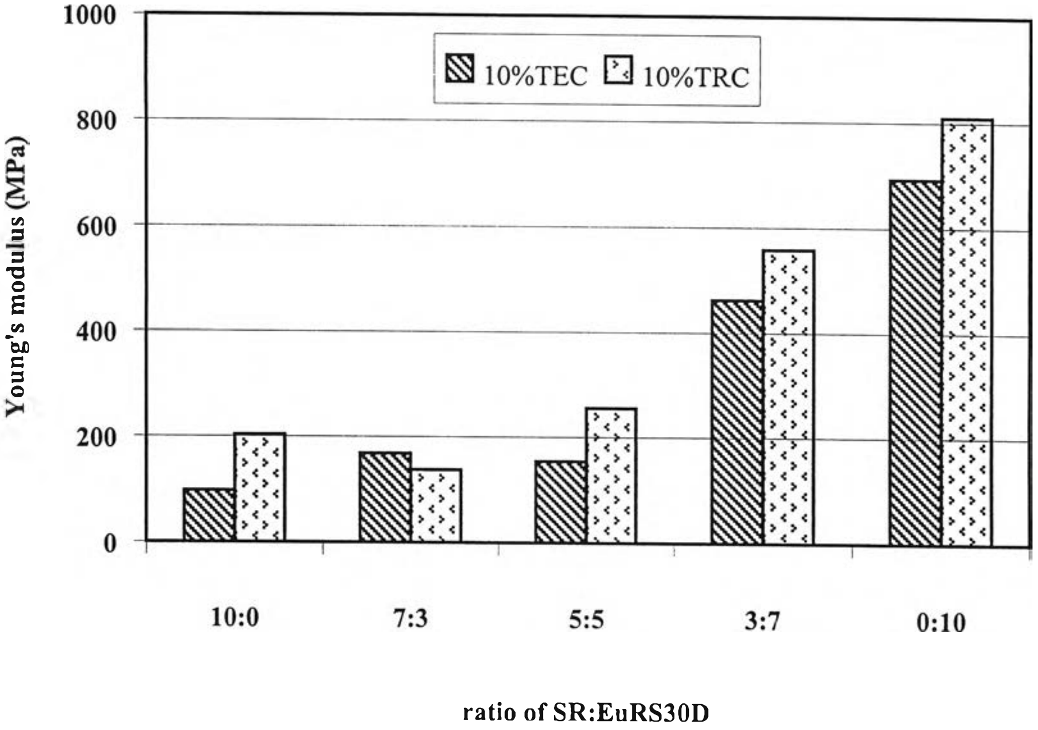


Figure 57 Young's modulus of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10%TEC and 10%TRC in aqueous system

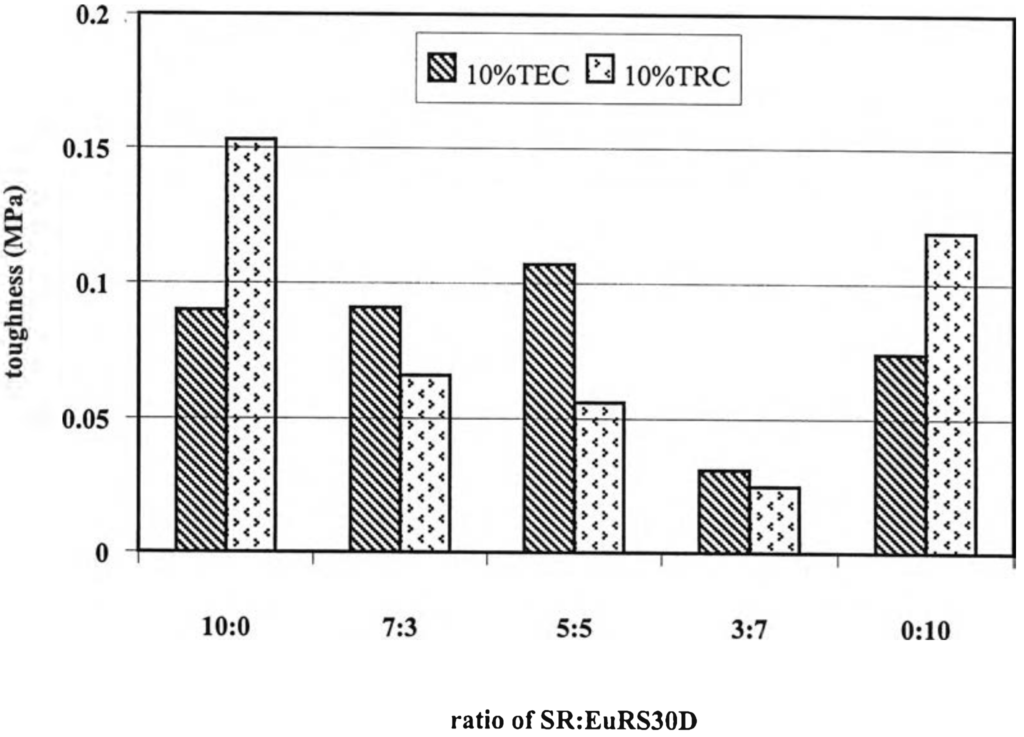


Figure 58 Toughness of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10%TEC and 10%TRC in aqueous system

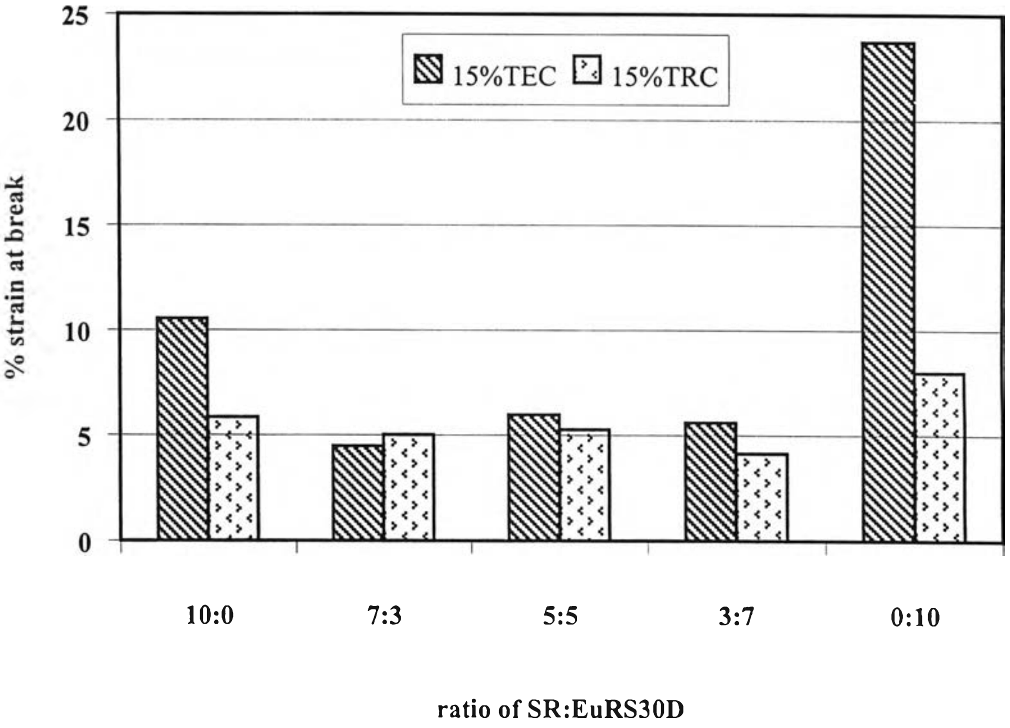


Figure 59 % Strain at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 15%TEC and 15%TRC in aqueous system

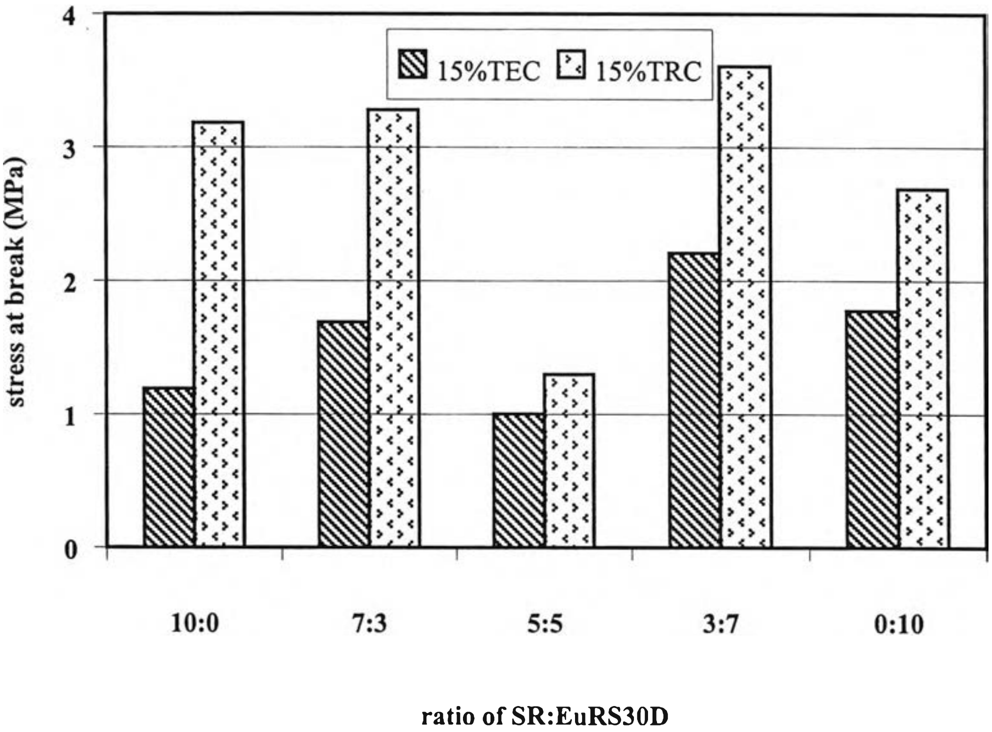


Figure 60 Stress at break of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 15%TEC and 15%TRC in aqueous system

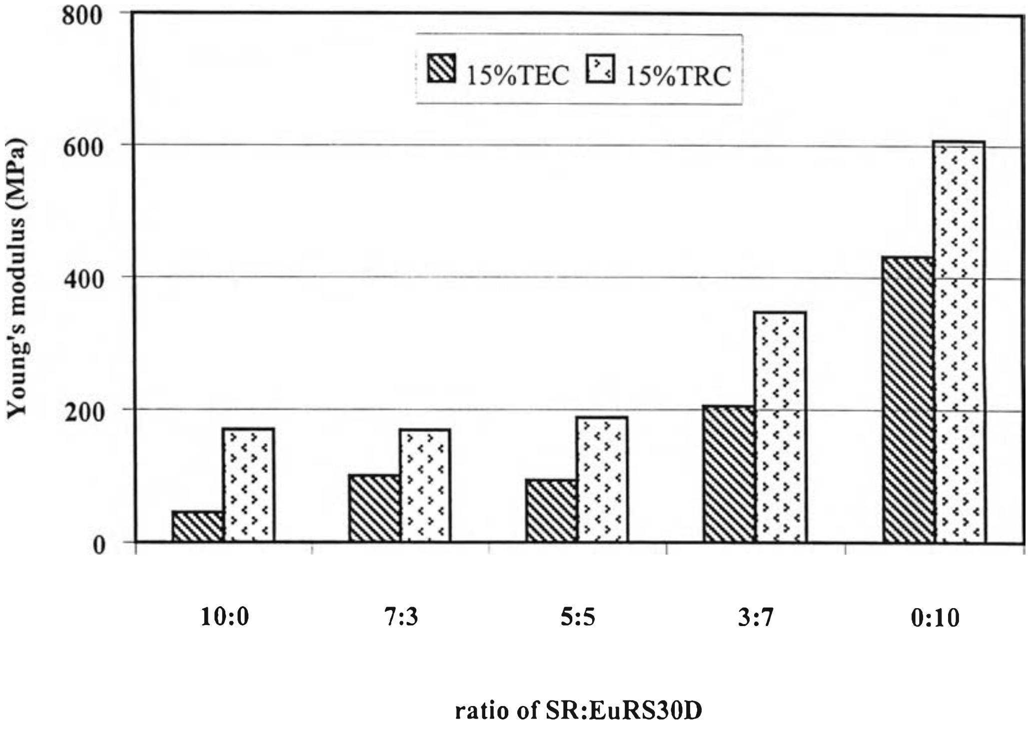


Figure 61 Young's modulus of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 15%TEC and 15%TRC in aqueous system

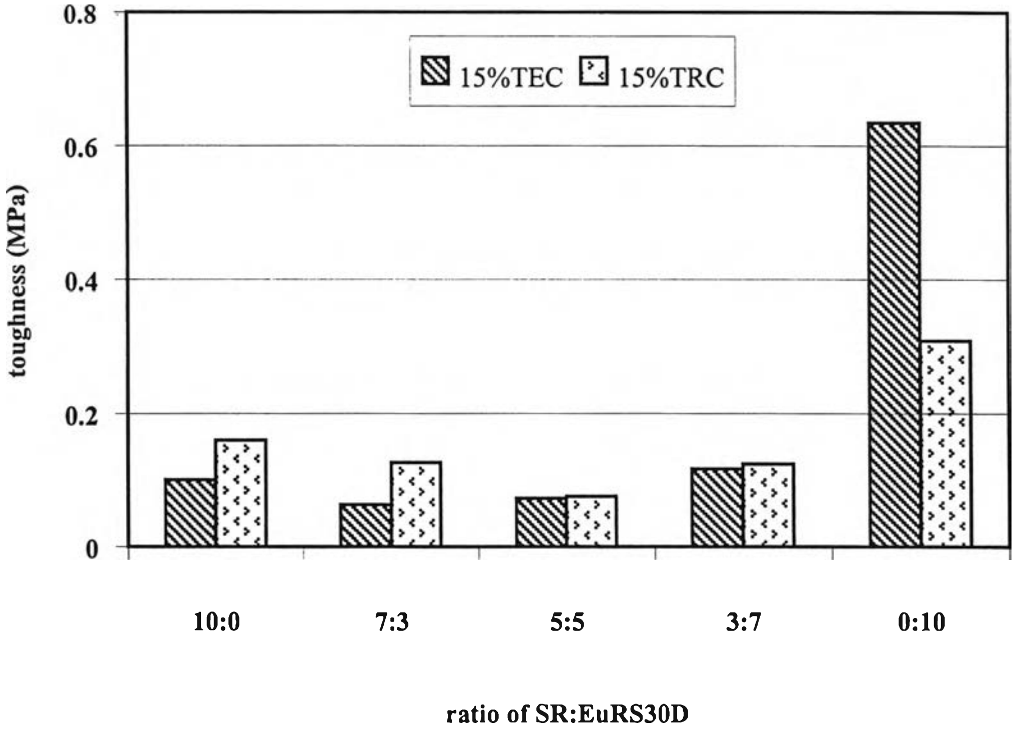


Figure 62 Toughness of films between SR:EuRS30D at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 15%TEC and 15%TRC in aqueous system

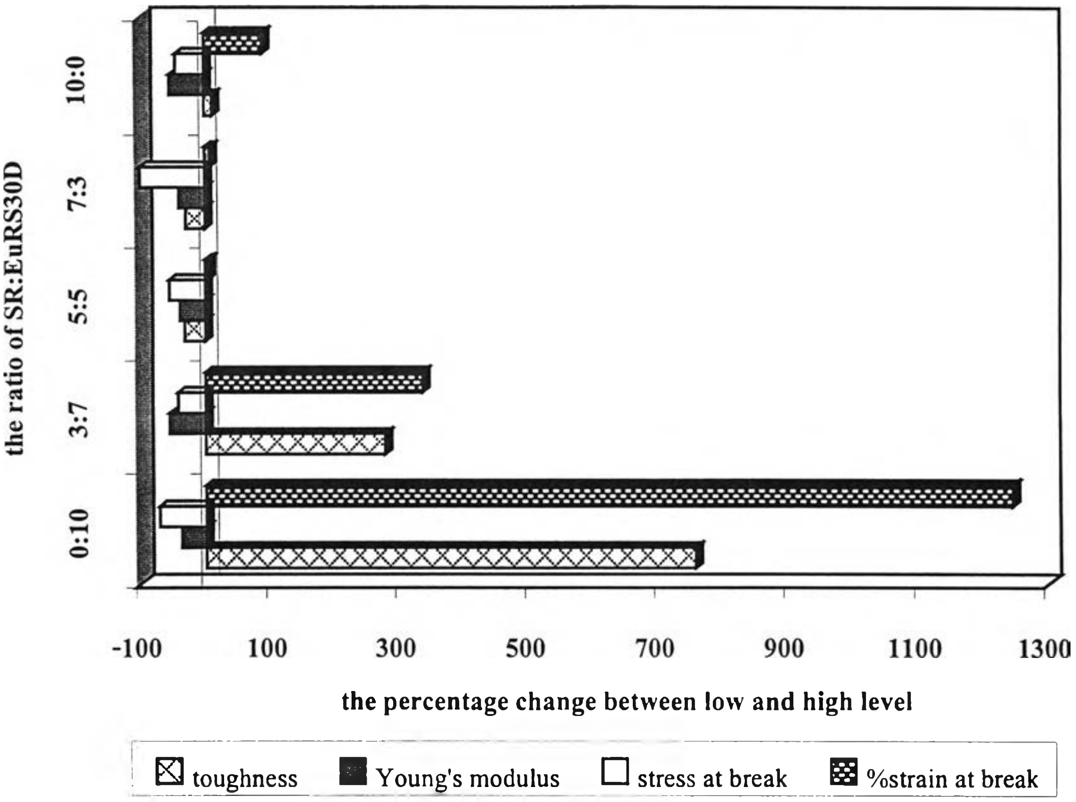


Figure 63 The percentage change in various mechanical properties when triethyl citrate content is increased from 10 to 15%

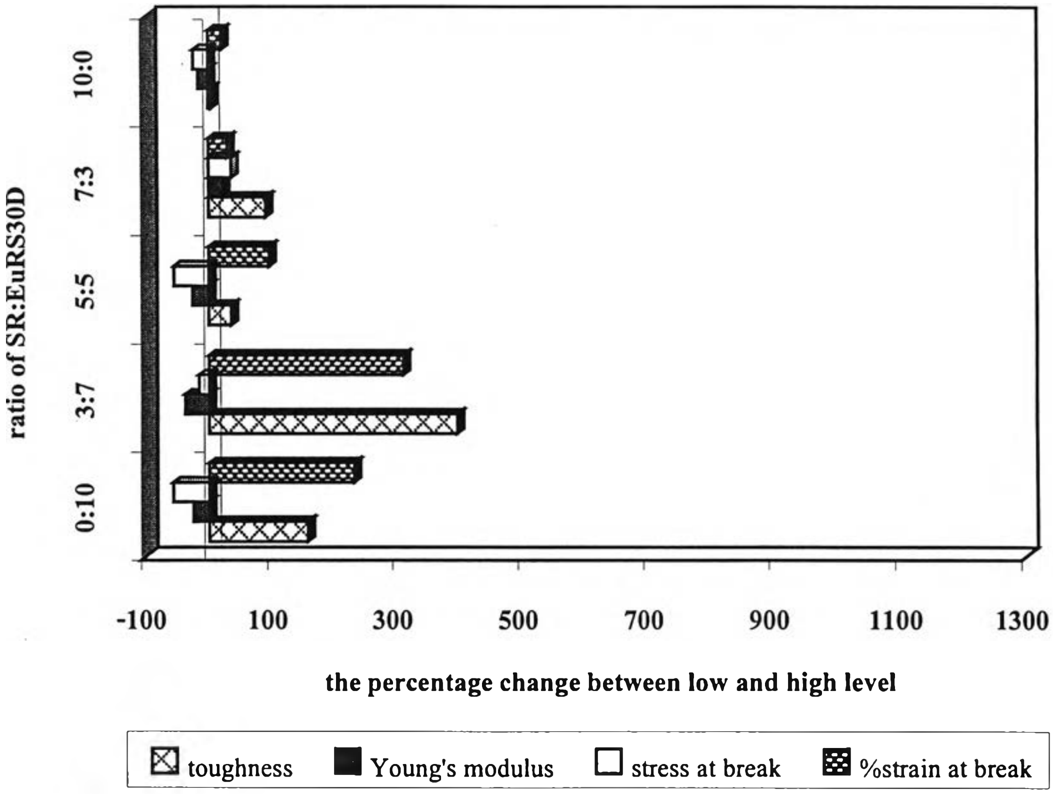


Figure 64 The percentage change in various mechanical properties when triacetin content is increased from 10 to 15%

Table 16 The percent change of the various mechanical properties of films plasticized with 15% level as compared to the films at the 10% plasticizer content level.

Mechanical propertie	Plasticizer type	Percent change of SR:EuRS30D with ratio				
		10:0	7:3	5:5	3:7	0:10
% Strain at break	TEC	90.26	7.75	4.21	335.25	1244.41
	TRC	21.54	30.25	96.35	310.82	231.27
Stress at break	TEC	-43.93	-99.99	-55.66	-42.26	-71.60
	TRC	-23.66	36.45	-55.59	-15.98	-56.97
Young's modulus	TEC	-53.65	-40.17	-39.12	-55.51	-37.65
	TRC	-16.18	23.22	-26.29	-37.79	-24.96
Toughness	TEC	12.22	-29.67	-31.78	277.42	756.76
	TRC	4.58	90.91	35.71	396.00	156.66

association coefficient values of triethyl citrate and triacetin with Aquacoat® were 5.70 and 3.14 and these values of triethyl citrate and triacetin with Eudragit®RS30D were 4.09 and 3.00, respectively. The higher association coefficient with Aquacoat® and Eudragit®RS30D resulted in the more effectiveness. Additionally, triacetin has higher water solubility so the higher amount of triacetin was in the aqueous phase more than the polymer phase (Bodmeier and Paeratakul, 1997). Similar results were obtained by Hutchings et al. (1994). Aquacoat® films were prepared using plasticizers from the class including the citrate esters or triacetin, the lowest modulus values were obtained for free films prepared using triethyl citrate or tributyl citrate. These two plasticizers have free hydroxyl groups while acetyl triethyl citrate, acetyl tributyl citrate and triacetin are completely esterified molecules. Another reason that as found by Gutierrez-Rocca and McGinity (1994) was the loss of triacetin after equilibrium. Eudragit®L100-55 and L30D films containing the water soluble and insoluble citrate ester plasticizers demonstrated a minimal loss, i.e. less than 5% from initial amount added was lost after 90 days. On the other hand, all films containing triacetin demonstrated a loss of approximate 10%. This triacetin loss indicated a tendency for triacetin either to evaporate or to degrade under normal ambient temperature.

The results obtained from photomicrograph studies were in agreement with mechanical properties that dibutyl phthalate was the efficient plasticizer for ethylcellulose film while triethyl citrate was the efficient plasticizer for Eudragit® RS100 in organic system due to the higher smoothness of film. For aqueous dispersion system, triethyl citrate was also the effective plasticizer for aqueous dispersion system when compared to triacetin as plasticizer because of the smoother and denser of triethyl citrate-plasticized films.

3.3.3 Effect of proportion of polymer

The impact of various ratios of two polymers on mechanical properties was considered only with triethyl citrate containing films at the same level of plasticizer in order to exclude the effect of plasticizer. Figures 65-68 demonstrated all the mechanical properties of blended films with low level of plasticizer in organic system and aqueous system. At a plasticizer level of 10% triethyl citrate, higher % strain and toughness including lower Young's modulus and stress at break were observed for Surelease®. Its properties showed by a soft and tough film.

For Eudragit®RS30D, lower % strain at break with high toughness was seen while higher stress at break and Young's modulus were observed. It displayed slightly harder and tough. When considered the properties of blended films in aqueous system, % strain at break, stress at break, Young's modulus and toughness of the mixture films between Surelease®: Eudragit®RS30D in the ratio of 7:3 and 5:5 were not much changed when contrasted to the pure Surelease® film whereas the blended film at the ratio of 3:7 was affected by the higher portion of Eudragit®RS30D. This blended film displayed very low values of % strain at break and toughness and high values of stress at

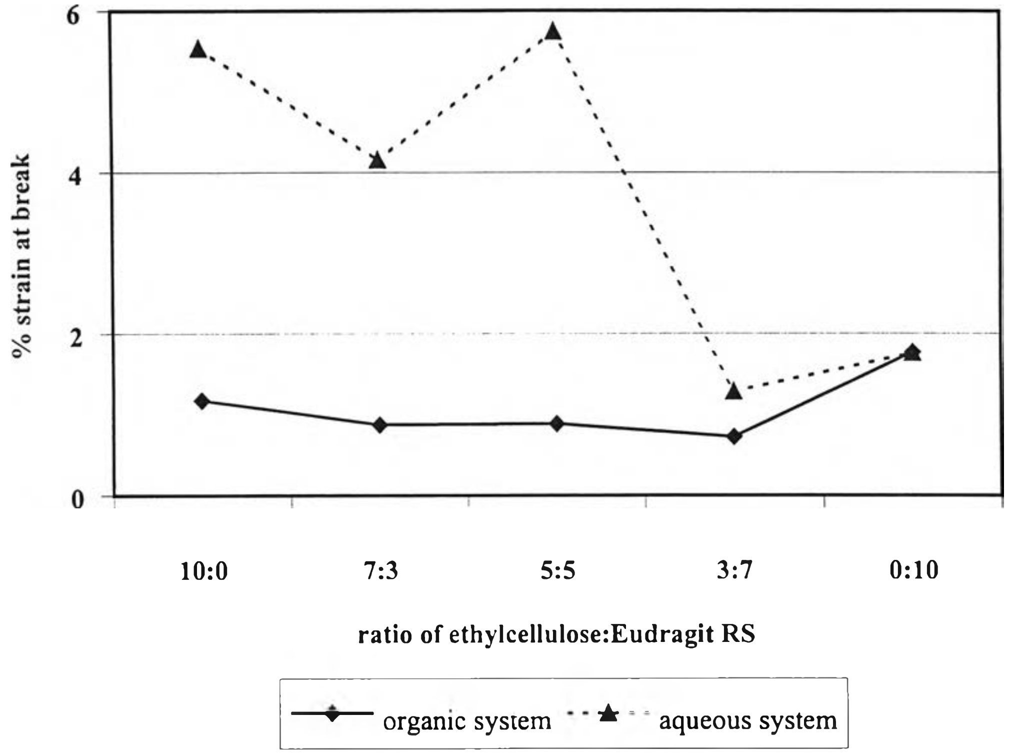


Figure 65 % Strain at break of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% TEC in organic system and aqueous system

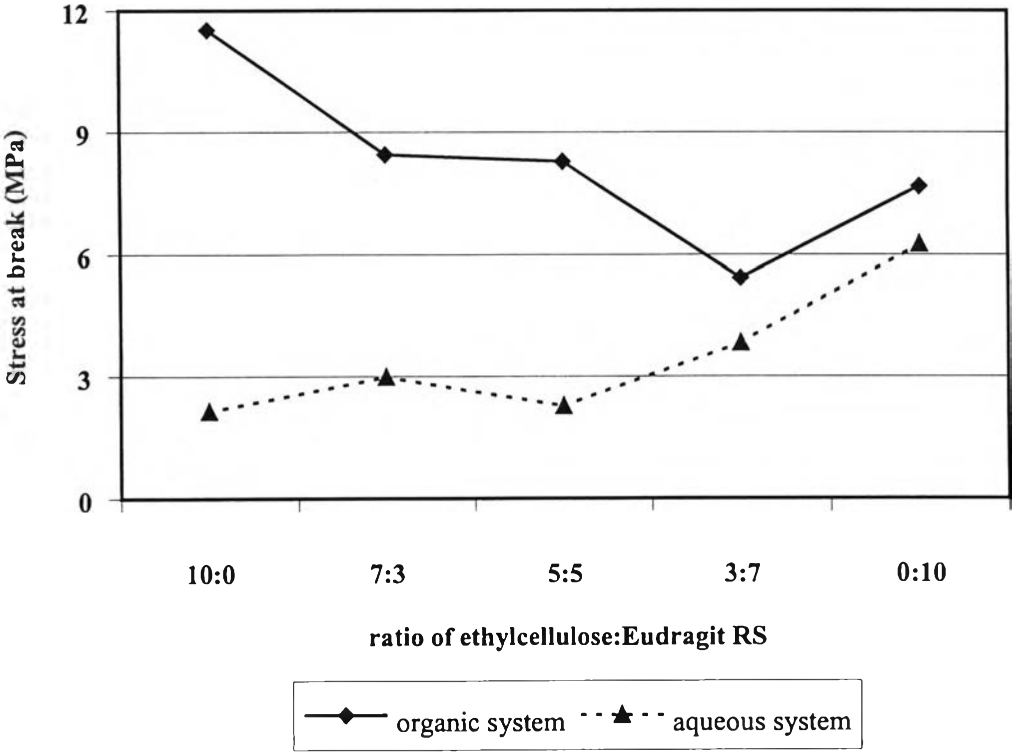


Figure 66 Stress at break of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% TEC in organic system and aqueous system

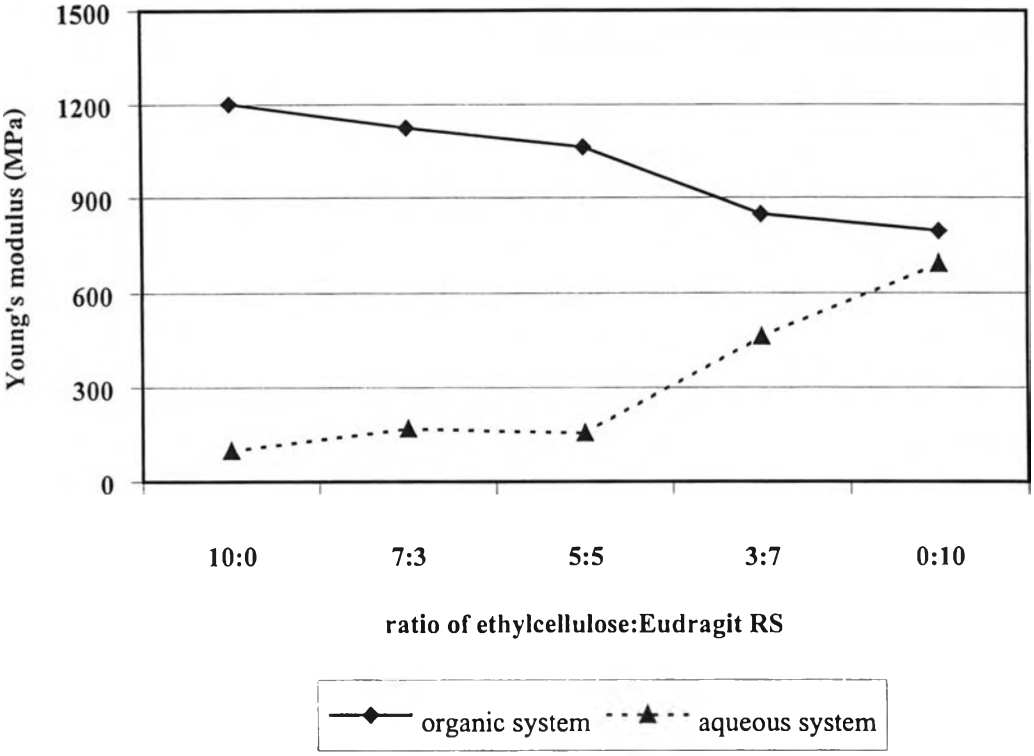


Figure 67 Young's modulus of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% TEC in organic system and aqueous system

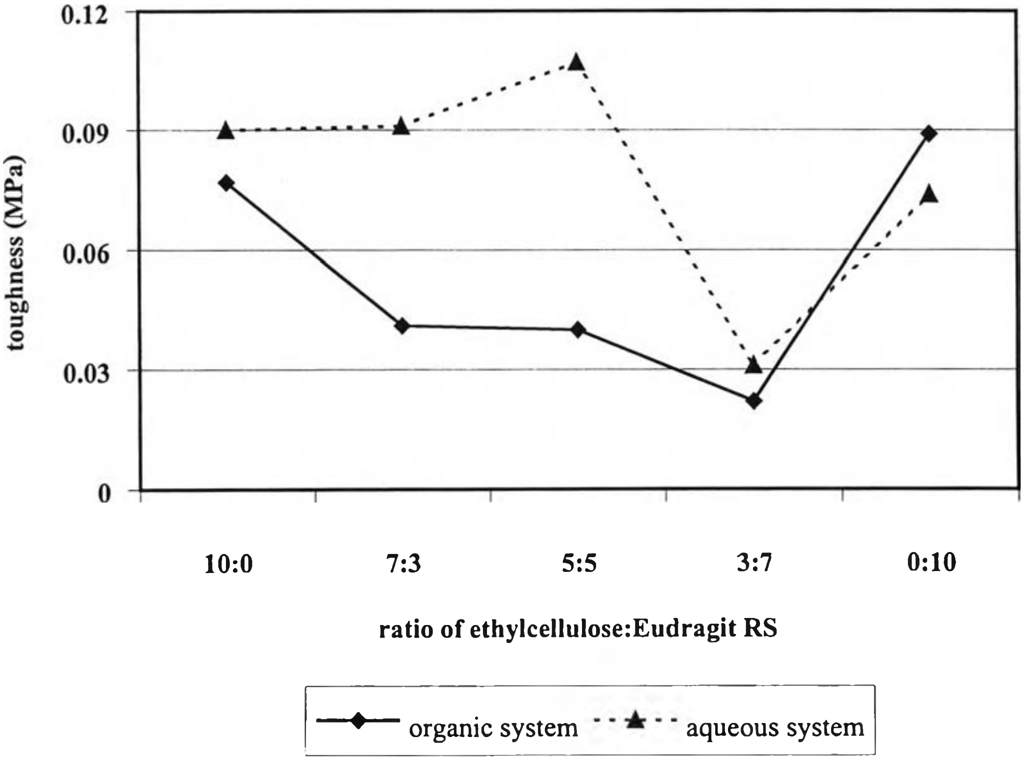


Figure 68 Toughness of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 10% TEC in organic system and aqueous system

break and Young's modulus. These values could be observed by weakness and slight hardness of film in this ratio. In the part of organic system, a slightly tough and hard film of ethylcellulose film was obtained as indicated by moderate value of toughness and higher values of stress at break and Young's modulus.

The mechanical properties of Eudragit®RS100 film were similar to the mechanical properties of Eudragit®RS30D so Eudragit®RS100 film had the same characteristic as Eudragit®RS30D film. Increasing the amount of Eudragit®RS100 in the blended films led to a continuous reduction of stress at break, Young'a modulus and toughness whereas % strain at break was slightly changed. The addition of Eudragit® RS30D to the blended films in aqueous system provided hard and brittle films and the blended films with a higher amount of Eudragit®RS100 produced soft and weak films. In this manner, the combined films at the ratio of 3:7 in both systems exhibited the most weakness and brittle appearance corresponding with the characteristics of film during testing. Some samples in this ratio appeared jagged edges eventhough the samples were cut with carefulness. Nevertheless, the alteration of mechanical properties of mixed films in aqueous system was in higher degree than in organic system. It was due to Surelease® which is an ethylcellulose dispersion already plasticized with fractionated coconut oil. Additionally, ethylcellulose pseudolatexes are stabilized with ammonium oleate which can be converted to oleic acid and then acts as a plasticizer (Bodmeier and Paeratakul, 1994a). So the mixing of the two polymers in various ratios in aqueous system was not only the change in the proper amount of the two polymers but also the change in the amount of plasticizers in the mixture. Consequently, the high values of % strain at break and toughness in aqueous system were observed in the blended films with the fraction of Surelease® up to 50%. % Strain at break and toughness of films with Surelease®: Eudragit®RS30D in the ratio of 3:7 were dramatically changed to the lowest value. It appeared that the combined film with higher fraction of Eudragit®RS30D more than 50% showed a hard and brittle characteristic.

Figures 69-72 exhibit the mechanical properties of the blended films with high level of plasticizer both in organic and aqueous systems. When considered the films from organic system, increasing the proportion of Eudragit®RS100 in mixed films with 20% triethyl citrate resulted a slight increase in % strain at break but the opposite effected on stress at break and Young's modulus. So the addition of Eudragit®RS100 in organic films caused softer and weaker film. The pure Eudragit®RS100 film appeared high values of % strain at break and toughness because of the efficiency of triethyl citrate at higher level.

In the part of aqueous system, mixed films with higher portion of Eudragit®RS30D plasticized with 15% triethyl citrate gave slightly higher toughness values including Young's modulus values whereas no apparent difference in % strain at break and stress at break values was seen. Hence, the increasing of Eudragit®RS30D resulted in slightly harder and tougher film except pure Surelease® and Eudragit®RS30D films which exhibited much tougher than blended films. The incorporation of Eudragit® RS100 in ethylcellulose films could lead to softer film. The result was corresponded to earlier study (Phuapradit et al., 1995). The addition of Eudragit®RL100 to the cellulose acetate membranes containing dibutyl sebacate caused a significant decrease in the tensile strength, percent elongation and modulus of elasticity, thus providing weaker and softer membranes.

