CHAPTER III

RESULTS

Part I

The Alteration of Physicochemical Properties of Chitosan Solution and Cast Film: The Effect of Organic Acid, Treatment Condition, Plasticizer, Water Anionic Dye and Pigment

1. The Effect of Organic Acid on Some Properties of Chitosan Solutions

At a mole ratio of glucosamine unit:acid 1:1.2, all acids could solubilize chitosan powder to obtain clear solutions. The viscosities of 5% w/w of chitosan in different acid solutions are presented in Table *86*, Appendix B. The viscosity time profiles during 24 hours illustrated in Figure *3* showed that the viscosities of solutions were quite stable in the range of 104.28 to 138.12 cps. At 24 hours, the viscosity values of chitosan solutions containing citric or malic acids were rather less than those of the others.

The pH's of chitosan solutions using acetic, citric, formic, glycolic, lactic, malic and propionic acid as solubilizers were 4.64±0.05, 2.96±0.03, 3.74±0.02, 3.77±0.01, 4.50±0.03, 3.15±0.03 and 4.85±0.05, respectively as shown in Figure *4* (Table *87* in Appendix B).

2. The Effect of Organic Acid and Treatment Condition on Physicochemical Properties of Chitosan Films

Dry chitosan salt films were easily peeled off from petri dish. The freshly prepared films were slightly yellowish. Most prepared films were clear, non-tacky and transparent, except chitosan formate and glycolate films which were less transparent. Chitosan citrate and malate films were slightly brittle.

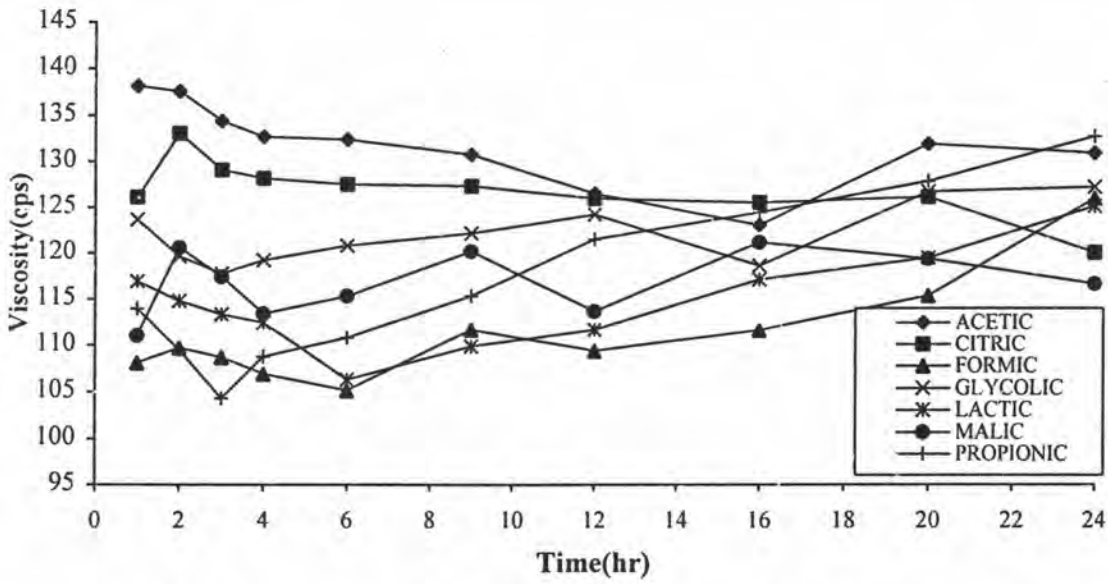


Figure 3. The viscosity of 5% w/w chitosan in various acid solutions (n=3).

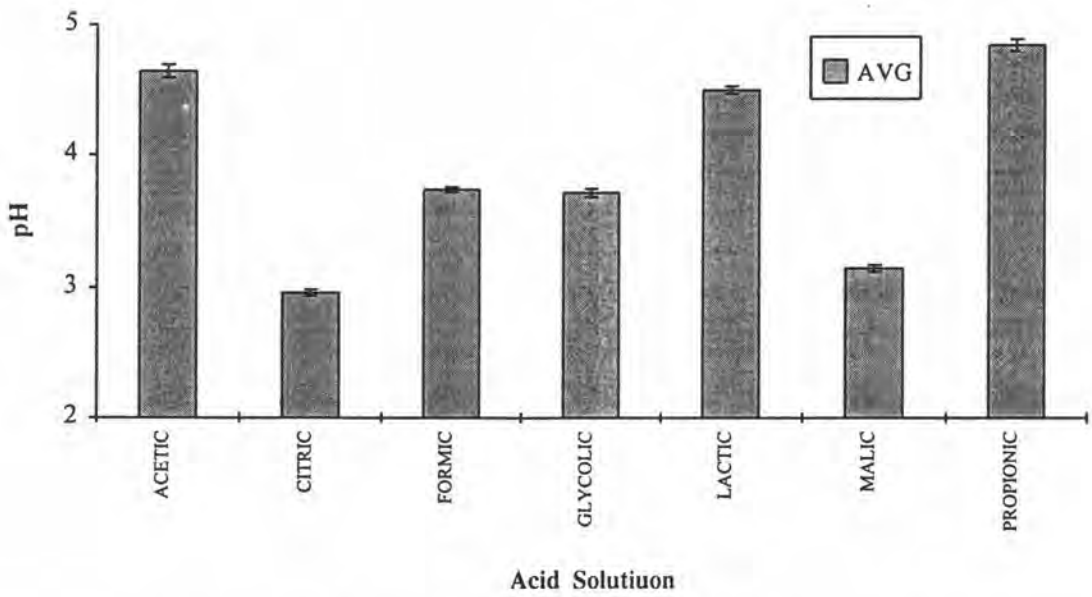


Figure 4. The pH of 5% w/w chitosan in various acid solutions at 24 hrs (n=3).

2.1. Water Sorption and Dissolution

All freshly prepared chitosan films could be readily dissolved in deionized water and HCl buffer pH 1.2 solution. The high swelling of free films was virtually observed before they were softened and eventually dissolved. Chitosan propionate film took longer time to dissolve than the others. The above observation was also found in case of the films after kept in vacuum for 168 hours and the films after drying at 60°C in hot air oven for 168 or 360 hours. However chitosan acetate film after kept at 60°C for 360 hours still remained its integrity but its water sorption and dissolution were very high. The freshly prepared or neutralized films after moist heat treatment could be readily dissolved in HCl buffer pH 1.2. The water sorption and dissolution in deionized water of the neutralized films after moist heat treatment for 168 hours was less than those of freshly prepared as presented in Table *5*.

In phosphate buffer the films still remained their integrities. The water sorption values of freshly prepared films of chitosan acetate, formate, glycolate, lactate, malate and propionate were 87.77±13.62, 48.56±5.33, 127.40±25.84, 38.91±6.23, 136.27±66.93 and 95.06±9.64 respectively and their dissolution values were -4.77±0.77, 5.28±1.75, 15.98±6.39, 8.83±1.32, 34.71±12.12 and -4.09±1.78 respectively. After kept in hot air oven for 168 or 360 hours, the water sorption and dissolution in phosphate buffer were also decreased.

The water sorption and dissolution of moist heat treated chitosan films are presented in Figures *5-10* (Tables *88* and *89* in Appendix B). After moist heat treatment, the water sorption and dissolution of most films in three media were noticeably decreased. Some could not be measured due to being soft gel or fragmentation. The water sorption and dissolution of treated films after different time interval of treatment depicted in Figures 5 and 6, showed that the films after exposure to moist heat noticeably decreased in water sorption and dissolution in deionized water. The value of these two parameters, water sorption and dissolution, was decreased to nearly stable after treatment longer than 24 hours. However the dissolution of chitosan citrate and malate films were still high and much higher than those of the others. Low % water sorption of chitosan citrate came from the high solubility in deionized water and resulted in the weight loss during water sorption test.

After exposure to moist heat, chitosan propionate film exhibited the lowest water sorption and dissolution which were less than 20.66±4.42%. The water sorption and dissolution values were nearly stable after 12 hours treatment. The dissolution of treated films in deionized water could be ranked: chitosan propionate<acetate<formate <lactate<glycolate<malate<citrate.

The tendency of water sorption and dissolution of treated chitosan salt films when using HCl buffer solution pH 1.2 as immersion medium was similar to that in deionized water except that the values of water sorption and dissolution were higher as shown in Figures 7 and 8. The water sorption and dissolution of film treated for 12-48 hours in deionized water and acid solution of chitosan citrate and malate could not be measured since they became soft gel which was difficult to handle. This observation was also found in the case of chitosan glycolate after treatment for 12 hours. Due to its

Table 5 Water sorption and dissolution of freshly prepared chitosan salt films and after kept in different condition.

Chitosan Salt Film	In Deionized Water		In HCl buffer pH 1.2		In Phosphate Buffer pH 6.8	
	WS(%)	%Dissolution	WS(%)	%Dissolution	WS(%)	%Dissolution
Acetate						
Freshly Prepared	*	*	*	*	87.77±13.62	-4.77±0.77
Vacuum 168 hrs.	*	*	*	*	93.10±6.96	-9.02±1.05
60°C 168 hrs.	*	*	*	*	87.82±9.39	-10.92±5.56
60°C 360 hrs.	1382.64±421.89	49.77±8.94	*	*	60.06±7.25	-4.23±0.85
Neutralized [a]	51.25±5.88	4.03±1.05	*	*	62.95±3.64	-5.69±0.82
Neutralized [b]	45.29±5.65	1.92±0.55	*	*	77.57±4.74	-17.42±0.95
Citrate						
Freshly Prepared	*	*	*	*	*	*
Vacuum 168 hrs.	*	*	*	*	*	*
60°C 168 hrs.	*	*	*	*	75.39±14.24	45.57±1.30
60°C 360 hrs.	-	-	-	-	108.95±33.65	50.44±3.05
Neutralized [a]	-	-	-	-	-	-
Neutralized [b]	-	-	-	-	-	-
Formate						
Freshly Prepared	*	*	*	*	48.56±5.33	5.28±1.75
Vacuum 168 hrs.	*	*	*	*	35.92±8.17	-2.17±0.57
60°C 168 hrs.	*	*	*	*	21.68±3.76	-2.24±1.25
60°C 360 hrs.	-	-	-	-	-	-
Neutralized [a]	-	-	*	*	38.36±5.91	-0.77+0.79
Neutralized [b]	-	-	*	*	36.99±6.75	0.05+1.86
Glycolate						
Freshly Prepared	*	*	*	*	127.40±25.84	15.98±6.39
Vacuum 168 hrs.	*	*	*	*	124.01±8.02	19.01±1.09
60°C 168 hrs.	-	-	-	-	60.39±6.39	-1.05±1.06
60°C 360 hrs.	*	*	*	*	60.65±9.58	9.91±2.37
Neutralized [a]	-	-	*	*	56.09±6.37	9.91±1.69
Neutralized [b]	-	-	*	*	52.68±6.00	7.65±1.71
Lactate						
Freshly Prepared	*	*	*	*		
Vacuum 168 hrs.	*	*	*	*	197.17±23.60	11.43±2.06
60°C 168 hrs.	*	*	*	*	157.49±20.44	13.81±1.00
60°C 360 hrs.	-	-	-	-	103.06±12.97	14.31±1.59
Neutralized [a]	-	-	*	*	139.23±10.48	11.96±2.45
Neutralized [b]	-	-	*	*	135.26±14.90	12.77±2.05
Malate						
Freshly Prepared	*	*	*	*	136.27±66.93	34.71±12.12
Vacuum 168 hrs.	*	*	*	*	127.61±16.04	33.21±2.69
60°C 168 hrs.	*	*	*	*	126.20±13.68	29.04±0.93
60°C 360 hrs.	-	-	-	-	-	-
Neutralized [a]	-	-	-	-	-	-
Neutralized [b]	-	-	-	-	-	-
Propionate						
Freshly Prepared	*	*	*	*	95.06±9.64	-4.09±1.78
Vacuum 168 hrs.	*	*	*	*	50.15±7.62	-2.01±1.10
60°C 168 hrs.	-	-	-	-	60.39±6.39	-1.05±1.06
60°C 360 hrs.	*	*	*	*	52.68±19.74	0.28±1.06
Neutralized [a]	-	-	*	*	50.19±2.76	-1.17±1.02
Neutralized [b]	-	-	*	*	49.51±3.96	-0.46±1.01

*The film was dissolved

-Not measured

[a]Freshly prepared

[b]After moist heat treatment for 168 hrs.

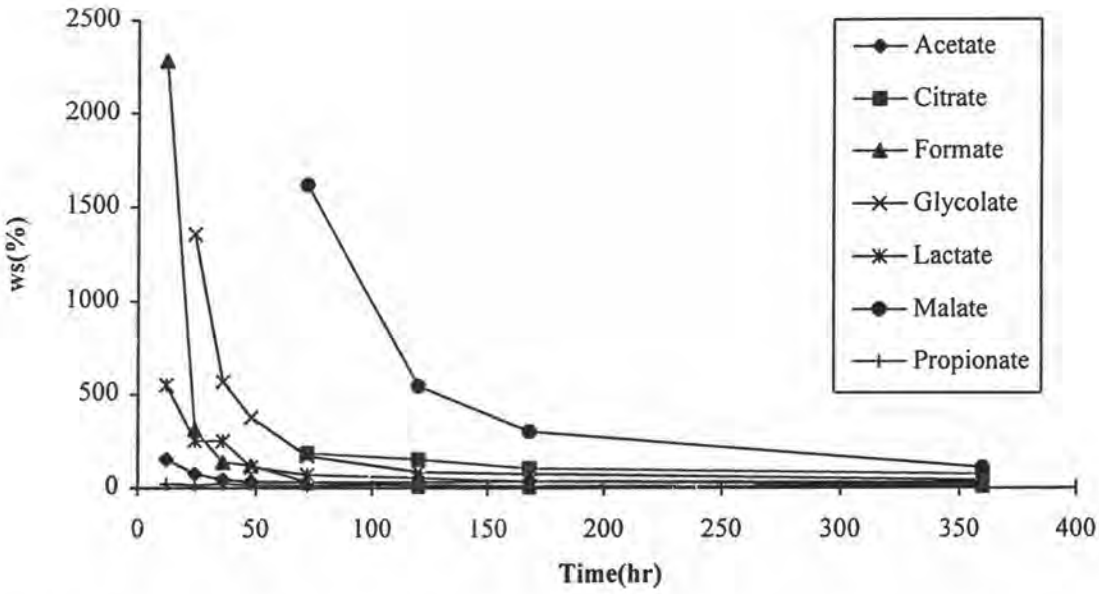


Figure 5 Water sorption (WS) of chitosan salt films after exposured moist heat at 60°C at different time intervals in deionized water (n=6).

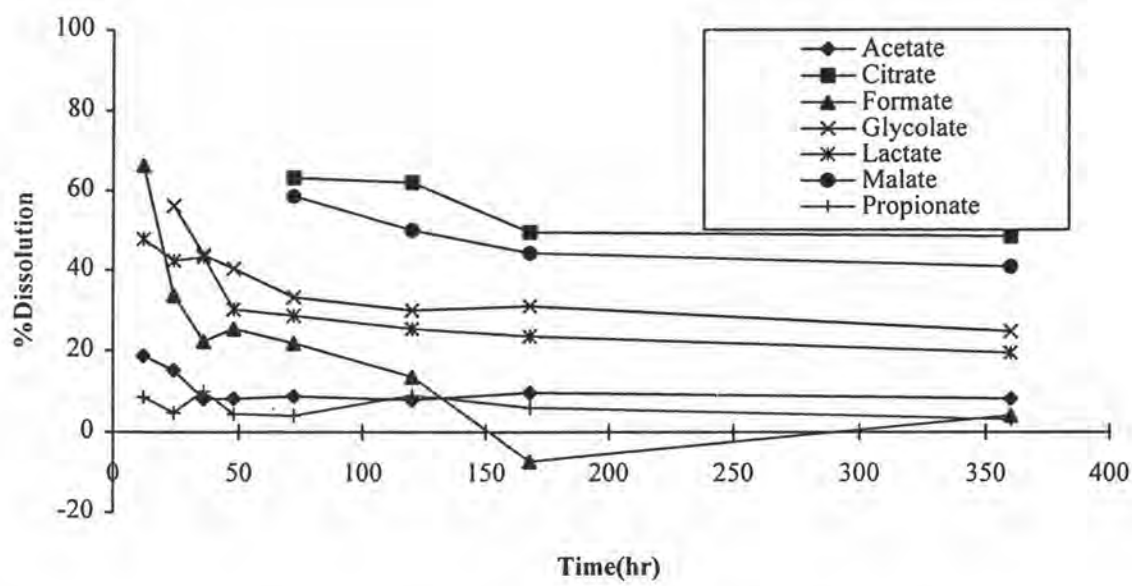


Figure 6 Dissolution of chitosan salt films after exposured moist heat at 60°C at different time intervals in deionized water (n=6).

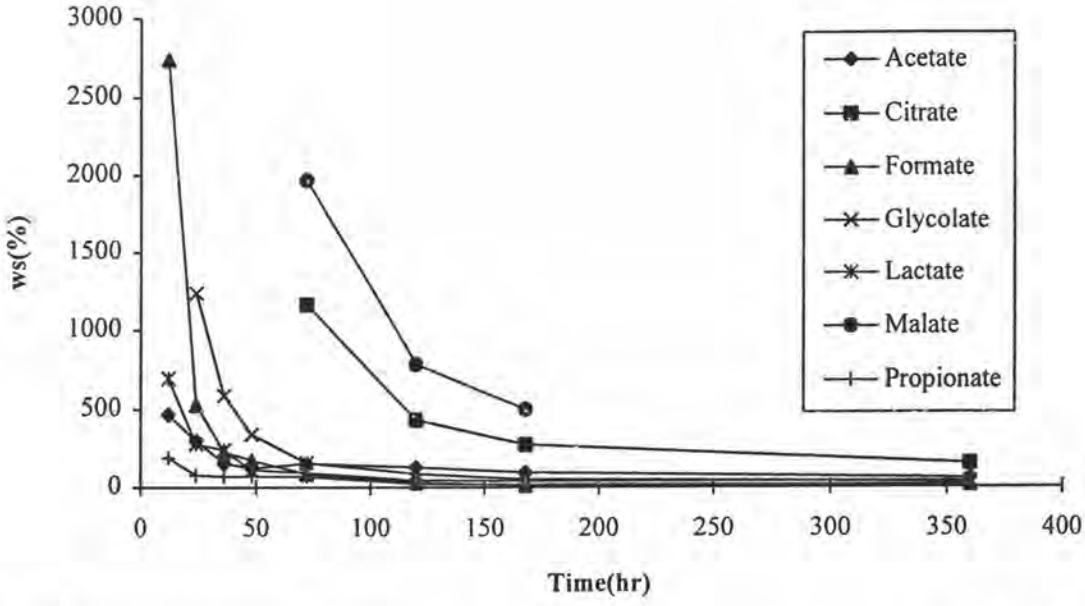


Figure 7 Water sorption (WS) of chitosan salt films after exposured moist heat at 60°C at different time intervals in HCl buffer pH 1.2 (n=6).

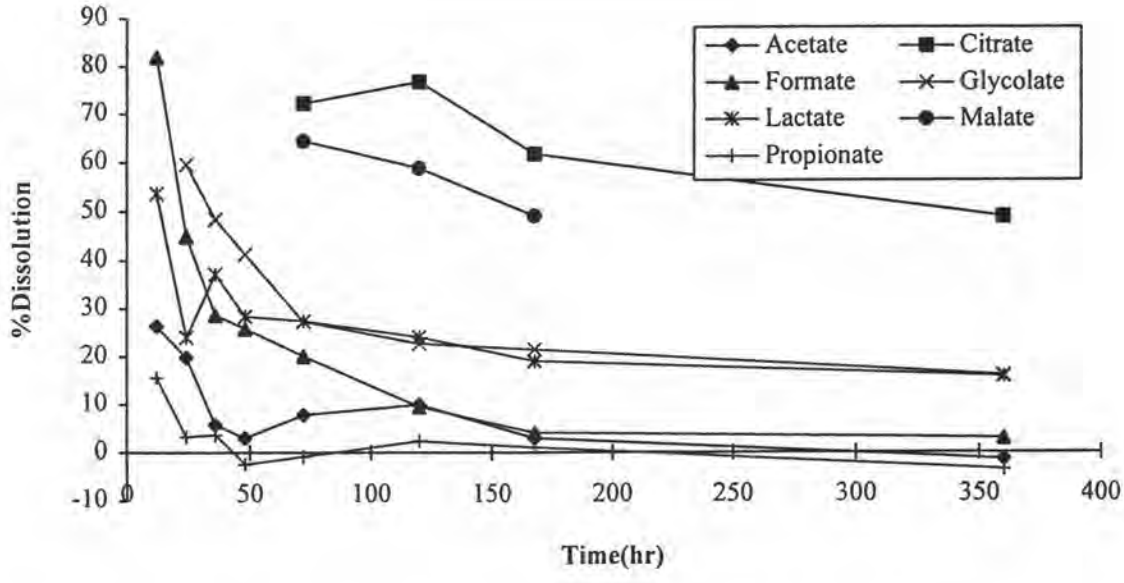


Figure 8 Dissolution of chitosan salt films after exposured moist heat at 60°C at different time intervals in HCl buffer pH 1.2 (n=6).

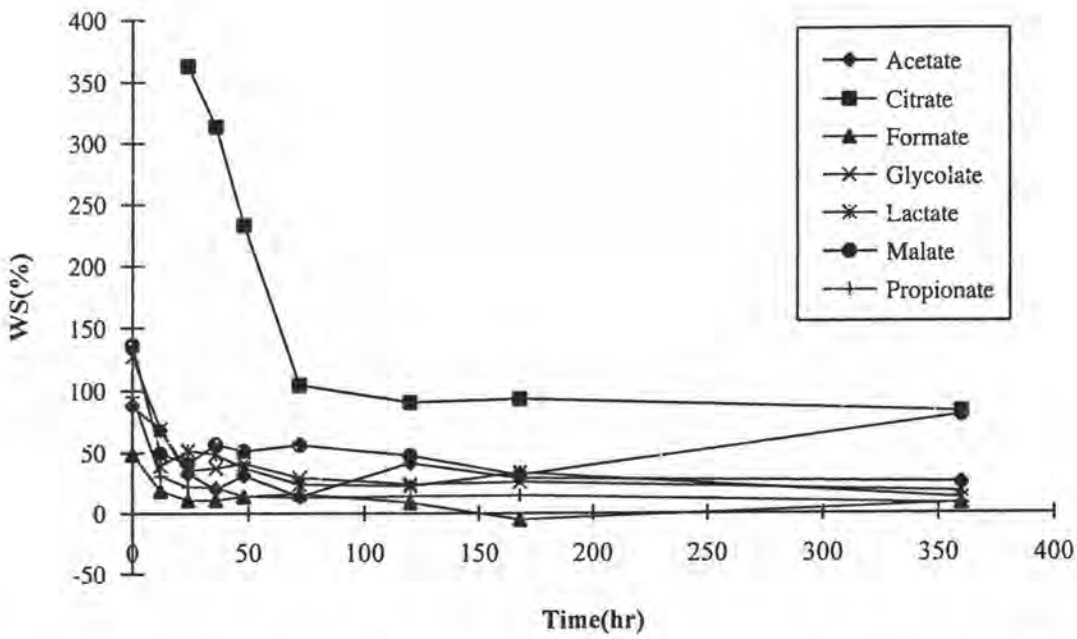


Figure 9 Water sorption (WS) of chitosan salt films after exposured moist heat at 60°C at different time intervals in phosphate buffer pH 6.8 (n=6).

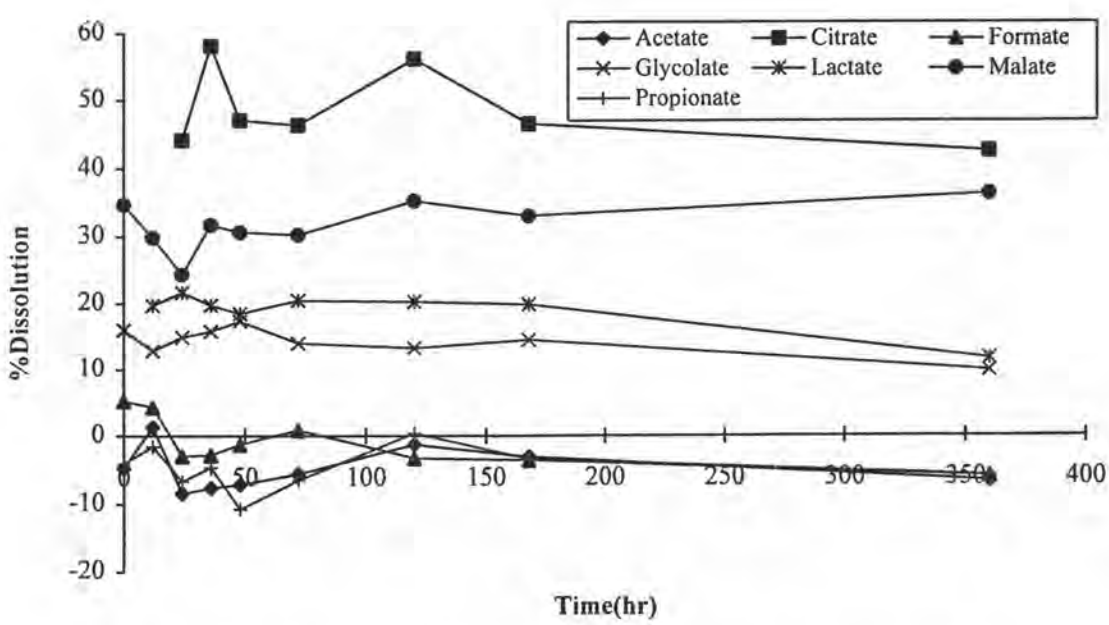


Figure 10 Dissolution of chitosan salt films after exposured moist heat at 60°C at different time intervals in phosphate buffer pH 6.8 (n=6).

disintegration to small fragments in acid solution, chitosan malate film after treatment for 360 hours could not be measured for water sorption and dissolution.

The ranking of dissolution of treated films in acid solution was similar to that of in deionized water as followed: chitosan propionate<acetate<formate<lactate <glycolate<malate<citrate. The water sorption of chitosan propionate film after treatment for 12 and 360 hours was 191.32±40.09 and 12.70±2.86 respectively. After treatment for 72 hours the water sorption and dissolution of all treated films tended to be stable. The dissolution of chitosan acetate, formate and propionate films after moist heat treatment for 360 hours was nearly negligible in both deionized water and acid solution.

When treated films were immersed in phosphate buffer most of them still remained their integrity except chitosan citrate and malate films which they became turbid soft gel. The dissolution of both films was still high. The decrease in water sorption and dissolution of other films could also be observed as illustrated in Figures *9* and *10*, however their dissolution values were slightly changed. The dissolution of some films was of negative value as also seen in case of freshly prepared films. The order of film solubility in phosphate buffer could be ranked as chitosan acetate≈propionate<formate <glycolate<lactate<malate<citrate.

Figures *11*, *13* and *15* (Table *90* in Appendix B) showed the % ws and Figures *12*, *14* and *16* (Table *91* in Appendix B) showed the dissolution of films treated at 130°C after immersion in deionised water, HCl buffer pH 1.2 and phosphate buffer pH 6.8 respectively. Four chitosan salt films, chitosan acetate, citrate, formate and propionate, were chosen to treat with dry heat at 130°C for 1 to 12 hours. The longer exposure to dry heat, the more decrease in water sorption was obtained. It was also found that dissolution tended to decrease in both deionized water and acid solution. The water sorption and dissolution values of dry heat treated films for 12 hours were higher than those of films after moist heat treatment for 360 hours. The dry heat with temperature of 130°C caused chitosan films to be easily disintegrated into small fragments after immersion in immersion fluids, whereas moist heat treated films still remained their integrity. Unexpectedly, both water sorption and dissolution of chitosan citrate were much lower than those of using moist heat in both deionized water and acid solution. The dry heat treatment did not markedly affect the water sorption and dissolution of the films after immersion in phosphate buffer. The lowering in water sorption and dissolution of chitosan formate than those of chitosan acetate and propionate films could be clearly observed.

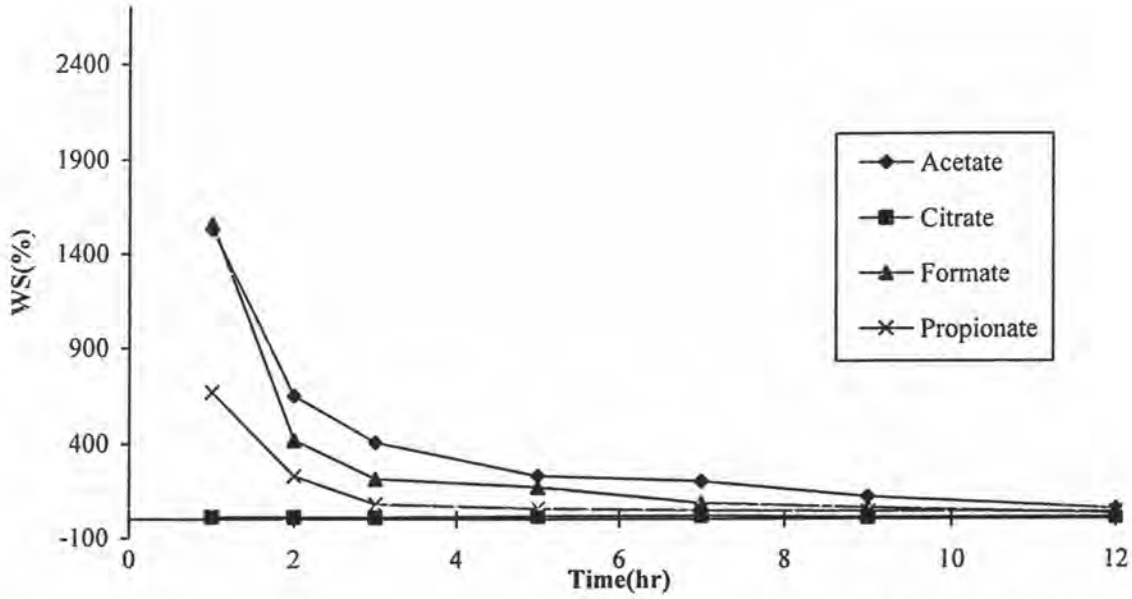


Figure 11 Water sorption (WS) of chitosan salt films after exposured dry heat at 130°C at differnt time interval in deionized water (n=6).

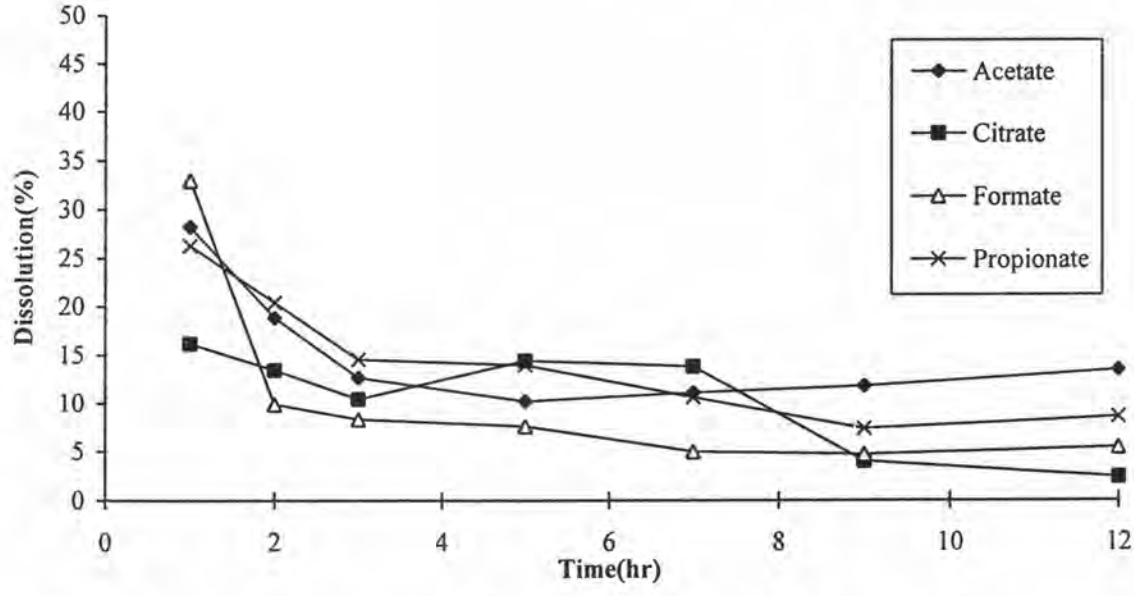


Figure 12 Dissolution of chitosan salt films after exposured dry heat at 130°C at differnt time interval in deionized water (n=6).

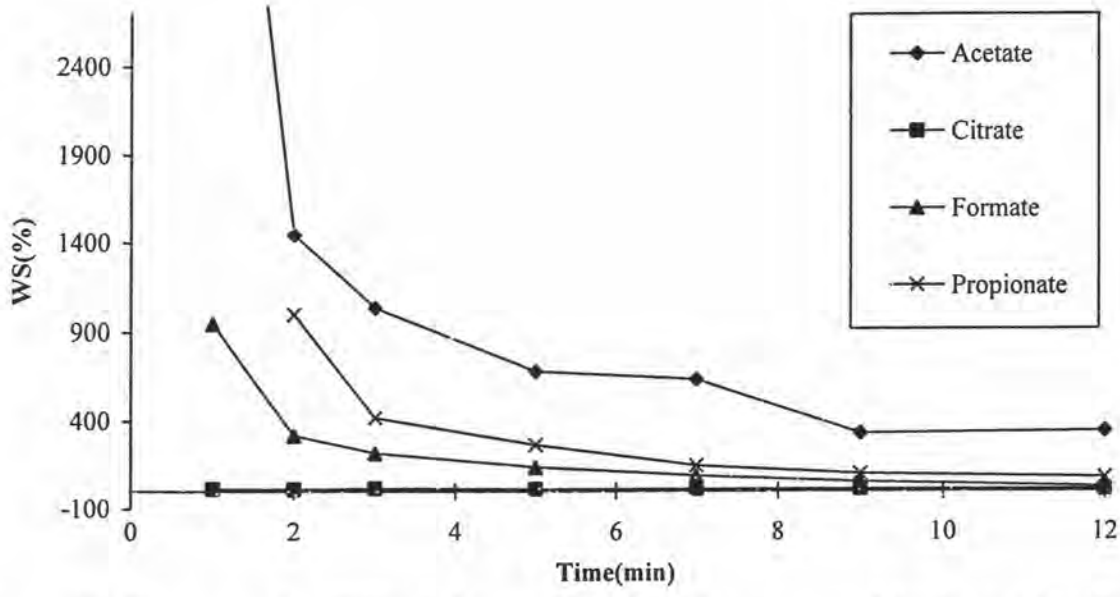


Figure 13 Water sorption (WS) of chitosan salt films after exposured dry heat at 130°C at differnt time interval in HCl buffer pH 1.2 (n=6).

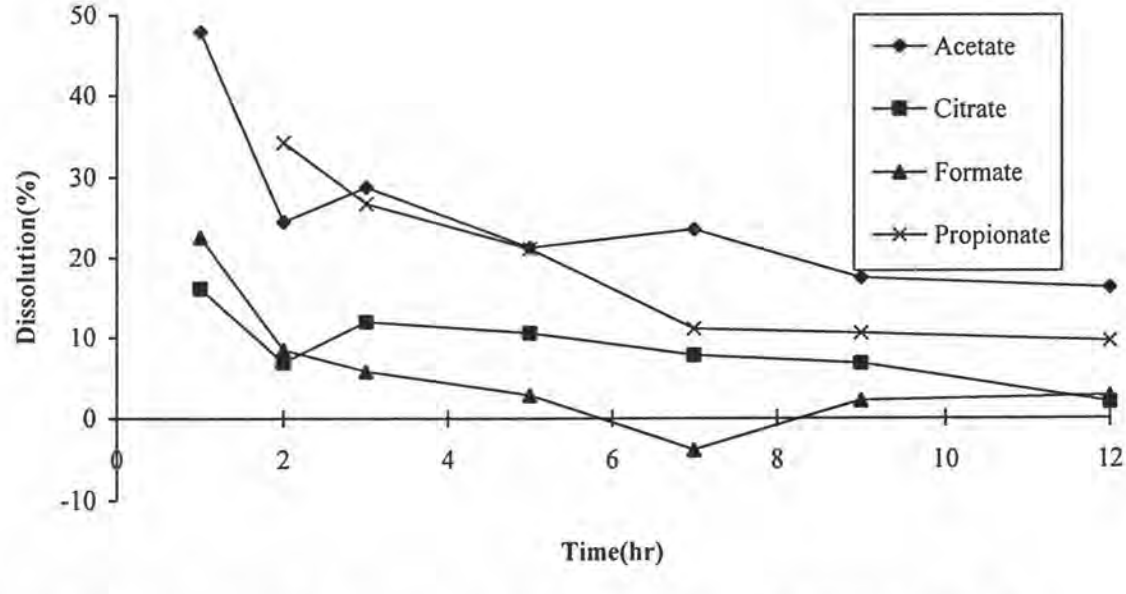


Figure 14 Dissolution of chitosan salt films after exposured dry heat at 130°C at differnt time interval in HCl buffer pH 1.2 (n=6).

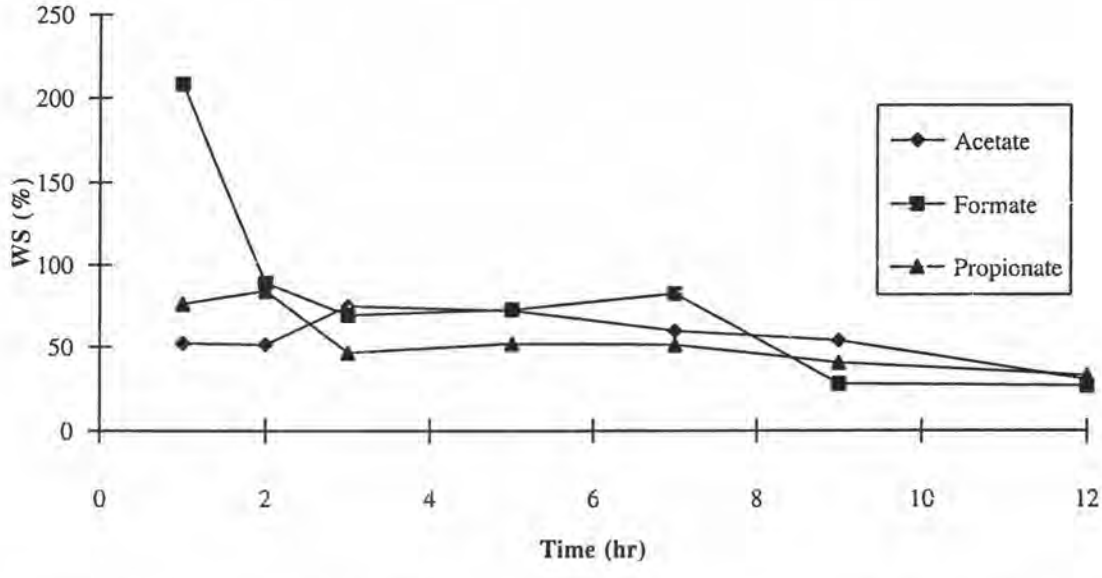


Figure 15 Water sorption (WS) of chitosan salt films after exposured dry heat at130°C at differnt time interval in phosphate buffer pH 6.8 (n=6).

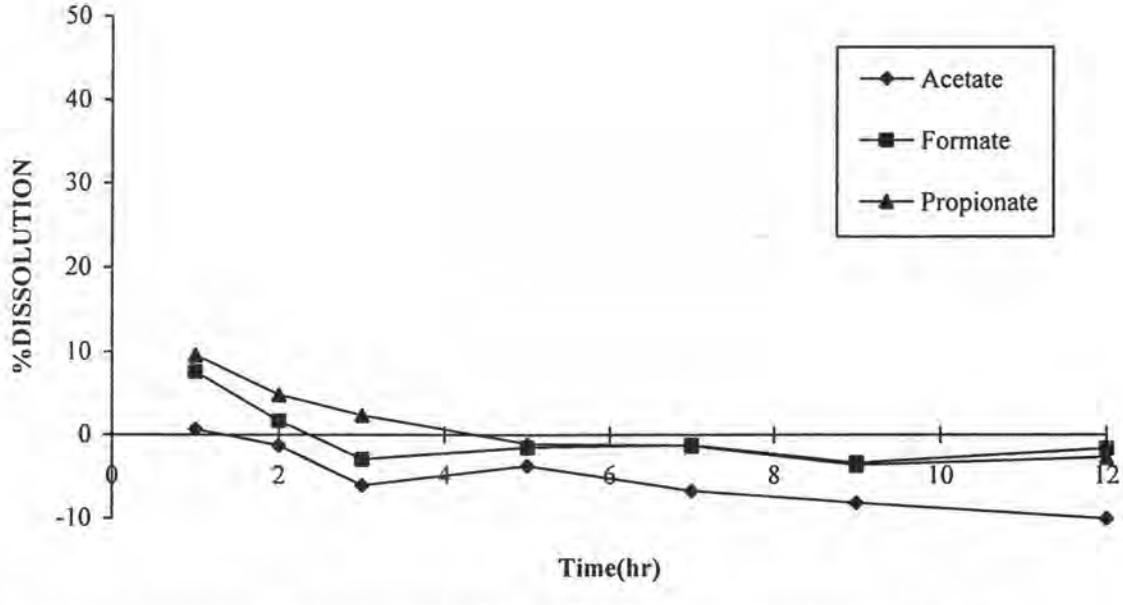


Figure 16 Dissolution of chitosan salt films after exposured dry heat at 130°C at differnt time interval in phosphate buffer pH 6.8(n=6).

2.2 Fourier Transform Infrared (FT-IR) Studies

The FT-IR spectrum of chitosan powder in Figure 17 showed the peak at 1588 cm^{-1} indicating NH_2 deformation overlapped with the amide II band at 1558 cm^{-1}. The peak at 1655 cm^{-1} was amide I band. The broad band centered at 3450 cm^{-1} was O-H stretching and the peak nearly to 2990 cm^{-1} was C-H stretching band. No difference in FT-IR spectra was observed after chitosan powder was exposed to moist heat for 12 to 360 hours or kept in hot air oven at 60°C for 168 hours.

The FT-IR spectra of pure acids used in this study are illustrated in Figures *18-20* and the FT-IR spectra of physical mixtures between chitosan and solid acids are shown in Figure *21*. It was found that the peaks of solid acids were dominant in spectra of physical mixtures with the except of diffraction of the physical mixture between chitosan and glycolic acid which showed the peak of both substances in FT-IR spectrum.

The evidence from FT-IR spectra of freshly prepared chitosan acetate and propionate films as shown in Figures *22* and *28* respectively exhibited the peaks at 1514 and 1615 cm^{-1} which indicated to $-NH_3^+$ band but the band at 1588 cm^{-1} indicating $-NH_2$ deformation was disappeared. The peak at 1556 cm^{-1} of acids which were presented in the carboxylate form of COO^- could be observed. Considerably, the amide II band and carboxylate band appeared in the same region and amide I band still appeared in spectra at 1655 cm^{-1}. Additionally, the carbonyl absorption peak of pure acetic and propionic acid which should be found at wavelength number higher than 1700 cm^{-1} did not appear in the spectra of these films. After exposure to moist heat, the $-NH_3^+$ band and carboxylate band had a tendency to regress with time. Another interesting observation arising from spectra concerned that the longer exposure to moist heat, the stronger intensity of peak at 1655 cm^{-1} was appeared.

The occurrence of broad band between 1550-1650 cm^{-1} in the FT-IR spectra of chitosan formate film hindered the interesting peaks in this region as shown in Figure *24*. No carbonyl peak of formic acid was presented at 1710 cm^{-1}. The spectra of chitosan citrate, glycolate, lactate and malate in Figures *23, 25, 26* and *27* respectively apparently showed the acidic carbonyl absorption peak at 1710, 1729, 1718 and 1724 cm^{-1} respectively. The carbonyl peaks of chitosan citrate and malate still remained after treatment with moist heat, whereas those from chitosan glycolate and lactate were regressed with time and finally disappeared after 168 hours treatment. Moreover, chitosan glycolate and lactate films tended to exhibit higher peak intensity after longer time of treatment indicated an increase in degree of crystallinity.

The cast films after vacuum for 168 hours or dried heat at 60°C for 168 or 360 hours did not much affect the FT-IR absorption of chitosan film as shown in Figures *29-33*. The spectra showed only slight regression peak intensity of 1558 cm^{-1}. Effect of dry heat at 130°C on chitosan film was interesting. Chitosan acetate, citrate, formate and propionate films were subjected to this dry heat and their FT-IR spectra are shown in Figures *29, 30, 31* and *33* respectively. The shoulder peak at 1741 cm^{-1} was appeared in FT-IR spectra of chitosan acetate and propionate films while the amide II peak at 1558 cm^{-1} still remained after exposure to dry heat at 130°C. Whereas after exposure to the temperature at 130°C, chitosan formate showed the amide band at 1655 cm^{-1} but there

was no presence of carbonyl band over the wave number of 1700 cm^{-1}. It appeared that all peak intensities of chitosan citrate were regressed after exposure to dry heat at 130°C.

Chitosan films prepared by using different acids neutralized with 0.5 N sodium phosphate solution had the FT-IR absorption pattern similar to that of chitosan powder as shown in Figure *34*.

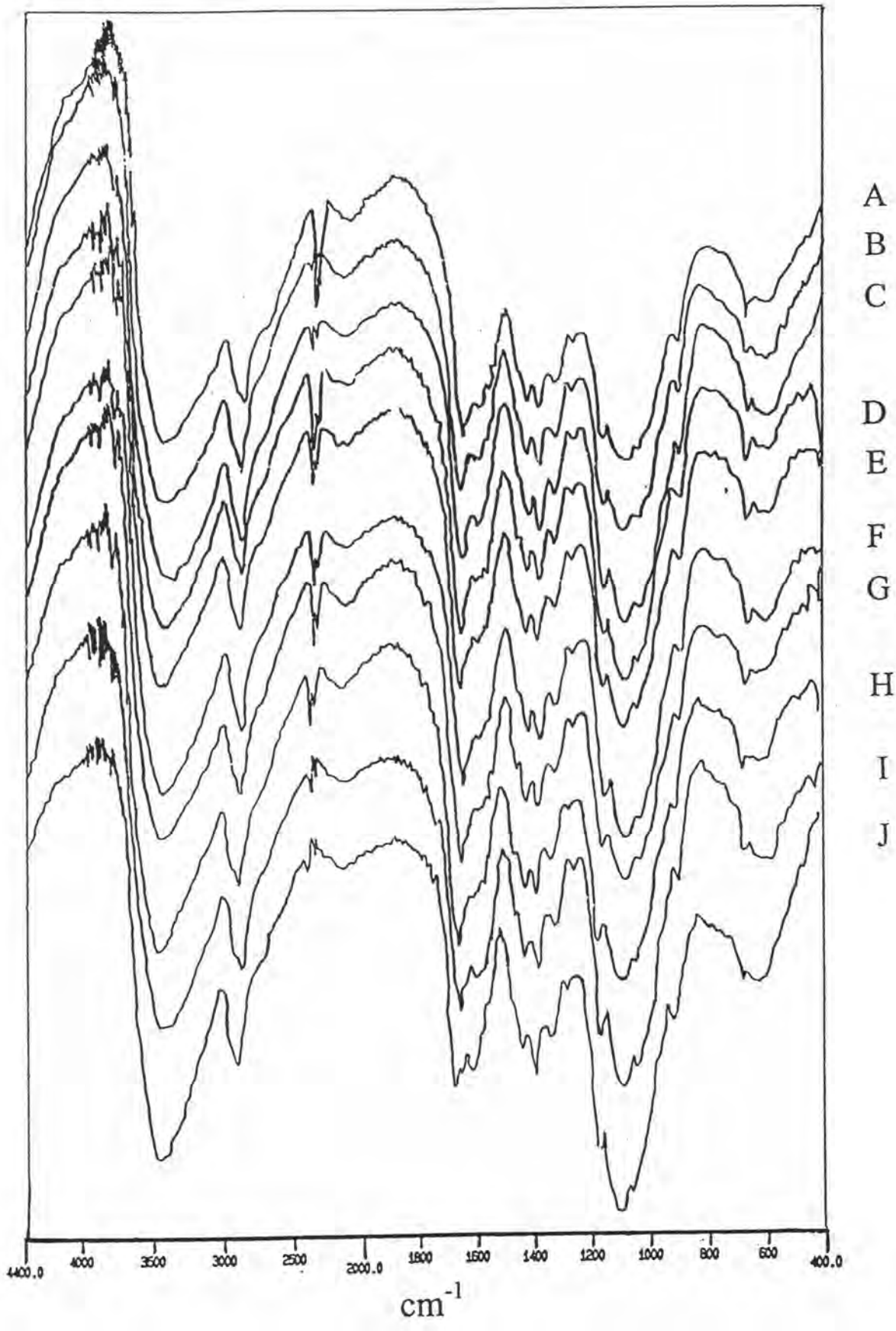


Figure 17 FT-IR spectra of chitosan powders (A) untreated; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs. and (J) after exposed to dry heat at 60°C 168 hrs.

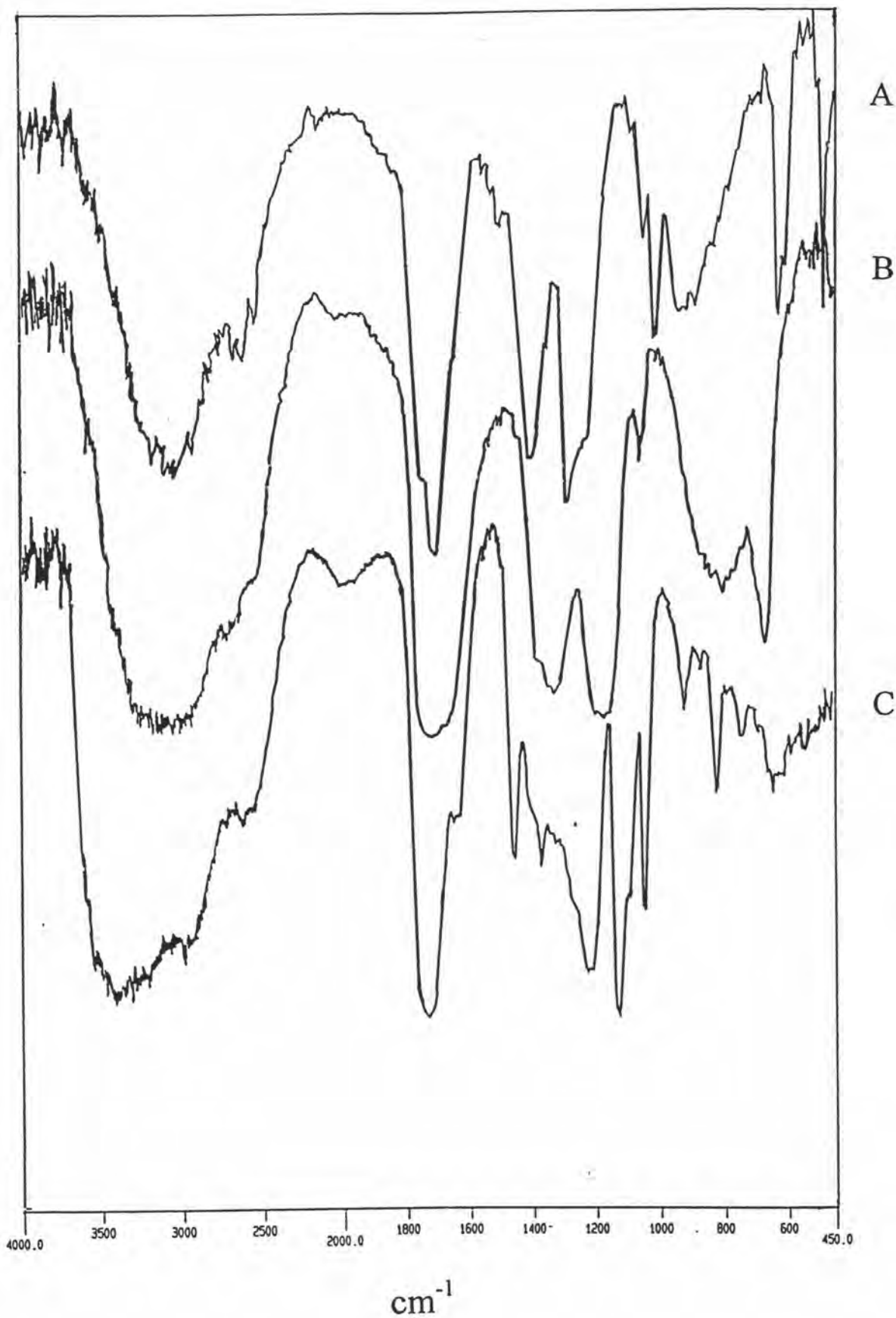


Figure 18 FT-IR spectra of (A) acetic acid; (B) formic acid and (C) lactic acid.

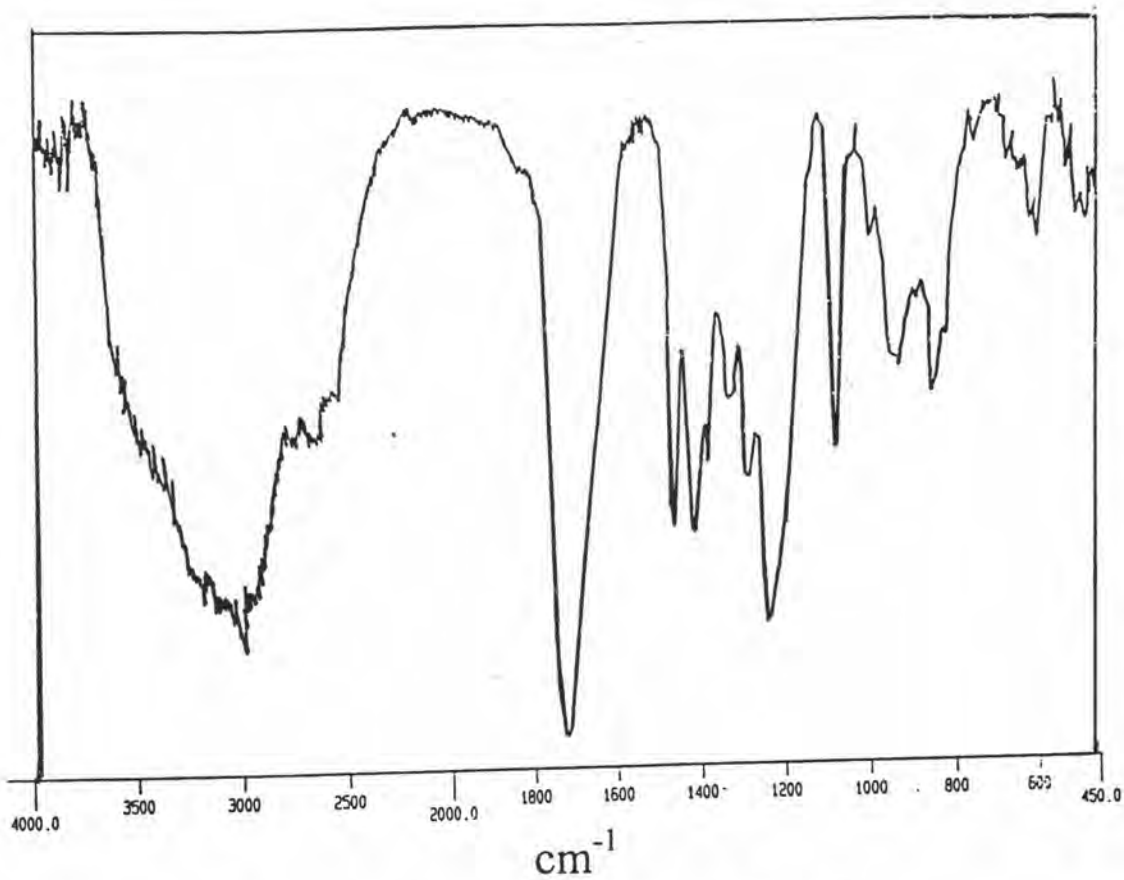


Figure 19 FT-IR spectra of (A) propionic acid.

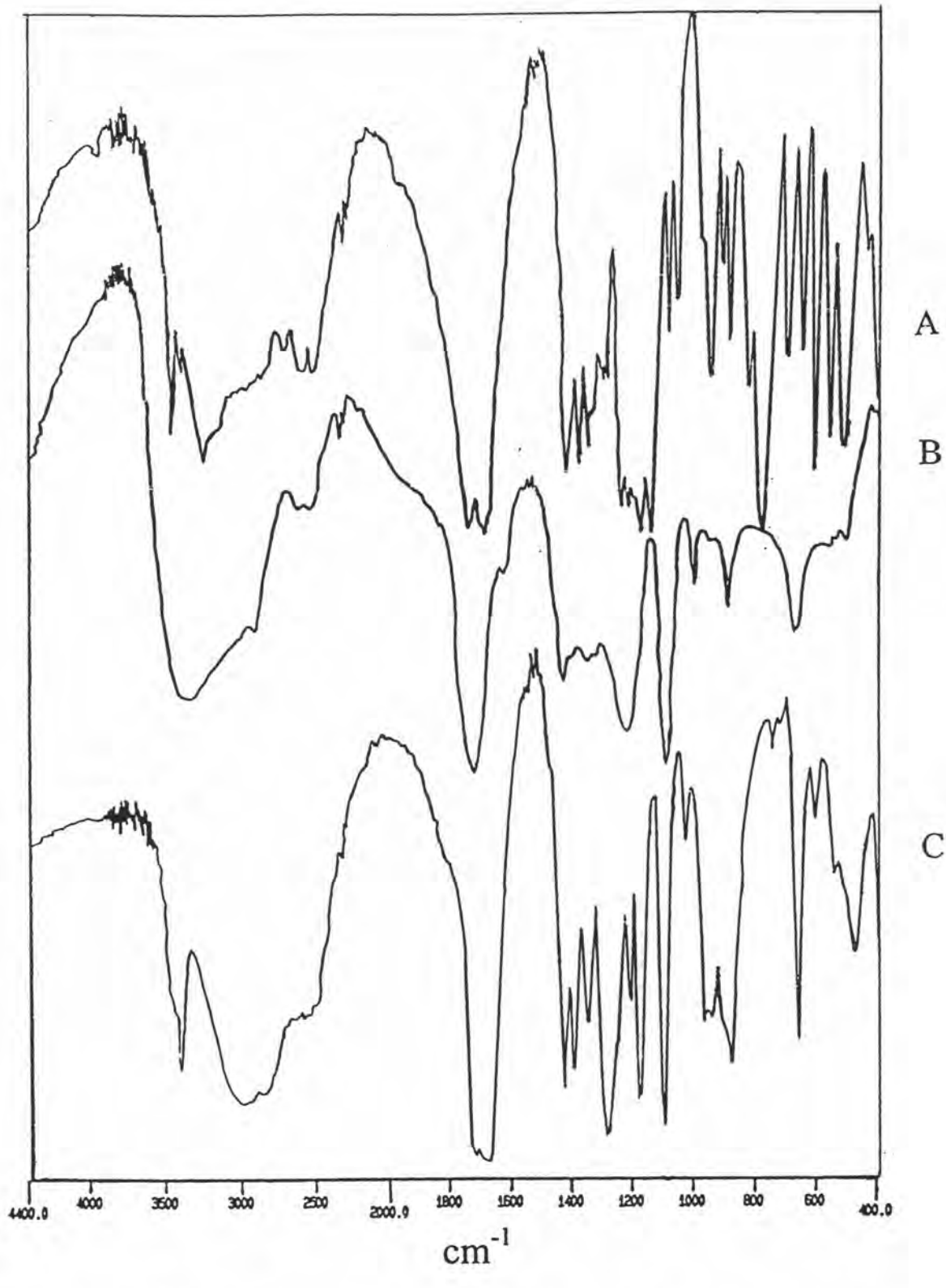


Figure 20 FT-IR spectra of (A) citric acid; (B) glycolic acid and (C) malic acid.

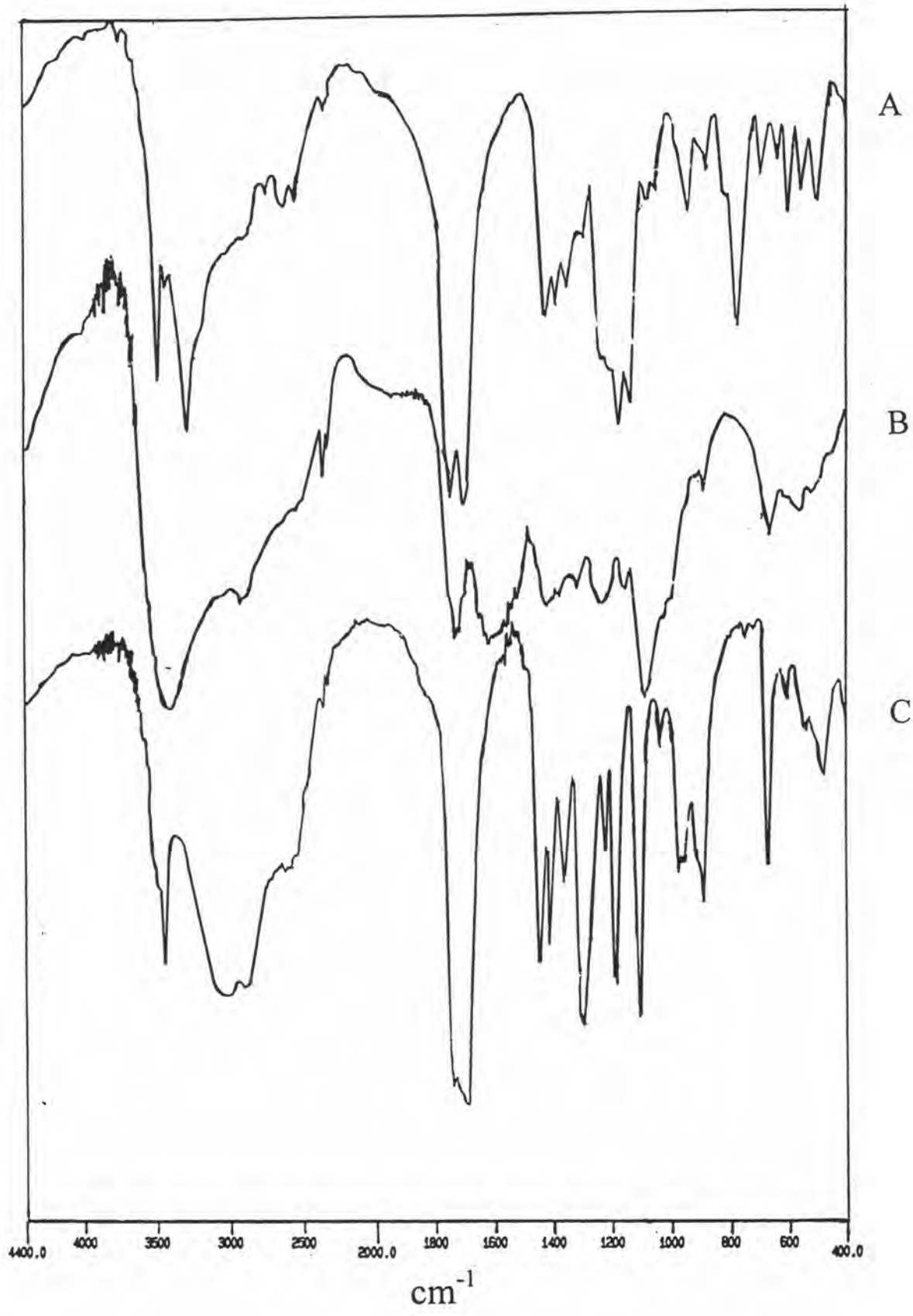


Figure 21 FT-IR spectra of physical mixture between (A) chitosan and citric acid; (B) chitosan and glycolic acid and (C) chitosan and malic acid.