In agreement with the result of microscopic views of films prepared from organic system, an increase in proportion of Eudragit®RS100 led to an increase in softness shown by smoother appearance. The result of the photomicrographs of films prepared from aqueous dispersion system was also correlated to the result of mechanical properties. The combined films prepared from aqueous dispersion system did not display a smoother surface with increasing fraction of Eudragit®RS30D. The mixture of films between Surelease® and Eudragit®RS30D could not improve better film properties when contrasted to the single film.

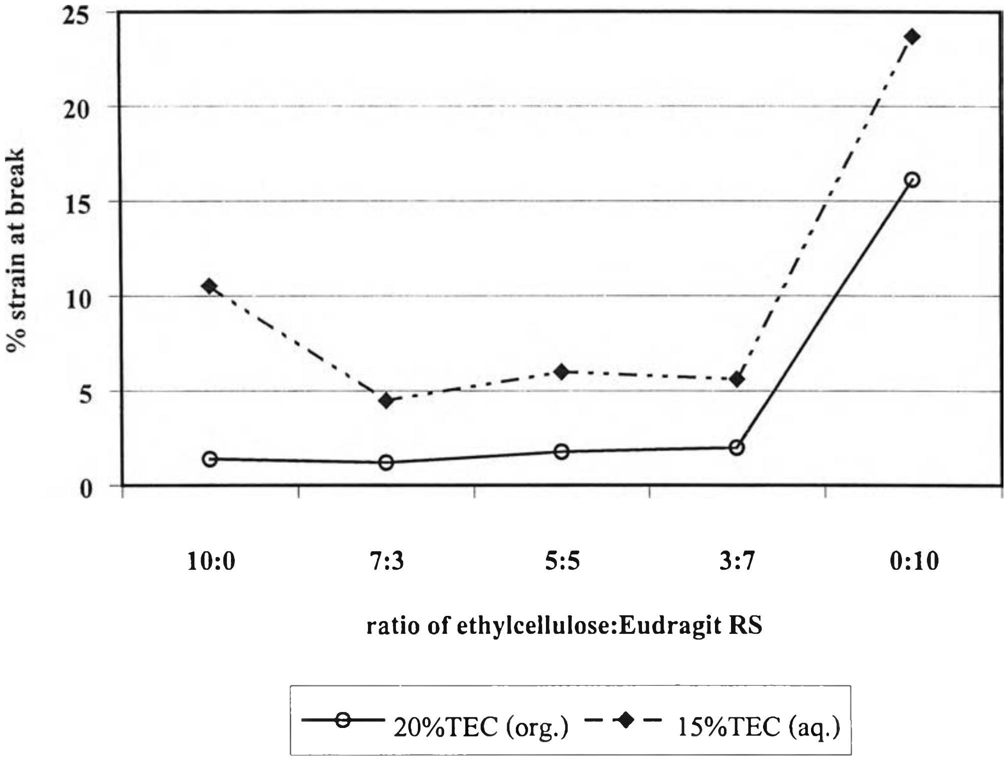


Figure 69 % Strain at break of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% TEC in organic system and 15% TEC in aqueous system

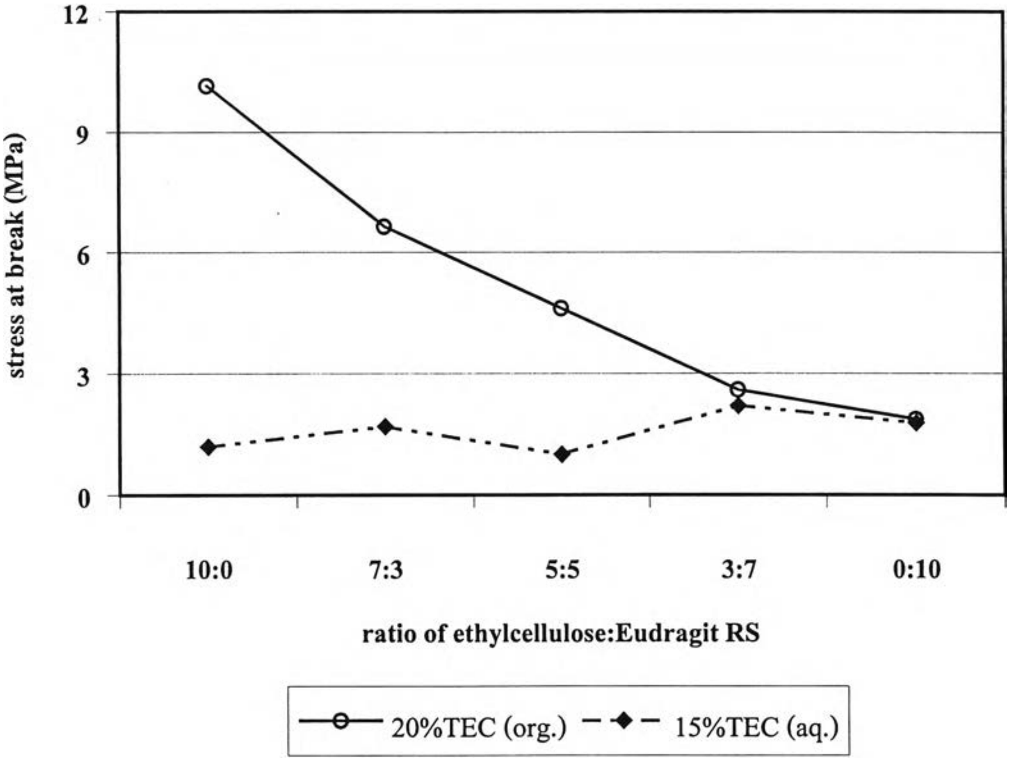


Figure 70 Stress at break of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% TEC in organic system and 15% TEC in aqueous system

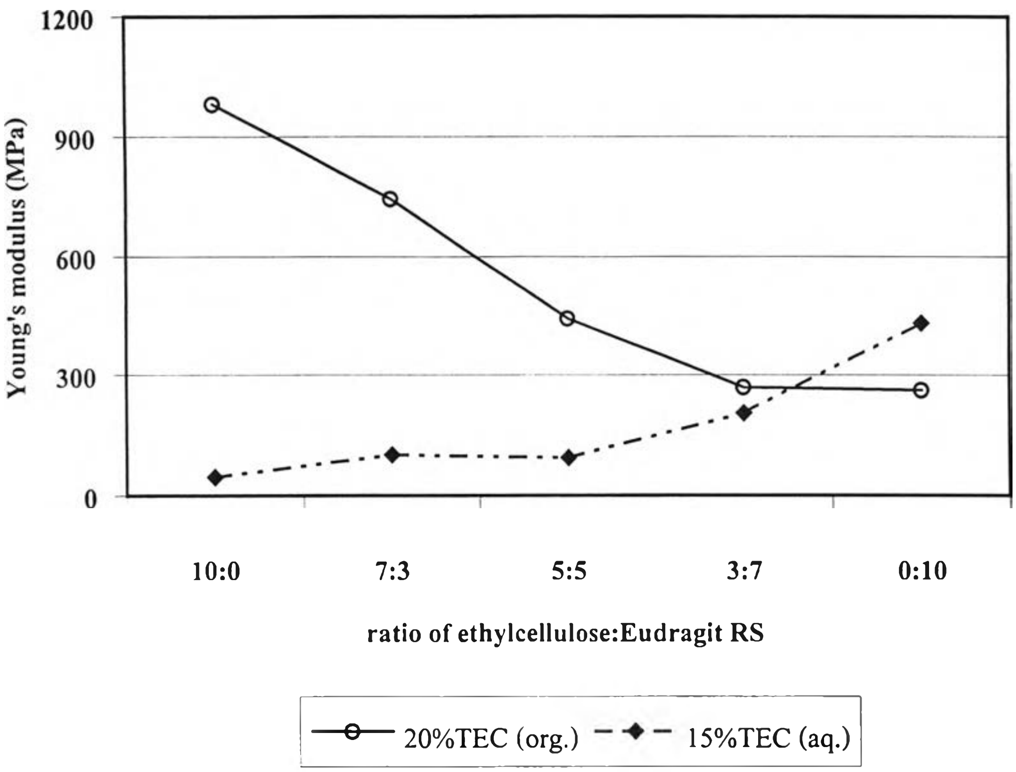


Figure 71 Young's modulus of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% TEC in organic system and 15% TEC in aqueous system

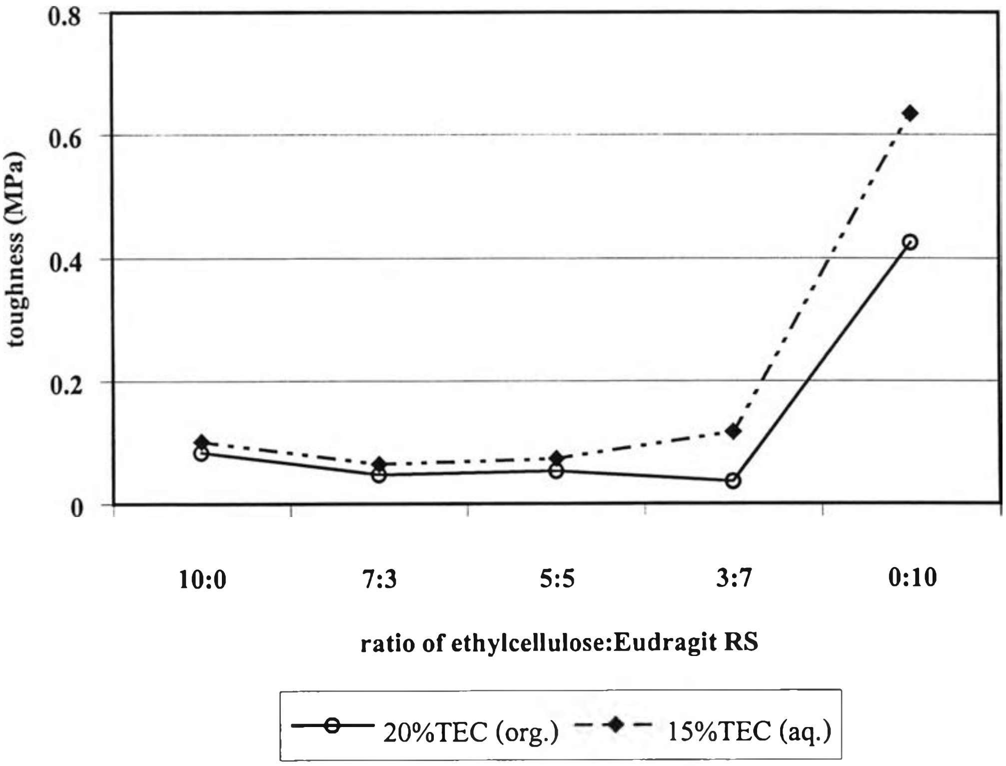


Figure 72 Toughness of films between EC:EuRS at the ratio of 10:0, 7:3, 5:5, 3:7 and 0:10 with 20% TEC in organic system and 15% TEC in aqueous system

3.3.4 Effect of organic system and aqueous system on mechanical properties

The influence of different systems on mechanical properties is also presented in Figures 65-72. The films prepared from aqueous system displayed the higher values of % strain at break and toughness corresponded with lower values of stress at break and Young's modulus. The difference values of mechanical properties with higher level of plasticizer were seen less evidently than those with lower level of plasticizer. Softer and tougher films could be produced from aqueous dispersion system due to the difference in the nature of the aqueous dispersion system and organic system. Additionally, Surelease® which is completely plasticized by fractionated coconut oil could influence on the mechanical properties. Another reason was the effect of water in the formulation.

Aulton and Abdul-Razzak (1981) have explained the competition of water for active sites. Water competes for bonding sites (i.e., free hydroxyl group), thus reducing the number of polymer-polymer contacts. The water acts as a plasticizer. Thus, polymer chains are more free for random movement and greater coalescence is possible. This may be related to the existence of solvent residues. They can increase the mobility of the polymeric chain by causing an increase in free volume. This increase in free volume will enable the polymer chains to move and orient themselves parallel to the direction of flow, causing the polymeric film to behave like a tough and ductile material (Gutierrez-Rocca and McGinity, 1993). Hence, both water and solvent residues can act as a plasticizer. The difference in the mechanical properties of films in organic system and films in aqueous system could be explained with the evaporation rate of solvent and water. The evaporation rate of the organic solvent was higher than the evaporation rate of water regardless of the different temperature. In the same duration of time, the quantity of water remaining in the films was more than the quantity of organic solvent thereafter enhancing the polymer segmental mobility by water.

However, all of film formulations prepared from aqueous dispersion system did not appeared better features or smoother surfaces than those prepared from organic system. Only the formulations of pure Surelease®and the polymer blends with the ratio of 7:3 (Surelease®: Eudragit®RS30D) presented better microscopic views.

3.4 Dissolution study of propranolol hydrochloride pellets

The dissolution data of all formulations of coated pellets in both acid buffer pH 1.2 and phosphate buffer pH 6.8 are summarized in Tables 25-37 (Appendix D). The drug release profiles in the above dissolution medium were plotted between the cumulative percent of drug release against time.

3.4.1 Uncoated pellets

The dissolution data of propranolol hydrochloride from uncoated pellets are tabulated in Table 25 (Appendix D) and the release profiles in both acid buffer pH 1.2 and phosphate buffer pH 6.8 are presented in Figure 73. The drug release characteristics of both media were nearly identical. The cumulative percent of drug release was almost completed within 30 minutes

3.4.2 Effect of proportion of polymer on the release profile

The coating of the combined films between ethylcellulose and Eudragit®RS100 is possible in any proportions. The effect of blending between ethylcellulose and Eudragit®RS100 on the drug release profile in both acid buffer and phosphate buffer is exhibited in Figures 74-81. The drug release was dramatically increased with the incorporation of Eudragit®RS100 in the coating formulation. A significant increase in membrane permeability was observed when greater than 30% of Eudragit®RS100 was added to the ethylcellulose membrane. The results were consistent

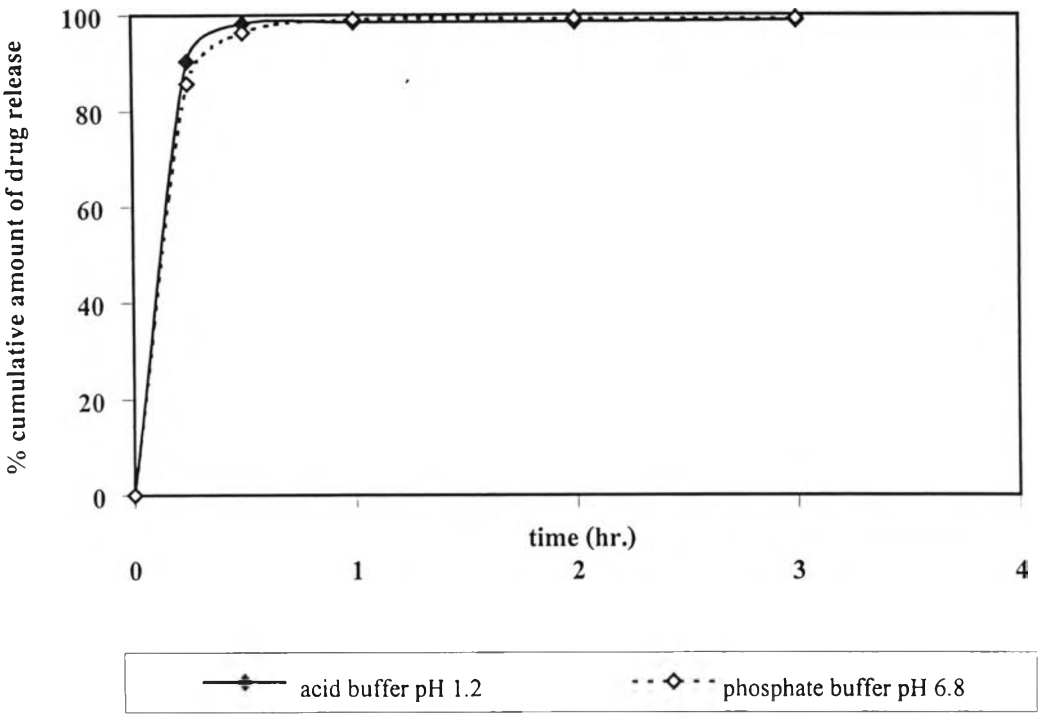


Figure 73 Release profiles of uncoat pellets in acid buffer pH 1.2 and phosphate buffer pH 6.8

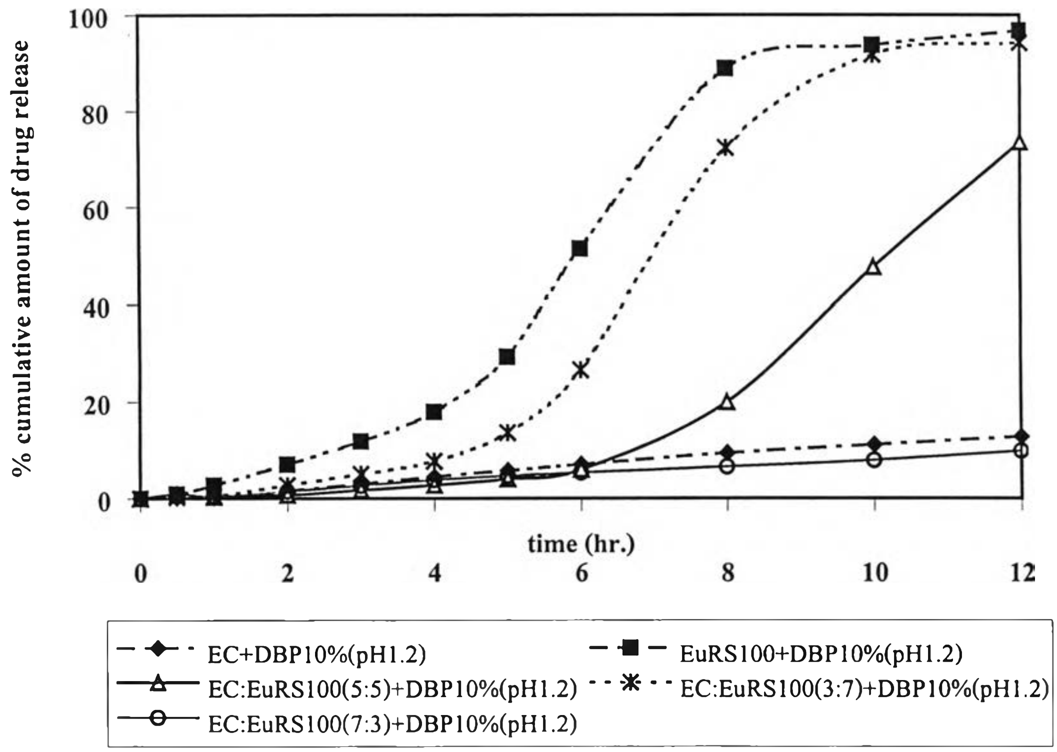


Figure 74 Release profiles of coated pellets of formulations A1, A3, A5, A7, A9 in acid buffer

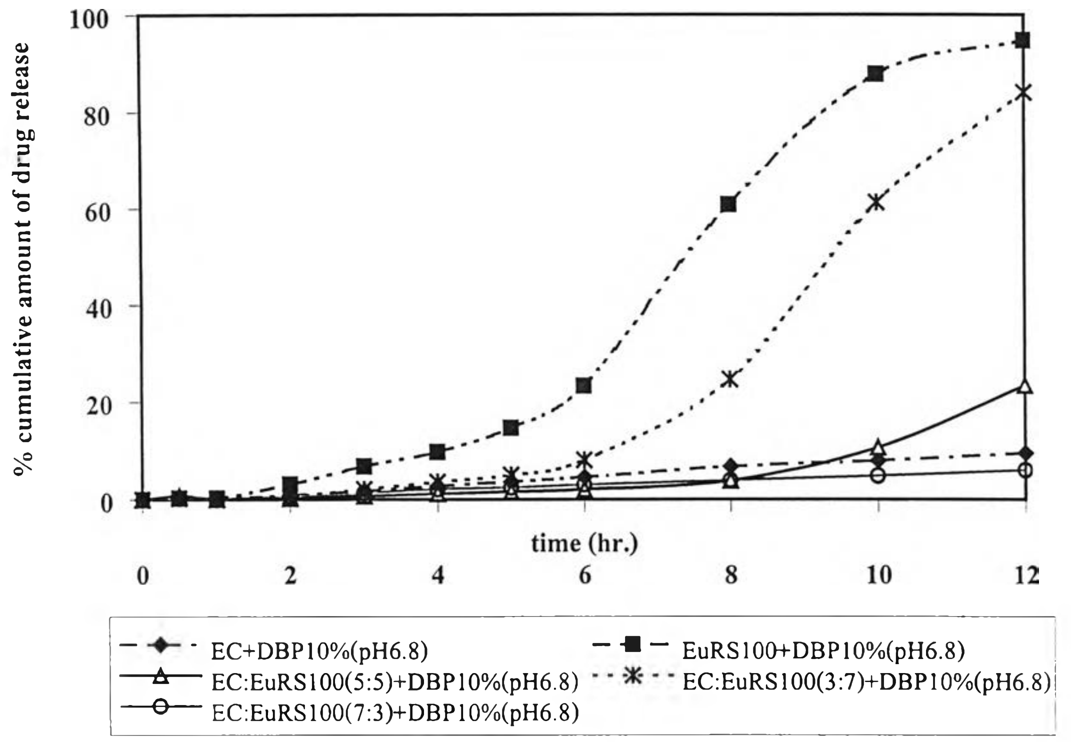


Figure 75 Release profiles of coated pellets of formulations A1, A3, A5, A7, A9 in phosphate buffer

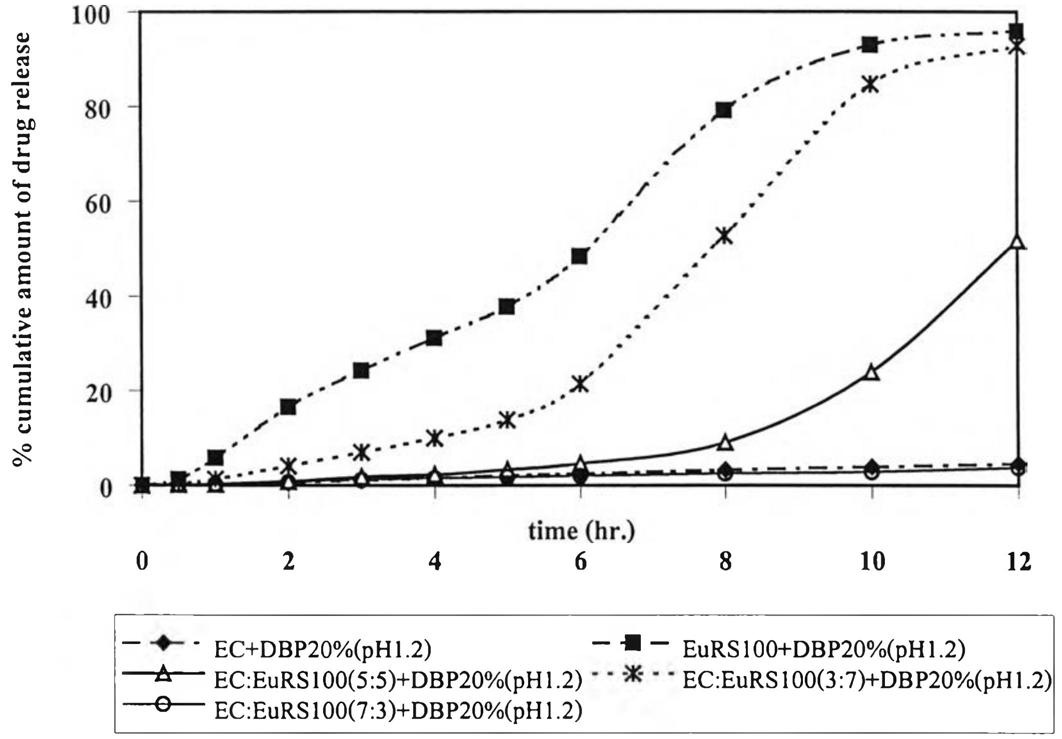


Figure 76 Release profiles of coated pellets of formulations A2, A4, A6, A8, A10 in acid buffer

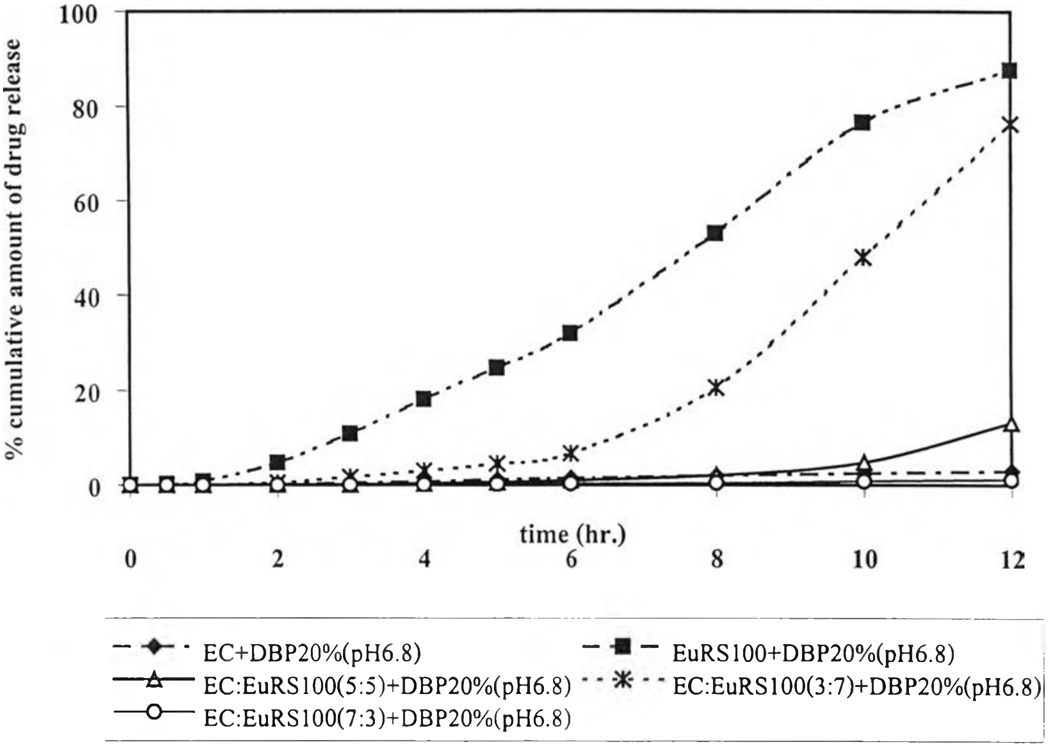


Figure 77 Release profiles of coated pellets of formulations A2, A4, A6, A8, A10 in phosphate buffer

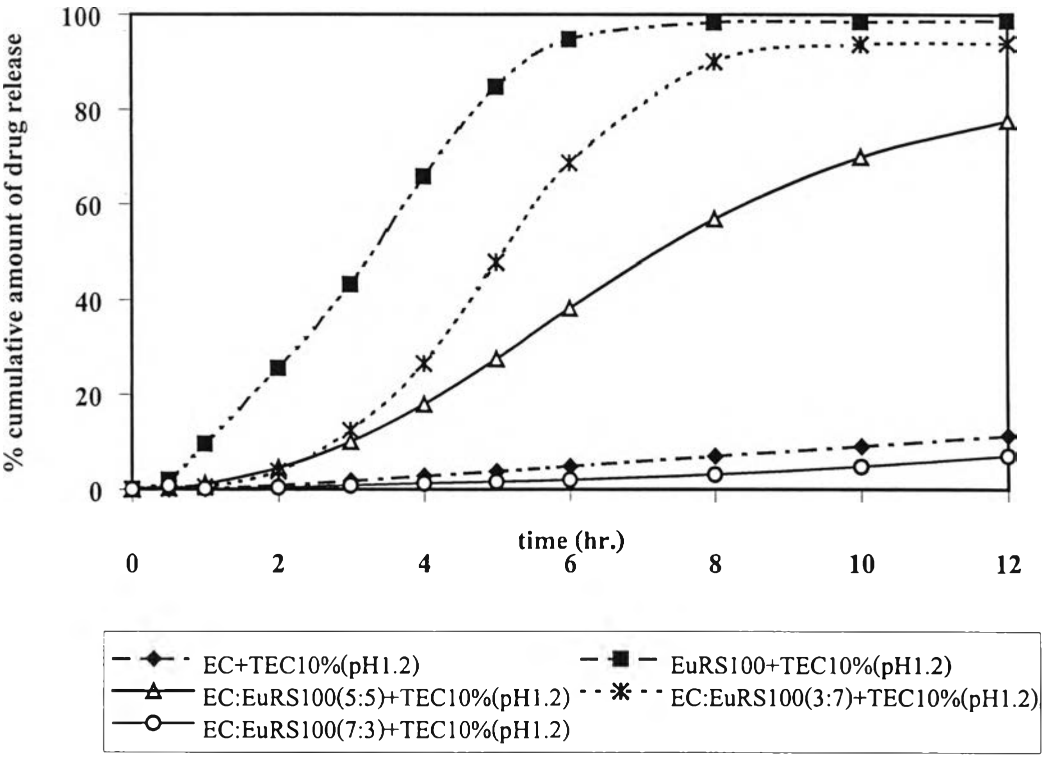


Figure 78 Release profiles of coated pellets formulations of A11, A13, A15, A17, A19 in acid buffer

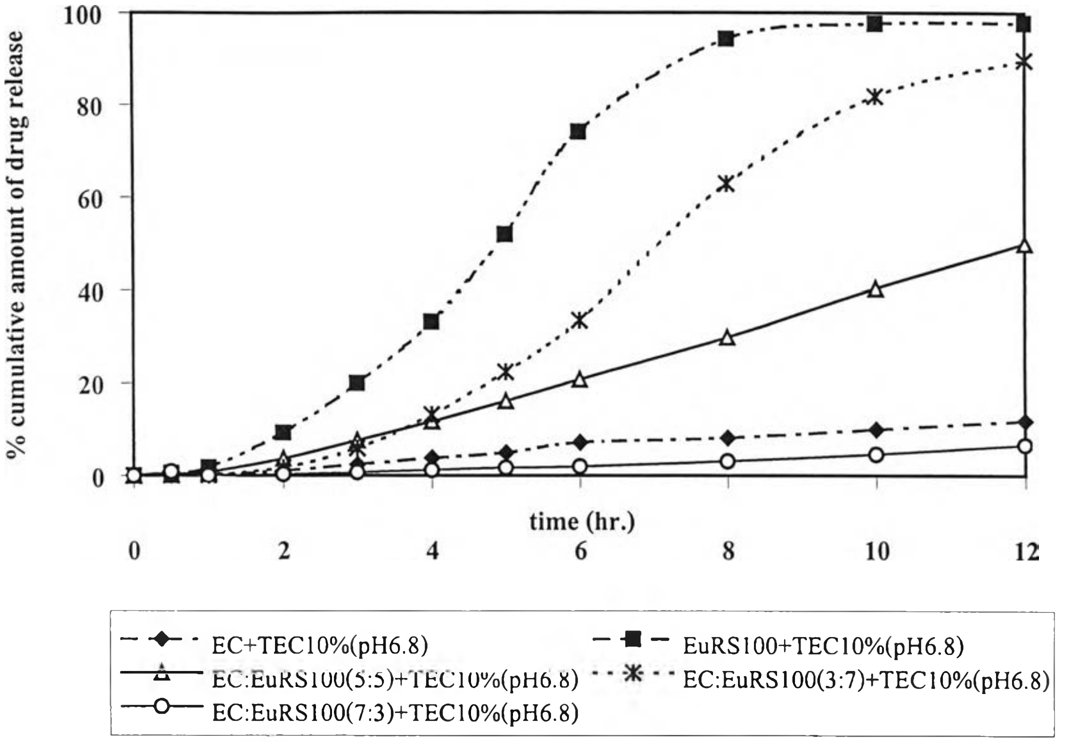


Figure 79 Release profiles of coated pellets of formulations A11, A13, A15, A17, A19 in phosphat buffer

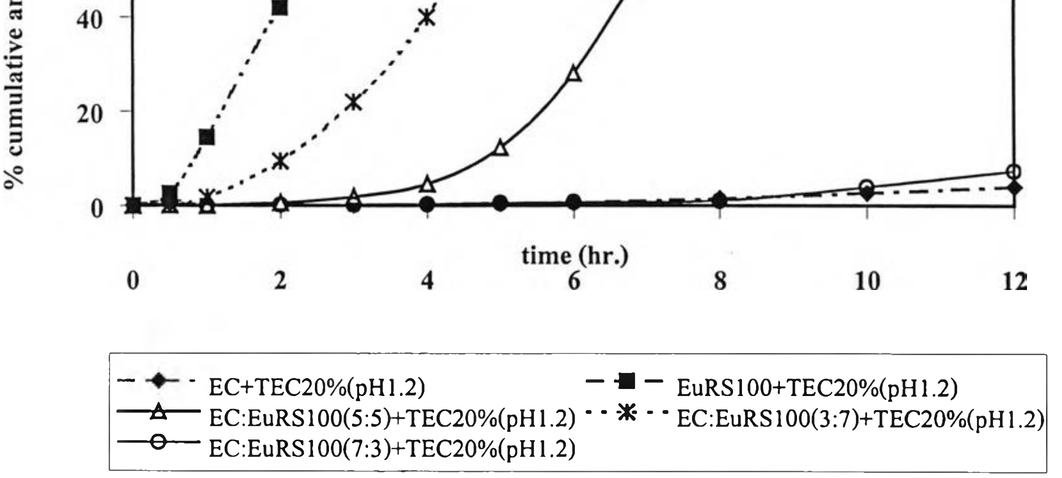


Figure 80 Release profiles of coated pellets of formulations A12, A14, A16, A18, A20 in acid buffer

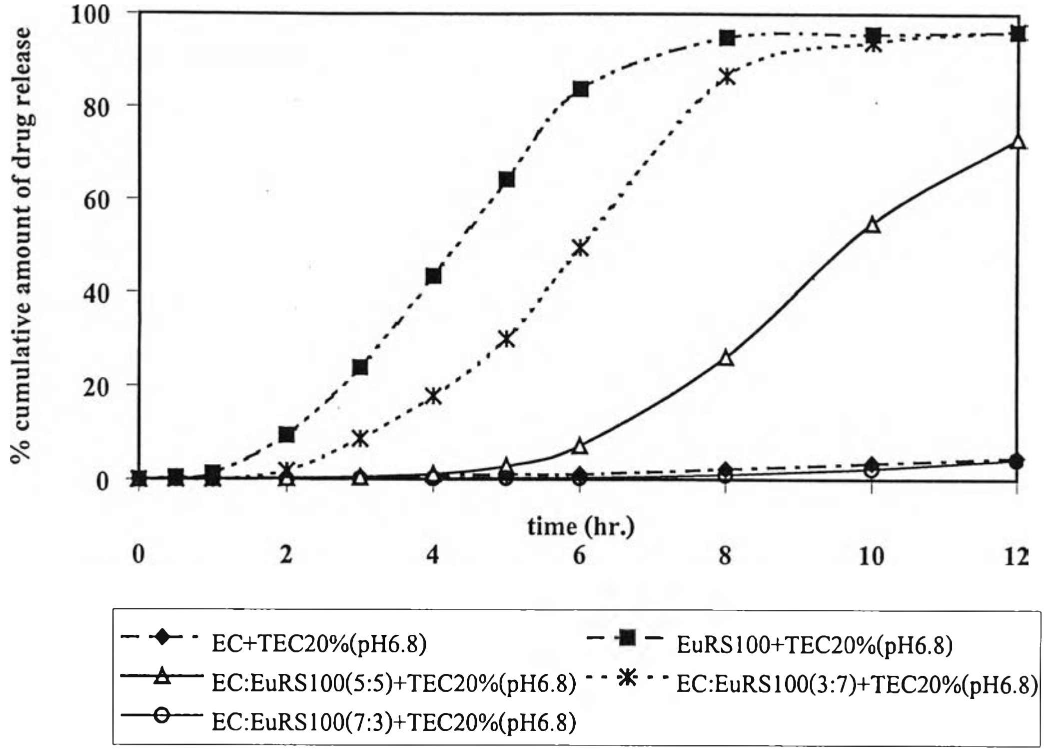


Figure 81 Release profiles of coated pellets formulations A12, A14, A16, A18, A20 in phosphate buffer

with a previous study by Phuapradit et al. (1995). The addition of Eudragit®RL100 at 10% level to the cellulose acetate or ethylcellulose membranes could modify the release profile by increasing the permeability. The effect was more outstanding in the case of the ethylcellulose membranes.

The drug release profiles of Eudragit®RS100 coated pellets with 10% dibutyl phthalate in both media had a sigmoidal shape with three phases like the diltiazem HCl beads coated with Eudragit®RS and RL30D and plasticized with acetyl tributyl citrate (Bodmeier et al., 1996). The shorter lag time of Eudragit®RS100 coated pellets with higher level of dibutyl phthalate was displayed in Figures 76-77. The pellet coated with the portion of ethylcellulose more than 50% and plasticized with 10% and 20% dibutyl phthalate showed very slow release profiles (Figures 74-77). Therefore, the mixture films of Eudragit®RS100 and ethylcellulose had the parallel profile which was similar to profile of each polymer. This parallel profile depended on which higher proportion of each polymer was incorporated in the mixture films. However, the drug release pattern of ethylcellulose and Eudragit®RS100 in the ratio of 5:5 plasticized with dibutyl phthalate in phosphate buffer did not show increasing permeability (Figures 75 and 77). Additionally the mixing of 30% Eudragit®RS100 did not alter the permeability of the combined film.

The pellets coated with Eudragit®RS100 containing 10% triethyl citrate displayed short lag time at the first period, a second stage of rapid release and a third stage of slow release (Figures 78 and 79). Consequently, the incorporation of ethylcellulose could prolong lag time at the first period and this effect was more pronounced when the higher amount of triethyl citrate was employed (Figures 80 and 81). The second stage of rapid release of the mixture films with Eudragit®RS100 more than 30% was appeared due to the influence of higher quantity of triethyl citrate.

Figures 82-89 show the effect of different ratios of Surelease®and Eudragit®RS30D on the release characteristics of propranolol hydrochloride pellets. Increasing the proportion of Eudragit®RS30D resulted in increasing permeability. The drug release rate was significantly accelerated when 30% of Eudragit®RS30D was used. The pellets coated with Eudragit®RS30D and with Surelease®: Eudragit®RS30D in the ratio of 5:5 released all the drug within 2 hours and 4 hours, respectively. The incorporation of Eudragit®RS30D only 30% could cause very rapid drug release which did not happen in the corresponding proportion of Eudragit®RS100 in organic system. The outstanding lag phase of pellets coated with aqueous dispersion formulations was not observed eventhough the incorporation of Surelease® at 70% level. The most prominent lag time in this system occurred in the pellets coated with mixture film in the ratio of 7:3 and plasticized with 15% triethyl citrate (Figures 84 and 85).

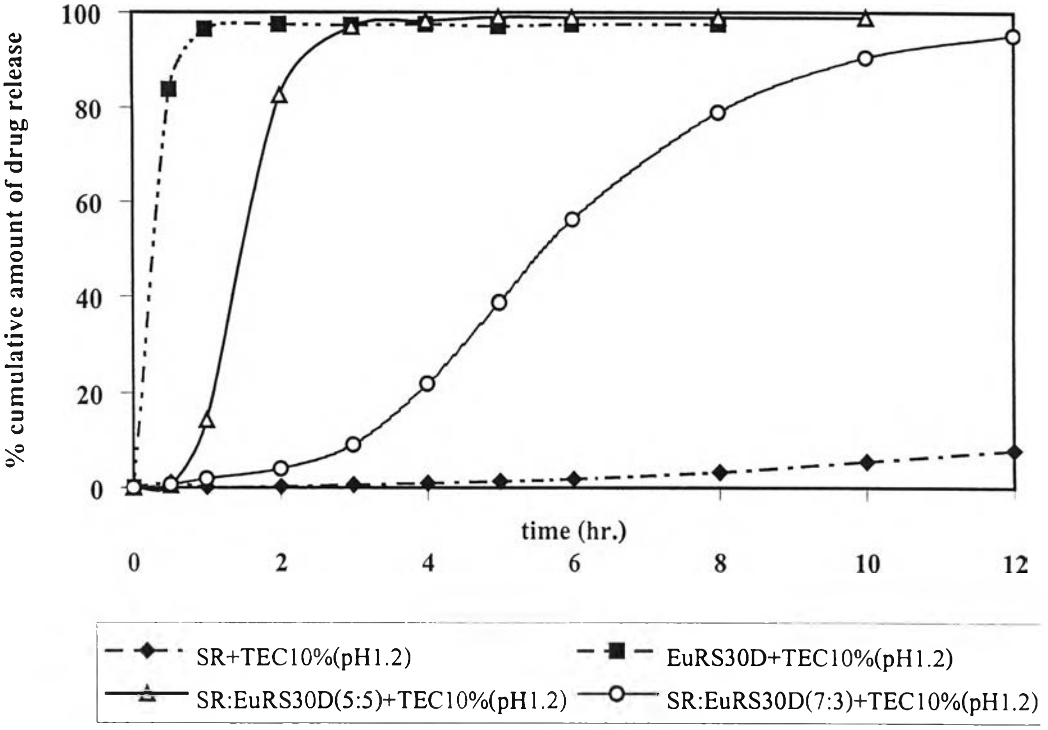


Figure 82 Release profiles of coated pellets of formulations B1, B3, B5, B9 in acid buffer

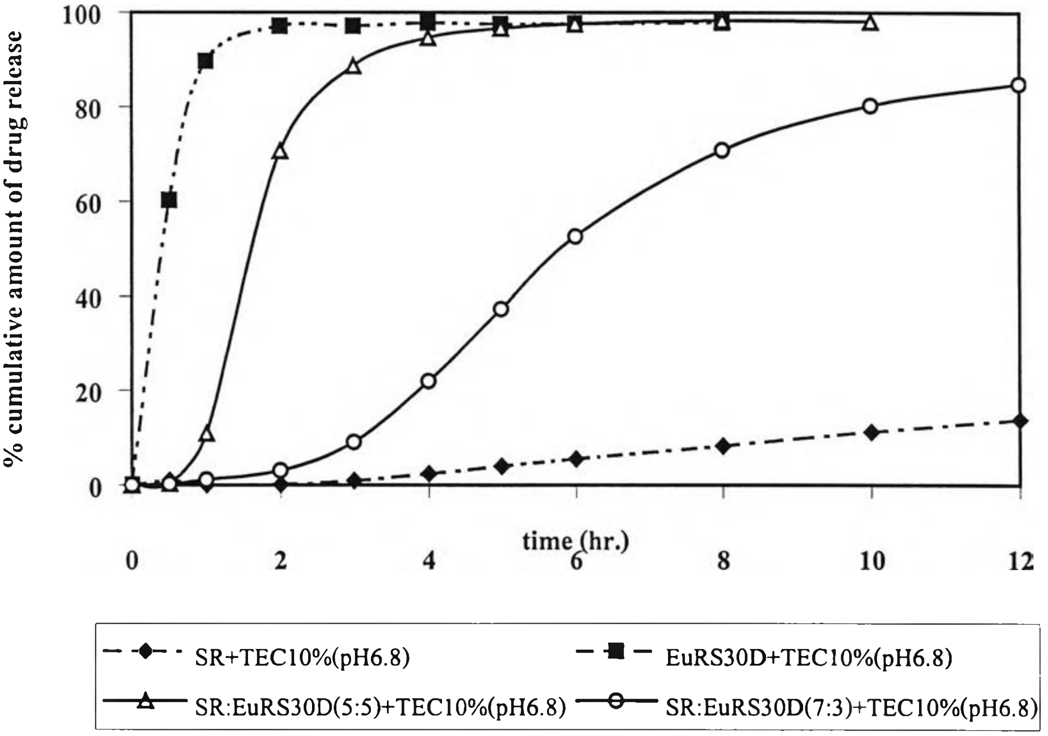


Figure 83 Release profiles of coated pellets of formulations B1, B3, B5, B9 in phosphate buffer

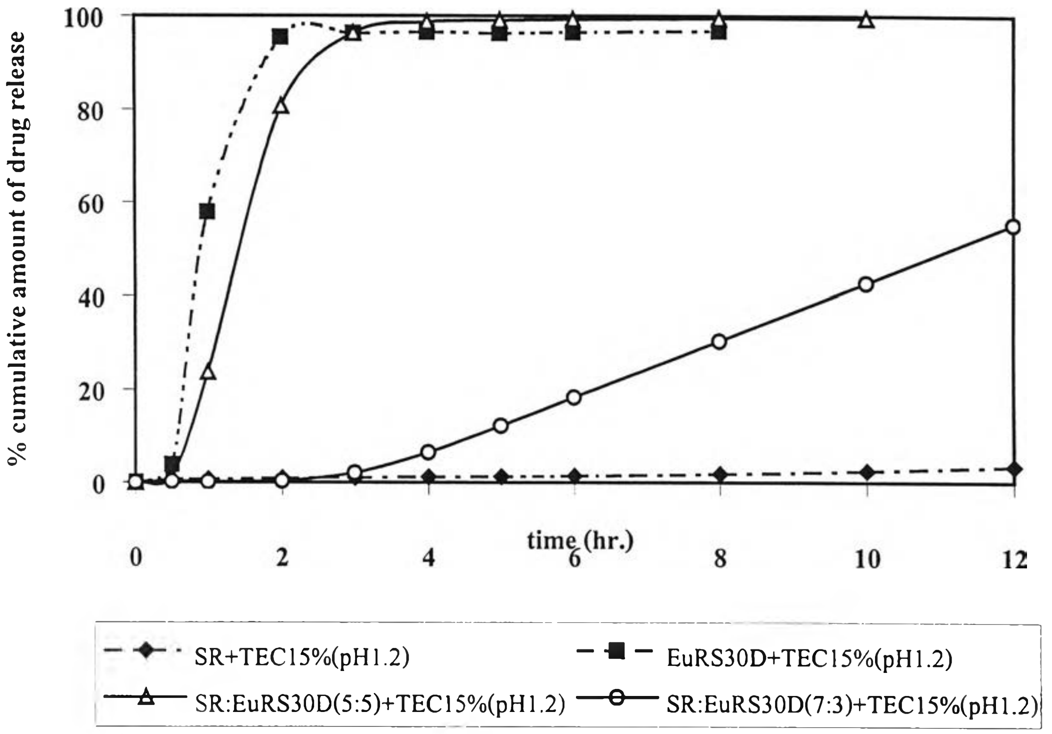


Figure 84 Release profiles of coated pellets of formulations B2, B4, B6, B10 in acid buffer

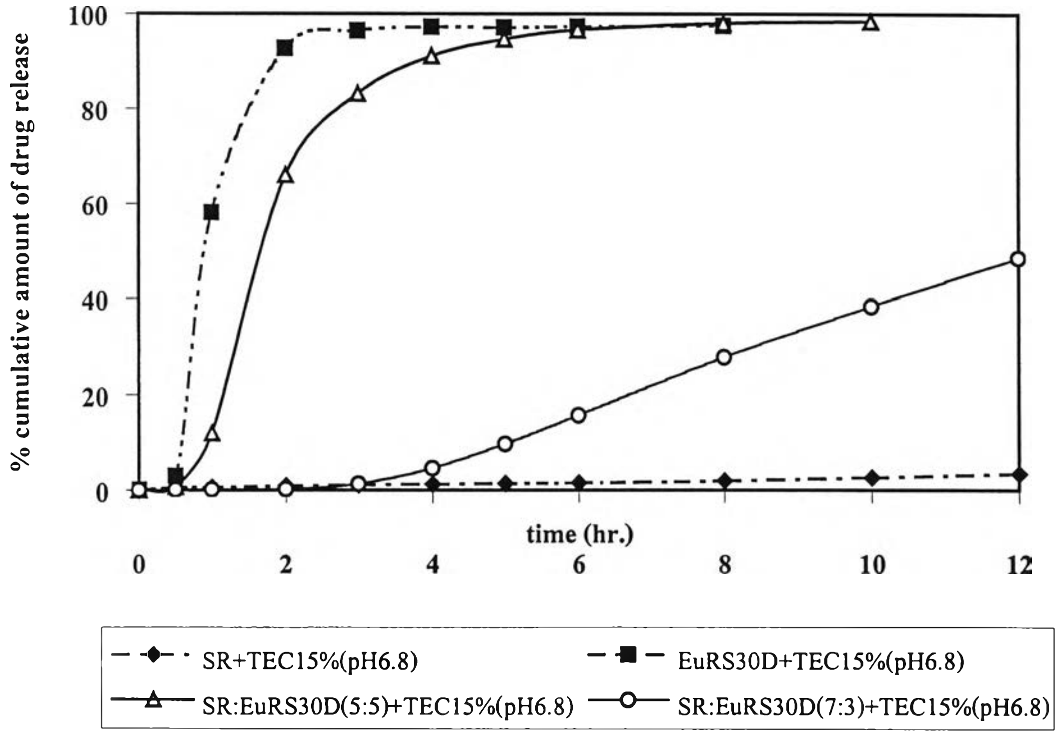


Figure 85 Release profiles of coated pellets of formulations B2, B4, B6, B10 in phosphate buffer

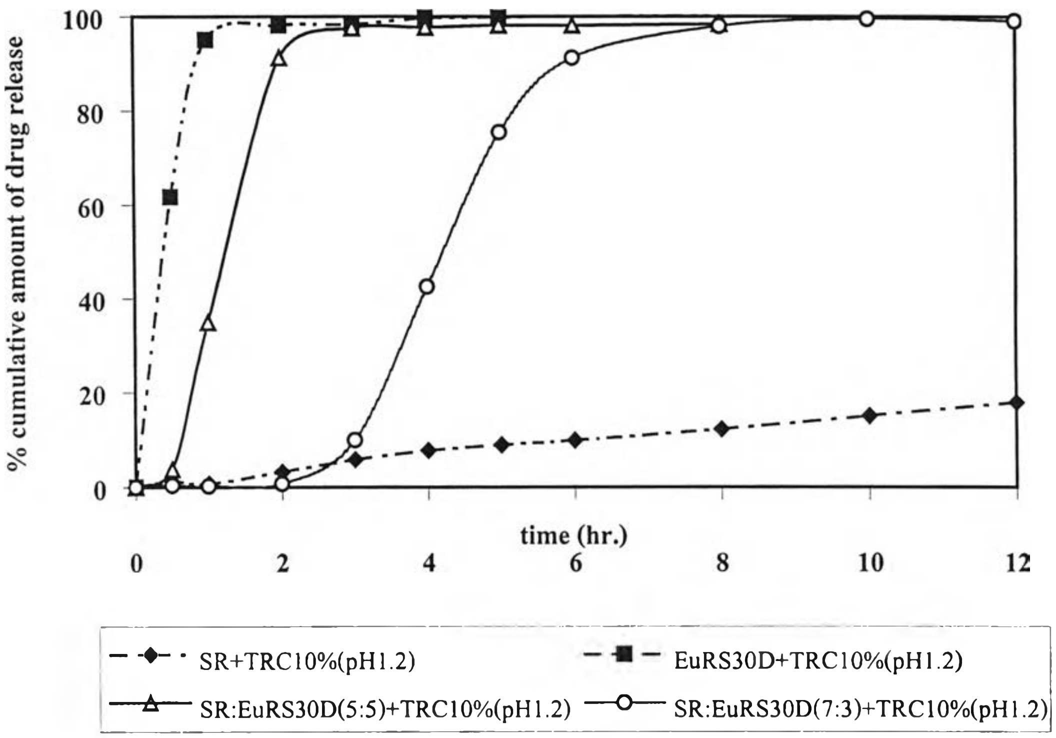


Figure 86 Release profiles of coated pellets of formulations B11, B13, B15, B19 in acid buffer

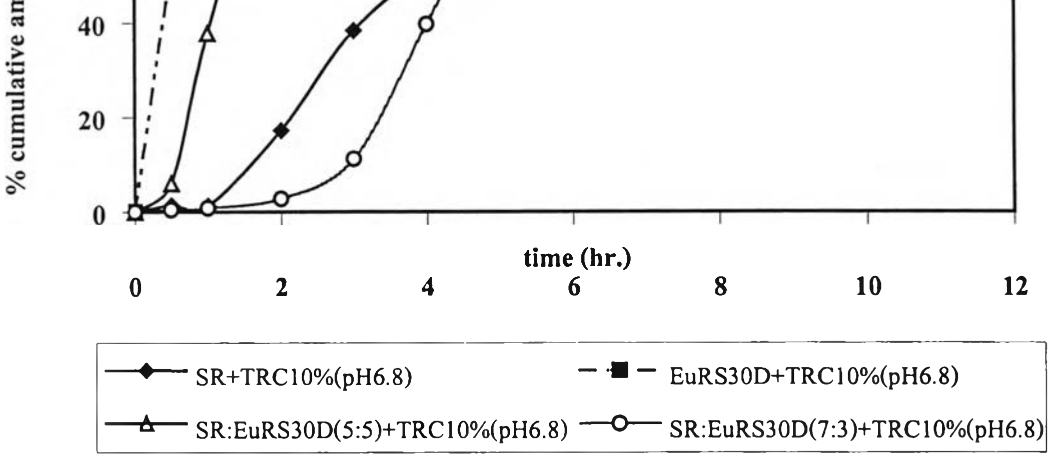


Figure 87 Release profiles of coated pellets of formulations B11, B13, B15, B19 in phosphate buffer

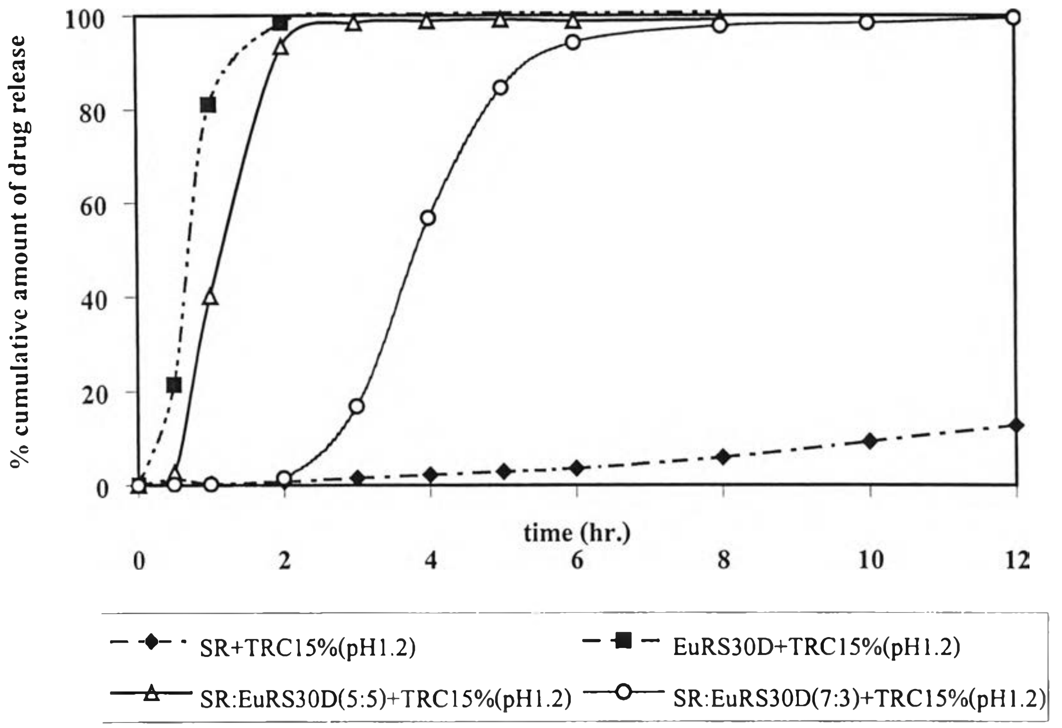


Figure 88 Release profiles of coated pellets of formulations B12, B14, B16, B20 in acid buffer

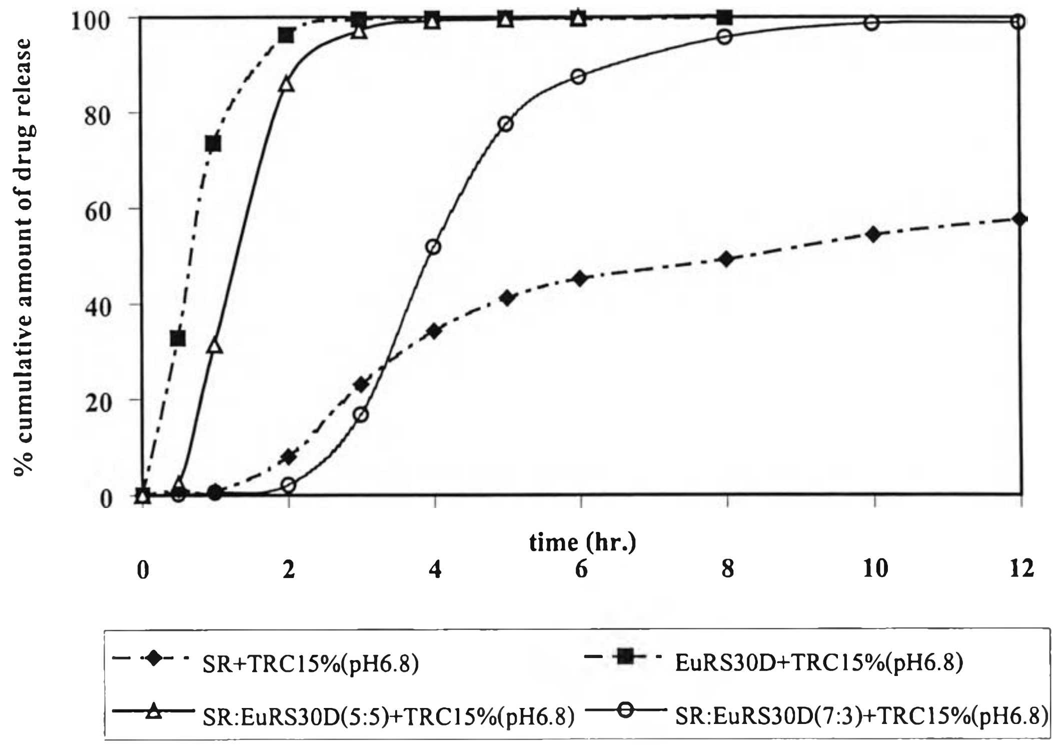


Figure 89 Release profiles of coated pellets of formulations B12, B14, B16, B20 in phosphate buffer

When considered the mechanical properties of the polymer blends in both systems, the higher quantity of Eudragit®RS100 led to softer and weaker of the mixed films and the higher amount of Eudragit®RS30D led to harder and more brittle of the mixed films. These appearances of the blended films did not correlate with the characteristics of drug release because the single Eudragit®RS that displayed the fastest of drug release was tougher than the polymer blends.

The changing permeability characteristics of blended films could be explained by the properties of Eudragit®RS type as described by Bodmeier and Paeratakul (1990a). Eudragit®RS type is copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The ammonium groups are responsible for the permeability and swelling of these water insoluble films. The penetration of water from the surrounding medium into the core, and diffusion of the dissolved drug molecules from the core into the lumen of the digestive tract, occurs preferentially via hydrated hydrophilic pathways (Dittgen, Durrani, and Lehmann, 1997). The increase of permeability by addition of Eudragit®RS type was evidently observed in the films prepared from aqueous dispersion system. This finding could be explained by a lack of a suitable curing period to optimise the coalescence of Eudragit®RS30D. Hence, the properties of Eudragit®RS30D film could not be equivalent to the properties of Eudragit®RS100 film in the similar coating conditions.

3.4.3 Effect of pH of dissolution medium on the release profile

The drug release profiles of the coated pellets in acid buffer pH 1.2 and in phosphate buffer pH 6.8 are presented in Figures 90-99. The profiles from formulations A1, A2, A11 and A12 containing ethylcellulose with two levels of dibutyl phthalate and triethyl citrate in both media were found to be nearly identical and superimposable (Figures 90, 91). The drug release characteristics of formulations A1 and A2 obtained from phosphate buffer pH 6.8 appeared to be slightly slower than those

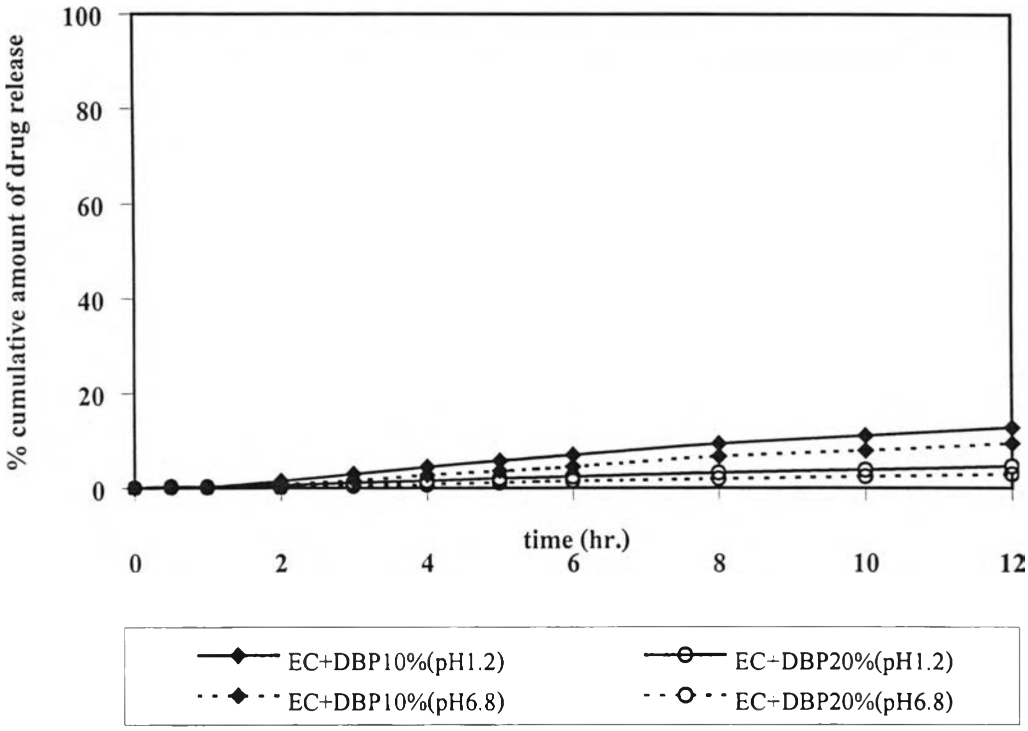


Figure 90 Release profiles of coated pellets of formulations A1 and A2 in acid buffer pH 1.2 and phosphate buffer pH 6.8

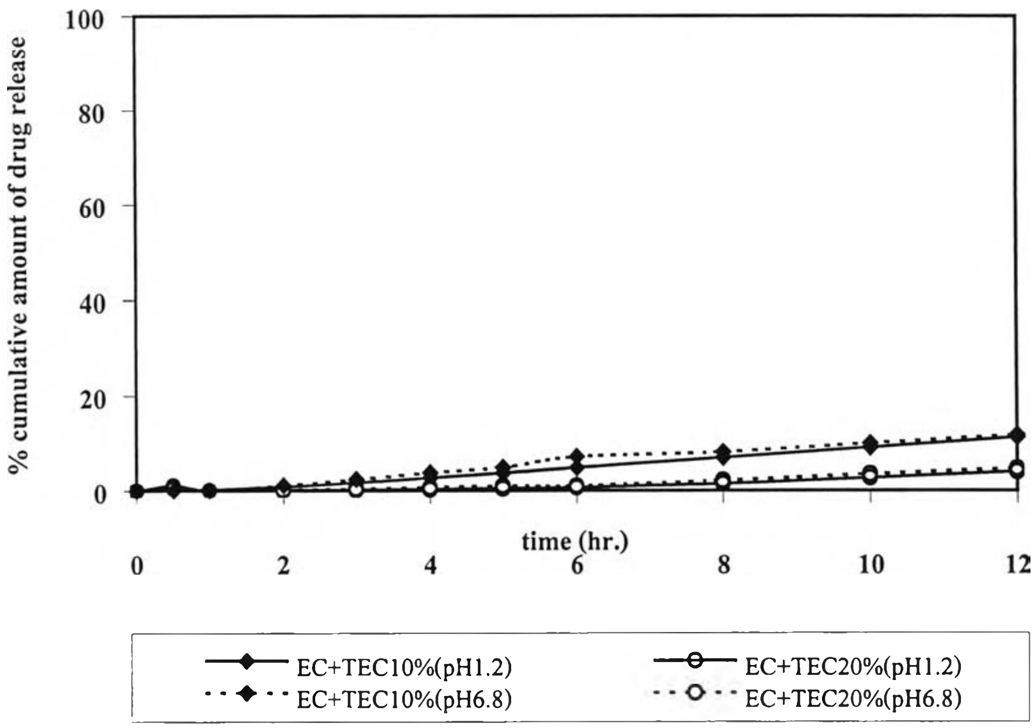


Figure 91 Release profiles of coated pellets of formulations A11 and A12 in acid buffer pH 1.2 and phosphate buffer pH 6.8

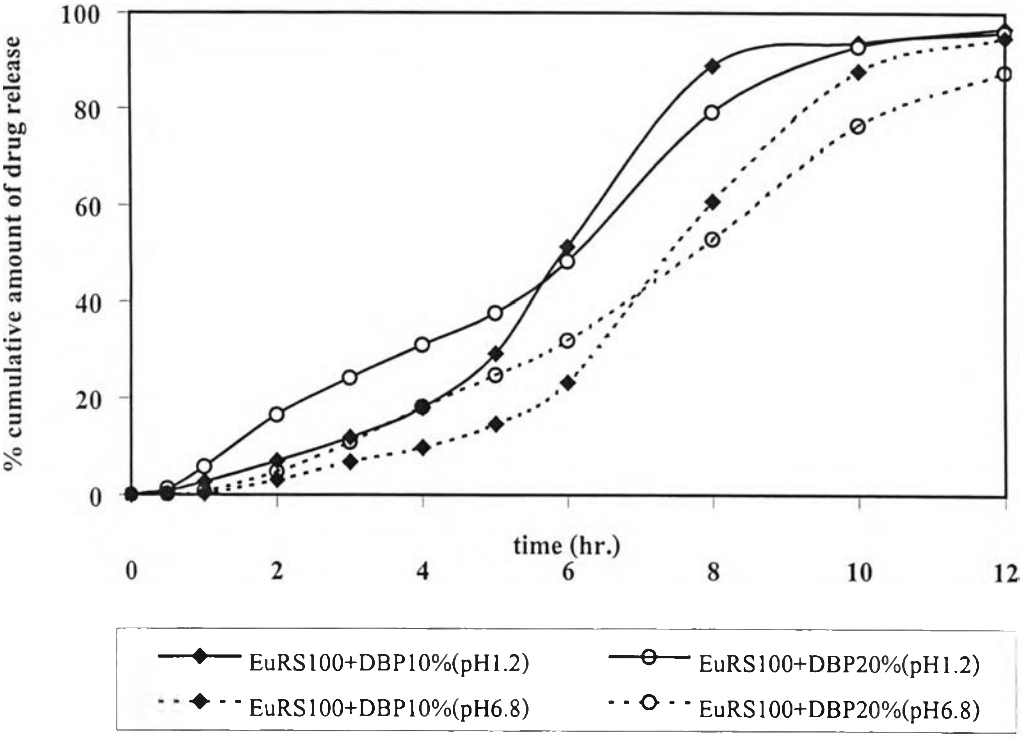


Figure 92 Release profiles of coated pellets of formulations A3 and A4 in acid buffer pH 1.2 and phosphate buffer pH 6.8

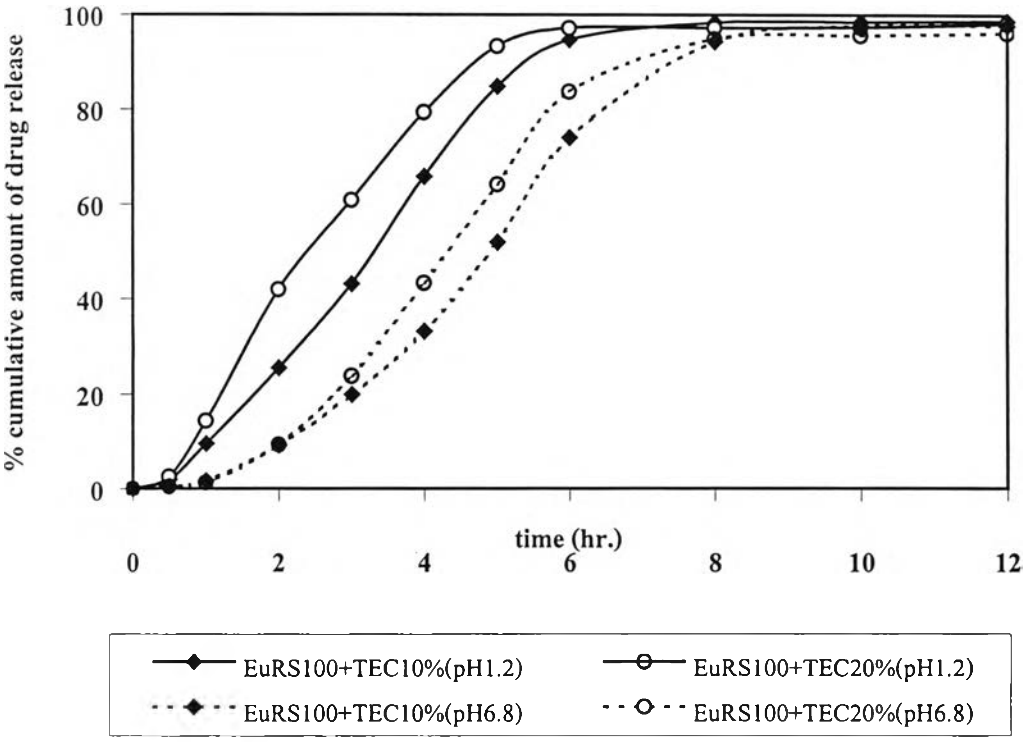


Figure 93 Release profiles of coated pellets of formulations A13 and A14 in acid buffer pH 1.2 and phosphate buffer pH 6.8

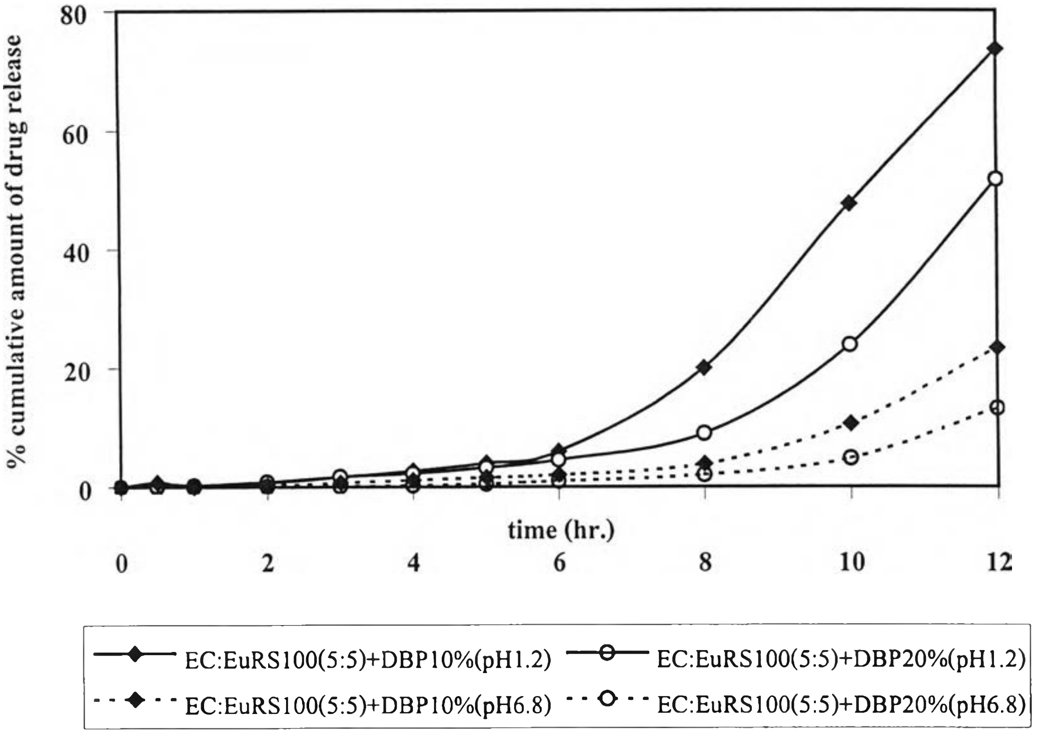


Figure 94 Release profiles of coated pellets of formulations A5 and A6 in acid buffer pH 1.2 and phosphate buffer pH 6.8

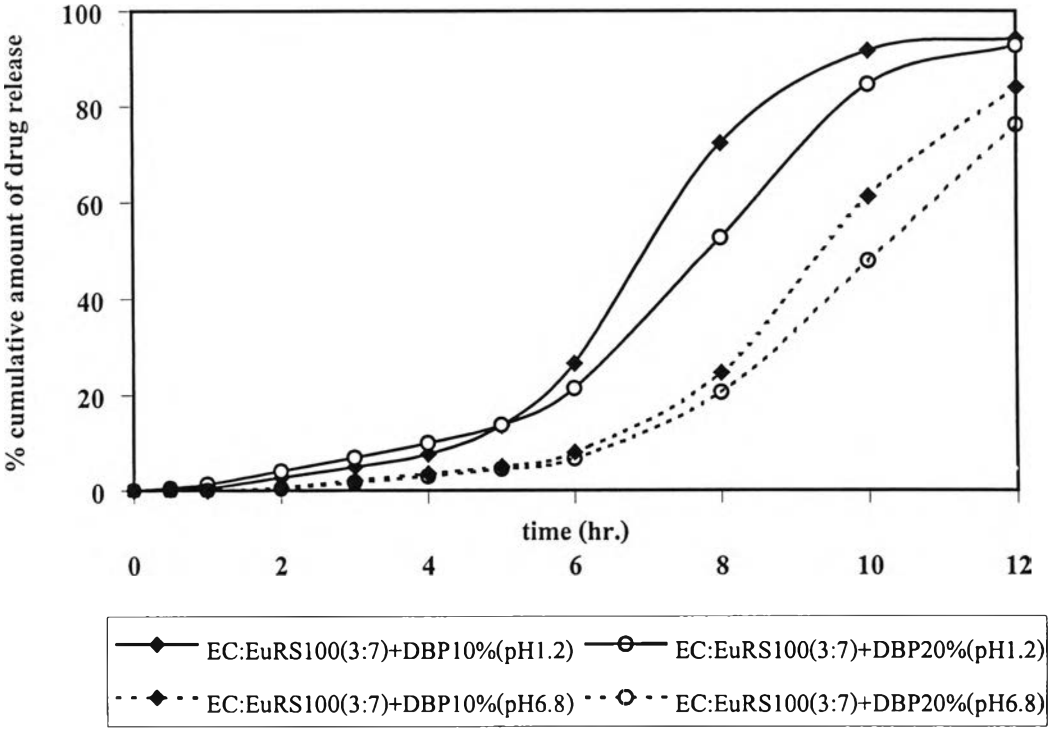


Figure 95 Release profiles of coated pellets of formulations A7 and A8 in acid buffer pH 1.2 and phosphate buffer pH 6.8