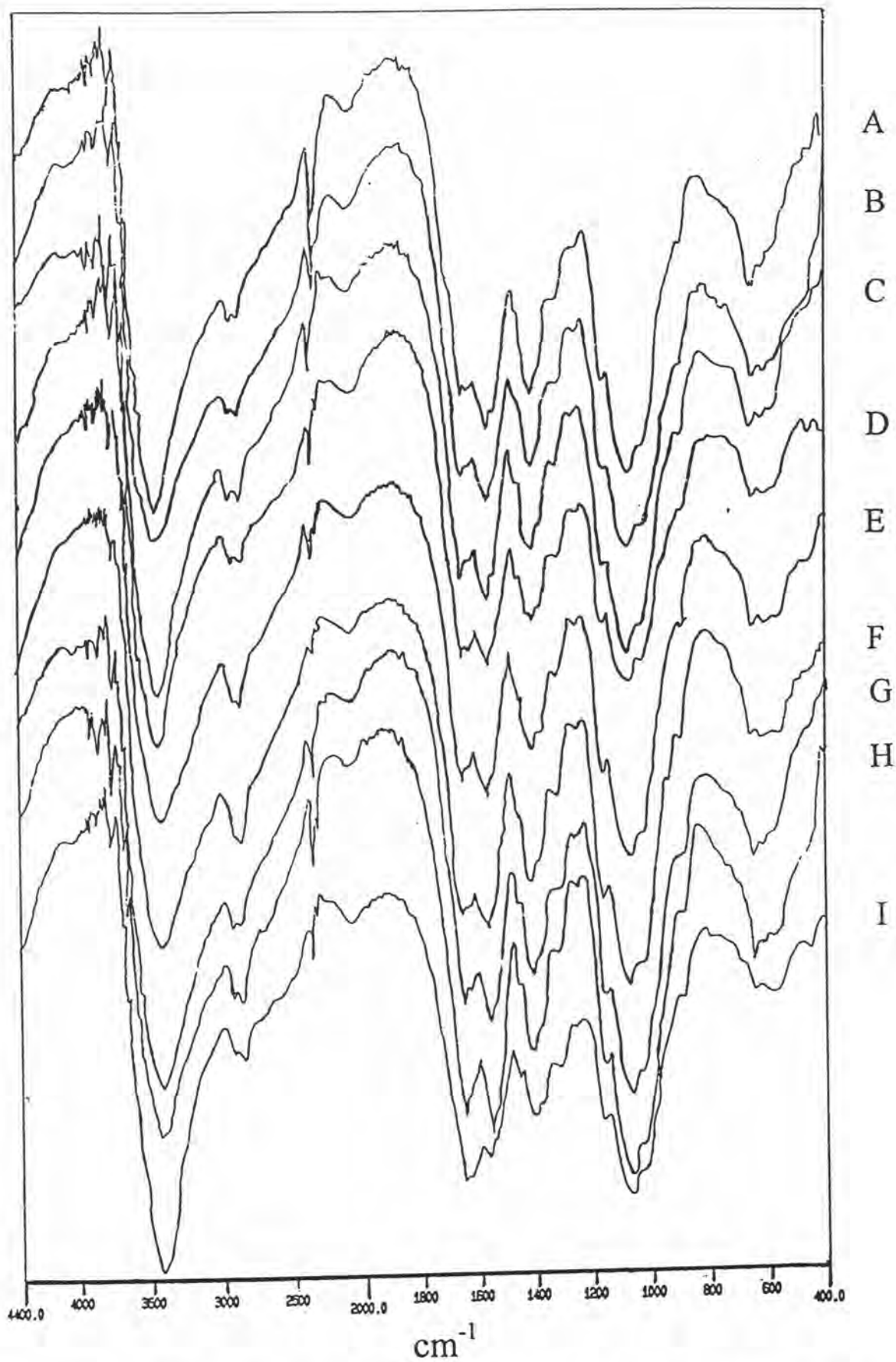


Figure 22 FT-IR spectra of chitosan acetate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

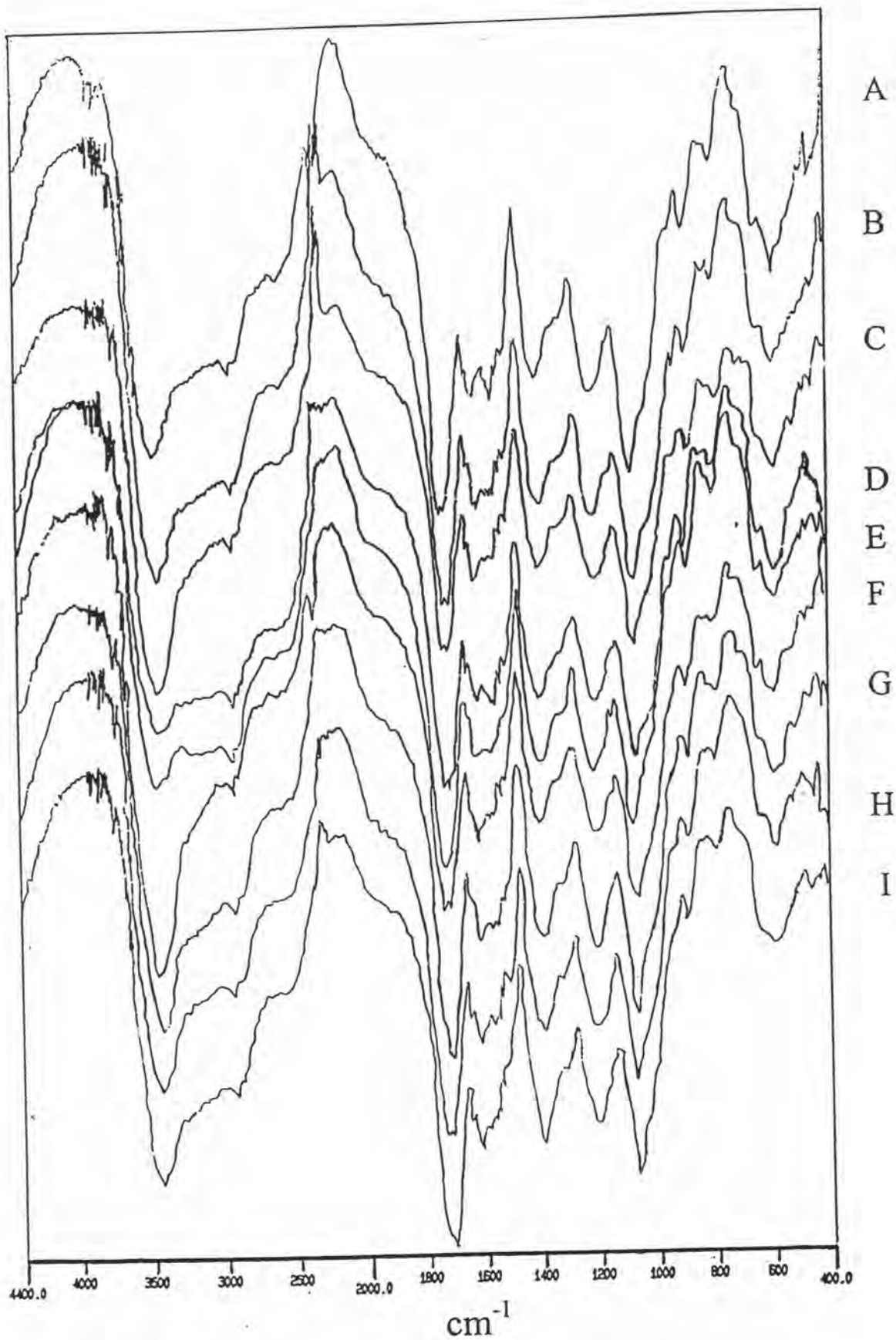


Figure 23 FT-IR spectra of chitosan citrate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

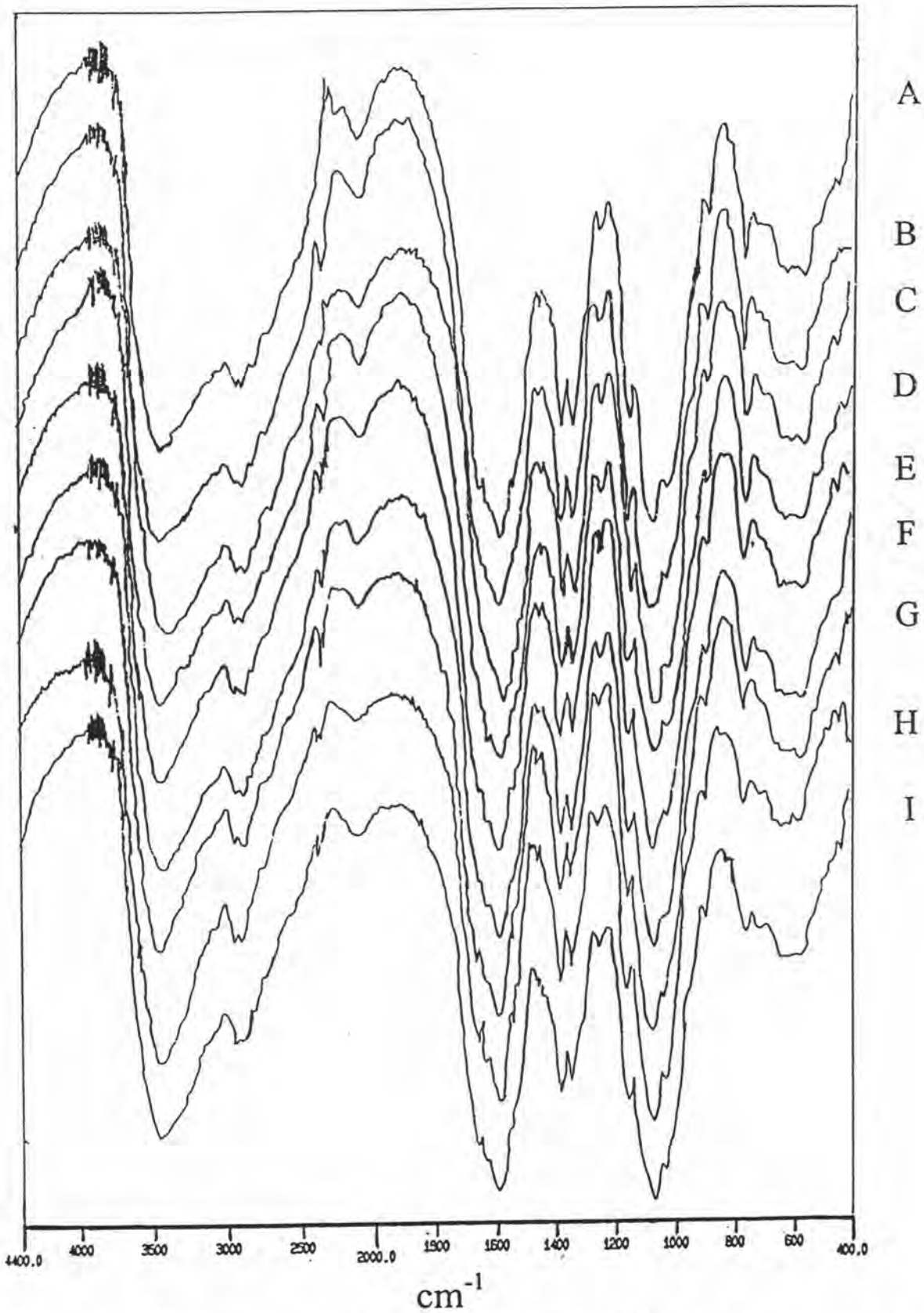


Figure 24 FT-IR spectra of chitosan formate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

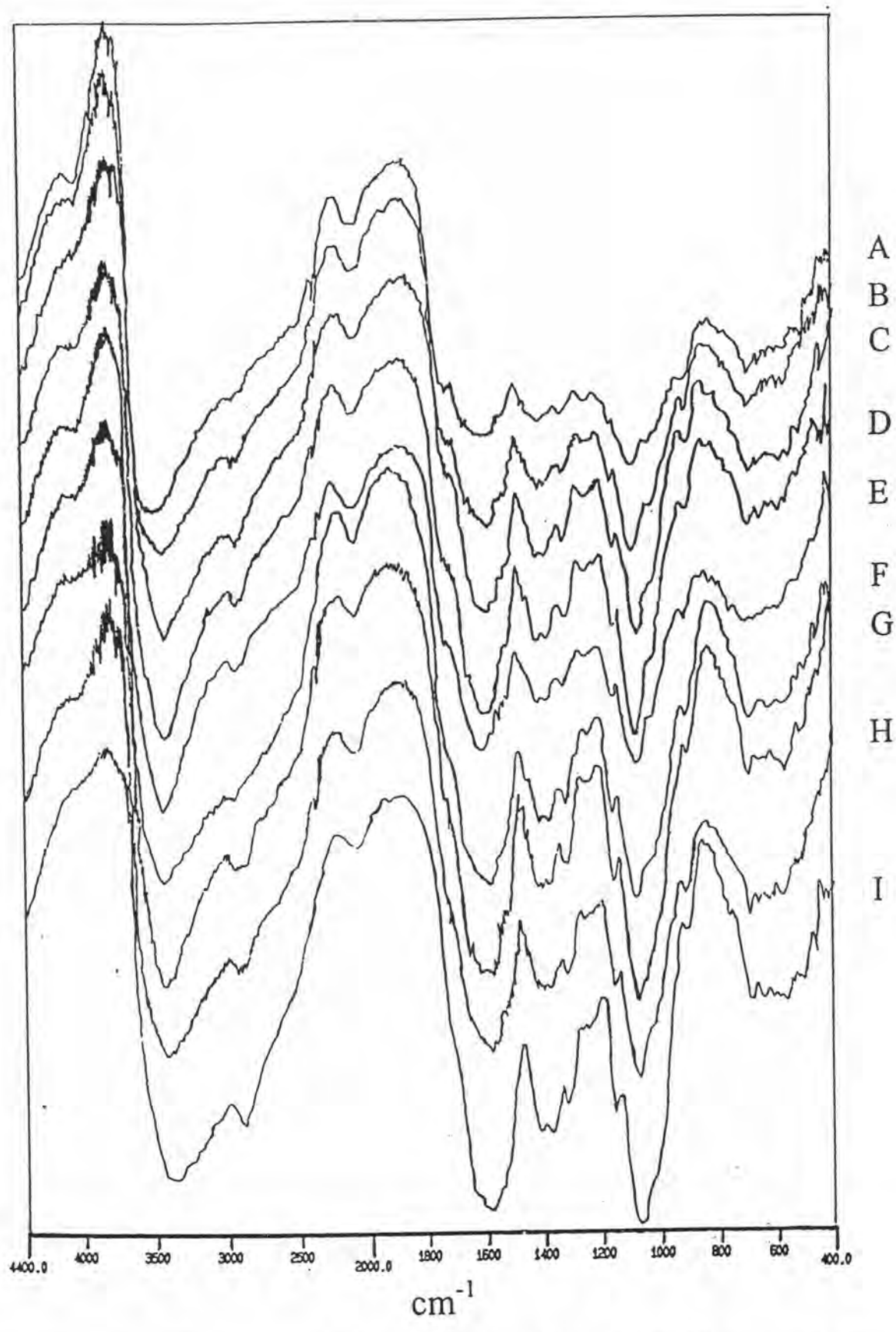


Figure 25 FT-IR spectra of chitosan glycolate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

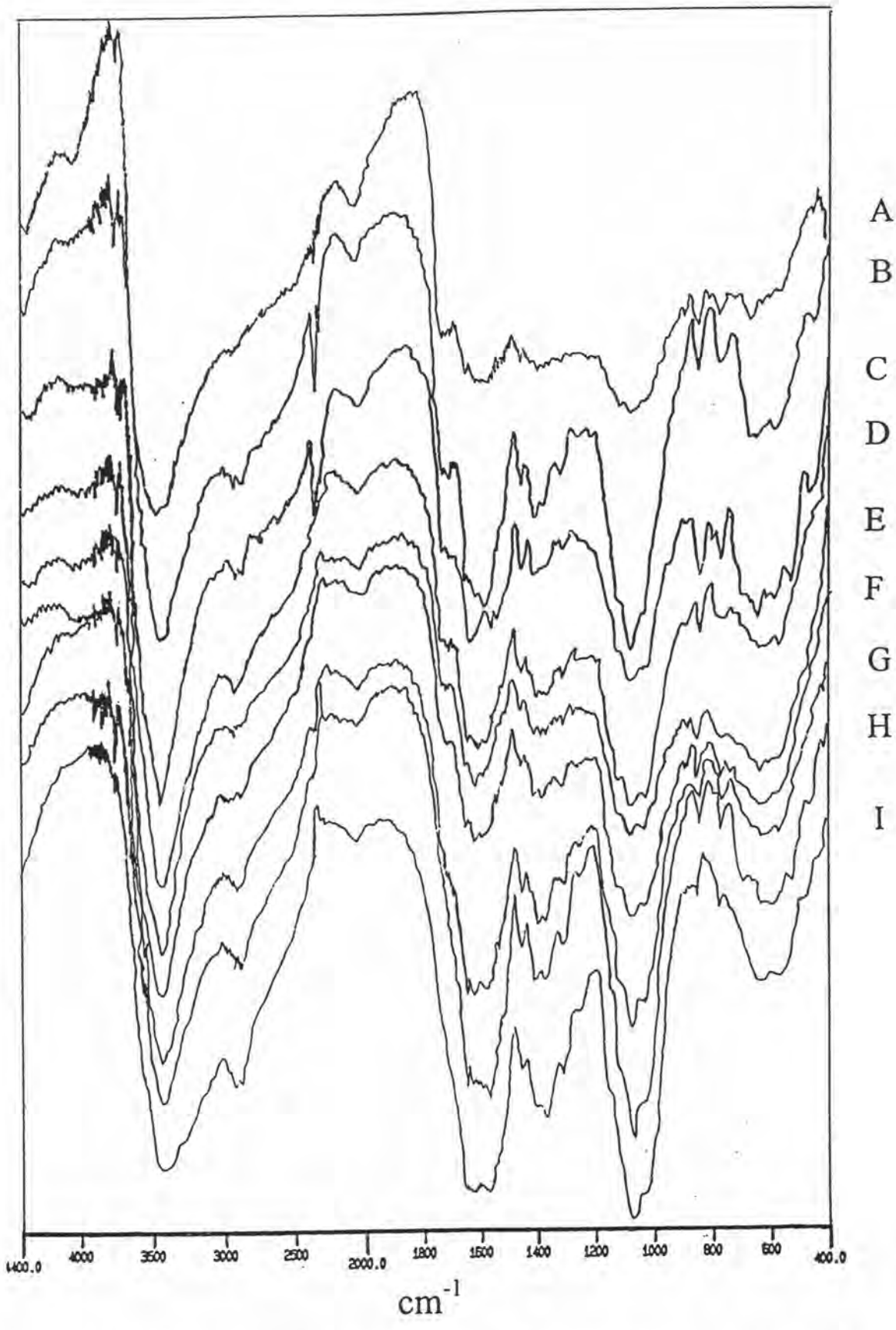


Figure 26 FT-IR spectra of chitosan lactate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

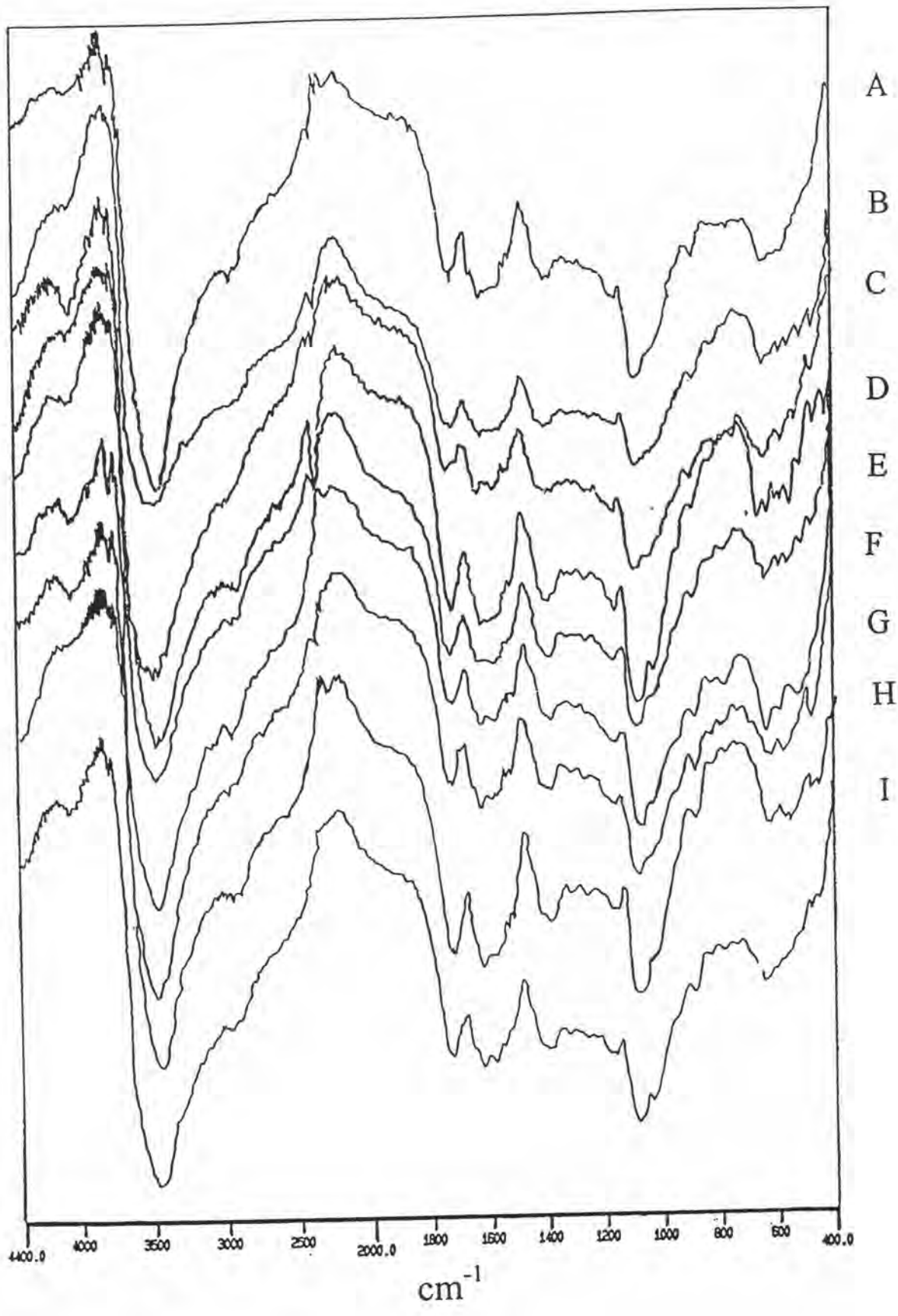


Figure 27 FT-IR spectra of chitosan malate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

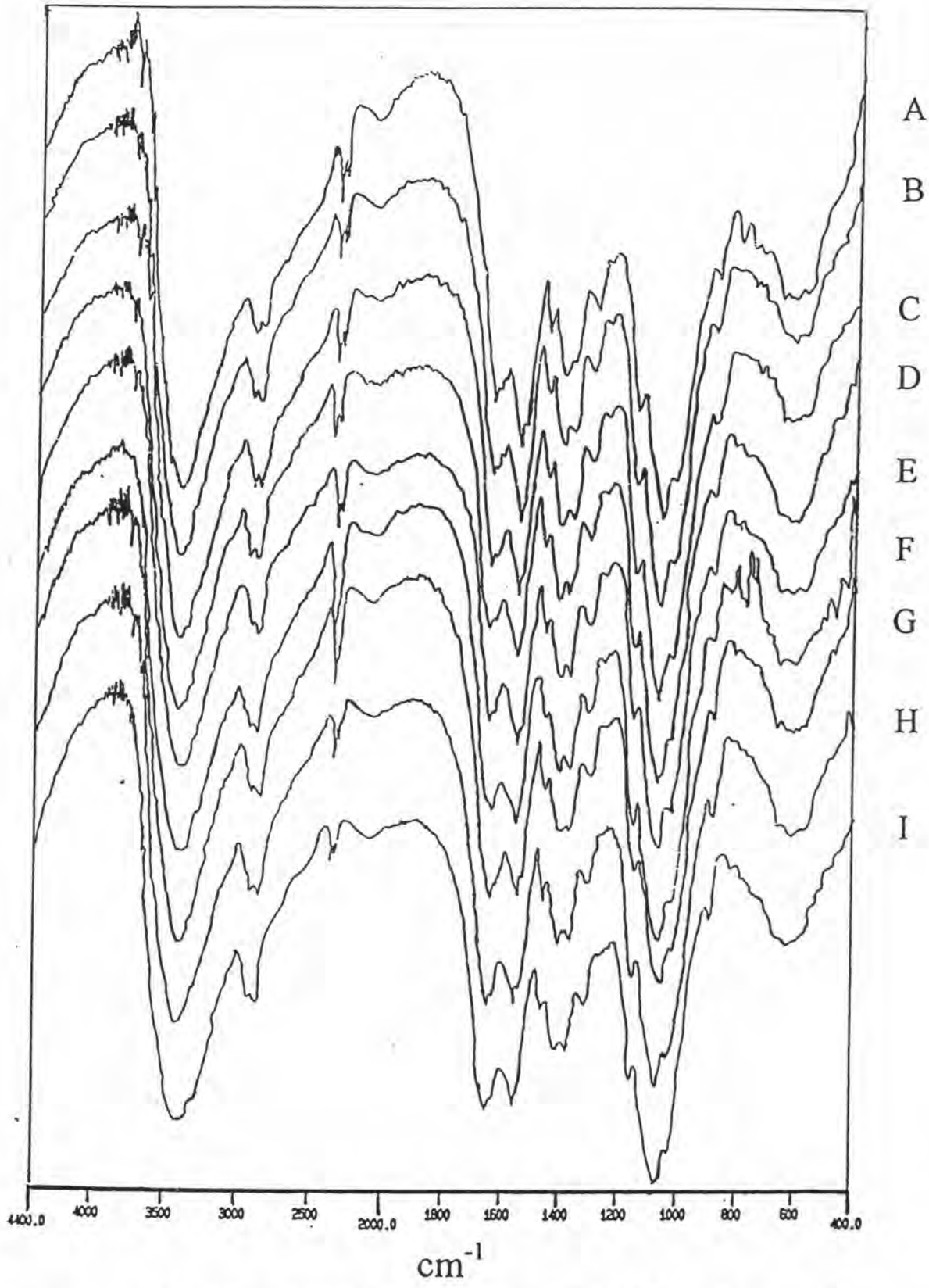


Figure 28 FT-IR spectra of chitosan propionate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs. (F). 72 hrs.; (G) 120 hrs.; (H) 168 hrs and (I) 360 hrs.

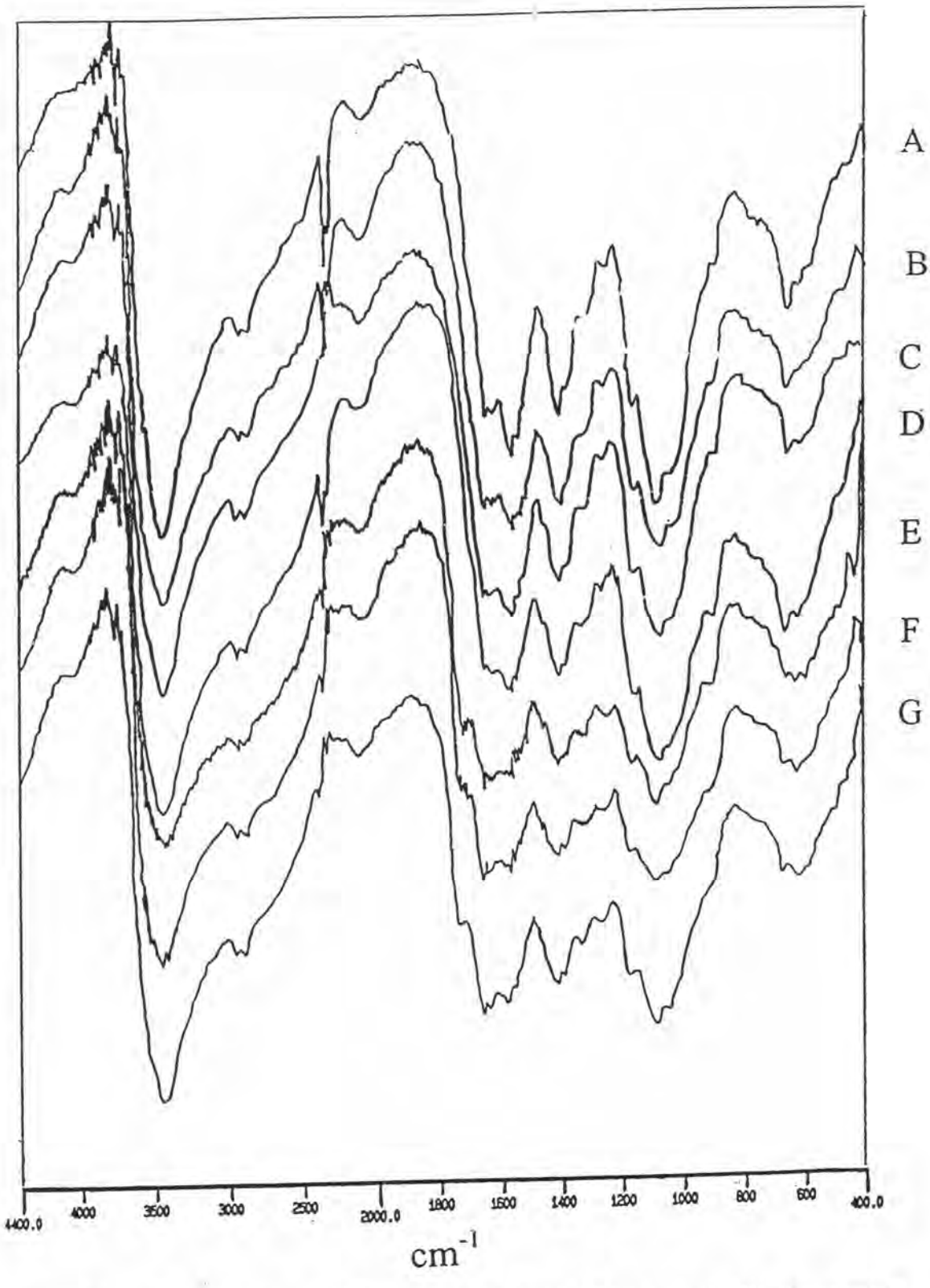


Figure 29 FT-IR spectra of chitosan acetate films (A) untreated; (B) after kept in vacuum 168 hrs.; after exposed to dry heat at 60°C (C) 168 hrs.; (D) 360 hrs.; after exposed to dry heat at 130°C (E) 5 hrs.; (F) 9 hrs. and (G) 12 hrs.

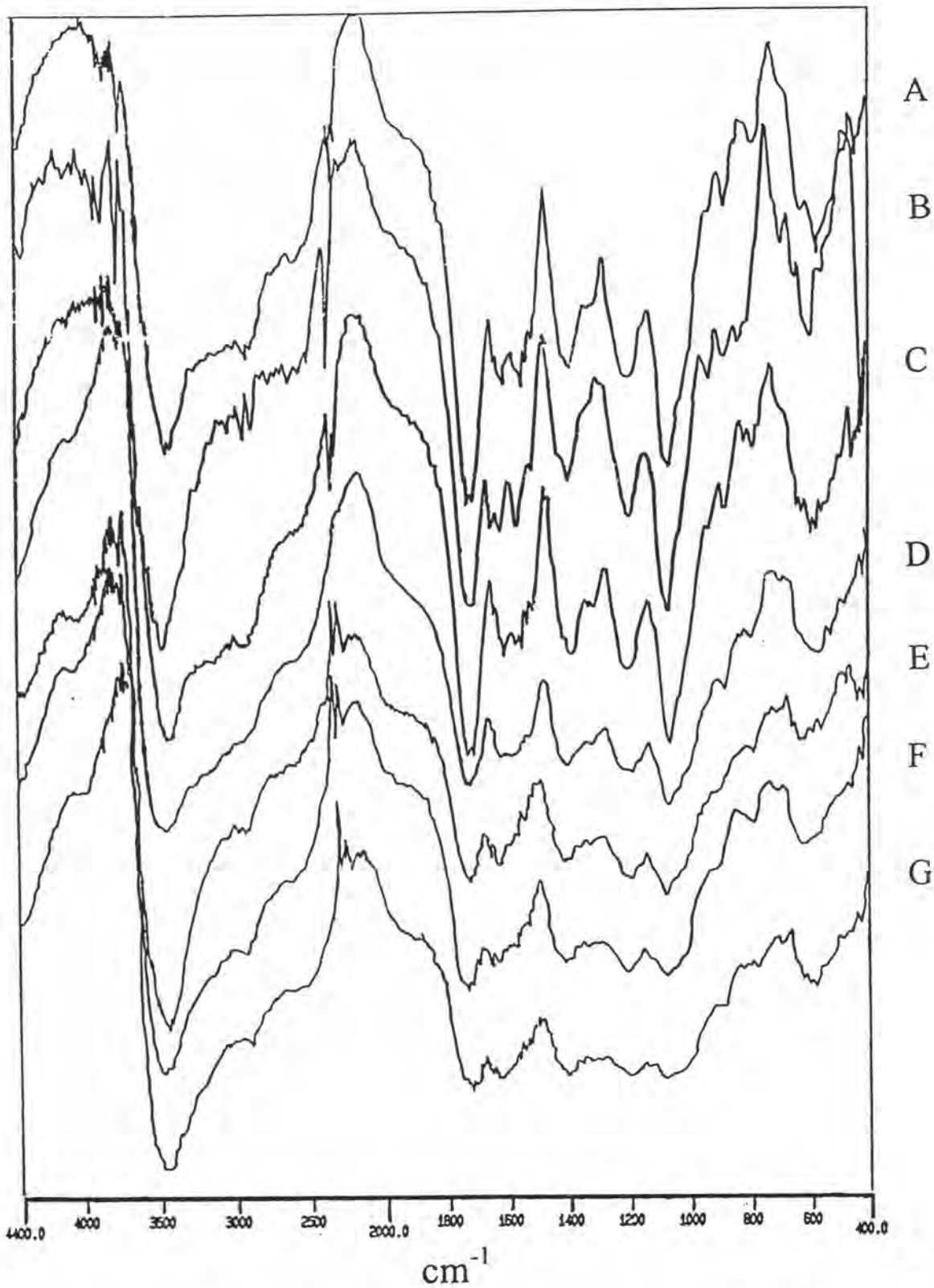


Figure 30 FT-IR spectra of chitosan citrate films (A) untreated; (B) after kept in vacuum 168 hrs.; after exposed to dry heat at 60°C (C) 168 hrs.; (D) 360 hrs.; after exposed to dry heat at 130°C (E) 5 hrs.; (F) 9 hrs. and (G) 12 hrs.

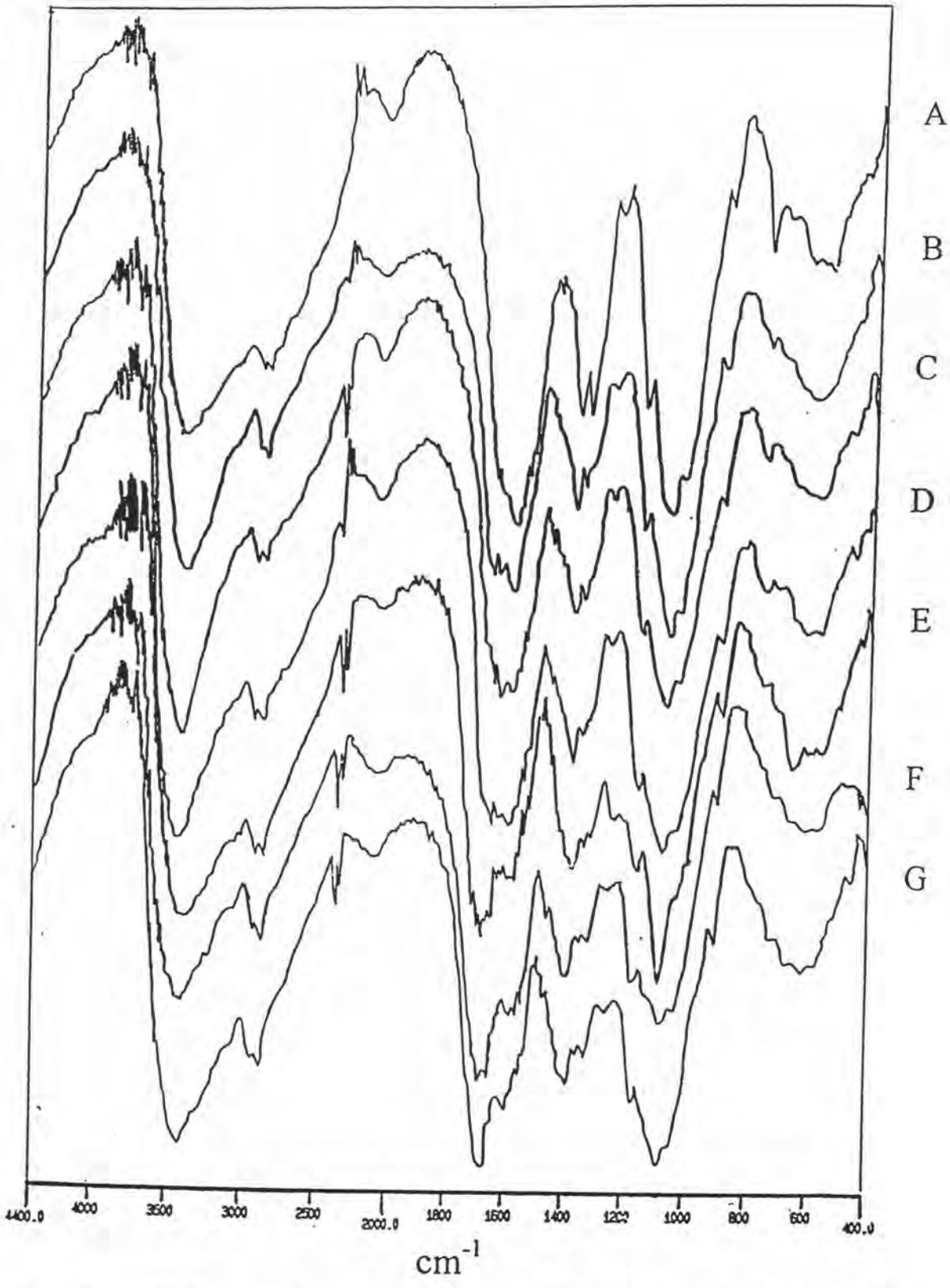


Figure 31 FT-IR spectra of chitosan formate films (A) untreated; (B) after kept in vacuum 168 hrs.; after exposed to dry heat at 60°C (C) 168 hrs.; (D) 360 hrs.; after exposed to dry heat at 130°C (E) 5 hrs.; (F) 9 hrs. and (G) 12 hrs.

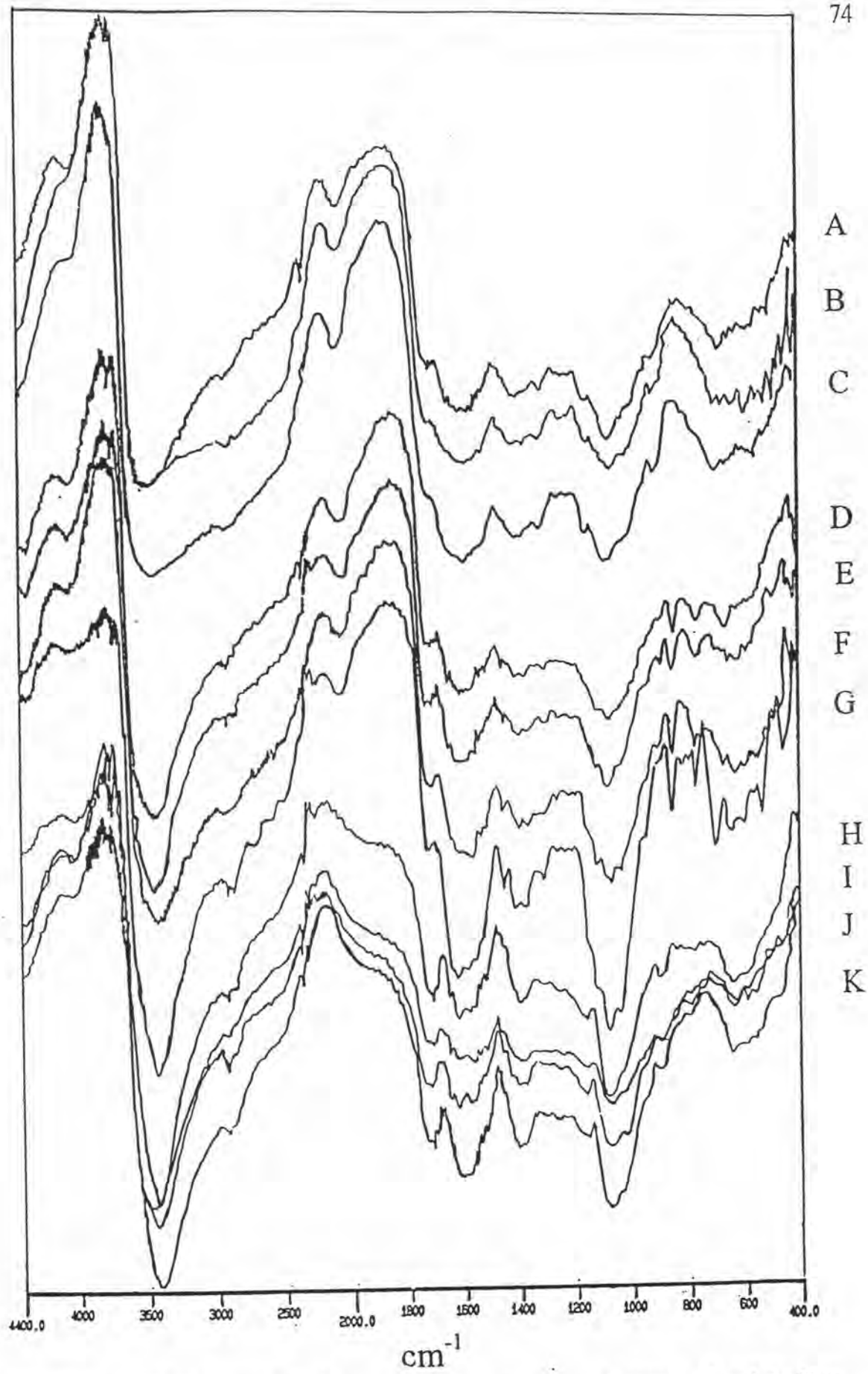


Figure 32 FT-IR spectra of chitosan films (A) untreated chitosan glycolate film; (B) chitosan glycolate after kept in vacuum 168 hrs.; (C) chitosan glycolate film after exposed to dry heat at 60°C 168 hrs.; (D) untreated chitosan lactate film; (E) chitosan lactate film after kept in vacuum 168 hrs.; (F) chitosan lactate film after exposed to dry heat at 60°C 168 hrs. and (G) 360 hrs.; (H) untreated chitosan malate; (I) chitosan malate film after kept in vacuum 168 hrs.; chitosan malate film after exposed to dry heat at 60°C (J) 168 hrs and 360 hrs.

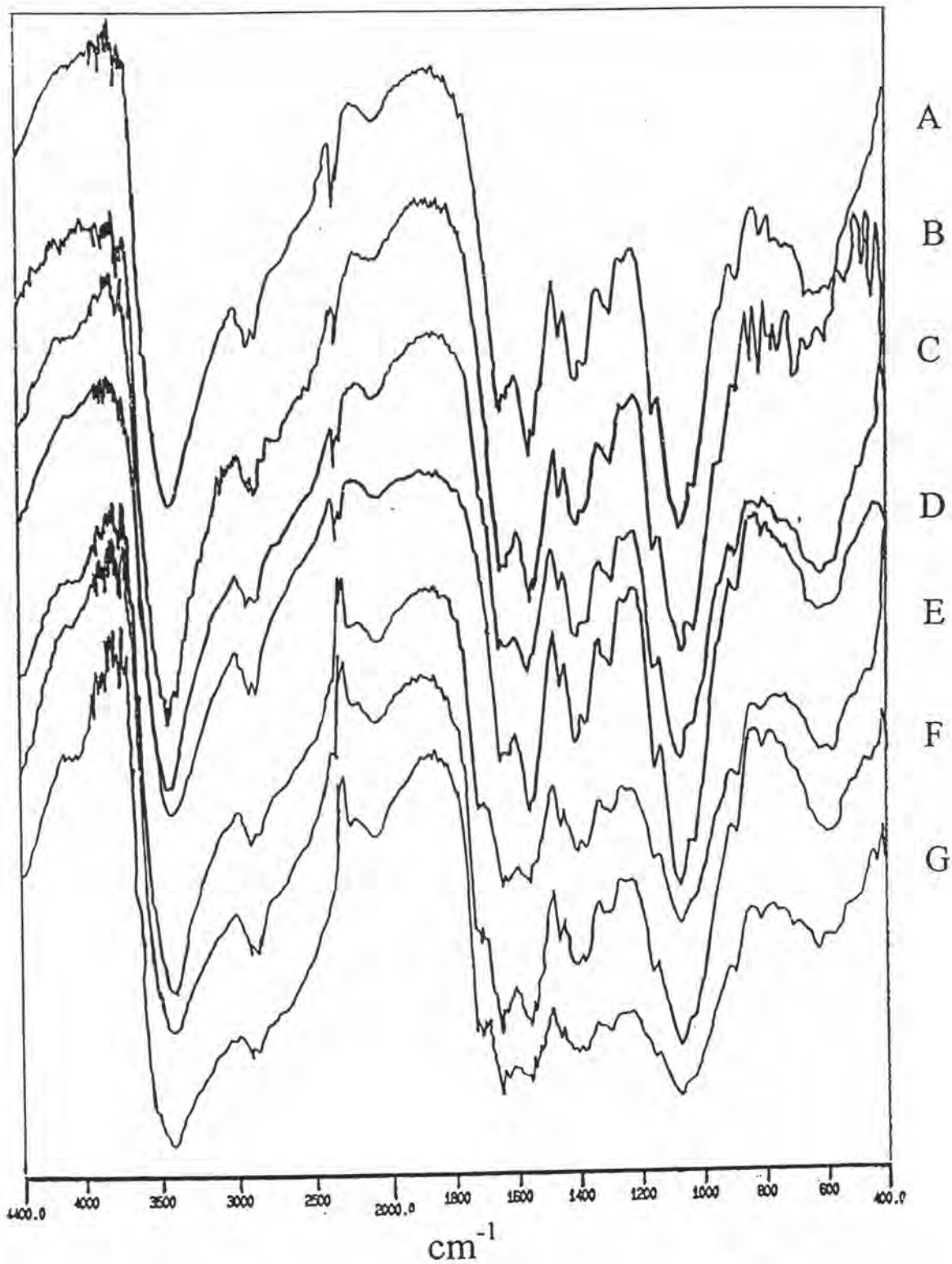


Figure 33 FT-IR spectra of chitosan propionate films (A) untreated; (B) after kept in vacuum 168 hrs.; after exposed to dry heat at 60°C (C) 168 hrs.; (D) 360 hrs.; after exposed to dry heat at 130°C (E) 5 hrs.; (F) 9 hrs. and (G) 12 hrs.

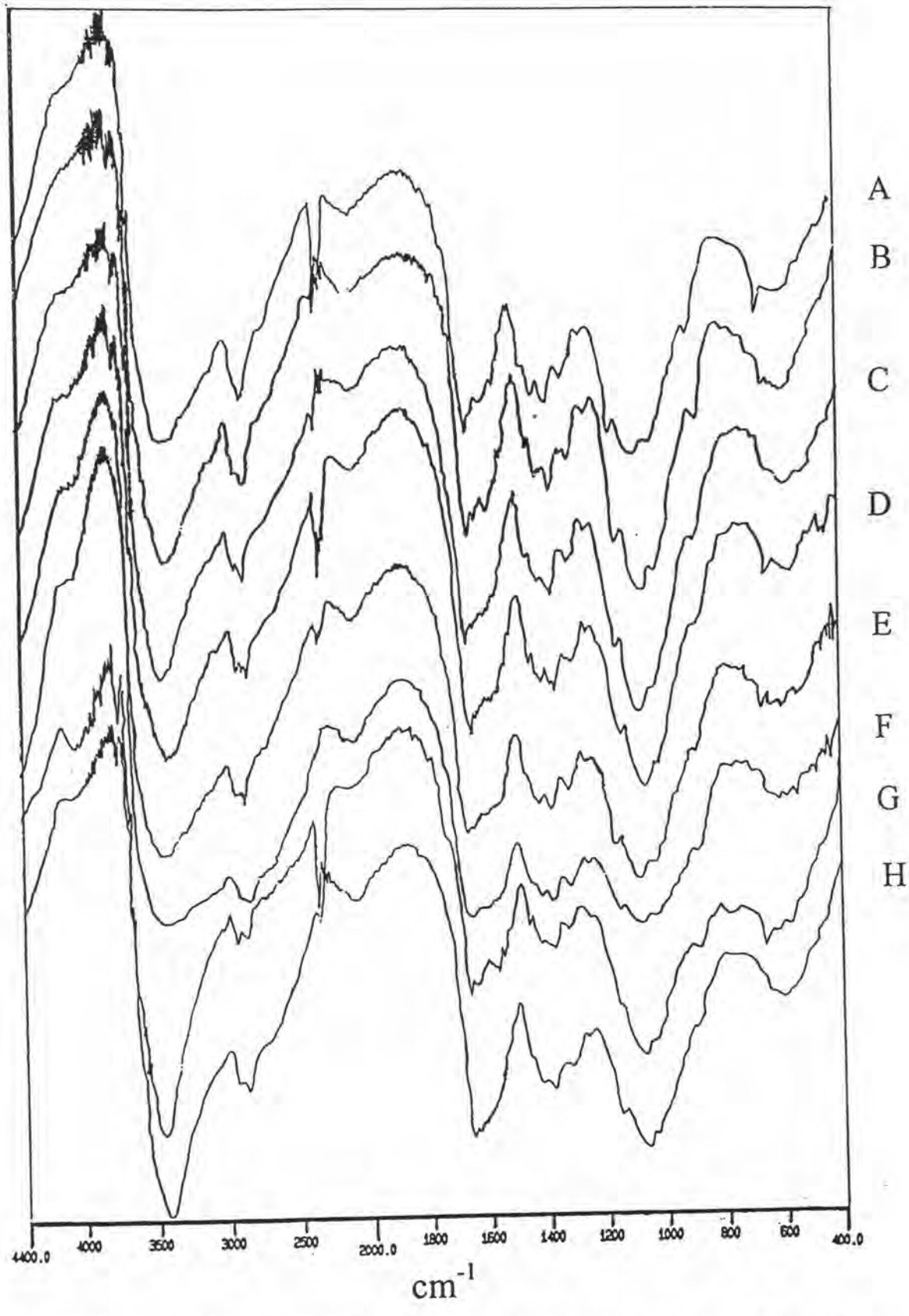


Figure 34 FT-IR spectra of (A) chitosan powders; neutralised film of (B) chitosan acetate; (C) chitosan citrate; (D) chitosan formate; (E) chitosan glycolate; (F) chitosan lactate; (G) chitosan malate and (H) chitosan propionate.

2.3 Powder X-ray Diffraction Studies

From the powder X-ray diffractogram, chitosan powder had a major reflection at about 20° 2θ and a minor reflection at 10.6° 2θ. After moist heat treatment for 12 to 360 hours and dry heat treatment at 60°C for 168 and 360 hours, it was found that there was no change of X-ray diffraction pattern as presented in Figure *35*.

By comparison, the diffractograms of chitosan citrate, glycolate and malate films were different from that of chitosan powder, and those of pure solid acids and their physical mixtures. The physical mixture between chitosan and solid acids showed the combination signal peak of the two compounds as shown in Figures *36-38*. However the peak intensity of glycolic acid in physical mixture was notably regressed as shown in Figures *37*.

The high crystalline structure of pure solid acids was changed to amorphous state after casting and shown in hallow pattern in diffractogram. Several diffraction patterns of chitosan salt were found, depending on acid used (Figures *39-45*). The crystallinity of salt form was less than neutral form of chitosan powder. No apparent dominant sharp peak appeared in diffractogram of chitosan citrate film indicated that citric acid and chitosan were in amorphous state and these moist heat treated films showed diffractogram similar to that of freshly prepared.

The X-ray diffraction of chitosan acetate film showed dominant reflections at 23° 2θ, 18.3° 2θ and 11.8° 2θ. After moist heat exposure there was an appearance of reflection at 21.7° 2θ whereas the reflection at 11.8° 2θ was decreased with time as illustrated in Figure *39*.

The longer chitosan formate films were exposed to moist heat, the more pronounce was the peak near 20° 2θ and the less was the reflection at 12.4° 2θ (Figure *41*). This result was similar to the cases of chitosan glycolate and malate films as shown in Figures *42* and *44* respectively. However, there was no significant change in intensity of minor peak at 11.9° 2θ of chitosan glycolate films. Additionally, the reflection at 11.2° 2θ of treated chitosan malate films was disappeared.

The dominant reflection at 18.3° 2θ of moist heat treated chitosan lactate films was clearly seen in Figure *43* whereas this reflection could not be observed in freshly prepared film or film after exposure the heat at 60°C 168 or 360 hours and after kept in vacuum 168 hours. The dominant reflection of moist heat treated chitosan propionate films was narrower than those of freshly prepared film or films after kept in vacuum or in hot air oven at 60°C for 168 or 360 hours as presented in Figure *45*. Thus, chitosan lactate and propionate films showed a tendency to increase crystallinity after exposure to moist heat.

Using dry heat at 60°C for 168 and 360 hours made significant decrease in the intensity of minor reflection of chitosan acetate and formate at 11.8° 2θ and 12.4° 2θ respectively. The result was also detected in case of using lactic and propionic acids but not in case of using glycolic acid. However, the disappearance of reflection at 11.2° 2θ of chitosan malate films after moist heat treatment was found. The powder X-ray

diffractograms of chitosan acetate, citrate, formate and propionate films after dry heat at 130°C for 9 hours as depicted in Figure *46* revealed that these treated films were obvious to be amorphous phase. The peak at 15° 2θ representing the anhydrous form of chitosan was not evidently detected in any prepared films in this study.

Neutralised chitosan films showing the diffraction pattern similar to chitosan powder indicated there was a conversion from chitosan salt to neutral form as illustrated in Figures *47* and *48*. The diffractogram of neutralized chitosan lactate film was notably different from the others since the reflection at about 10° 2θ was obviously dominant as shown in Figure *47*.

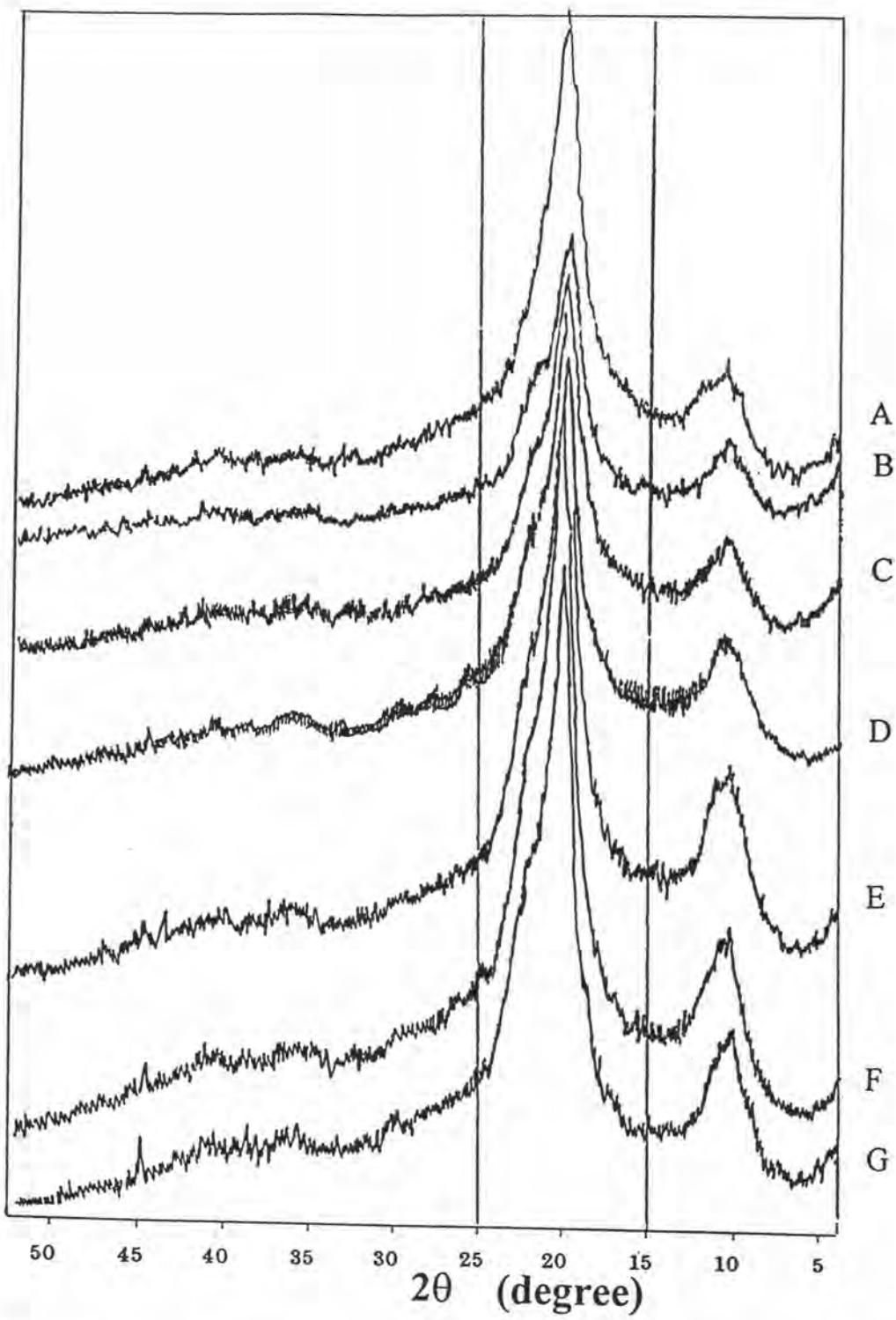


Figure 35 X-ray diffractograms of chitosan powders (A) untreated; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; after exposure to dry heat at 60°C (J) 168 hrs. and (K) 360 hrs.

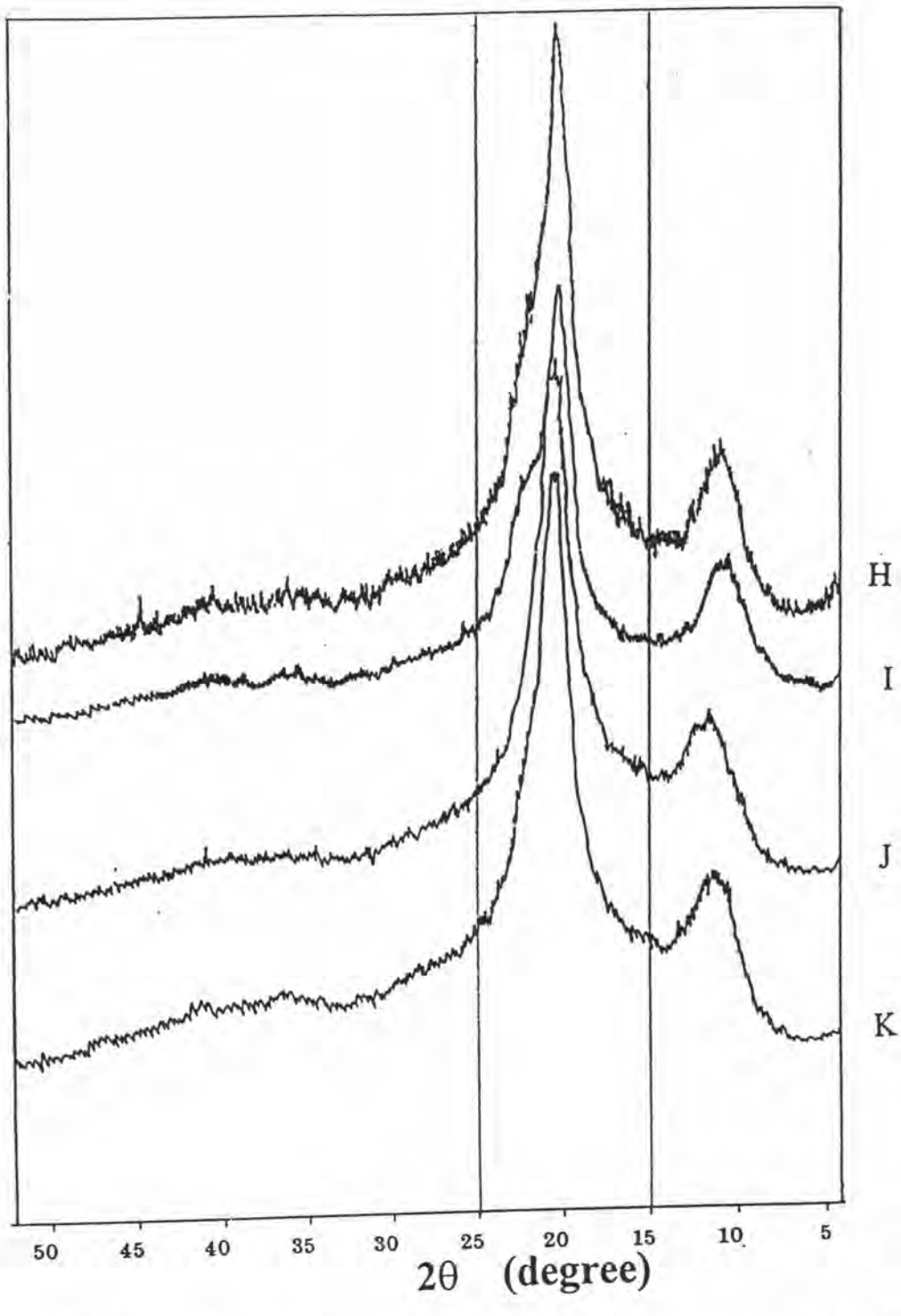


Figure 35 X-ray diffractograms of chitosan powders (A) untreated; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; after exposed to dry heat at 60°C (J) 168 hrs. and (K) 360 hrs. (continue).

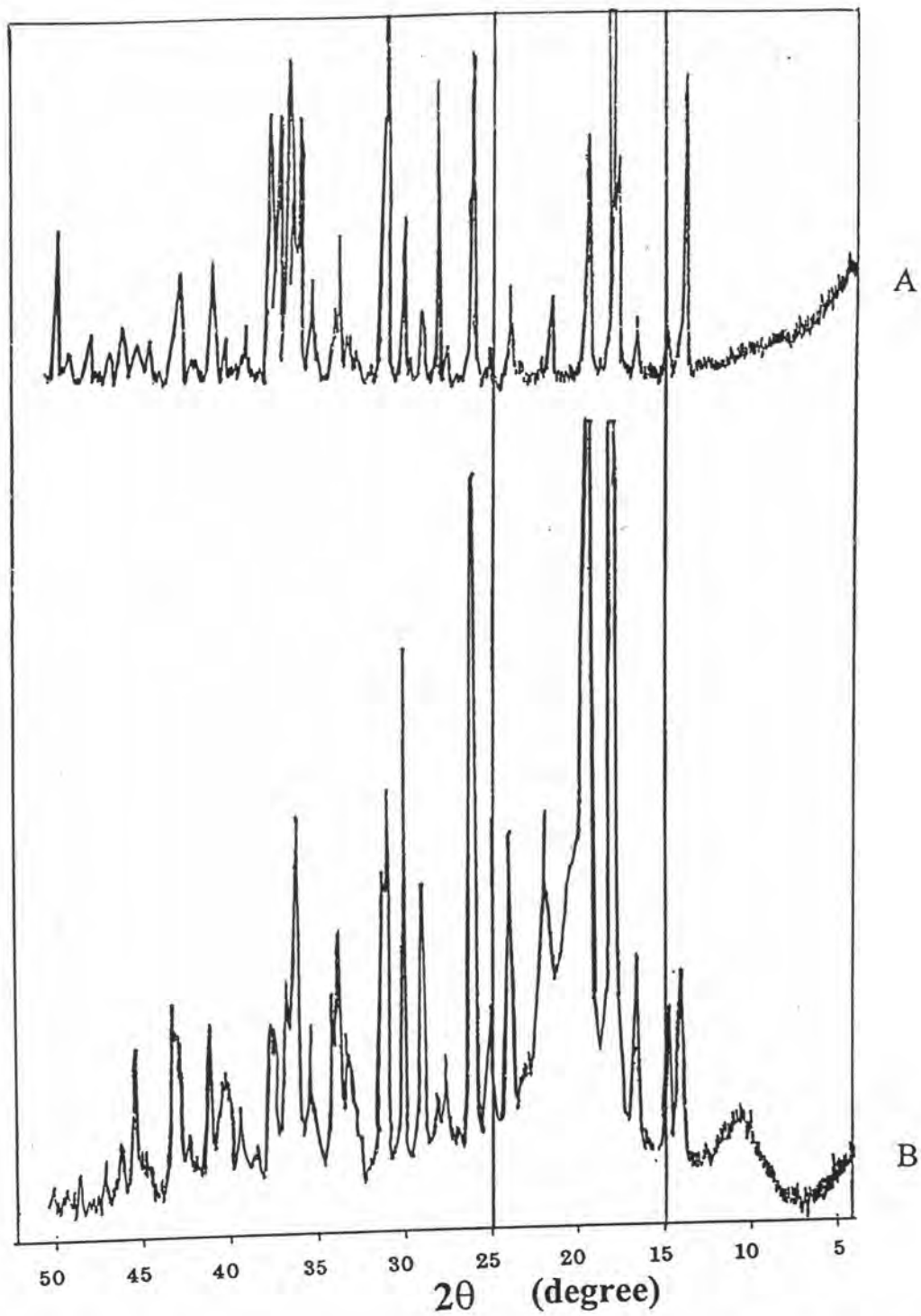


Figure 36 X-ray diffractograms of (A) citric acid; (B) physical mixture between chitosan and citric acid.

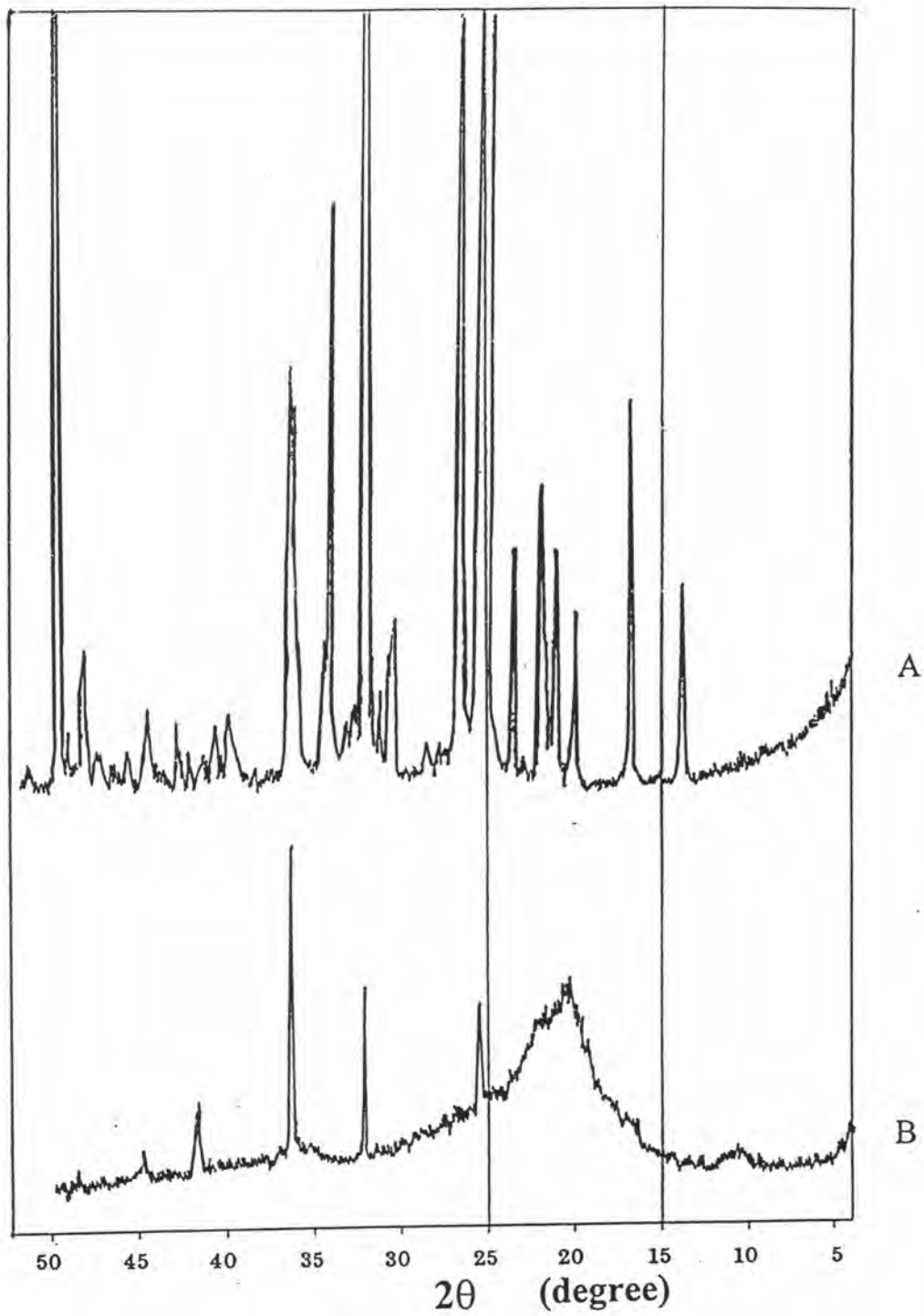


Figure 37 X-ray diffractograms of (A) glycolic acid; (B) physical mixture between chitosan and glycolic acid.

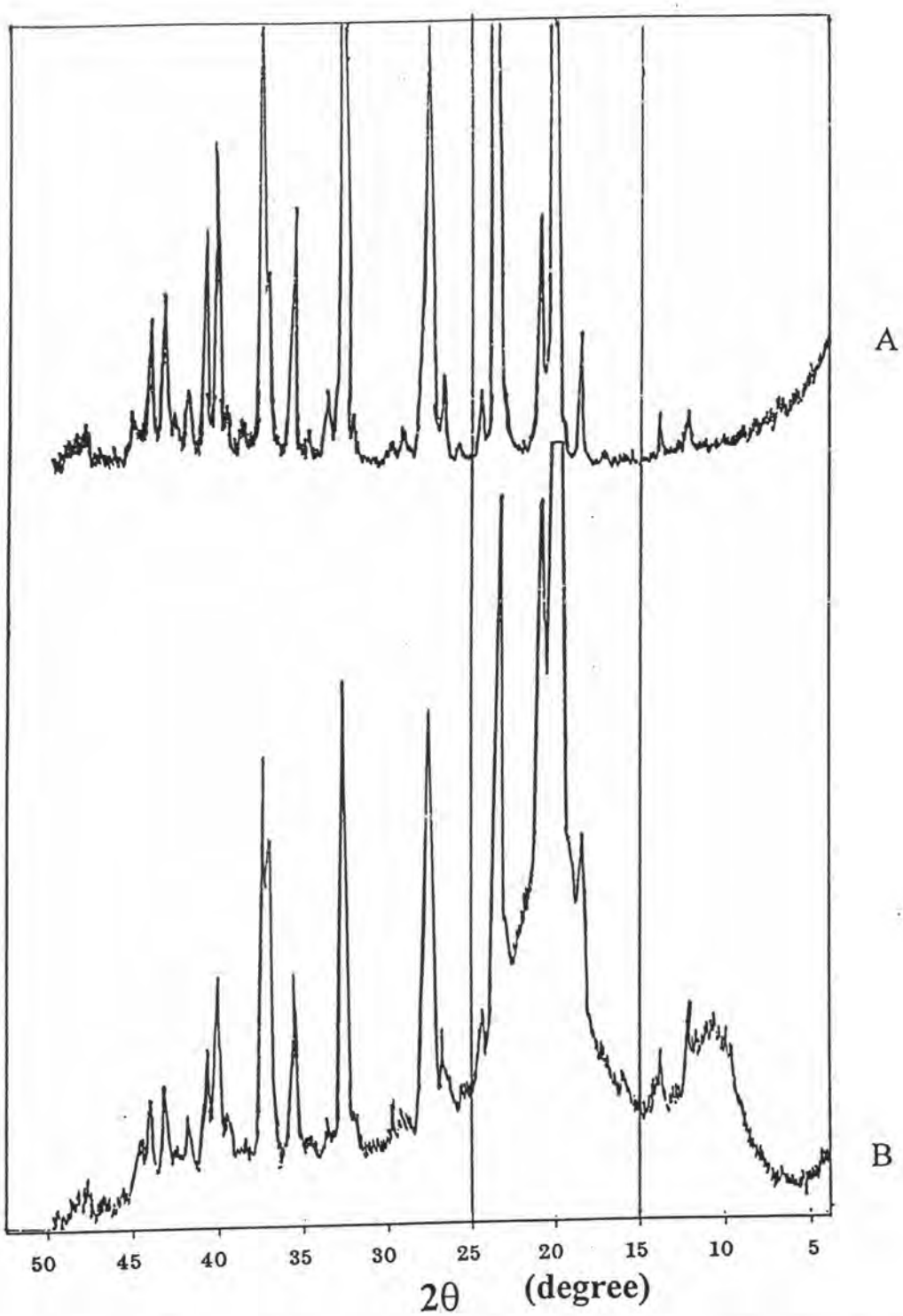


Figure 38 X-ray diffractograms of (A) malic acid; (B) physical mixture between chitosan and malic acid.

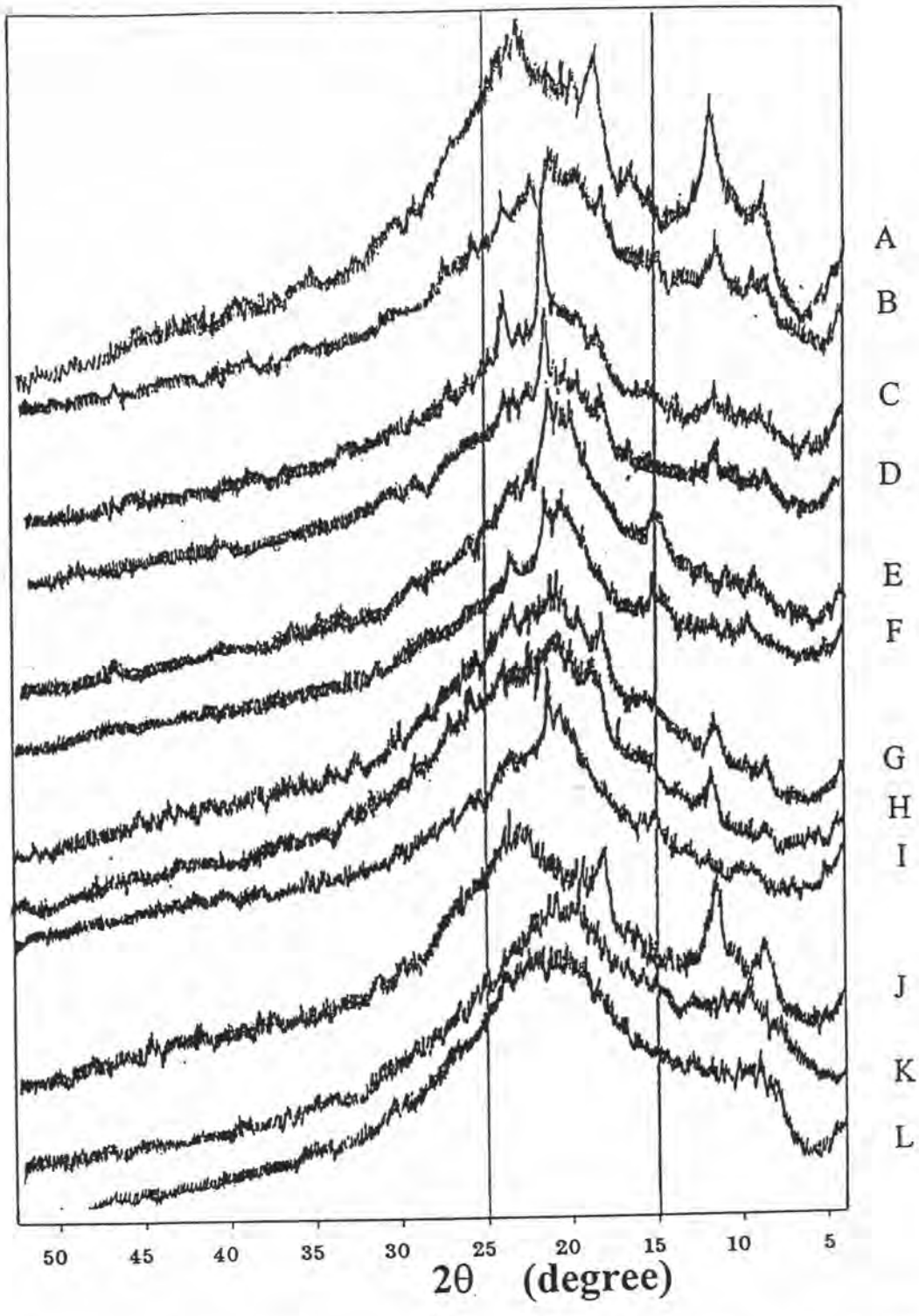


Figure 39 X-ray diffractograms of chitosan acetate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; (J) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (K) 168 hrs. and (L) 360 hrs.

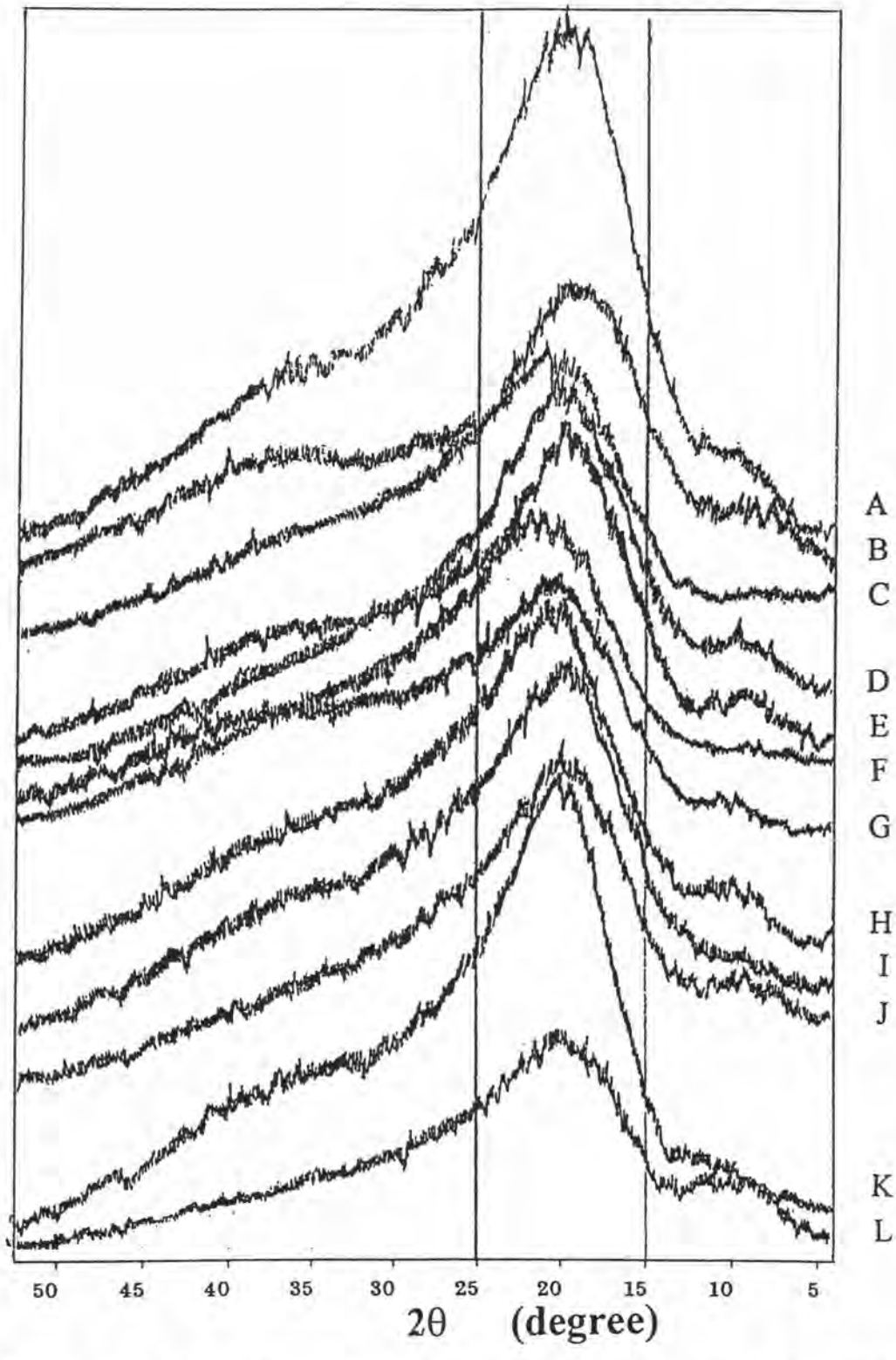


Figure 40 X-ray diffractograms of chitosan citrate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; (J) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (K) 168 hrs. and (L) 360 hrs.

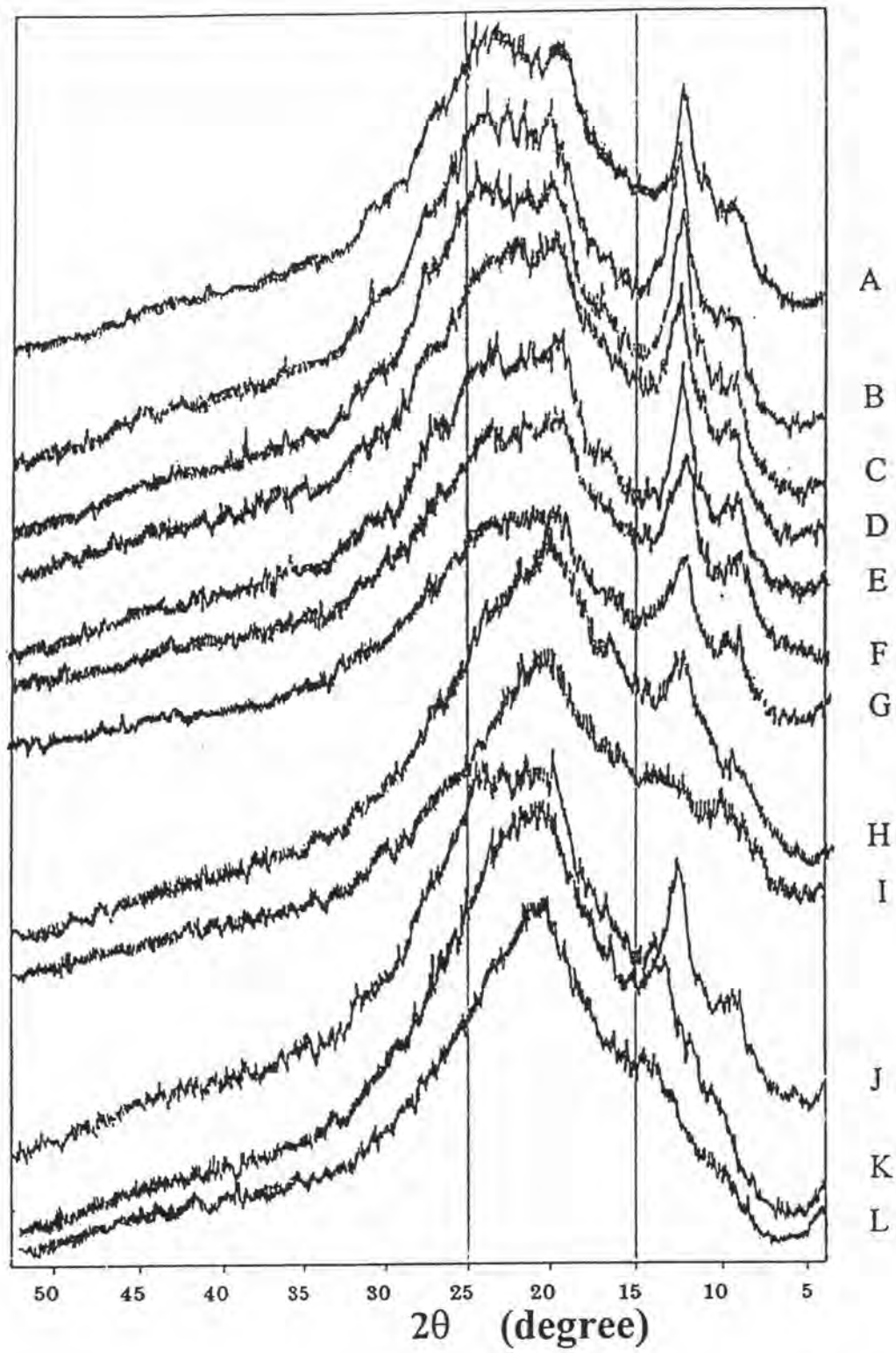


Figure 41 X-ray diffractograms of chitosan formate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; (J) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (K) 168 hrs. and (L) 360 hrs.

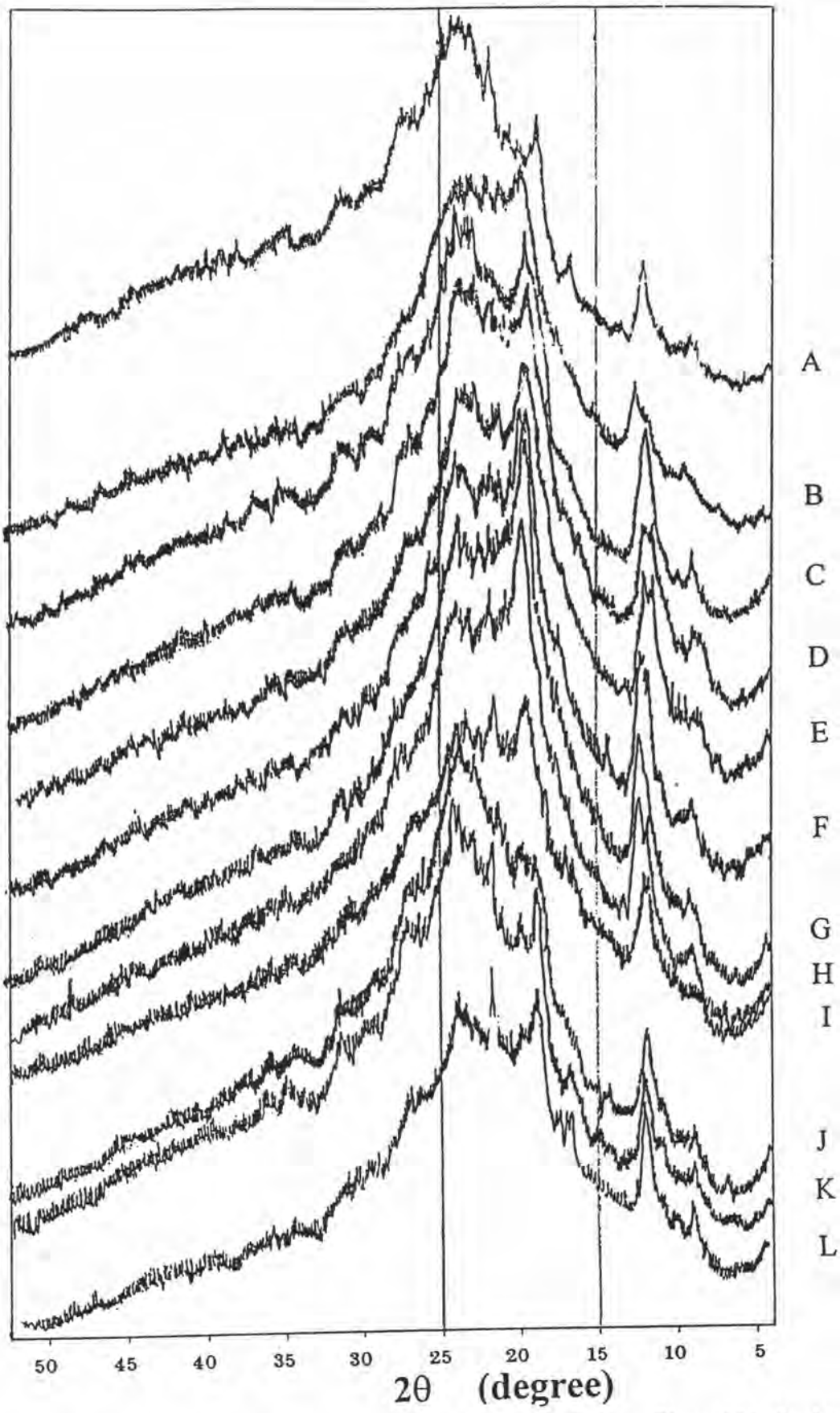


Figure 42 X-ray diffractograms of chitosan glycolate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; (J) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (K) 168 hrs. and (L) 360 hrs.

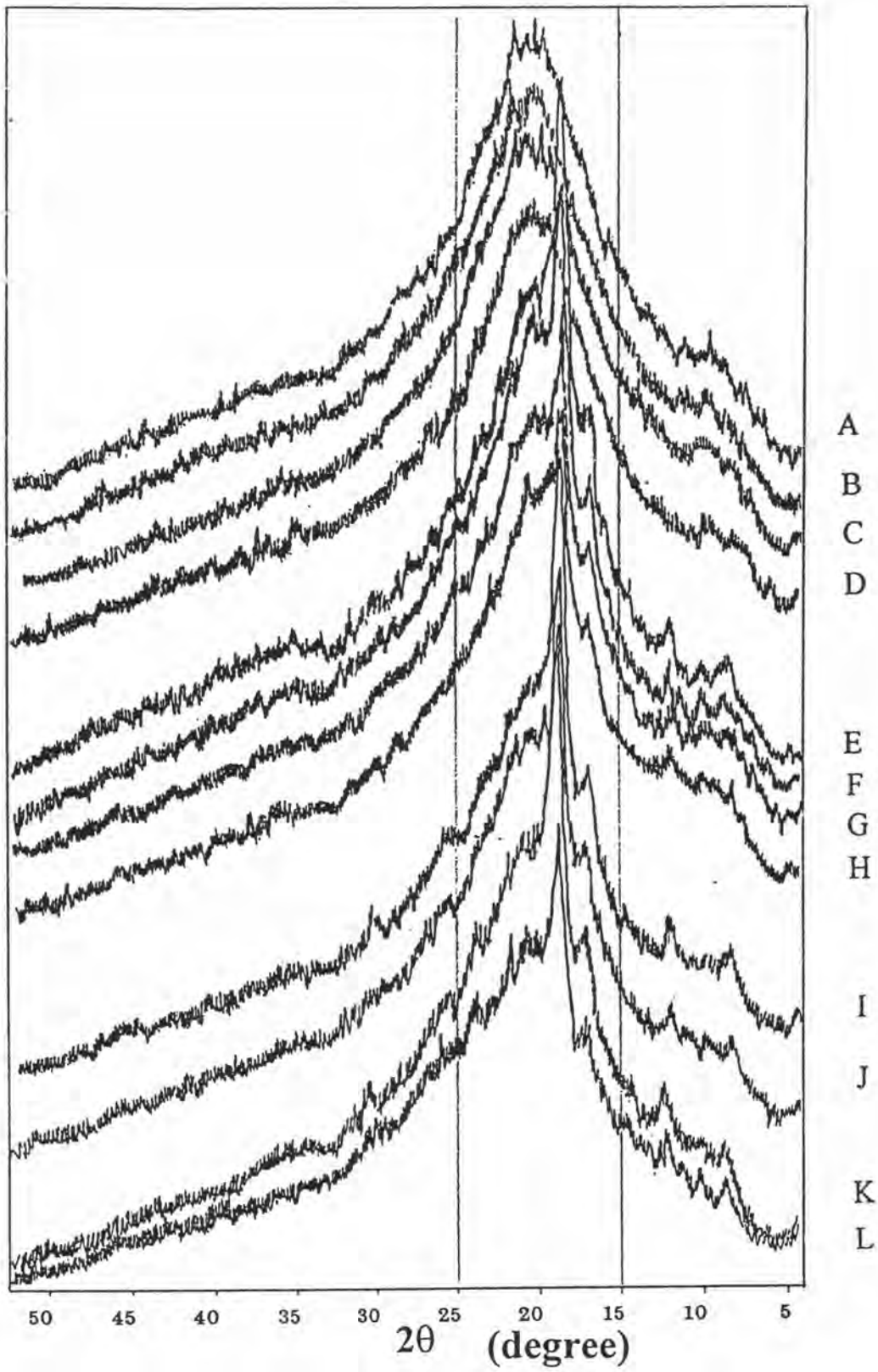


Figure 43 X-ray diffractograms of chitosan lactate films (A) freshly prepared; (B) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (C). 168 hrs. and (D) 360 hrs; after exposed to moist heat (E) 12 hrs.; (F) 24 hrs.; (G) 36 hrs.; (H) 48 hrs.; (I) 72 hrs.; (J) 120 hrs.; (K) 168 hrs. and (L) 360 hrs.

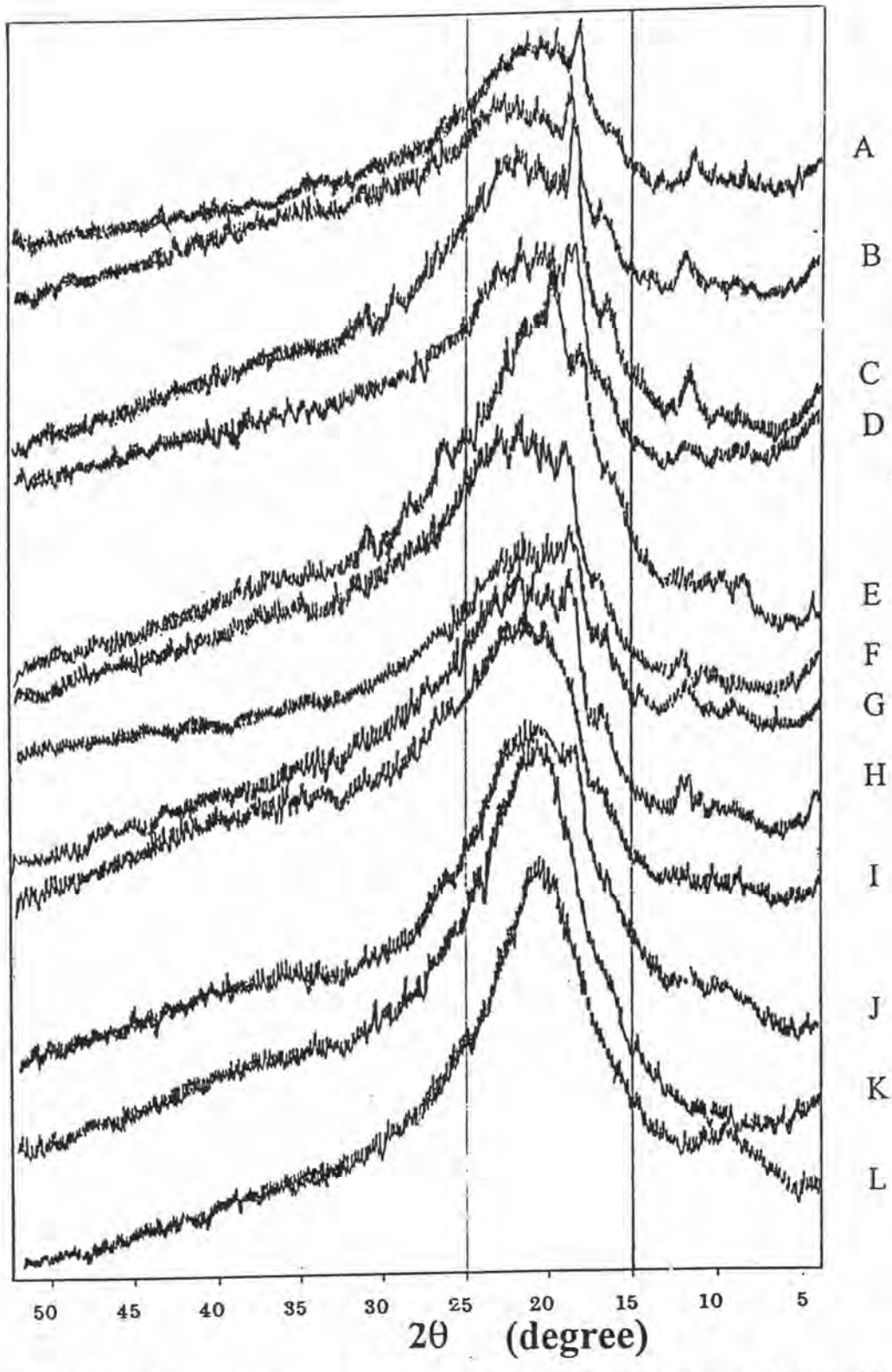


Figure 44 X-ray diffractograms of chitosan malate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; (J) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (K) 168 hrs. and (L) 360 hrs.

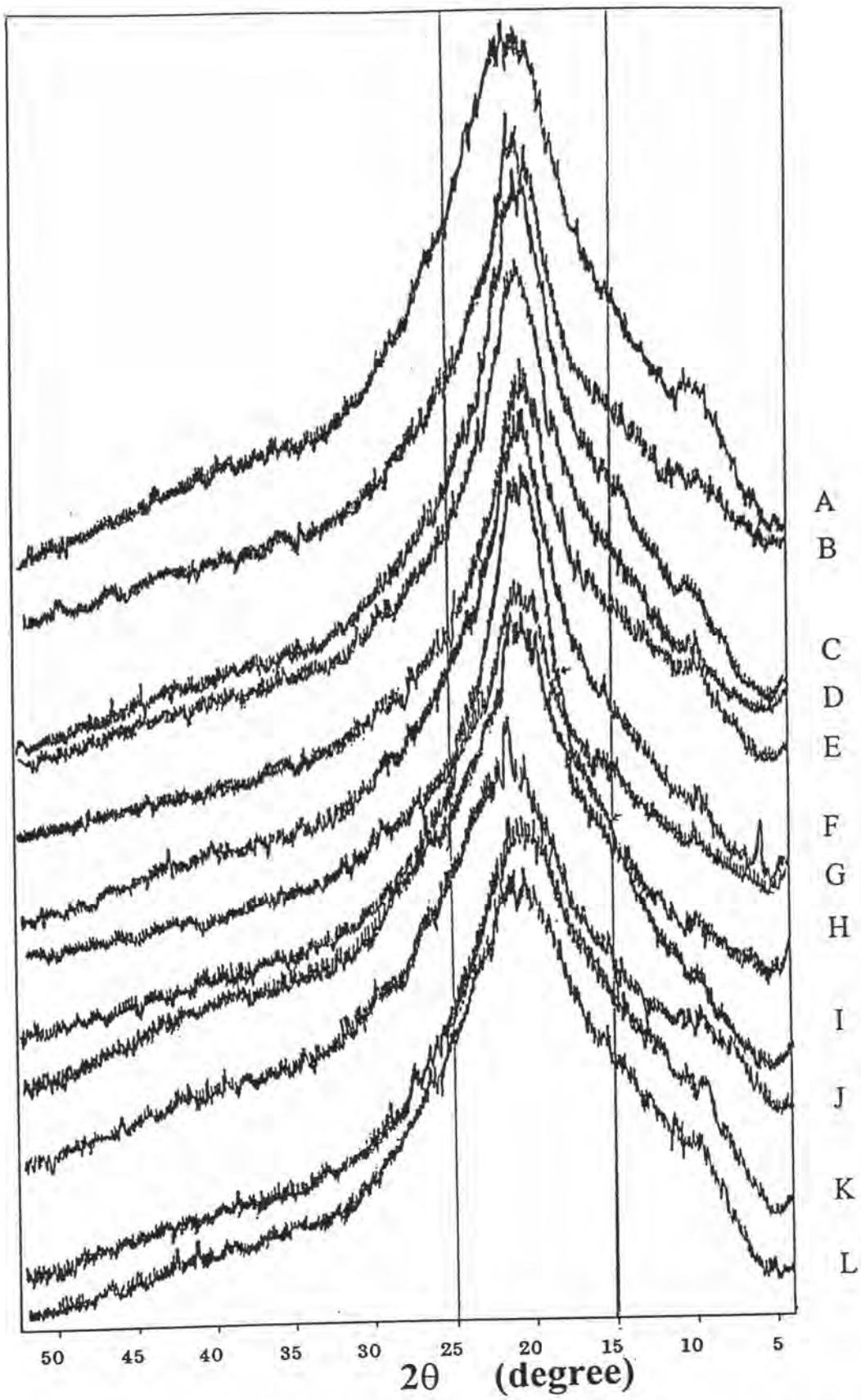


Figure 45 X-ray diffractograms of chitosan propionate films (A) freshly prepared; after exposed to moist heat (B) 12 hrs.; (C) 24 hrs.; (D) 36 hrs.; (E) 48 hrs.; (F) 72 hrs.; (G) 120 hrs.; (H) 168 hrs.; (I) 360 hrs.; (J) after kept in vacuum 168 hrs; after exposed to dry heat at 60°C (K) 168 hrs. and (L) 360 hrs.

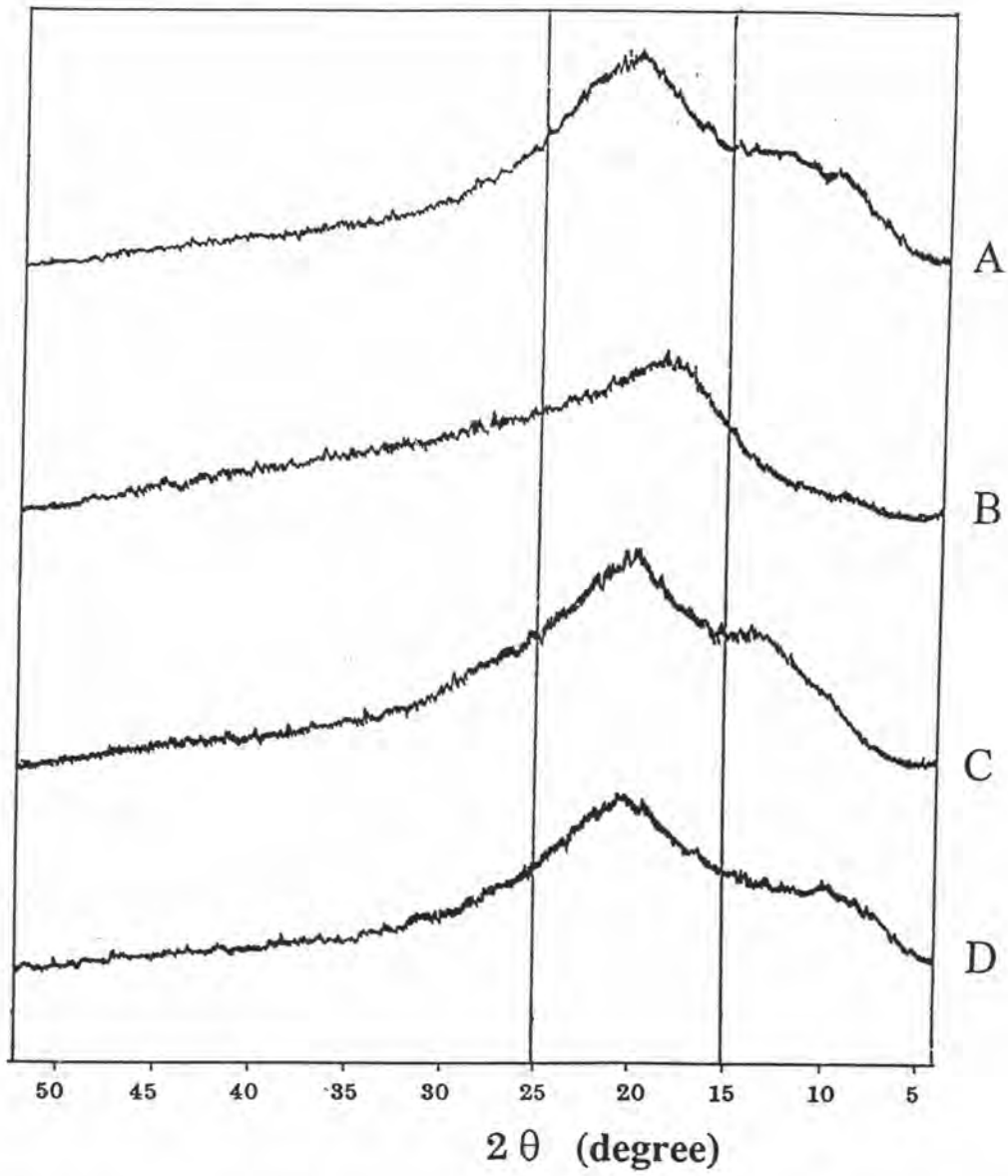


Figure 46 X-ray diffractograms of film after exposed to dry heat at 130°C for 9 hrs.(A) chitosan acetate; (B) chitosan citrate; (C) chitosan formate and (D) propionate.

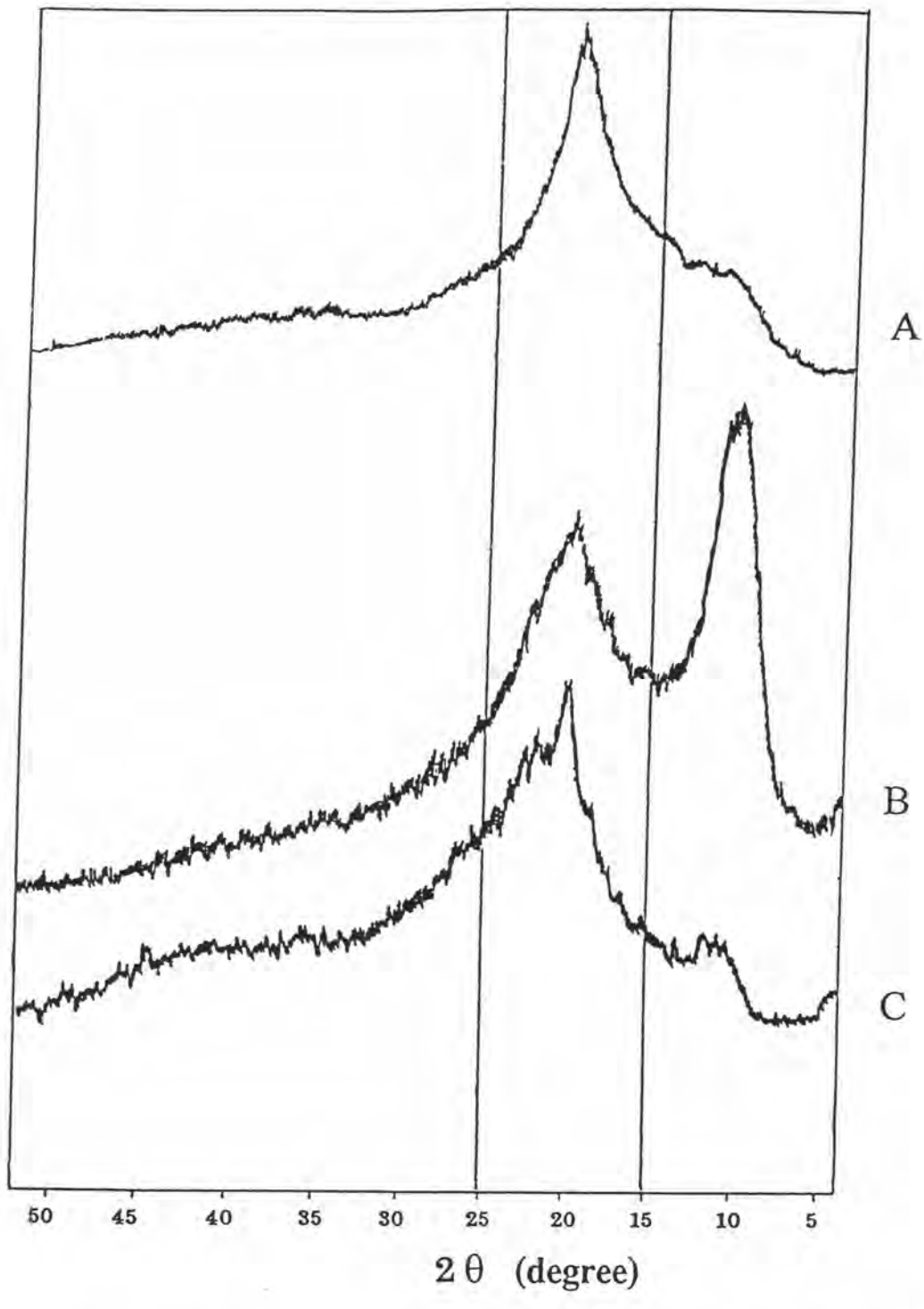


Figure 47 X-ray diffractograms of neutralized chitosan acetate film (A); chitosan lactate film (B) and chitosan malate film (C)

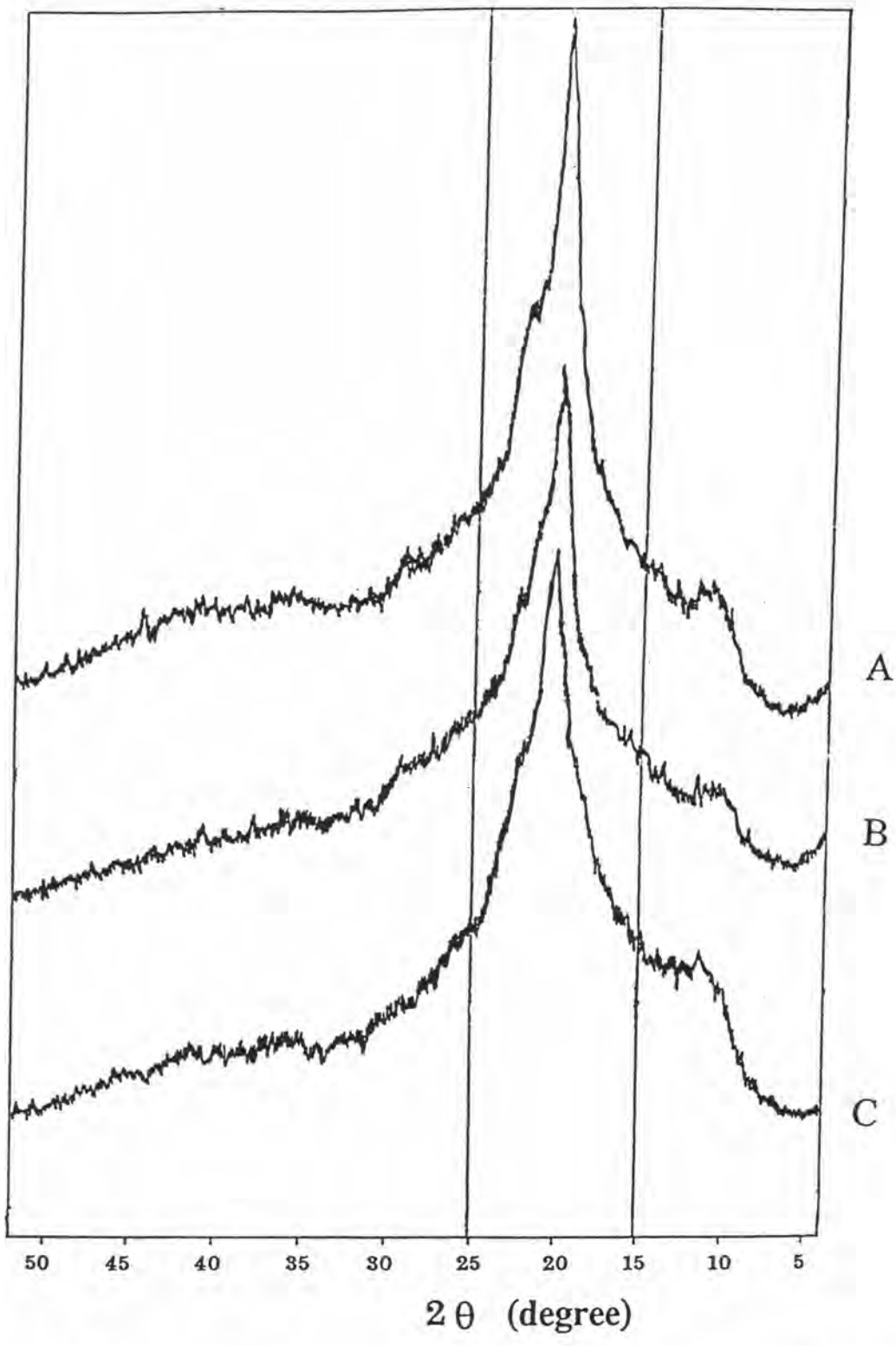


Figure 48 X-ray diffractograms of neutralized chitosan formate film (A); chitosan glycolate film (B) and chitosan propionate film (C)

2.4 Differential Scanning Calorimetry Studies

The endothermic and exothermic peaks from DSC curves are summarized in Table *6* and shown in Figures *49-58*. The endothermic peak appearing nearly to 100 °C was associated with the loss of water. Chitosan powder had an exothermic peak appearing at temperature of 306.9°C corresponding to the decomposition temperature of this polymer.

The chitosan powder after moist heat treatment did not show any obvious alteration of decomposition temperature. The sharp endothermic peak representing the melting point of citric, glycolic and malic acids was appeared at 159.5, 74.0 and 136.2°C respectively. The DSC curve of physical mixture showed the peak shifts and the presence of new peak as summarized in Table *6*. In case of physical mixture between chitosan and citric or malic acid, the decomposition peak still appeared nearly to the same position, but in the thermogram of physical mixture between chitosan and glycolic acid it was shifted to the lower temperature of 294.8°C.

Exothermic peaks of freshly prepared chitosan acetate, formate, glycolate, lactate and propionate films were clearly shifted to lower temperature compared to that of chitosan powder. The films after treatment with moist heat for 72, 168 and 360 hours had the exothermic peak slightly shifted to higher temperature compared to that of freshly prepared film. However it was still lower than that of chitosan powder. Broad endothermic peak at temperature about 200°C was clearly observed in DSC curve of chitosan glycolate and lactate and could also be detected in DSC curve of chitosan acetate and propionate films. The appearance of endothermic peak of chitosan formate was different from that of chitosan acetate, glycolate, lactate and propionate films. The endothermic peak of chitosan formate was occurred at about 160°C.

Chitosan citrate and malate films showed exothermic peaks at 361.0°C and 344.8°C respectively which were higher than other films. These moist heat treated films had exothermic peak at temperature slightly less than those of freshly prepared films. The broad endothermic peak of chitosan citrate and malate films appeared at about 178°C and 187°C respectively.

Table 6 The temperature of endothermic and exothermic peaks from DSC curves of chitosan powder, acids, physical mixture and chitosan films.

Test Specimen	Duration of Moist Heat Treatment (hr)	Temperature (°C)	
		Endothermic Peak	Exothermic Peak
Chitosan powder	-	86.3	306.9
Chitosan powder	360	108.6	305.8
Citric acid	-	159.5, 214.8	
Glycolic acid	-	74.0, 158.9, 362.6	
Malic acid	-	136.2, 292.6	
Phy[1] chitosan:citric	-	77.9, 156.0, 173.1,199.8	307.9
Phy[1] chitosan:glycolic	-	94.8, 208.0	294.8
Phy[1] chitosan:malic	-	92.6, 130.3, 181.2, 212.7	135.6, 307.8
Chitosan acetate	-	99.3	282.8
	72	87	294
	168	96.8	294.3
	360	95.5	296.3
Chtosan citrate	-	172.9	361
	72	94.9, 177.6	359.6
	168	90.9, 177.5	358
	360	71.9, 179.2	*
Chitosan formate	-	84.2, 158.9	305
	72	86.8, 159.8	305
	168	83.8, 159.8	311
	360	83.8,159.8	*
Chitosan glycolate	-	92.6, 197.0	277.5
	72	80.2, 199.2	280.3
	168	104.1, 205.6	277.1
	360	95.7, 196.3	280.2
Chitosan lactate	-	93.5, 191.4	303
	72	92.0, 201.2	*
	168	84.5, 198.1	*
	360	87.9, 198.1	*
Chitosan malate	-	97.1, 186.3	344.8
	72	111.0, 187.5	344
	168	104.0, 187.5	343.7
	360	186.1	342.5
Chitosan propionate	-	89.7	278.2
	72	77.8	289.5
	168	81	288.5
	360	83.1	290.6

* = Very broad peak

- = No treatment or freshly prepared

[1] = Physical mixture

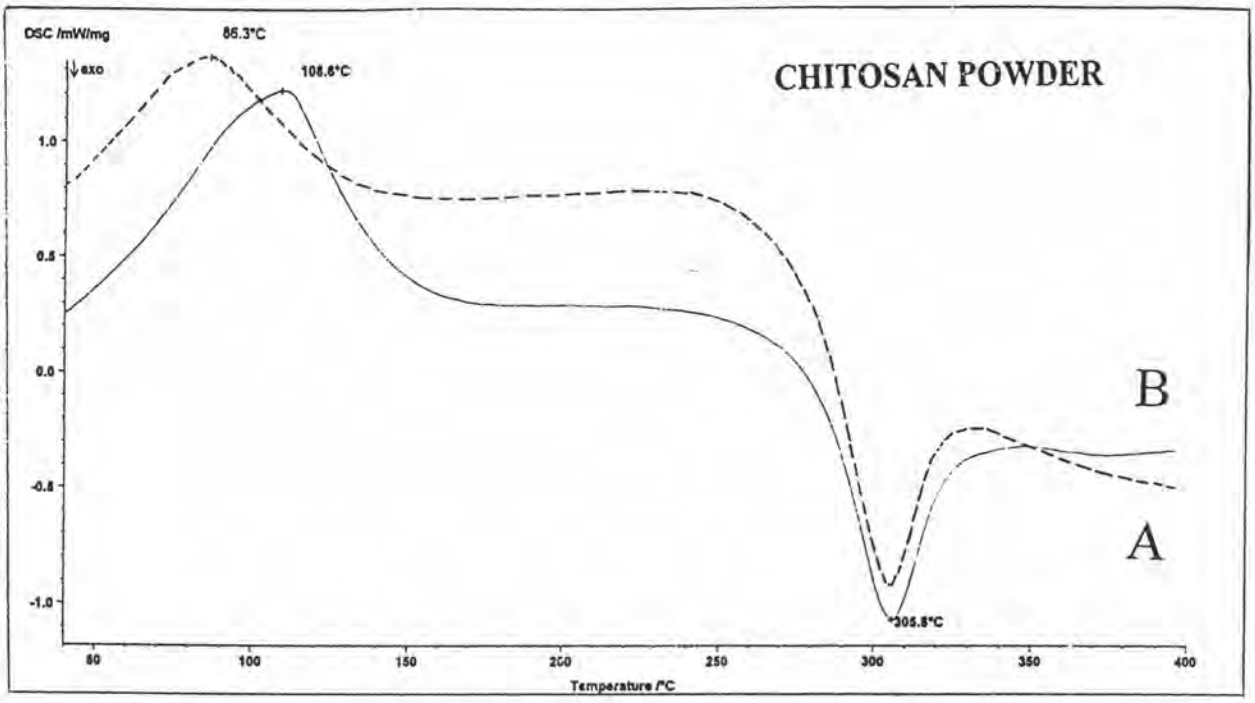


Figure 49 DSC thermograms of chitosan powder (A) untreated and (B) after exposed to moist heat at 60°C for 360 hrs.

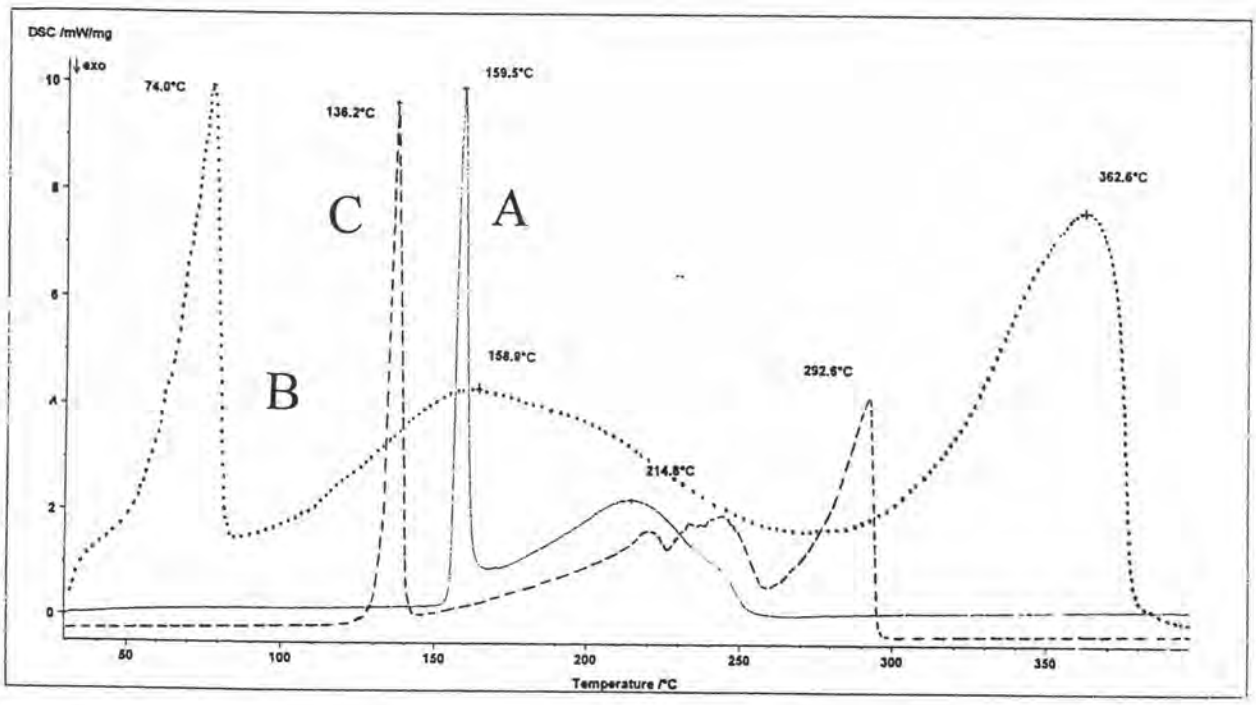


Figure 50 DSC thermograms of (A) citric acid; (B) glycolic acid and (C) malic acid.

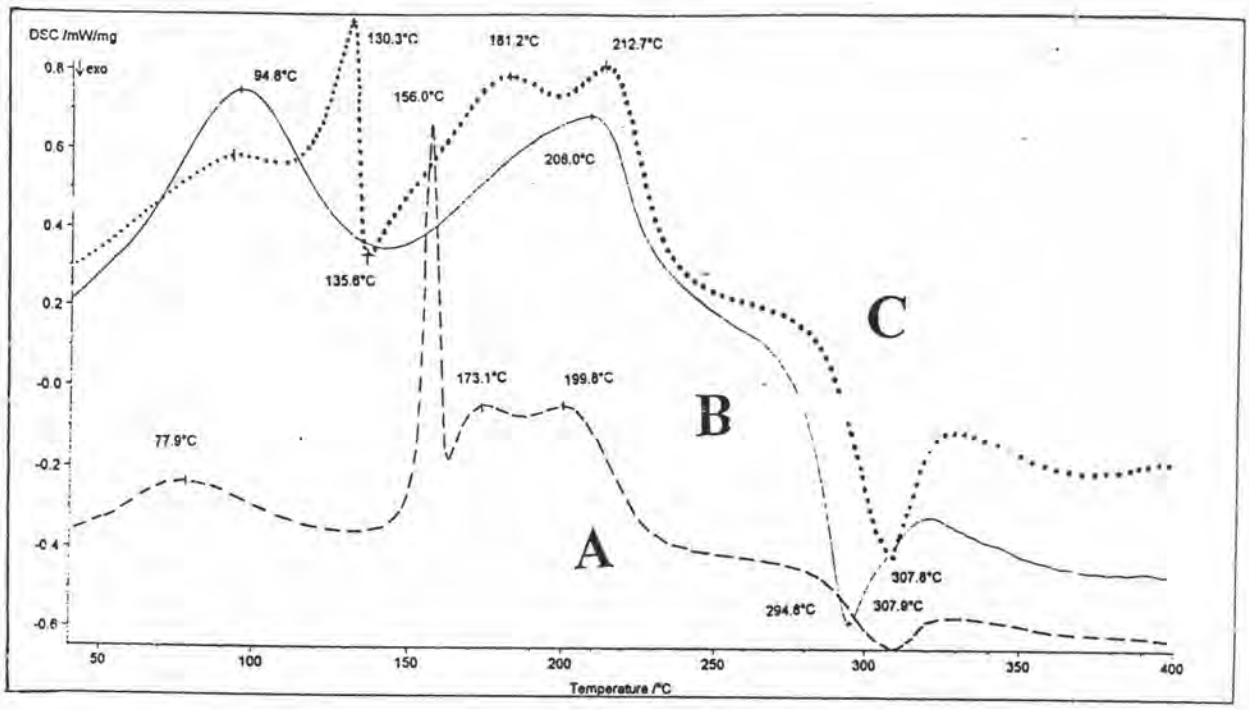


Figure 51 DSC thermograms of physical mixtures between (A) chitosan-citric acid; (B) chitosan-glycolic acid and (C) chitosan-malic acid.

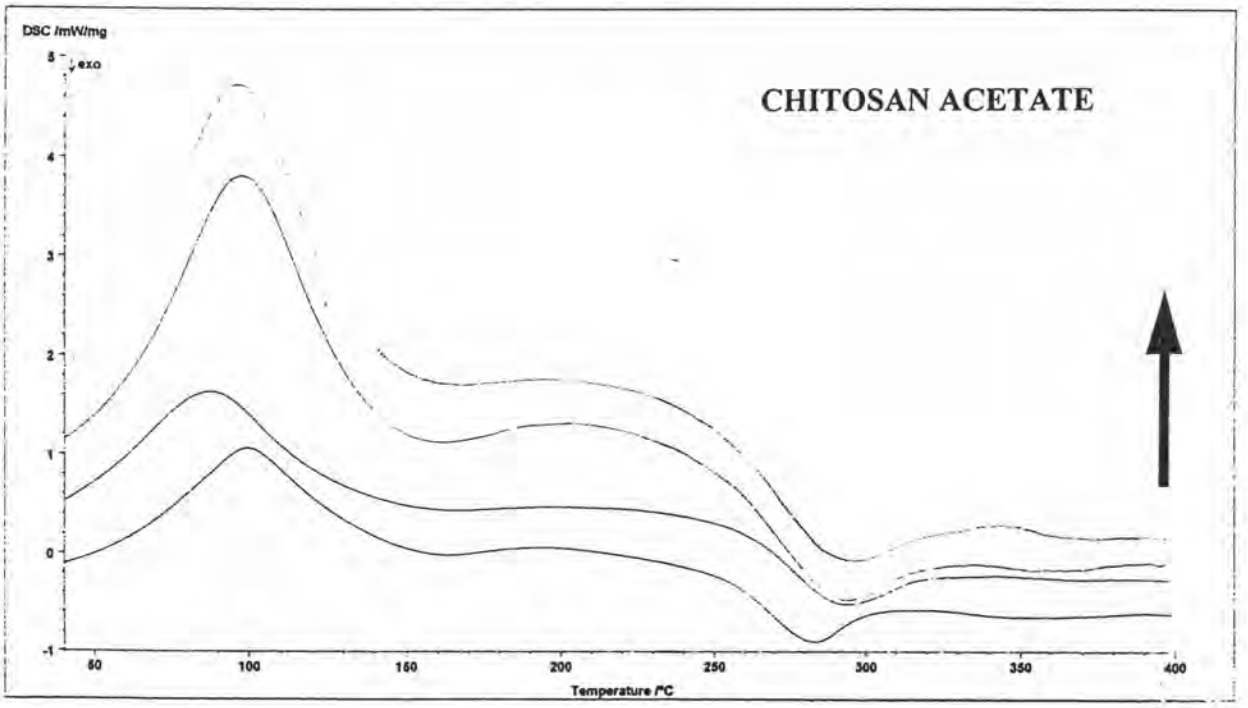


Figure 52 DSC thermograms of chitosan acetate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

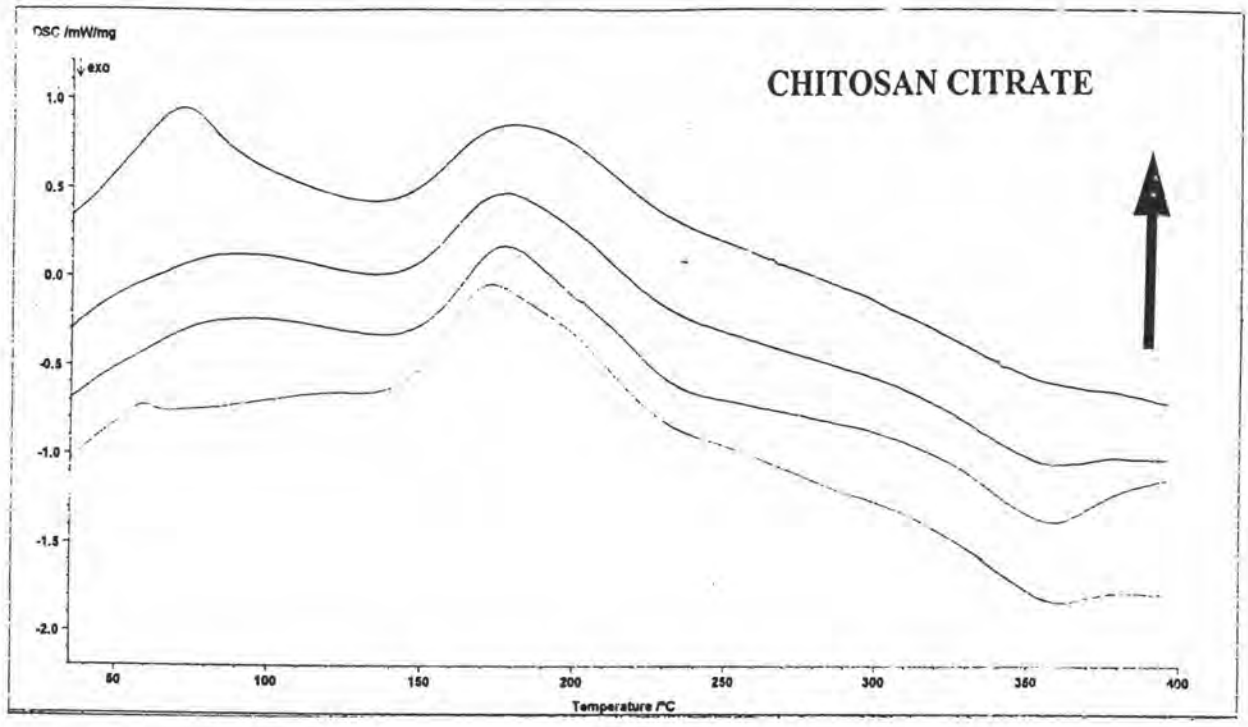


Figure 53 DSC thermograms of chitosan citrate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

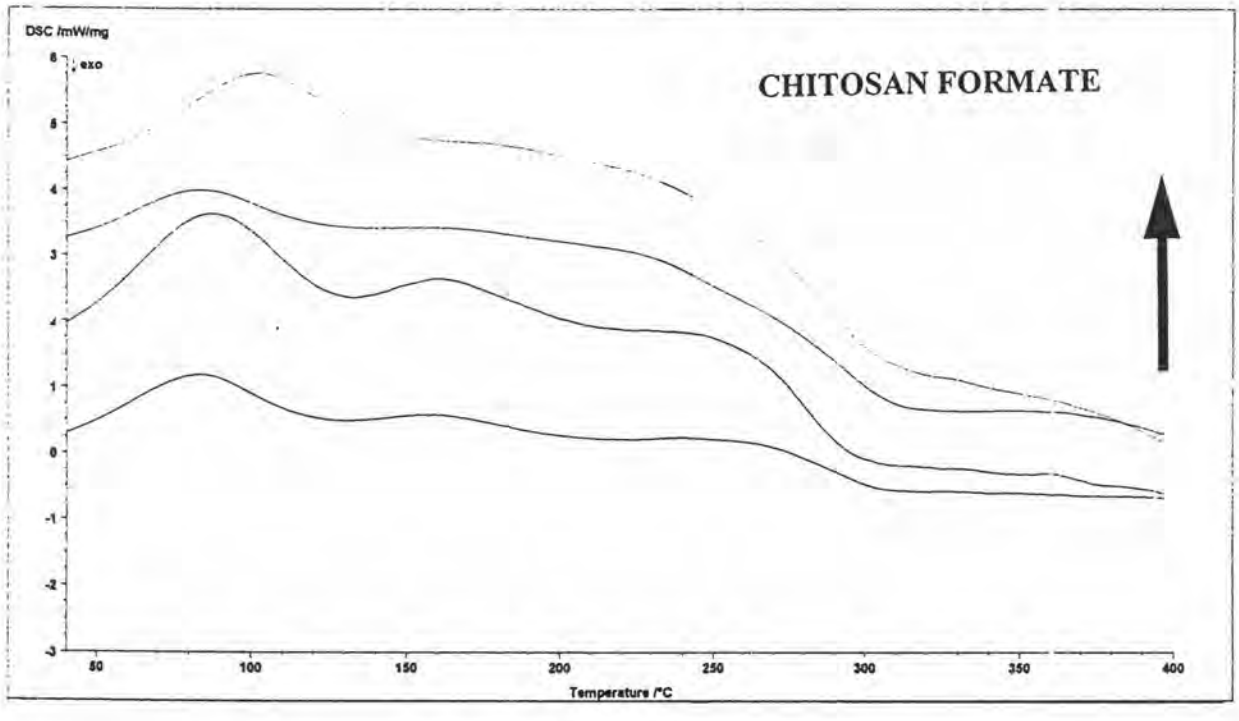


Figure 54 DSC thermograms of chitosan formate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

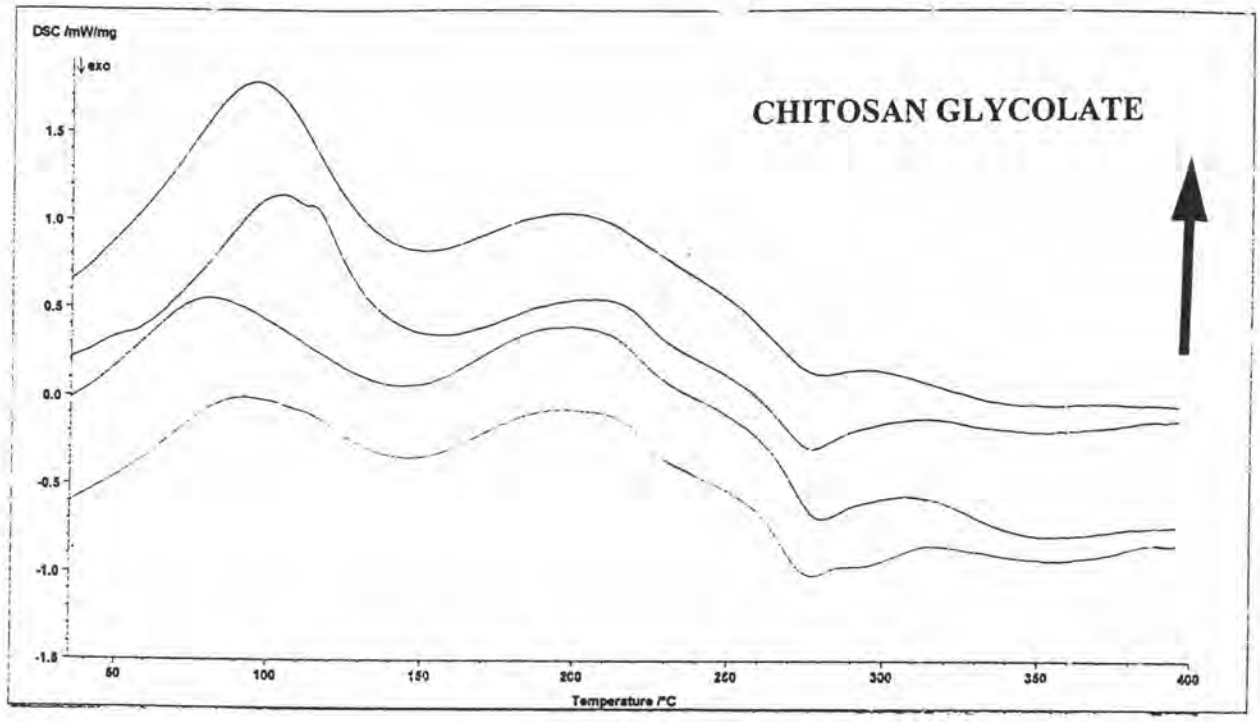


Figure 55 DSC thermograms of chitosan glycolate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

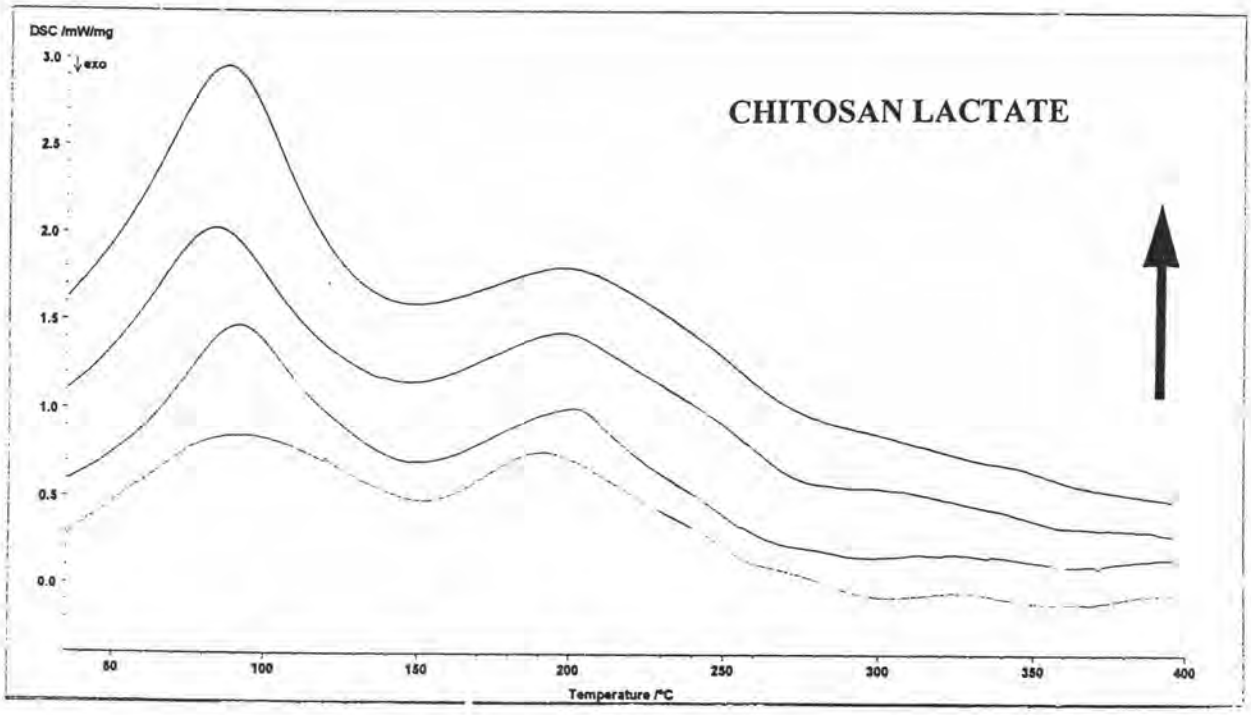


Figure 56 DSC thermograms of chitosan lactate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

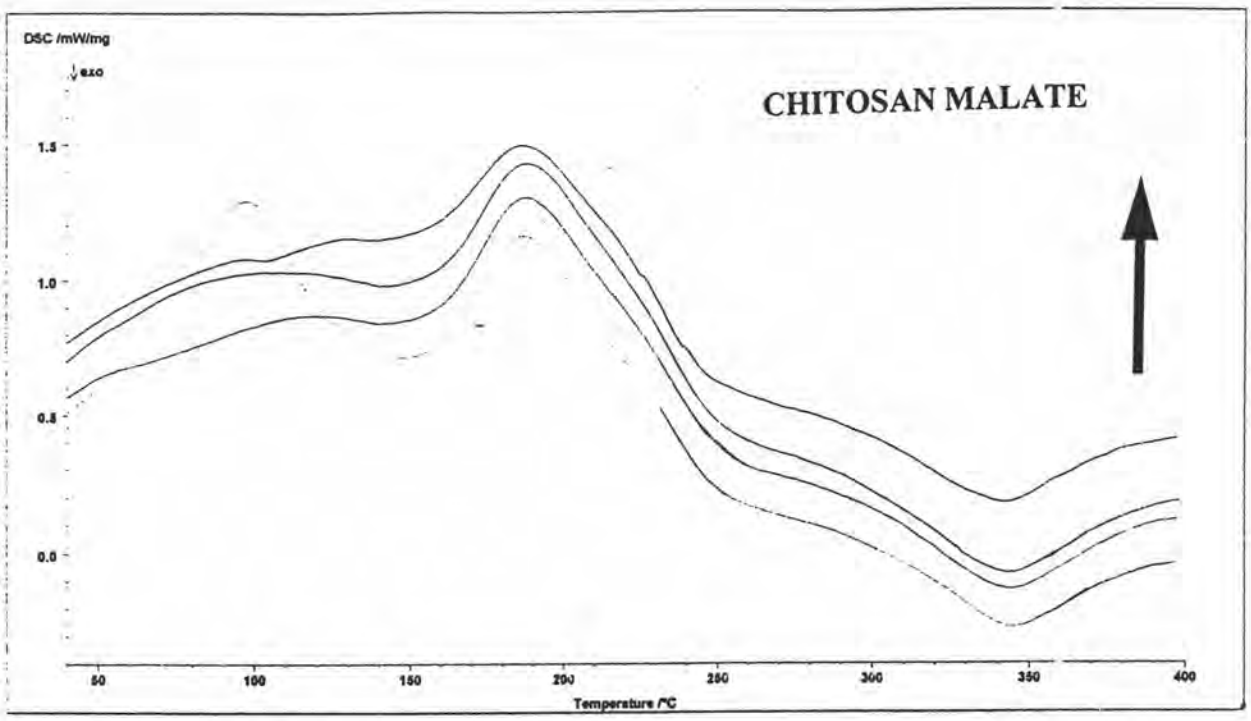


Figure 57 DSC thermograms of chitosan malate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

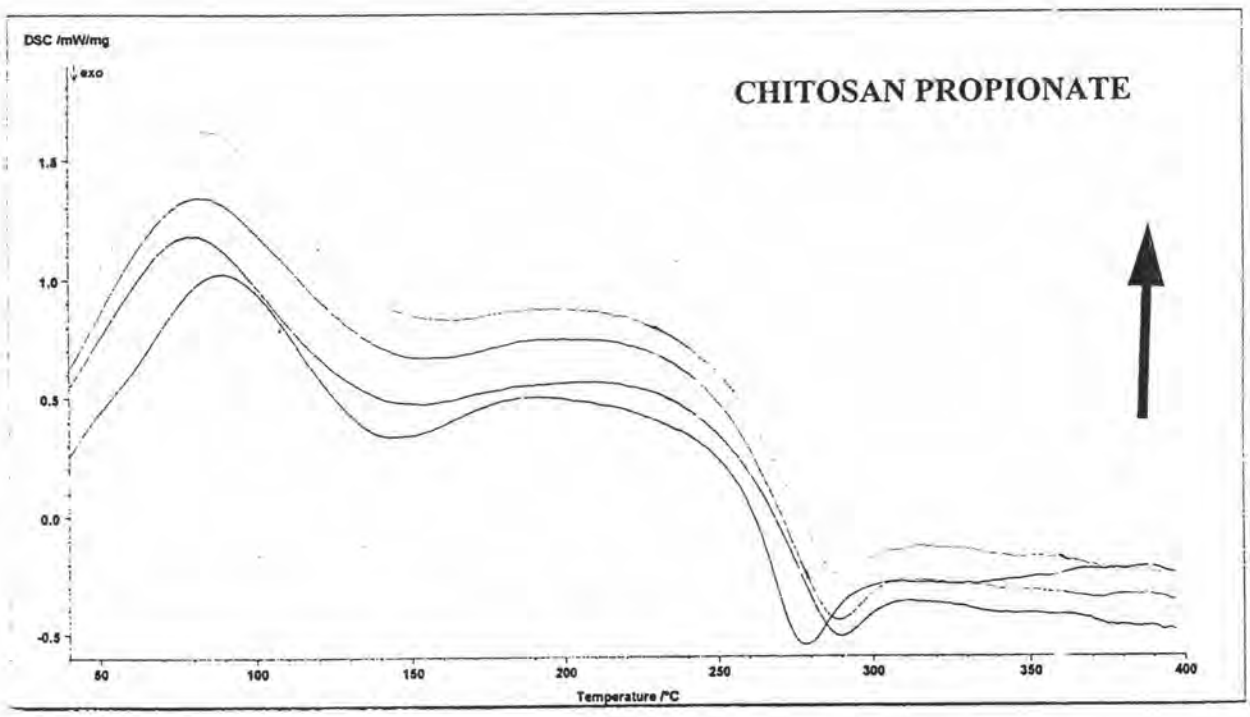


Figure 58 DSC thermograms of chitosan propionate films: freshly prepared and after exposed to moist heat at 60°C for 72, 168 and 360 hrs. (upward).