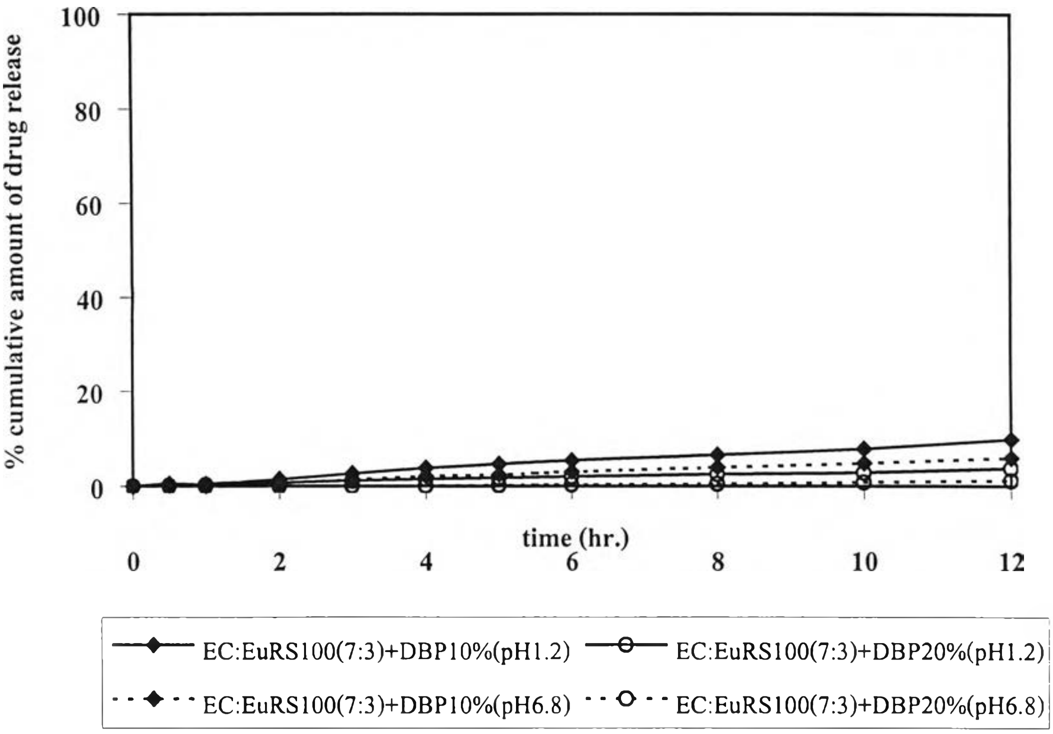


Figure 96 Release profiles of coated pellets of formulations A9 and A10 in acid buffer pH 1.2 and phosphate buffer pH 6.8

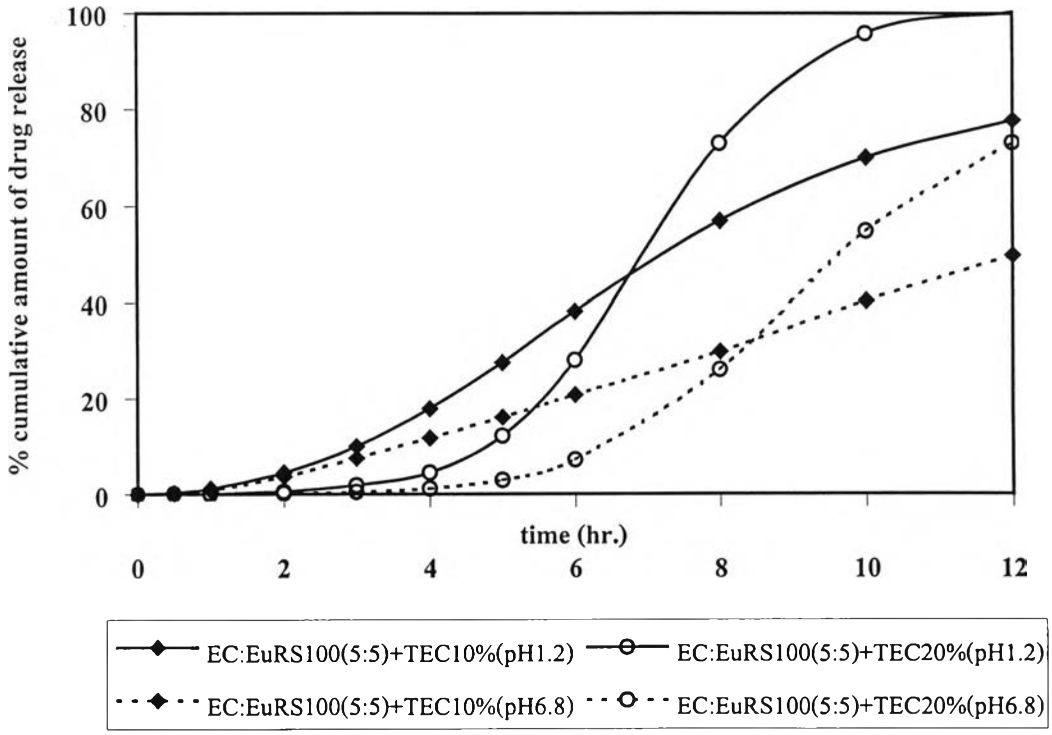


Figure 97 Release profiles of coated pellets of formulations A15 and A16 in acid buffer pH 1.2 and phosphate buffer pH 6.8

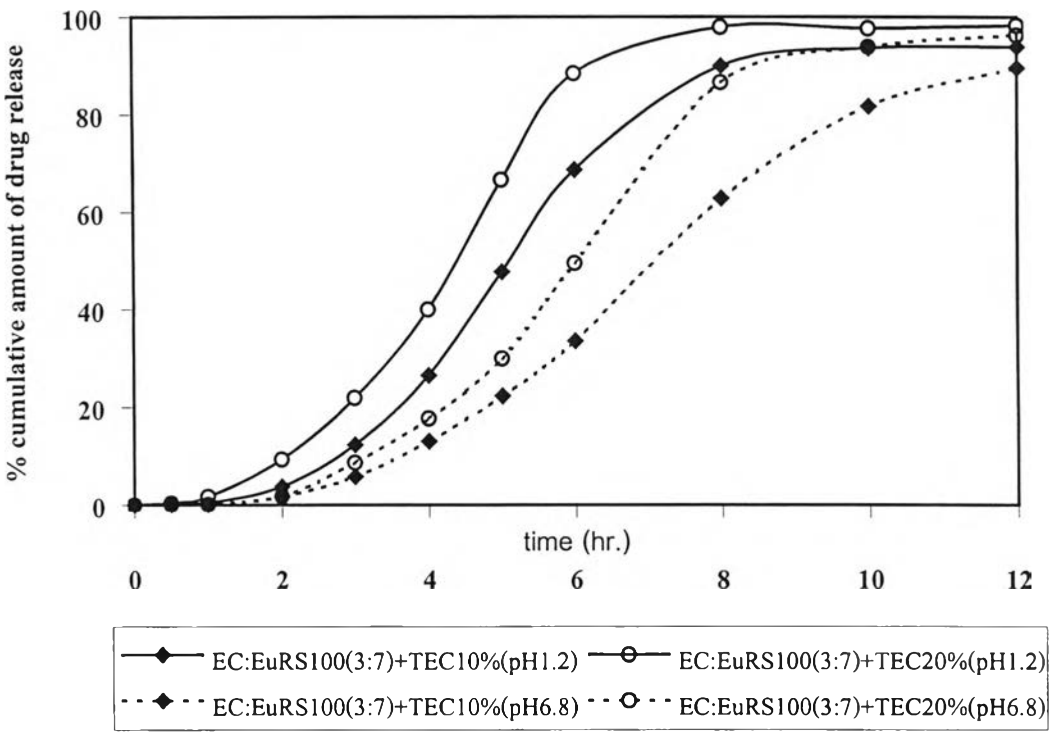


Figure 98 Release profiles of coated pellets of formulations A17 and A18 in acid buffer pH 1.2 and phosphate buffer pH 6.8

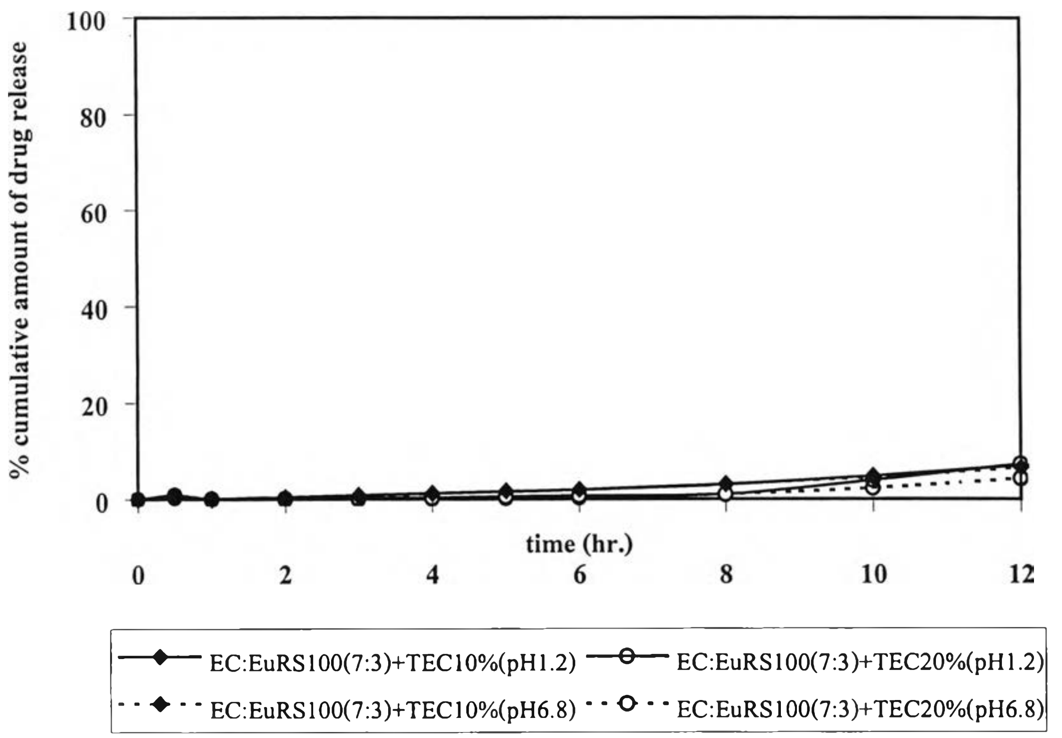


Figure 99 Release profiles of coated pellets of formulations A19 and A20 in acid buffer pH 1.2 and phosphate buffer pH 6.8

from acid buffer pH 1.2 whereas the drug release characteristics of formulation A11 and A12 obtained from acid buffer pH 1.2 appeared to be slightly slower than those from phosphate buffer pH 6.8. However, there was no marked difference of each formulation in acid buffer and phosphate buffer. Thus drug release characteristics of formulations A1, A2, A11 and A12 were independent of the dissolution medium.

Figures 92 and 93 illustrate the effect of dissolution medium on drug release profiles from the pellets coated with Eudragit®RS100 plasticized with dibutyl phthalate and triethyl citrate (formulations A3, A4, A13, A14). Drug release in acid buffer pH 1.2 was clearly faster than drug release in phosphate buffer pH 6.8. Moreover, the release profiles were observed to be parallel, indicating similar drug release pattern.

The different release profiles between two media of the formulations with blended polymer are exhibited in Figures 94-99 which were obviously different between release profiles in acid buffer and those in phosphate buffer except the formulations A9, A10, A19 and A20. This study, therefore, indicated that the coated pellets displayed more pH-dependent drug release characteristics when high proportion of Eudragit®RS100 was incorporated in the formulations.

The drug release characteristics of the coated pellets employing the aqueous polymeric dispersion are shown in Figures 100-107. Drug release from formulation B1 containing Surelease® with 10% level of triethyl citrate displayed a slightly higher drug release in phosphate buffer than in acid buffer. But comparison of drug release in formulation B2 with higher level of triethyl citrate indicated identical drug release profiles between two media (Figure 100). The release profiles of propranolol hydrochloride from Surelease® coated pellets with triacetin as plasticizer were obviously faster in phosphate buffer than in acid buffer (Figure 101).

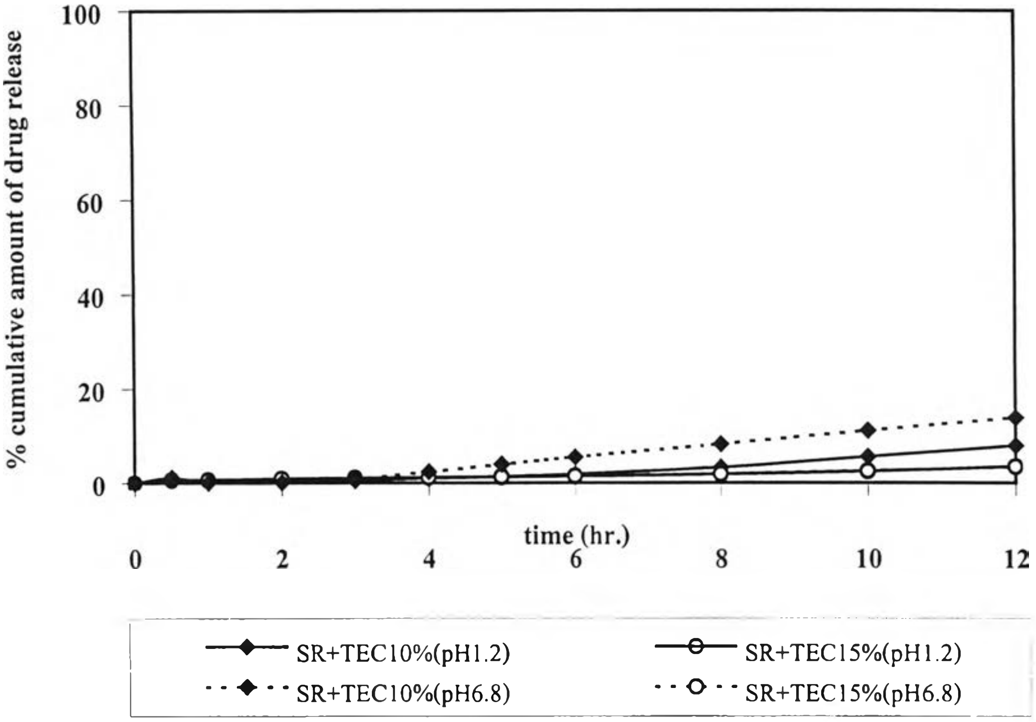


Figure 100 Release profiles of coated pellets of formulations B1 and B2 in acid buffer pH 1.2 and phosphate buffer pH 6.8

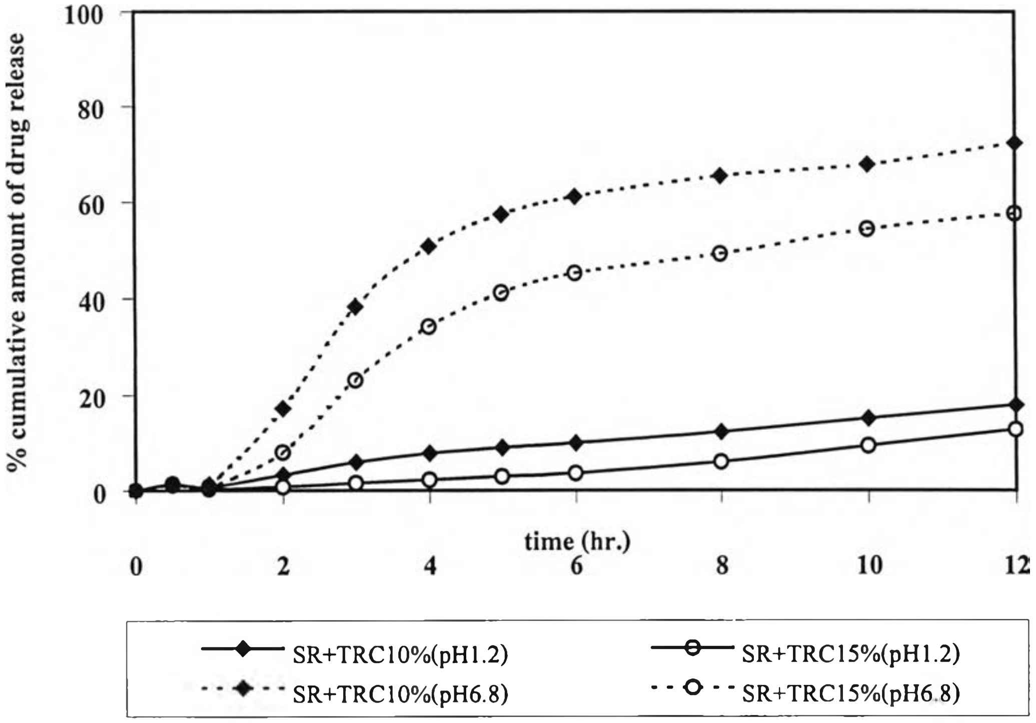


Figure 101 Release profiles of coated pellets of formulations B11 and B12 in acid buffer pH 1.2 and phosphate buffer pH 6.8

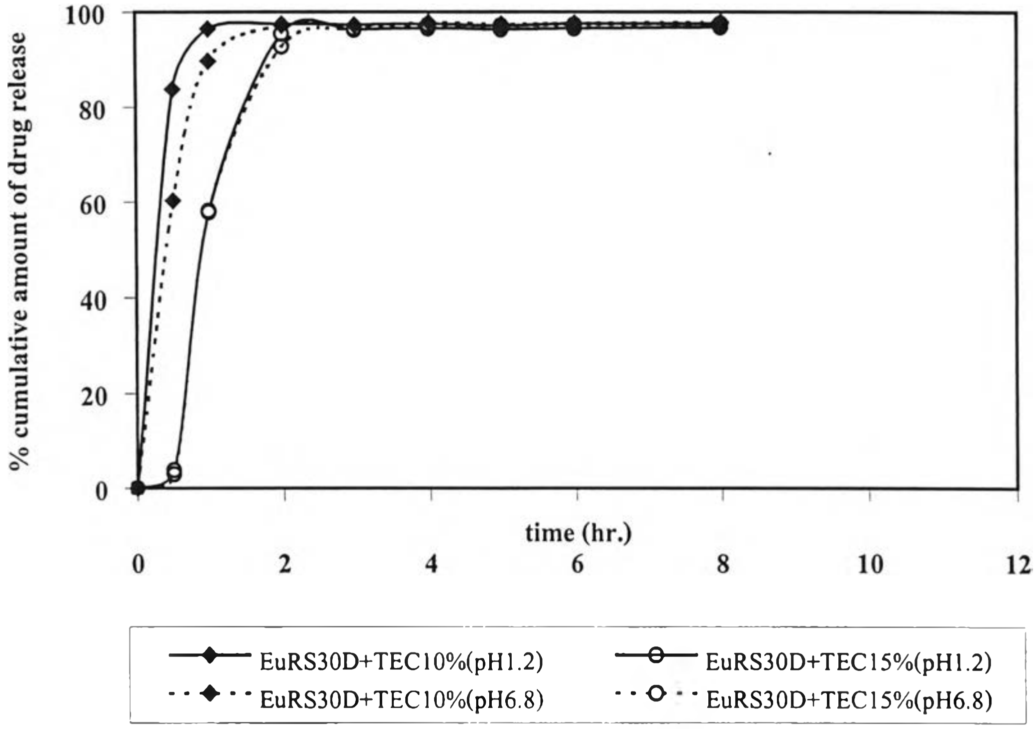


Figure 102 Release profiles of coated pellets of formulations B3 and B4 in acid buffer pH 1.2 and phosphate buffer pH 6.8

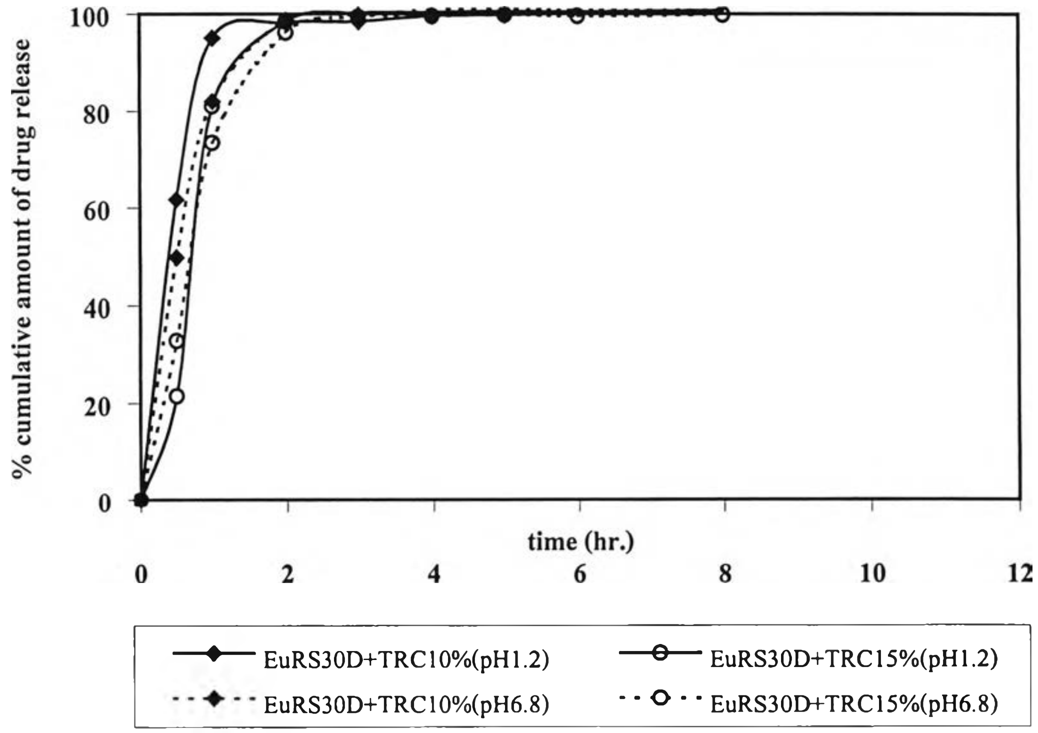


Figure 103 Release profiles of coated pellets of formulations B13 and B14 in acid buffer pH 1.2 and phosphate buffer pH 6.8

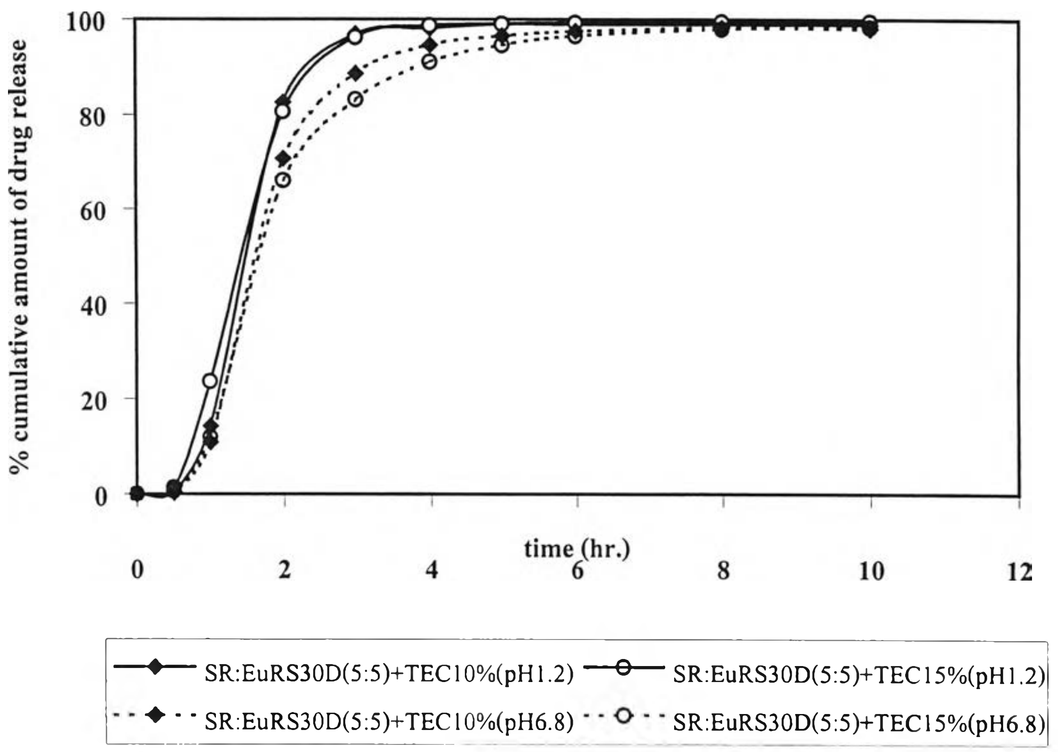


Figure 104 Release profiles of coated pellets of formulations B5 and B6 in acid buffer pH 1.2 and phosphate buffer pH 6.8

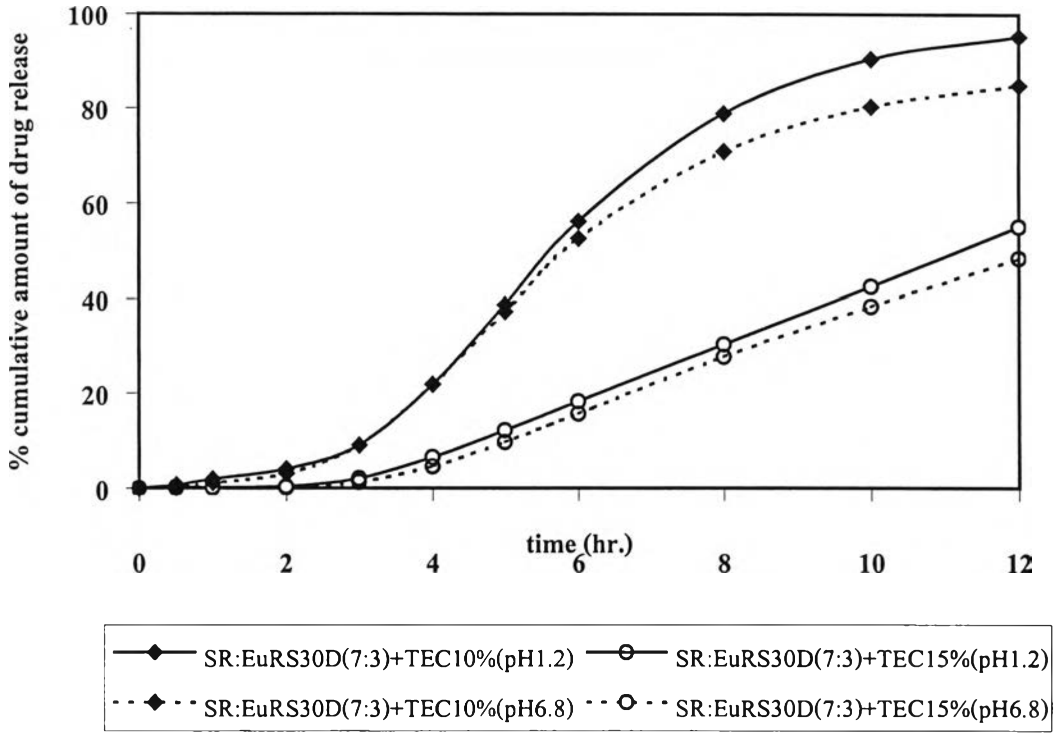


Figure 105 Release profiles of coated pellets of formulations B9 and B10 in acid buffer pH 1.2 and phosphate buffer pH 6.8

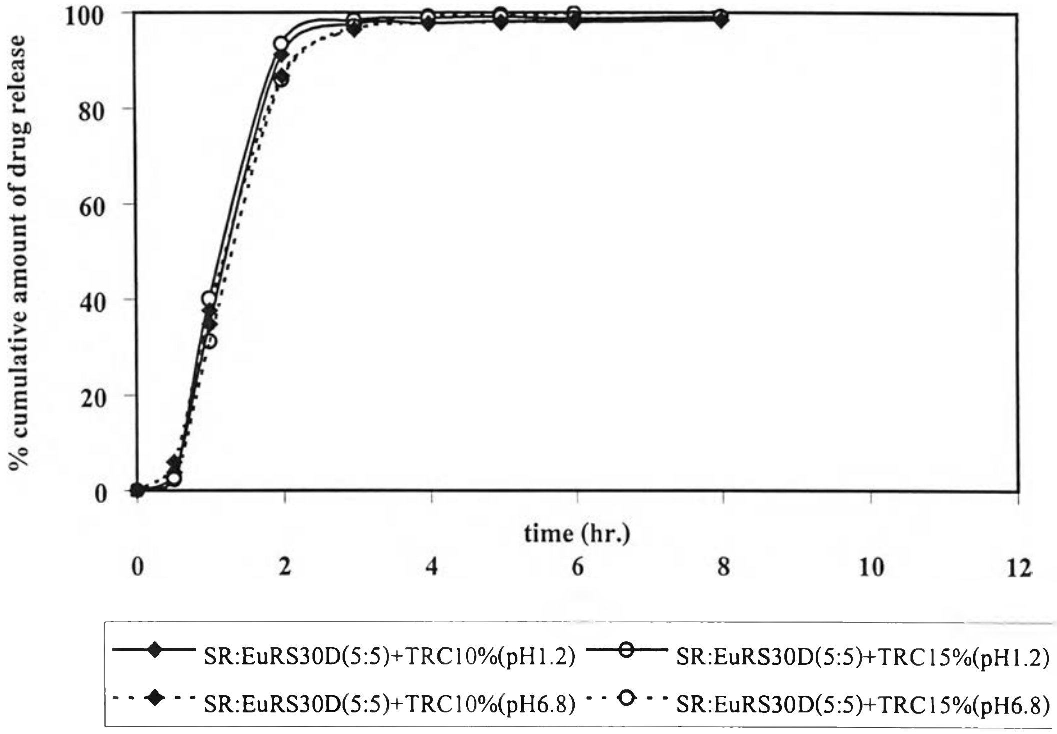


Figure 106 Release profiles of coated pellets of formulations B15 and B16 in acid buffer pH 1.2 and phosphate buffer pH 6.8

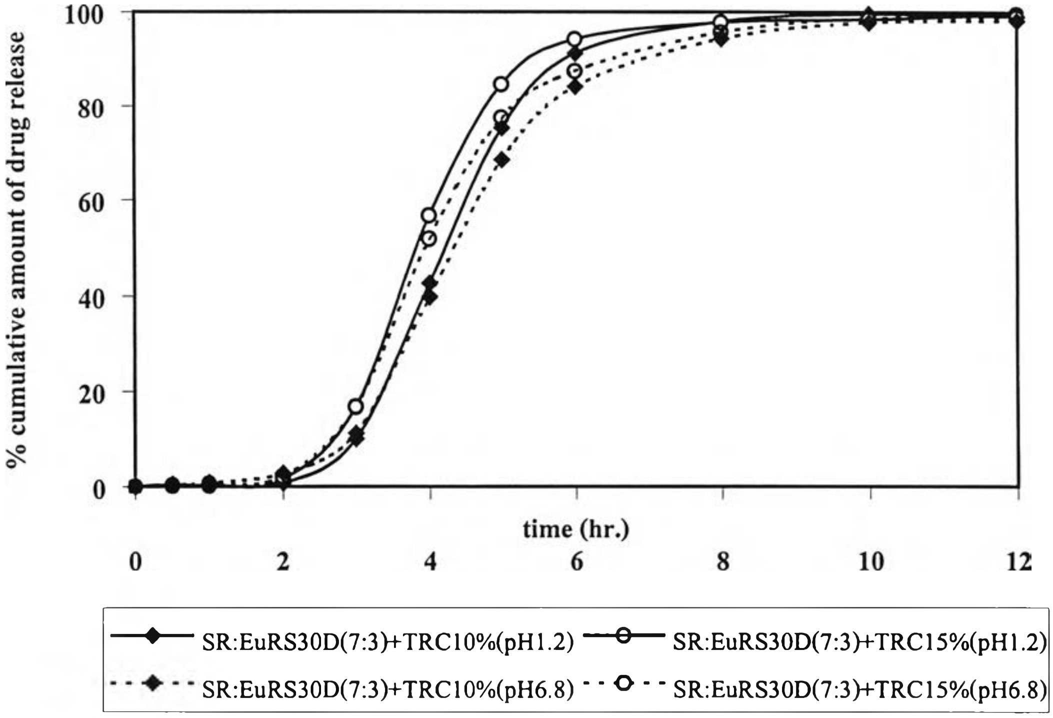


Figure 107 Release profiles of coated pellets of formulations B19 and B20 in acid buffer pH 1.2 and phosphate buffer pH 6.8

For the pellets coated with Eudragit®RS30D, the release profiles in phosphate buffer were slightly slower than those from acid buffer (Figures 102-103). The corresponding trend was also observed in the coated pellets with blended polymers (Figures 104-107).

The results of pellets coated with ethylcellulose and Surelease® plasticized with 15% triethyl citrate (Figures 90, 91 and 100) were consistent with a previous study by Iyer et al. (1990). They had concluded that drug release profiles of pellets coated with ethylcellulose using dibutyl sebacate as plasticizer and Surelease® appeared to be pH-independent. However, the result of pellets coated with Surelease® using triacetin as plasticizer did not agree with the previous research. This observation of a higher release profile in phosphate buffer could probably be explained by the mechanism of release. Shah et al. (1994) had summarized the drug release mechanism when higher coating level of Surelease® was operated. At higher coating level, drug release was controlled by partition of the drug through the membrane. Hence, the release rate depended on the polymer/dissolution medium partition coefficient. The partition mechanism favored the preferential transportation molecules that were neutral in character. As a result, molecules that were in solution and un-ionized partition in, diffuse through, and partition out of the membrane at a faster rate than highly ionized species. The degree of ionization depended on the pH of the dissolution medium and the pKa of the drug molecules (Iyer et al., 1990). Since propranolol HCl is a weak base, the unionized fraction of propranolol HCl is increased with increasing pH of the vehicle (Coutel-Egros et al, 1992). The increasing of unionized fraction of propranolol HCl resulted in the higher drug release in phosphate buffer than in acid buffer.

The pellets coated with Surelease® plasticized by 10% triethyl citrate displayed slightly faster release in phosphate buffer than in acid buffer while the drug releases in both media of pellets coated with Surelease® plasticized by 15% triethyl citrate were identical. The drug releases of pellets coated with Surelease® plasticized by

10% and 15% triacetin in phosphate buffer were obviously higher than that in acid buffer. The data in this experiment supported the impact on release rate of higher level of plasticizers. When the higher amount of plasticizer was used, no difference of drug release between both media was observed in the formulation of Surelease® with triethyl citrate whereas the difference of drug release between two media with lesser extent was found in the formulation of Surelease® with triacetin.

Furthermore, the release profiles of Surelease® coated pellets with triacetin in phosphate buffer exhibited a relatively constant slow release after an initial fast release (Figure 101). The fast release at the first stage may be caused by the high level of pores after leaching out of triacetin and the later slow release was due to the resistance of drug through the film of well-coated pellets. However, the results suggested that the kinetics of the Surelease® coated pellets may be quite different when coating film contained a different plasticizer. Hence, it could not clearly explain mechanisms why greater difference of drug release between two media in Surelease® coated pellets with triacetin was found.

The increased drug release characterictics of pellets coated with Eudragit®RS type with an increase in dissolution medium acidity could be explained by the solubility property of propranolol HCl. The release profiles of Eudragit®RS type followed the trend observed for the solubility data which propranolol HCl could be soluble 199.908 mg/ml in dissolution fluid pH 1.2 and 6.624 mg/ml in dissolution fluid pH 7.5 at 37 °C (Rekhi et al., 1989). Govender et al. (1997) stated that dosage forms with Eudragit®RS30D exhibiting pH-independent permeability property might give rise to pH-dependent permeablility due to the enhanced solubility of salbutamol which was often affected by the pH. Chang and Hsiao (1989) also reported pH-dependent drug-release characteristics from theophylline pellets coated with Eudragit®RS pseudolatex, which possesses pH-independent permeability properties. Additionally, the pH-dependent permeability of Eudragit®RS100 was corresponded with the results of Coowanitwong (1997). Drug release characteristics of propranolol HCl in acid buffer also were faster than those in phosphate buffer.