2.5 Solid State ^{13}Carbon Nuclear Magnetic Resonance Spectroscopy

The signals from solid state ^{13}C NMR analysis of powderous chitosan, untreated and heat treated chitosan acetate are presented in Figures *59* and *60* respectively. The peaks representing the carbon 1-6 of glucosamine unit is indicated in Figure *59*. This structural identification was reported by some investigators (Imai et al., 1991; Tokura, 1994). Carbon of CH_3 group on acetamido functionality raised signals at 23 ppm and carbon of N-acetyl CO group appeared the signal at 173 ppm. These two peaks confirmed that there were acetamido groups remaining in chitosan used in this study (% deacetylation 85.91). The spectra of untreated chitosan acetate film neutralized with 1 N NaOH solution was similar to that of chitosan powder, except that the peak of $C_{4,5}$ nearly fused to the sharp peak of $C_{5,3}$.

The longer moist heat treatment on chitosan acetate, the more was the peak intensity at 23 and 173 ppm. The enhancement of peak intensity was also observed in case of using dry heat treatment at 130°C for 9 hours. Integrated peak height ratio of all spectra are shown in Table *7*. The peak $C_{4,5}$ nearly fused with the sharp peak of $C_{5,3}$ was also seen in case of heat treated chitosan acetate film. The aforementioned characteristics were also occurred in case of chitosan propionate as illustrated in Figure *60*, however dry heat treated sample was not tested.

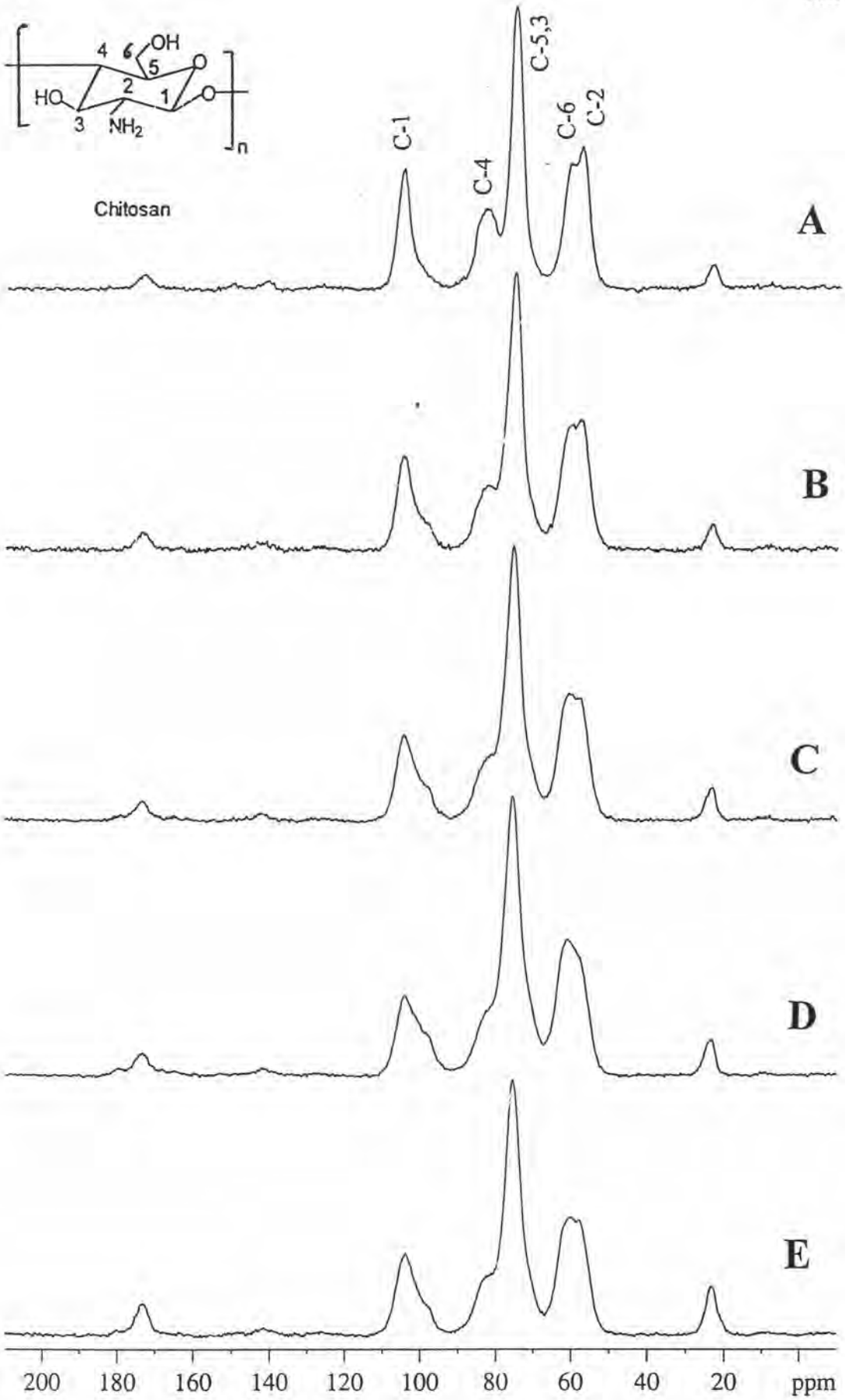


Figure 59 Solid state ^{13}C NMR spectra of (A) chitosan; and chitosan acetate (B) untreated; after moist heat treatment at 60°C for (C) 24 hrs.; (D). 72 hrs. and (E) after dry heat at 130°C for 9 hrs.

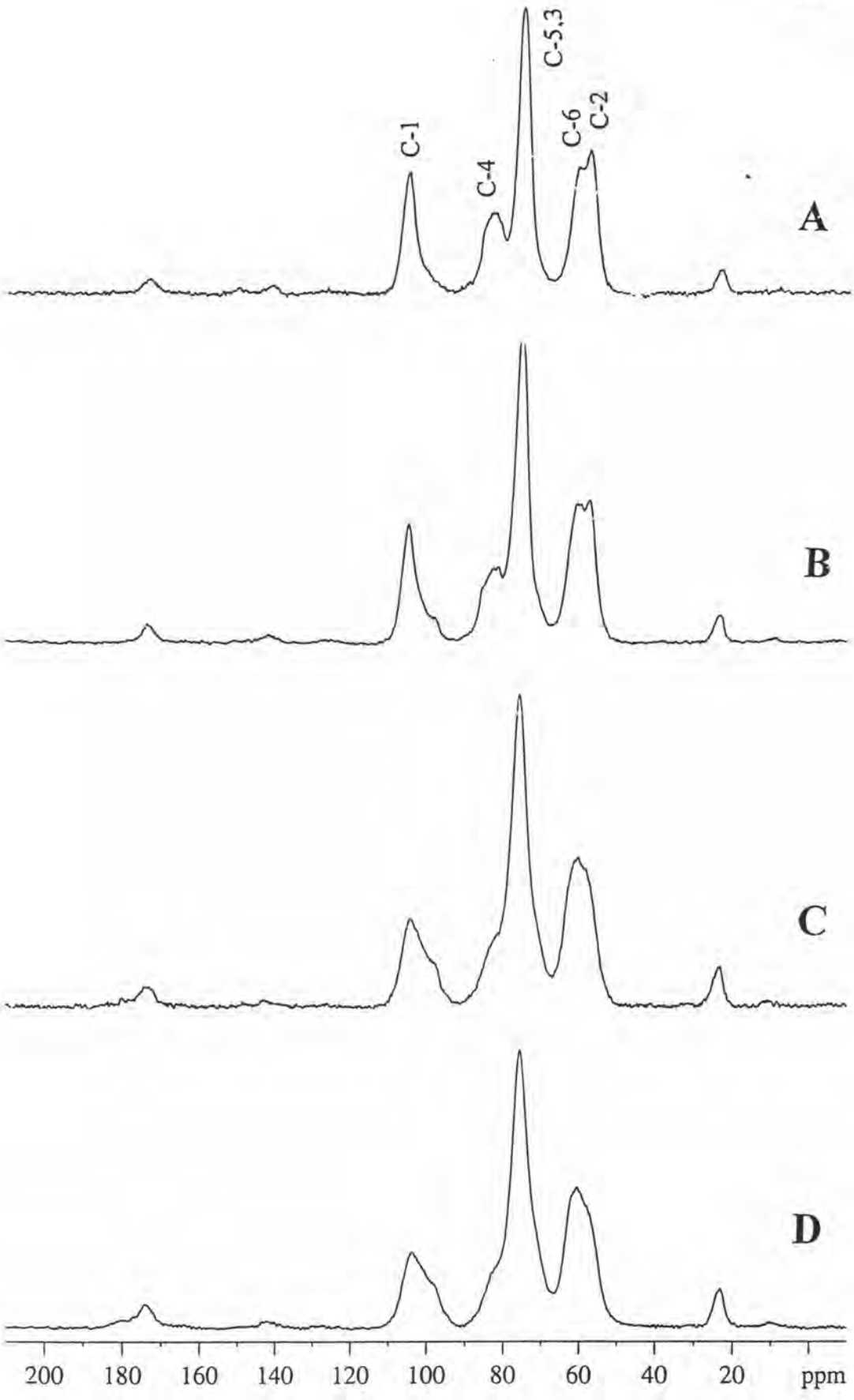


Figure 60 Solid state ^{13}C NMR spectra of (A) chitosan; and chitosan propionate (B) untreated; after moist heat treatment at 60°C for (C) 24 hrs.; (D) 72 hrs.

Table 7 Peak area ratio from solid state ^{13}C NMR spectra of chitosan powder and chitosan film

Sample	Peak Area Ratio	
	23 ppm/105 ppm	173 ppm/105 ppm
Chitosan	0.097	0.08
Chitosan Acetate	0.094	0.073
Chitosan Acetate After Moist Heat Treatment at 60°C 75%RH for 24 hrs	0.169	0.119
Chitosan Acetate After Moist Heat Treatment at 60°C 75%RH for 72 hrs	0.164	0.156
Chitosan Acetate Dry Heat Treatment at 130°C for 9 hrs	0.306	0.217
Chitosan Propionate	0.103	0.102
Chitosan Propionate After Moist Heat Treatment at 60°C 75%RH for 24 hrs	0.177	0.121
Chitosan Propionate After Moist Heat Treatment at 60°C 75%RH for 72 hrs	0.198	0.192

2.6 UV-VIS Absorption Studies

The wavelength with the absorbance of chitosan films when fixed the absorbance at 1.5 is shown in Figure *61* (Table *92* in Appendix B). As time interval of treatment with moist heat was longer, the absorbing frequency was shifted to a higher wavelength and the film was more yellowish. However, the treated films were still optically clear. The shift to higher wavelength of UV-VIS absorption of chitosan citrate, glycolate, lactate and malate films were higher than those of chitosan acetate, formate and propionate films when fixed the absorbance at 1.5. By comparison, chitosan formate film showed the lowest wavelength and its film color was less yellowish than other chitosan films after treatment for 360 hours. This observation was also found in case of using temperature at 130°C as shown in Figure *62* (Table *93* in Appendix B), however shift to higher wavelength were less than those of using moist heat.

2.7 Moisture Sorption

The effect of type of chitosan salt and duration of moist heat treatment on moisture sorption is presented in Figure *63* (Table *94*, in Appendix B). Degree of moisture sorption of freshly prepared could be ranked as chitosan propionate<acetate <malate<citrate<lactate<formate<glycolate. Chitosan propionate and chitosan acetate films showed a tendency to increase moisture sorption, especially, after moist heat treatment at the initial stage (0-36 hours). However, duration of treatment slightly affected to moisture sorption of other films.

From the previous report, the result showed that type of organic acid, treatment method and duration of treatment affected the physico-chemical properties of chitosan films. Due to higher water sorption and dissolution and the greater remaining of these film properties after heat treatment, chitosan citrate and chitosan malate were selected as film formers to prepare fast release coated tablet in further studies. Whereas chitosan acetate and chitosan propionate were selected to prepare extended coated tablet since they could evidently alter to be insoluble form after heat treatment which potentially acted as barrier and prolonged drug release. Propranolol hydrochloride was utilized as model drug.

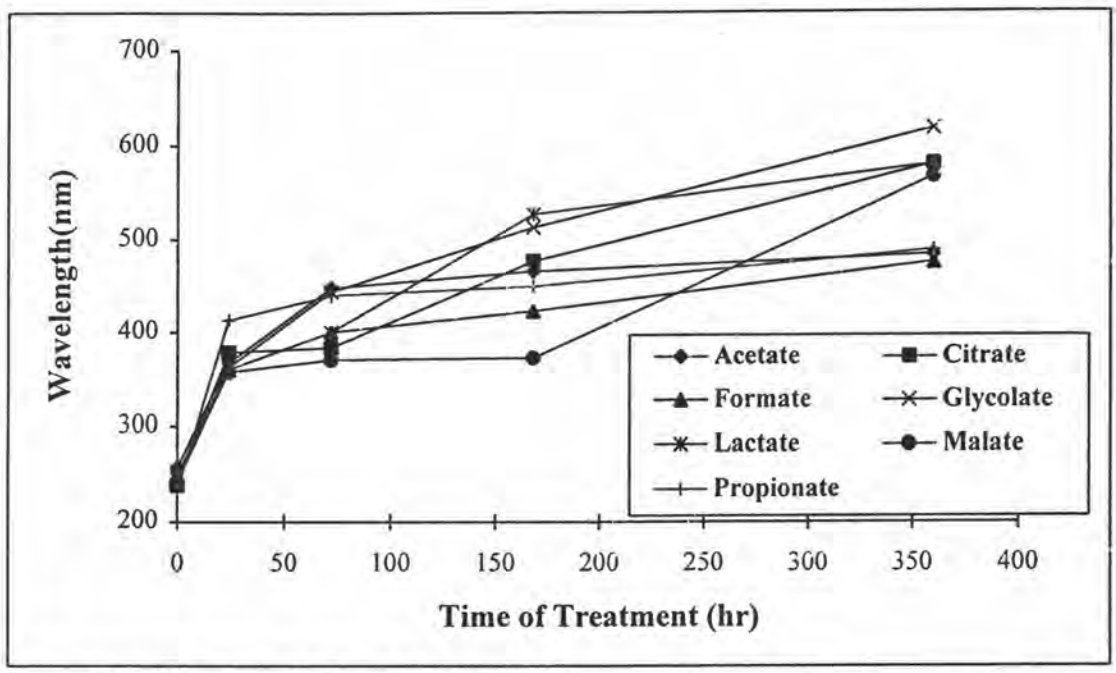


Figure 61 Wavelength from UV-VISIBLE spectrophotometric measurement at absorbance of 1.5 of chitosan films at different time interval after moist heat treatment at 60°C 75% RH.

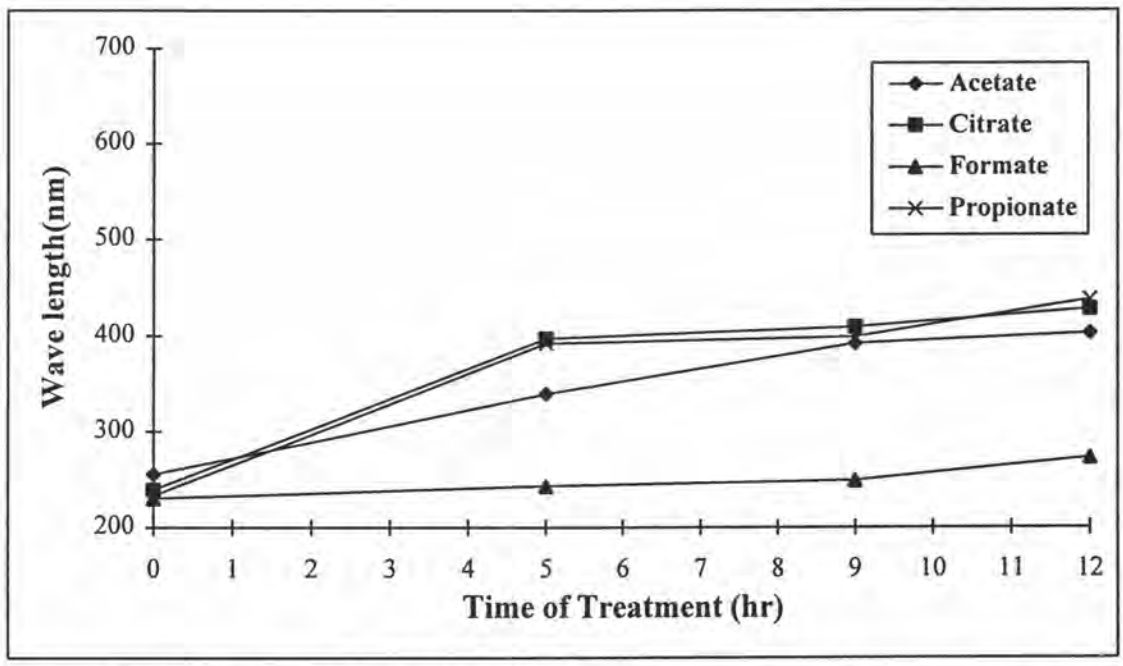


Figure 62 Wavelength from UV-VISIBLE spectrophotometric measurement at absorbance of 1.5 of chitosan films at different time interval after dry heat treatment at 130°C.

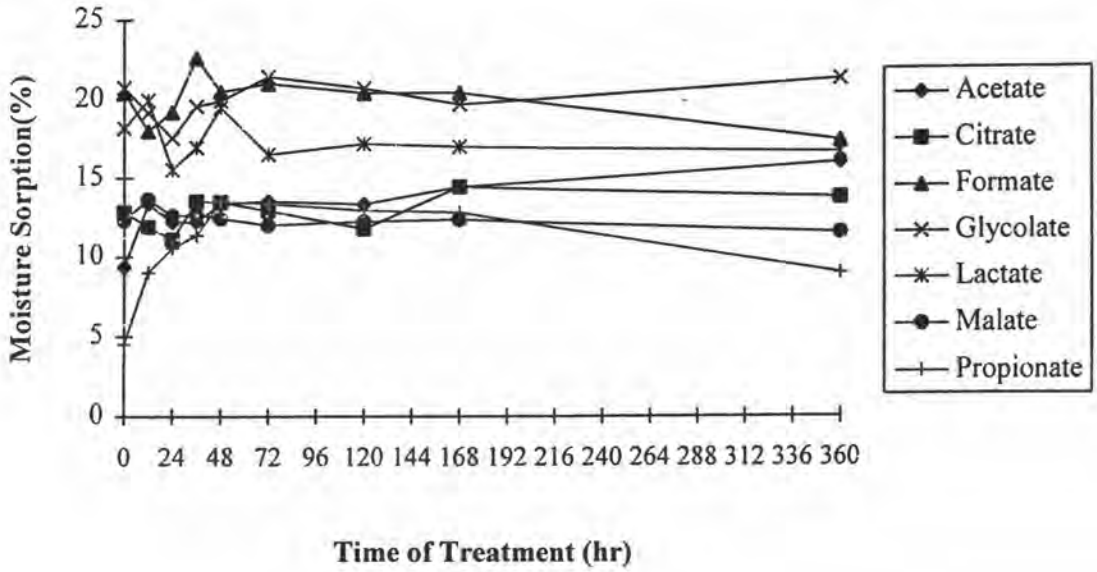


Figure 63 Moisture sorption of chitosan salt films after moist heat treatment for different time intervals (n=6).

3. Effect of Plasticizer on Physicochemical Properties of Chitosan Film

3.1 Physical Appearances

Some physical characteristics of cast films are shown in Tables *8-11*. The chitosan citrate, propionate, malate and acetate solutions yielded a glossy and transparent cast films. Chitosan acetate and propionate films were easily peeled off from petri dish and exhibited moderate flexibility and neither precipitation nor bleeding was detected. Chitosan citrate film was more difficultly peeled off and more sticky than chitosan malate film. These two latter cast films were less flexible than chitosan acetate and chitosan propionate films.

Cast films plasticized with glycerin and propylene glycol showed the satisfactory appearance, since there was transparent and neither precipitation nor bleeding was found as shown in Tables *8-11*. Nevertheless, the chitosan citrate film was rather sticky after plasticized with low concentration of these substances at as shown in Table *8*. An increase in the amount of glycerin provided more flexibility of chitosan citrate, malate, acetate and propionate films. Whereas propylene glycol provided the moderate flexibility at higher concentration. Thus addition of glycerin and propylene glycol could produce satisfactory film characteristics except at low concentration. Whereas incompatibility between chitosan citrate or chitosan propionate, and other plasticizers (PEG 400, 1450 and 6000, triacetin and triethyl citrate) was appeared such as bleeding, precipitation and translucence as presented in Tables *8* and *9*. From this result, it was indicated that both plasticizers, glycerin and propylene glycol, provided the compatibility and good plasticizing behavior for chitosan films thus they were selected for further investigation. Although cast films incorporated with PEG 6000 showed some incompatibility as shown in Tables *8* and *9*, these films were very glossy and thus their mechanical properties were further investigated.

Microscopic nature of unplasticized and plasticized chitosan films was conducted by using a microscope to support the compatibility or incompatibility between this polymeric salt and plasticizer. Clear and no phase separation were noticeable in unplasticized chitosan citrate film as illustrated in Figure *64(A)* and chitosan propionate film as presented in Figure *65(A)* or these films plasticized with glycerin or propylene glycol as shown in Figures *64(B)* and *(C)* and *65(B)* and *(C)*. Therefore this evidence also confirmed the good compatibility between chitosan salts and glycerin or propylene glycol detected from the observation of physical appearances. The dark spots appeared in photographs of films plasticized with glycerin and propylene glycol was the defect during took a photograph since the spots occurred at the same position.

Chitosan films plasticized with other substances (PEG 400, 1450, 6000, triacetin and triethyl citrate) exhibited the occurrence of phase separation as presented in Figures *64(D)* to *(H)* and *65(D)* to *(H)*. Degree of phase separation depended on the level of plasticizer incorporated. Phase separation was more obvious in films added with those substances at 35% w/w than those films added at 15% w/w. Many droplets of liquid were evidently found on surface of chitosan citrate films plasticized with PEG 400 and PEG 1450 and chitosan propionate film plasticized with PEG 400. The precipitation was

Table 8 Some physical characteristics of chitosan citrate films before and after incorporated with different amount of plasticizers.

Plasticizer	yellow color	transparency	glossy	precipitation	sticky	flexibility	bleeding
Unplasticized	++	+	++	−	−	+	−
Glycerin							
5%	++	+	++	−	+	+	−
15%	++	+	++	−	−	++	−
25%	++	+	++	−	−	+++	−
35%	++	+	++	−	−	++++	−
45%	++	+	++	−	−	++++	−
PEG 400							
5%	++	+	+	−	++	++	−
15%	++	+	+	−	++	++	∓
25%	++	−	+	−	+	++	+++
35%	++	−	+	−	−	++	+++
PEG 1450							
5%	++	+	+++	−	−	++	−
15%	++	−	+++	−	−	++	−
25%	++	−	+++	−	−	++	−
35%	++	−	+++	−	−	++	−
PEG 6000							
5%	++	−	+++	−	−	+	−
15%	++	−	+++	−	−	++	−
25%	++	−	++++	−	−	++	−
35%	++	−	++++	−	−	++	−
45%	++	−	++++	∓	−	+	−
Propylene Glycol							
5%	++	+	++	−	+++	++	−
15%	++	+	++	−	−	+++	−
25%	++	+	++	−	−	+++	−
35%	++	+	++	−	−	+++	−
45%	++	+	++	−	−	+++	−
Triacetin							
5%	++	−	++	−	+	++	−
15%	++	−	++	−	+	++	−
25%	++	−	++	−	+	++	−
35%	++	−	++	−	+	++	∓
Triethyl Citrate							
5%	++	−	++	−	+	++	−
15%	++	−	++	−	+	++	−
25%	++	−	++	−	−	++	+∓+
35%	++	−	++	−	−	++	++++

The symbols of (+) and (-) showed the appearance and no appearance, respectively, and the number of the symbols of (+) showed a degree of the appearance.

Table 9 Some physical characteristics of chitosan propionate films before and after incorporated with different amount of plasticizers.

Plasticizer	yellow color	transparency	glossy	precipitation	sticky	flexibility	bleeding
Unplasticized	++	+	+++	−	−	++	−
Glycerin							
5%	++	+	+++	−	−	+	−
15%	++	+	+++	−	−	+	−
25%	++	+	+++	−	−	++	−
35%	++	+	+++	−	−	+++	−
PEG 400							
5%	++	+	+	−	−	++	−
15%	++	+	+	−	−	++	−
25%	++	−	+	−	−	++	∓
35%	++	−	+	−	−	+	+++
PEG 1450							
5%	++	+	+++	−	−	++	−
15%	++	−	+++	−	−	++	−
25%	++	−	+++	−	−	++	−
35%	++	−	+++	∓	∓	+	−
PEG 6000							
5%	++	−	+++	−	−	++	−
15%	++	−	++++	−	−	++	−
25%	++	−	++++	∓	∓	+	−
35%	++	−	++++	+++	++	+	−
Propylene Glycol							
5%	++	+	+++	−	−	++	−
15%	++	+	+++	−	−	++	−
25%	++	+	+++	−	−	+++	−
35%	++	+	+++	−	−	+++	−
Triacetin							
5%	++	−	++	−	−	++	−
15%	++	−	+++	−	−	++	−
25%	++	−	+++	−	−	++	−
35%	++	−	+++	−	−	++	−
Triethyl Citrate							
5%	++	−	++	−	−	++	−
15%	++	−	+++	−	−	++	∓
25%	++	−	+++	−	−	++	+++
35%	++	−	+++	−	−	++	++++

The symbols of (+) and (-) showed the appearance and no appearance, respectively, and the number of the symbols of (+) showed a degree of the appearance.

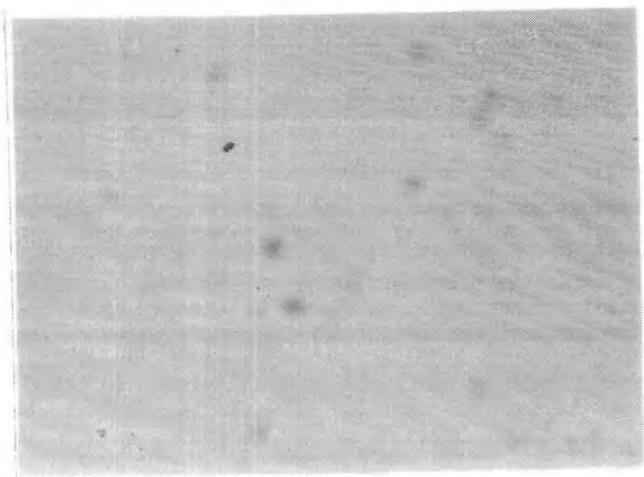
Table 10 Some physical characteristics of chitosan malate films before and after incorporated with different amount of plasticizers.

Plasticizer	yellow color	transparency	glossy	precipitation	sticky	flexibility	bleeding
Unplasticized	+++	+	++	–	–	+	–
Glycerin							
5%	+++	+	++	–	–	++	–
15%	+++	+	++	–	–	++	–
25%	+++	+	++	–	–	+++	–
35%	+++	+	++	–	–	++++	–
45%	+++	+	++	–	–	++++	–
Propylene Glycol							
5%	+++	+	++	–	–	++	–
15%	+++	+	++	–	–	++	–
25%	+++	+	++	–	–	++	–
35%	+++	+	++	–	–	+++	–
45%	+++	+	++	–		+++	–

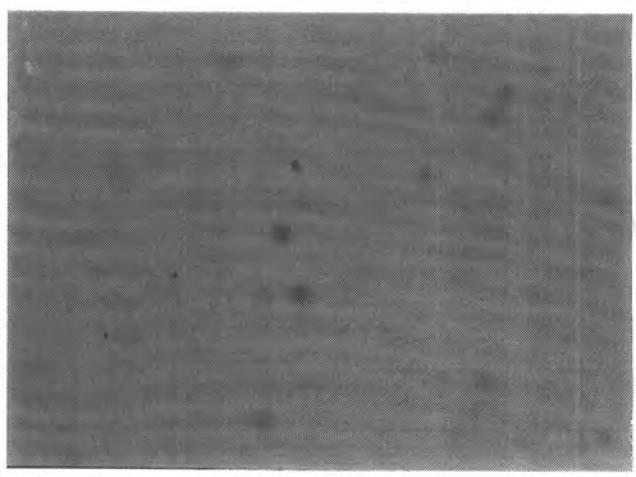
Table 11 Some physical characteristics of chitosan acetate films before and after incorporated with different amount of plasticizers.

Plasticizer	yellow color	transparency	glossy	precipitation	sticky	flexibility	bleeding
Unplasticized	++	+	+++	–	–	++	–
Glycerin							
5%	++	+	+++	–	–	+	–
15%	++	+	+++	–	–	++	–
25%	++	+	+++	–	–	+++	–
35%	++	+	+++	–	–	++++	–
45%	++	+	+++	–	–	++++	–
Propylene Glycol							
5%	++	+	+++	–	–	+	–
15%	++	+	+++	–	–	++	–
25%	++	+	+++	–	–	++	–
35%	++	+	+++	–	–	+++	–
45%	++	+	+++	–		+++	–

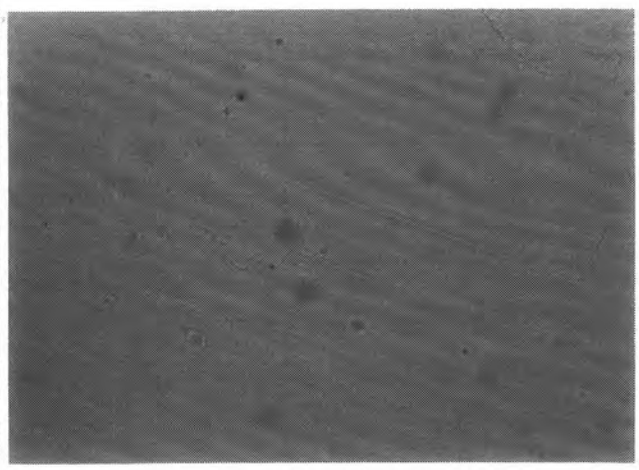
The symbols of (+) and (-) showed the appearance and no appearance, respectively, and the number of the symbols of (+) showed a degree of the appearance.



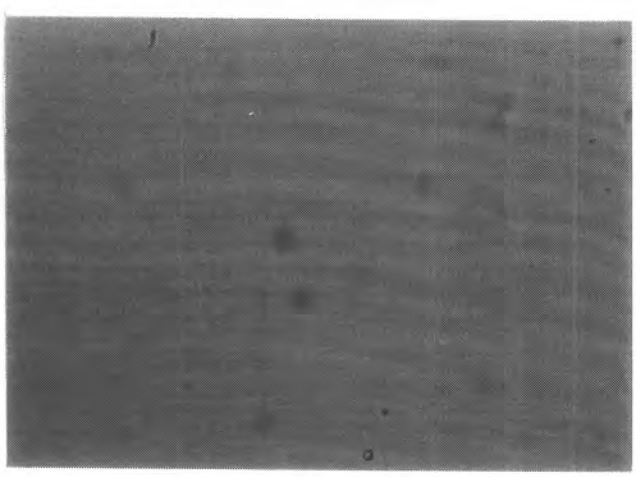
(A)



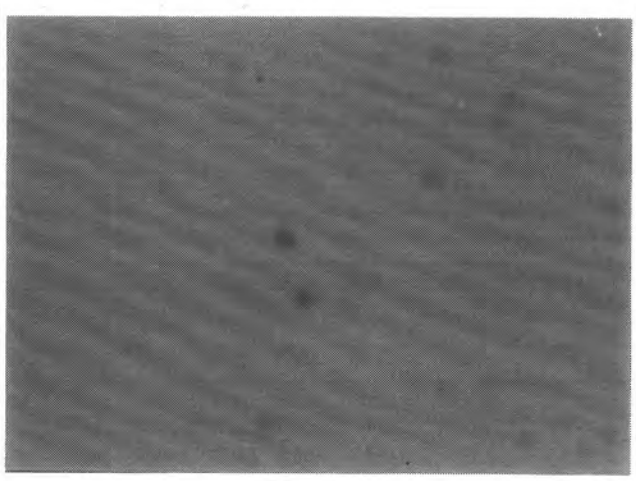
(B(a))



(B(b))



(C(a))



(C(b))

Figure 64 Photomicrographs of chitosan citrate films (A) unplasticized and plasticized with (B) glycerin; (C) propylene glycol; (D) PEG 400; (E) PEG 1450; (F) PEG 6000; (G) triacetin and (H) triethyl citrate at concentration of (a) 15% and (b) 35%.

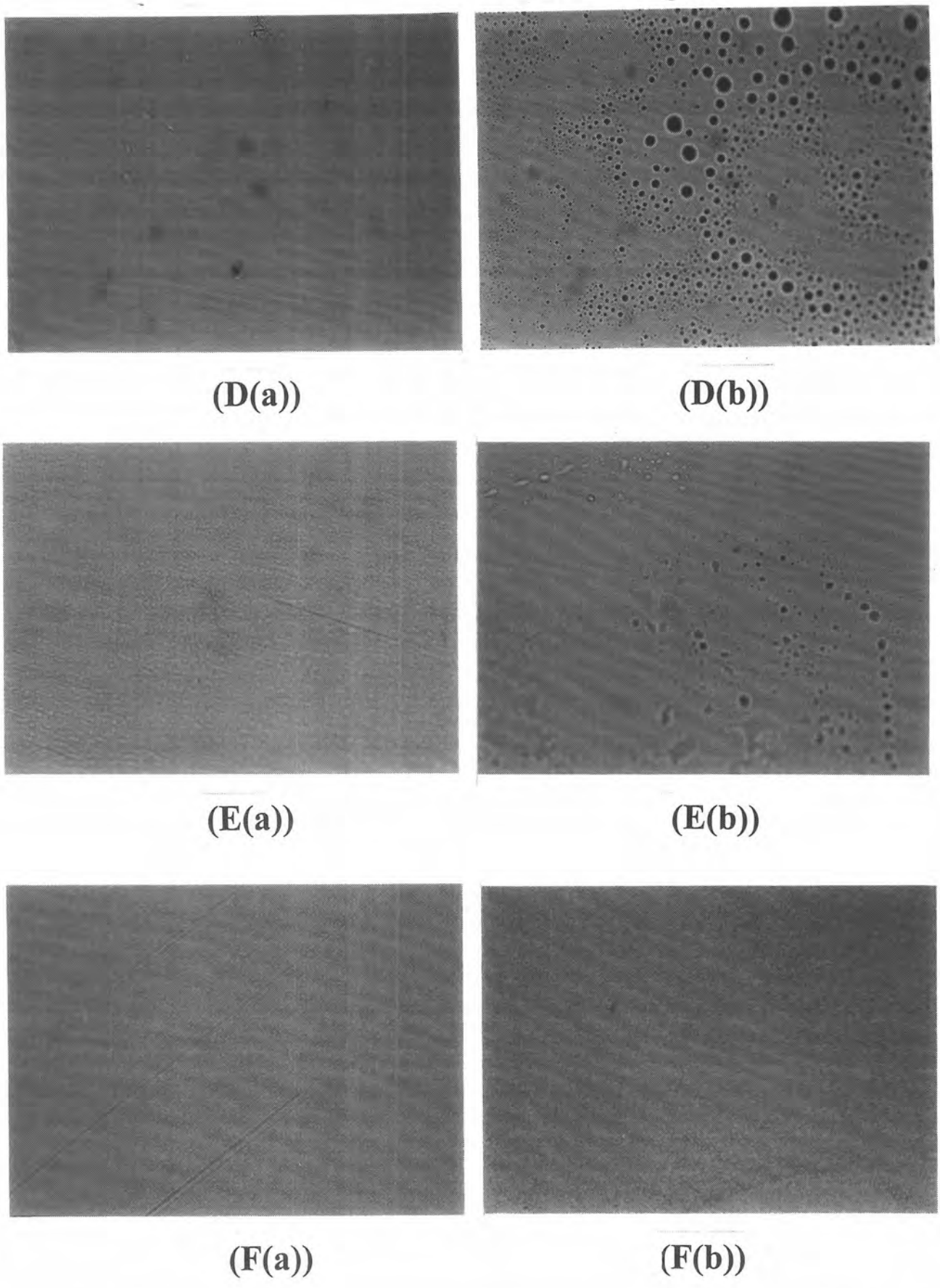


Figure 64 Photomicrographs of chitosan citrate films (A) unplasticized and plasticized with (B) glycerin; (C) propylene glycol; (D) PEG 400; (E) PEG 1450; (F) PEG 6000; (G) triacetin and (H) triethyl citrate at concentration of (a) 15% and (b) 35% (continue).

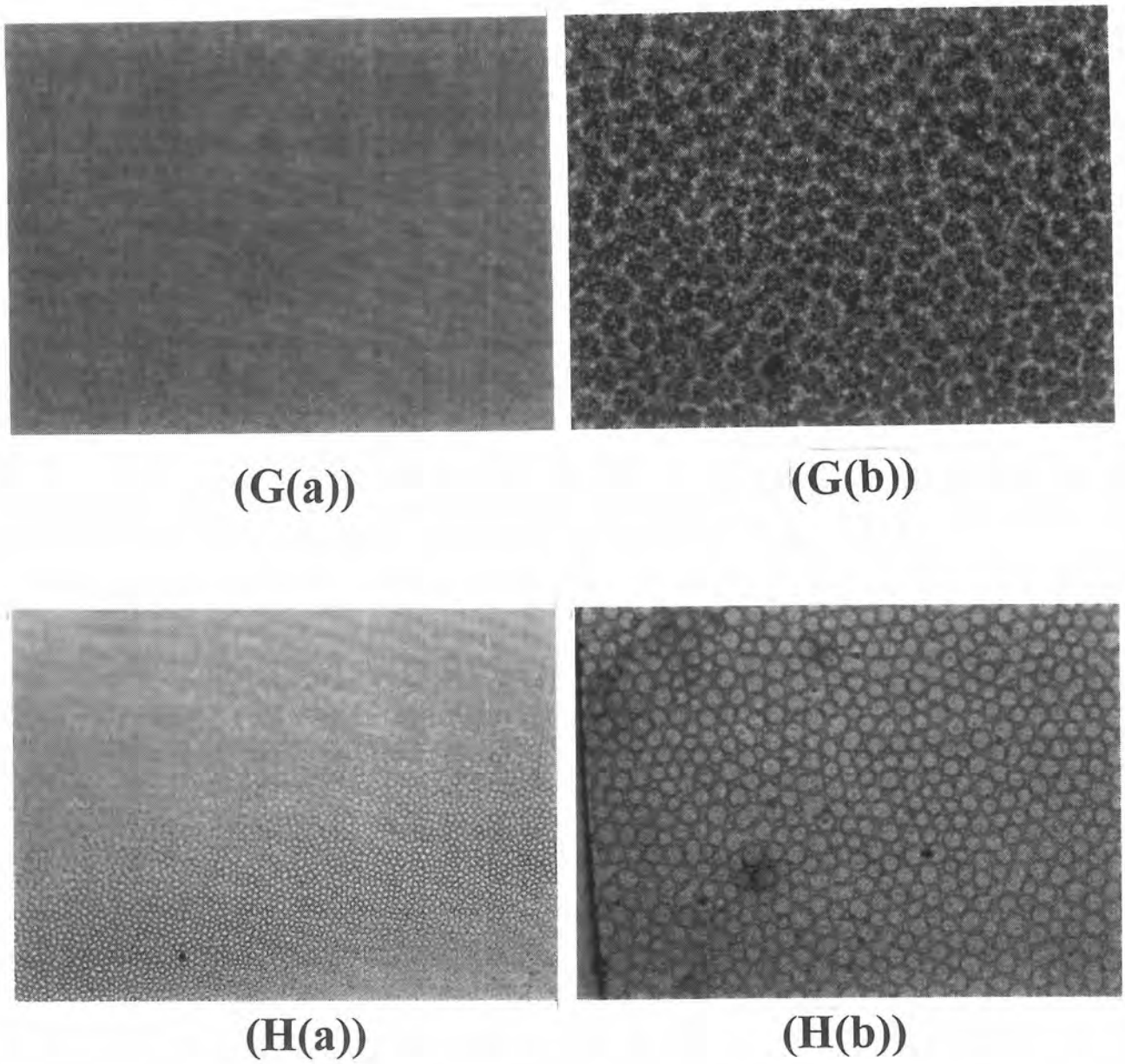


Figure 64 Photomicrographs of chitosan citrate films (A) unplasticized and plasticized with (B) glycerin; (C) propylene glycol; (D) PEG 400; (E) PEG 1450; (F) PEG 6000; (G) triacetin and (H) triethyl citrate at concentration of (a) 15% and (b) 35% (continue).

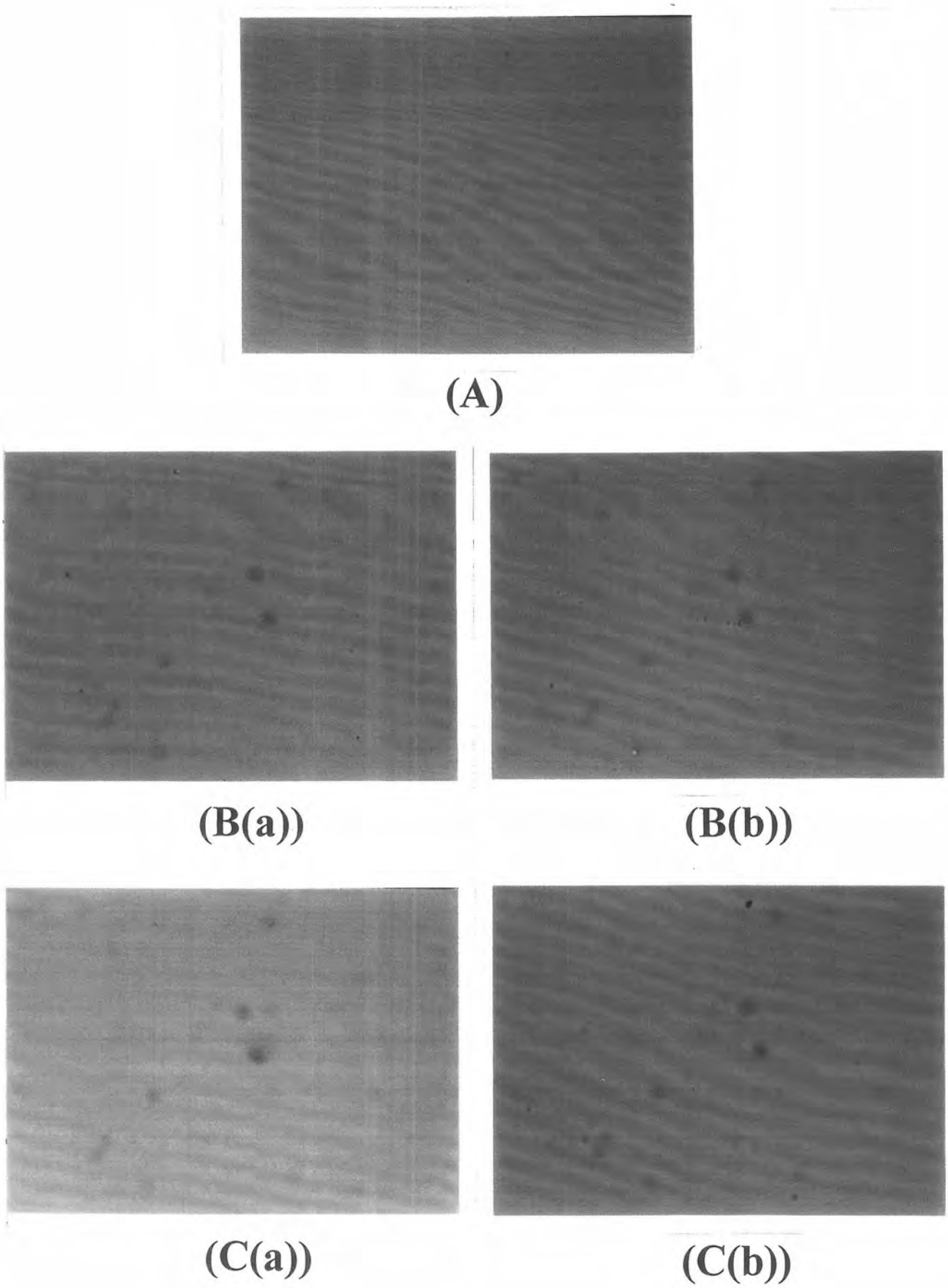
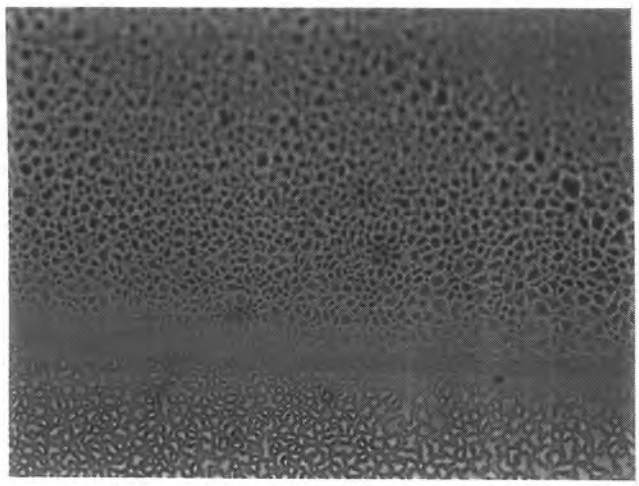
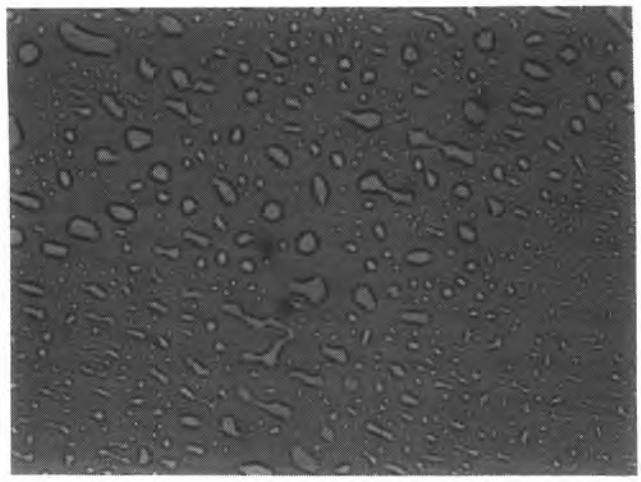


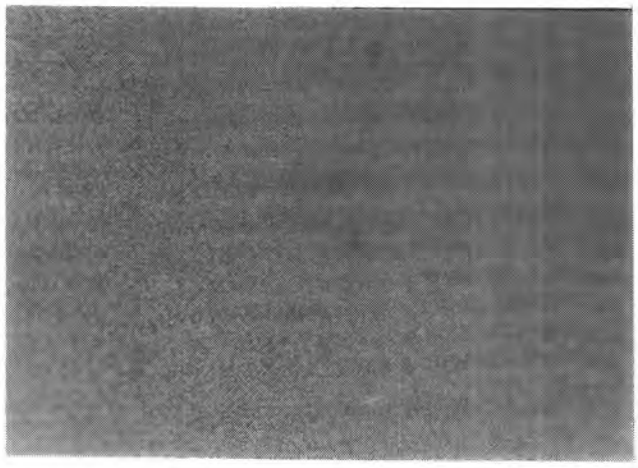
Figure 65 Photomicrographs of chitosan propionate films (A) unplasticized and plasticized with (B) glycerin; (C) propylene glycol; (D) PEG 400; (E) PEG 1450; (F) PEG 6000; (G) triacetin and (H) triethyl citrate at concentration of (a) 15% and (b) 35%.



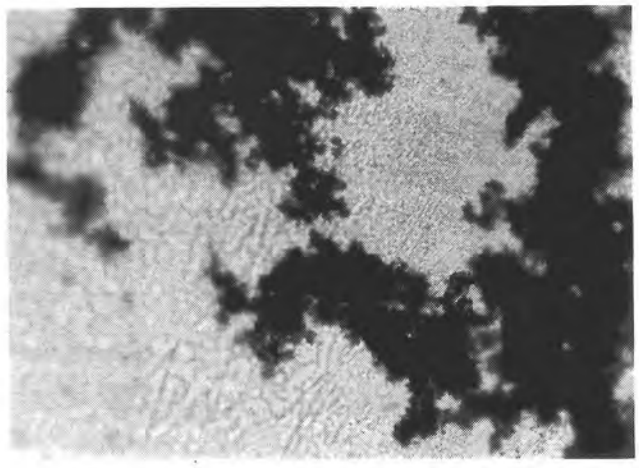
(D(a))



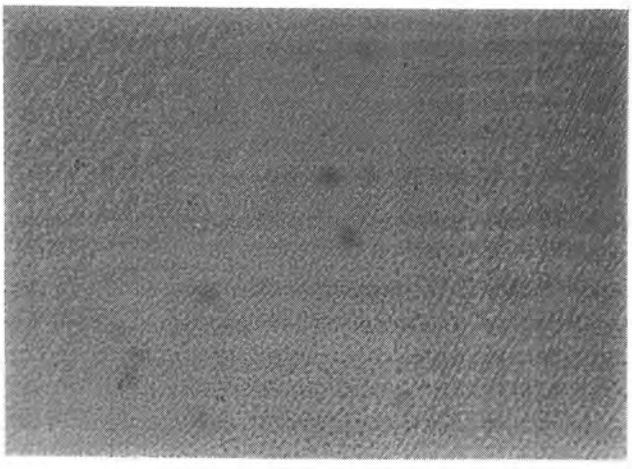
(D(b))



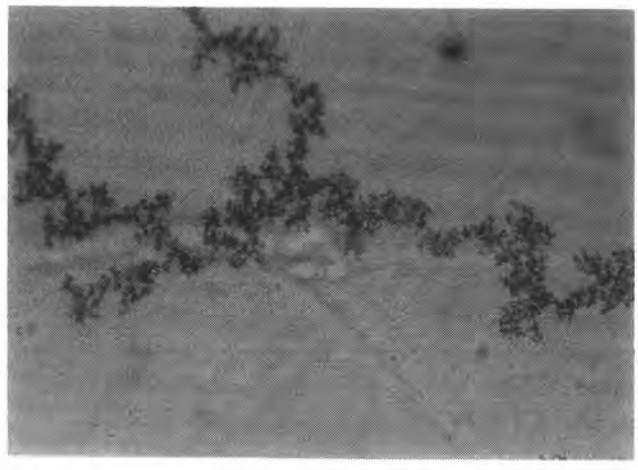
(E(a))



(E(b))



(F(a))



(F(b))

Figure 65 Photomicrographs of chitosan propionate films (A) unplasticized and plasticized with (B) glycerin; (C) propylene glycol; (D) PEG 400; (E) PEG 1450; (F) PEG 6000; (G) triacetin and (H) triethyl citrate at concentration of (a) 15% and (b) 35% (continue).

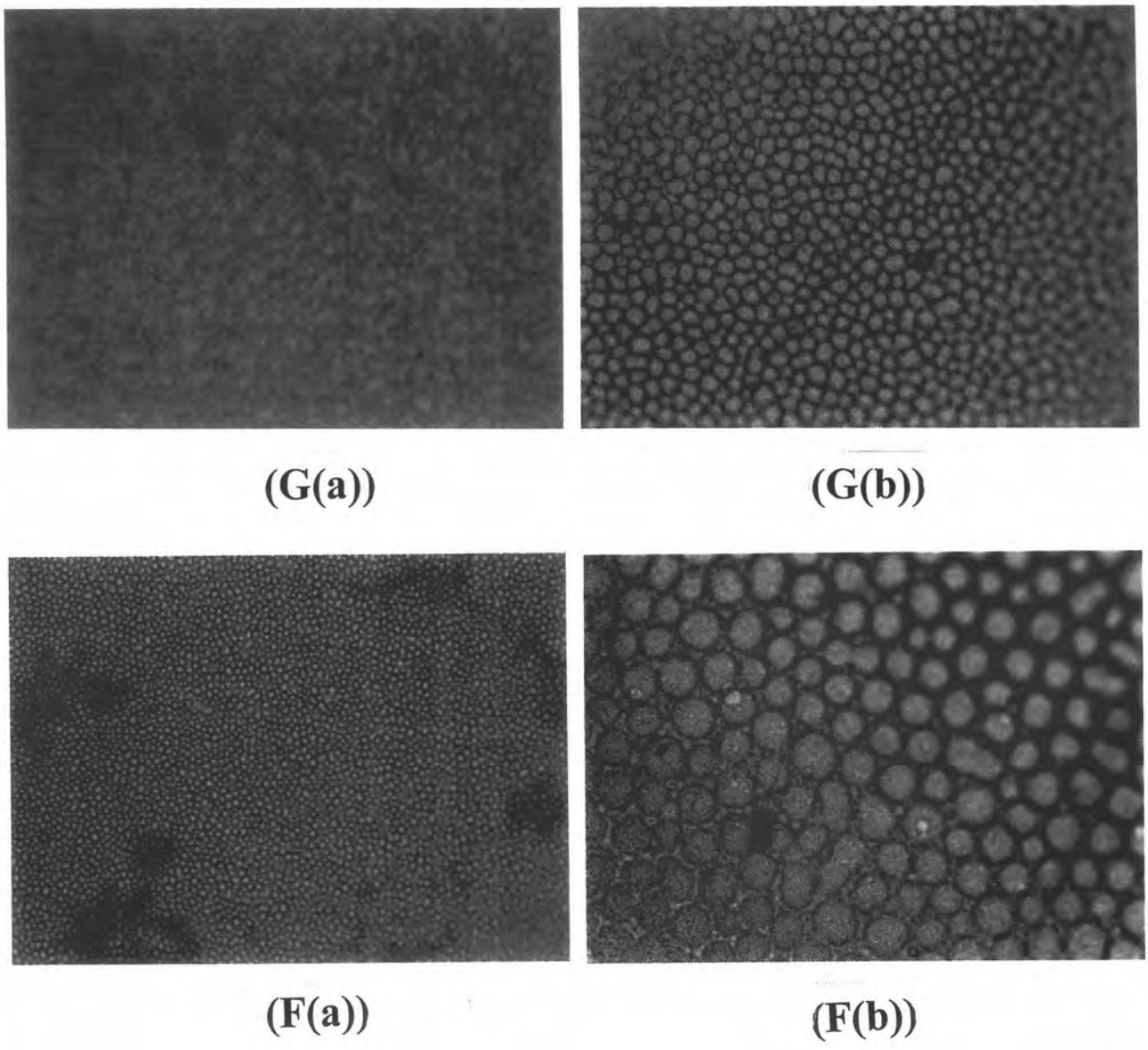


Figure 65 Photomicrographs of chitosan propionate films (A) unplasticized and plasticized with (B) glycerin; (C) propylene glycol; (D) PEG 400; (E) PEG 1450; (F) PEG 6000; (G) triacetin and (H) triethyl citrate at concentration of (a) 15% and (b) 35% (continue).

appeared in chitosan propionate film plasticized with PEG 1450 and PEG 6000 at concentration of 35% w/w. There were many rather circle particles dispersed in both chitosan salt films plasticized with triacetin and triethyl citrate. This result indicated and supported the incompatibility between chitosan salt and various plasticizers: PEG 400, 1450, 6000, triacetin and triethyl citrate.

3. 2 Mechanical Properties of Cast Film

3. 2. 1 Chitosan Citrate and Chitosan Malate Films

The effect of plasticizer on mechanical properties of chitosan citrate and malate films depended on type and amount of plasticizer used as shown in Figures *66-69* (Tables *95, 97, 99, 101* in Appendix B). Typical stress-percent strain profiles are illustrated in Figures *250-254* (Appendix B).

Unplasticized chitosan malate film had stress at break, Young's modulus, maximum percent strain and toughness which were obviously greater than unplasticized chitosan citrate film. An enhancement of glycerin extensively increased maximum percent strain and diminished the Young' s modulus and stress at break of chitosan citrate and malate films. An incorporation of glycerin at the concentration of 25 % w/w and 15 % w/w based on chitosan in chitosan citrate and malate films respectively provided the maximum toughness of prepared films. Loading glycerin at the concentration of 45% obviously decreased the toughness of chitosan citrate and chitosan malate films.

In contrast, when higher amount of PEG 6000 was incorporated into chitosan citrate film, decrease in maximum percent strain, and toughness, and increase in Young's modulus and stress were found. Because of the brittleness of cast film after incorporation of this substance, PEG 6000 was not a suitable plasticizer for chitosan film.

Films plasticized with propylene glycol still remained high stress at break and slightly decreased in Young' s modulus and slightly increased in maximum percent strain, so that these plasticized cast film exhibited the high toughness. The small decrease in the toughness of chitosan citrate film plasticized with low concentration propylene glycol was also found. By comparison, the toughness value at the same type and concentration of plasticizer demonstrated that unplasticized and plasticized chitosan malate films were stronger than those of chitosan citrate films.

Besides good physical appearance and compatibility, good mechanical properties especially toughness was to consider for the selection of suitable plasticizers for chitosan films. This study selected propylene glycol and glycerin at the concentration of 25% w/w based on polymer for the plasticization of chitosan citrate and malate film since they provided relatively high value of toughness and provide good physical appearance and compatibility.

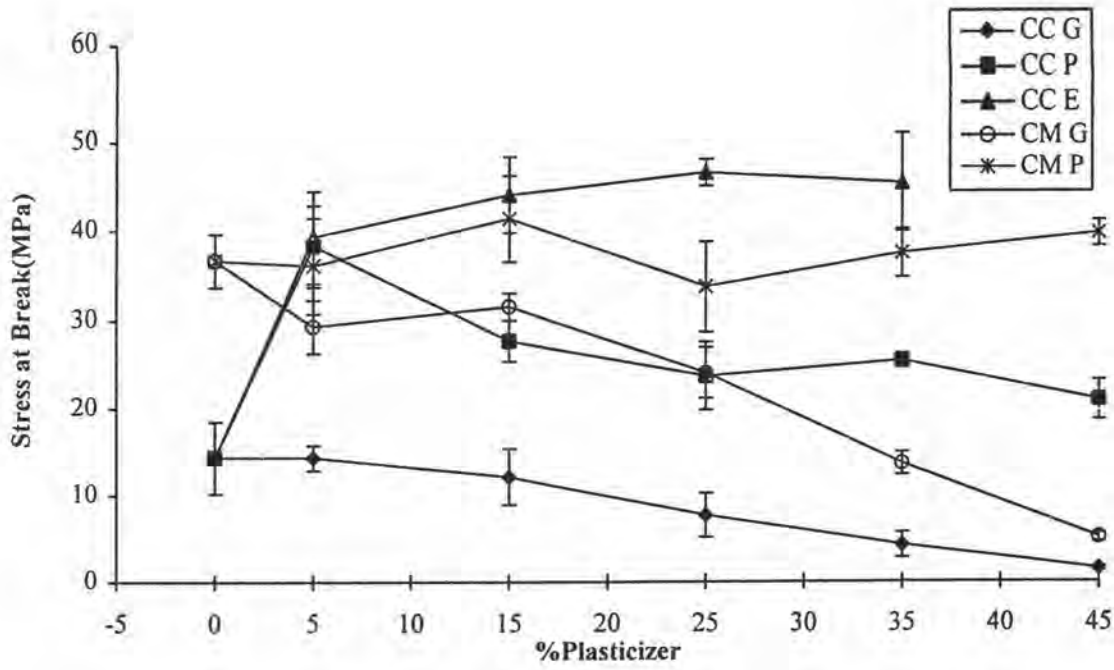


Figure 66 Stress at break of chitosan citrate and chitosan malate cast films plasticized with different amount of plasticizer (n=6).