Since the Eudragit®RS type displays pH-dependent permeability properties, these properties have impacted on the coated pellet with the blended polymers. The polymer blends in organic system showed the drug release profiles in phosphate buffer which slower than those in acid buffer with the exception of ethylcellulose: Eudragit®RS100 in the ratio of 7:3 which showed no difference of drug release profiles between in acid buffer and in phosphate buffer. It may be due to the outstanding effect of ethylcellulose in organic system on the blended film in this ratio. Therefore, drug release profiles of two media were not different. The mixtures of films in aqueous dispersion system illustrated similar tendency that faster drug release profiles in acid buffer than in phosphate buffer were found. It could be explained by the influence of Eudragit®RS30D as described before. Additionally, lower quantity of Surelease® in the mixed films could not perform the same mechanism as the formulation with pure Surelease®.

3.4.4 Effect of plasticizer amount on the release profile

Figures 90, 92 and 94-96 also depict the effect of plasticizer amount on the dissolution profiles of formulations using dibutyl phthalate as plasticizer. There was a tendency that higher level of plasticizer causing lower permeability of drug. However, at first period of the drug release between formulations A3 and A4 displays faster release when higher level of dibutyl phthalate was employed (Figure 92). Considering the mechanical properties, an increase in the ductility and toughness of films corresponded with a decrease in the strength and stiffness of films was due to increasing quantity of plasticizer.

Plasticizers are added to induce and enhance the coalescence of the colloidal polymer particles into a homogeneous film by reducing the glass transition and minimum film formation temperature (Bodmeier and Paeratakul, 1994a). The level of the plasticizer has an accelerating effect on the speed of film formation. Hence, the drug release profiles were reduced by increasing plasticizer amount. These findings agreed with Schmidt and Niemann (1993) that an increase of dibutyl phthalate from 10% to 20% led to an excellent enteric coating of Eudragit®L30D and the maximum drug release was reduced from 40 to 4%.

However, the result of pellets coated with Eudragit®RS100 with higher level of dibutyl phthalate disagreed with the previous study. The coated pellet with Eudragit®RS100 containing 20% dibutyl phthalate showed faster release in the first period whereas the release profile of the final period in each buffer of this formulation showed slower drug release than the Eudragit®RS100 coated pellets with lower amount of dibutyl phthalate (Figure 92). Lippold, Sutter and Lippold (1989) explained that faster release of higher level of dibutyl sebacate result because of the increased polymer mobility with occurred during processing. Upon cooling, it was proposed that the polymer chains remained in this "metastable state", so release occurred more rapidly. However, Eudragit®RS100 with 20% dibutyl phthalate also illustrated tougher film than one with 10% dibutyl phthalate and this effect resulted from a greater degree of coalescence. Therefore, a reduction in the rate of final period was observed

There were various effects of higher level of triethyl citrate on the release profiles in formulations A11-A20 that were displayed in Figures 91, 93 and 97-99. Figures 91 and 99 illustrate effect of higher level of triethyl citrate resulted in slightly slower release rate. The trends observed for the effect of plasticizer amount were in agreement with results from Hutchings and Sakr (1994) for Aquacoat film prepared in which triethyl citrate, acetyl triethyl citrate, tributyl citrate or dimethyl sebacate were used as plasticizer. Higher levels of plasticizer caused a reduction in the rate of drug release. Whereas the level of triethyl citrate was increased, the formulation with higher proportion of Eudragit®RS100 more than 50% exhibited faster release rate (Figures 93, 98). In the formulation with ethylcellulose: Eudragit®RS100 in the ratio of 5:5, drug release profiles were characterized by a slow phase followed by a rapid phase when higher level of triethyl citrate was used (Figure 97). When considered the dry film properties of these formulations, an increasing amount of triethyl citrate led to decreased stress at break and Young's modulus. This impact was more outstanding with increasing the portion of Eudragit®RS100 (Figures 34, 38). Hence, the films with higher portion of Eudragit®RS100 exhibit less stiffness and soft characteristic.

Plasticizer amount changed the mechanical properties of free films significantly. In addition, triethyl citrate, the water soluble plasticizer was leached in dissolution medium from free films. An enhance drug release by using a more hydrophilic plasticizer could be explained by an increase in water permeability which was further increased by plasticizer leaching (Schultz et al., 1997). The weakening of the films with higher level of triethyl citrate upon exposure to aqueous media could be explained with the hydration or water uptake of the polymeric films and the leaching of the water soluble plasticizer, triethyl citrate. The percent of triethyl citrate remaining in the film based on the original triethyl citrate concentration decreased sharply with increasing triethyl citrate concentration (Bodmeier and Paeratakul, 1993). The results of the present study offer support for the belief that soft film which may obtain from higher level of plasticizer or higher portion of Eudragit®RS100 can cause rapid leaching of water soluble plasticizer.

The leaching of triethyl citrate at 20% level therefore presented by increasing permeability in the formulation with Eudragit®RS100 higher than 50% but the formulation with Eudragit®RS100 lower than 50% showed the different trend due to the mechanical strength of ethylcellulose film. For the formulation with 50% Eudragit® RS100 at 20% of triethyl citrate, the lower permeability at first period was shown due to the retardation of ethylcellulose and the higher permeability was followed due to the hydration or swelling of ethylcellulose in the polymer blends when it was contacted with the dissolution medium for a duration of time. For that reason, softer film occurred and led to leaching of triethyl citrate at the end of release profile. Leaching of triethyl citrate from the film might be ranked in the following order : Eudragit®RS100 ≈ the polymer blends in the ratio of 3:7 > the polymer blends in the ratio of 5:5 > the polymer blends in the ratio of 7:3 ≈ ethylcellulose. The leaching from polymers was affected by the softness of polymer. The order of the softness of the films, as measured by stress at break and Young's modulus correlated well with the order of leaching (Figures 34, 38).

The results with higher level of plasticizer between triethyl citrate and triacetin were illustrated in Figures 100-107. The slower release profiles were observed when using higher level of both triethyl citrate and triacetin. The slightly slower release rates when employing higher level of plasticizer are also observed in Figures 102-104. The four drug release profiles in Figure 106 are almost identical, they are all nearly superimposable and similar. However, release profiles of formulation B20 in Figure 107 depict faster release than release profiles of formulation B19.

The obtained results indicated that the higher level of triethyl citrate and triacetin from 10% to 15% led to lower permeabilities of films in aqueous dispersion system. Triethyl citrate had more pronounced effect than triacetin to retard drug release. As in previous study, at low plasticizer concentrations, the latex particles were insufficiently plasticized resulted in faster release (Bodmeier and Paeratakul, 1990a). The 10 – 30 % plasticizer range of water soluble plasticizer was enough for good film formation. The leaching out of water soluble plasticizer occurred evidently at higher plasticizer levels more than 30%. On the other hand, the slightly higher permeability of blended film in formulation B20 with higher level of triacetin was probably due to the leaching of the triacetin with higher amount than triethyl citrate (Figure 107). Because triacetin has higher solubility than triethyl citrate, hence, triacetin can leach out at higher quantity than triethyl citrate at the same concentration.

The leaching out of triethyl citrate in films prepared from aqueous dispersion system occurred with less quantity than the leaching out of triethyl citrate in films prepared from organic system. In agreement with Goodhart et al. (1984), increasing amounts of triethyl citrate in Aquacoat® films resulted in a decreased drug release in the plasticizer range investigated. In contrast, the solute diffusivity in ethylcellulose films cast from solution increased with increasing amounts of triethyl citrate because of leaching of the plasticizer.

3.4.5 Effect of plasticizer type on the release profile

The effectiveness of equivalent amount of dibutyl phthalate and triethyl citrate as plasticizers in retarding drug release of pellets coated with various formulations from organic system was compared. As shown in Figures 108-117, dibutyl phthalate was capable of retarding drug release than an equivalent quantity of triethyl citrate. These results were no obvious difference between dibutyl phthalate and triethyl citrate in the formulations with ethylcellulose and ethylcellulose: Eudragit®RS100 at the ratio of 7:3 in both media (Figures 108, 109, 116 and 117). However, the other formulations with dibutyl phthalate as plasticizer had the capacity to decrease film permeability to a greater extent during dissolution testing.

The mechanical properties of the single polymer and the blended polemers at 10% level of plasticizer showed that dibutyl phthalate-plasticized films with higher portion of ethylcellulose more than 30% produced hard and tough film. In comparison with triethyl citrate-plasticized films, it displayed hard and tough film with higher portion of Eudragit®RS100 (more than 50%). When higher quantity of plasticizer was used, triethyl citrate-plasticized films of all formulations gave softer and tougher

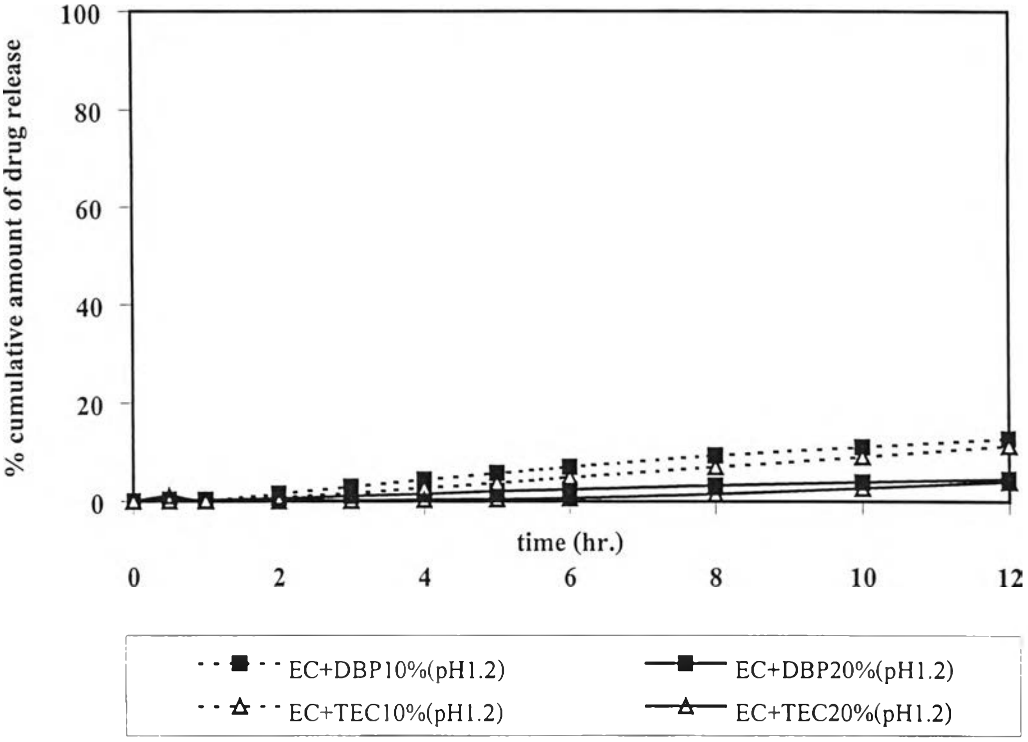


Figure 108 Release profiles of coated pellets of formulations A1, A2, A11, A12 in acid buffer

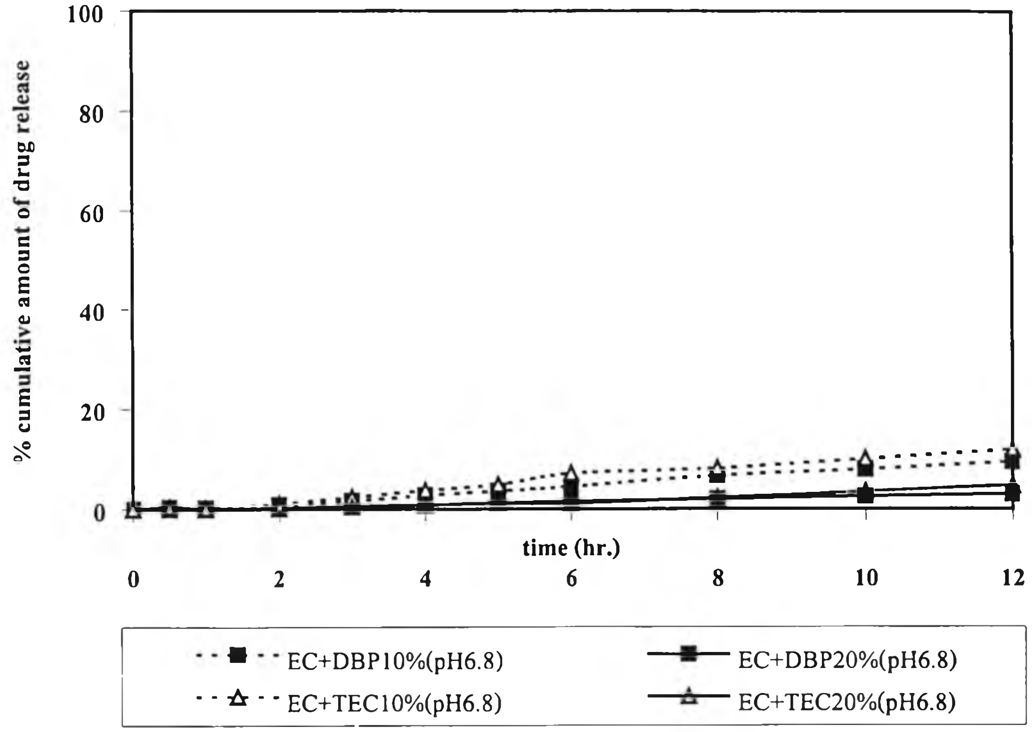


Figure 109 Release profiles of coated pellets of formulations A1, A2, A11, A12 in phosphate buffer

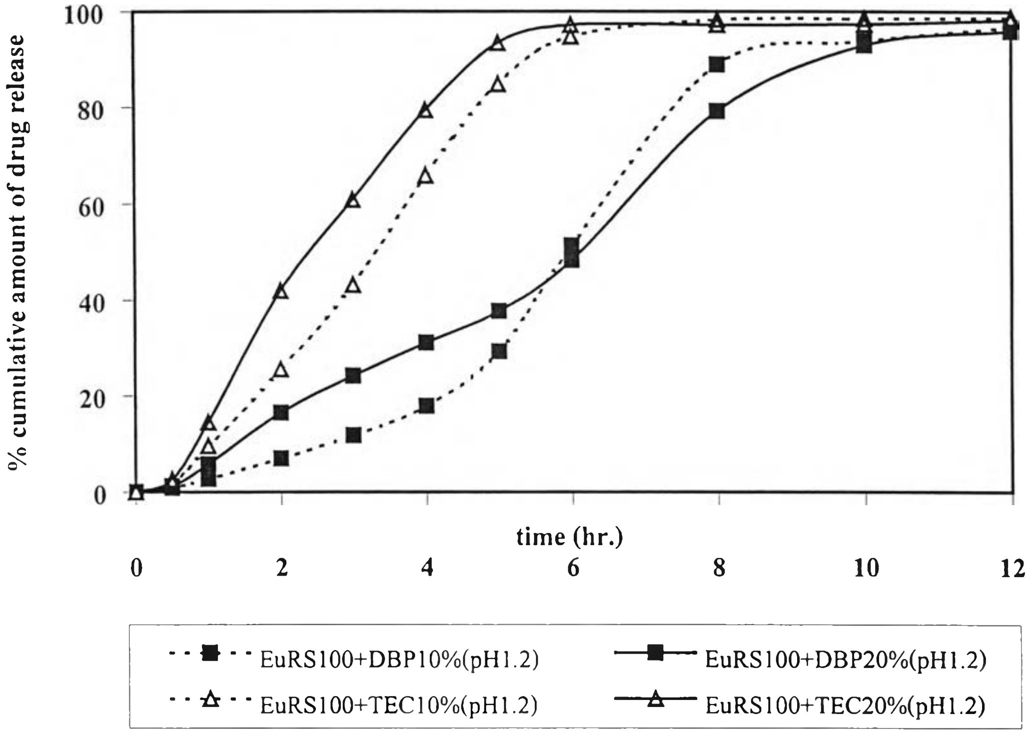


Figure 110 Release profiles of coated pellets of formulations A3, A4, A13, A14 in acid buffer

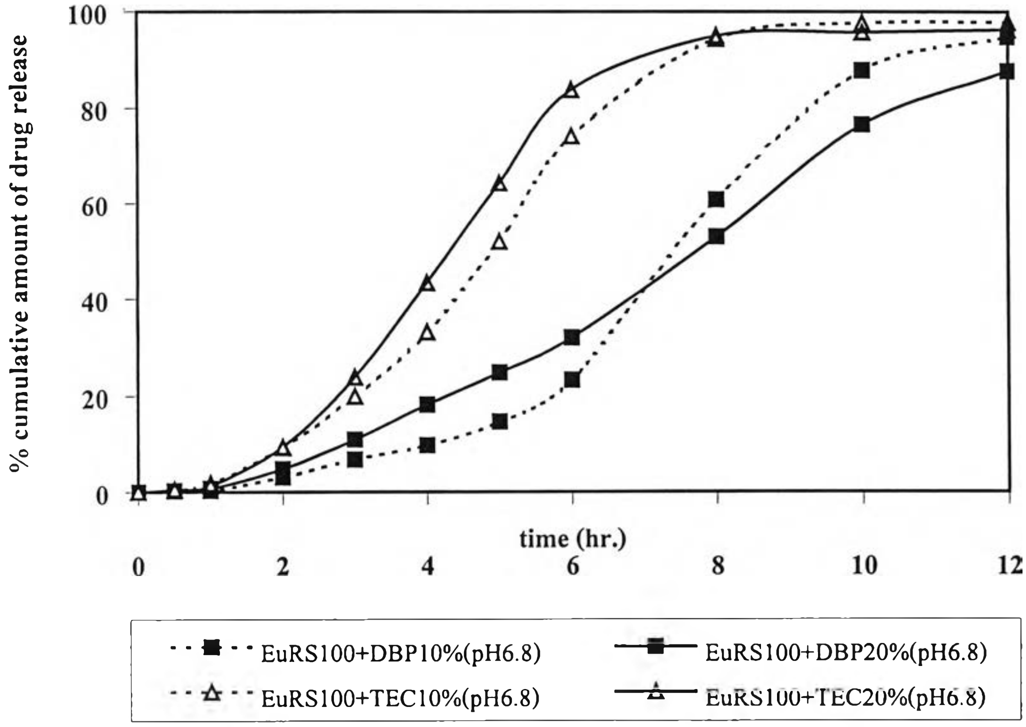


Figure 111 Release profiles of coated pellets of formulations A3, A4, A13, A14 in phosphate buffer

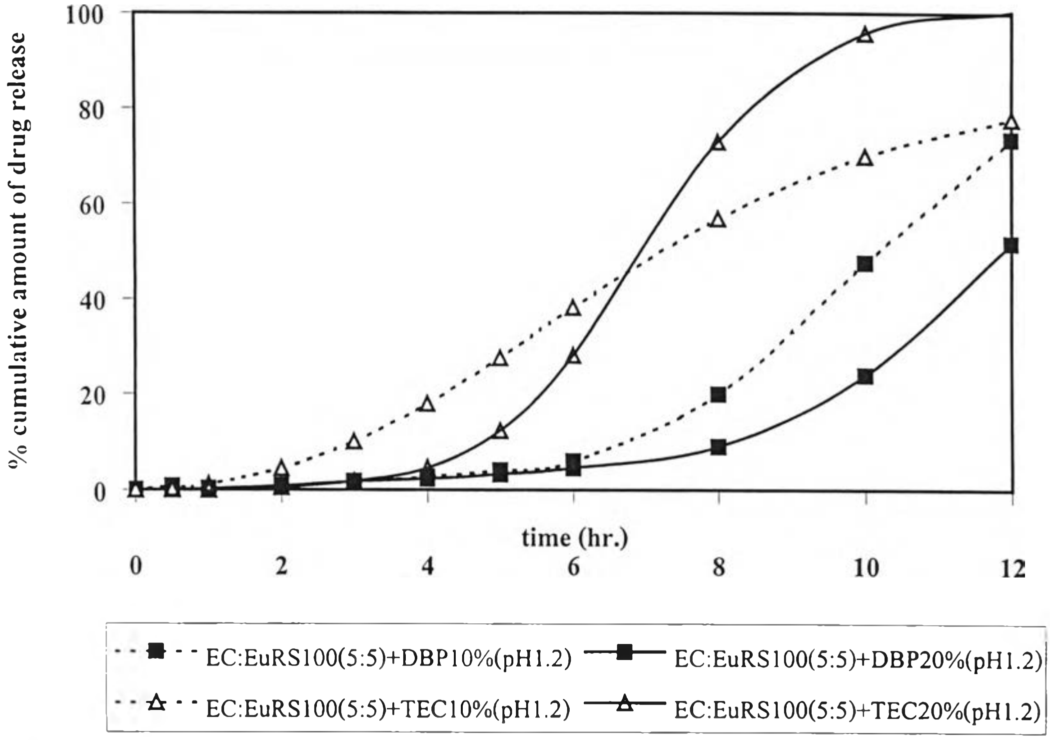


Figure 112 Release profiles of coated pellets of formulations A5, A6, A15, A16 in acid buffer

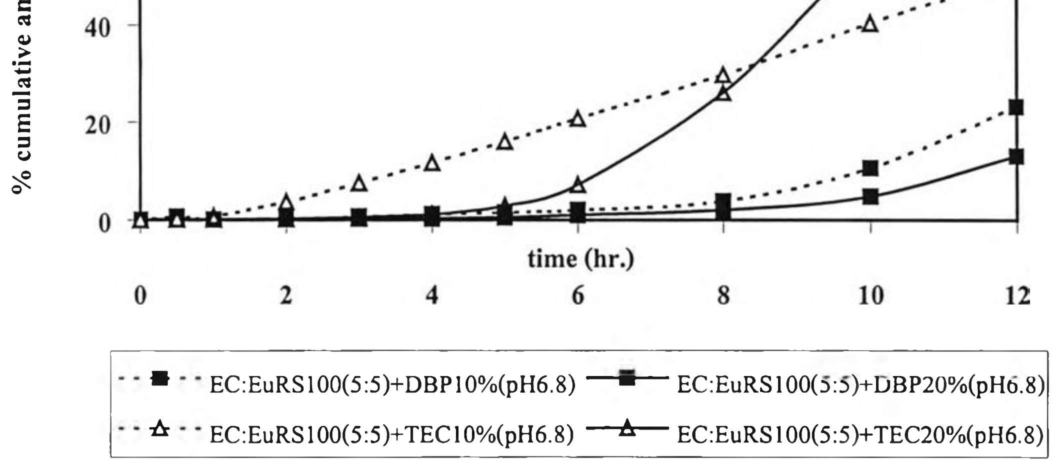


Figure 113 Release profiles of coated pellets of formulations A5, A6, A15, A16 in phosphate buffer

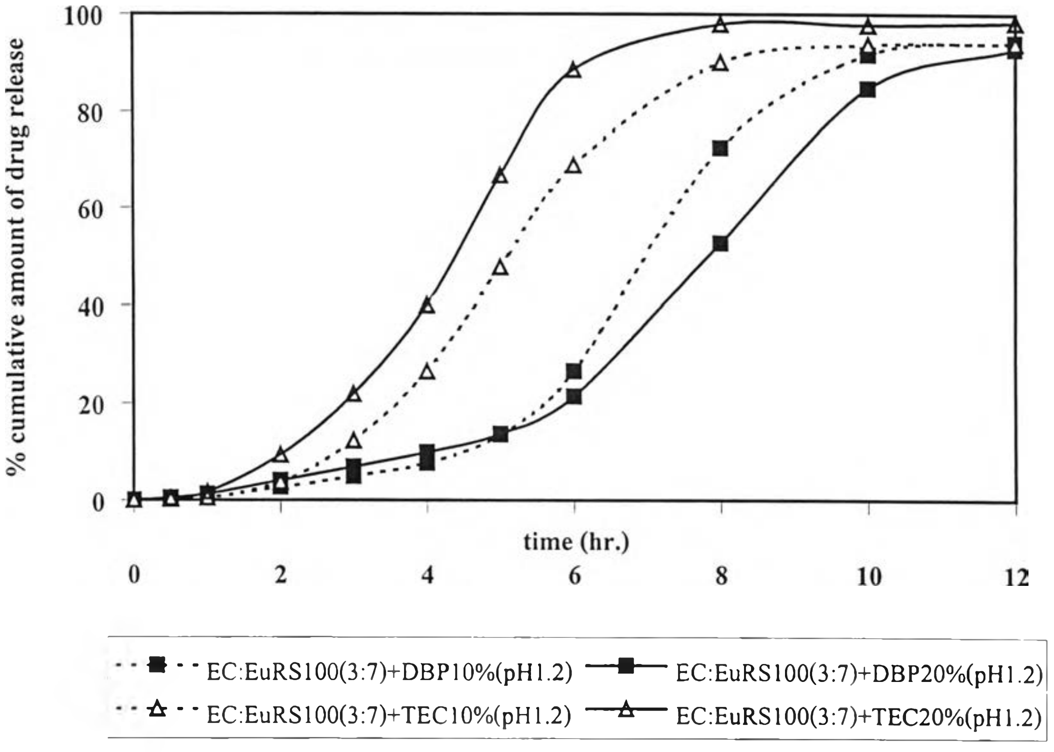


Figure 114 Release profiles of coated pellets of formulations A7, A8, A17, A18 in acid buffer

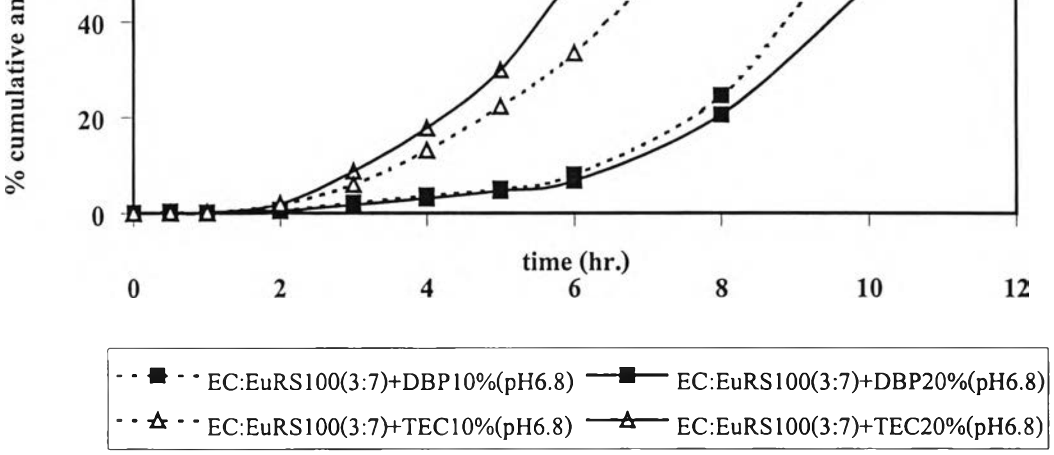


Figure 115 Release profiles of coated pellets of formulations A7, A8, A17, A18 in phosphate buffer

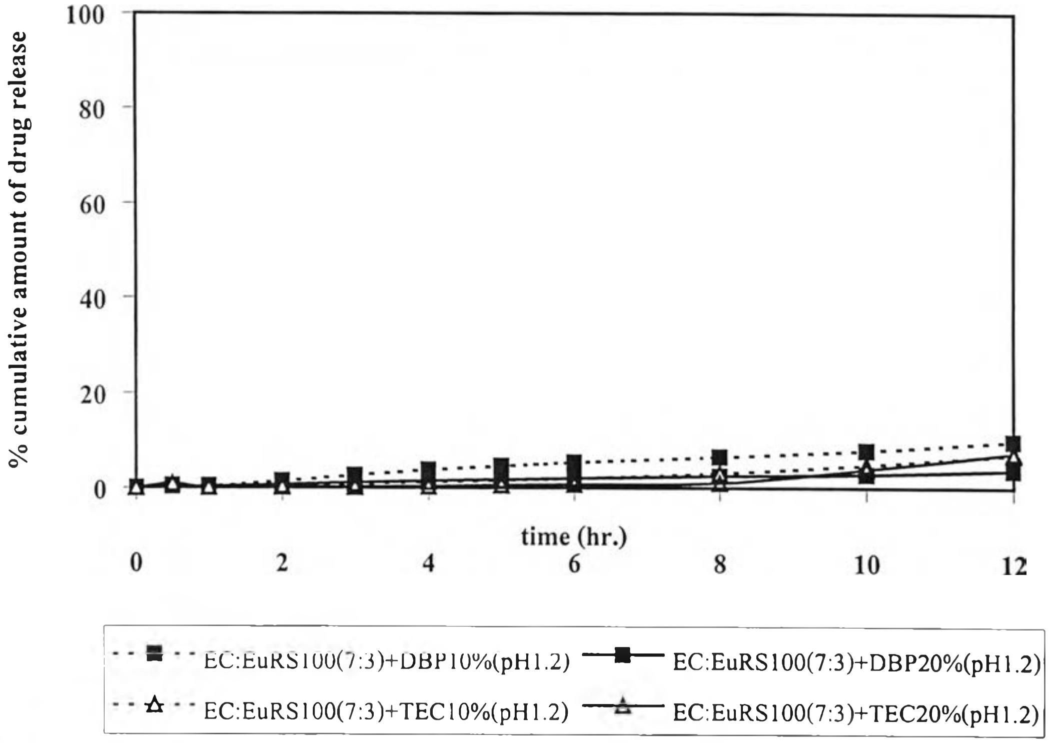


Figure 116 Release profiles of coated pellets of formulations A9, A10, A19, A20 in acid buffer

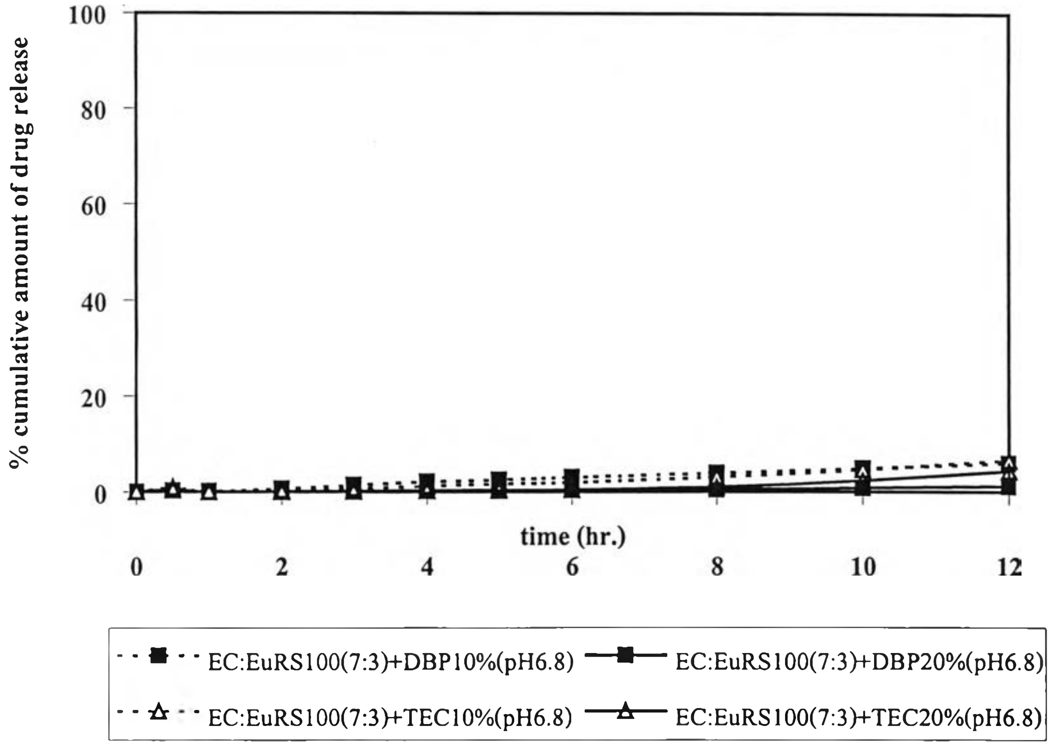


Figure 117 Release profiles of coated pellets of formulations A9, A10, A19, A20 in phosphate buffer

films than dibutyl phthalate-plasticized films. However, the dried film properties prepared by casting method were different from the wetted film properties in dissolution medium due to the leaching out of triethyl citrate.

In previous studies, films of Eudragit®L30D plasticized with dibutyl phthalate were less permeable than films containing the same amount of triethyl citrate (Schmidt and Niemann, 1992; Maul and Schmidt, 1995). They explained by the more hydrophobic properties of dibutyl phthalate remaining undissolved in the film whereas the more hydrophilic triethyl citrate was eluted from the coating. This present study was also supported by mechanical properties of wet and dry films (Bodmeier and Paeratakul, 1993, 1994a). Polymeric films of Eudragit®RS30D plasticized with water insoluble plasticizer, possessed some similarities in their mechanical properties in both dry and wet states. These results were due to the complete retention of the water insoluble plasticizer in the films. On the other hand, the puncture strength of wet films plasticized with water soluble plasticizer was reduced when compared to that of the dry films due to the leaching of water soluble plasticizer from the films during exposure to the aqueous medium.

The influence of two types of water soluble plasticizers (triethyl citrate and triacetin) on drug release characteristic is presented in Figures 118-125. From the result, it could be seen that coated pellets in formulation with Surelease® gave different effect of various types of water soluble plasticizer (Figures 118-119). The Surelease® coated pellets incorporated with triethyl citrate could retard drug release more than those with triacetin. The coated pellets with Surelease®: Eudragit®RS30D in the ratio of 7:3 displayed a slower release when these formulations contained triethyl citrate (Figures 124-125). Nevertheless, no marked difference was observed in the formulations with Eudragit®RS30D and with Surelease®: Eudragit®RS30D in the ratio of 5:5 (Figures 120-123). From the result of mechanical property testing, almost all of

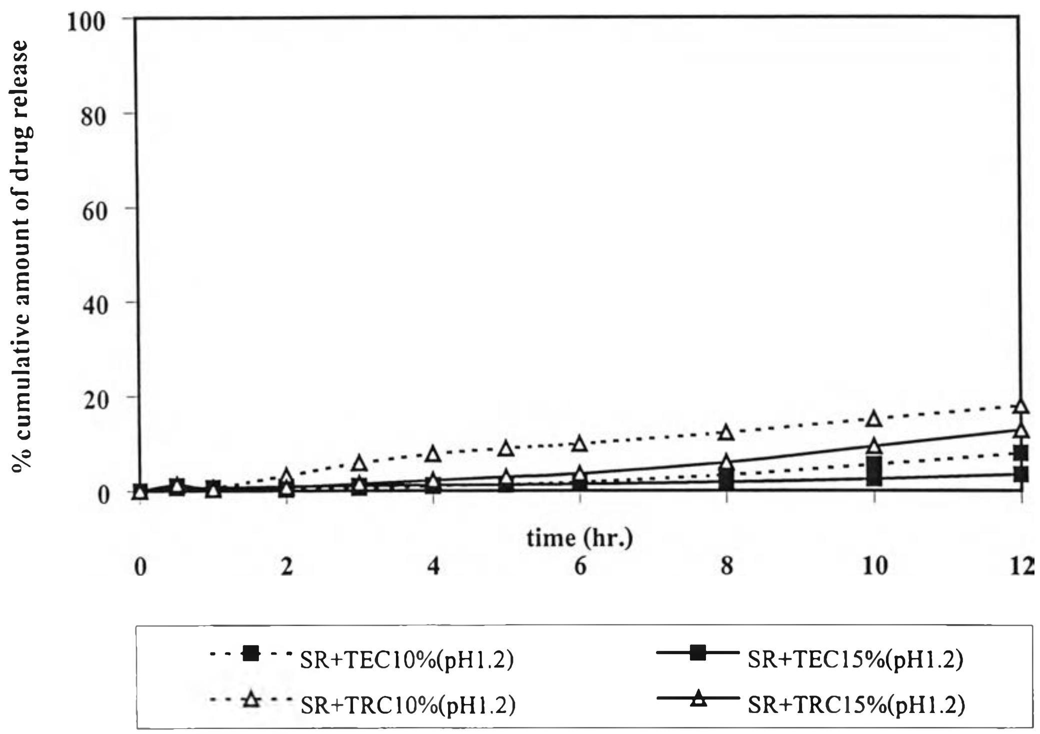


Figure 118 Release profiles of coated pellets of formulations B1, B2, B11, B12 in acid buffer

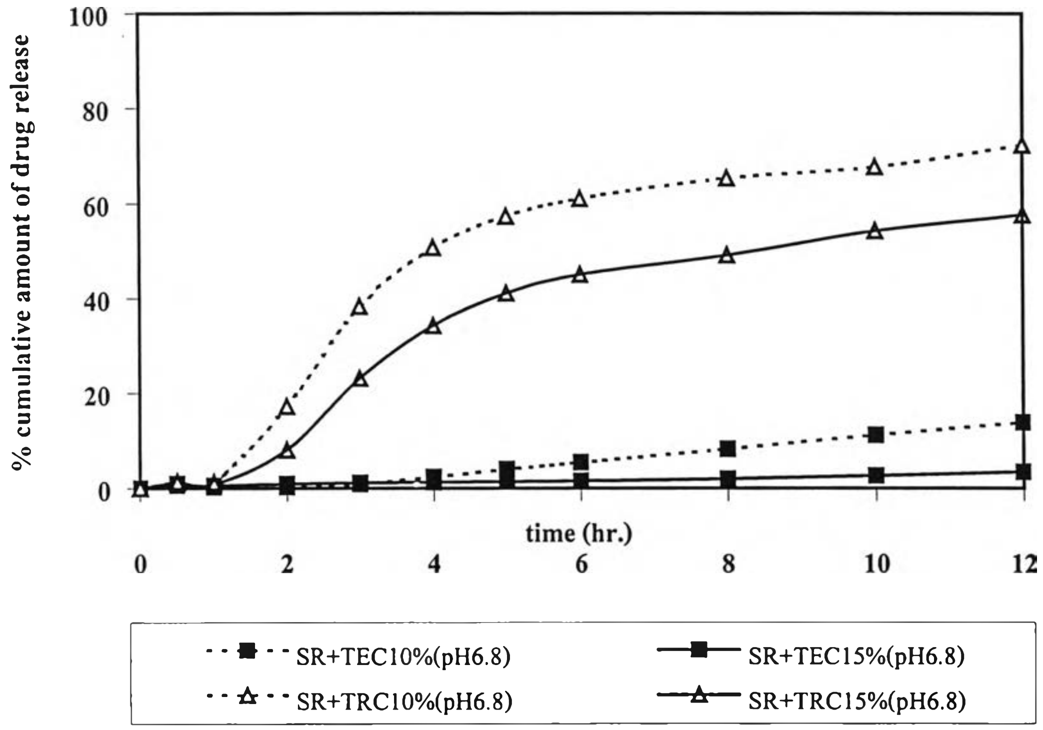


Figure 119 Release profiles of coated pellets of formulations B1, B2, B11, B12 in phosphate buffer

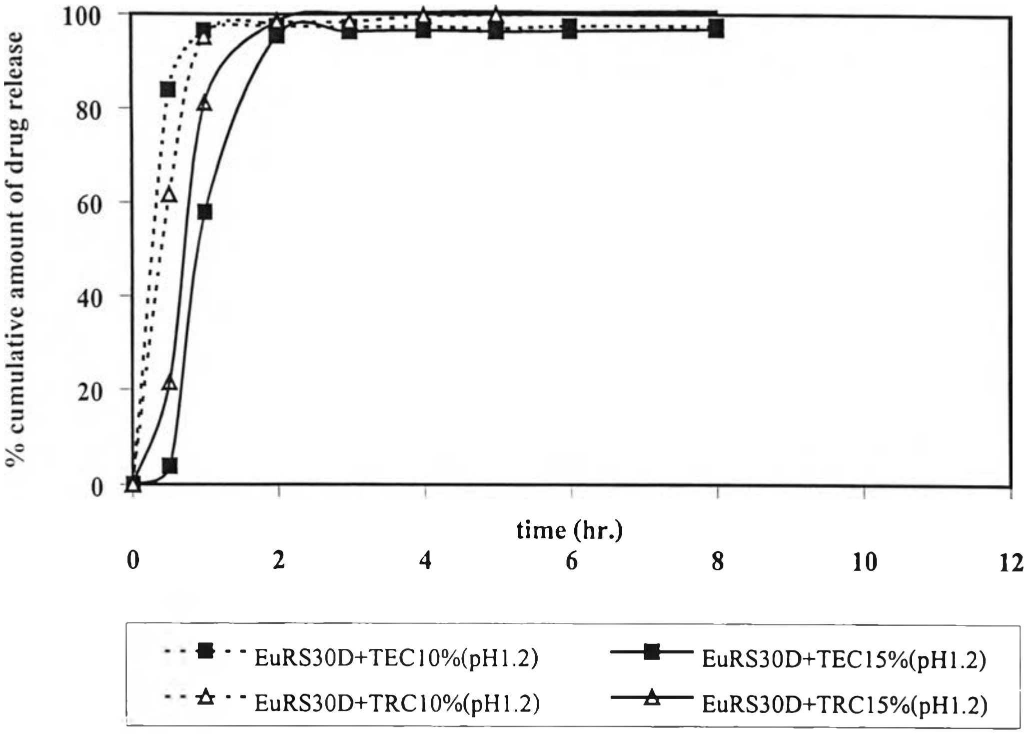


Figure 120 Release profiles of coated pellets of formulations B3, B4, B13, B14 in acid buffer

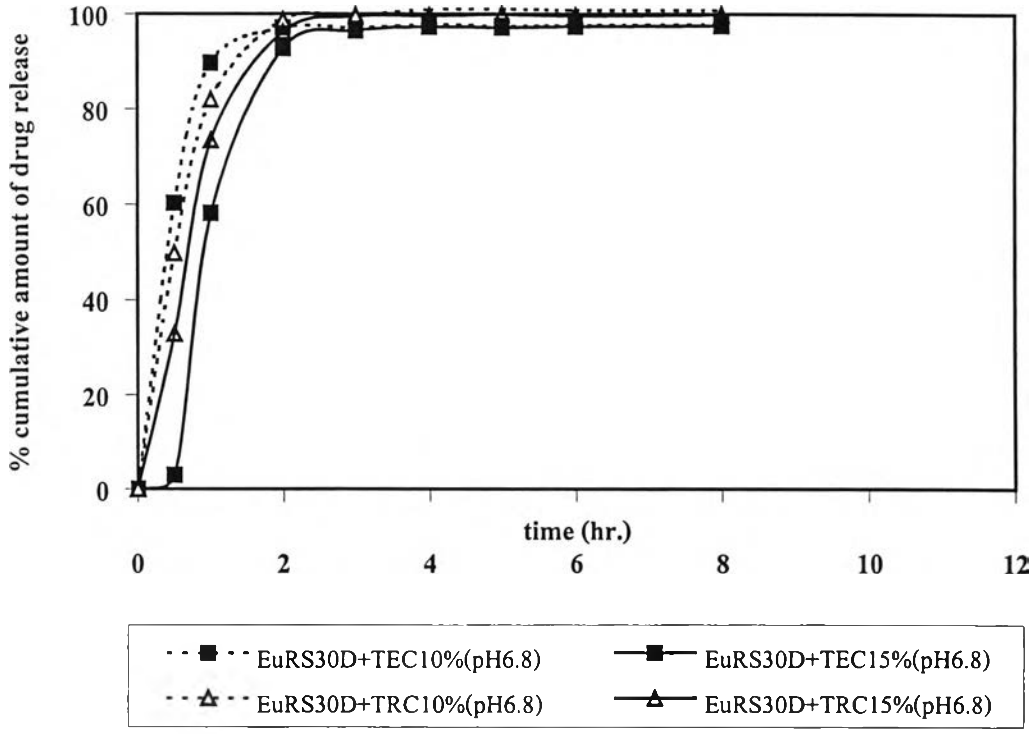


Figure 121 Release profiles of coated pellets of formulations B3, B4, B13, B14 in phosphate buffer

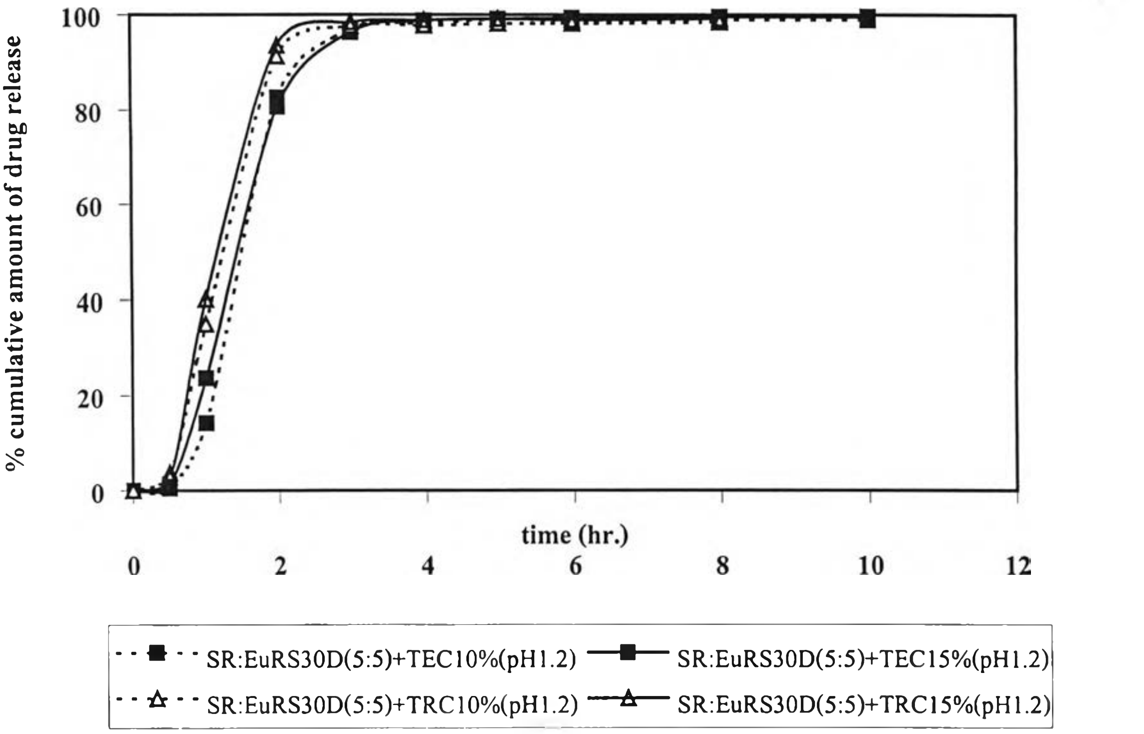


Figure 122 Release profiles of coated pellets of formulations B5, B6, B15, B16 in acid buffer

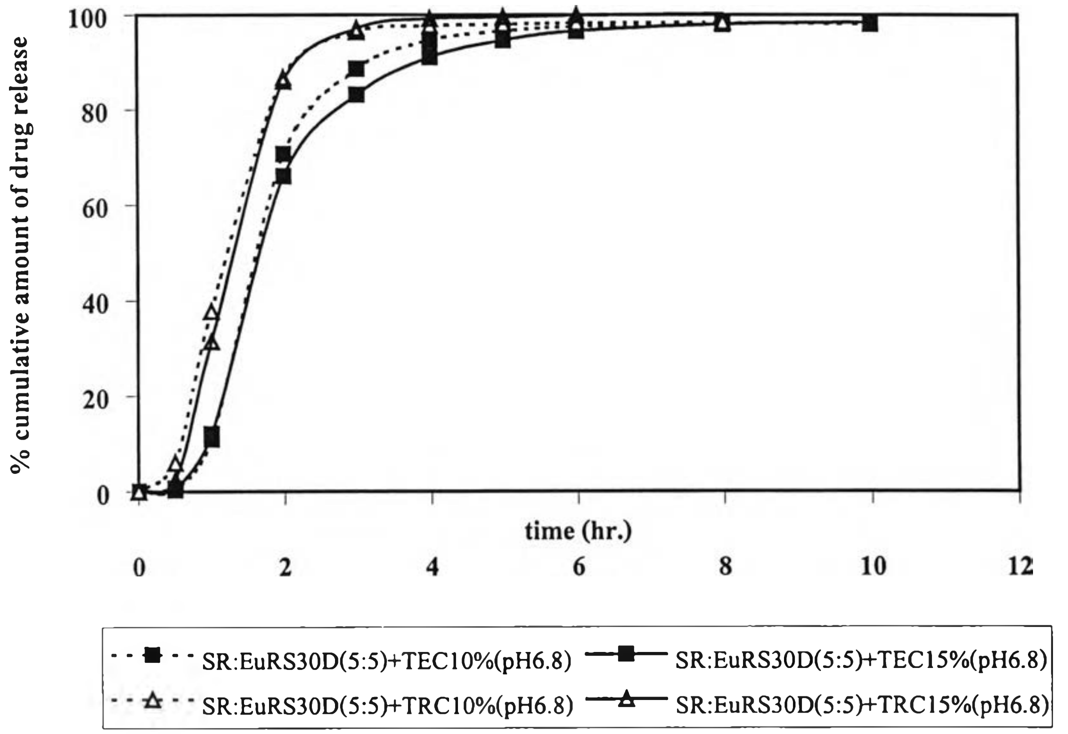


Figure 123 Release profiles of coated pellets of formulations B5, B6, B15, B16 in phosphate buffer

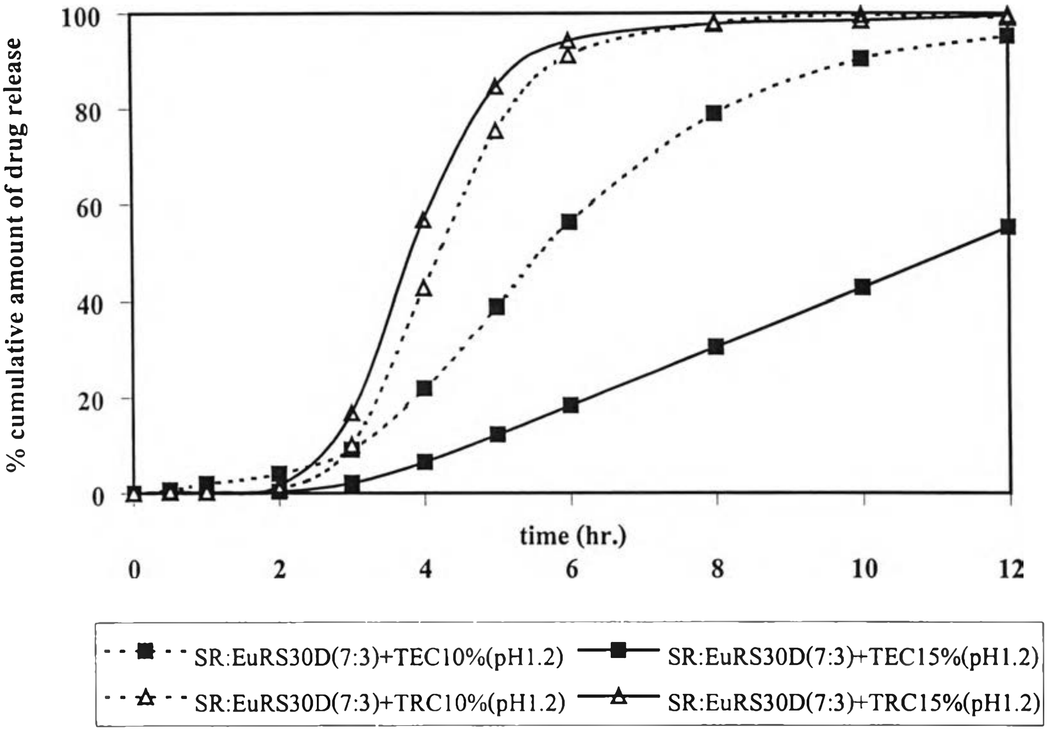


Figure 124 Release profiles of coated pellets of formulations B9, B10, B19, B20 in acid buffer

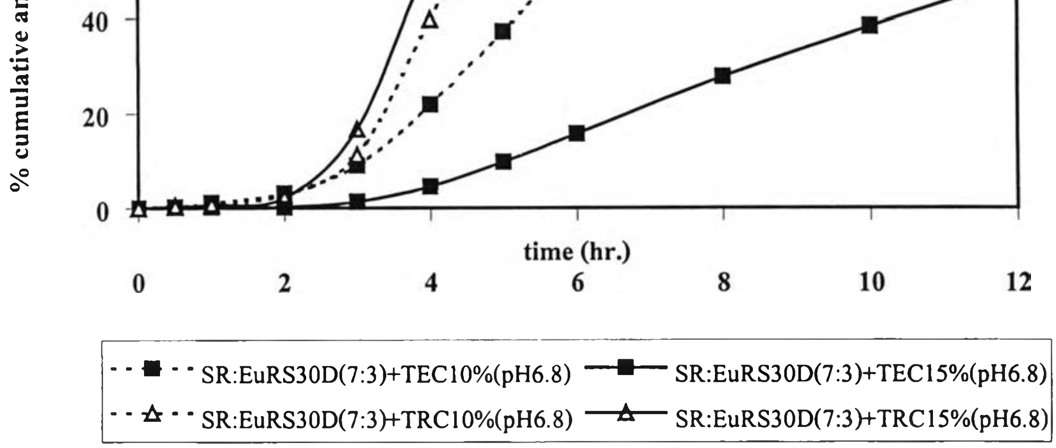


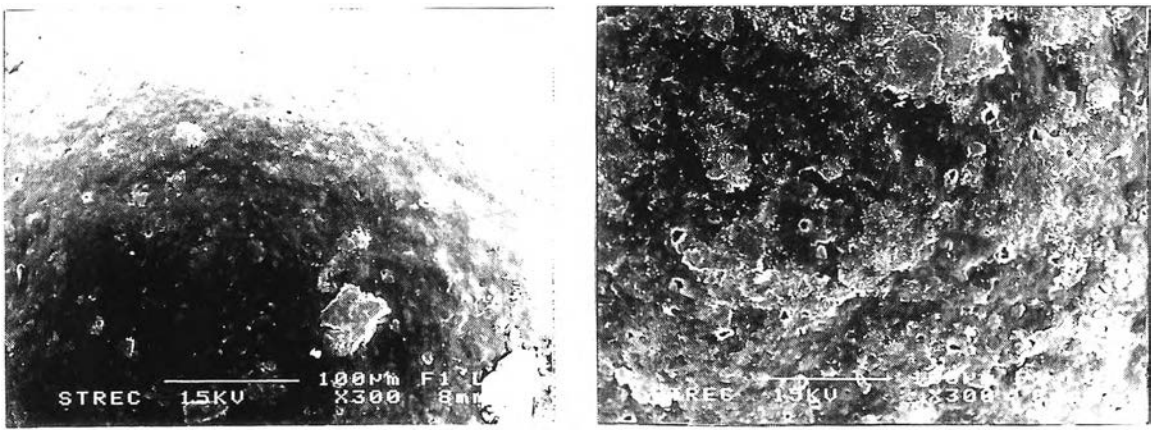
Figure 125 Release profiles of coated pellets of formulations B9, B10, B19, B20 in phosphate buffer

the polymer blends in aqueous dispersion system containing triethyl citrate were softer and tougher than the polymer blends containing triacetin.

As described previously, triethyl citrate had more efficient than triacetin due to extensive partitioning into the colloidal particles. Hence, triethyl citrate may enhance film coalescence better than triacetin resulted in slower drug release. Furthermore, Bodmeier and Paeratakul (1992) had described about the leaching of water soluble plasticizer between triethyl citrate and triacetin. Triacetin could leach faster from the Eudragit®L films than triethyl citrate because of higher solubility in the dissolution medium when compared to triethyl citrate (triacetin, 77.8 ± 0.5 mg/ml and triethyl citrate, 55.4 ± 0.0 mg/ml). The more leaching out of triacetin led to the formation of many pores during dissolution, which enhanced the access of the dissolution medium to the pellet cores. These results were confirmed by the photomicrographs of Surelease® and Eudragit®RS30D plasticized with 15% level of triethyl citrate contrasted with those plasticized with the same level of triacetin after dissolution in acid buffer (Figure 126).

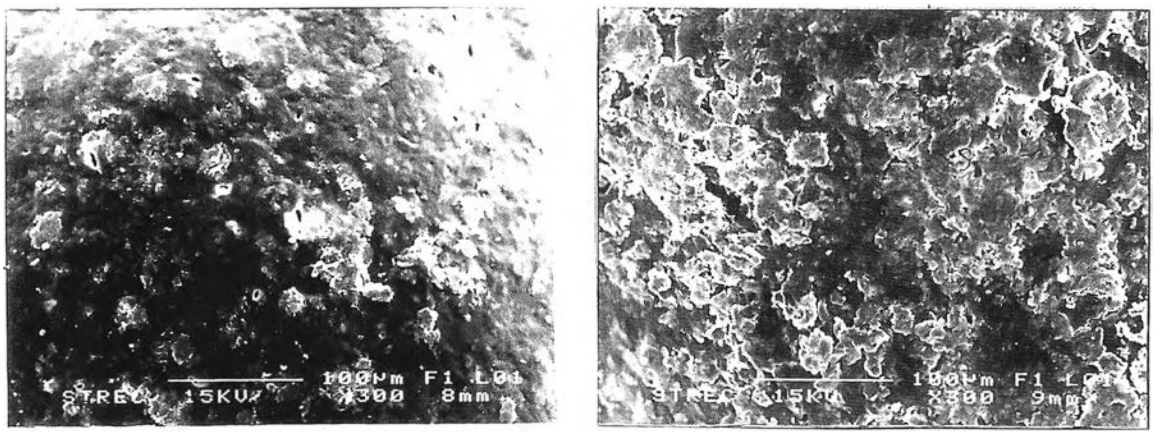
3.4.6 Effect of organic system and aqueous system on the release profile

Many researchers suggested that the coalescence of pseudolatex films were incomplete after the coating procedure. The slower drug release observed after postcoating of coated pellets with optimum conditions (Gilligan and Po, 1991; Govender and Dangor, 1997). Drying of the Eudragit®RS30D coated pellets in the chamber for another 15 minutes at the coating temperature may be not enough to form homogeneous and continuous polymer films. For that reason, the properties of Eudragit®RS30D coated pellets could not be comparable to the properties of Eudragit® RS100. On the other hand, Eudragit®RS30D films from casting method were comparable to Eudragit®RS100 films due to the different conditions. Both systems of Eudragit®RS films were dried overnight at coating temperature to prepare dry casting



SR + TEC

SR + TRC



EuRS30D + TEC

EuRS30D + TRC

Figure 126 Photomicrographs of pellets coated with Surelease® and Eudragit®RS30D plasticized with 15% TEC compared with those plasticized with 15% TRC after dissolution in acid medium films. Hence, the permeability of Eudragit®RS30D in this study may be inferior to the genuine permeability of Eudragit®RS30D in term of retarding effect.

A comparison of the dissolution profiles between organic and aqueous dispersion system formulation at the same ratio of polymer was presented in Figures 127-134. No difference between release profiles of coated pellets with pure ethylcellulose in both organic and aqueous dispersion systems was detectable (Figures 127-128). When higher level of triethyl citrate was used, the coated pellets with pure ethylcellulose in both systems also exhibited identical release characterictic (Figures 131 -132). These results could be explained by the effectiveness of triethyl citrate that can penetrate into the molecular level of polymer and completely coalition of polymer can occur easier from organic system than from aqueous dispersion system. Hence, the efficacy of ethylcellulose plasticized with triethyl citrate in organic system may be comparable to Surelease®which is already plasticized by fractionated coconut oil and extra plasticized by triethyl citrate.

The other formulations with pure Eudragit®RS or the different proportions of mixed films of ethylcellulose and Eudragit®RS illustrate the similar results (Figures 127-134). All formulations containing with Eudragit®RS30D displayed faster drug release profile than those with Eudragit®RS100. Bodmeier and Paeratakul (1990b) had explained these results by the different densities of the films. Films cast from the organic solution resulted in the thinnest film. This film was therefore denser or less porous than the latex-cast films. In addition to density, the slower drug release from organic solvent-cast films when compared to latex-cast films, could be explained with different microstructures of the films. The microstructure depended strongly on processing and formulation variables such as drying conditions and solvent composition.

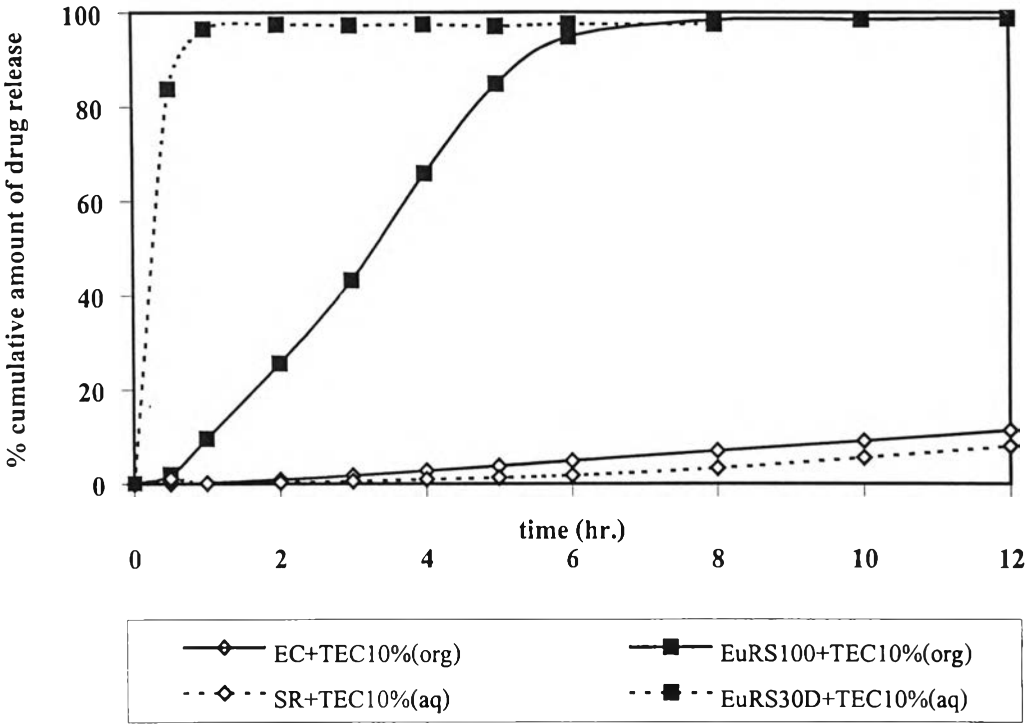


Figure 127 Release profiles of coated pellets of formulations A11, A13, B1, B3 in acid buffer

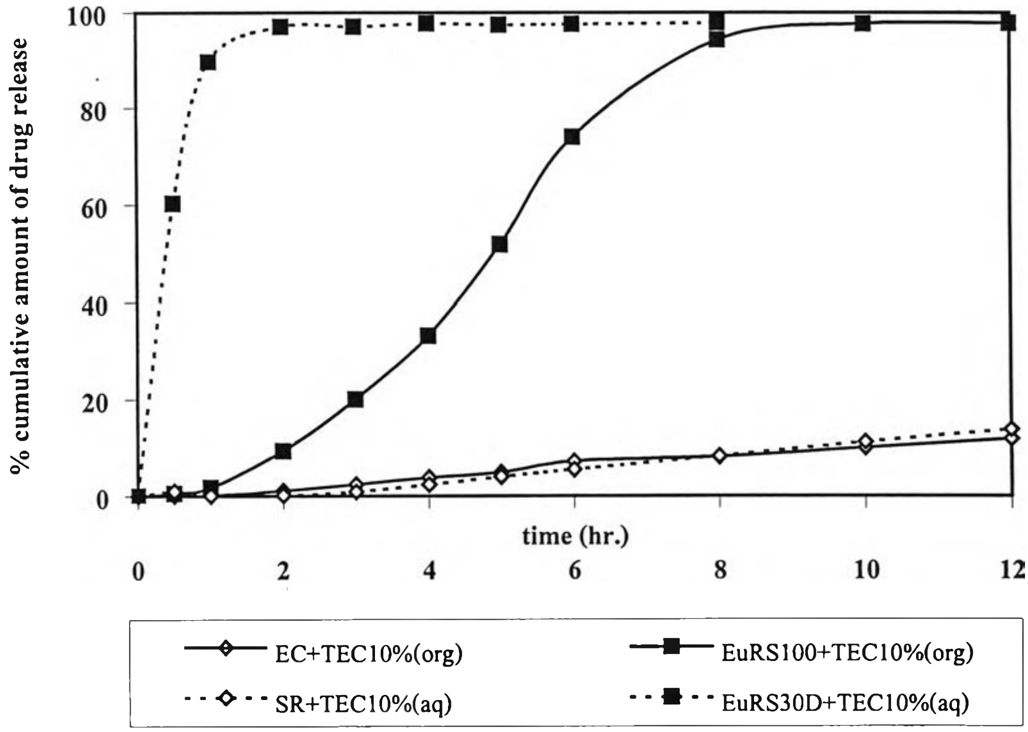


Figure 128 Release profiles of coated pellets of formulations A11, A13, B1, B3 in phosphate buffe

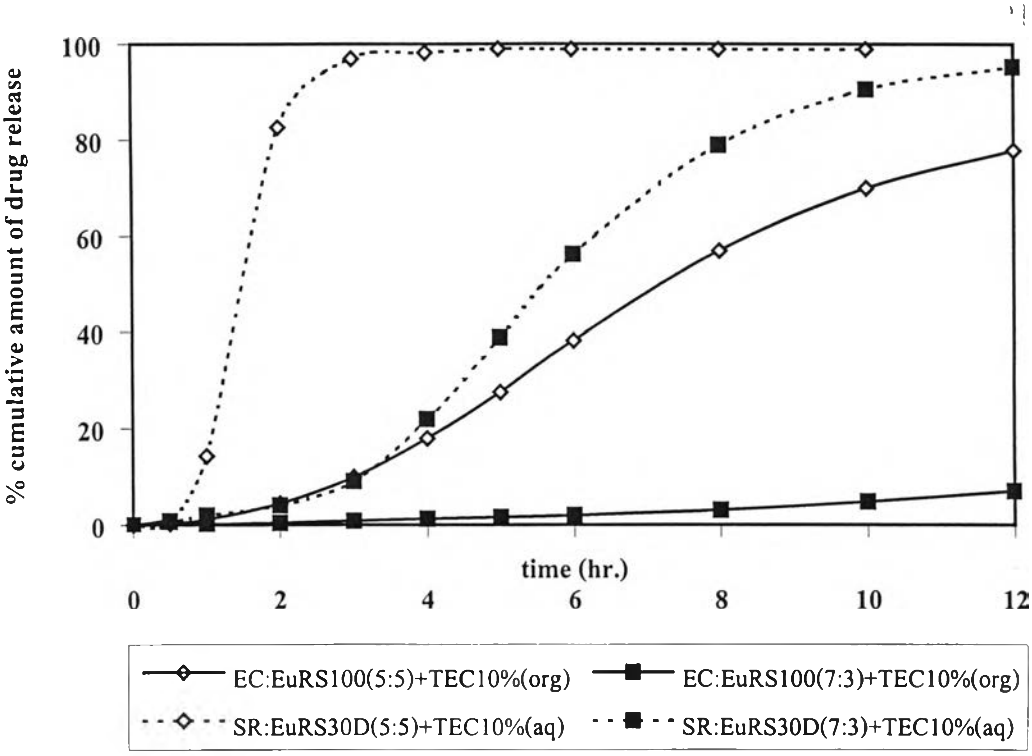


Figure 129 Release profiles of coated pellets of formulations A15, A19, B5, B9 in acid buffer

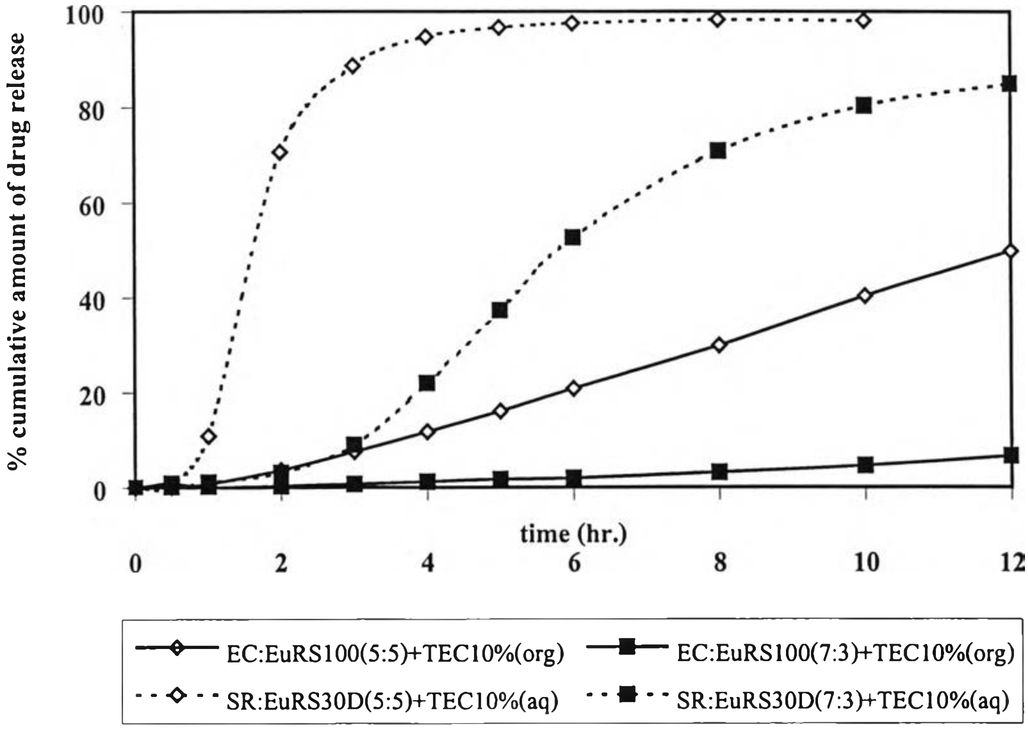


Figure 130 Release profiles of coated pellets of formulations A15, A19, B5, B9 in phosphate buffer

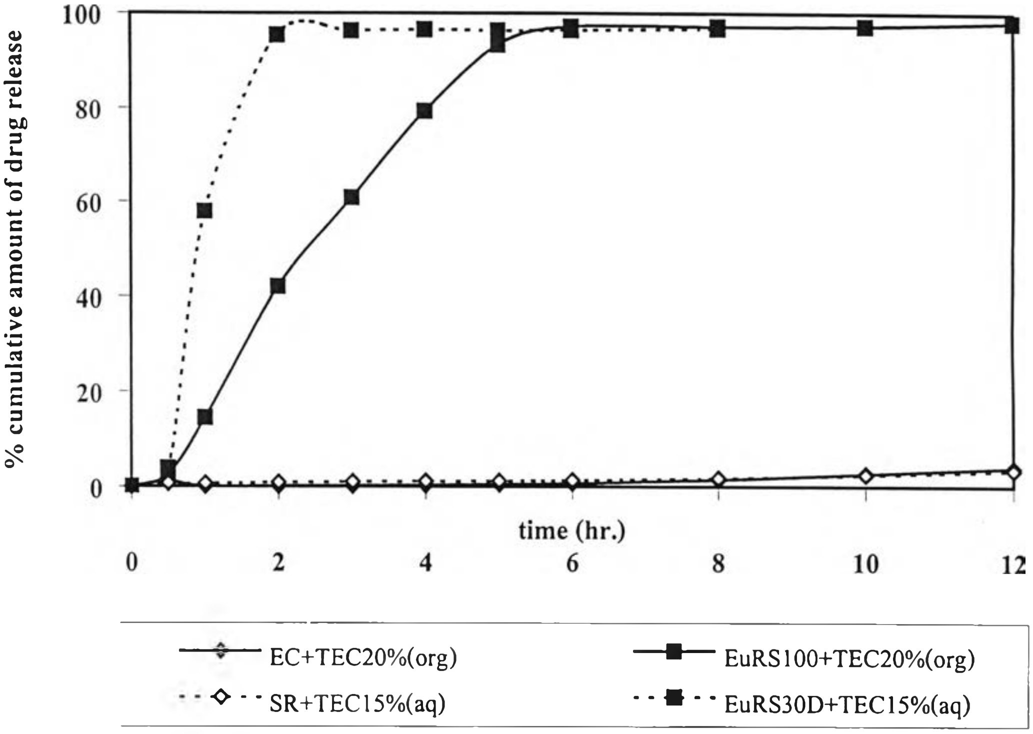


Figure 131 Release profiles of coated pellets of formulations A12, A14, B2, B4 in acid buffer

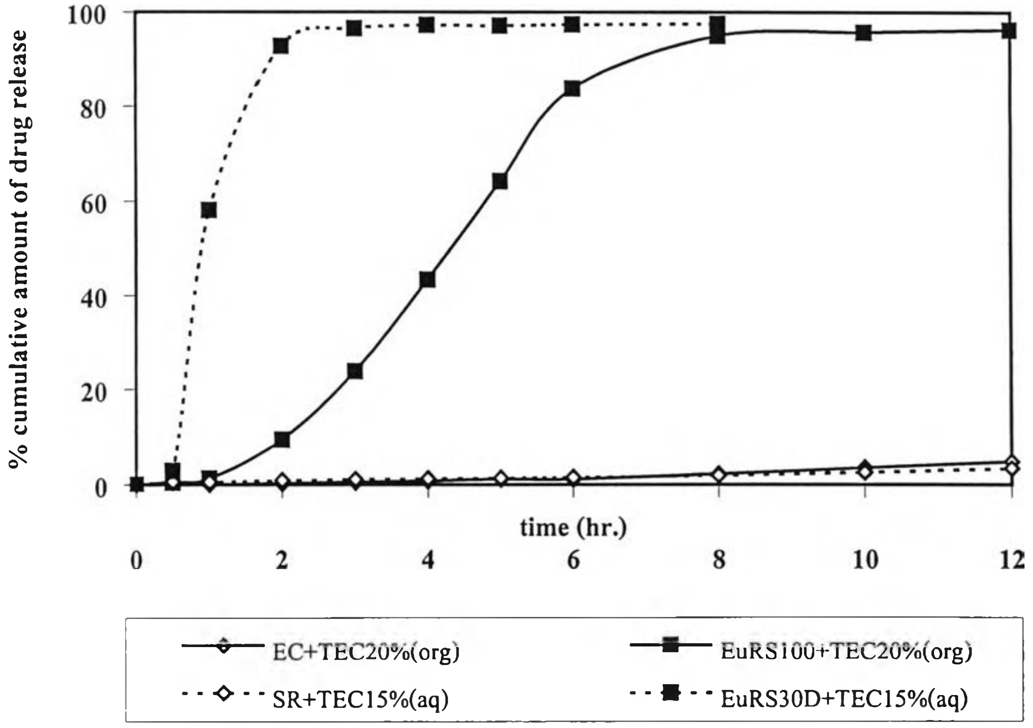


Figure 132 Release profiles of coated pellets of formulations A12, A14, B2, B4 in phosphate buffer

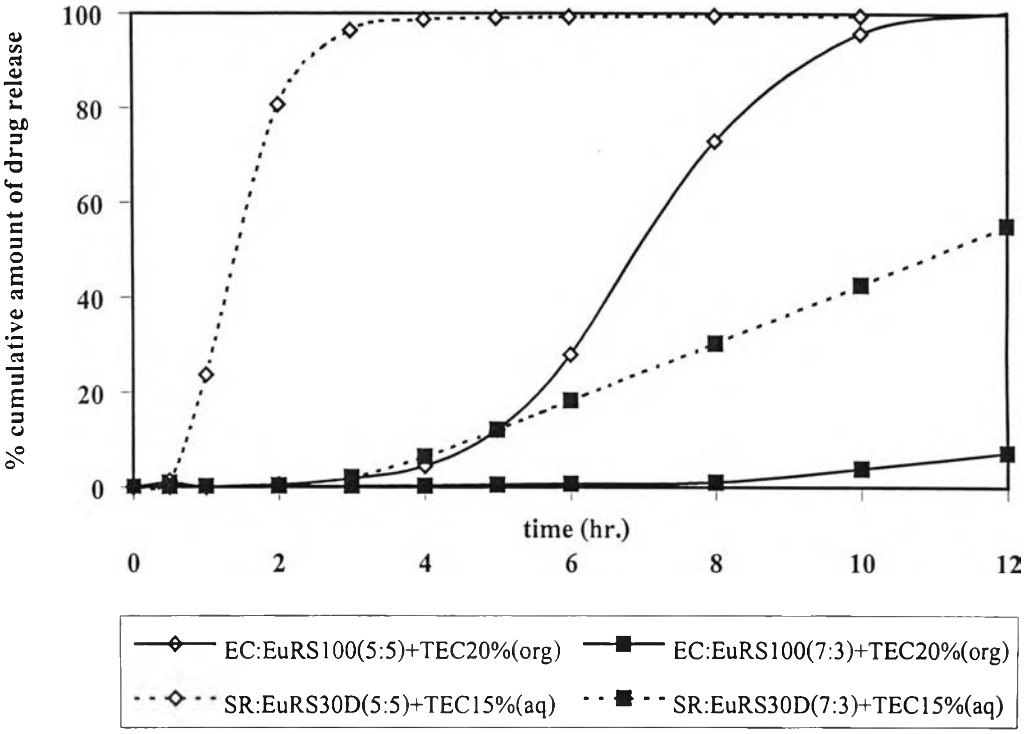


Figure 133 Release profiles of coated pellets of formulations A16, A20, B6, B10 in acid buffer

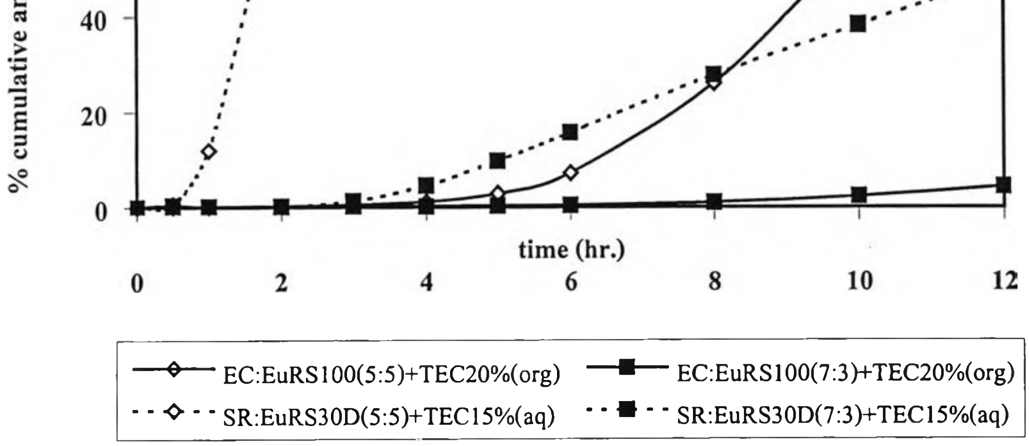


Figure 134 Release profiles of coated pellets of formulations A16, A20, B6, B10 in phosphate buffer

4. Evaluation of Physicochemical Properties of Casting Films

4.1 The powder X-ray diffraction analysis

The X-ray diffraction patterns were run by two equipments which were Jeol JDX-3530 and Rigaku Denki. The samples of films without antiadherent and films prepared from aqueous dispersion system were run by Jeol JDX-3530 whereas the samples of films prepared from organic system were run by Rigaku Denki.