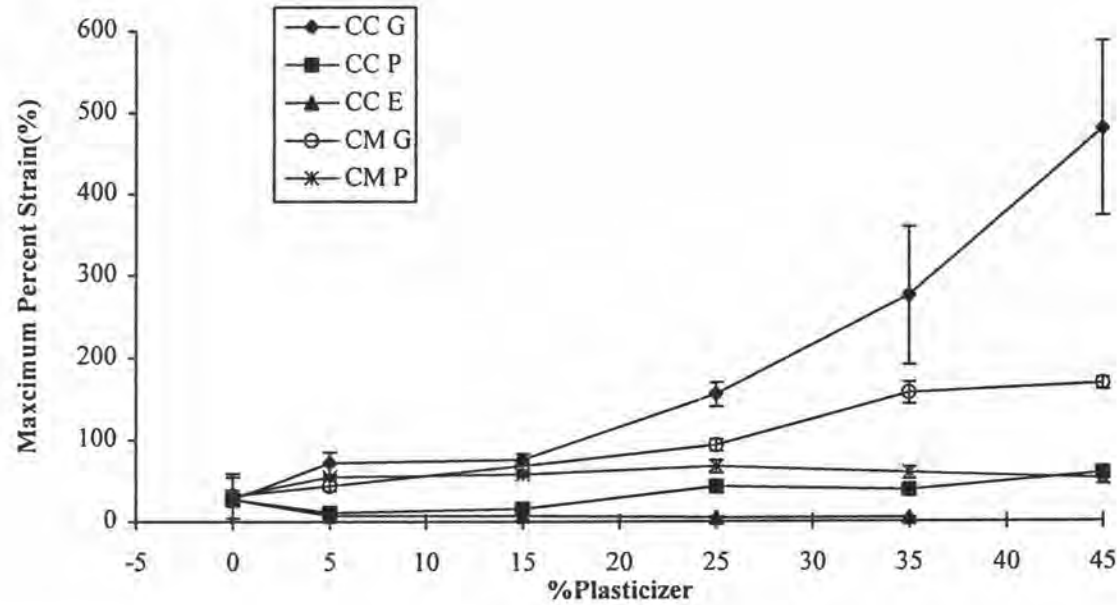


Figure 67 Maximum percent strain of chitosan citrate and chitosan malate cast films plasticized with different amount of plasticizers (n=6).

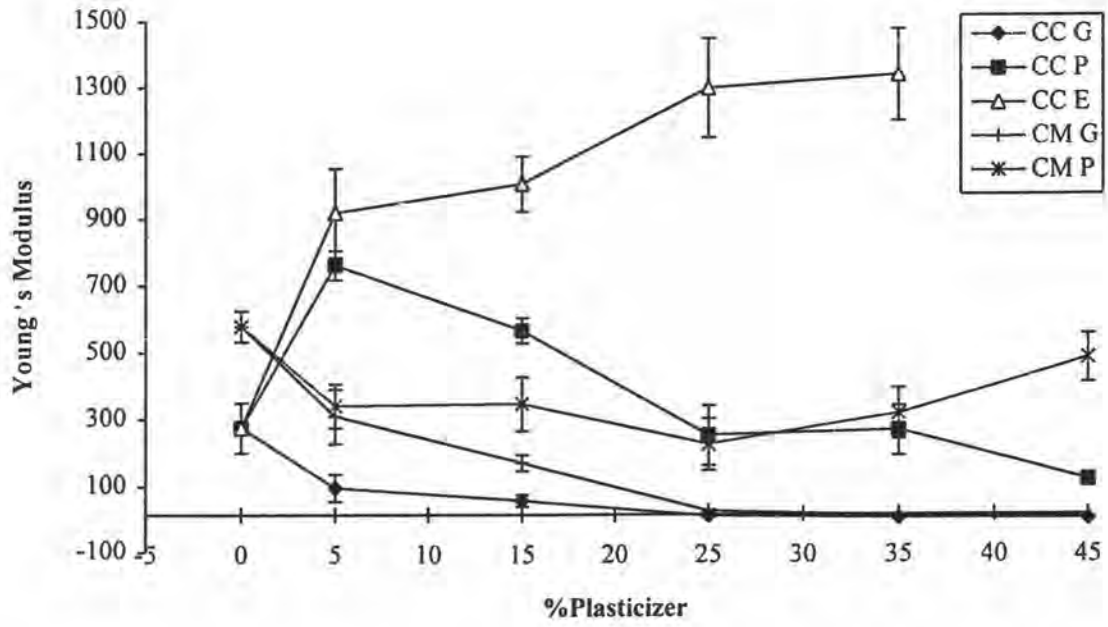


Figure 68 Young's Modulus of chitosan citrate and chitosan malate cast films plasticized. with different amount of plasticizers (n=6)

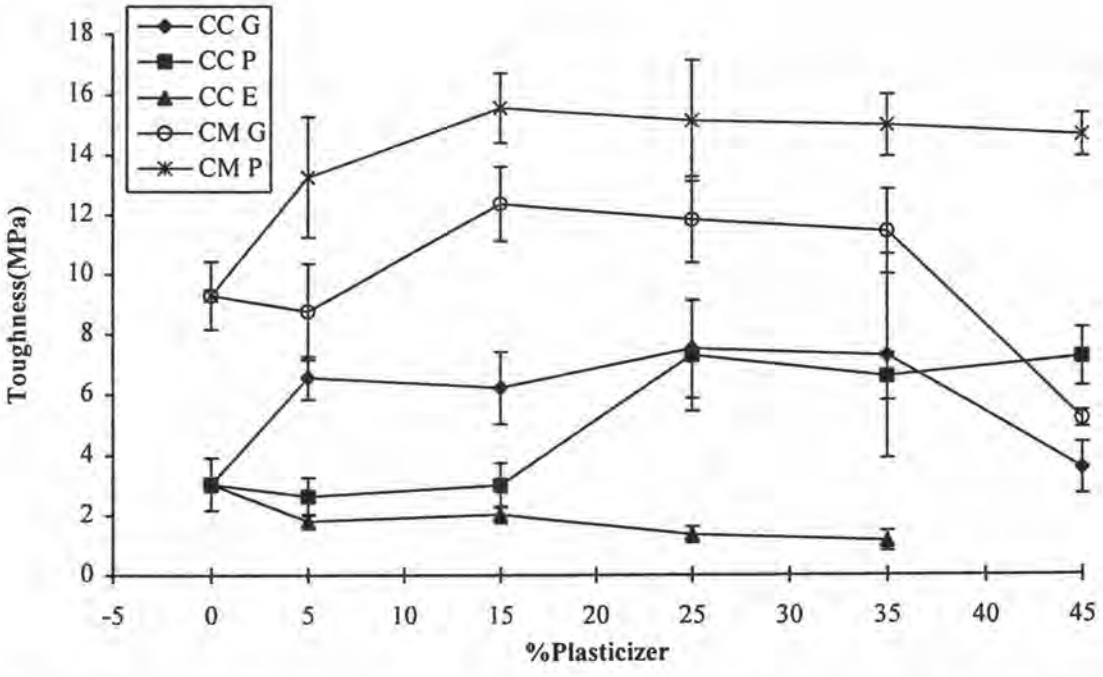


Table 69 Toughness of chitosan citrate and chitosan malate cast films plasticized with different amount of plasticizers (n=6).

3. 2. 2 Chitosan Acetate, Chitosan Formate and Chitosan Propionate Films

The relationship between the duration of moist heat treatment and mechanical properties of freshly prepared and moist heat treated chitosan acetate, formate and propionate films are presented in Figures *70-73* (Tables *103-114*, Appendix B). The typical stress-percent strain profiles are illustrated in Figure *255*, Appendix B.

The maximum percent strain, stress at break and toughness of freshly prepared chitosan propionate film were greater than those of freshly prepared chitosan acetate and formate films respectively. The Young's modulus of freshly prepared chitosan propionate film was higher than that of chitosan formate and chitosan acetate films respectively. The portion of profiles representing plasticity property of tested material was further decreased as the duration of moist heat treatment was elongated. The toughness and maximum percent strain were more decreased as the duration of treatment was longer and they were rather stable after treatment for 72 hours. The rate of decrement in toughness and maximum percent strain during 36 hours of treated chitosan acetate film was slower than that of treated chitosan propionate film and vice versa after 36 hours of treatment. After moist heat treatment for 36 hours, the stress at break and Young's modulus of treated chitosan formate film was lower than those of chitosan acetate and propionate films. Whereas the stress at break and Young's modulus of treated chitosan propionate films were higher than those of treated chitosan acetate films. However the duration of moist heat treatment did not markedly affect these values.

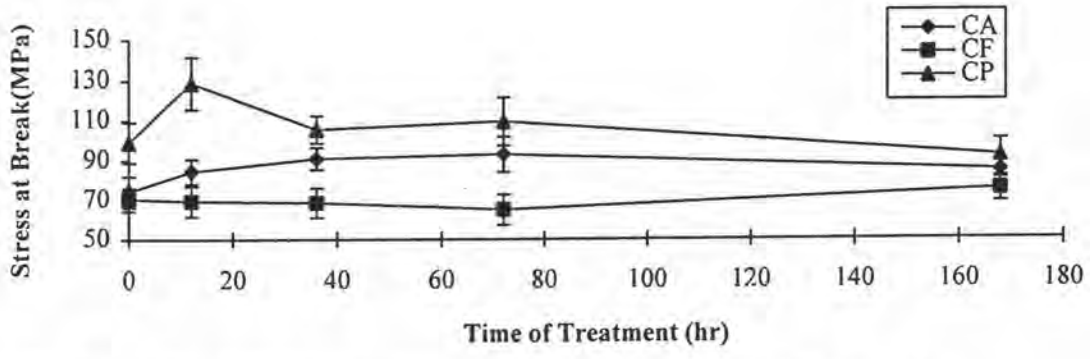


Figure 70 Stress at break of chitosan acetate, formate and propionatecast films before and after exposed to moist heat at 60°C 75%RH for different time intervals (n=6)

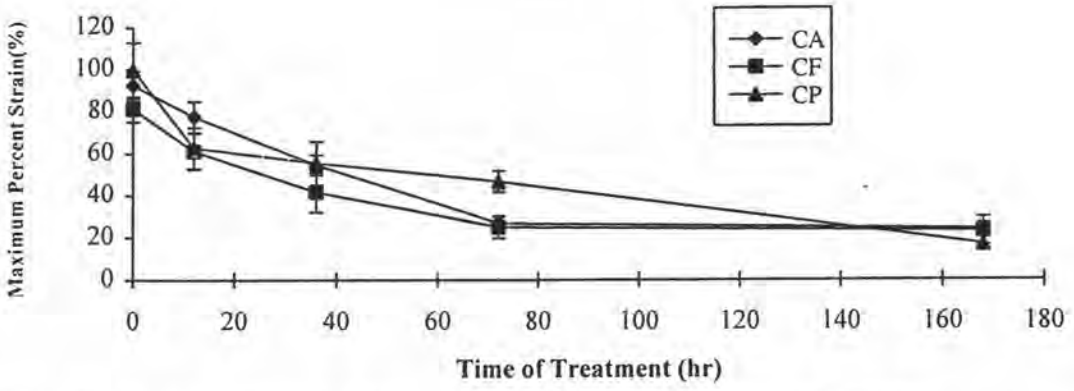


Figure 71 Maximum percent strain of chitosan acetate, formate and propionate films before and after exposed to moist heat treatment at 60°C 75%RH for different time intervals (n=6).

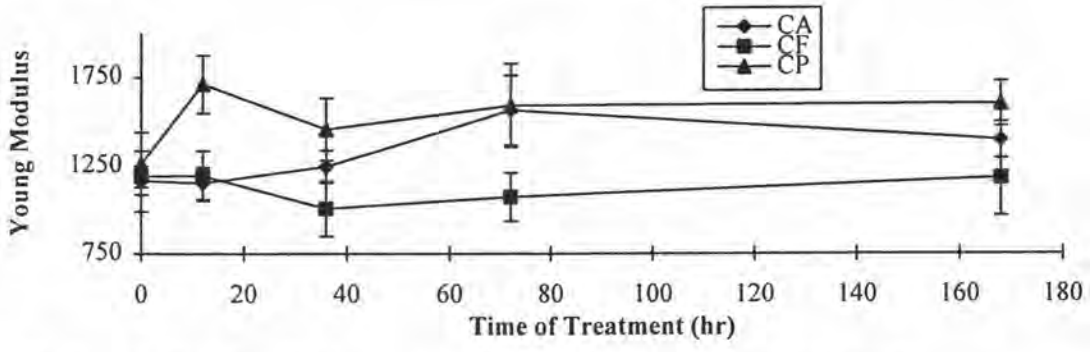


Figure 72 Young's Modulus of chitosan acetate, formate and propionate film before and after exposed to moist heat treatment at 60°C 75%RH for different time intervals (n=6).

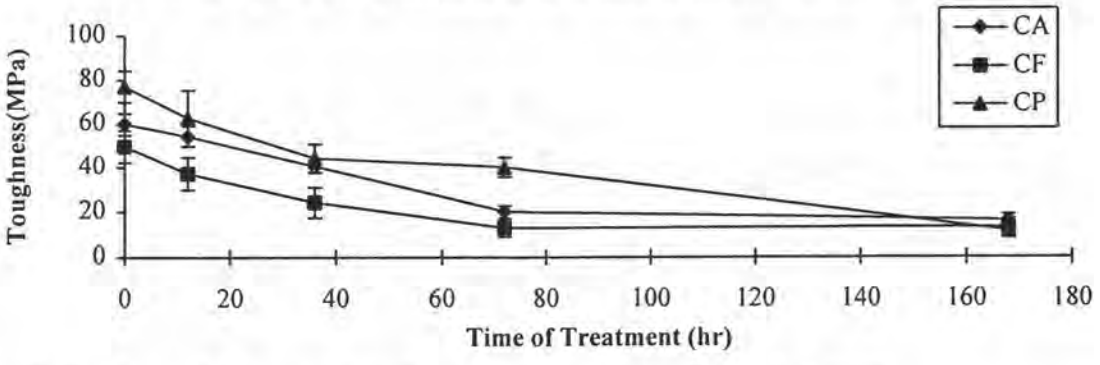


Figure 73 Toughness of chitosan acetate, formate and propionate cast films before and after exposed to moist heat treatment at 60°C 75%RH for different time intervals (n=6).

4. Effect of Water Soluble Dye and Pigment on Physicochemical Properties of Chitosan Citrate Solution and Cast Film

4.1. The Compatibility Between Chitosan Citrate Solution and Water Soluble Anionic Dyes

The chitosan citrate solution containing propylene glycol at concentration of 25 % w/w based on chitosan was yellowish. By visual observation, brilliant blue and green FS solutions could be readily miscible with this solution at concentration of 0.02-1.00%w/w based on chitosan providing the brilliant and distinctive color. While the precipitated matter was obviously appeared after mixing chitosan citrate solution and ponceau 4R and tartrazine solutions which the concentrations were more than 0.02% w/w. Sunset yellow solution was unable to be miscible with chitosan citrate solution at concentration between 0.02-1.00% w/w since during mixing, insoluble matter was suddenly occurred. Also the colloid like characteristic was appeared in mixture between erythrosine of every concentrations and chitosan citrate solution. These results are summarized in Table *12*.

This result indicated that these anionic dye solutions except brilliant blue or green FS solutions could not be compatible with chitosan citrate solution. Sunset yellow solution showed the incompatibility with chitosan citrate solution. Ponceau 4R and tartrazine solutions showed poorly compatibility as presented in Table *12*. At higher concentration (0.05-1.00% w/w) these two dyes were incompatible with chitosan citrate solution.

The good compatibility between chitosan citrate solution and brilliant blue at concentration (0.02-1.00% w/w) was detected. Another interesting finding was green FS, the combined color between brilliant blue and tartrazine in the ratio of 3:22, at the concentration up to 1.00% w/w based on chitosan remained miscible with chitosan solution. These color concentrations of brilliant blue and green FS in chitosan solution provided high tinctorial strength enough to employ in pharmaceuticals and cosmetic products. This preliminary study showed that these two color solutions could be miscible with chitosan citrate solution and could provide brilliant colored solution.

Chitosan citrate films plasticized with 25 %w/w of propylene glycol based on polymer and colored with brilliant blue and green FS at the concentration of 0.25, 0.50 and 1.00% w/w of chitosan was still glossy and moderate flexible and transparent. Neither bleeding nor precipitation was found as presented in Table *13*.

Chitosan citrate films plasticized with 25 %w/w of propylene glycol based on polymer and colored with 0.5 %w/w of brilliant blue based on polymer incorporated with talcum showed glossy surface and vice versa for the films incorporated with titanium dioxide especially as the amount of pigment was increased. Increase in the amount of titanium dioxide notably reduced the color intensity of brilliant blue compared with that of talcum. These results are shown in Table *14*.

Table 12 Miscibility between water soluble dye solutions and chitosan citrate solution.

Dye	Conc. of dye solution (% w/w of chitosan)				
	0.02	0.05	0.20	0.50	1.00
Brilliant blue	readily miscible	readily miscible	readily miscible	readily miscible	miscible
Erythrosine	colloid like	colloid like	colloid like	colloid like	colloid like
Green FS	readily miscible	readily miscible	miscible	miscible	miscible
Ponceau 4R	miscible	precipitate	precipitate	precipitate	precipitate
Sunset yellow	precipitate	precipitate	precipitate	precipitate	precipitate
Tartrazine	miscible	precipitate	precipitate	precipitate	precipitate

Table 13 Physical characteristics of chitosan citrate films plasticized with propylene glycol 25% colored with different amount of water soluble dyes.

Color	color	transparency	glossy	precipitation	sticky	flexibility	bleeding
Green FS							
0.25%	++	+	++	–	–	++	–
0.50%	+++	+	++	–	–	++	–
1.00%	++++	+	++	–	–	++	–
Brilliant Blue							
0.25%	++	+	++	–	–	++	–
0.50%	+++	+	++	–	–	++	–
1.00%	++++	+	++	–	–	++	–

The symbols of (+) and (-) showed the appearance and no appearance, respectively, and the number of the symbols of (+) showed a degree of the appearance.

Table 14 Physical characteristics of chitosan citrate films plasticized with propylene glycol 25% colored with brilliant blue 0.5% and pigmented with different amount of pigments.

Pigment	color	transparency	glossy	precipitation	sticky	flexibility	bleeding
Talcum							
15%	+++	+	++	–	–	++	–
30%	+++	+	+++	–	–	++	–
45%	+++	-	++++	–	–	+++	–
Titanium Dioxide							
15%	++	–	++	–	–	++	–
30%	+	–	++	–	–	++	–
45%	+	–	+	–	–	++	–

The symbols of (+) and (-) showed the appearance and no appearance, respectively, and the number of the symbols of (+) showed a degree of the appearance.

4. 2 Mechanical Properties of Cast Film

The effect of talcum or titanium dioxide on mechanical properties of colored and plasticized chitosan citrate film are presented in Figures *74-77* (Tables *96, 98, 100* and *102*, Appendix B). Typical stress-percent strain profiles are presented in Figures *256* and *257* (Appendix B). The stress at break, maximum percent strain, Young's modulus and toughness of chitosan citrate film plasticized with 25 %w/w of propylene glycol and colored with brilliant blue were slightly greater than that of non-colored film. At low concentration of 15% w/w talcum and titanium dioxide based on polymer, the stress at break, maximum percent strain and toughness of pigmented films were greater than those of unpigmented films or pigmented with higher amount of these pigments. Cast films containing titanium dioxide at 30 and 45% w/w of polymer showed great diminution of maximum percent strain, and toughness. Stress at break was also markedly lowered after adding this pigment. This result was also found in the case of incorporation with talcum but the degree of lowering was less than the incorporation of titanium dioxide and % strain and toughness after adding talcum were still higher than unpigmented cast film. By comparison at the same concentration, the Young' s modulus of films pigmented with talcum was higher than that of films pigmented with titanium dioxide.

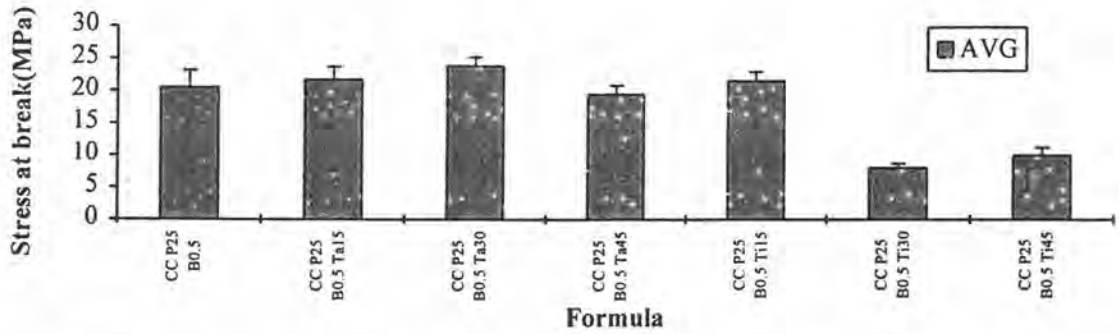


Figure 74 Stress at break of plasticized chitosan citrate cast films colored with brilliant blue 0.5% w/w of polymer and pigmented with different amount of talcum or titanium dioxide (n=6).

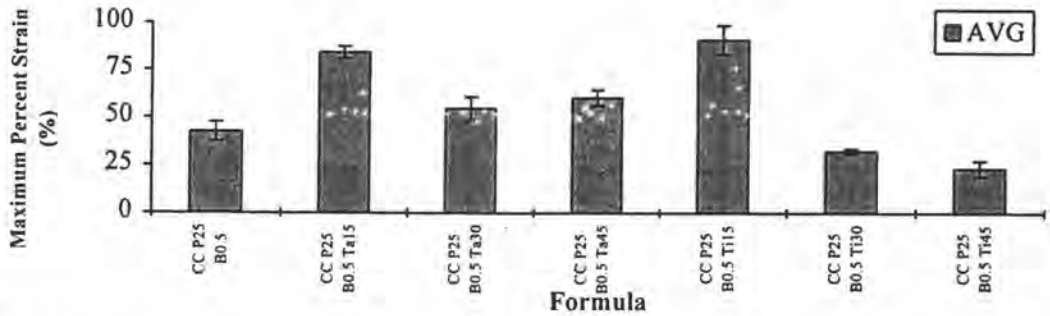


Figure 75 Maximum percent strain of plasticized chitosan citrate cast films colored with brilliant blue 0.5% w/w of polymer and pigmented with different amount of talcum or titanium dioxide (n=6).

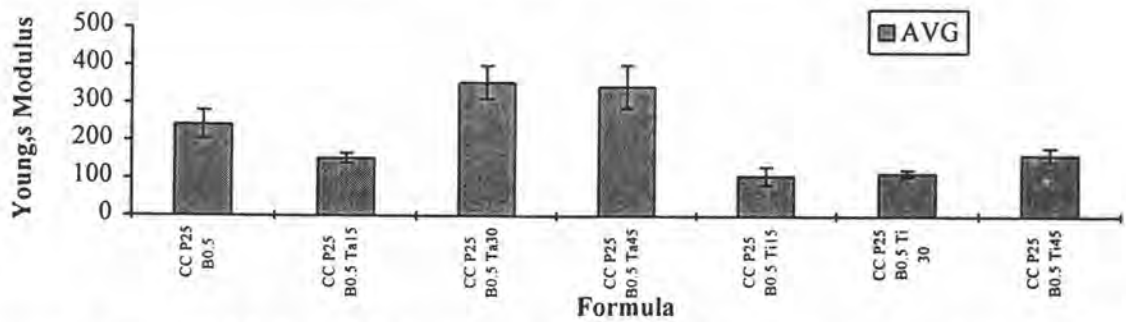


Figure 76 Young' s Modulus of plasticized chitosan citrate cast films colored with brilliant blue 0.5% w/w of polymer and pigmented with different amount of talcum or titanium dioxide (n=6).

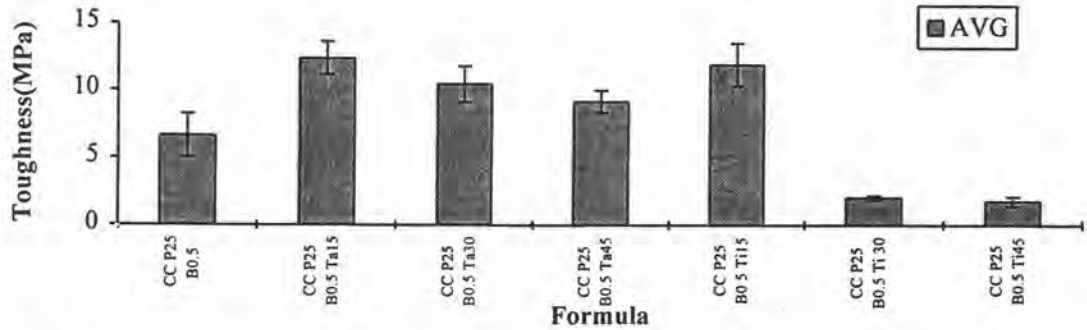


Table 77 Toughness of plasticized chitosan citrate cast films colored with brilliant blue 0.5%w/w of polymer and pigmented with different amount of talcum or titanium dioxide (n=6)

4. 3 The Moisture Sorption

An addition of brilliant blue slightly decreased the moisture sorption of chitosan citrate film and this evidence was more prominent after incorporation of pigments. This result is illustrated in Figure *78* (Table *115*, Appendix B). Talcum exhibited this tendency more obviously than titanium dioxide.

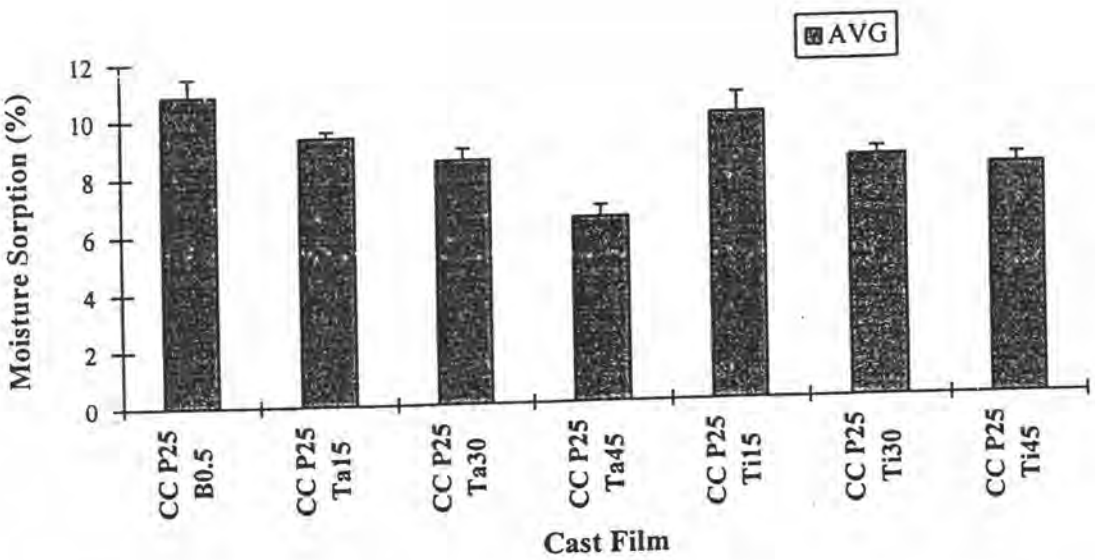


Figure 78 Moisture sorption of chitosan citrate films unplasticized and plasticized with propylene glycol 25% and colored with brilliant blue 0.5% w/w of polymer and pigmented with talcum and titanium dioxide at different concentrations (n=6)

Part II

Propranolol HCl Coated Tablet Using Chitosan As Film Former and Drug Release Study: Approach to Fast and Extended Release

1 Physical Appearance of Film Coated Tablet

The photographs of core tablets are shown in Figures *79A(a)* and *(b)*. After coating, the unplasticized and plasticized coated tablets using chitosan citrate and chitosan malate films as film former were off-white and glossy. The photographs of tablets coated with chitosan citrate film plasticized with propylene glycol 25% are depicted in Figure *79 B*. The colored coated tablets exhibited the smoothness and uniformity of colored film (Figure *79C* to *80A*). Color migration could not be observed in surface of coated tablets. Tablets coated with chitosan citrate film pigmented with talcum exhibited very glossy and elegant brilliant color greater than that pigmented with titanium dioxide. The surface of tablets coated with film pigmented with titanium dioxide was rather rugged. This characteristic was more dominant as the amount of this pigment was augmented. The photographs of tablets coated with films pigmented with talcum 30% and titanium dioxide 30% are shown in Figures *80B* and *80C* respectively. However no color migration was detected in surface of tablets coated with colored film pigmented with talcum and titanium dioxide. After kept in bottle and kept at 45°C 75%RH, and after kept at room temperature for one year, the physical appearance of coated tablets was not altered. Whereas the color of coated tablets was more yellowish after direct exposure this accelerated condition.

The tablets coated with unplasticized and plasticized chitosan acetate and propionate films were yellowish and glossy. The surface of film coated tablets was rough with less glossiness and yellowish color after introducing magnesium stearate to chitosan acetate film. This unsatisfactory characteristic was more dominant as the amount of magnesium stearate was increased. The incorporation of castor oil at concentration 15% w/w based on chitosan could enhance the smoothness and glossy of chitosan acetate film containing magnesium stearate 45% w/w of polymer as presented in Figure *81A*. As well as castor oil, the addition of triacetin (15, 30 and 45%) and diethyl phthalate (15%) could enhance the smoothness and glossy but not in case of an addition of propylene glycol (30%). An addition of urea at different concentrations did not alter the physical appearance of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15%, except that the color was less yellowish as shown in Figure *81C*. Whereas an addition of HPMC 45% provided the rather rough and less glossy surface.

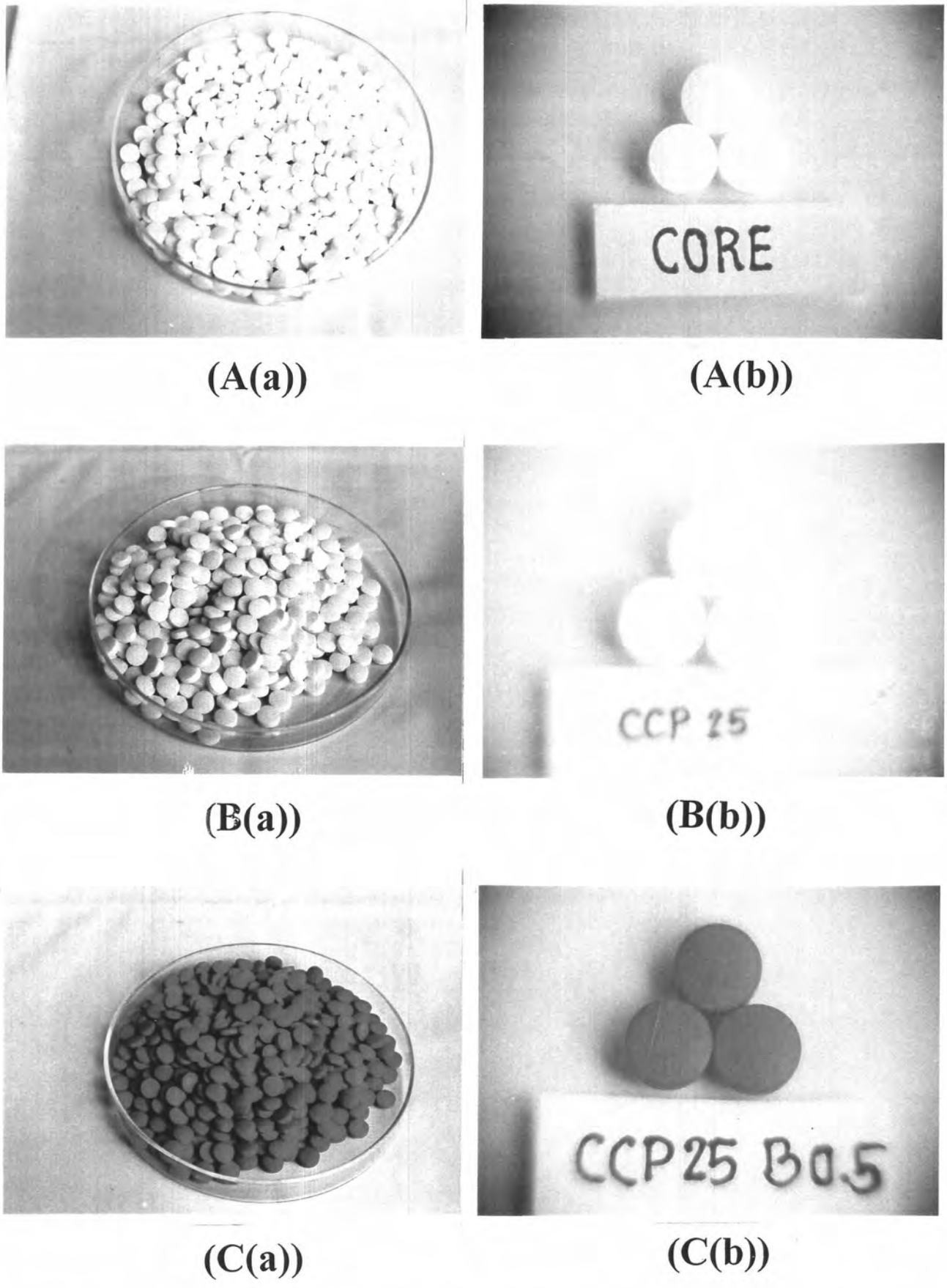
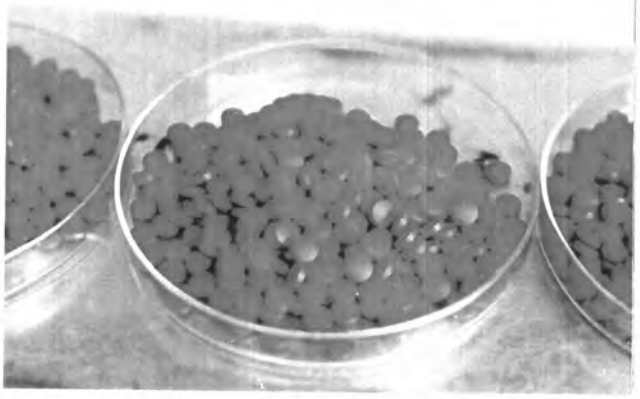


Figure 79 Photographs of core tablets (A) and tablets coated with chitosan citrate film plasticized with propylene glycol 25% (CC P25) (B) and tablets coated with chitosan citrate film plasticized with propylene glycol 25% colored with brilliant blue 0.5% (CC P25 B0.5) (C) ((a) low magnification and (b) high magnification).

(A(a))

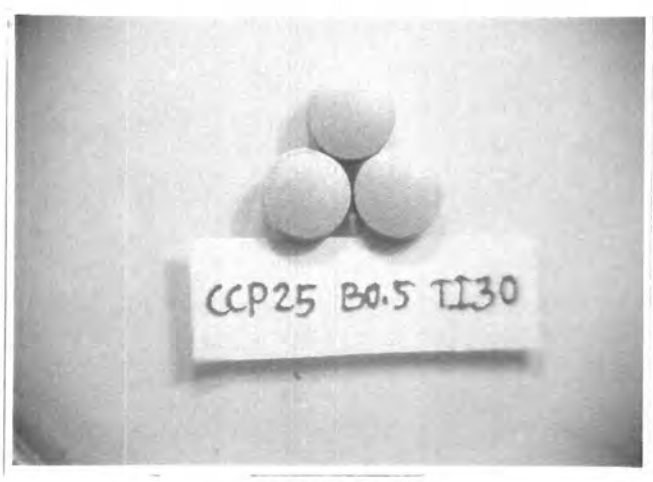
(A(b))



(B(a))

(B(b))

(C(a))



(C(b))

Figure 80 Photographs of tablets coated with chitosan citrate film plasticized with propylene glycol 25% colored with green FS 0.5% (CC P25 G0.5) (A); tablets coated with chitosan citrate film plasticized with propylene glycol 25% colored with brilliant blue 0.5% and pigmented with talcum 30%(CC P25 B0.5 Ti30) (B) and titanium dioxide 30% (CC P25 B0.5 Ti30) (C) ((a) low magnification and (b) high magnification).

Tablets coated with chitosan acetate film containing talcum was more smooth and glossy than that film containing titanium dioxide. Titanium dioxide at concentration of 45% could reduce the yellowish of coated tablet due to its whiteness.

Dry heat treatment at 60°C for 7 days only slightly enhanced color intensity of tablets coated with chitosan acetate film containing the additives whereas the moist heat treatment gradually deepened the color of coated tablet as shown in Figures *81B* and *81D*. The more increase in the temperature or time interval of moist heat treatment, the more increase in the color intensity was visually observed.

The defects such as cracking, splitting and picking of most coated tablets were not observed, except that there was the picking during coating the tablets with film coating preparation containing titanium dioxide.

2. Weight Variation

The weight variation of core and coated tablets are presented in Tables *116-131* to in Appendix C. Weight variation values of core and coated tablets were all within the limit of USP standard (%CV <7.5). Weight variation of coated tablets containing model drug 40 and 80 mg was 0.9-3.4% and 0.9-2.8% respectively.

3. Friability

The percent friability of core and coated tablets are shown in Tables *132-140* in Appendix C. Most coated tablets were not friable and shown that the weight was slightly increased during friability test. This evidence also found in case of tablets coated with CA film however after addition of film additives into this film coat, the friability was negligible. The friability was also minute or negligible in case of coated tablets after exposure accelerated condition or after kept at room temperature for one year.

4. Diameter and Film Thickness

The diameter and film thickness are presented in Tables *141-179* in Appendix C. The more increase in coating level, the greater was the diameter of tablets and the thicker was the film coat. The diameter of tablets coated with chitosan citrate and chitosan malate films was greater after exposure to accelerated condition. Whereas it was slightly changed after kept at room temperature for one year. The diameter of most tablets coated with CA film containing or without film additives was decreased after heat treatment.

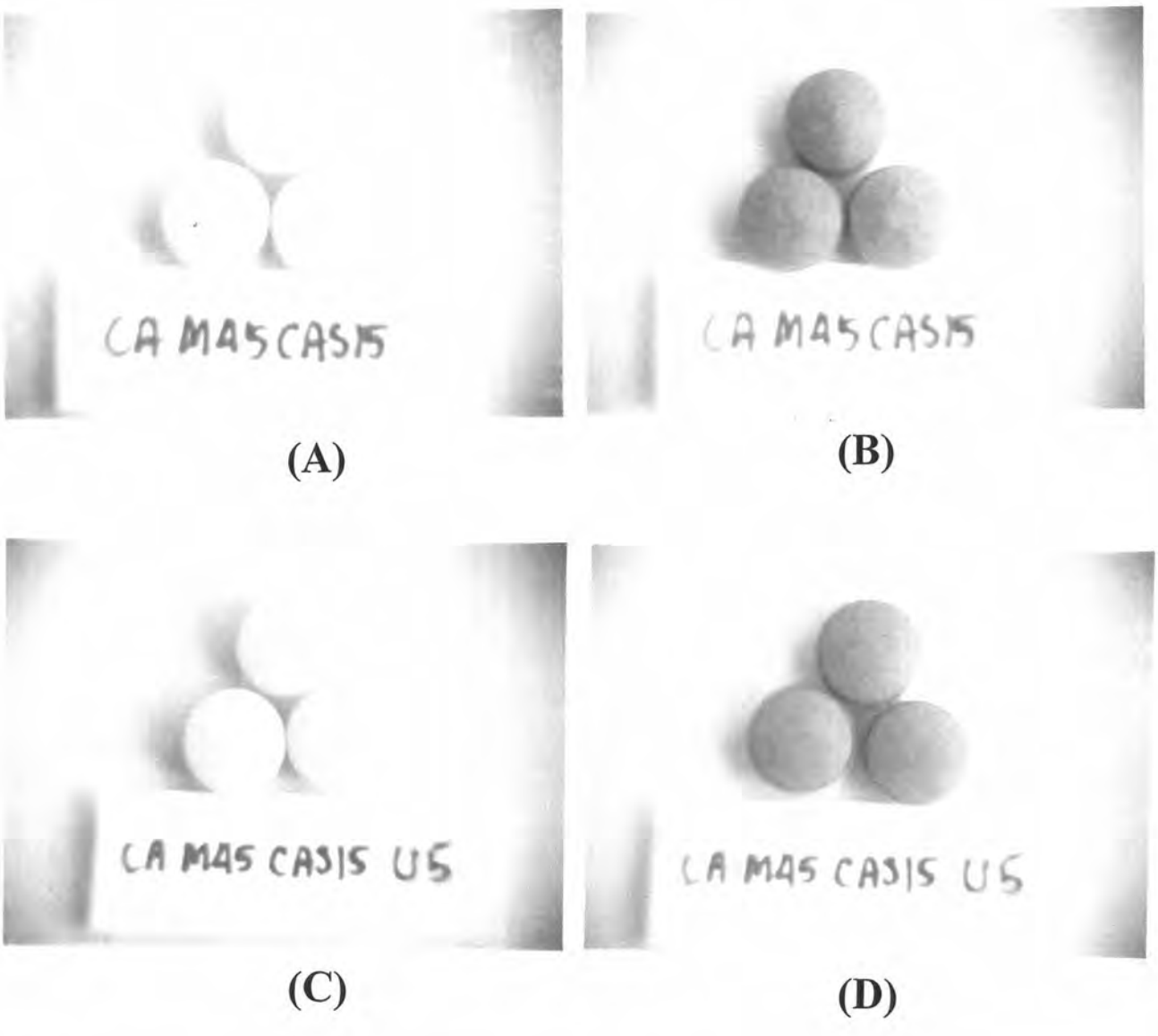


Figure 81 Photographs of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% (CA M45 Cas15) (A) freshly prepared (B) after moist heat treatment at 60°c for 24 hrs. and tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea 45, 15 and 5% respectively (CA M45 Cas15 U5) (C) freshly prepared and (D) after moist heat treatment at 60°C for 24 hrs.

5. Hardness

5. 1 Tablets Coated with Chitosan Citrate and Chitosan Malate Films

The average means of hardness of core and coated tablets are shown in Tables *180-193* in Appendix C. The hardness of coated tablets was higher than that of core tablet. An enhancement of coating level enhanced the hardness of tablets coated with chitosan citrate and chitosan malate films. Coating with chitosan malate film promoted the higher hardness of coated tablet than using chitosan citrate as shown in Figures *82* and *83*.

The hardness of core tablet was increased after exposure to accelerated condition and the hardness of treated coated tablet was also nearly to that of core tablet as presented in Figure *82* and Tables *182, 183* and *184* in Appendix C. The hardness of tablets coated with chitosan film by fixing the coating level based on amount of chitosan instead of chitosan salt are presented in Tables *185, 186* and *187* (Appendix C) . It was found that at coating level of 3 %w/w (based on amount of chitosan) the hardness of tablets coated with chitosan citrate and malate is nearly to 20 Kp. An increased amount of propylene glycol in chitosan citrate film coated tablets did not change the hardness as presented in Table *187*. While an addition of color and pigment into plasticized chitosan citrate coated tablets slightly decreased the hardness as shown in Table *188*. The hardness was also slightly decreased after storage in accelerated condition for 7 days or at room temperature for one year as shown in Tables *189-193*. However the accelerated condition did not markedly affect to the hardness of tablets coated with chitosan citrate or chitosan malate films consisting with or without different additive.

5. 2 Tablets Coated with Chitosan Acetate Film

The average means of hardness of core and coated tablets are shown in Tables *194-222* in Appendix C. The hardness of coated tablets was notably higher than that of core tablet. Enhancement of coating level of chitosan acetate film also enhanced the hardness of coated tablets as shown in Figure *84* (Table *194* in Appendix C). The hardness of coated tablets after peeling chitosan acetate film around them off are presented in Figure *84* (Table *196*, Appendix C). From this experimental data, by comparison, the enhancement of hardness of coated tablets was markedly less than that before film peeling. This result was also found in case of using chitosan acetate film plasticized with glycerin as shown in Figure *85* (Table *197*, Appendix C). Plasticization of chitosan acetate film with glycerin 25% decreased the hardness of coated tablet.

The hardness of tablets coated with chitosan acetate film containing different additives are presented in Table *198*, Appendix C. An incorporation of additive in chitosan acetate film decreased the hardness of tablets compared to that of tablets coated with plain chitosan acetate film at the same coating level. Plasticization the chitosan acetate film containing magnesium stearate 45% with castor oil, triacetin, propylene glycol and diethyl phthalate reduced the hardness of coated tablets as presented in Table *198* (Appendix C). These tablets had the hardness nearly to 20 Kp after peeling

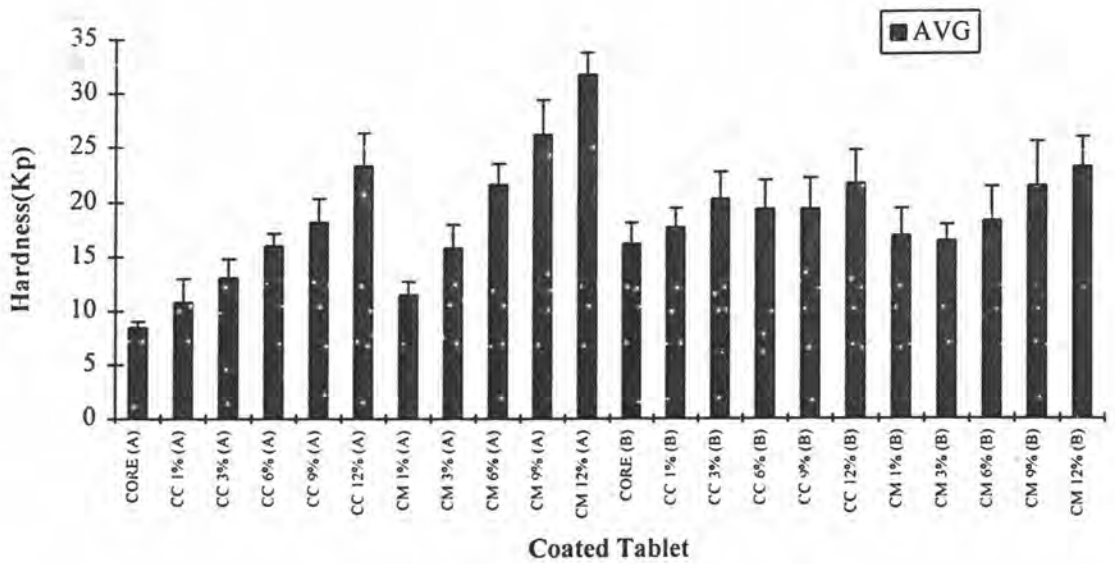


Figure 82 Hardness of core tablet and tablets coated with chitosan citrate and chitosan malate films with different coating level %w/w of polymeric salt : (A) freshly prepared and (B) after direct exposure to accelerated condition for 7 days (n=10).

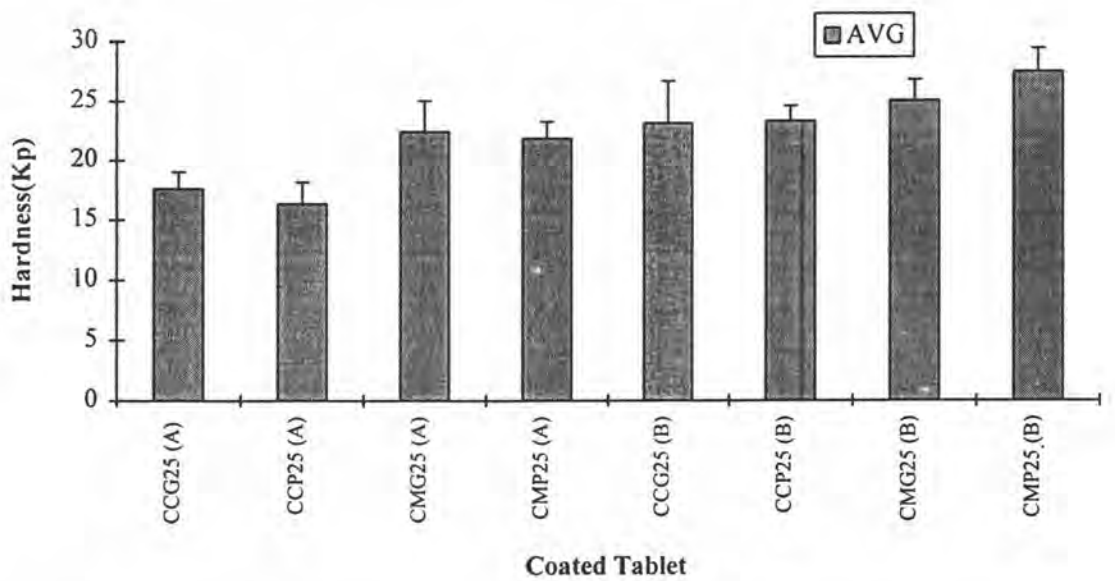


Figure 83 Hardness of tablets coated with chitosan citrate and chitosan malate films plasticized with glycerin and propylene glycol at concentration of 25% w/w of polymer at coating level 6%w/w of polymeric salt: (A) freshly prepared and (B) after direct exposure to accelerated condition (n=10).

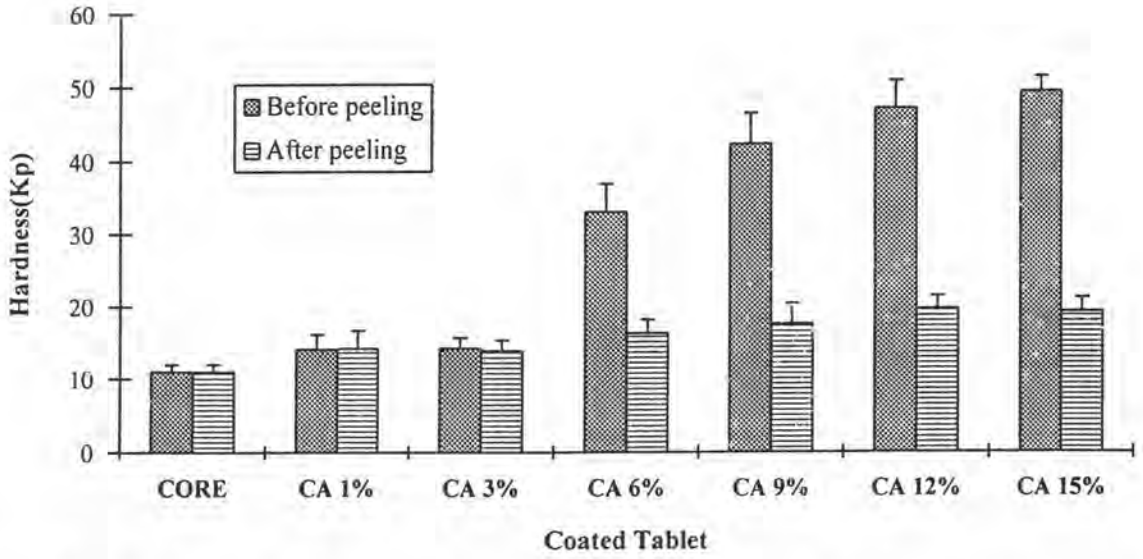


Figure 84 Hardness of tablets coated with different coating level of chitosan acetate film before and after peeling their films (n=10).

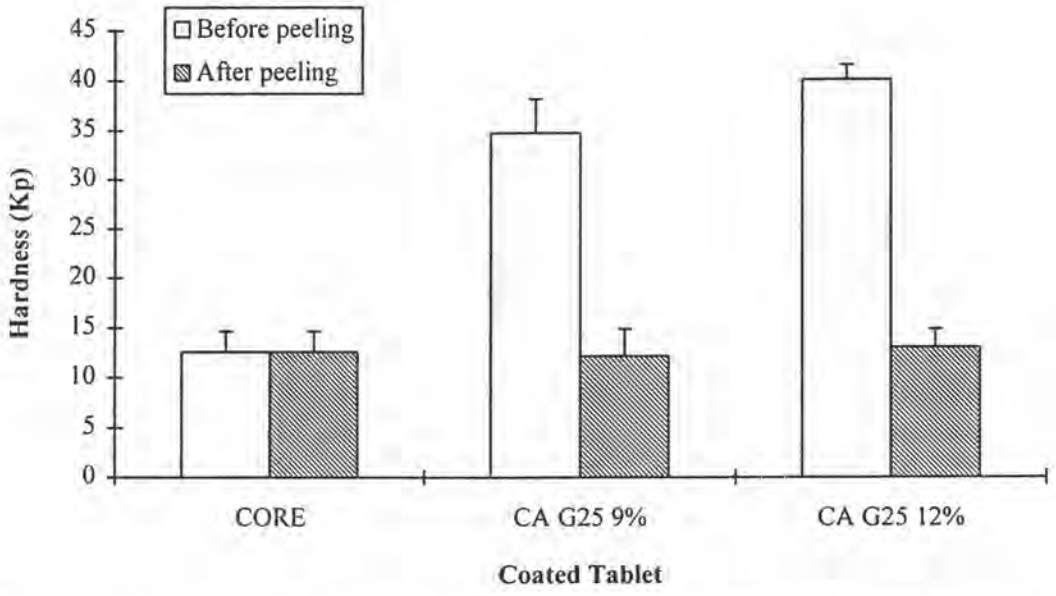


Figure 85 Hardness of tablets coated with different coating level of chitosan acetate film plasticized with glycerin at concentration of 25% w/w of polymer before and after peeling their films (n=10).

their film coat as presented in Table *199* (Appendix C). This result was similar to the case of tablet coated with this film without additive. Dry heat at 60°c for one week did not markedly affect the hardness of these coated tablets as shown in Table *200* (Appendix C). Hardness of tablets coated with chitosan acetate film containing magnesium stearate, talcum, titanium dioxide was not markedly altered after moist heat treatment as shown in Tables *201-205* (Appendix C), except that of tablets coated with chitosan acetate film containing magnesium stearate plasticized with triacetin, propylene glycol and diethyl phthalate was reduced after long moist heat treatment as presented in Tables *207-211* (Appendix C).

An enhancement of coating level had a tendency to increase the hardness of tablets coated with chitosan acetate film containing magnesium stearate and castor oil at concentration of 45 and 15 % w/w or tablet coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5% w/w as shown in Tables *212* and *218* (Appendix C) whereas moist heat treatment did not markedly affect to the hardness of tablets coated with these films as presented in Tables *213, 215* and *219* (Appendix C). The hardness of the latter type coated tablet had a tendency to decrease as the moisture content during moist heat treatment was increased as shown in Table *220* (Appendix C). An increased amount of urea reduced the hardness of coated tablet as shown in Table *214* (Appendix C) and moist heat treatment could not markedly alter the hardness aspresented in Table *215* (Appendix C). The hardness of tablets coated with CA M45 Cas15 film containing different amount of urea after film peeling was nearly to 20 Kp as shown in Table *216* (Appendix C). The hardness of selected coated tablets as shown in Tables *221* and *222* (Appendix C) was not markedly alter after storage in bottle and kept in accelerated condition and at room temperature for one year.

6. Adhesion Between Chitosan Film and Core tablet

Typical stress-displacement curves from adhesion test are presented in Figures *258* to *264* (Appendix C), and the data of average peeling strength, modulus and energy to break point are shown in Tables *223-237* (Appendix C).

6. 1 Tablets Coated with Chitosan Citrate and Chitosan Malate Films

Average peeling strength, modulus and energy to break point measured from the adhesion test of tablets coated with chitosan citrate film at different coating levels (% w/w based on chitosan salt) were greater than that of chitosan malate as presented in Figures *86, 87* and *88*. Exceptionally, the modulus from adhesion test of tablet coated with chitosan citrate plasticized with 25% glycerin (CC G25) was lower than that of tablet coated with chitosan malate film plasticized with 25% glycerin (CM G25) as shown in Figure *90*. The tendency to increase in average peeling strength and energy to break point, and decrease in modulus was found when increasing in coating level in case of chitosan citrate film coated tablets but not in case of chitosan malate film coated tablets which their test values were not notably changed by varying coating level as shown in Figures *86, 87* and *188*.

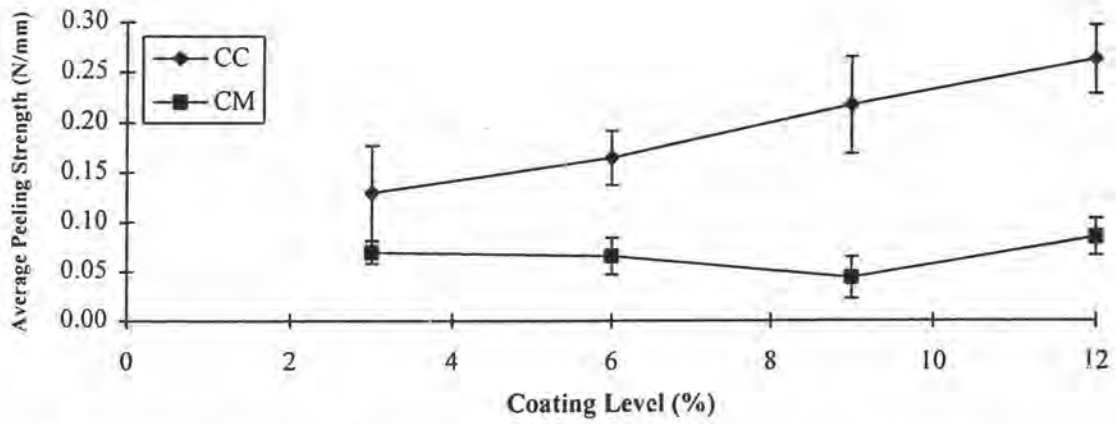


Figure 86 Average peeling strength from adhesion test of tablets coated with different coating levels of chitosan citrate film (CC) and chitosan malate film (CM) at different coating levels (w/w of polymeric salt)(n=6).

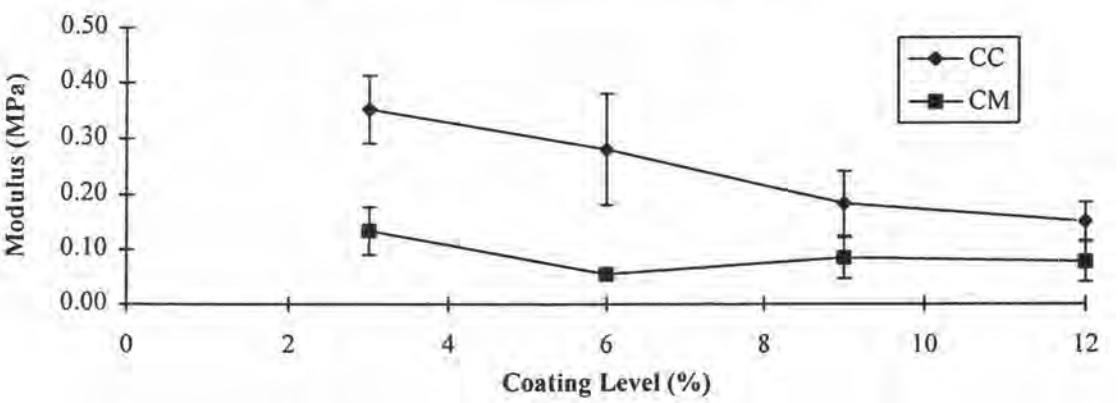


Figure 87 Modulus from adhesion test of tablets coated with different coating levels of of chitosan citrate film (CC) and chitosan malate film (CM) at different coating levels (w/w of polymeric salt)(n=6).

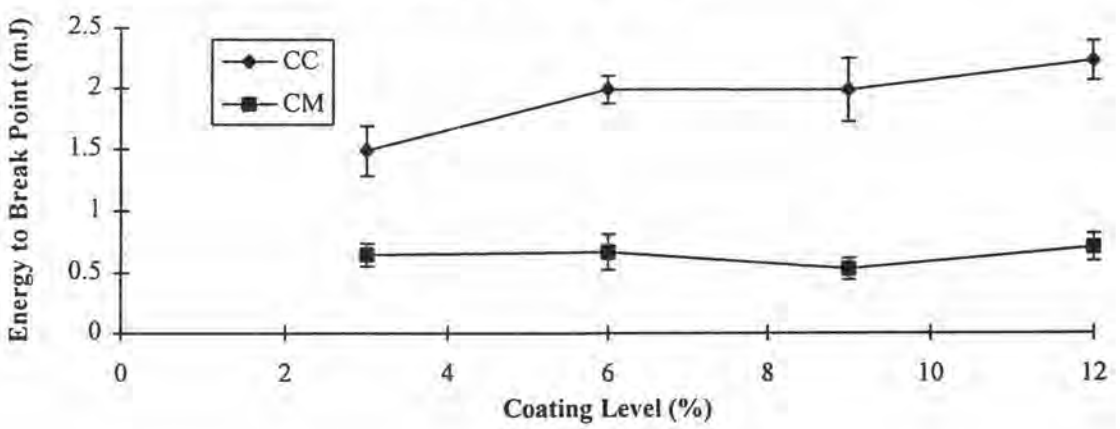


Figure 88 Energy to break point from adhesion test of tablets coated with different coating levels of chitosan citrate film (CC) and chitosan malate film (CM) at different coating levels (w/w of polymeric salt)(n=6).

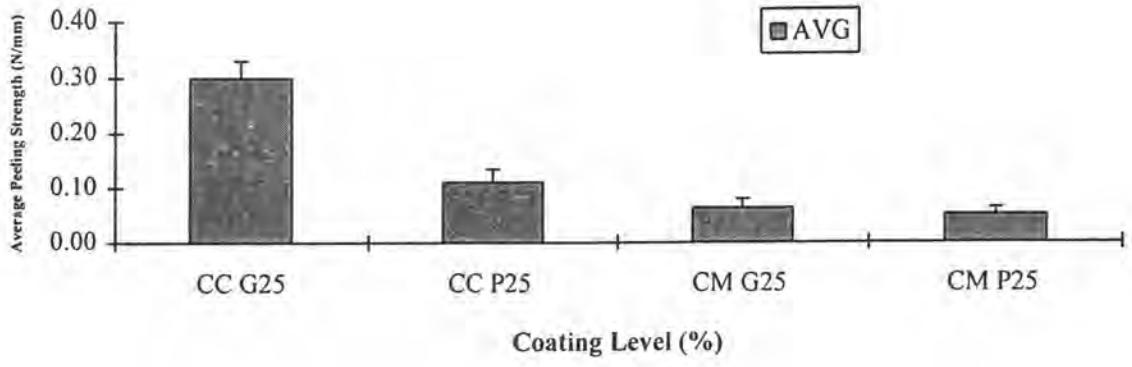


Figure 89 Average peeling strength from adhesion test of tablets coated with chitosan citrate film plasticized with glycerin 25%(CC G25) and propylene glycol 25% (CC P25); and chitosan malate film plasticized with glycerin 25% (CM G25) andpropylene glycol 25% (CM P25) at coating level of 6% w/w of polymeric salt (n=6).

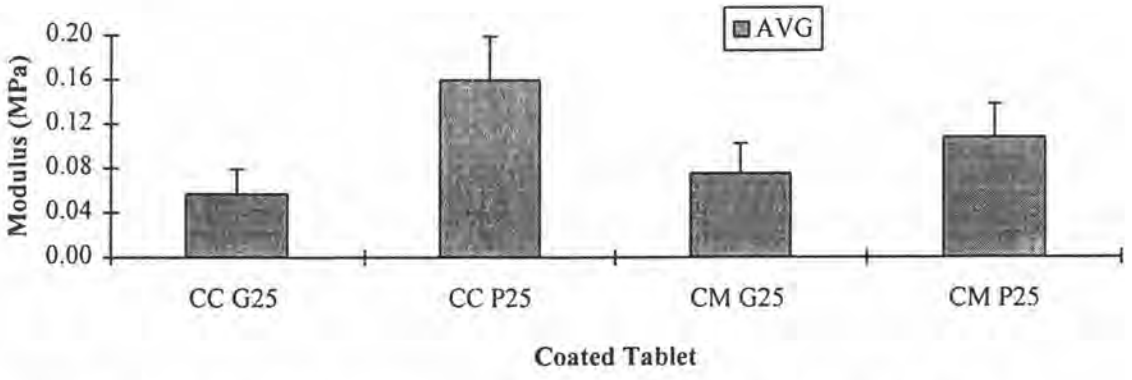


Figure 90 Modulus from adhesion test of tablets coated with chitosan citrate film plasticized with glycerin 25%(CC G25) and propylene glycol 25% (CC P25); and chitosan malate film plasticized with glycerin 25% (CM G25) and propylene glycol 25% (CM P25) at coating level of 6% w/w of polymeric salt (n=6).

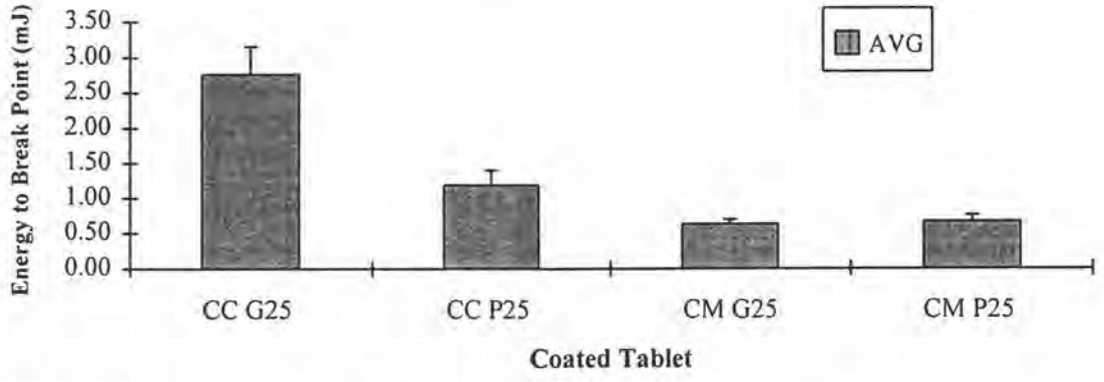


Figure 91 Energy to break point from adhesion test of tablets coated with chitosan citrate film plasticized with glycerin 25%(CC G25) and propylene glycol 25% (CC P25); and chitosan malate film plasticized with glycerin 25% (CM G25) and propylene glycol 25%(CM P25) at coating level of 6%w/w of polymeric salt(n=6).

The result clearly demonstrated that addition of glycerin in chitosan citrate film enhanced adhesion greater than propylene glycol, however this effect was not seen in case of chitosan malate film coated tablet. The effect of glycerin on enhancement the adhesion was obviously seen in case of tablet coated with chitosan citrate film than that coated with chitosan malate film. This result was found both in case of tablets coated at 6% w/w of polymeric salt and 3% w/w of polymer as presented in Figures *89-94*.

Tablets coated with chitosan citrate film (plasticized with propylene glycol at concentration of 25% w/w of polymer) colored with brilliant blue at concentration 0.5% w/w of polymer showed slightly lower the energy to break point and slightly higher average peeling strength and modulus than that of non-colored film as illustrated in Figures *95-97*. Tablets coated with pigmented films showed the values of average peeling strength and energy to break point nearly to that of non-pigmented film coated tablets as illustrated in Figures *95* and *97*. Except, tablets coated with colored film pigmented with talcum 45% showed the greater values of average peeling strength and energy to break point greater than those of other pigmented film coated tablets. Tablets coated with films pigmented with titanium dioxide exhibited the lower energy to break point than those using talcum. The modulus of tablets coated with film pigmented with 15% titanium dioxide was greater than that of the the others as presented in Figure *96*.

6. 2 Tablets Coated with Chitosan Acetate Film

Very low values of average peeling strength and energy to break point were found in case of using chitosan acetate film. The lower of these values was observed when increasing coating level from 1 to 6% w/w of polymeric salt as presented in Figures *98* and *100* and the modulus values are shown in Figure *99*. The adhesion could not assess when coating level was more than 6% since the film was rather thick and hard and therefore it was difficult to handle during peeling test. By comparison, at coating level of 3% w/w of polymer, the values of average peeling strength, modulus and energy to break point measured from tablet coated with chitosan acetate film were extensively less than those coated with chitosan citrate film and chitosan malate film.

7. Uniformity of Dosage Unit

From the determination of uniformity of dosage unit, it revealed that core and coated tablets was uniform in dosage unit as presented in Tables *238-246* (Appendix C). The average drug content and %CV from the determination of uniformity of dosage unit of tablets were 96.01-108.16% and 0.57-3.62% respectively. All of them conformed the limit of USP XXIII (drug content 85-115% and %CV$\leq$6%).