The representative X-ray diffraction pattern for ethylcellulose, Surelease®, Eudragit®RS type and the blended film between two polymers in the ratio of 5:5 with 10% plasticizer were depicted in Figures 135-136. The ethylcellulose and Eudragit®RS type polymers are amorphous in nature due to the absence of complete steroregularity and the presence of bulky side groups (Jenquin and McGinity, 1994). The samples with pure polymer and blended polymer with the ratio of 5:5 showed halo shape baseline in powder X-ray diffraction. The ethylcellulose film in both systems demonstrated two broad bands between 5° and 25° 2θ while the Eudragit®RS film in both systems showed one broad band between 10° and 25° 2θ. The patterns of the mixture polymers of ethylcellulose and Eudragit®RS in both systems displayed the integrated band of two pure polymers. It could not be observed any change in the blended polymer with the ratio of 5:5.

From X-ray diffraction patterns of talcum, magnesium stearate, pure polymer of ethylcellulose, Eudragit®RS100 and blended polymers plasticized with 20% dibutyl phthalate and triethyl citrate (Figures 137-138), it can be seen that every pure polymer and blended polymers with antiadherents produced the same characteristic peaks of talcum and magnesium stearate. The weak intensity of magnesium stearate that was displayed in the pure polymer and blended polymers was due to the minimal

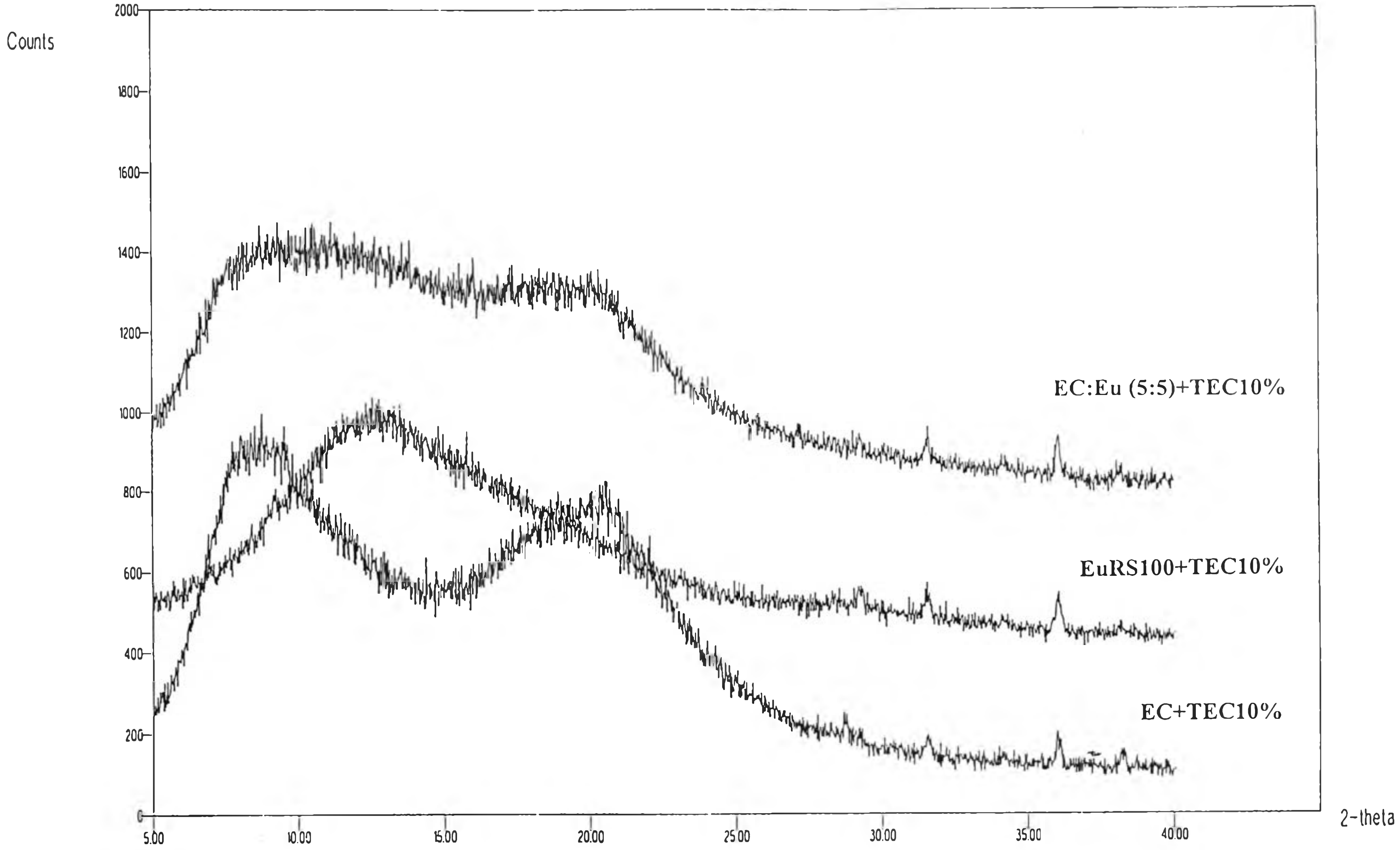


Figure 135 X-ray diffractograms of ethylcellulose (EC), Eudragit®RS100 (EuRS100, Eu) and blended film at the ratio of 5:5 with triethyl citrate (TEC) 10% by using Jeol JDX-3530

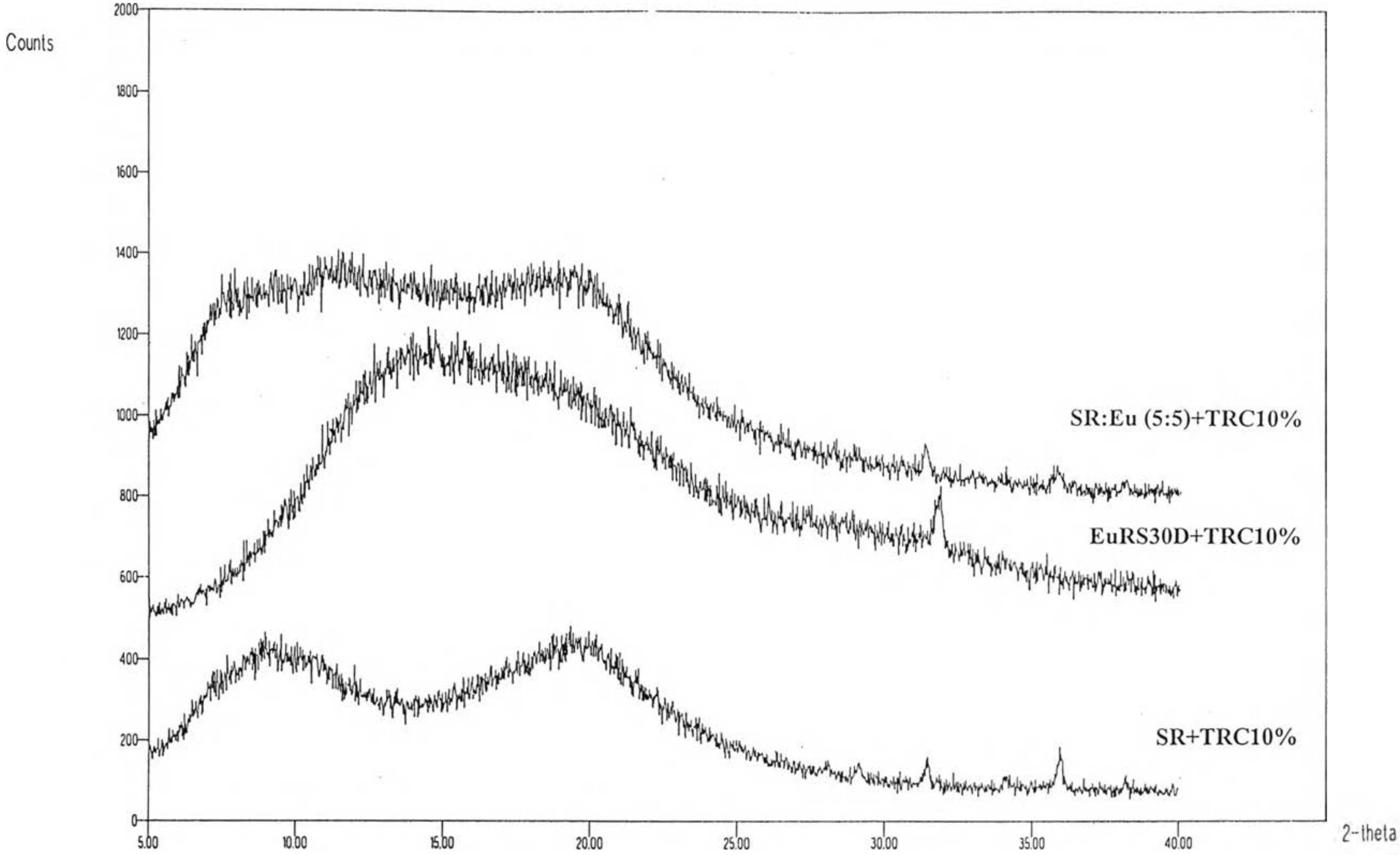


Figure 136 X-ray diffractograms of Surelease®(SR), Eudragit®RS30D (EuRS30D, Eu) and blended film at the ratio of 5:5 with triacetin (TRC) 10% by using Jeol JDX-3530

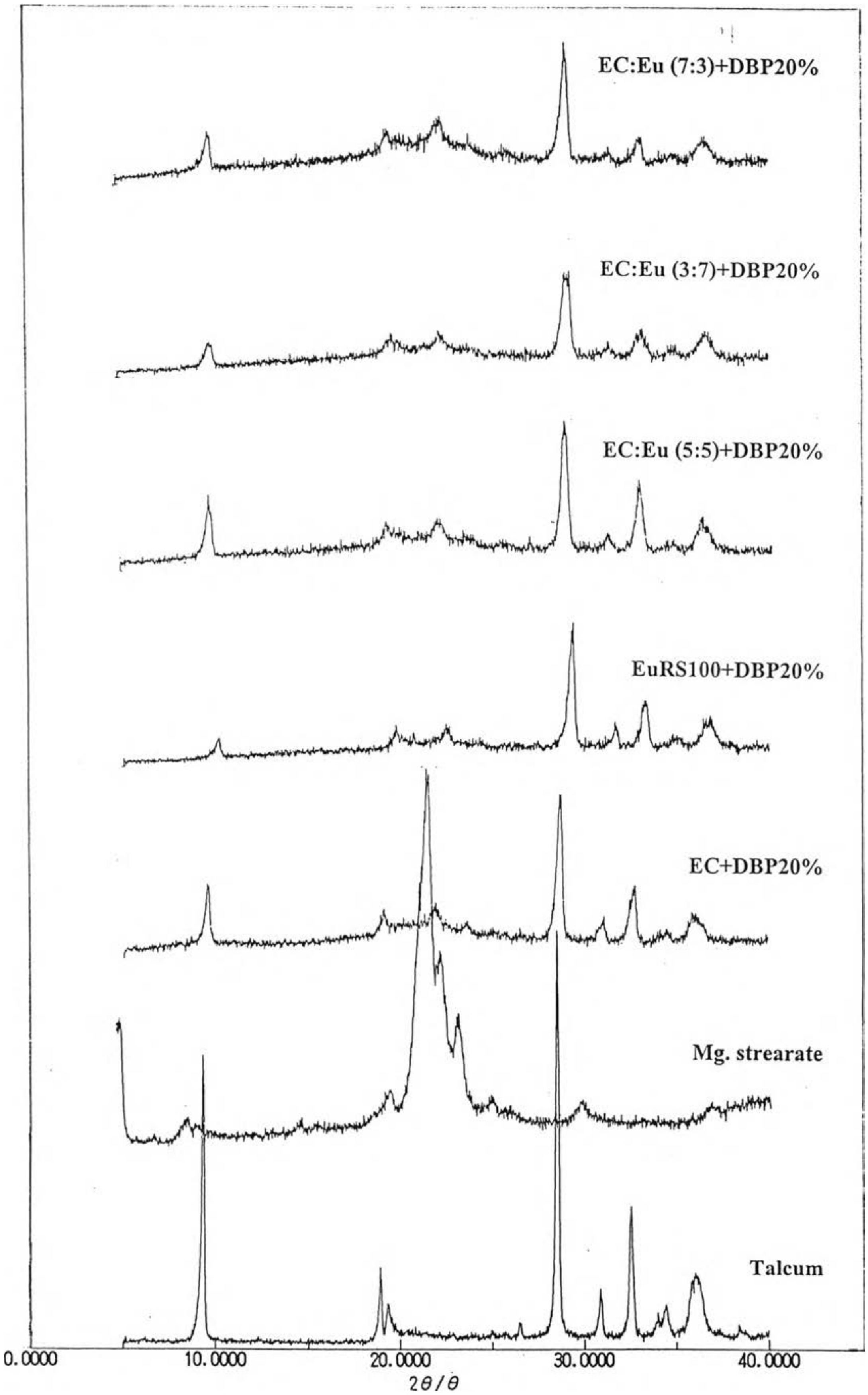


Figure 137 X-ray diffractograms of talcum, magnesium stearate and blended films prepared from ethylcellulose (EC) and Eudragit®RS100 (EuRS100, Eu) at the various ratios with antiadherents and dibutyl phthalate (DBP) 20% by using Rigaku Denki (Miniflex).

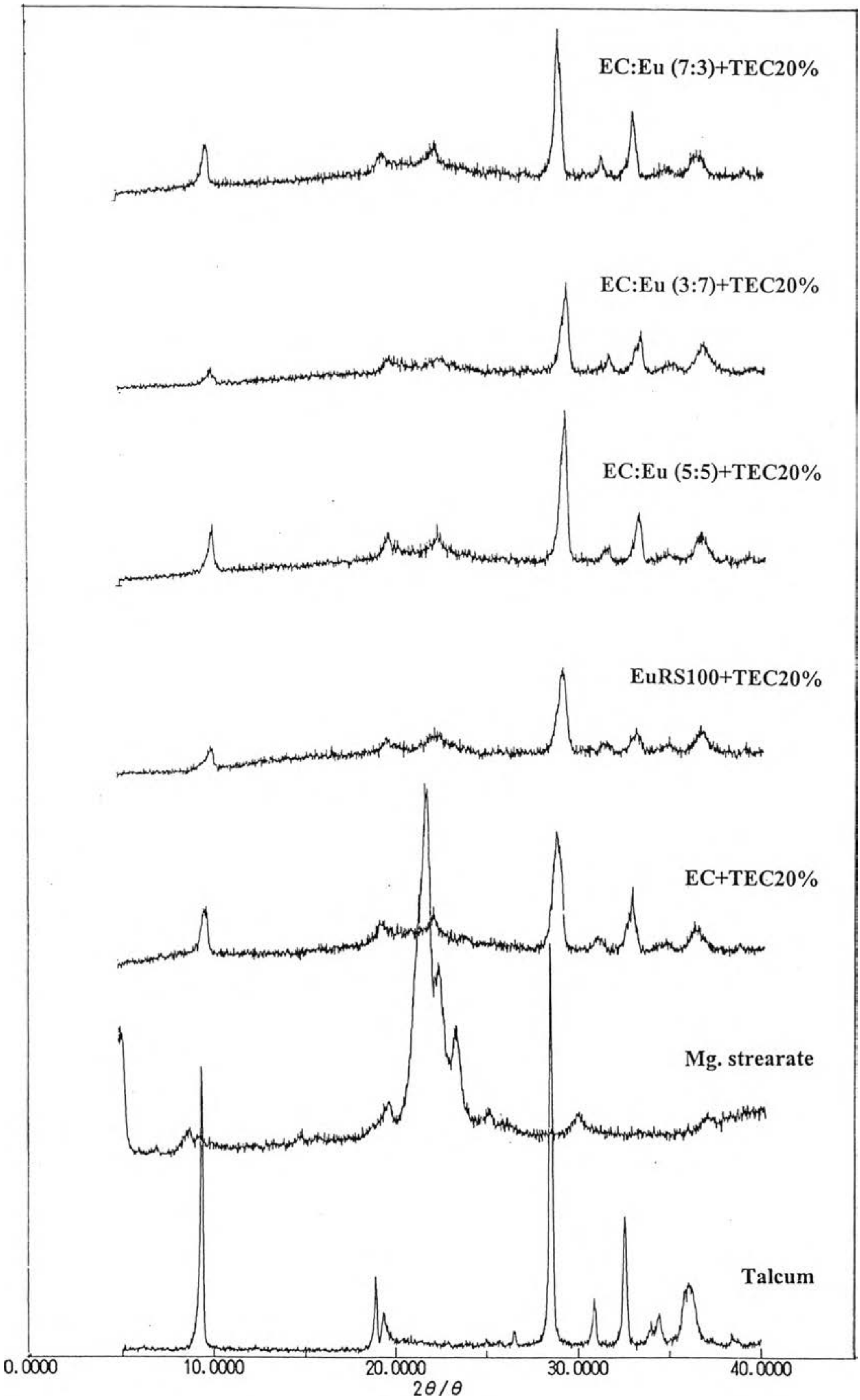


Figure 138 X-ray diffractograms of talcum, magnesium stearate and blended films prepared from ethylcellulose (EC) and Eudragit®RS100 (EuRS100, Eu) at the various ratios with antiadherents and triethyl citrate (TEC) 20% by using Rigaku Denki (Miniflex).

quantity of magnesium stearate. Slightly higher baseline was observed in all formulations. The diffraction patterns of talcum, single polymer of Surelease® or Eudragit®RS30D and blended polymers with talcum and 15% level of plasticizers are seen in Figures 139 and 140. The slightly higher baseline was still observed in all formulations. The single polymer of Surelease® or Eudragit®RS30D and blended polymers with talcum and 15% plasticizers contained sharp diffraction peaks of talcum in powder X-ray diffraction. The slightly higher baseline of films might be the effect of diffraction pattern of polymers. From all these results, it could be deduced that various ratios of blended polymers had no effect on changing of the X-ray diffraction patterns. On the other hand, the data could be concluded that at least 90%, there were no interaction between the two polymers in both systems.

However the film prepared from organic system and aqueous dispersion system exhibited different X-ray diffraction patterns (Figures 137-140). All characteristic peaks of antiadherent in films prepared from organic system were shifted in the same direction to the right position whereas those peaks of antiadherent in films prepared from aqueous system were shifted to the left position. These results could be explained by the different methods of specimen preparation according to the different types of instrument used. The samples from organic system measured by Rigaku Denki were cut up and packed into a thin rectangular quartz slide by the other cover slide. Nevertheless, the smooth surface could not operate and the slightly lower plane occurred from base of the quartz slide. The samples from aqueous dispersion system measured by Jeol JDX-3530 were cut in a rectangular size and put into the sample holder by using removable adhesive. The slightly higher plane from base of the sample holder was observed because of the method used to fix the films by removable adhesive.

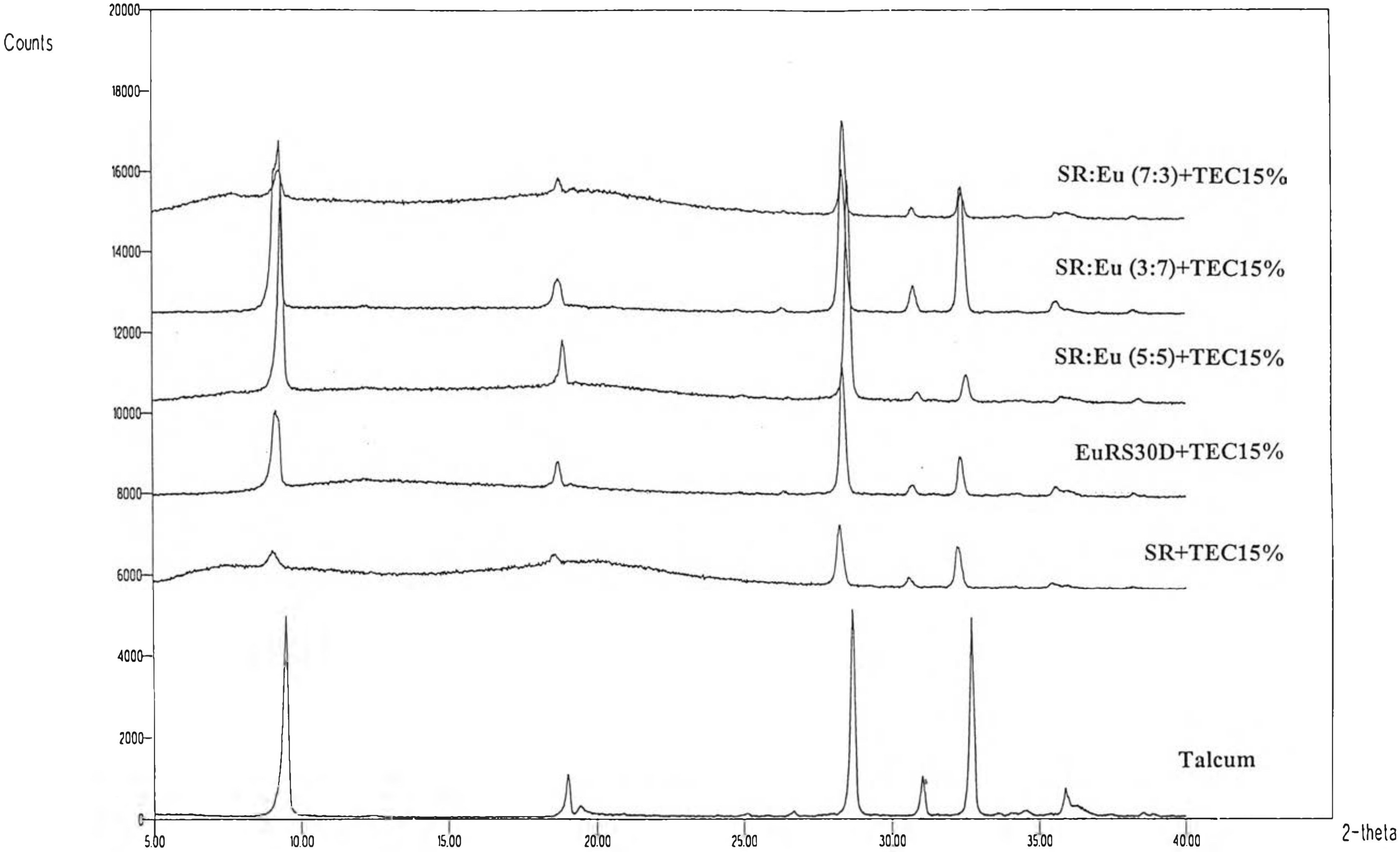


Figure 139 X-ray diffractograms of talcum and blended films prepared from Surelease® (SR) and Eudragit®RS30D (EuRS30D, Eu) at the various ratios with talcum and triethyl citrate (TEC) 15% by using Jeol JDX-3530

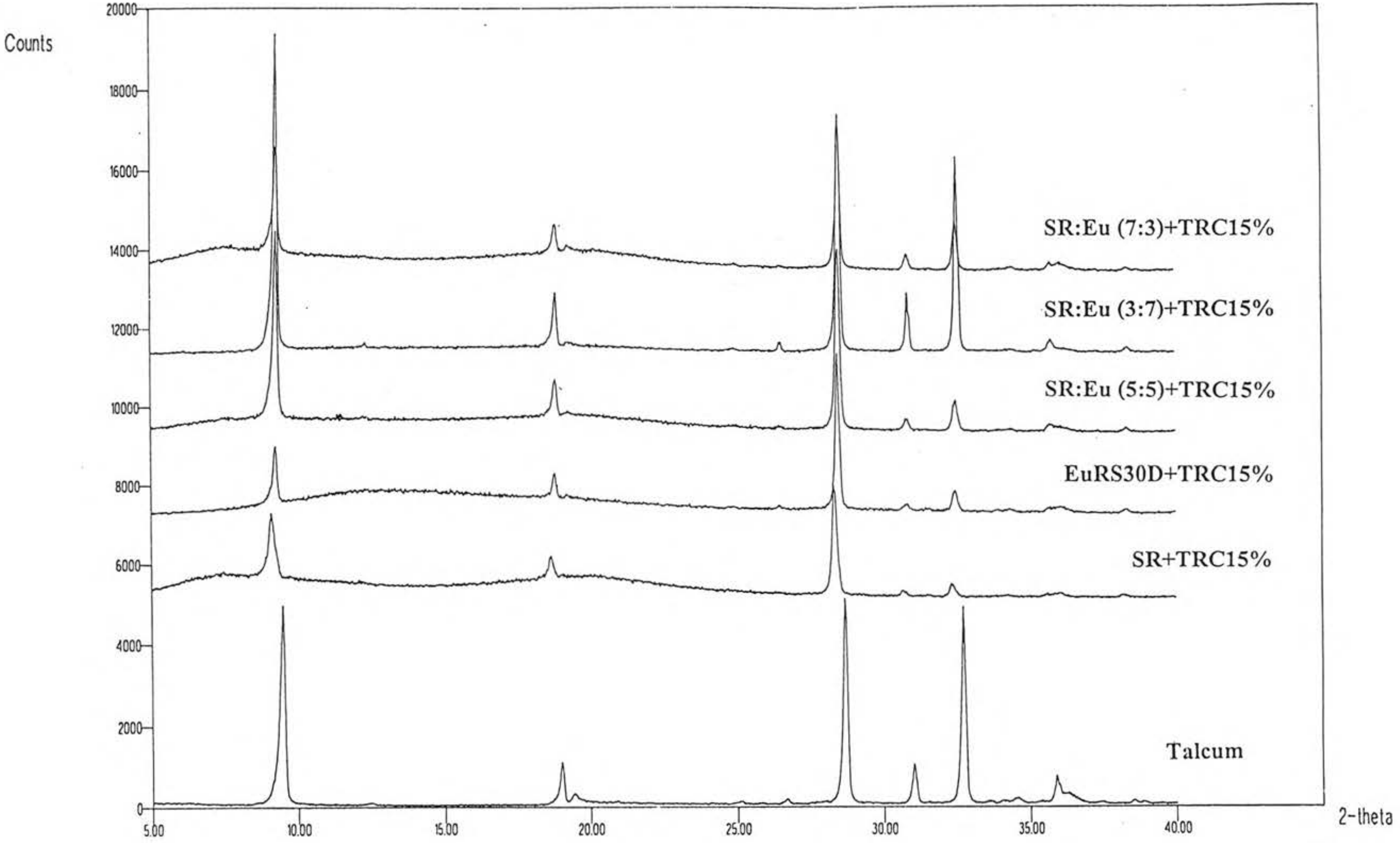


Figure 140 X-ray diffractograms of talcum and blended films prepared from Surelease® (SR) and Eudragit®RS30D (EuRS30D, Eu) at the various ratios with talcum and triacetin (TRC) 15% by using Jeol JDX-3530

4.2 The infrared spectroscopy

The IR spectra of ethylcellulose, Eudragit®RS type and the blended polymers with various ratios are depicted in Figures 141-142. The principle peaks of ethylcellulose were observed at the wavenumbers of 1056, 1107, 2974 and 3473 cm^{-1}. The peaks at 1056 and 1107 were resulted from C-O stretching vibrations. The C-H stretching was observed at 2974 cm^{-1} and the broad absorption band at 3473 cm^{-1} was observed due to O-H stretching. The peaks of Surelease® displayed in Figure 142 were similar as ethylcellulose but it shown splitting peaks at 2863, 2923 and 2974 cm^{-1}. Furthermore the peak at 1745 was resulted from C=O stretching. This peak may be due to the other materials in Surelease® such as fractionated coconut oil or oleic acid. The principle peaks of Eudragit®RS type in both organic and aqueous system were at the wavenumbers of 1144, 1240, 1384, 1447, 1734, 2952 and 2988 cm^{-1}. The peaks of Eudragit®RS at 1140 and 1240 cm^{-1} resulted from C–O stretching vibrations. The peaks at 1384 and 1450 cm^{-1} were resulted from C–H bending. The C=O stretching of the ester groups was occurred at about 1734 $cm^{-1}$and the C–H stretching peaks were represented at 2952 and 2988 cm^{-1}.