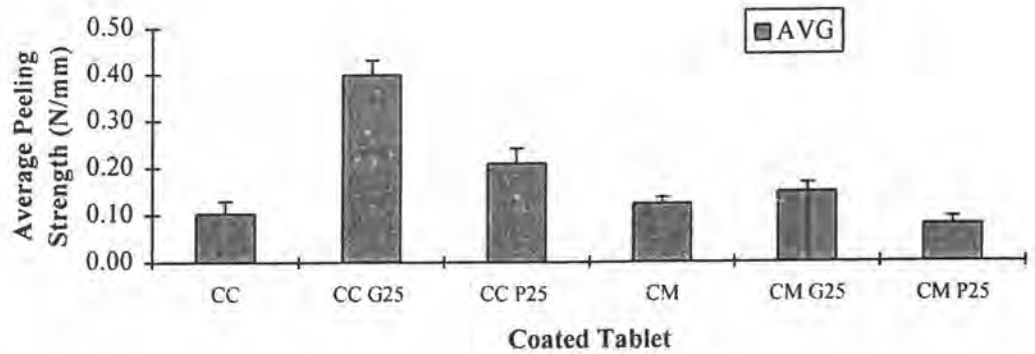


Figure 92 Average peeling strength from adhesion test of tablets coated with unplasticized chitosan citrate film (CC); chitosan citrate film plasticized with glycerin 25% (CC G25) and propylene glycol 25% (CC P25); and unplasticized chitosan malate film (CM): chitosan malate film plasticized with glycerin 25% (CM G25) and propylene glycol 25%(CM P25) at coating level of 3%w/w of polymer(n=6).

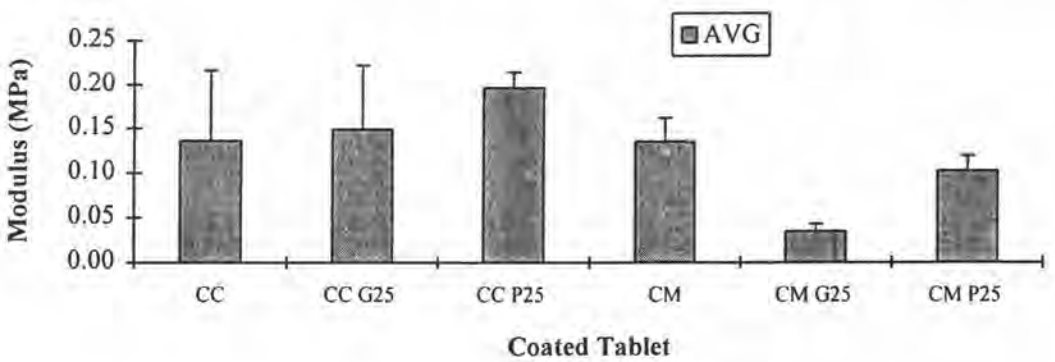


Figure 93 Modulus from adhesion test of tablets coated with unplasticized chitosan citrate film (CC); chitosan citrate film plasticized with glycerin 25% (CC G25) and propylene glycol 25% (CC P25); and unplasticized chitosan malate film (CM); chitosan malate film plasticized with glycerin 25% (CM G25) and propylene glycol 25% (CM P25) at coating level of 3% w/w of polymer (n=6).

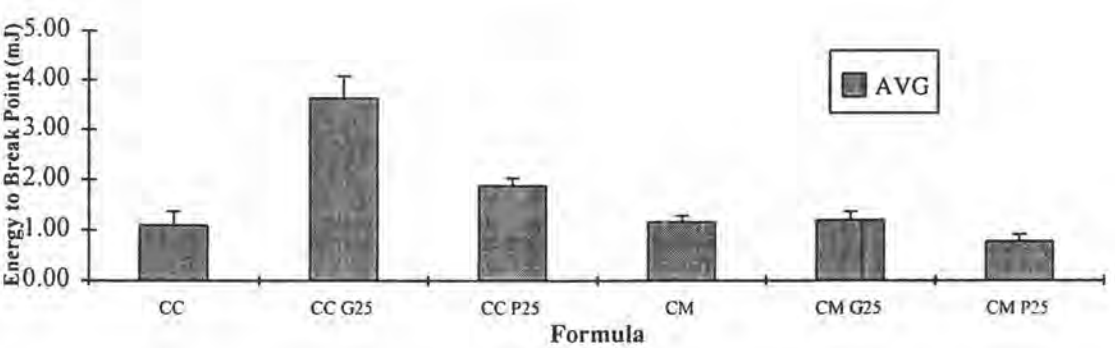


Figure 94 Energy to break point from adhesion test of tablets coated with unplasticized chitosan citrate film (CC); chitosan citrate film plasticized with glycerin 25% (CC G25) and propylene glycol 25% (CC P25); and unplasticized chitosan malate film (CM); chitosan malate film plasticized with glycerin 25% (CM G25) and propylene glycol 25%(CM P25) at coating level of 3% w/w of polymer (n=6).

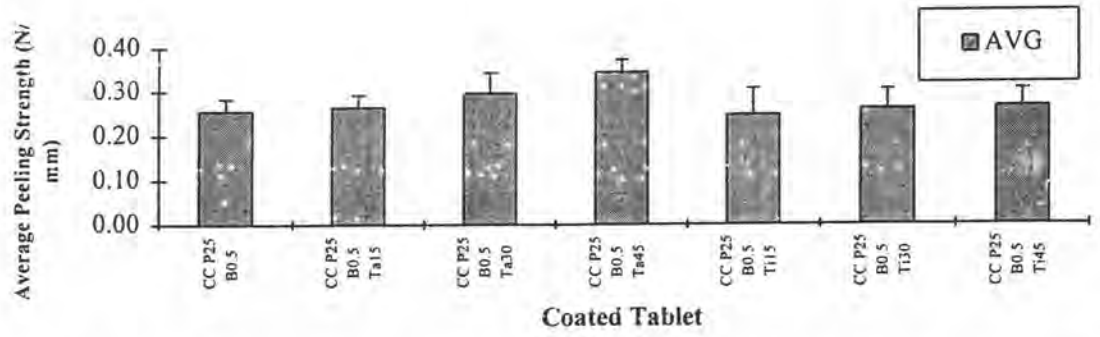


Figure 95 Average peeling strength from adhesion test of tablets coated with chitosan citrate film plasticized with glycerin 25%and colored with brilliant blue 0.5% (CC P25 B0.5); chitosan citrate film plasticied with propylene glycol 25% and colored with brillianr blue 0.5% and pigmented with talcum 15% (CC P25 B0.5 Ta15); 30% (CC P25 B0.5 Ta30); 45% (CC P25 B0.5 Ta45) and titanium dioxide 15% (CC P25 B0.5 Ti15); 30% (CC P25 B0.5 Ti30) and 45% (CC P25 B0.5 Ti45) (n=6).

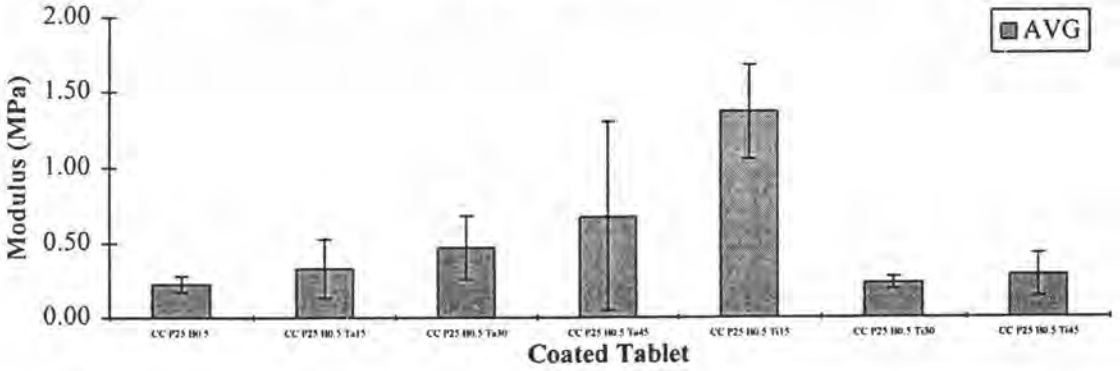


Figure 96 Modulus from adhesion test of tablets coated with chitosan citrate film plasticized with glycerin 25%and colored with brilliant blue 0.5% (CC P25 B0.5); chitosan citrate film plasticied with propylene glycol 25% and colored with brillianr blue 0.5% and pigmented with talcum 15% (CC P25 B0.5 Ta15); 30% (CC P25 B0.5 Ta30); 45% (CC P25 B0.5 Ta45) and titanium dioxide 15% (CC P25 B0.5 Ti15); 30% (CC P25 B0.5 Ti30) and 45% (CC P25 B0.5 Ti45) (n=6).

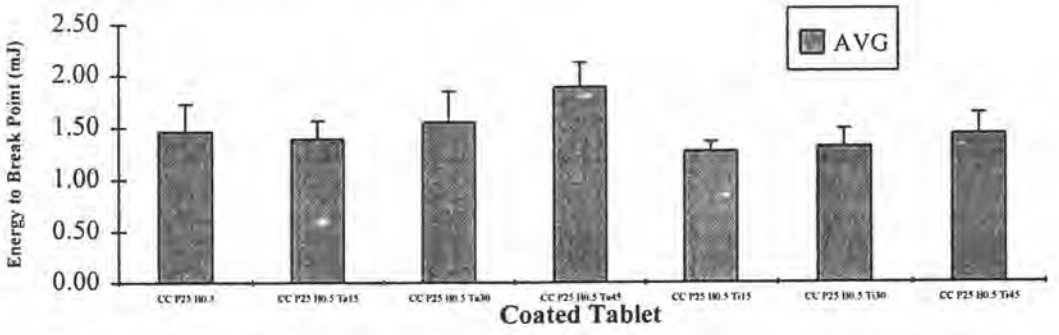


Figure 97 Energy to break point from adhesion test of tablets coated with chitosan citrate film plasticized with glycerin 25%and colored with brilliant blue 0.5% (CC P25 B0.5); chitosan citrate film plasticied with propylene glycol 25% and colored with brillianr blue 0.5% and pigmented with talcum 15% (CC P25 B0.5 Ta15); 30% (CC P25 B0.5 Ta30); 45% (CC P25 B0.5 Ta45) and titanium dioxide 15% (CC P25 B0.5 Ti15); 30% (CC P25 B0.5 Ti30) and 45% (CC P25 B0.5 Ti45) (n=6).

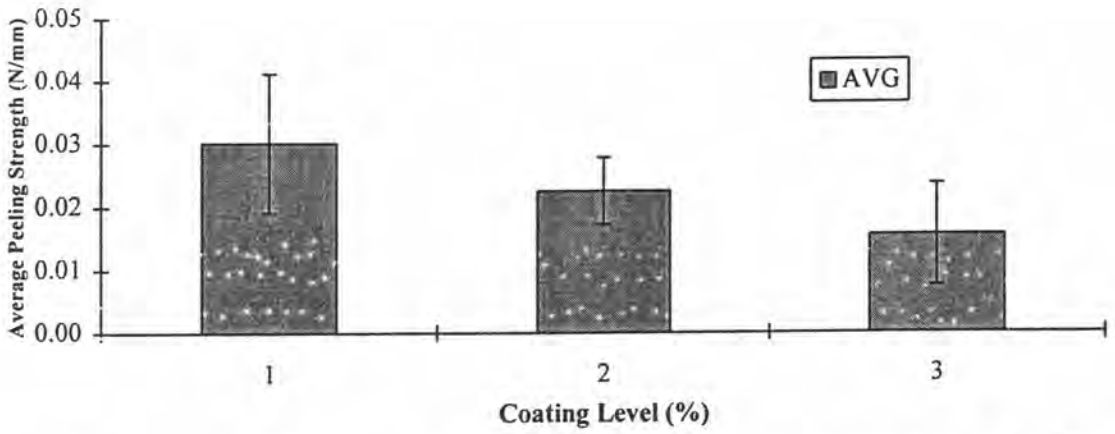


Figure 98 Average peeling strength from adhesion test of tablets coated with different coating levels of chitosan acetate film at different coating levels base on polymer (n=6).

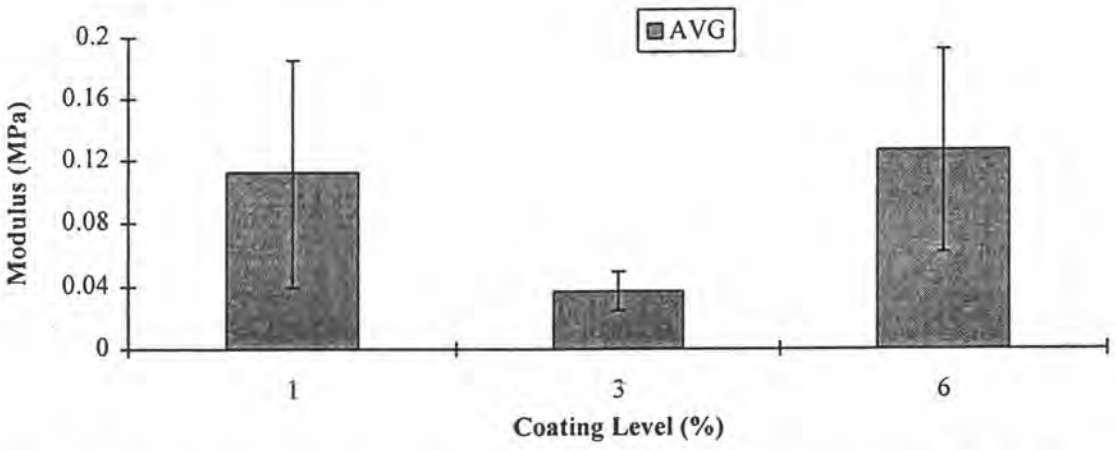


Figure 99 Modulus from adhesion test of tablets coated with different coating levels of chitosan acetate film at different coating levels base on polymer(n=6).

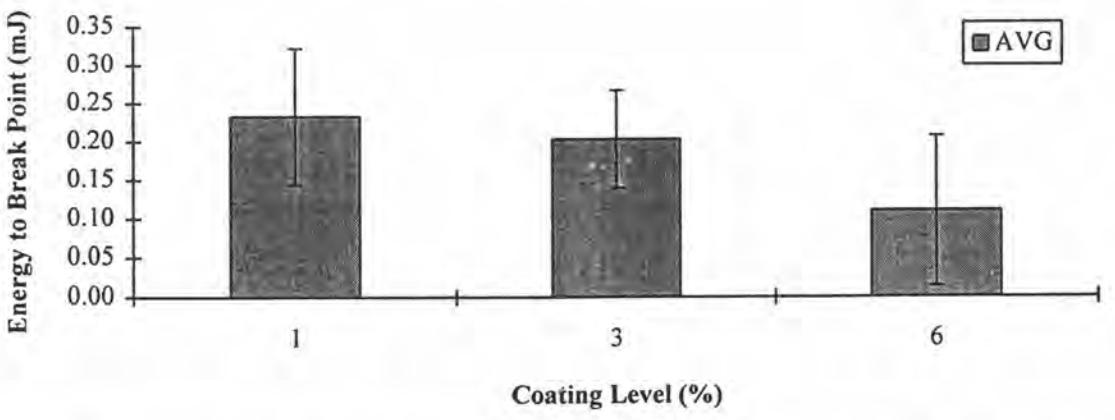


Figure 100 Energy to break point from adhesion test of tablets coated with different coating levels of chitosan acetate film at different coating levels base on polymer (n=6).

8. The Drug Content

From the analysis of drug content of core and coated tablets before and after kept in bottle at 75% RH 45°C for one month or at room temperature for one year, it revealed that propranolol HCl in core and coated tablets was in range 90-110% as shown in Tables *247-256* (Appendix C). All of them also conformed the monograph in USPXXIII because they contained not less than 90% and not more than 110% of label amount.

The amount of film additives especially talcum, titanium dioxide and magnesium stearate did not affect to the stability of this encapsulated drug. In addition, duration or the amount of %RH of moist heat treatment did not decrease the drug content as shown in Tables *252-254* (Appendix C). The drug content of core and coated tablets did not obviously decrease after exposure to accelerated condition or aging at room temperature.

9. Disintegration Time

9. 1 Tablets Coated with Chitosan Citrate and Chitosan Malate Films

The disintegration time (DT) of core and coated tablets are presented in Tables *254-268* (Appendix C). The DT of core tablet containing propranolol HCl 40 mg was 4.12 $\pm$ 0.25 minute. The DT of tablets coated with chitosan citrate and chitosan malate films in deionized water was longer than that of core tablet. The increasing of coating level showed a tendency to prolong the DT as illustrated in Figure *101*. After direct exposure to accelerated condition (45°C 75% RH), the DT of tablets coated with coating level of 1 and 3% of chitosan citrate and 1% of chitosan malate films was longer than 30 minutes as presented in Table *258* (Appendix C). Plasticized film coated tablets exhibited slightly longer DT than that of unplasticized film coated tablet. The DT was decreased after incorporating pigment in plasticized and colored chitosan citrate films. The small change in DT of plasticized and colored film coated tablets pigmented with talcum and titanium dioxide after kept in bottle in accelerated condition was observed, however, the direct exposure to accelerated condition mostly affected to the coated tablets. Whereas there was the slight change of DT of coated tablets after kept at room temperature for one year as shown in Tables *267* and *268* (Appendix C).

9. 2 Tablets Coated with Chitosan Acetate Film

The DT of core and coated tablets are shown in Tables *269-278* (Appendix C). The DT of core containing 80 mg propranolol HCl was 9.98$\pm$0.68 minutes . Tablets coated with chitosan acetate film showed the longer DT than core tablet. The higher increase in amount of coating level of chitosan, the longer was the DT as illustrated in Figure *102* (Table *269*, Appendix C). By comparison at the same coating level, the DT of tablets coated with chitosan acetate film plasticized with glycerin was shorter than that of tablets coated with unplasticized chitosan acetate film as presented in Table *274*

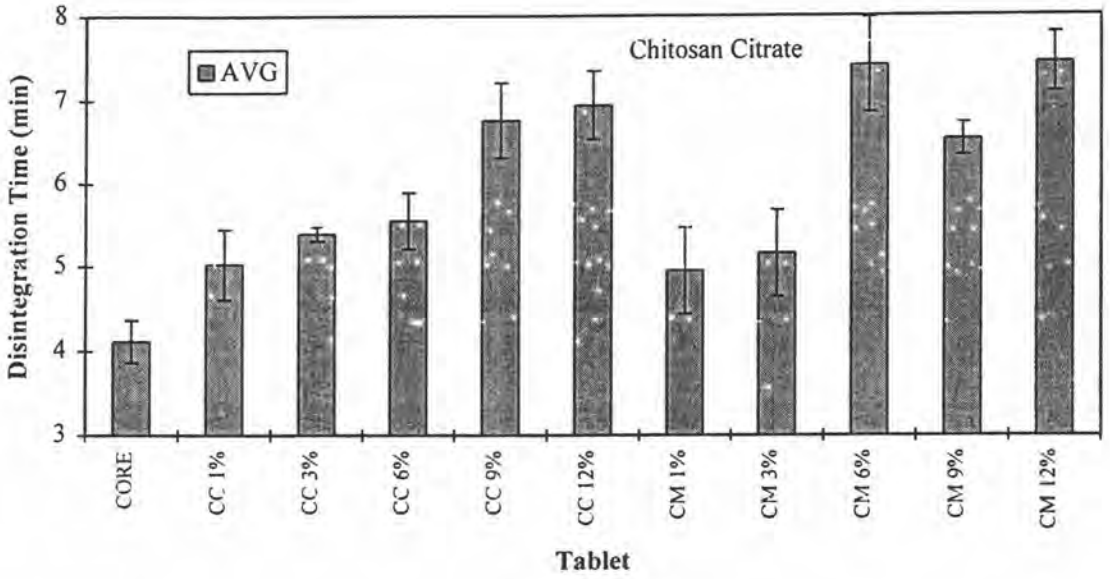


Figure 101 Disintegration time of core and tablets coated with chitosan citrate film at different coating levels (n=6).

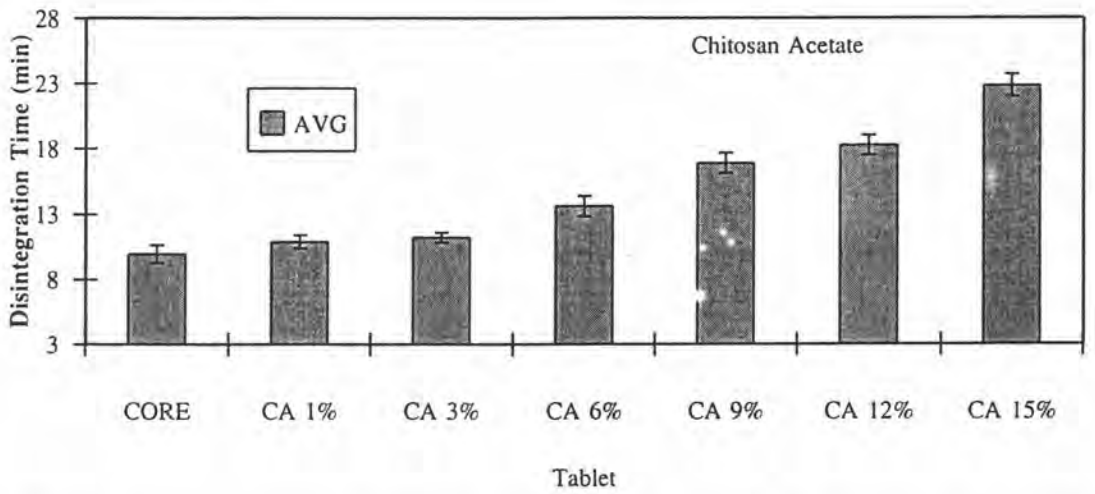


Figure 102 Disintegration time of core tablet and tablets coated with chitosan acetate film at different coating levels (n=6).

(Appendix C). Because of the gelling forming property of chitosan film, the higher amount of coat would provide the thicker gel layer around core tablet before this gel dissolving and this result was related to the longer DT in deionized water.

After moist heat treatment at 60°C 75% RH, the tablets coated with chitosan acetate film were more yellowish. The degree of yellowish was increased after longer treatment. The brittle film was observed after treatment for 12 hours and that the DT was shorter than that of freshly prepared coated tablets, except that of 3% of film coat. The DT of some coated tablets after treatment for 36 hours was longer than 30 minutes and coated tablets after treatment for 72 hours was longer than 30 minutes. Plasticized chitosan acetate film coated tablets with glycerin showed the same result as found in unplasticized film coated tablet These DT values of coated tablets after moist heat treatment are shown in Tables *270*-273 and *275-276* (Appendix C).

The DT of tablets coated with chitosan acetate film containing talcum was longer than that of the films containing titanium dioxide or castor oil as shown in Table *277* (Appendix C). Freshly prepared, most heat treated and dry heat treated tablets coated with chitosan acetate film containing magnesium stearate 45, 60, 75% and combination between magnesium stearate 45% and castor oil 15% was longer than 30 minutes. At coating level of 12 % w/w of polymer, the DT of tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5% w/w of polymer was shorter than that coated at coating level of 9% w/w, and at higher coating level the DT was longer than 30 minutes as presented in Table *278* (Appendix C). The DT of freshly prepared and moist heat treated tablets coated with chitosan acetate film containing magnesium stearate 45%, castor oil 15% and different amount of urea or HPMC 45% at coating level of 15% w/w of polymer was longer than 30 minutes.

10. Drug Release Study

10. 1 Fast Release Preparation

The drug release profiles of core and coated tablets and cumulative % drug release are depicted in Figure *103-134* and shown in Tables *279-299* (Appendix C)

10. 1. 1 Effect of Coating Level of Polymeric Salt and Plasticizer

The drug release profiles of tablets coated with chitosan citrate film and chitosan malate film at various coating levels (% w/w of polymeric salt) are shown in Figure *103* and *104*. The more increase in coating level, the slower was the drug release due to the longer lag time. The long lag time was more prominent in release profile of tablets coated with chitosan malate especially at high coating level. The drug release from these coated tablets conformed to the monograph in USP XXIII, not less than 75% of drug dissolved in 30 minutes. Drug liberation from all coated tablets was slower than that from core tablet. Core tablet exhibited the highest drug release at each time interval and the release profile in acidic medium was similar to that in basic medium. This result indicated that the medicament released from core tablet was not affected by the pH of dissolution medium.

In basic environment, the retardation of drug release from film coated tablets was noticeable as shown in Figures *105* and *106* and the increase in coating level resulted in more prolongation of drug release especially the drug release from tablets coated with chitosan malate film which the release of tablets coated with high coating level could be sustainable to 12 hours. Whereas more than 75% of loaded drug could be liberated within 30 minutes in basic medium from all chitosan citrate film coated tablets. These release characteristics indicated that the drug release from tablets coated with chitosan citrate film was pH sensitive less than that from chitosan malate film. However it should be considered that this comparison was relied on the same coating level of chitosan salt.

The release behaviors of tablets coated with chitosan salt films plasticized with glycerin or propylene glycol at concentration of 25% w/w based on chitosan at coating level of 6% of polymeric salt in acidic and alkaline dissolution fluids (Figures *107*and *108* respectively) were still similar to that of the above formula. The influence of type of plasticizer on drug release did not apparently found.

After direct exposure to accelerated condition at 45°C 75% RH for 7 days, the release profile of these treated coated tablets in acidic medium are presented in Figures *109* and *110*. The fast release in acidic medium at coating level 3-12 % w/w was obtained both in case of using chitosan citrate or malate as film former. This result was associated to the disintegration of treated film at higher coating level in acidic medium. Meanwhile, at 1% coating level, the retardation of drug release was obtained

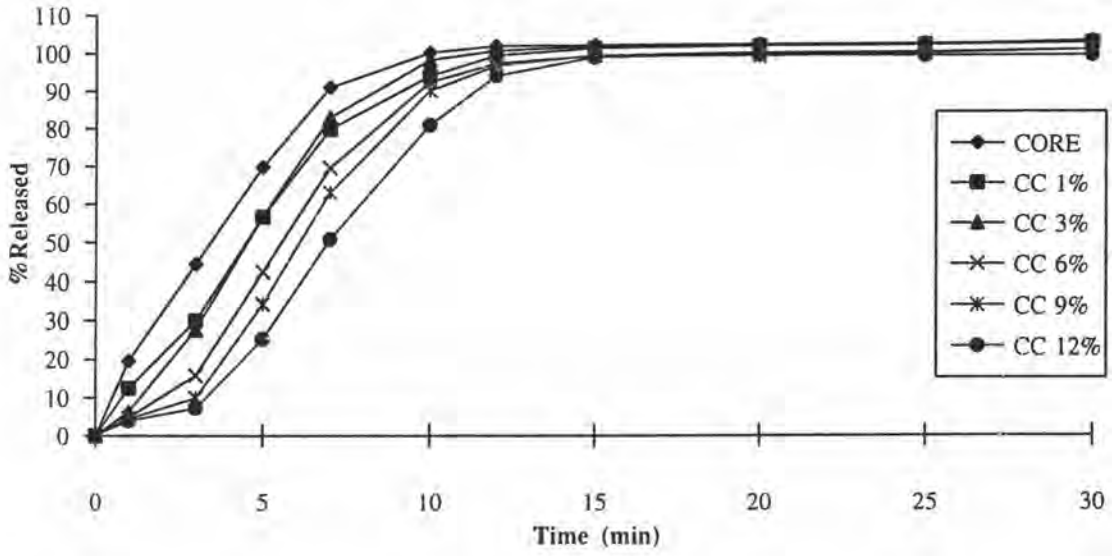


Figure 103 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate film at different coating level in dilute HCl acid (n=6).

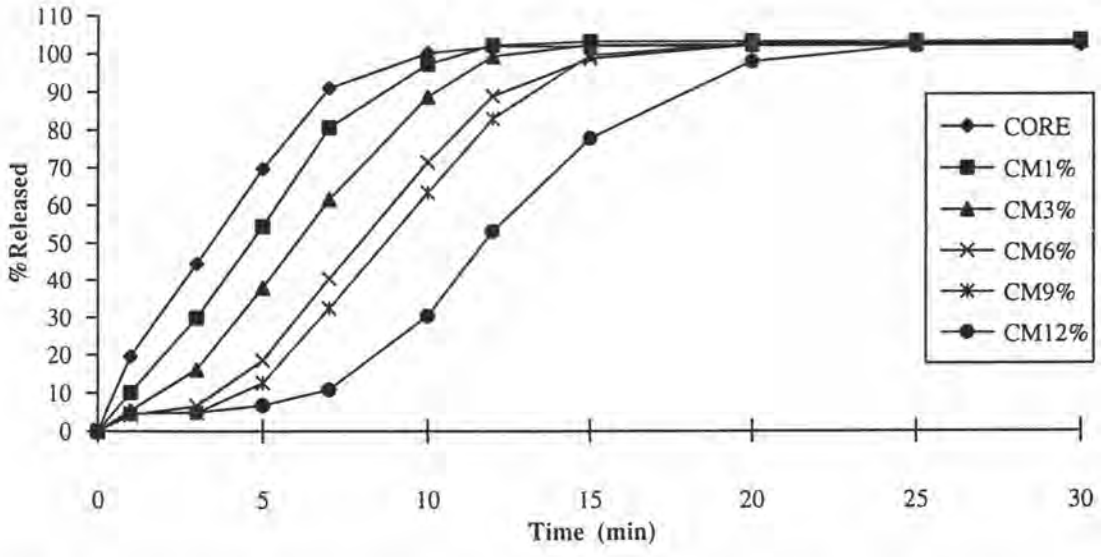


Figure 104 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan malate film at different coating level in dilute HCl acid (n=6).

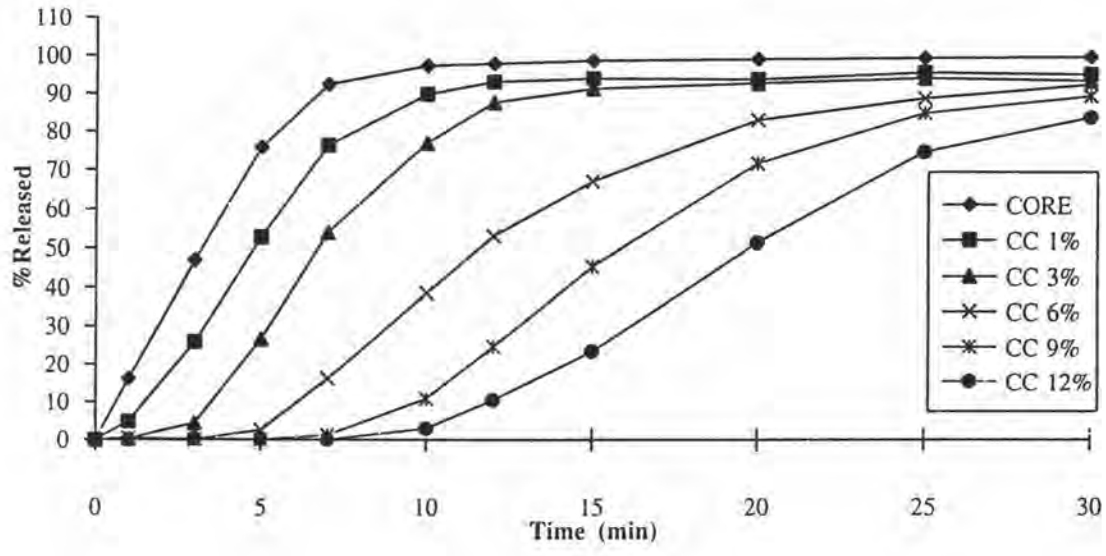


Figure 105 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate film at different coating level in phosphate buffer pH 6.8 (n=6).

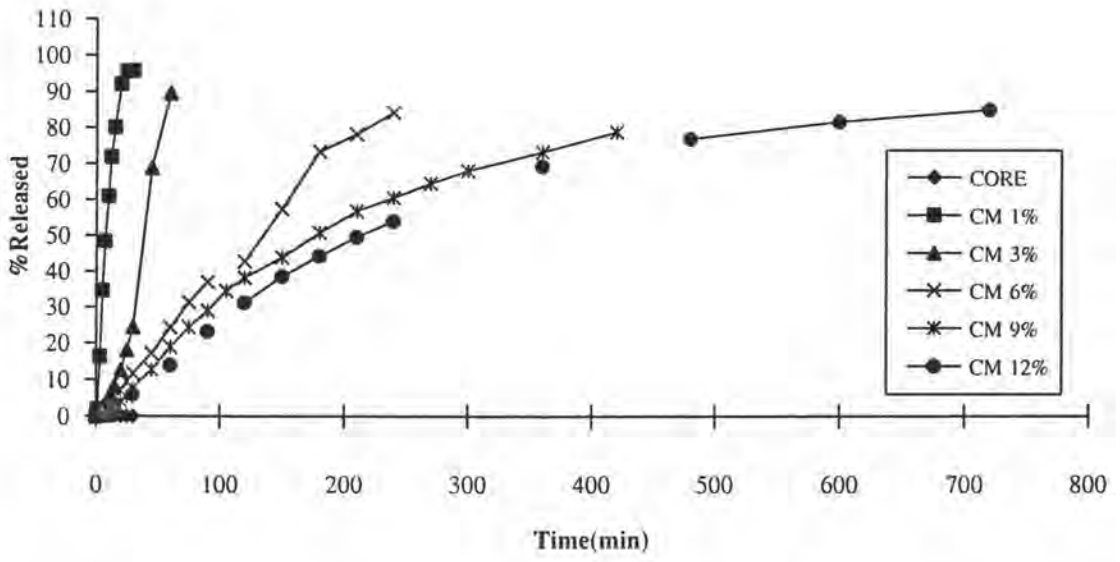


Figure 106 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan malate film at different coating level in phosphate buffer pH 6.8 (n=6).

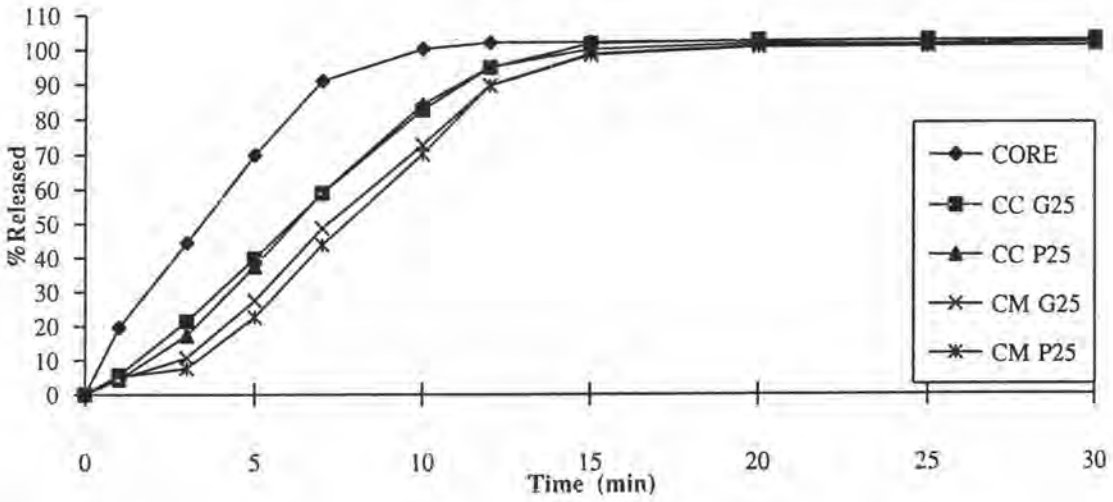


Figure 107 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate filmand chitosan malate film plasicized with glycerin and propylene glycol 25% w/w at coating level of 6 % w/w of chitosan salt in dilute HCl acid (n=6).

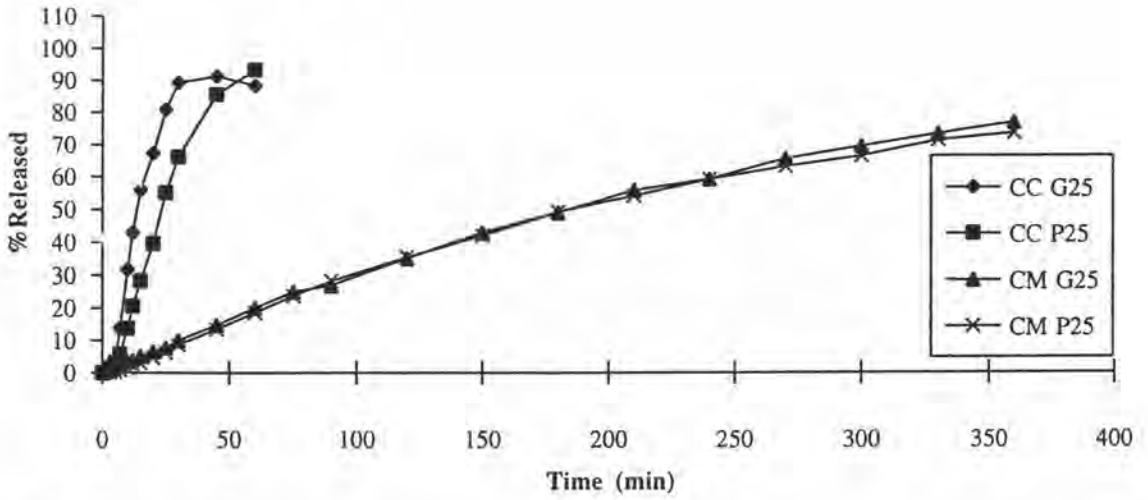


Figure 108 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate filmand chitosan malate film plasicized with glycerin and propylene glycol 25% w/w at coating level of 6 % w/w of chitosan salt in phosphate buffer pH 6.8 (n=6)

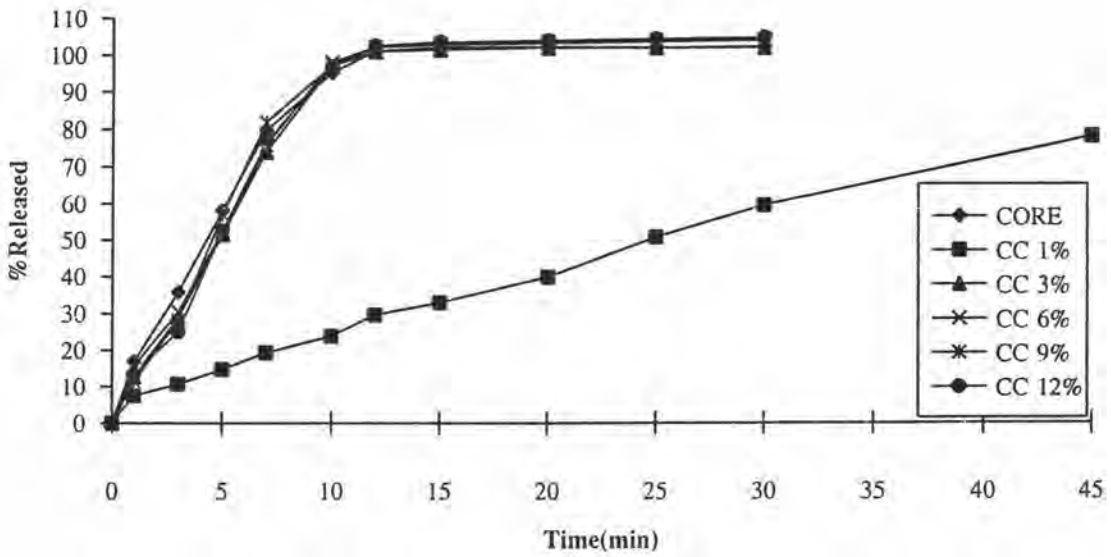


Figure 109 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate film at different coating level after direct exposure accelerated condition for 7 days in dilute HCl acid (n=6).

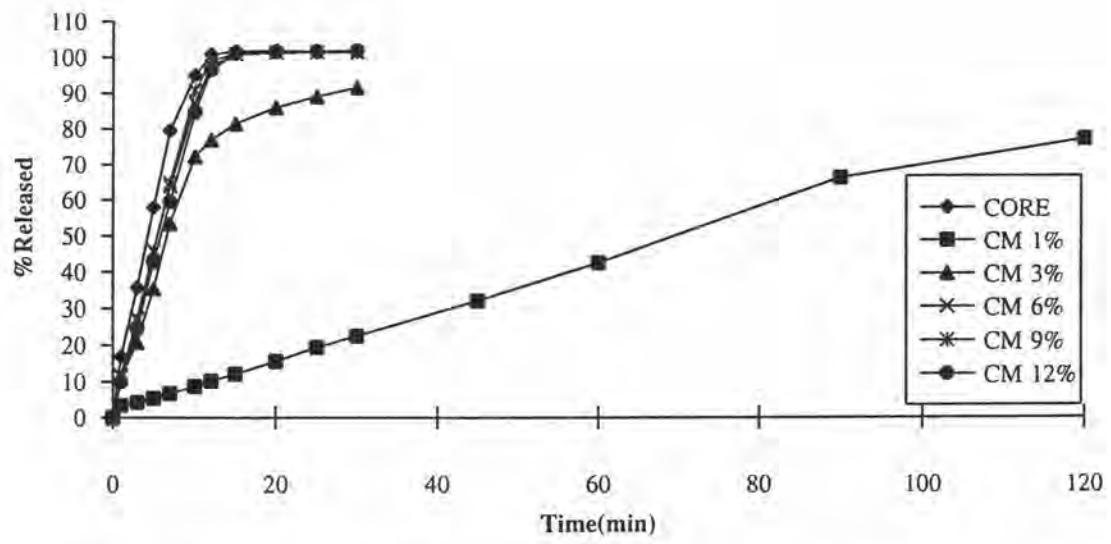


Figure 110 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan malate film at different coating level after direct exposure accelerated condition for 7 days in dilute HCl acid (n=6).

which it should be related to the adhesion force between surface of less soluble treated chitosan citrate film and surface of core tablet.

In basic dissolution medium, the more apparent retardation of drug release after exposure accelerated condition was greater than that of freshly prepared as presented in Figures *111* and *112*. This related to the undergo less solubility of treated chitosan film in release medium. This release characteristic was also observed in film coated tablets plasticized with glycerin and propylene glycol as shown in Figures *113* and *114*. Tablets coated with film plasticized with glycerin after exposure to accelerated condition exhibited the drug release slower than the others both in acidic and basic environment.

More yellowish than that of plasticized with propylene glycol after exposure accelerated condition of tablets coated with chitosan films plasticized with glycerin was observed and this alteration should be related to the less soluble form of this treated film coated tablets.

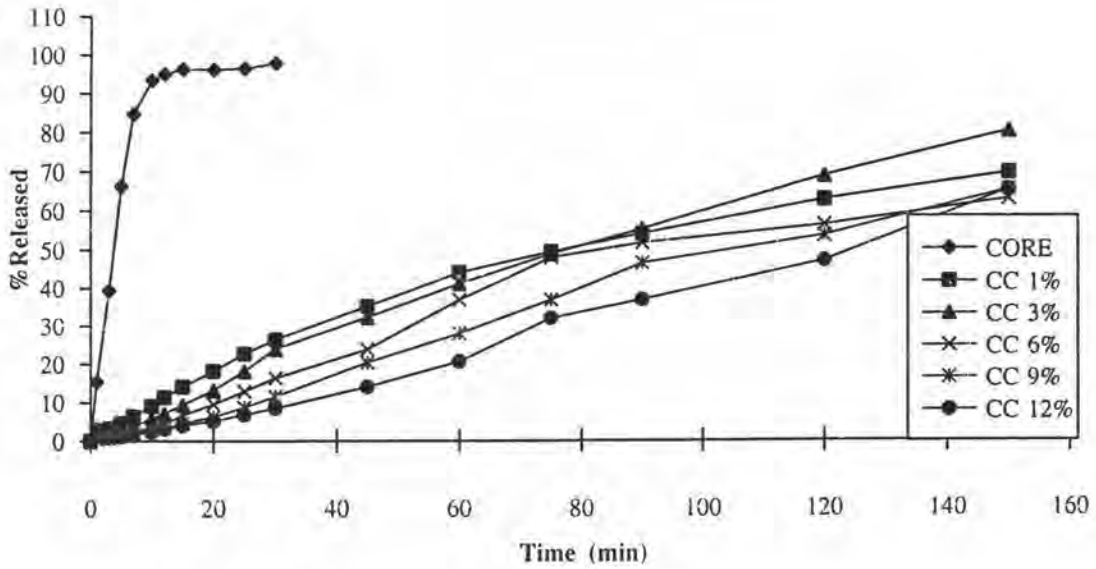


Figure 111 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate film at different coating level after direct exposure accelerated condition for 7 days in phosphate buffer pH 6.8 (n=6).

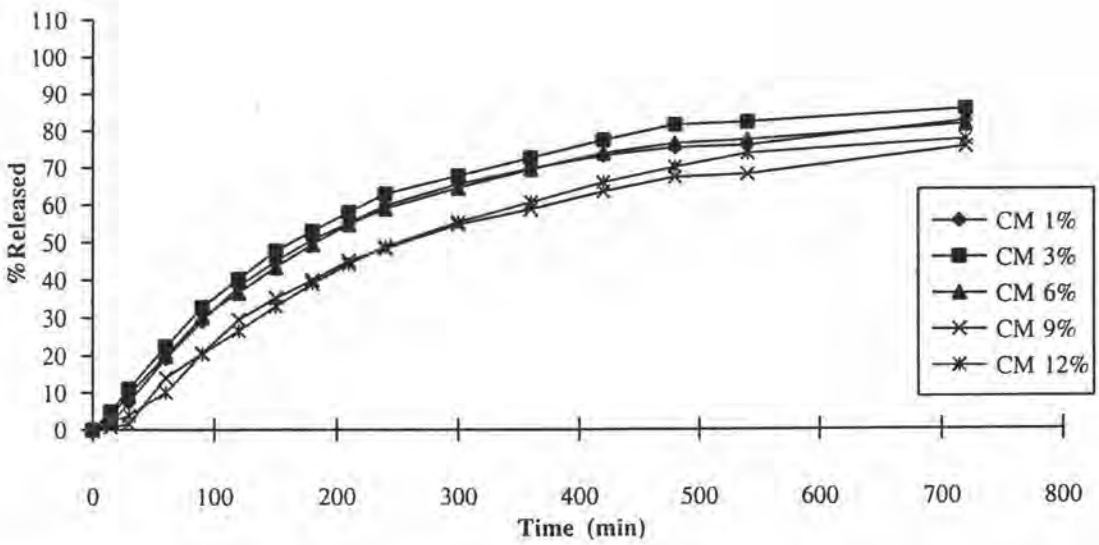


Figure 112 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan malate film at different coating level after direct exposure accelerated condition for 7 days in phosphate buffer pH 6.8 (n=6).

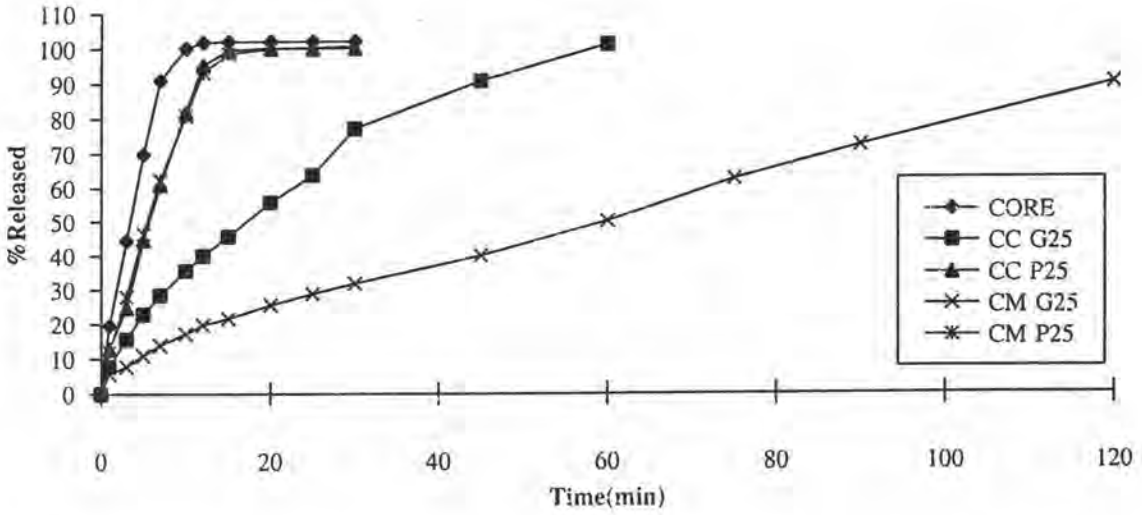


Figure 113 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate film and chitosan malate film plasicized with glycerin and propylene glycol 25%w/w at coating level of 6 % w/w of chitosan salt after direct exposure accelerated condition for 7 days in dilute HCl acid (n=6).

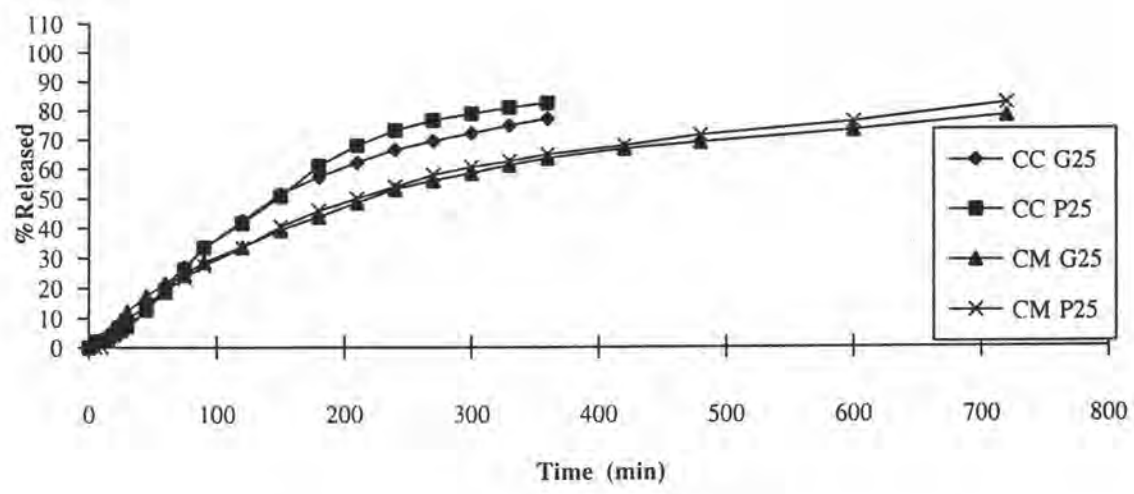


Figure 114 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan citrate film and chitosan malate film plasicized with glycerin and propylene glycol 25%w/w at coating level of 6 % w/w of chitosan salt after direct exposure accelerated condition for 7 days in phosphate buffer pH 6.8 (n=6)

10. 1. 2 Effect of Type of Polymeric Salt and Plasticizer

In order to investigate the effect of polymer not the polymeric salt on drug release behavior, the coating level was controlled to increase as by weight of 3% w/w based on chitosan. Similar release profile of tablets coated with unplasticized and plasticized chitosan citrate and chitosan malate films in acidic medium are shown in Figure *115*. However, the noticeable prolongation of drug release from tablet coated with chitosan malate film in basic medium was still appeared, especially from tablet coated with chitosan malate film plasticized with propylene glycol as shown in Figure *116*. After direct exposure to accelerated condition, the tablets coated with film plasticized with glycerin showed more retardation of drug release in acidic medium and the more noticeably slower drug release of all accelerated formula in basic environment was also detected as shown in Figures *117* and *118* respectively.

10. 1. 3 Effect of Amount of Propylene Glycol

No obvious change in release characteristic by varying the amount of propylene glycol was found in acidic medium, whereas the faster drug release in basic medium was found as the amount of propylene glycol was more increased as shown in Figures *119* and *120* respectively. Nevertheless, in basic medium, the rather long lag time was obviously appeared.

10. 1. 4 Effect of color

Color incorporation slightly slowered drug release in acidic medium as depicted in Figure *121*. In contrast, the release from tablets coated with colored chitosan film (plasticizer with propylene glycol) was apparently faster than that of tablet coated with non colored film in alkaline dissolution fluid.

The effect of storage condition on drug release was also investigated. It was found that there was no noticeable change in drug release of coated tablets after kept in bottle at 45°C 75% RH for 7 days as depicted in Figures *126* or *127*. The longer storage at 45°C 75% RH (1 month), the dominant slower drug release was observed, especially in case of colored coated tablets as depicted in Figures *128* or *129*. Film coated tablets colored with green FS exhibited the slower drug release than that of coated tablets colored with brilliant blue. This evidence was more dominant when coated tablets were directly exposed to the above condition as illustrated in Figures *130* or *131*.

10. 1. 5 Effect of Pigment on Drug Release

Pigment incorporation slightly enhanced drug liberation in acidic medium, but no obvious change in drug release profile by varying amount of pigment was found as presented in Figures *122* and *123*. In basic environment, the higher amount of talcum enhanced drug release and after incorporated talcum 45% w/w the release was greater than that of unpigmented coated tablets. At concentration of 15 and

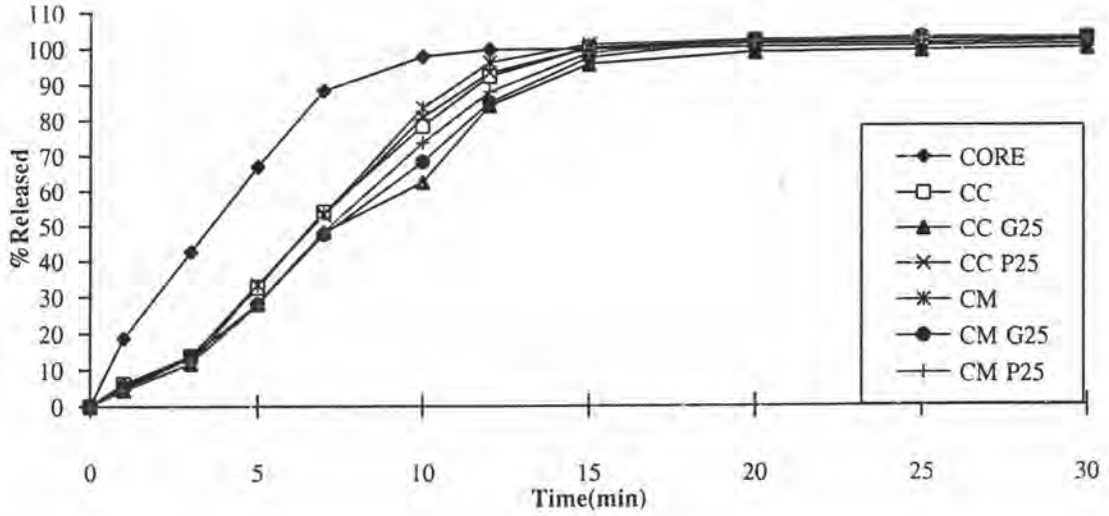


Figure 115 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film and malate film unplasticized or plasticized with glycerin and propylene glycol at 25% w/w at coating level of 3%w/w of chitosan in dilute HCl acid (n=6).

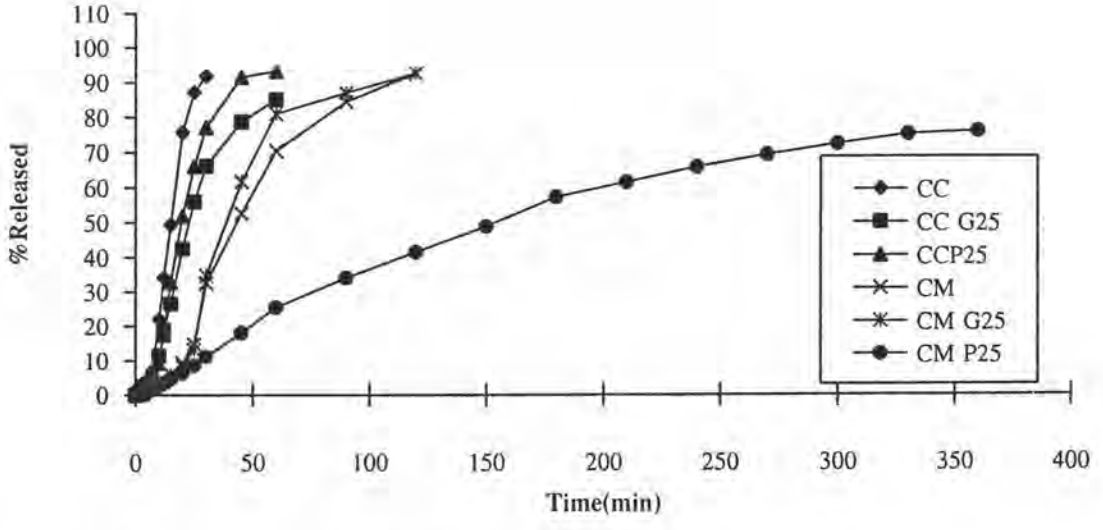


Figure 116 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film and malate film unplasticized or plasticized with glycerin and propylene glycol at 25% w/w at coating level of 3%w/w of chitosan in phosphate buffer pH 6.8 (n=6).

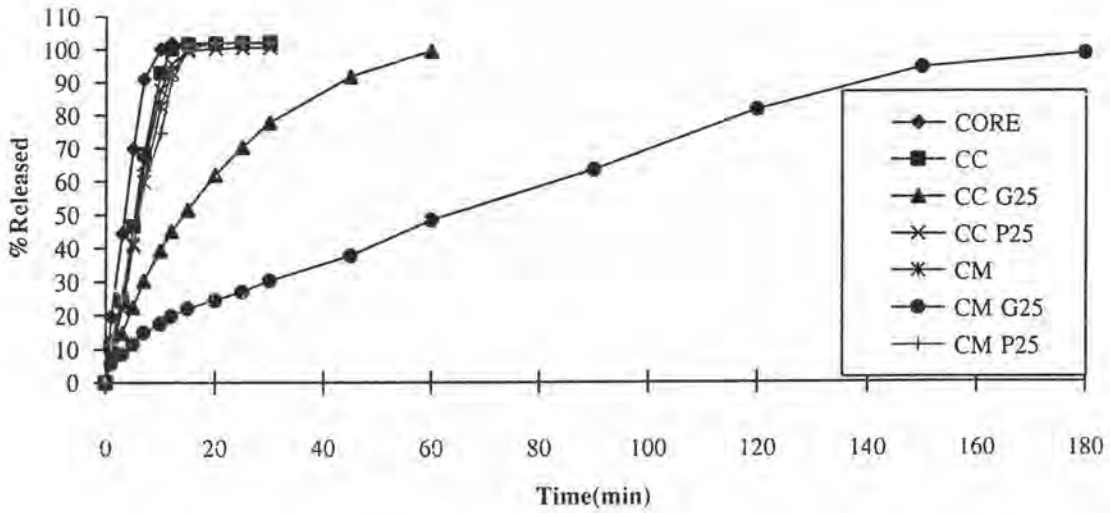


Figure 117 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film and malate film unplasticized or plasticized with glycerin and propylene glycol at 25% w/w at coating level of 3%w/w of chitosan after direct exposure accelerated condition for 7 days in dilute HCl acid (n=6).

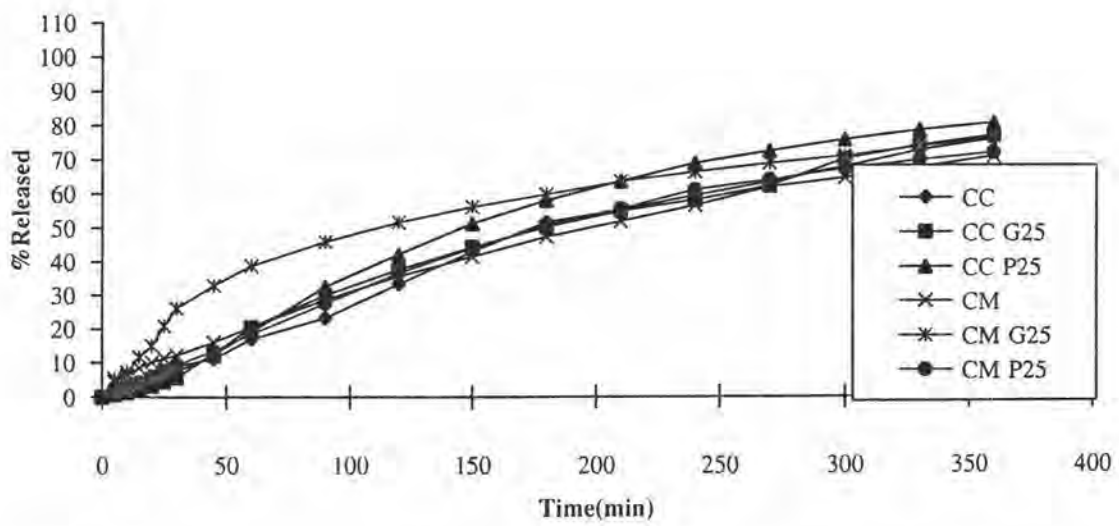


Figure 118 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film and malate film unplasticized or plasticized with glycerin and propylene glycol at 25% w/w at coating level of 3%w/w of chitosan after direct exposure accelerated condition for 7 days in phosphate buffer pH 6.8 (n=6).

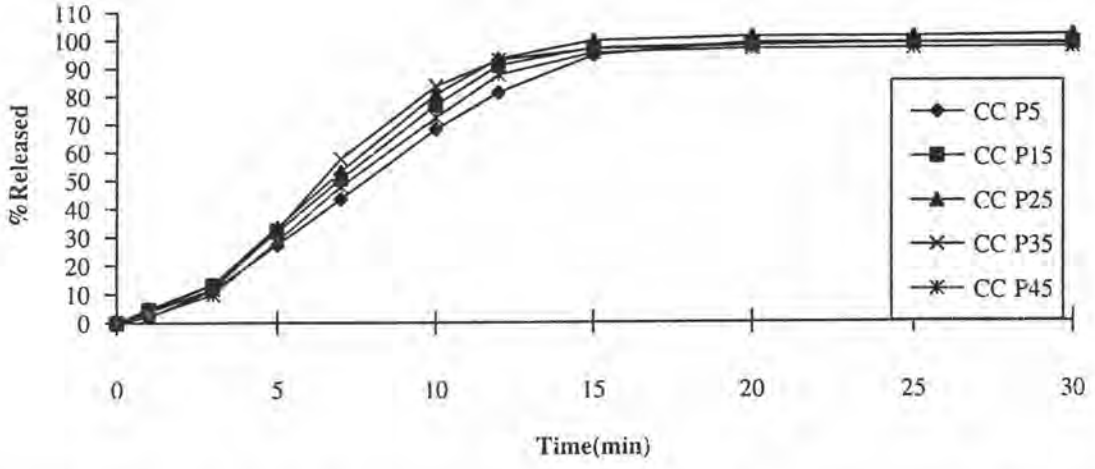


Figure 119 Effect of the level of propylene glycol on drug release from tablets coated with chitosan citrate film at coating level of 3% w/w of chitosan in dilute HCl acid(n=6).

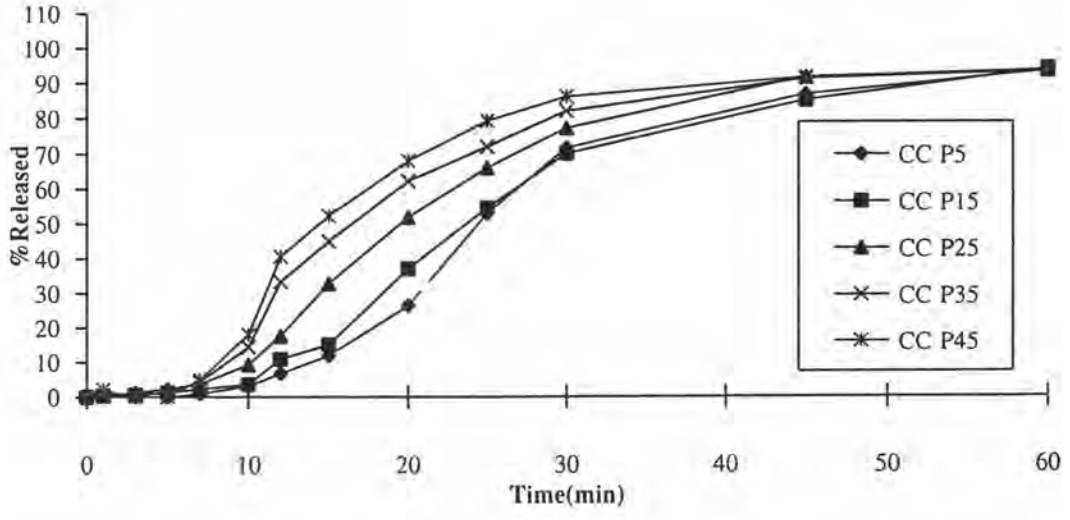


Figure 120 Effect of the level of propylene glycol on drug release from tablets coated with chitosan citrate film at coating level of 3%w/w of chitosan in phosphate buffer pH 6.8 (n=6).

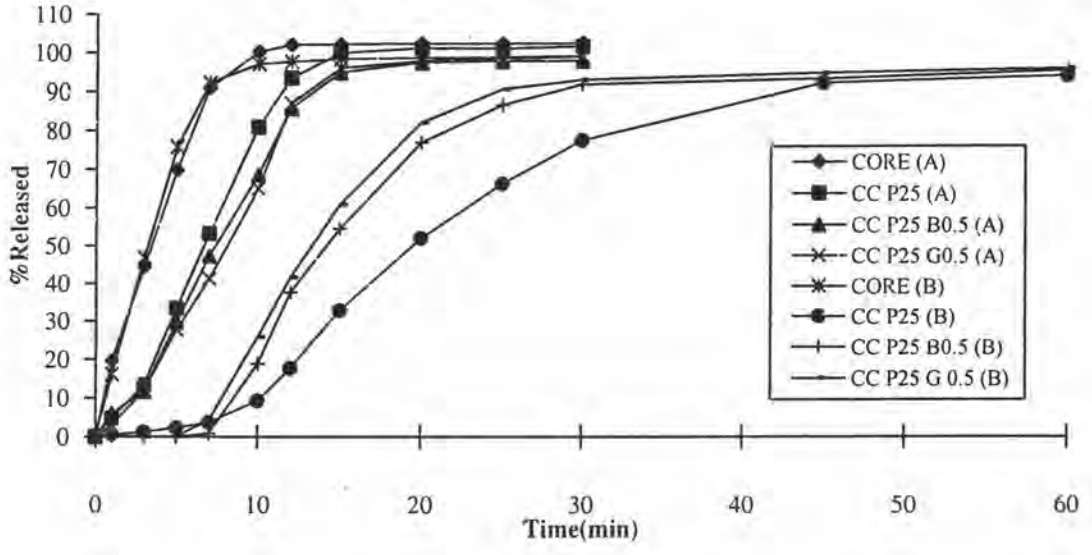


Figure 121 The dissolution profiles of propranolol HCl of core tablet and tablets coated with chitosan citrate film plasticized with propylene glycol 25% w/w of polymer and tablets coated with chitosan citrate film plasticized with propylene glycol 25% w/w of polymer and colored with brilliant blue or green FS at concentration of 0.50 % w/w of polymer in (A) dilute HCl acid and (B) phosphate buffer pH 6.8 (n=6).

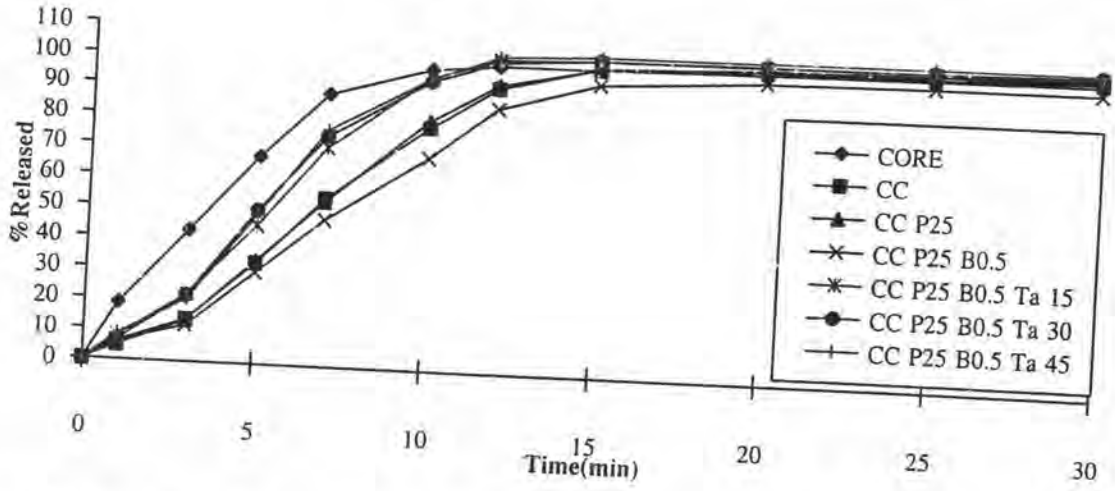


Figure 122 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film unplasticizied and plasticized with propylene glycol at concentration of 25 % w/w of polymer, and unpigmented and pigmented with different concentration of talcum colored with brilliant blue 0.5% w/w of polymer at coating level 3%w/w of chitosan in dilute HCl acid (n=6).

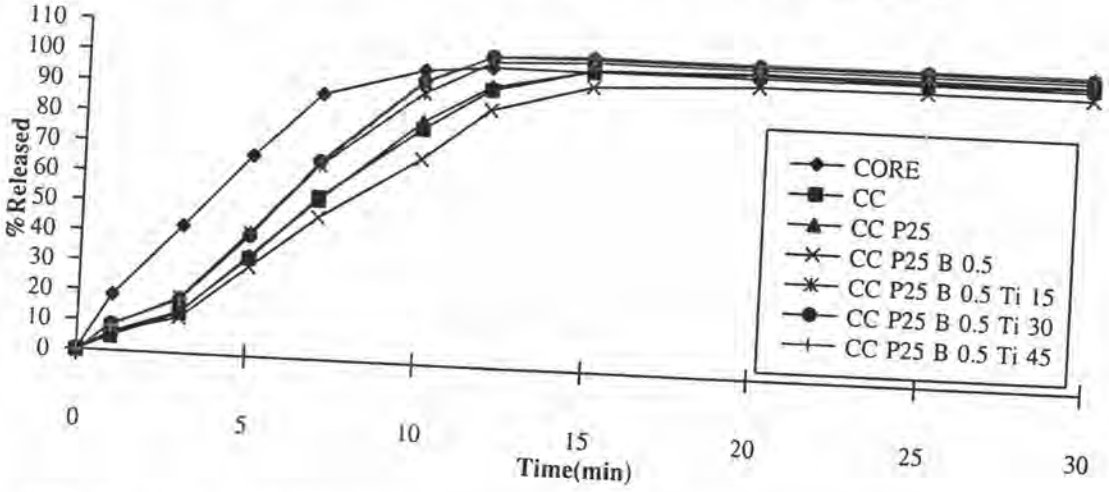


Figure 123 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of titanium dioxide colored with brilliant blue 0.5% w/w of polymer at coating level 3%w/w of chitosan in dilute HCl acid (n=6).

30 % w/w, talcum slowered the drug release compared to that unplasticized film coated tablet as shown in Figure *124*. Incorporation of titanium dioxide showed a tendency to retard the drug release in basic medium as shown in Figure *125*.

After kept coated tablets in brown airtight glass bottle at 45°C 75% RH for one week and one month, the drug release was retested. After kept for one week, the drug release profile was similar to that of freshly prepared as presented in Figures *126* and *127*. The more retardation of drug release was found after storage for one month as depicted in Figures *128* and *129*. In comparison, the drug release from coated tablets using talcum as pigment remained to conformed the criteria of USP XXIII, but the film coated tablets using titanium dioxide was not passed this standard.

Noticeable retardation of drug release from coated tablets pigmented with talcum after direct exposure to accelerated condition is shown in Figure *130*. The retardation of drug release was found in case of using titanium dioxide but an increased amount of this material reduced the retardation as presented in Figure *131*.

The drug release profiles of core and coated tablets after kept at room temperature for one year are depicted in Figures *132, 133* and. *134*. The drug release of stored core tablets was slower than that of freshly prepared. The drug release profiles of aged coated tablets were similar to those of freshly prepared coated tablets. The drug release profiles reached the plateau stage at about 15 minutes. Except that the drug release from tablets coated with chitosan malate film plasticized with glycerin was slower than the other. Nevertheless the drug release from all formula conformed the criteria relied on USP XXIII.

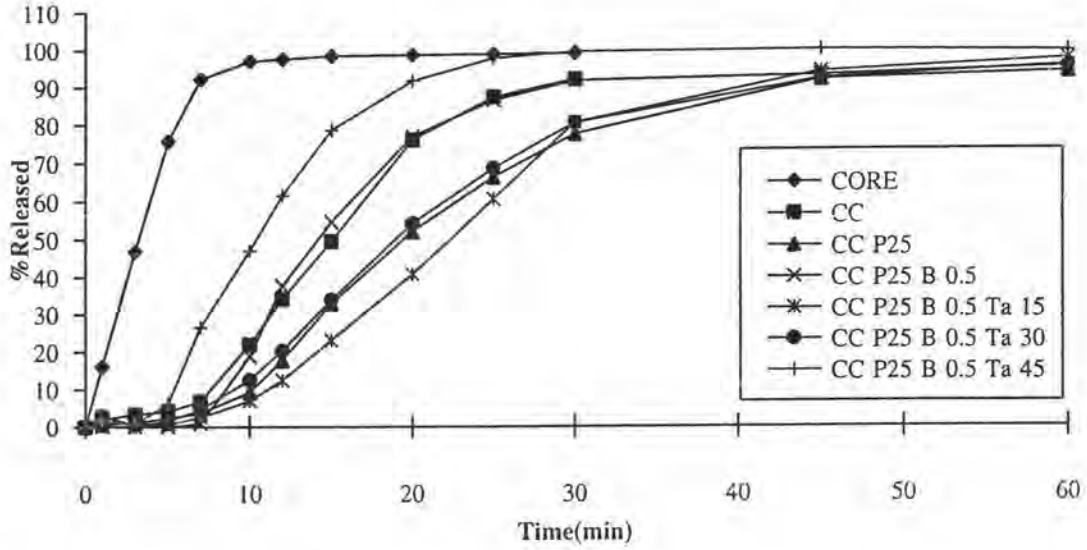


Figure 124 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of talcum colored with brilliant blue 0.5% w/w of polymer at coating level 3%w/w of chitosan in phosphate buffer pH 6.8 (n=6).

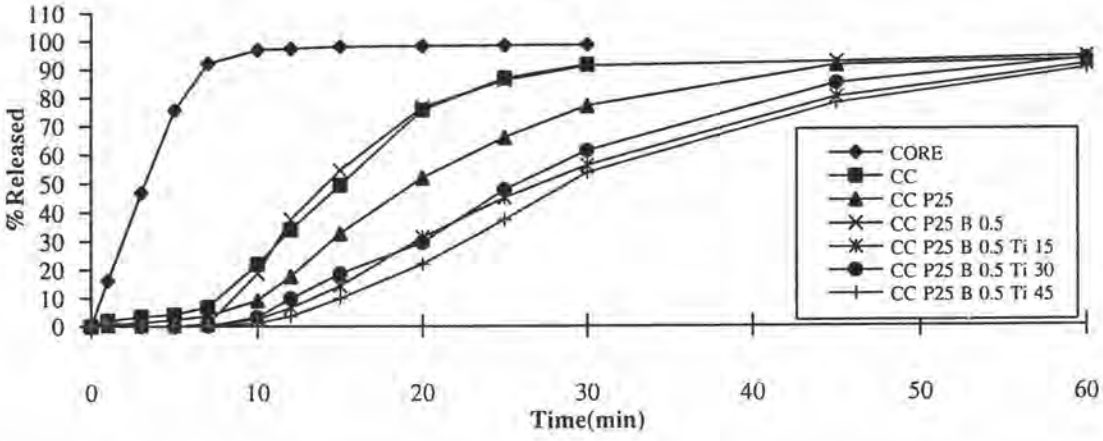


Figure 125 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of titanium dioxide colored with brilliant blue 0.5% w/w of polymer at coating level 3%w/w of chitosan in phosphate buffer pH 6.8 (n=6).

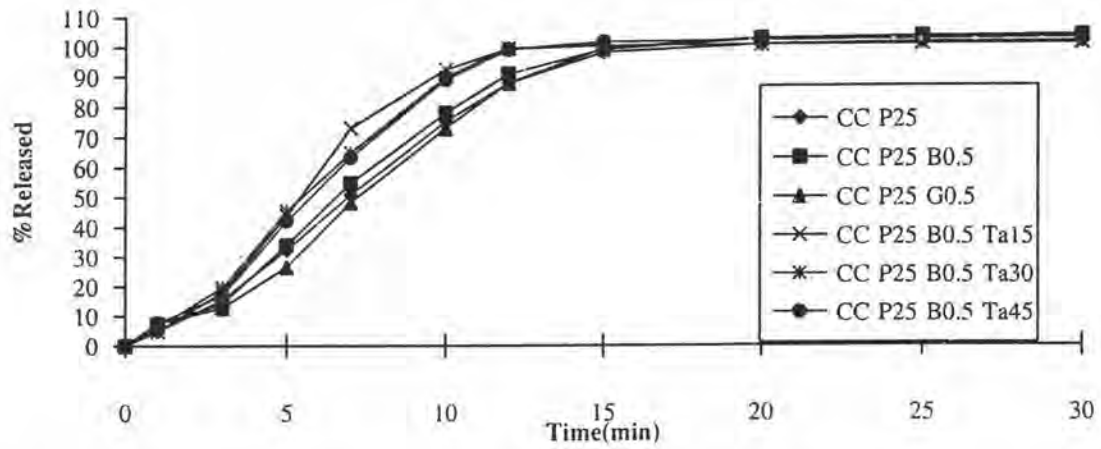


Figure 126 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of talcum and colored with brilliant blue 0.5% w/w of polymer at coating level 3% w/w of chitosan after kept in bottle and kept in accelerated condition for 7 days in diluteHCl acid (n=6).

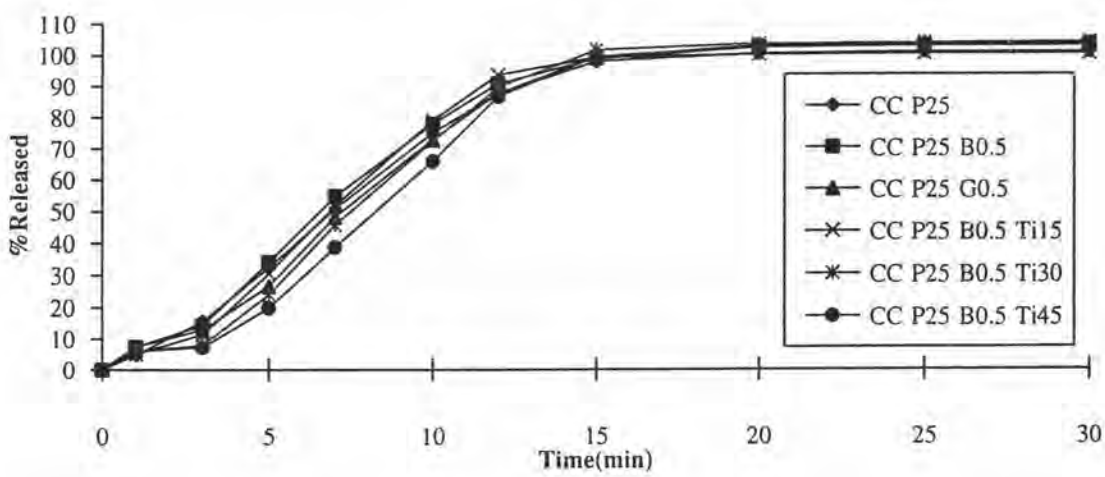


Figure 127 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of titanium dioxide and colored with brilliant blue 0.5% w/w of polymer at coating level 3% w/w of chitosan after kept in bottle and kept in accelerated condition for 7 days in diluteHCl acid (n=6).

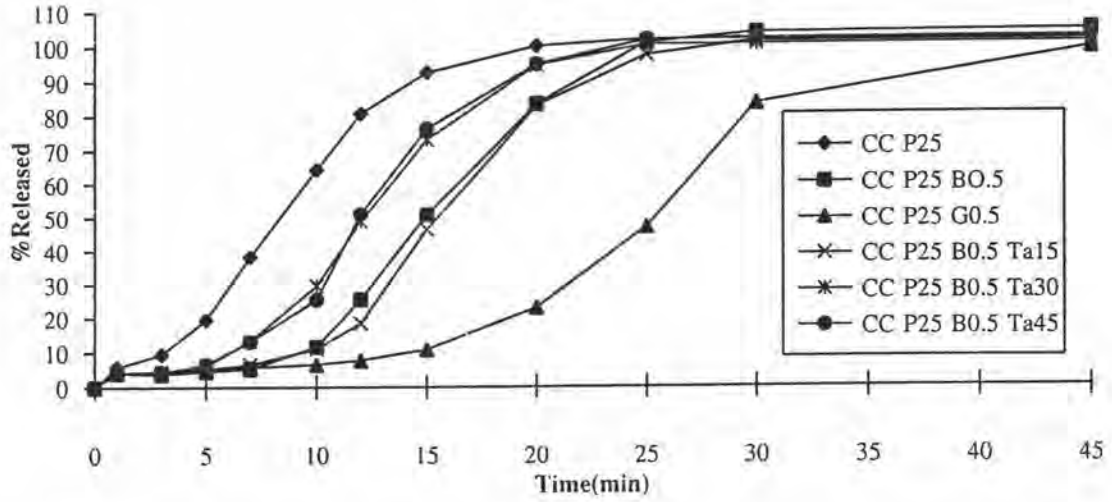


Figure 128 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 %w/w of polymer and unpigmented or pigmented with different concentration of talcum colored with brilliant blue 0.5% w/w of polymer at coating level 3%w/w of chitosan after kept in bottle and kept in accelerated conditionfor one month in dilute HCl acid (n=6).

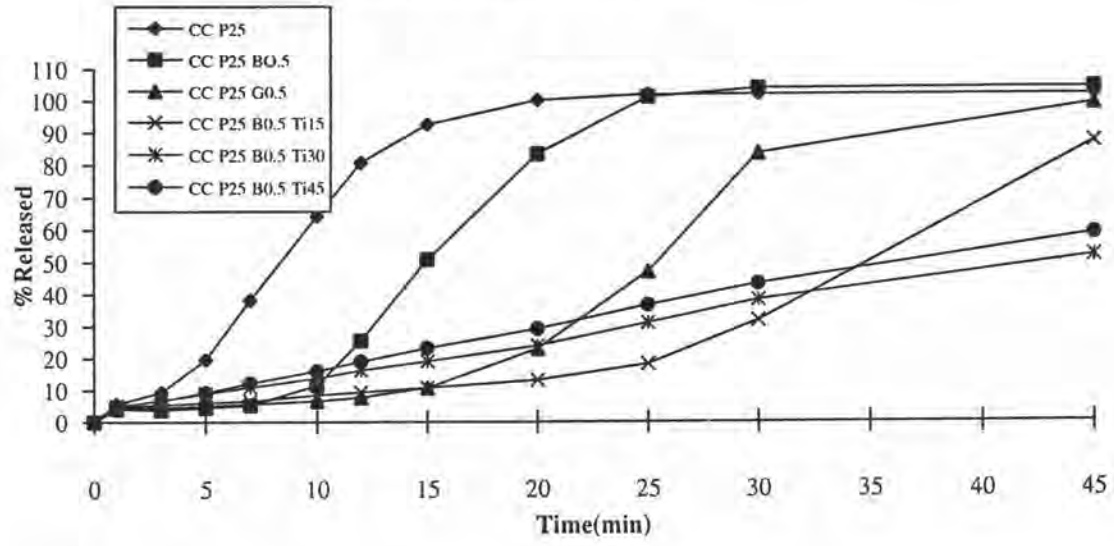


Figure 129 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 %w/w of polymer and unpigmented or pigmented with different concentration of titanium dioxide colored with brilliant blue 0.5% w/w of polymer at coating level 3%w/w of chitosan after kept in bottle and kept in accelerated conditionfor one month in dilute HCl acid (n=6).

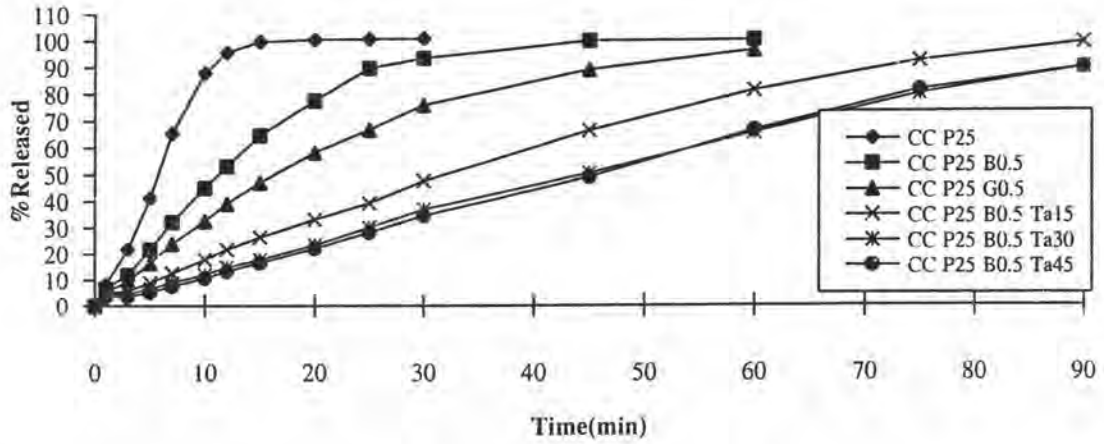


Figure 130 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of talcum colored with brilliant blue 0.5% w/w of polymer at coating level 3% w/w of chitosan after direct exposure to accelerated condition for 7 days in dilute HCl acid (n=6).

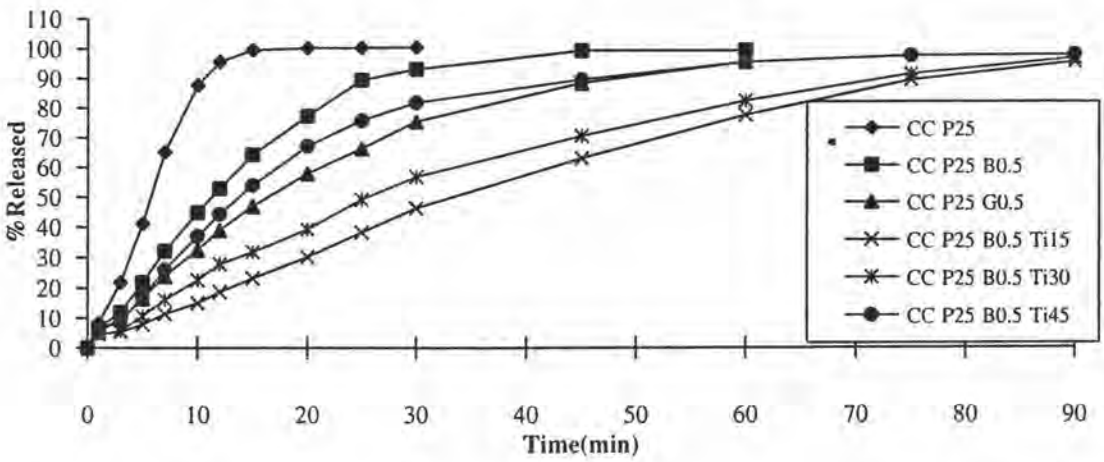


Figure 131 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of titanium dioxide colored with brilliant blue 0.5% w/w of polymer at coating level 3% w/w of chitosan after direct exposure to accelerated condition for 7 days in dilute HCl acid (n=6).

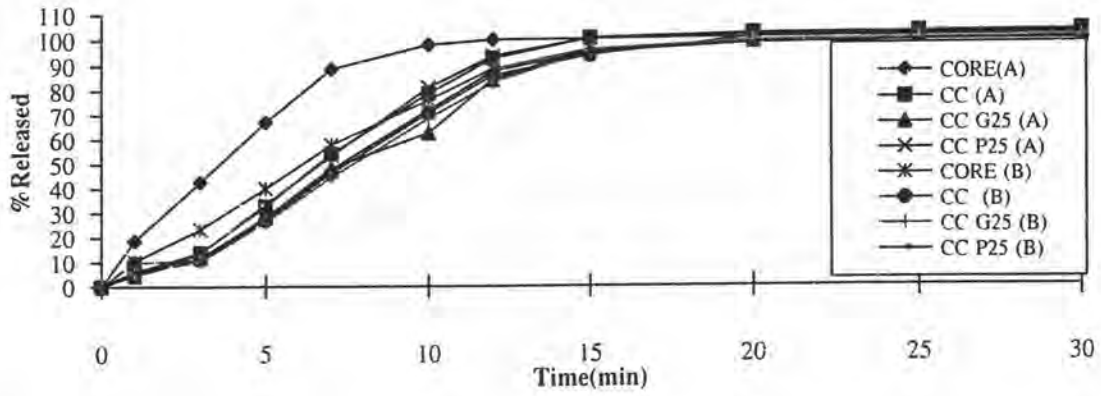


Figure 132 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan citrate plasticized or plasticized with glycerin and propylene glycol at 25% w/w at coating level of 3%w/w of chitosan in dilute HCl acid: (A) freshly prepared and (B) after kept at room temperatue for one year (n=6).

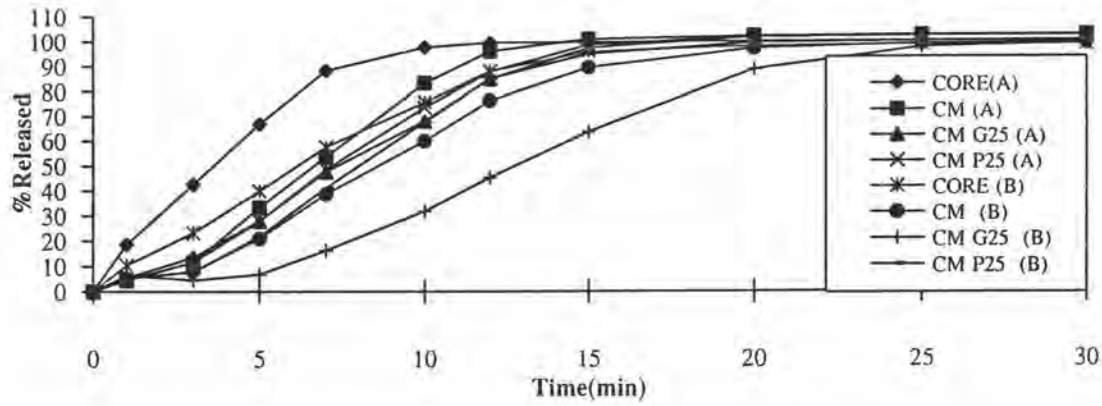


Figure 133 The dissolution profiles of propranolol HCl from core tablet and tablets coated with chitosan malate unplasticized or plasticized with glycerin and propylene glycol at 25% w/w at coating level of 3%w/w of chitosan in dilute HCl acid: (A) freshly prepared and (B) after kept at room temperatue for one year (n=6).

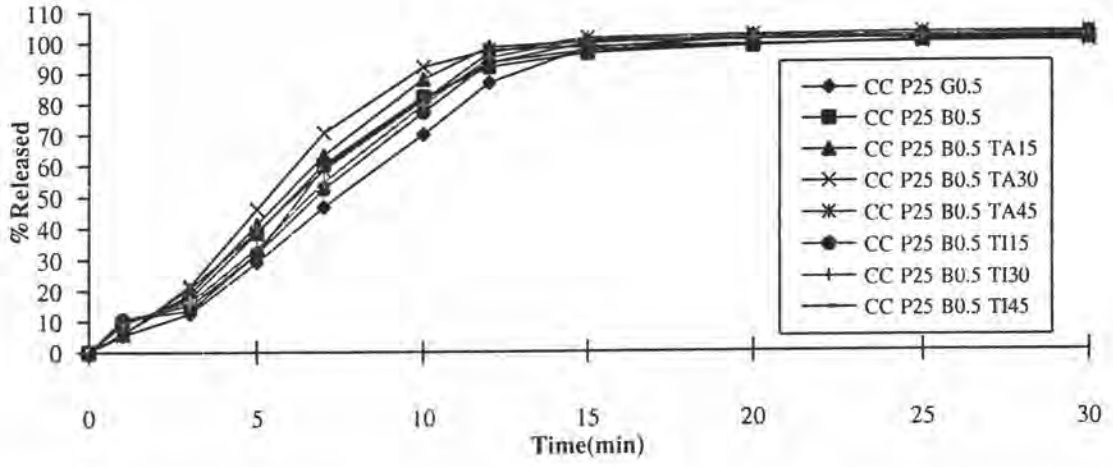


Figure 134 The dissolution profiles of propranolol HCl from tablets coated with chitosan citrate film unplasticizied or plasticized with propylene glycol at concentration of 25 % w/w of polymer and unpigmented or pigmented with different concentration of talcum colored with brilliant blue 0.5% w/w of polymer at coating level 3% w/w of chitosan after kept at room temperature for one year in dilute HCl acid (n=6).

10. 2 Extended Release Preparation

The drug release profiles of core and coated tablets and cumulative % drug release are illustrated in Figures *135-176* and shown in Tables *300-342* (Appendix C).

10. 2. 1 Effect of Coating Level of Chitosan Acetate Film on Drug Release

The greater coating level of chitosan acetate film onto core tablet, the more retardation of drug release due to the longer lag time was appeared as depicted in Figure *135*. Lag time in release profiles was shorten by adding glycerin into coating component as shown in Figure *136*. Drug release from chitosan propionate film coated tablet also had the lag time. Addition of triacetin slightly enhanced the drug release meanwhile sorbitol slightly slowered the drug release as depicted in Figure *137*.

Sustainable release of medicament could be achieved in basic dissolution medium. The near zero order release was found during 10-70 % drug release. The more retardation of drug release could be attained by enhancement of coating level as presented in Figure *138*.

Basically, administration of oral sustained release dosage form had to pass the stomach before movement further to the next gastrointestinal part, hence the product must withstand and control drug release in both acid and basic environment of gastrointestinal tract. Freshly prepared chitosan acetate and propionate films could effectively control drug release in basic medium while exhibited fast release in acid medium. Therefore it was difficult and seem impossible to use this film as the barrier for oral sustained release product. Nevertheless due to the effectiveness for control medicament in basic environment, it may repeat to coat chitosan film coated tablet with enteric coating film former to prolong the release both in acidic and basic environment but this method was not included in this present study.

In order to obtain the extended release film coated tablets, chitosan acetate and chitosan propionate film coated tablets were prepared with various coating levels, different treated methods (dry or moist heat treatment) and various time intervals of treatment, however these coated tablets could not show desirable release characteristic. The film coat was so brittle after treatment and thus it could not prolong the drug release. Many plasticizers (propylene glycol, glycerin, sorbitol and triacetin) were added to the coating formulation, but they still could not extend drug release as shown in Tables *306* and *307* in Appendix C. This result should be related to the volatility of plasticizer during heat treatment which the remainder was less than to plasticize or the hydrophilic nature of these plasticizers which could not plasticize the treated polymeric films. Castor oil was also selected for plasticizing at concentration of 15% w/w based on chitosan since at more than this concentration it would separate from the coating solution. However an addition of only this hydrophobic substance could not retard drug release. From this investigation, it also showed that after heat treatment chitosan propionate film on core tablet was more obviously brittle and yellowish than that

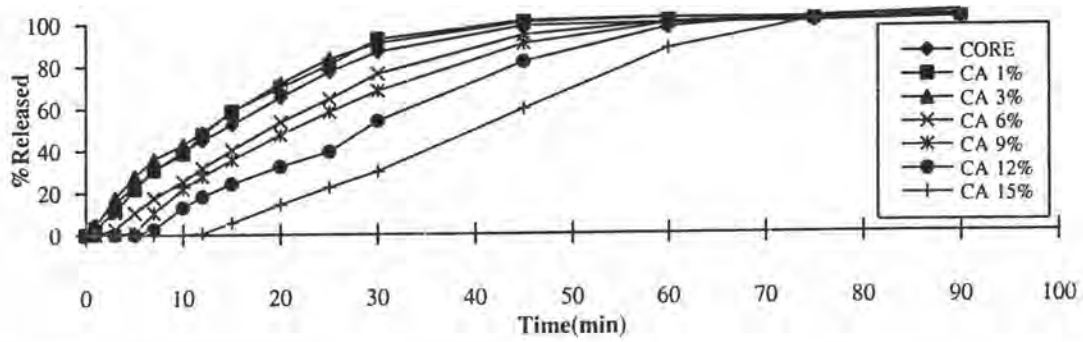


Figure 135 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan acetate film at different coating level in HCl buffer pH 1.2 (n=6).

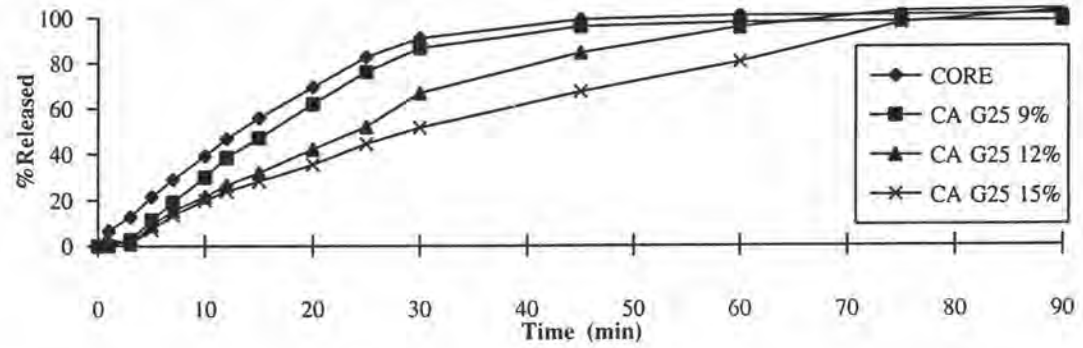


Figure 136 The dissolution profiles of propranolol HCl from core and tablets coated with chitosan acetate film plasticized with glycerin at concentration of 25 % w/w of polymer at different coating level in HCl buffer pH 1.2 (n=6).

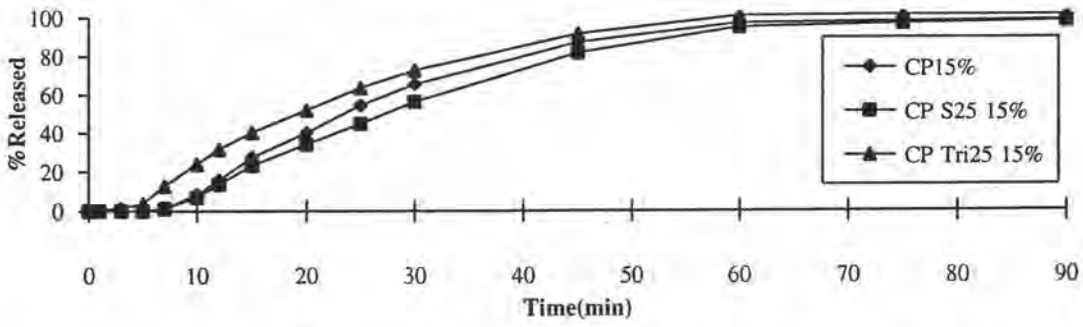


Figure 137 The dissolution profiles of propranolol HCl from tablets coated with chitosan propionate film non plasticized and plasticized with triacetin and sorbitol at concentrationof 25 % w/w of polymer at coating level 15 % w/w of polymer in HCl buffer pH 1.2 (n=6).

of chitosan acetate, hence the continual study selected to modify chitosan acetate film for preparing sustainable release coated tablets. Other hydrophobic substances were incorporated in chitosan acetate film in order to develop the sustainable drug release. These materials included: magnesium stearate, talcum and titanium dioxide. The release characteristics of drug from tablets coated with chitosan acetate film incorporated with these substances prior or after heat treatment were evaluated .

10. 2. 2 Effect of Incorporated Additives

The effect of some additives: castor oil, magnesium stearate, talcum and titanium dioxide incorporated in chitosan acetate film on drug release was illustrated in Figure *139*. Freshly prepared tablets coated with chitosan acetate film containing the above additives still exhibited the fast drug release in acidic medium. The amount of drug release was nearly depleted at about 90 minutes.

Combination between magnesium stearate and castor oil in chitosan acetate film could prolong medicament release in acidic medium to about 8 hours as presented in Figure *140*. Additionally, the coating level of this coating component affected the retardation of drug release. The longer drug release was achieved as the amount of the film coat was increased as depicted in Figure *141*. By visual observation during drug release test, the dissolution of chitosan acetate film containing magnesium stearate and castor oil was slower than those of films containing or without magnesium stearate respectively.

Combination between magnesium stearate 45% and propylene glycol, diethyl phthalate or triacetin in chitosan acetate film could slightly prolong drug release in acid medium as shown in Figure *140*. Plasticization with triacetin could prolong drug release greater than propylene glycol and diethyl phthalate respectively.

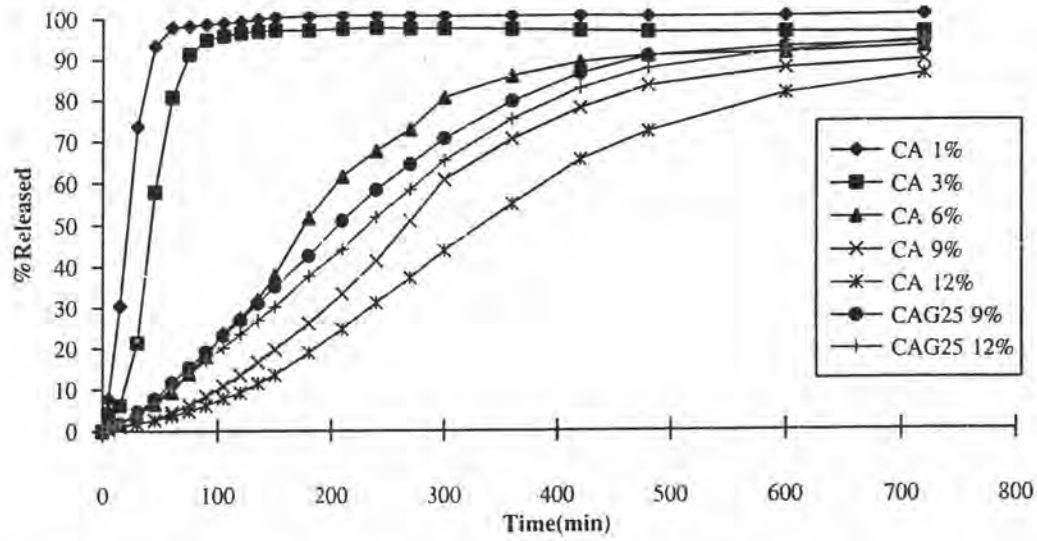


Figure 138 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film unplasticized or plasticized with glycerin a concentration of 25 % w/w of polymer at different coating level in phosphate buffer pH 6.8 (n=3).

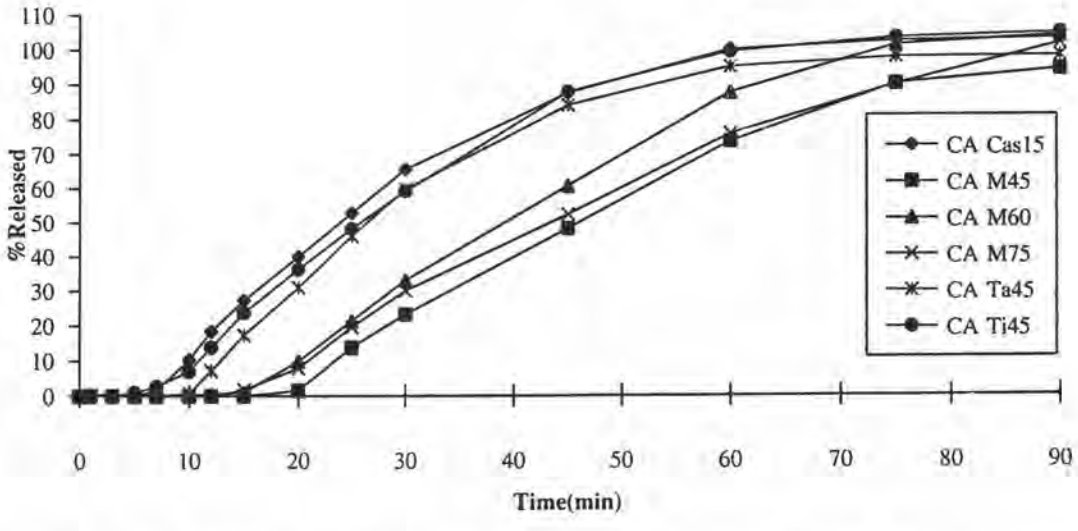


Figure 139 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing some additives at coating level of 15 % w/w of polymer in HCl buffer pH 1.2 (n=6).

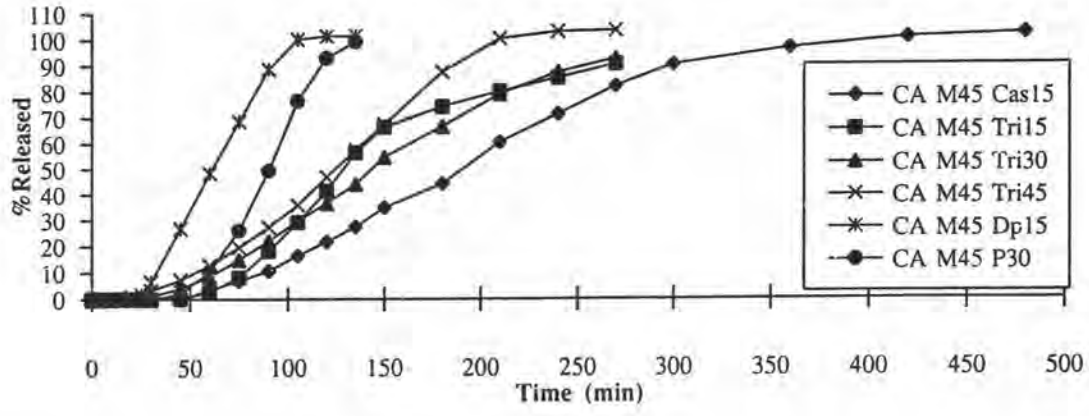


Figure 140 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 45 % w/w of polymer and different plasticizers at coating level of 15 % w/w of polymer in HCL buffer pH 1.2 (n=6).

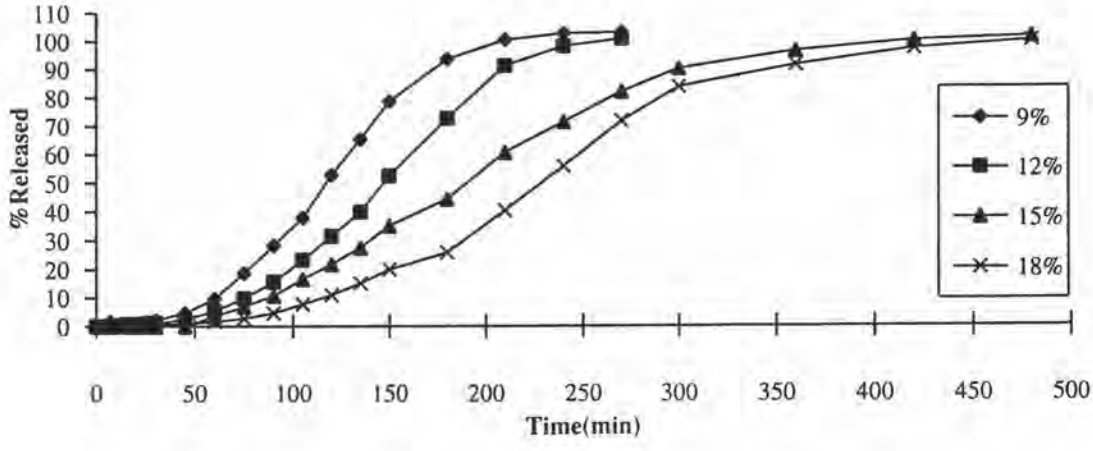


Figure 141 The dissolution profiles of propranolol HCl of freshly prepared tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% w/w in HCl buffer pH 1.2 (n=6)

10. 2. 3 Effect of Dry Heat Treatment

Dry heat treatment at 60°C for 7 days could extend drug release in pH change system of tablets coated with film containing magnesium stearate at different concentrations, talcum at concentration of 45% and combination of magnesium stearate and castor oil as depicted in Figure *142*. However the desired sustainable drug release did not achieve, since the drug release reached the plateau at about 7 hours.

The more increased amount of magnesium stearate did not affect the release as well as the duration of dry heat treatment as illustrated in Figures *143* and *144*respectively. Dry heat treatment could extend drug release of tablets coated with chitosan acetate film containing castor oil or titanium dioxide as depicted in Figures *145* and *146* respectively. The longer duration of treatment could greater extend the drug release, however the drug was completely released within only 240 minutes.

By comparison, after dry heat treatment for 7 days, tablets coated with chitosan acetate film containing magnesium stearate 45% plasticized with castor oil 15% could prolong drug release greater than those plasticized with diethyl phthalate 15%, triacetin 15% and propylene glycol 30% respectively as presented in Figure *147*.

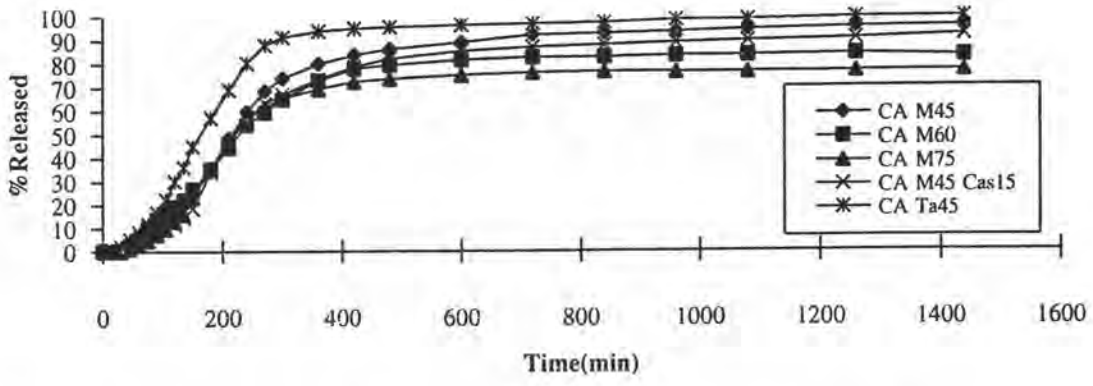


Figure 142 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing different additives at coating level of 15 % w/w of polymer after exposure dry heat at 60°C for 7 days in pH change system (n=3).

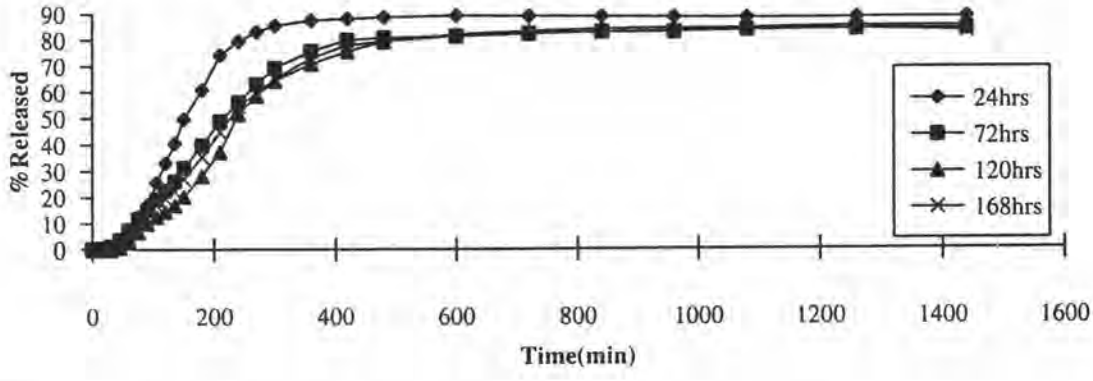


Figure 143 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate 60 % w/w of polymer at coating level of 15 % w/w of polymer after dry heat at 60°C at different time interval in pH change system (n=3).

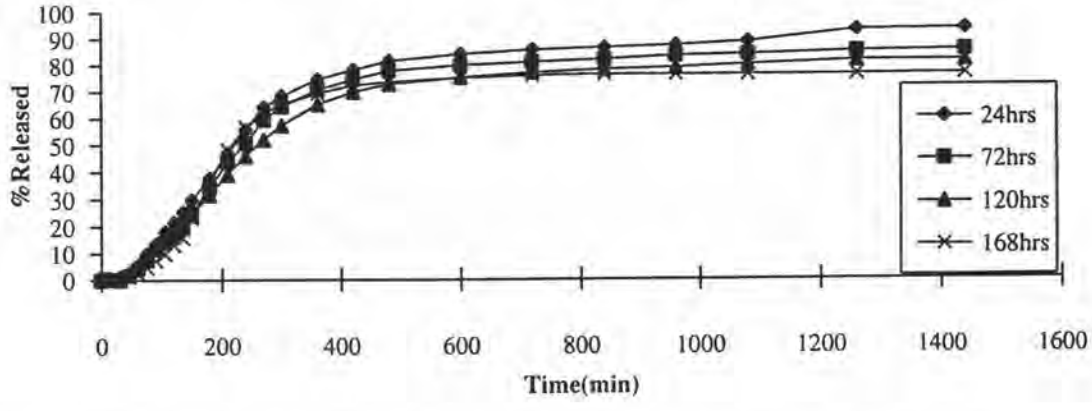


Figure 144 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate 75 % w/w of polymer at coating level of 15 % w/w of polymer after dry heat at 60°C for different time interval in pH change system (n=3).

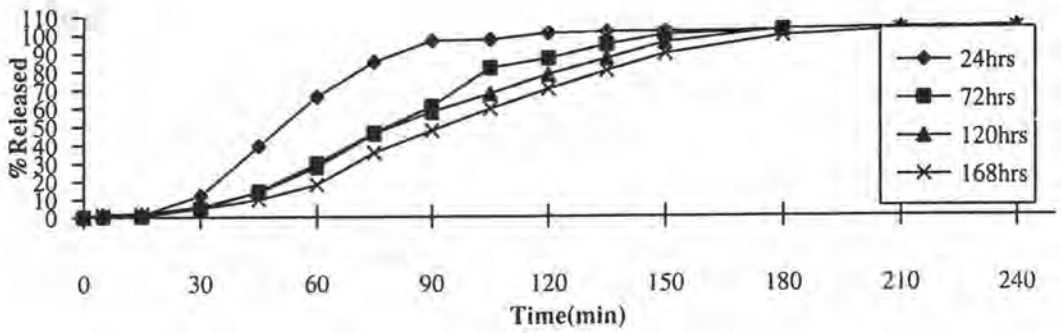


Figure 145 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing castor oil 15%w/w of polymer at coating level of 15 % w/w of polymer after exposure dry heat at 60°C for different time interval in pH change system (n=3).

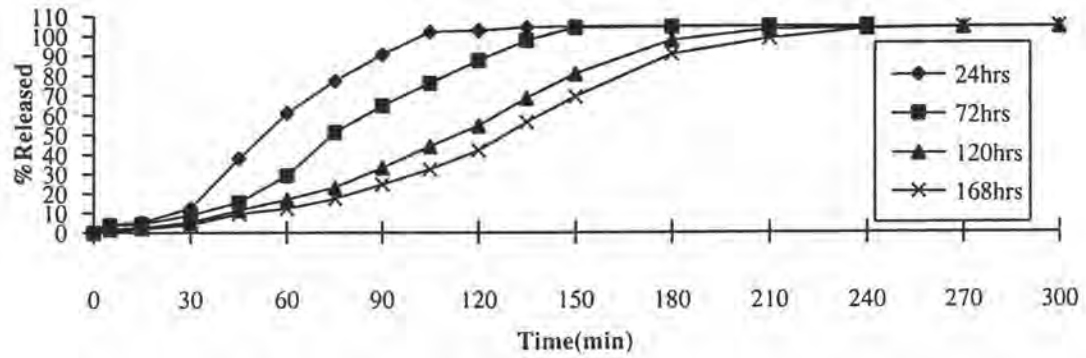


Figure 146 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing titanium dioxide 45%w/w of polymer at coating level of 15 % w/w of polymer after exposure dry heat at 60°C for different time interval in pH change system (n=3).

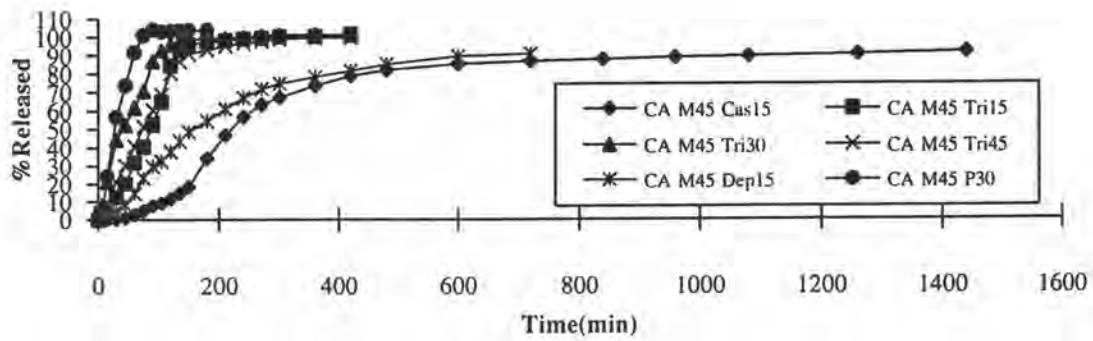


Figure 147 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate containing magnesium stearate 45 % w/w and different plasticizers at coating level of 15 %w/w of polymer after exposure dry heat at 60°C for 7 days in pH change system (n=3).

10. 2. 4 Effect of Moist Heat Treatment on Drug Release

Moist heat at 45°C 75% RH insufficiently prolonged drug release from the system coated with chitosan acetate film incorporated with magnesium stearate at concentration of 45 % w/w, whereas moist heat at 60°C 75% RH could obviously promote *in vitro* sustainable release as presented in Figures *148* and *149* respectively. The capability to sustain drug release also depended on the treatment period. The longer period of treatment, the more prolong drug release was obtained. This efficiency of moist heat to prolong drug release was also obtainable in case of using magnesium stearate at concentration of 60 and 75 % w/w, and additionally moist heat at 45°C could also promote *in vitro* sustainable release as shown in Figures *150* and *151* respectively. An increased amount of magnesium stearate could enhance the prolongation of drug release and treatment with moist heat at 60°C could effectively extend drug release more than that of 45°C.

An incorporation of talcum into chitosan acetate film could prolong drug release both after treatment with moist heat at 45°C and 60°C, and degree of retardation was enhanced when the temperature or duration of treatment was increased as depicted in Figures *152* and *153*. Considerably, it was found that the drug could be liberated from the device up to 100% at 24 hours. By comparison upon moist heat at 60 °C, the prolongation of drug release using film containing magnesium stearate 45% was greater than that using film containing talcum 45%. The %drug release at 7 hours of coated tablets after treatment at 60°C for 24, 72 and 120 hours of CA M45 was 77.86±0.88, 53.20±3.76, 51.95±7.20 and CA Ta45 was 83.93±3.89, 72.33±3.04 and 59.94±1.19 respectively. Meanwhile, only moist heat at 60°C for long period (72 and 120 hours) could prolong drug release from tablets coated with film containing titanium dioxide as illustrated in Figure *154*.

Combination between magnesium stearate at concentration of 45% w/w and castor oil at concentration of 15% w/w more effectively protracted drug release than using only magnesium stearate, and sustainable release characteristic could be attained when using moist heat both at 45°C and 60°C as shown in Figures *155* and *156*. After treatment for 168 hours, the drug release was slightly greater than that after treatment for 120 hours both treated with moist heat at 45°C or 60°C.

The effect of coating level on drug release from tablets coated with CA M45 Cas15 film after moist heat treatment for 24 hours was investigated with pH change method. It was found that an increase in coating level exhibited a tendency to prolong drug release as shown in Figure *157*. The rather long lag time still presented, nevertheless, when it was employed lower coating level.

Triacetin only at concentration 45% added in chitosan acetate film containing magnesium stearate could prolong the release after moist heat treatment at 45°C for 72 hours (Figure *158*) Using moist heat at 60°C, triacetin at concentration of 30% effectively prolong drug release more than other concentrations and plasticizing with triacetin at concentration of 15 % could not prolong drug release after treatment for 24 hours as shown in Figure *159*.

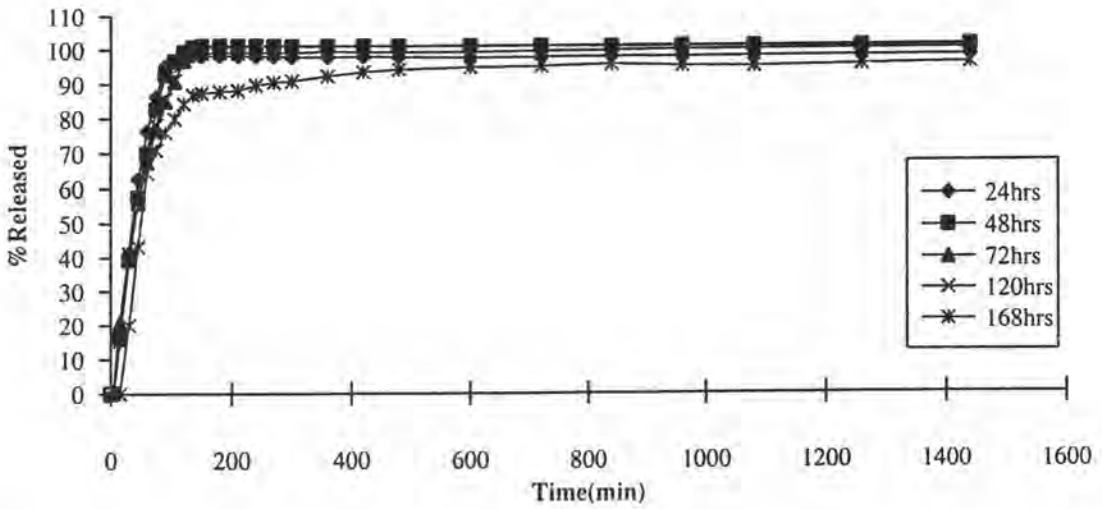


Figure 148 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 45% at coating level of 15% w/w of polymer after moist heat treatment at 45°C for different time interval in pH change system(n=3).

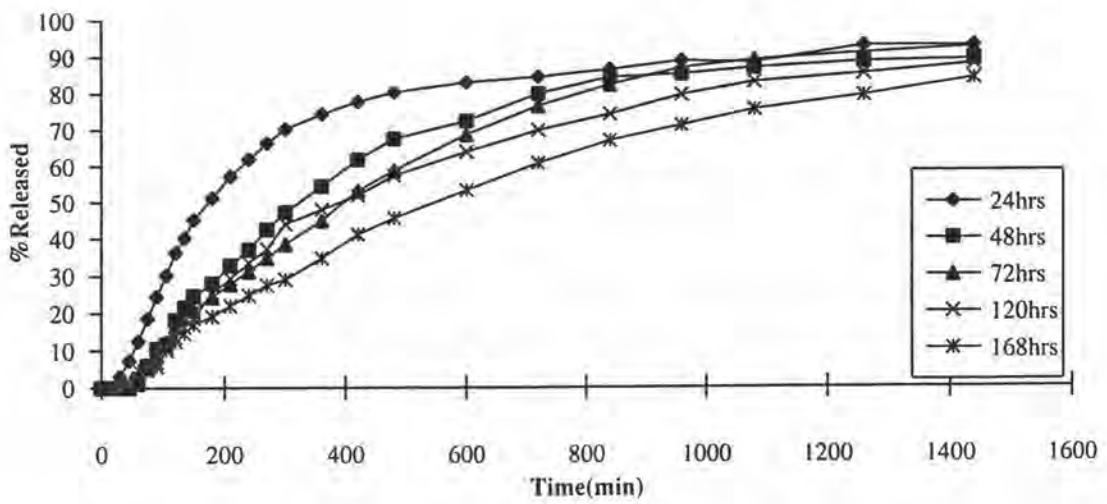


Figure 149 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 45% at coating level of 15% w/w of polymer after moist heat treatment at 60°C for different time interval in pH change system(n=3).

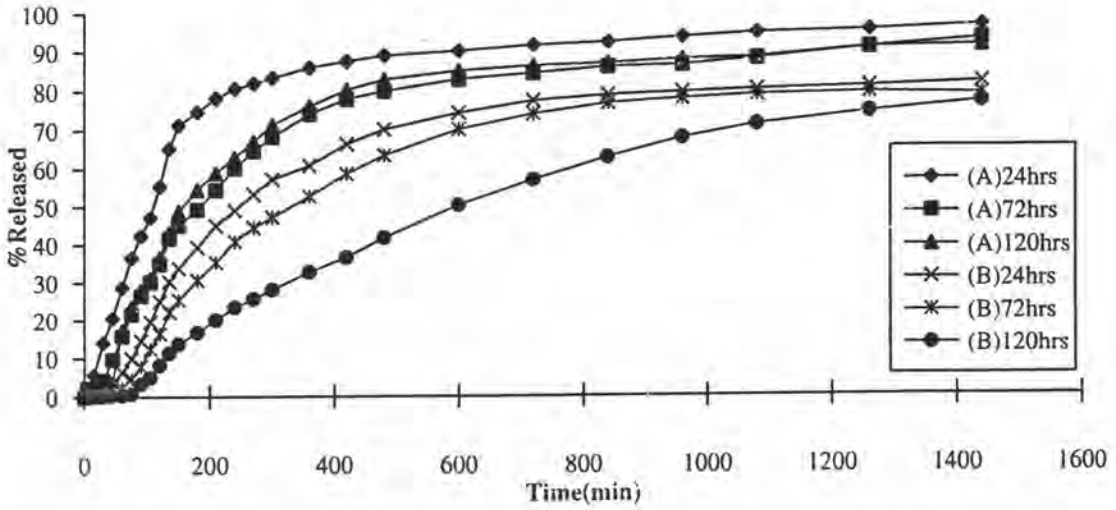


Figure 150 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 60% after moist heat treatment for different time interval at (A) 45°C and (B) 60°C in pH change system (n=3).

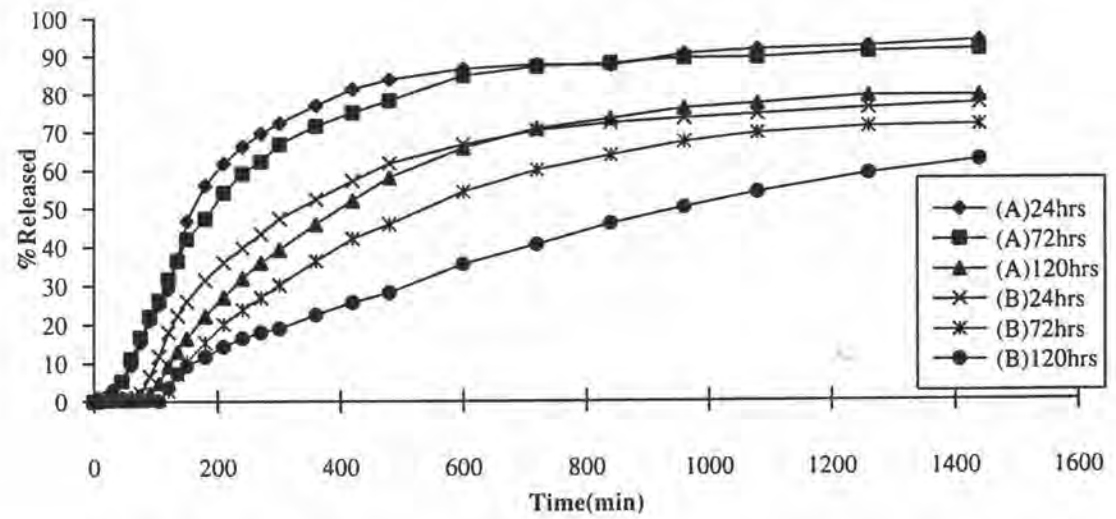


Figure 151 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 75% after moist heat treatment for different time interval at (A) 45°C and (B) 60°C in pH change system (n=3).

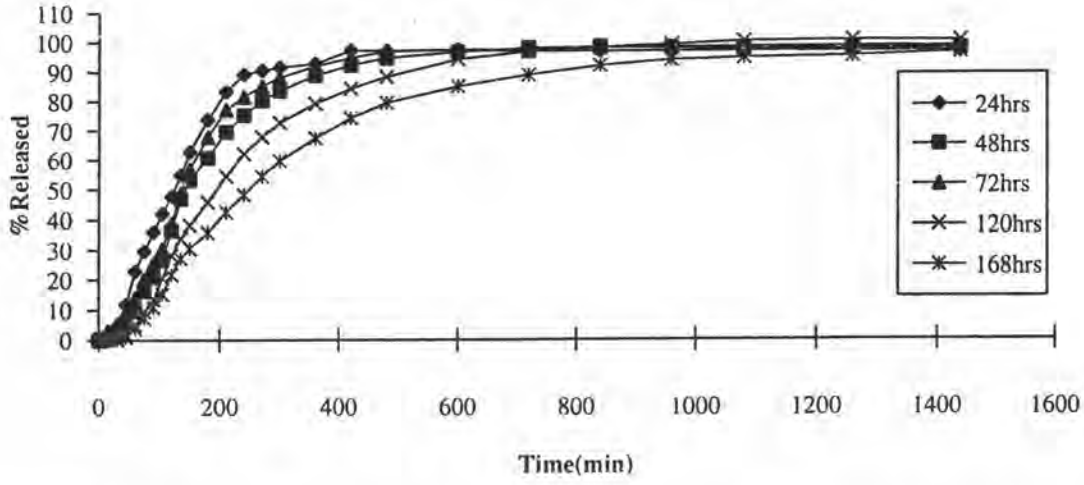


Figure 152 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing talcum 45% at coating level of 15% w/w of polymer after moist heat treatment at 45°C for different time interval in pH change system (n=3).

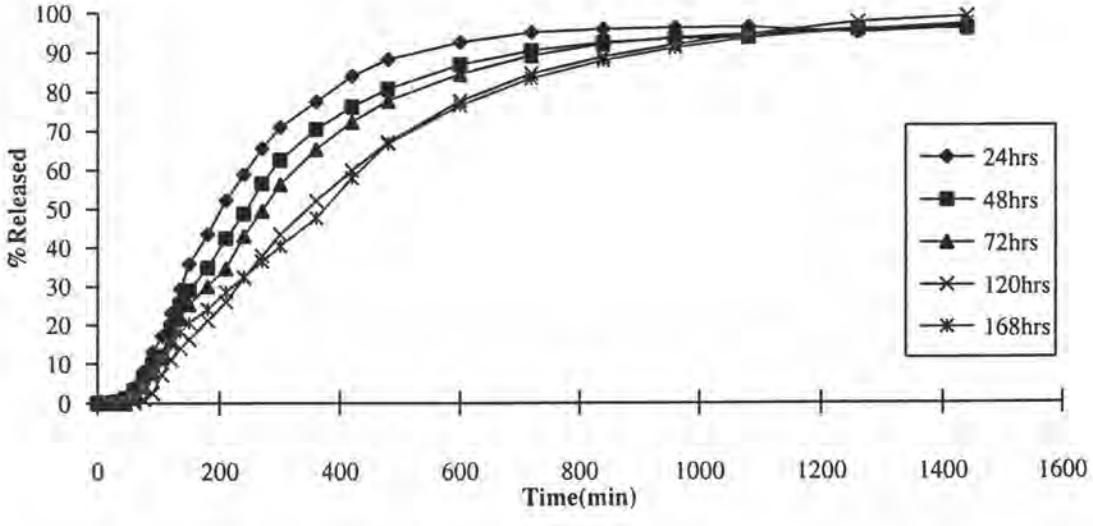


Figure 153 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing talcum 45% at coating level of 15% w/w of polymer after moist heat treatment at 60°C for different time interval in pH change system (n=3).

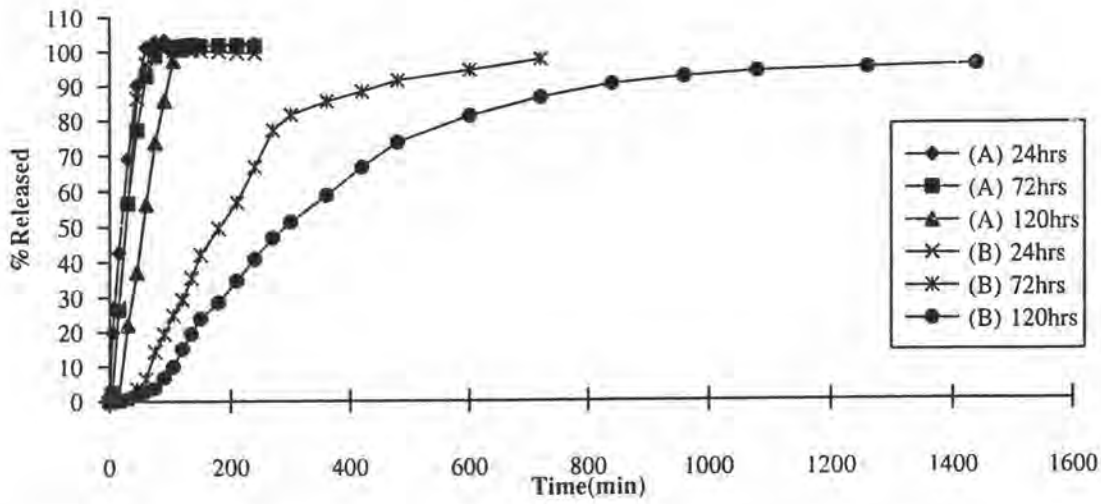


Figure 154 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing titanium dioxide 45% after moist heat treatment for different time interval at :(A) 45°C and(B) 60°C in pH change system (n=3).