The IR spectra of blended polymers between ethylcellulose and Eudragit®RS100 in various ratios showed the combination of ethylcellulose peaks and Eudragit®RS100 peaks (Figure 141). No additional band was observed with any ratios of the blended polymers. It could be concluded that no evidence of intermolecular chemical bonding between ethylcellulose and Eudragit®RS100. However, the emergence of additional band occurred at 805.52 cm^{-1} in the blended polymers from aqueous dispersion system that did not happen in organic system (Figures 142-143). This additional band would indicate a new chemical bond or a new functional group resulting from the differences in the components or the differences in the production process between the two systems. This band was evidently observed in the blended polymers with Surelease® and Eudragit®RS30D in the ratio of 3:7. These results may be

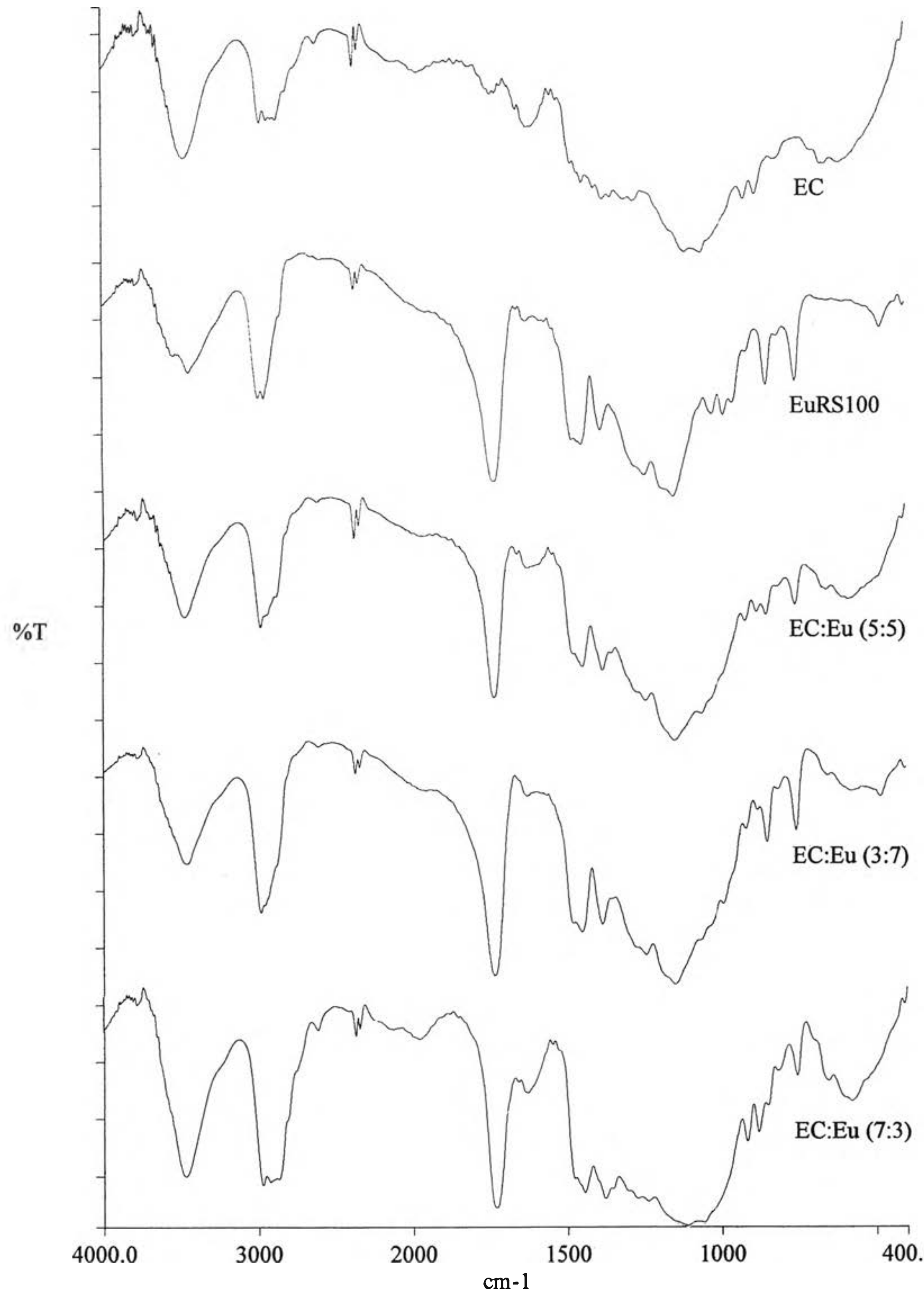


Figure 141 IR spectra of blended films prepared from ethylcellulose (EC) and Eudragit® RS100 (EuRS100, Eu) at the various ratios without antiadherents and plasticizer

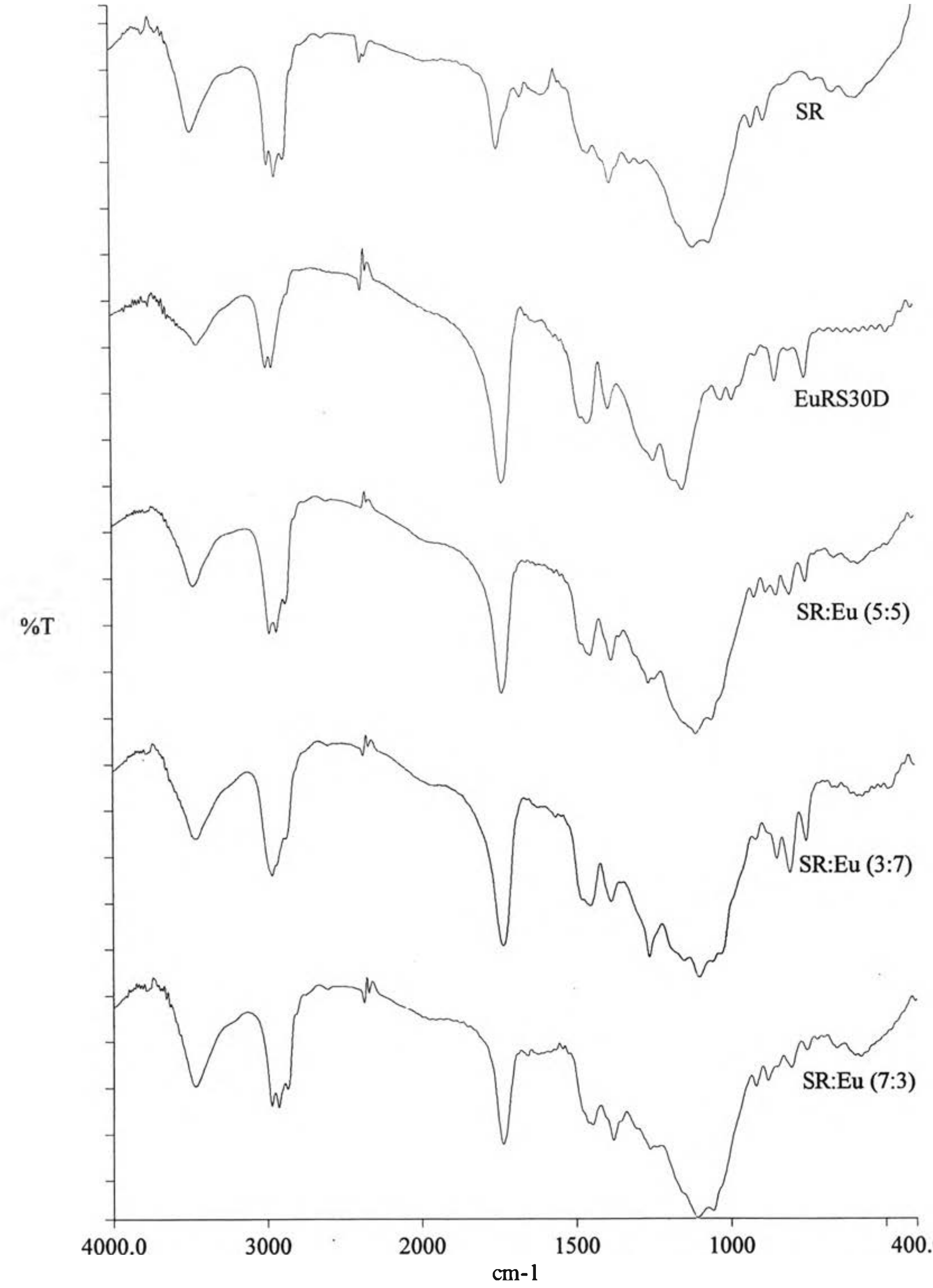


Figure 142 IR spectra of blended films prepared from Surelease® (SR) and Eudragit® RS30D (EuRS30D, Eu) at the various ratios without antiadherents and plasticizer

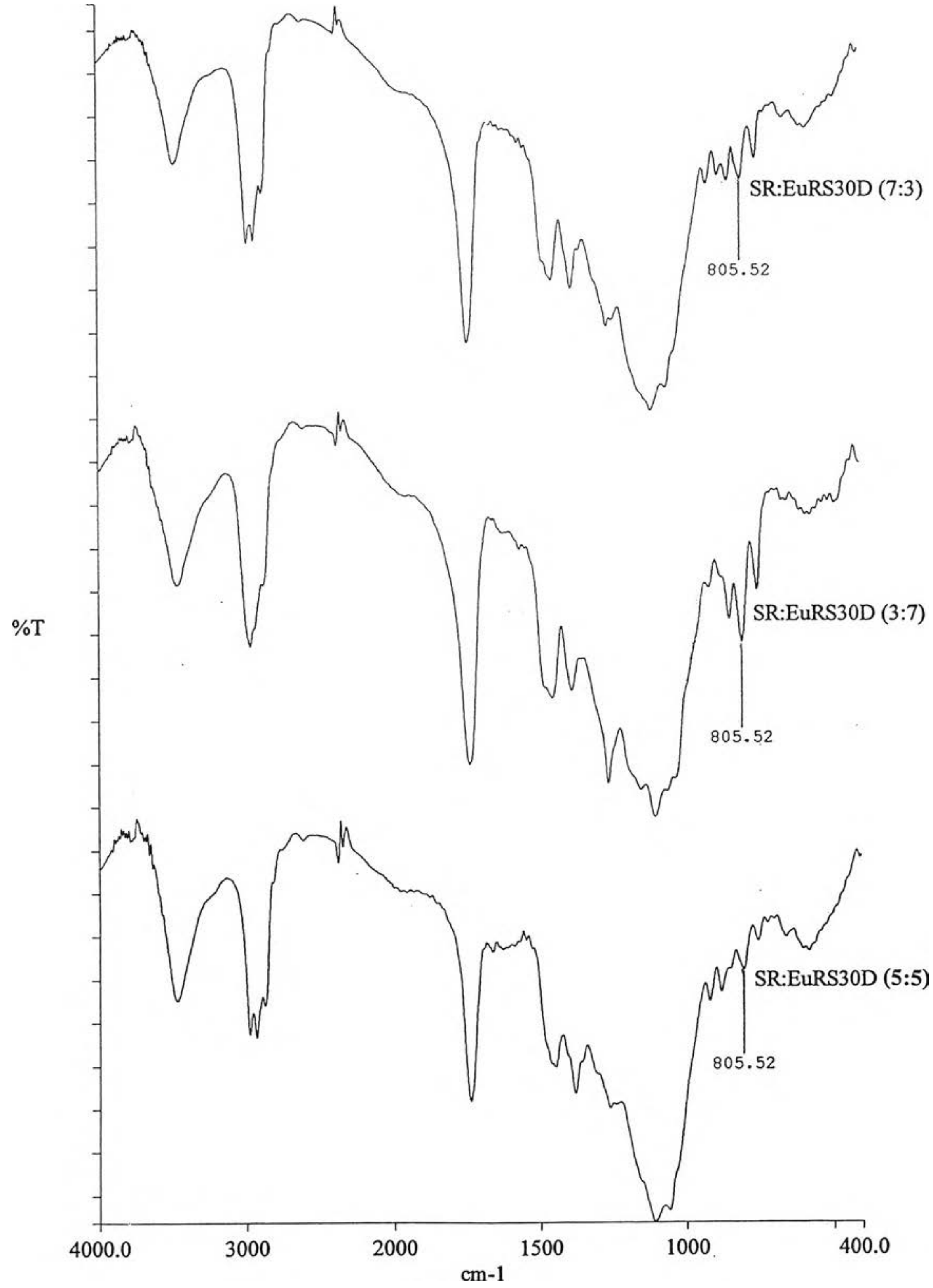


Figure 143 IR spectra of blended films between Surelease® (SR) and Eudragit®RS30D (EuRS30D) at the various ratios with labelled peak at 805.52 cm^{-1}

an explanation of why viscous appearance between Surelease® and Eudragit®RS30D was observed with every ratio and was outstanding in the blended film with the ratio of 3:7 because of interaction between two polymers in aqueous dispersion system.

Though the interaction between these two polymers occurred, they still could retard the drug release when compared with using Eudragit®RS30D alone. Nevertheless, the formulation of Surelease® and Eudragit®RS30D in the ratio of 3:7 could not be operated because of nozzle blockage. The intensity of the new peak at 805.52 cm^{-1} of the blended film with Surelease® and Eudragit®RS30D in the ratio of 3:7 was the most prominent peak. This result may explain the problem that occurred during experiment.

Figures 144-145 demonstrate the spectra of talcum, magnesium stearate and blended polymers in various ratios with dibutyl phthalate and triethyl citrate as plasticizer. The eminent peaks of talcum occurred in the mixed polymers with various ratios while no eminent peak of magnesium stearate was clearly observed. It was due to the quantity of talcum in the mixing films was much more than the quantity of magnesium stearate. In the case of aqueous dispersion system, the prominent peaks of talcum were also seen in the blended films with triethyl citrate and triacetin as plasticizer (Figures 146-147). The observation indicated no sign of interactions between antiadherents (talcum, magnesium stearate) and the blended polymers in any ratios because of no additional band or alternation in wavenumber position.

4.3 The differential scanning calorimetry

Measuring of the glass transition temperatures of films and blended films with and without additives by employing DSC was very difficult because no endothermic baseline shifts were observed. Also in the second heating of some samples, they did not indicate a shift in Tg. Despite the difficulties, Tg of ethylcellulose alone

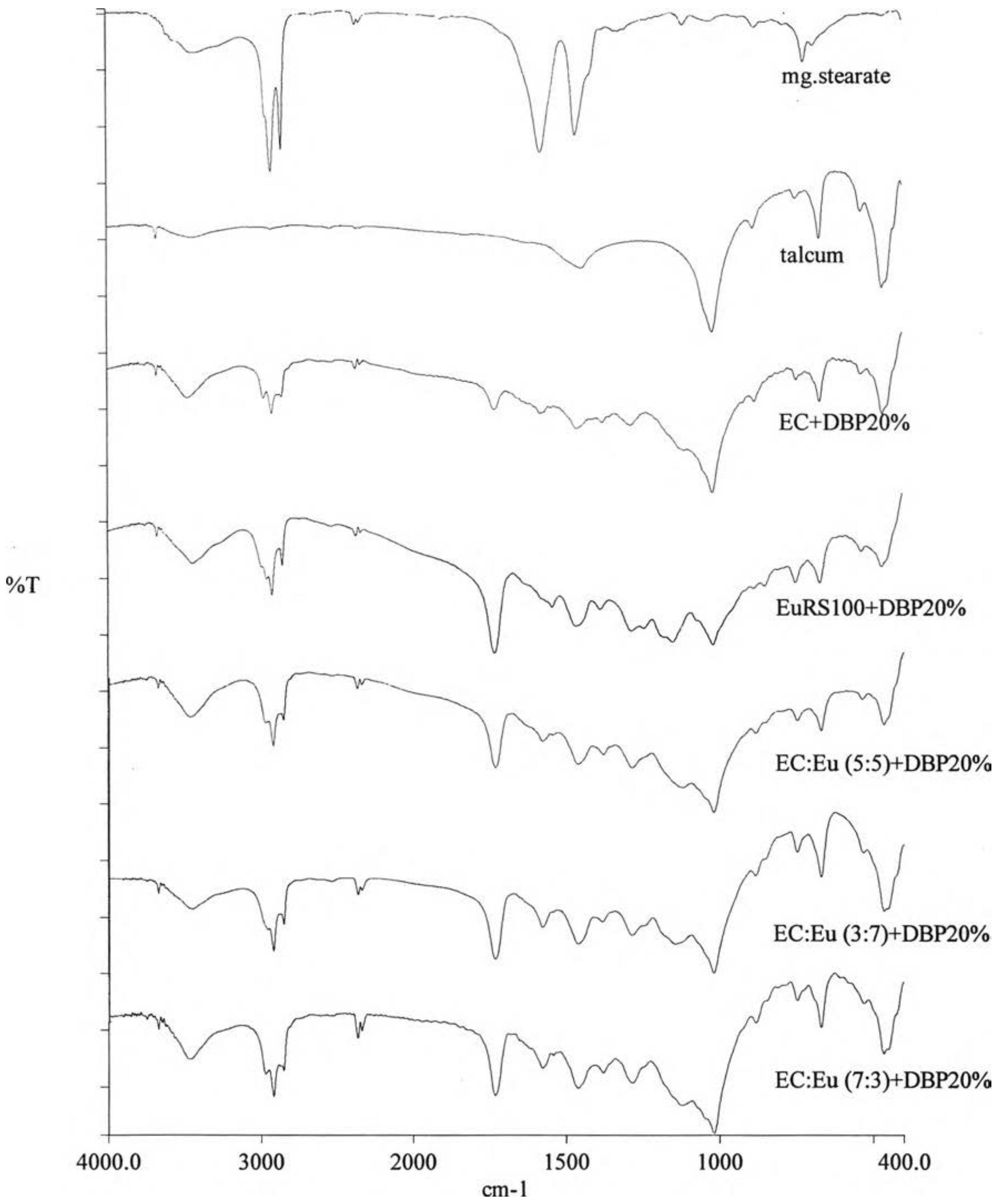


Figure 144 IR spectra of magnesium stearate, talcum and blended films prepared from ethylcellulose (EC) and Eudragit®RS100 (EuRS100, Eu) at the various ratios with antiadherents and dibutyl phthalate (DBP) 20%

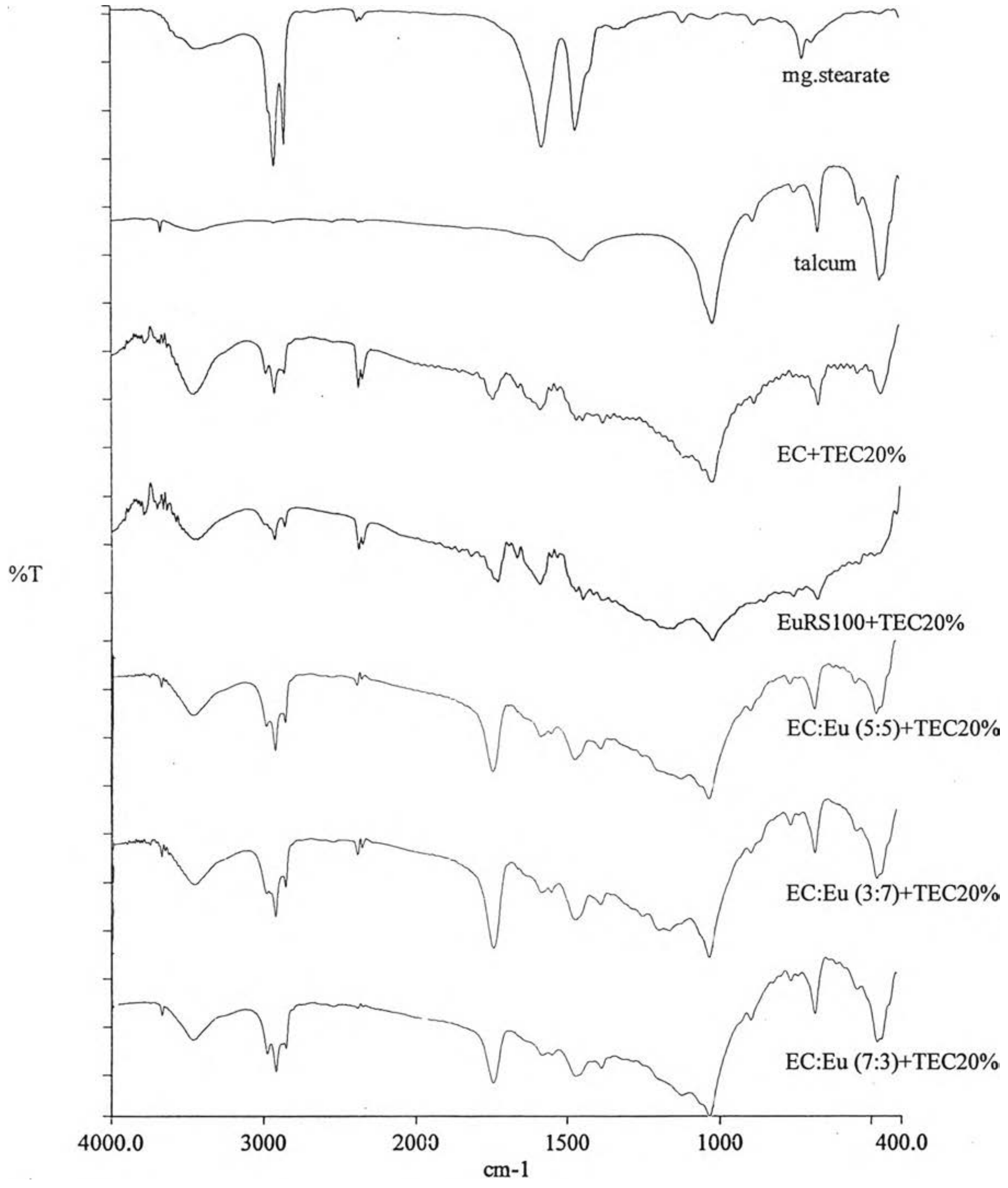


Figure 145 IR spectra of magnesium stearate, talcum and blended films prepared from ethylcellulose (EC) and Eudragit®RS100 (EuRS100, Eu) at the various ratios with antiadherents and triethyl citrate (TEC) 20%

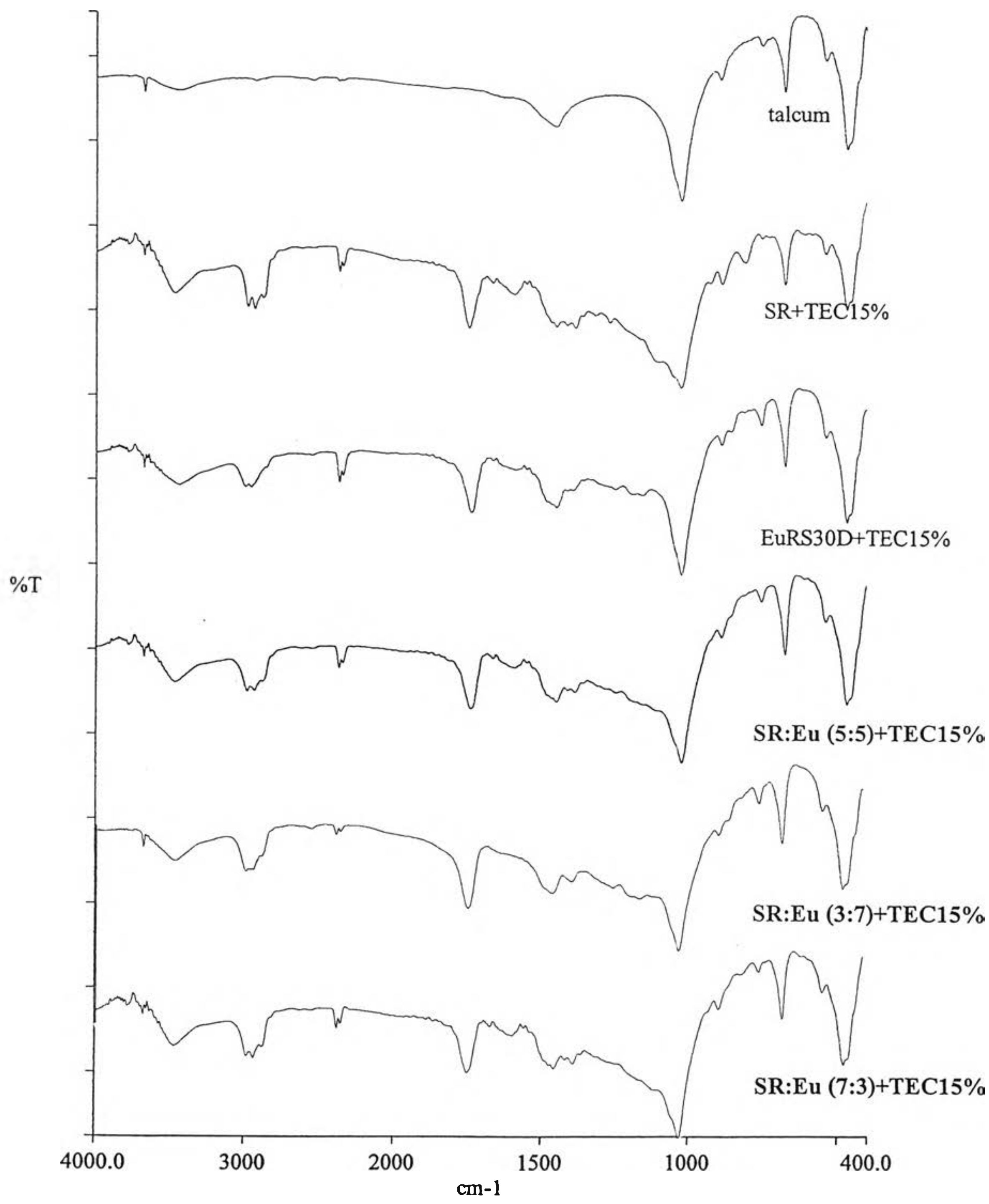


Figure 146 IR spectra of talcum and blended films prepared from Surelease® (SR) and Eudragit®RS30D (EuRS30D, Eu) at the various ratios with talcum and triethyl citrate (TEC) 15%

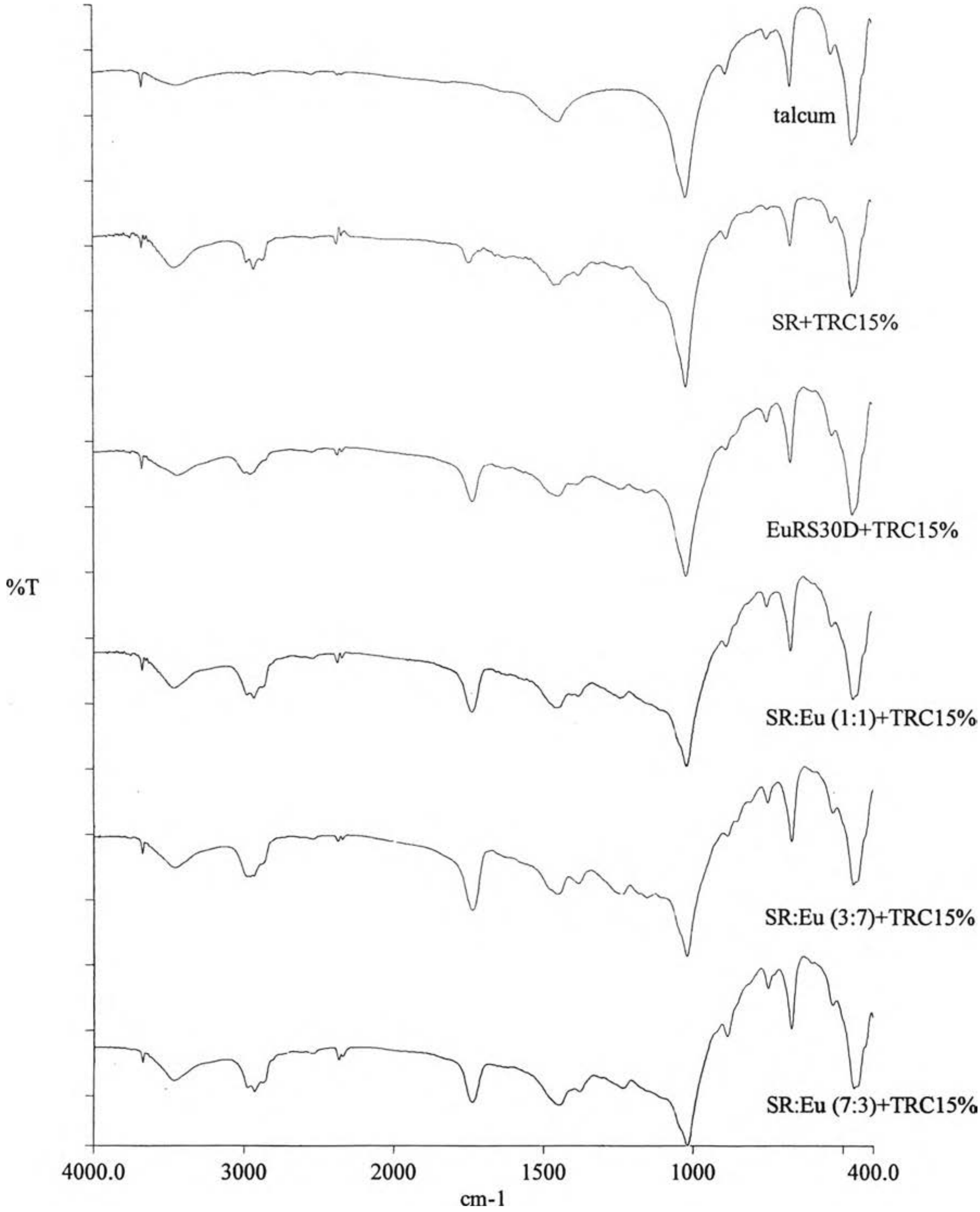


Figure 147 IR spectra of talcum and blended films prepared from Surelease® (SR) and Eudragit®RS30D (EuRS30D, Eu) at the various ratios with talcum and triacetin (TRC) 15%

could be measured by DSC at 126.34 °C (Figure 148) and Tg of blended film of ethylcellulose:Eudragit®RS100 in the ratio of 5:5 could be measured in the second heating at 125.41 °C (Figure 149). This measured Tg of ethylcellulose was lower than the previous measuring by Rowe et al. (1984) possibly due to different measuring methods employed. The Tg of ethylcellulose which was measured by the torsional braid pendulum was found to be 135 °C. No signal of Tg of Eudragit®RS100 was seen. The Tg of other films of Eudragit®RS100, Surelease®, Eudragit®RS30D and blended film between Surelease®:Eudragit®RS30D in the ratio of 5:5 could not be found. The Tg of Eudragit®RS type and Surelease® which was reported in the previous studies was 47 and 35 °C, respectively (Lehmann, 1989; Parikh et al., 1993a).

As described before, the influence of heating rate on the glass transition was an important parameter (Sakellariou et al., 1985; Fukuoka, Makita and Nakamura, 1989). Hence, the Eudragit®RS30D film without any additives was run again by varying scanning rate from 5, 10, 20 °C/min. These thermograms with three different heating rates are demonstrated in Figure 150. They displayed broad band that was enlarged and shifted to higher temperatures as the heating rate was increased. The thermogram from scanning rate 10 °C/min depicted better characteristic of a levelled baseline than the others so the heating rate at 10 °C/min was used for the films with antiadherent and plasticizer. Furthermore, the films of Eudragit®RS type alone and polymer blends in aqueous system showed rough baseline in the second heating without a baseline shift. Hence, the second heating was not operated in the films prepared from aqueous dispersion system.

All of the formulations: A1, A2, A3, A4, A5, A6, A11, A13, A15, B1, B2, B3, B4, B5, B6, B11, B13 and B15 were chosen for Tg measurement. For all the formulations, glass transition temperatures could not be determined by this method and by these conditions. The cause of this problem may be due to the size of the samples and their ability to distribute heat evenly. The various sizes of samples made by cutting may

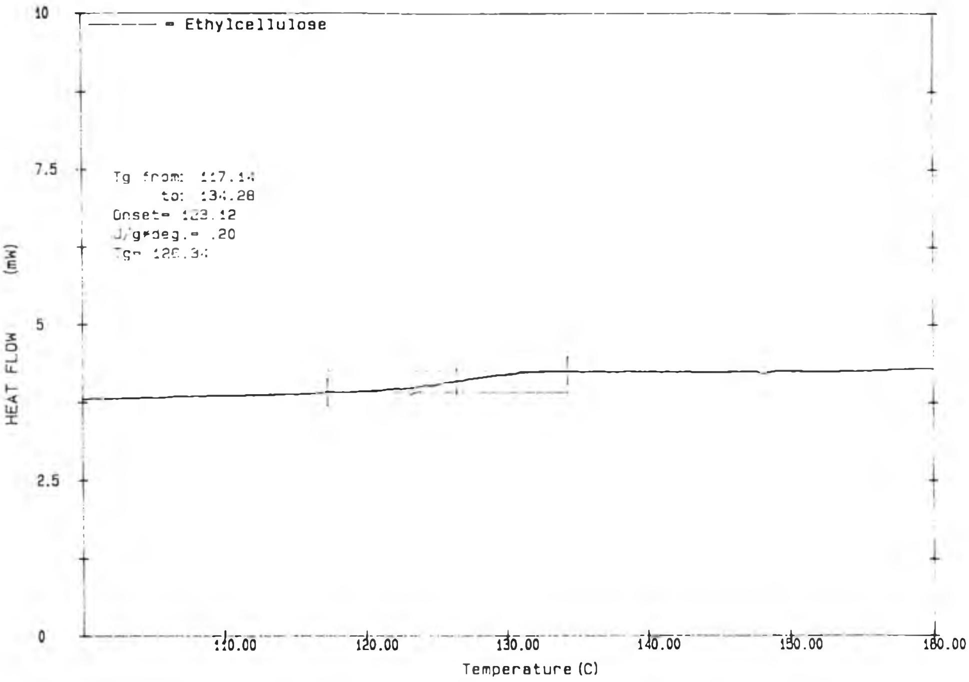


Figure 148 The glass transition temperature of ethylcellulose at scanning rate 10.0 °C/min.

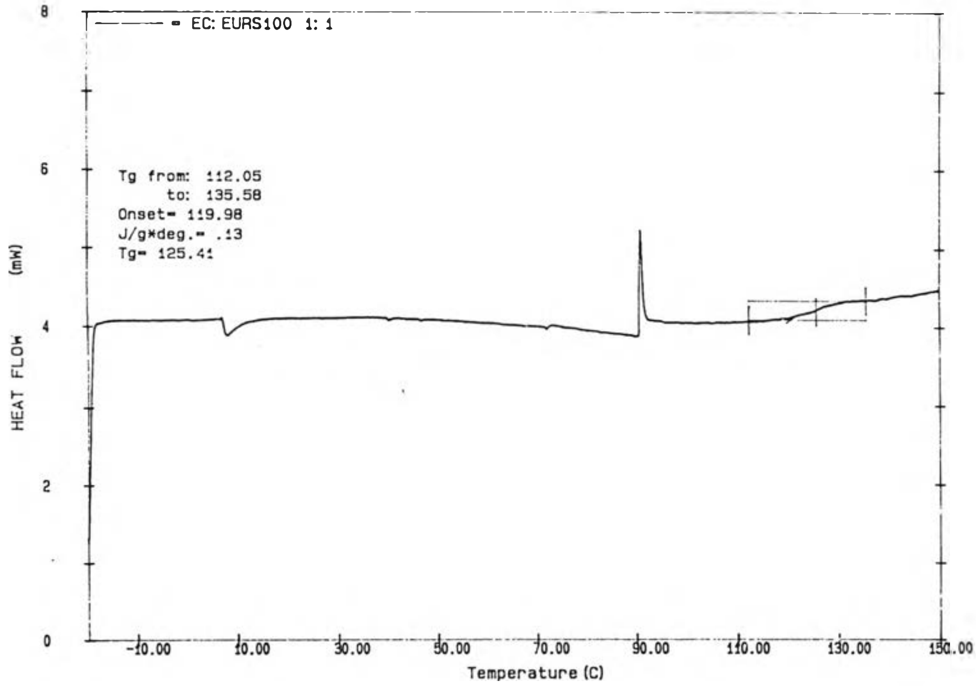


Figure 149 The glass transition temperature of ethylcellulose from blending film between ethylcellulose and Eudragit®RS100 with the ratio of 5:5 at scanning rate 10.0 °C/min.

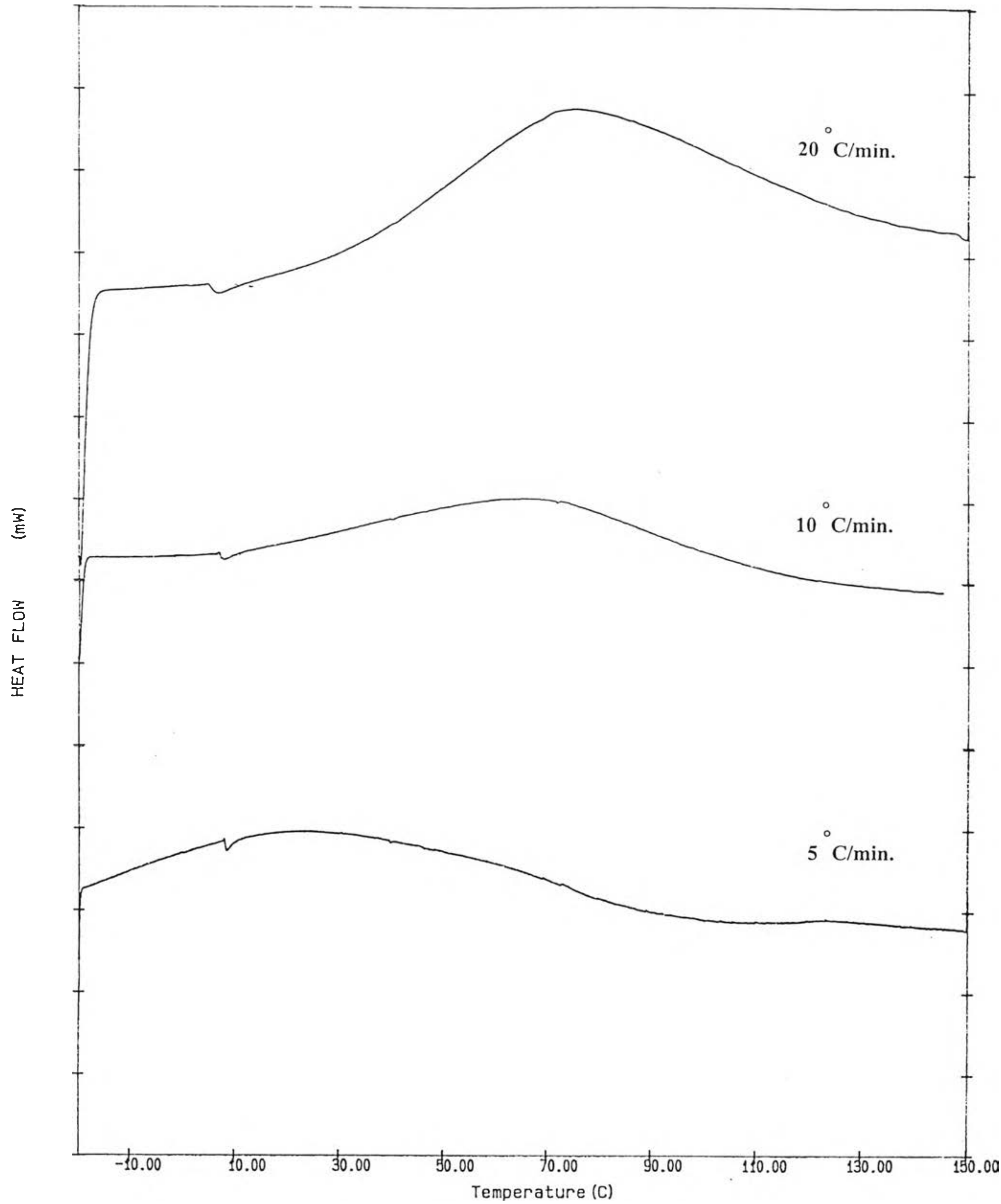


Figure 150 DSC thermograms of Eudragit®RS30D by varying scanning rate from 5, 10, 20 °C/min.

result in differences in the surface area causing uneven heat distribution within each piece of sample. Therefore, accurate and reproductible Tg could not be determined.

Lee and Knight (1965) had discussed the reasons for the inconsistencies that occurred in glass transition measurements, and concluded that the main factors were failure to establish near-equilibrium conditions during measurement, and secondly, the use of too great a rate of temperature change, faster than the changes in molecular arrangement. The first problem was difficult to overcome, but the second might be significantly reduced by employing very low rates of temperature change, in the region of 1 °C h^{-1}, which was impractical unless the approximate transition zone was known beforehand to enable final determinations to be made over very narrow temperature ranges. An additional cause of error was impurities in the sample, which typically include unreacted monomer, residual solvents used in sample preparation, and water, any of which might shift the transition temperature by as much as 40-50 °C (Porter and Ridgway, 1983).