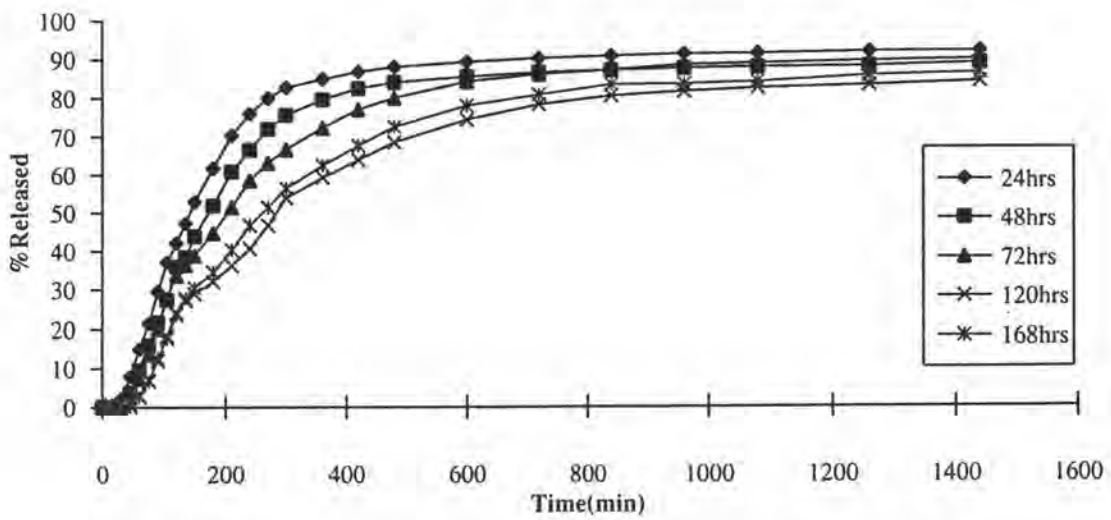


Figure 155 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% at coating level of 15% w/w of polymer after moist heat treatment at 45°C for different time interval in pH change system (n=3).

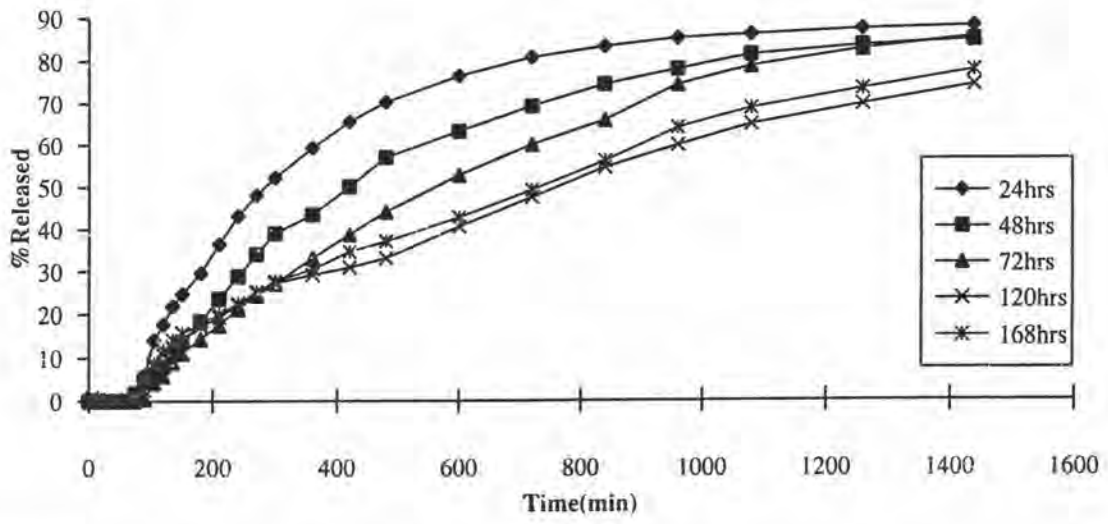


Figure 156 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% at coating level of 15% w/w of polymer after moist heat treatment at 60°C for different time interval in pH change system (n=3).

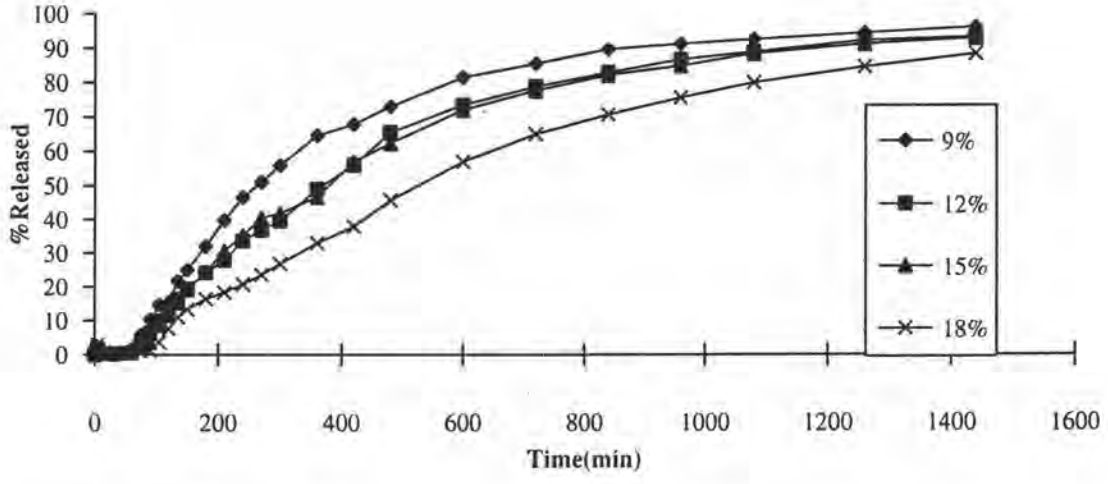


Figure 157 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15 % w/w of polymer at different coating level after moist heat treatment at 60°C for 24 hrs in pH change system (n=3).

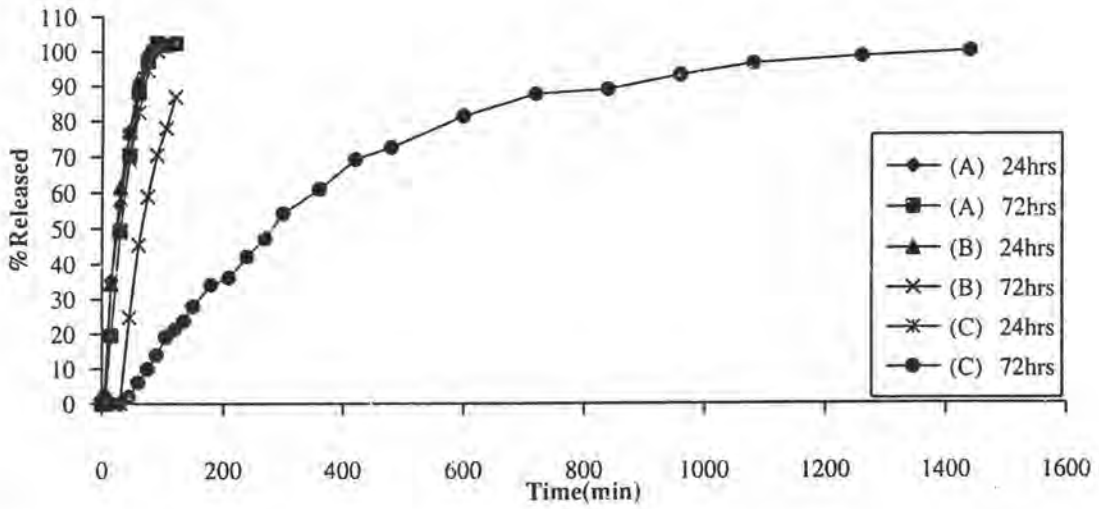


Figure 158 The dissolution profiles of propranolol HCl from tablet coated with chitosan acetate film containing magnesium stearate at concentration of 45 % and triacetin at concentration of (A) 15 %,(B) 30% and (C) 45% w/w at coating evel of 15 % w/w of polymer after moist heat treatment at 45°C for 24 and 72 hrs in pH change system (n=3).

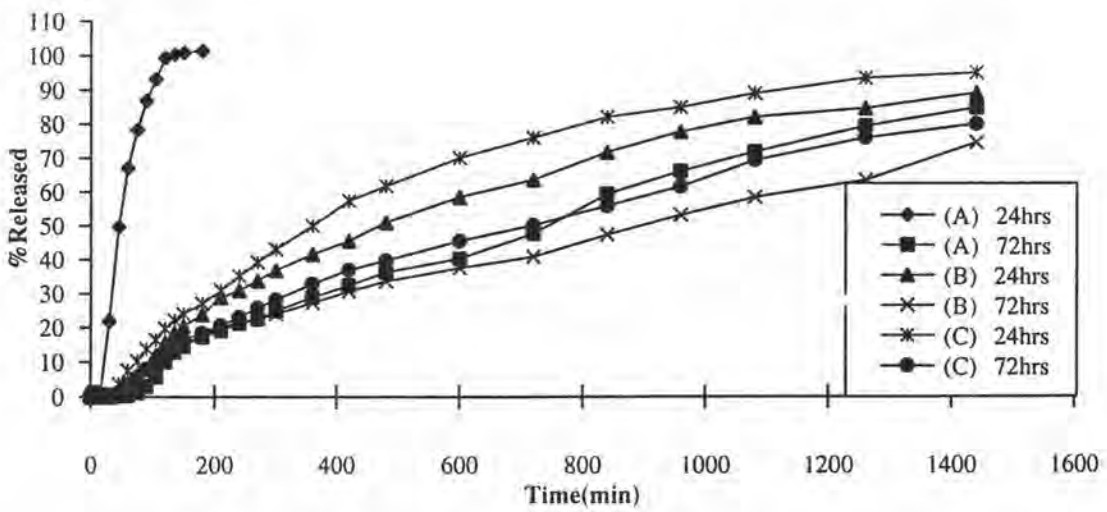


Figure 159 The dissolution profiles of propranolol HCl from tablet coated with chitosan acetate film containing magnesium stearate at concentration of 45 % and triacetin at concentration of (A) 15 %,(B) 30% and (C) 45% w/w at coating level of 15 % w/w of polymer after moist heat treatment at 60°C for 24 and 72 hrs in pH change system (n=3).

Only after moist heat treatment at 60°C, coating layer containing magnesium stearate at concentration of 45% w/w and adding with propylene glycol or diethyl phthalate could prolong drug release as shown in Figures *160* and *161*. The drug release after treatment for 72 hours was slower than that after treatment for 24 hours.

10. 2. 5 Effect of pH of Dissolution Medium

Some coated tablets treated with moist heat at 60°C were selected to further study the effect of pH of dissolution medium on drug release behavior. These treated coated tablets include: tablet coated with chitosan acetate film containing magnesium stearate at concentration of 45% (CA M45) and treated for 48 hours and tablet coated with chitosan acetate film containing magnesium stearate at concentration of 45% combined with castor oil at 15% (CA M45 Cas15) after treatment for 24 hours. Both these selected coated tablets had the drug dissolved in pH change system at each time interval conformed to the monograph in USP XXIII.

The latter type coated tablet exhibited more prolong drug release than the first type coated tablet in alkaline dissolution medium and both type coated tablets provided the greater delayed drug release in this medium than in acidic medium as shown in Figure *162*. These two type coated tablets liberated the medicament to the plateau stage at 12 hours and 24 hours in acidic and basic dissolution medium respectively. The drug liberation in acidic dissolution medium could be reached to 100%, whereas in basic medium the drug could be released at about 90% at 36 hours.

10. 2. 6 Effect of Osmolality of Dissolution Medium

In order to understand mechanism of drug release from above two treated coated tablets, the study of drug release in glucose solutions with different osmolalities was undertaken and compared with the drug release in deionized water. The determination of osmotic pressure by using freezing point-depression osmometer had been also reported by Herbig et al. (1995).

An enhancement of osmolality of glucose solution markedly retarded drug release and provided the longer lag time too. The lag time of later type coated tablet was longer than in the first case as presented in Figures *163* and *164*. All drug releases in glucose solutions were extensively slower and longer than those in deionized water.

The solubilities of propranolol HCl in different dissolution fluids, and pH's, viscosities and osmotic pressures of different dissolution fluids are presented in Table *15*. The solubility of this medicament in deionized water was greater than that in HCl buffer pH 1.2 and phosphate buffer pH 6.8 respectively. The more obviously decrease in solubility was observed as the molality of glucose solution was increased. The pH values of glucose solutions were nearly to 7.00, while that of

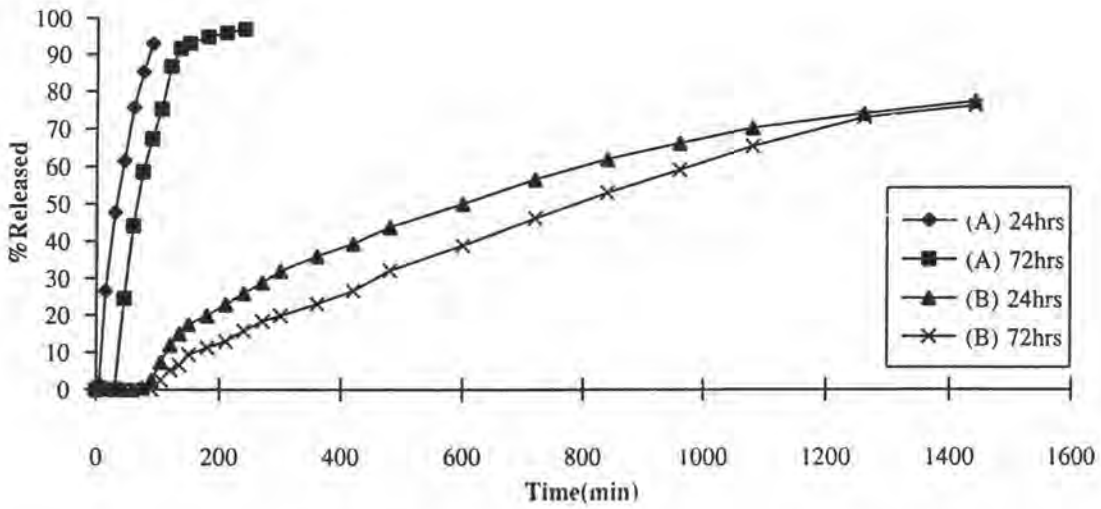


Figure 160 The dissolution profiles of propranolol HCl from tablet coated with chitosan acetate film containing magnesium stearate at concentration of 45 % and propylene glycol at concentration of 30 % w/w at coating evel of 15 % w/w of polymer after moist heat treatment at :(A) 45°C and (B) 60°C for 24 and 72 hrs in pH change system (n=3).

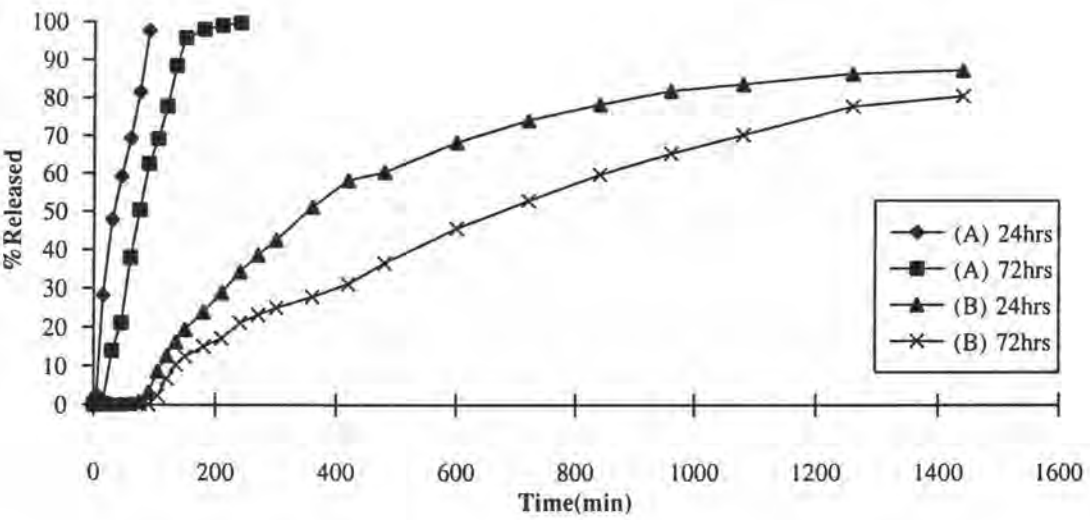


Figure 161 The dissolution profiles of propranolol HCl from tablet coated with chitosan acetate film containing magnesium stearate at concentration of 45 % and diethyl phthalate at concentration of 15 % w/w at coating level of 15 % w/w of polymer after moist heat treatment at : (A) 45°C and (B) 60°C for 24 and 72 hrs in pH change system (n=3).

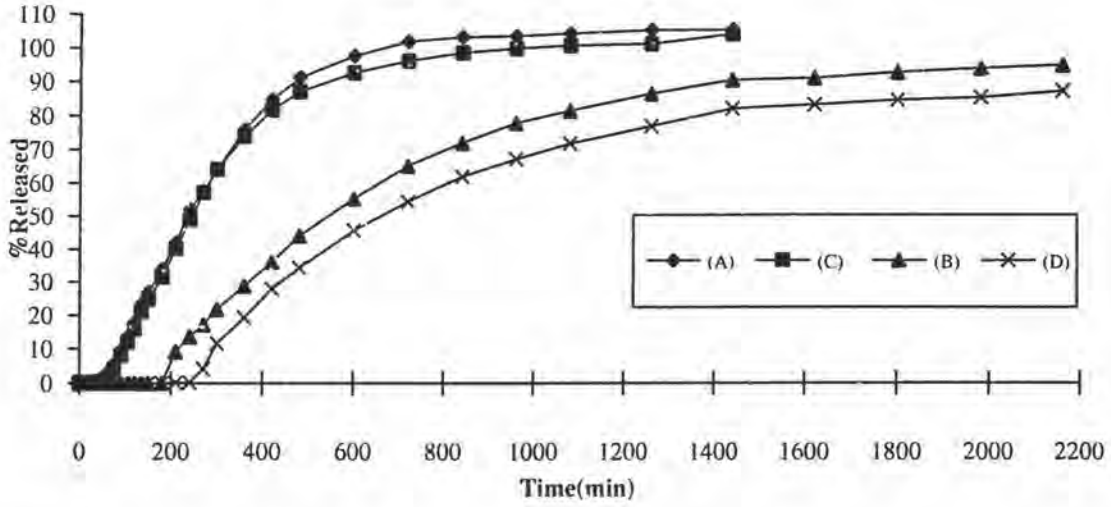


Figure 162 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing: magnesium stearate at concentration of 45% w/w after moist heat treatment at 60°C for 48 hrs. in: (A) HCl buffer pH 1.2 and (B) phosphate buffer pH 6.8 , and containing magnesium stearate and castor oil at concentration of 45 and 15 % w/w respectively after moist heat treatment at 60°C for 24 hrs. in :(C) HCl buffer pH 1.2 and (D) phosphate buffer pH 6.8 (n=3).

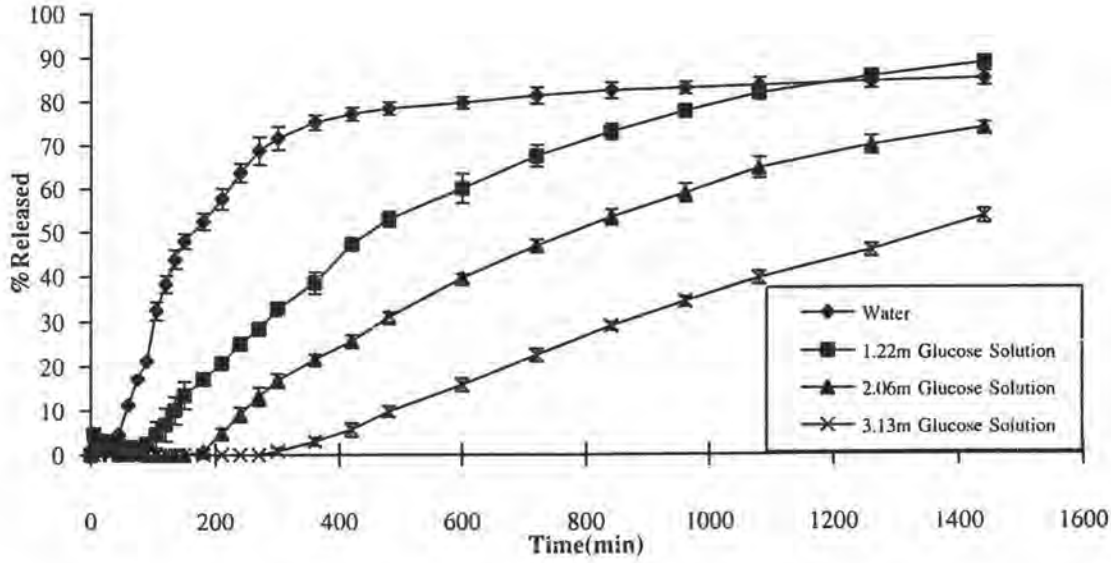


Figure 163 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate at concentration of 45 % w/w of polymer at coating level 15 % w/w of polymer after moist heat treatment at 60°C for 48 hrs in deionized water and glucose solutions with different osmolality (n=3).

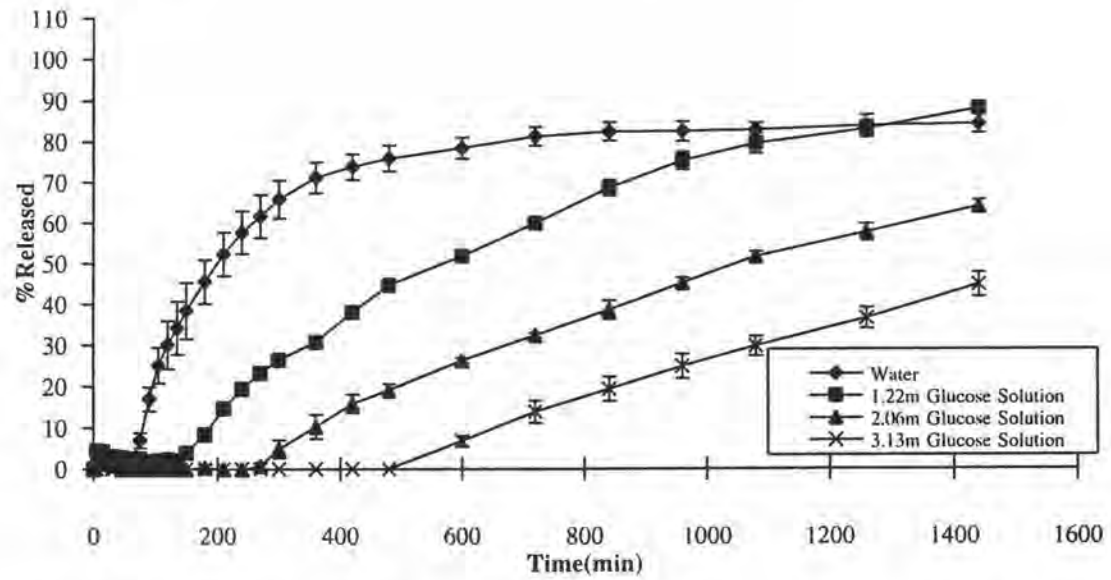


Figure 164 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate and castor oil at concentration of 45 and 15 % w/w of polymer at coating level 15 % w/w of polymer after moist heat treatment at 60°C for 24 hrs in deionized water and glucose solutions with different osmolality (n=3).

Table 15 Solubility, pH, viscosity, and osmotic pressure of different dissolution fluids and osmotic pressure of saturated component of core tablet and osmotic pressure difference of these dissolution fluids and saturated component of core tablet.

Dissolution fluid	Solubility (mg/ml)	pH	Viscosity (cps)	Osmotic Pressure (atm)	Osmotic Pressure difference (atm)
Deionized Water	272.73±1.06	6.22±0.05	1.31±0.07	0.13±0.03	88.95
HCl Solution pH 1.2	224.40±0.80	1.20±0.00	1.27±0.07	5.57±0.00	83.51
Phosphate Buffer pH 6.8	198.11±4.68	6.80±0.00	1.23±0.12	8.35±0.05	80.73
1.22 m Glucose	143.86±1.38	7.09±0.03	1.76±0.07	28.93±0.14	60.15
2.06 m Glucose	88.18±0.27	7.04±0.01	2.17±0.07	43.27±0.26	45.81
3.13 m Glucose	49.69±0.16	6.89±0.01	3.23±0.08	64.82±0.64	24.26
Saturated Core Component				89.08±0.00	0.00

deionized water was 6.22±0.05. The viscosity of dissolution fluids was quite low, nevertheless an increased molality of glucose solutions slightly enhanced the viscosity. Due to these dissolution media differing in osmotic pressure, thus there was an osmotic difference between the dissolution fluids and saturated component of core tablet. Osmotic pressure difference between saturated core component and deionized water was highest and greater than that between saturated core component, and acidic and basic dissolution fluids respectively as shown in Table *15*. Additionally, an increased molality of glucose solutions minimized the osmotic pressure difference.

10. 2. 7 Effect of Hydrophilic Substance Added in Film Coat

The obtained treated coated tablets always exhibited the long lag time and the drug liberation did not completely deplete from device. In order to minimize these unsatisfactory characteristics this study adjusted the composition of the chitosan acetate film by addition of some hydrophilic substances, urea and HPMC, at different concentration.

The dissolution characteristics of propranolol HCl from these freshly prepared coated tablets are presented in Figure *165*. The faster drug release in pH 1.2 buffer was found as the amount of urea in CA M45 Cas15 film was increased. Comparison at the same concentration, loading with HPMC at 45% in this film coat could extend the drug release greater than loading with urea. An increase in coating level of tablet coated with CA M45 Cas15 U5 film could prolong the drug release as illustrated in Figure *166*. The more extended release of coated tablets was observed when using pH change system as illustrated in Figure *167*. The study of drug release with pH change method of freshly prepared tablets coated with chitosan acetate film incorporated with magnesium stearate and adding castor oil or triacetin demonstrated that the release was rather prolonged as shown in Figure *167*. The degree of retardation of drug release promoted by castor oil was greater than triacetin. The drug release from tablets coated with film containing urea 5% was faster than that of tablets coated with film containing HPMC or film without urea. The tablets coated with film containing urea or HPMC could liberate the drug nearly to 100%. whereas those which were without hydrophilic matter released the drug nearly to 80% at 12 hours.

Incorporation of urea at 15, 30 and 45% or HPMC at 45% could shorten the lag time of drug release of these coated tablets after moist heat treatment and promoted the drug release up to 100%, but the release rate was also enhanced as presented in Figure *168*. To reduce the release rate the few amount of urea at concentration of 5% was employed. Coated tablet prepared with this composition could control drug liberation up to nearly 100 % and shorten the lag time to about 60 minutes. The effect of pH of dissolution medium on drug release was also investigated (Figure *169*) and the result agreed well with those of previous studies, except that the drug release from this latter coated tablets after treatment was faster. In deionized water, the drug liberation could be nearly to 100% and reached plateau stage at about 8 hours and the liberation was faster than the previous treated coated tablets that were without addition of hydrophilic substance (Figure *170*).

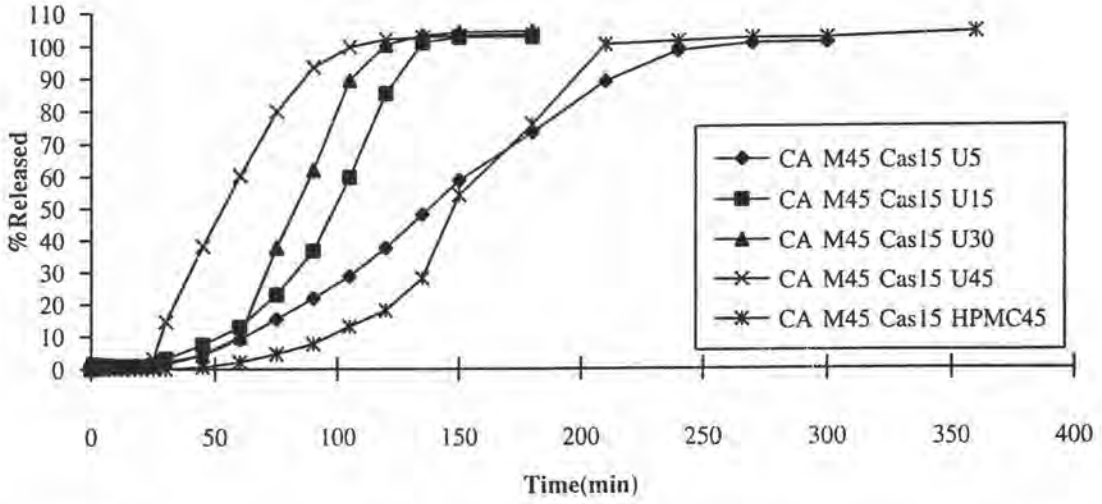


Figure 165 The dissolution profiles of propranolol HCl of freshly prepared tablets coated with chitosan acetate film containing magnesium stearate 45%, castor oil 15% and hydrophilic additive at coating level of 15 % w/w of polymer in HCl buffer pH 1.2 (n=6).

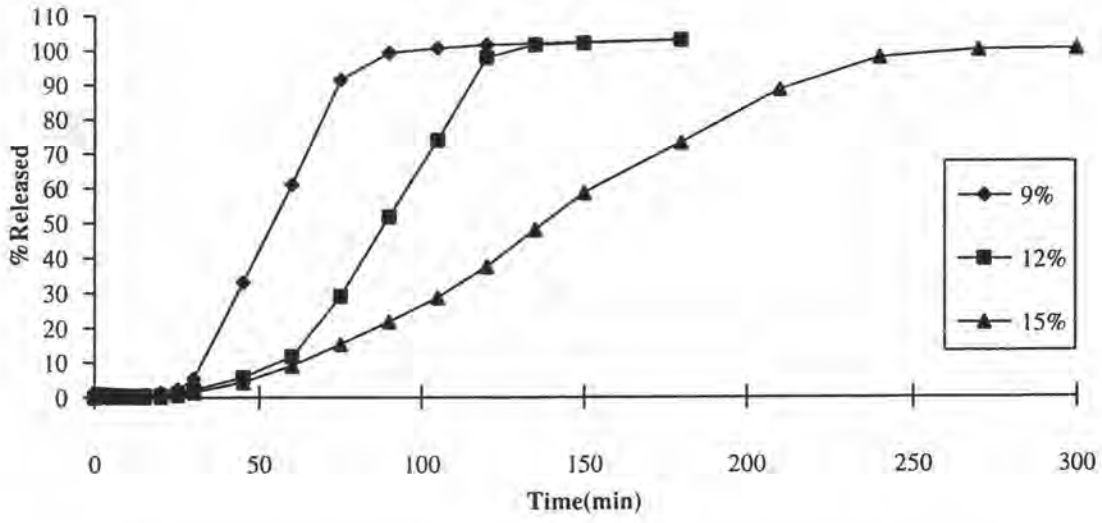


Figure 166 The dissolution profiles of propranolol HCl of freshly prepared tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea 45, 15 and 5 %w/w respectively at different coating level in HCl buffer pH 1.2 (n=6).

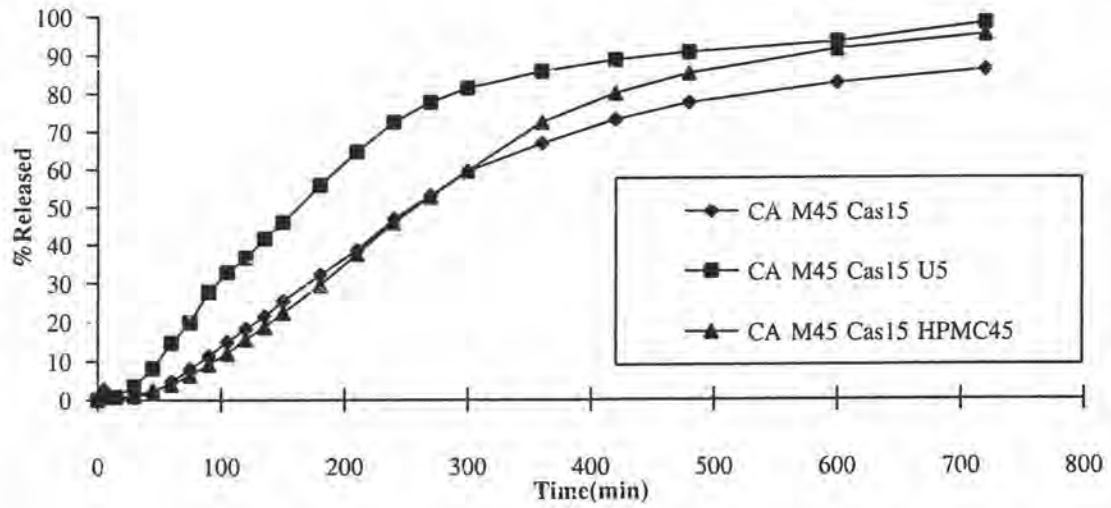


Figure 167 The dissolution profiles from propranolol HCl of freshly prepared tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15 % w/w with and without urea or HPMC at coating level 15% w/w of polymer in pH change system (n=6).

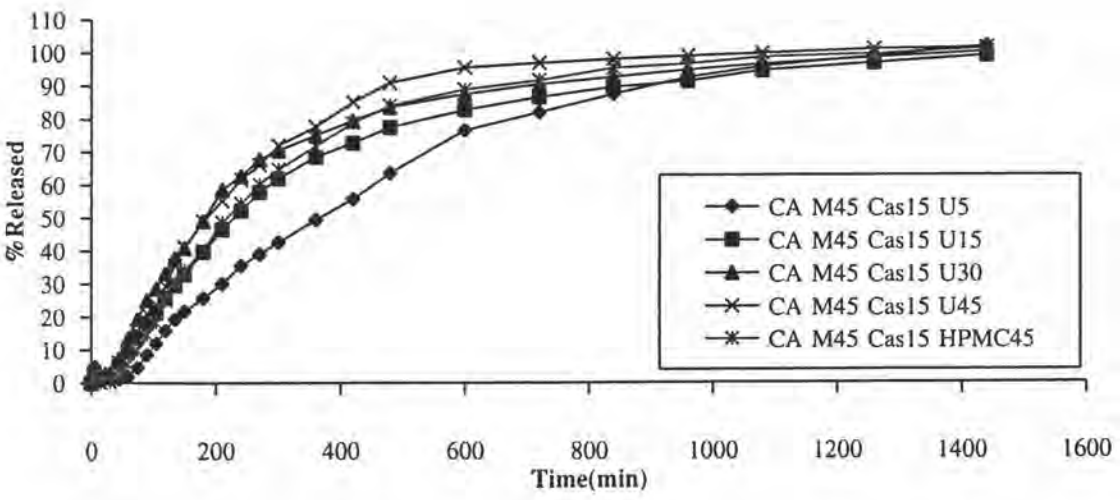


Figure 168 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% and urea 5, 15, 30 and 45% or HPMC 45% w/w of polymer at coating level 15% w/w of polymer after moist heat treatment at 60°C for 24 hrs in pH change system

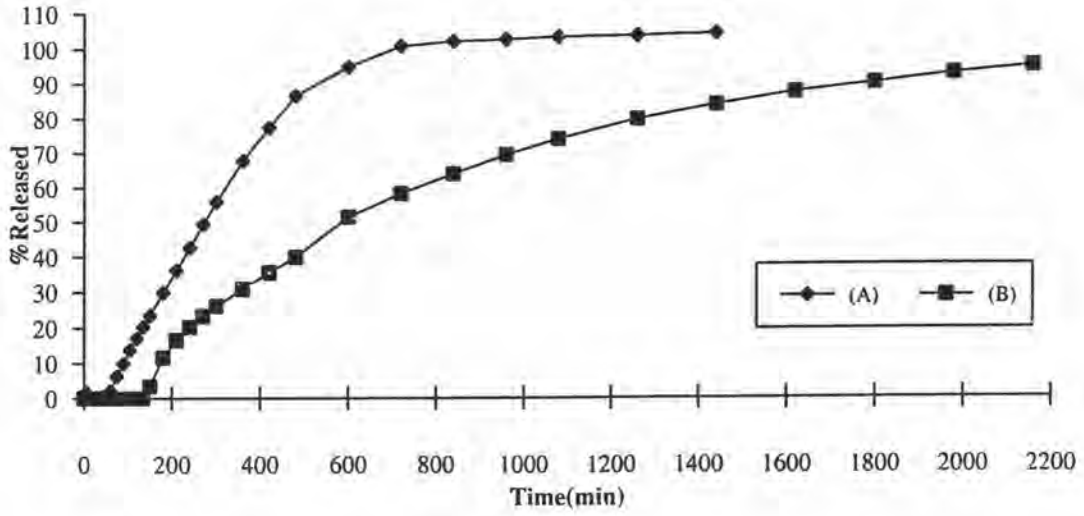


Figure 169 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing: magnesium stearate , castor oil and urea at concentration of 45, 15 and 5 % w/w of polymer respectively after moist heat treatment at 60°C for 24 hrs in :(A) HCl buffer pH 1.2 and (B) phosphate buffer pH 6.8(n=6).

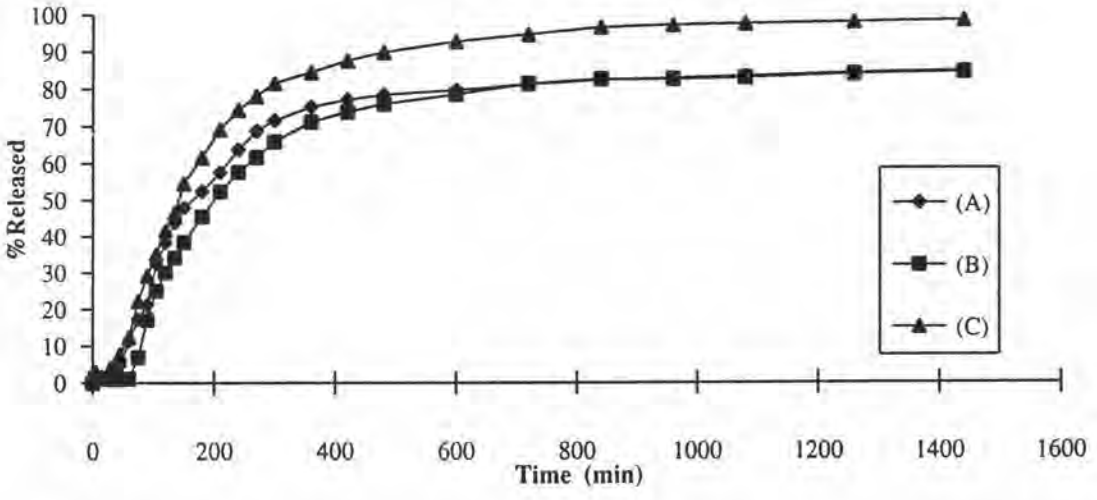


Figure 170 The dissolution profiles of propranolol HCl from tablets coated with (A) CA M45 after moist heat treatment at 60°C for 48 hrs (B) CA M45 Cas15 after moist heat treatment at 60°C for 24 hrs and (C) CA M45 Cas15 U5 after moist heat treatmentat 60°C for 24 hrs at coating level of 15%w/w of polymer in deionized water (n=3).

The effect of coating level on drug release from treated coated tablets was investigated with pH change method. An increase in coating level exhibited a tendency to prolong drug release as presented in Figure *171*.

10. 2. 8 Effect of Moisture Content During Heat Treatment

Moisture content during moist heat treatment affected the drug release of the treated coated tablet (using chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45,15 and 5% w/w of polymer respectively at coating level 15% w/w based on chitosan). The drug release from coated tablet treated at 60°c and under atmosphere of 95% RH was more slower than that using 80 % RH and 75 % RH respectively as shown in Figure *172*. Treatment at 0% RH 60°C exhibited the prolongation of drug release which the release rate was higher than that after treatment at 75, 80 and 95 % RH and also slightly faster than that of freshly prepared.

10. 2. 9 Comparison The Release Profile of Treated Coated Tablet and Commercial Product

The comparison between the drug release profile of prepared coated tablet and commercial product is depicted in Figure. *173*. The drug release of both preparations conformed the criteria of drug release at each time interval as remarked by USP XXIII. The extended drug release for 24 hours could be attained. The release profile of prepared coated tablet exhibited the lag time whereas no this characteristic was appeared in release profile of commercial product. The another distinctive characteristic was that the prepared coated tablet could liberate the encapsulated drug nearly to 100%, while commercial product liberated the drug only about 80% at 24 hours.

10. 2. 10 Effect of Ageing

The drug release profiles of CA M45 Cas15 coated tablets after kept in sealed amble bottle at 45°C in 75%RH atmosphere for one month and after kept at room temperature for one year compared to that of freshly prepared are displayed in Figure *174*. The aged coated tablets exhibited slightly faster drug release compared to that of freshly prepared. The 24 hours. moist heat treated CA M45 Cas15 coated tablets after kept in sealed amble bottle at 45°C in 75%RH atmosphere for one month exhibited slower drug release than that of freshly prepared and that of after kept at room temperature for one year as shown in Figure *175* . The drug released from 24 hours moist heat treated CA M45 Cas15 U5 coated tablets after kept in sealed amble bottle at 45 °C in 75%RH atmosphere for one year was slightly faster than that of freshly prepared as displayed in Figure *176*. All of these coated tablets had the drug dissolved in pH change system at each time interval conformed the monograph of USPXXIII.

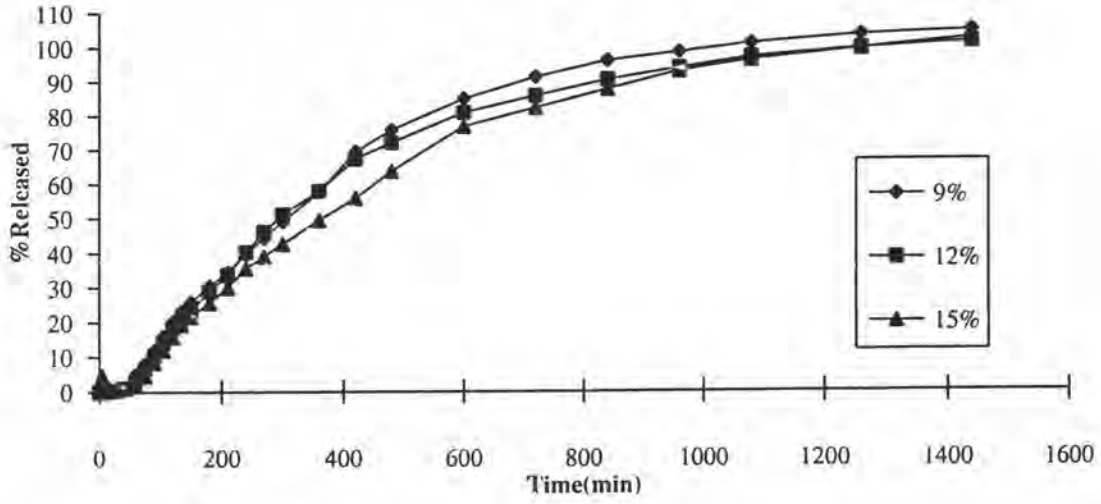


Figure 171 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration 45, 15 and 5% w/w of polymer after moist heat treatment at 60°C for 24 hrs in pH change system (n=3).

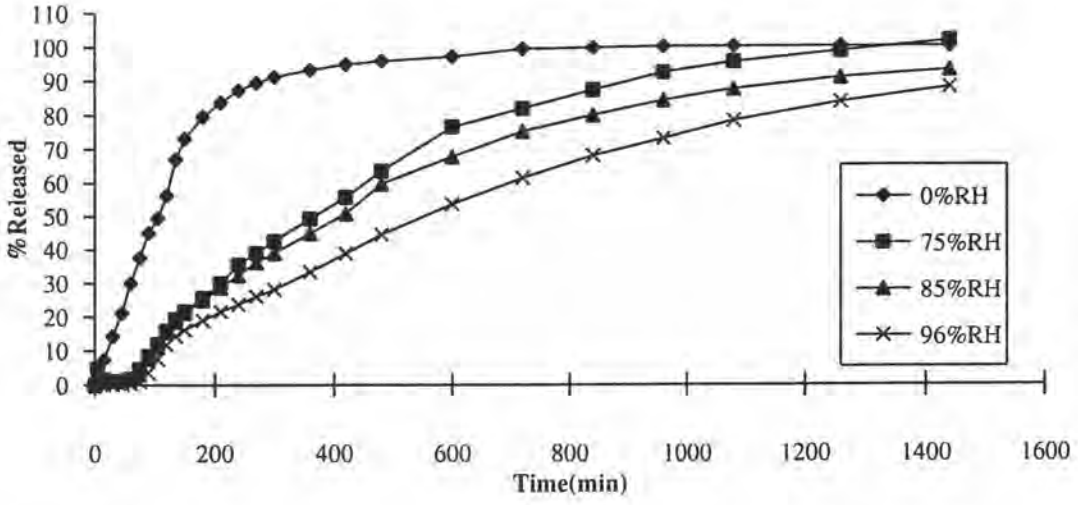


Figure 172 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate , castor oil and urea at concentration of 45, 15 and 5 % w/w of polymer at coating level 15% w/w of polymer after moist heat treatment at 60°C in 0, 75, 85 and 96 %RH in pH change system(n=6).

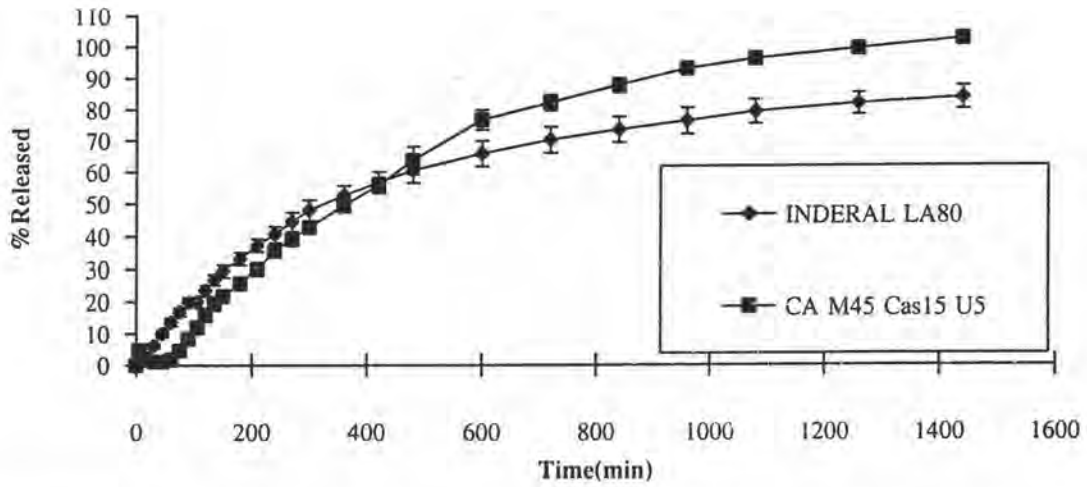


Figure 173 The dissolution profiles of propranolol HCl of commercial product (Inderal LA80) and tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5% w/w respectively at coating level 15% w/w of polymer after moist heat treatment at 60°C for 24 hrs in pH change system (n=6).

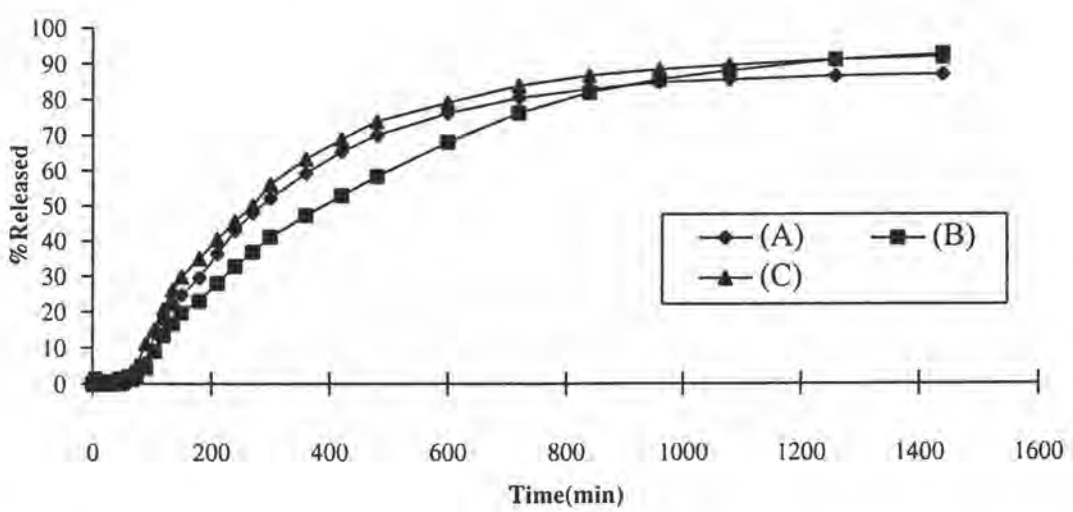


Figure 174 The dissolution profiles of propranolol HCl from tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% at coating level of 15% w/w of polymer after moist heat treatment at 60°C for 24 hrs (A) after treatment (B) after kept in bottle at 45°C 75%RH for 1 month and (C) after kept at room temperature for 1 year (n=6).

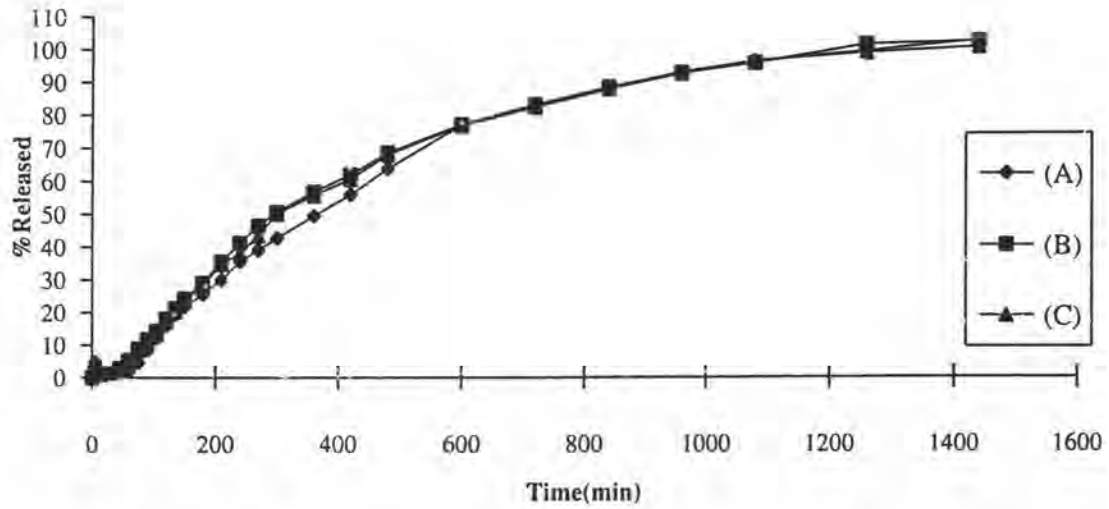


Figure 175 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate , castor oil and urea at concentration of 45, 15 and 5 % w/w of polymer at coating level 15% w/w of polymer after moist heat treatment at 60°C 75 %RH in pH change system: (A) after treatment; (B) after kept in bottle and kept at 60°C 75 %RH for one month and (C) after kept at room temperature for one year (n=6).

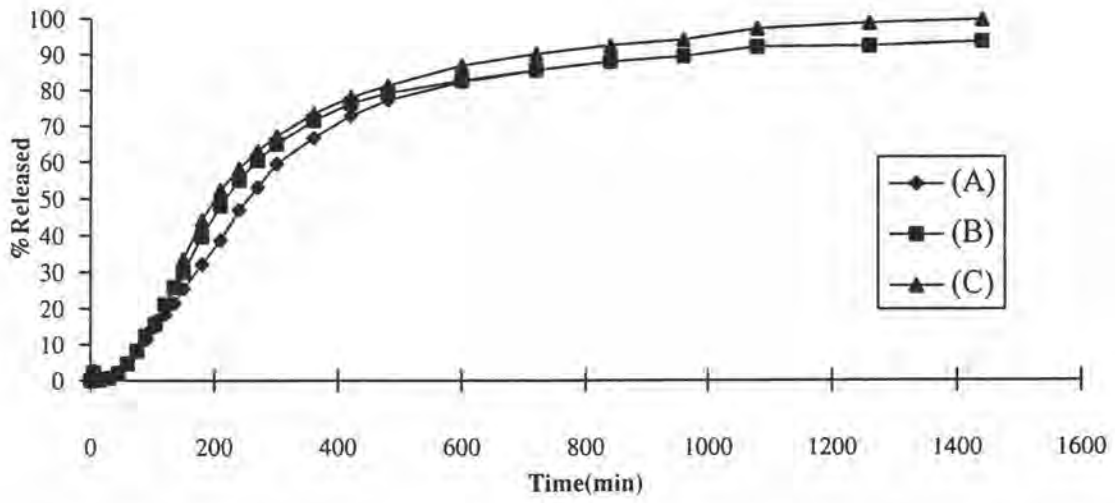


Figure 176 The dissolution profiles of propranolol HCl of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% w/w of polymer: (A) freshly prepared (B) after kept in bottle at 45°C 75%RH for one month and (C) after kept at room temperature for one year in pH change system (n=6).

10. 2. 11 % Weight Increase During Dissolution Test

It was found that the weight gain of coated tablet was clearly altered during dissolution experiment. An increased weight of freshly prepared coated tablets in acidic medium was very high as shown in Figure *177* (Table *346* and *347*, Appendix C) and was markedly greater than that of moist heat treated coated tablet as shown in Figures *178* and *179* (Tables 346 and 347, Appendix C)

Maximum % weight gain of freshly prepared in acidic medium of CA M45 CAS15 and CA M45 CAS15 U5 was 372.0±14.3 and 277.7±16.9% at 3 hours and 0.5 hours respectively. Whereas maximum % weight gain of in acidic medium and pH change system of coated tablets after 24 hours moist heat treatment of CA M45 CAS15 was 68.7±3.6 and 74.4±2.9, and that of CA M45 CAS 15 U5 was 53.7±5.4 and 50.3±2.1% and all of them occurred at 90 minutes. In basic medium, the maximum % weight gain was found at 6 and 3 hours for the first and later case at 50.4±2.2 and 24.3±2.8 % respectively. Maximum % weight gain of the latter case in three dissolution systems was less than that of first case.

After % weight gain reached to the maximum, it gradually decreased to the plateau stage, with the exception in pH change system. In this case, it was found a rapidly decreased % weight gain after changing pH from 1.2 to 6.8.

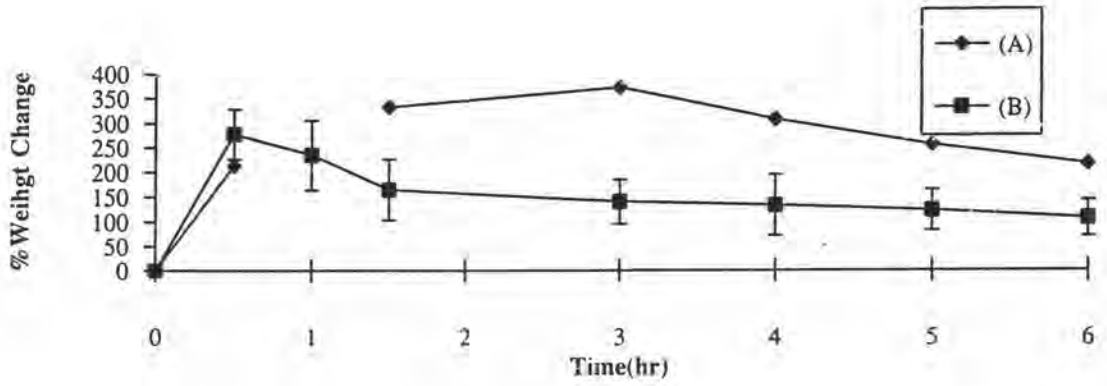


Figure 177 The weight change during dissolution test of freshly prepared tablets coated with : (A) chitosan acetate film containing magesium stearate and castor oil 45 and 15% w/w respectively and (B) chitosan acetate film containing magesium stearate, castor oil and urea at concentration 45, 15 and 5 % w/w at coating level of 15 % w/w of polymer in HCl buffer pH 1.2 (n=3).

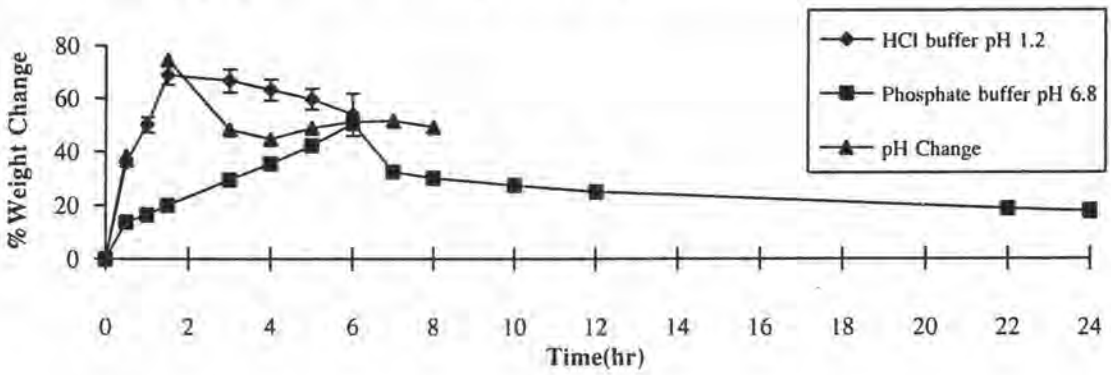


Figure 178 The weight change during dissolution test of tablets coated with chitosan acetate film containing magesium stearate and castor oil 45 and 15%w/w respectively at coating level of 15 % w/w of polymer after moist heat treatment at 60oC for 24 hrs in HCl buffer pH 1.2 , phosphate buffer pH 6.8 and pH change system(n=3).

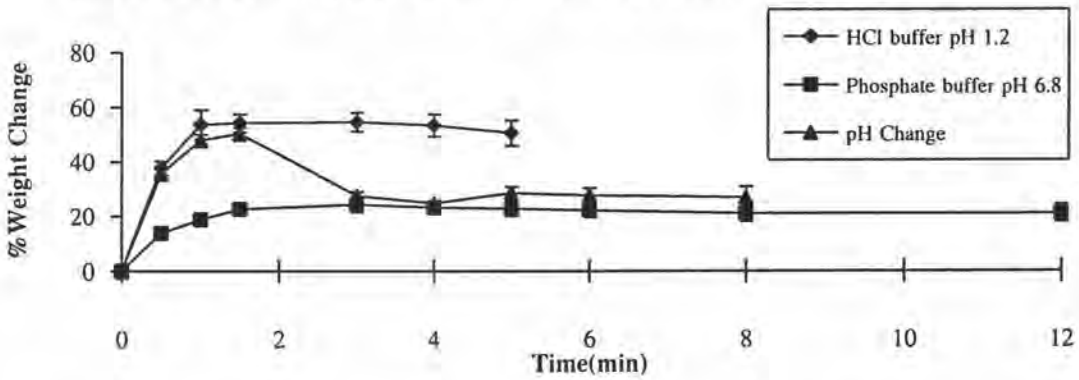


Figure 179 The weight change during dissolution test of tablets coated with chitosan acetate film containing magesium stearate, castor oil and urea 45 , 15 and 5 %w/w respectively at coating level of 15 % w/w of polymer after moist heat treatment at 60oC for 24 hrs in HCl buffer pH 1.2 , phosphate buffer pH 6.8 and pH change system (n=3).

11. Surface Topography

Scanning electron micrographs showing the surface topography of core and coated tablets are illustrated in Figures *180-188* and *190-197*. The rather rough surface of core tablet containing the compressed structure of added additives and medicament (40 mg of propranolol HCl) are depicted in Figures *180*A (a, b and c). The photomicrographs of tablets coated with chitosan citrate and chitosan malate at coating level of 6 and 12 % w/w of polymeric salt as presented in Figures *181-182* exhibited rather smooth surface and homogenous film onto core tablet. The chitosan citrate film seemed to be adhered onto core surface more tightly than that of chitosan malate film. The scanning electron micrographs of tablet coated with chitosan citrate at coating level of 3% w/w of polymer as shown in Figures *183*A (a, b and c) exhibited the rather smooth surface and some air bubble appeared within film texture. An incorporation of propylene glycol at concentration 25 and 45 % provided the smooth and no air bubble appeared within film texture after coating onto core tablet at coating level of 3% w/w of polymer as shown in Figures *183*B (a,b and c) and *184*A (a, b and c). Chitosan citrate film plasticized with propylene glycol and colored with brilliant blue or green FS remained to exhibit the rather smooth surface as illustrated in Figure *184*B and *185*A (a, b and c). The more increase in amount of talcum in plasticized and colored chitosan citrate film coated tablet, the higher were the amount of irregular shape particles dispersed in film texture and the rather rough surface were appeared as shown in Figures *185*B-*186*B. The talcum particles dispersed in cross-sectioned area were irregular and plate-like shape. This evidence was also seen in case of using titanium dioxide but the dispersed particles were noticeably smaller and in spherical shape as shown in Figures *187*A-*188*A. By a visual observation, all chitosan citrate and malate films were closely and tightly adhered to the surface of core tablet. The irregular shape and plate like particles of talcum are shown in Figures *189*A (a and b) whereas the very small spherical particles of titanium dioxide are depicted in Figures *189*B (a and b). Particle size of titanium dioxide was much smaller than that of talcum.

Scanning electron micrographs showing the surface topography of core tablet containing propranolol HCl 80 mg and other additives are illustrated in Figures *190*A (a, b and c). The rather rough surface of core tablet containing the compressed structure of drug and added additives was depicted. Scanning electron micrographs of chitosan acetate film onto propranolol HCl tablet are shown on Figures *190*B (a,b and c). The coated chitosan acetate film was quite smooth and homogeneous. The cross-sectioned texture of the coat was dense, smooth and homogeneous, and the micrograph of cross-sectioned area showed that the film was rather loosely adhered to the tablet surface. There were void spaces as boundary layer between core surface and film coat. The scanning electron micrographs showing the surface topography of tablets coated with chitosan acetate containing different additives are displayed in Figures *191-197*. The chitosan acetate film incorporated with magnesium stearate onto core tablet was rather rugged as depicted in Figures *191*A (a and b) and had many small void spaces within the cross-section area of film texture as illustrated in Figure *191*A (c). Addition of castor oil could minimize the defects since the surface was quite smooth and the amount of little void spaces was reduced as shown in Figures *191*B (a,b and c). Moist heat treatment at 60 °C promoted the smoothness of surface, but the void space within film texture was enlarged as presented in Figures *192*A (a, b and c). All these coated films were loosely

adhered to surface of core tablet. After dissolution test with pH change method, the film containing castor oil showed the rough surface, nevertheless the film was still intact as shown in Figures *192*B (a, b and c).

Small crystal like particles and rough surface in chitosan acetate film containing various additives (magnesium stearate, castor oil and urea at concentration of 45, 15 and 45 % w/w respectively) were detected in scanning electron micrographs in Figures *193*A (a, b and c). The more smooth surface was appeared after moisture treatment, but number of crystal like particles in cross-sectioned area markedly increased as shown in Figures *193*A (a, b and c). It was apparent that more swellable surface and large void spaces were detected in case of treated film containing urea at 45 % after dissolution testing with pH change method as shown in Figures *194*A (a, b and c).

The tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5 % w/w of polymer respectively exhibited smooth surface and dense film texture as presented in Figures *194*B (a, b and c). These film characteristic was not markedly changed after moist heat treatment as shown in Figures *195*A (a, b and c). Coated film was loosely adhered to the surface of core tablet. Surface topography of this coated tablet after dissolution test in pH change pH system, HCl buffer pH1.2, in phosphate buffer pH 6.8 at 24 hours are depicted in Figures *195*B and *196*A and *196*B respectively. After dissolution testing with pH change method, swollen surface and large spaces were found as shown in Figures *195*B (a, b and c) but this appearance was less than that of tablet coated with aforementioned film containing urea 45%. In addition, the cross-sectioned area showed many pits in film texture as illustrated in Figure *195*B (c). When using pH 1.2 buffer solution as release medium, more swollen and many large spaces in tested film were found as depicted in Figures *196* A (a, b and c). Meanwhile after dissolution testing at pH 6.8, less swollen film and fiber like sheet dispersed within film were obviously detected as shown in Figures *196*B (a, b and c). The rather smooth surface of abovementioned film coat after moist heat at 60°C at magnification of 3500 was detected in Figure *197*A (b). The swollen film and the presence of many pores on surface at lower and higher magnifications (75x and 3500x) were observed after dissolution in HCl buffer pH 1.2 as depicted in Figures *197*B (a and b). Whereas the less swollen film was detected after dissolution in phosphate buffer pH 6.8 at magnification of 3500 as shown in Figure *197*C (b).

Magnesium stearate used in this study was in irregular shape as depicted in Figures *198*A (a and b). After dispersion in dilute acetic acid, the particles of magnesium stearate were agglomerated and were partly fused together as shown in Figures *198*B (a and b).

12. Physicochemical Properties of Film Coat

12.1 Fourier Transform Infrared (FT-IR) Studies

FT-IR spectra of chitosan citrate plasticized with propylene glycol or colored with brilliant blue are illustrated in Figure *199*. An interaction between chitosan citrate and propylene glycol or brilliant blue was scarce since the prominent peaks of spectra did not shift. FT-IR spectra of talcum, titanium dioxide and brilliant blue are depicted in Figure *200*.

The more incorporation of talc and TiO_2 in chitosan citrate film, the more dominant was the enhancement of peak intensity at 666 cm^{-1} (O-Si-O bend) and 1010 cm^{-1} (Si-O stretch), and 620 cm^{-1} (0-Ti-0 bend) respectively as presented in Figures *201* and *202* respectively. No shift of prominent peaks was appeared, therefore, interaction between chitosan citrate and these pigments was not found. In addition, cast film and film peeled off from coated tablets had the same pattern of IR spectra as presented in Figure *203*.

The IR spectra of chitosan acetate film containing magnesium stearate and other additive (castor oil and urea) peeled off from coated tablets are depicted in Figure *204*.

The more dominant peaks occurred at the wavelength of 2914 and 2850 cm^{-1} in FT-IR spectra of magnesium stearate and stearic acid were the C-H symmetric and asymmetric stretching of hydrocarbon chains in stearic molecule. The peak appeared at 1577 cm^{-1} in FT-IR spectrum of magnesium stearate was the COO^- asymmetric stretching which indicated that the carbonyl group was in an ionized state in forming the magnesium salt of stearic. In other words, this broad band at 1577 cm^{-1} is assigned to the asymmetric metal carboxylate stretching vibration. These peak characteristics of metal stearate were indicated by Antony, Bhattacharya and De (1999). Whereas the C=O stretching of stearic acid was appeared at 1703 cm^{-1}. The broad peak around 3100-3600 cm^{-1} was the peak representing the water crystallization in magnesium stearate which this characteristic was not detected in FT-IR spectrum of stearic acid (Ertel and Carstensen, 1988 a). The small peak at about 1464 cm^{-1} was the CH_2 stretching found both in spectra of magnesium stearate and stearic acid as shown in Figures *204*A and B. The more increase in magnesium stearate loading, the higher was the intensity of this peak. The shoulder C=O stretching peak appeared at 1745.9 cm^{-1} of film containing castor oil (Figure *204*D) came from the carbonyl of esters which were the component of castor oil. Castor oil consisted of triglyceride of fatty acids. These fatty acids are approx. ricinoleic 87%, oleic 7%, linoleic 3%, pamitic 25, stearic 1% and dihydroxystearic trace amounts (Windholz, 1983).

There were the peak shifts to higher wavelengths (from 1655 to 1639 cm^{-1} and 1559 to 1539 cm^{-1}) after incorporation magnesium stearate in chitosan acetate film. The more increase in amount of urea, the broader peak around wavenumber 1550-1750 cm^{-1} was found and was more similar to that of pure urea. However, no much alteration was found in case of low amount of urea (5 and 15 %w/w of chitosan) as shown in Figure *205*.

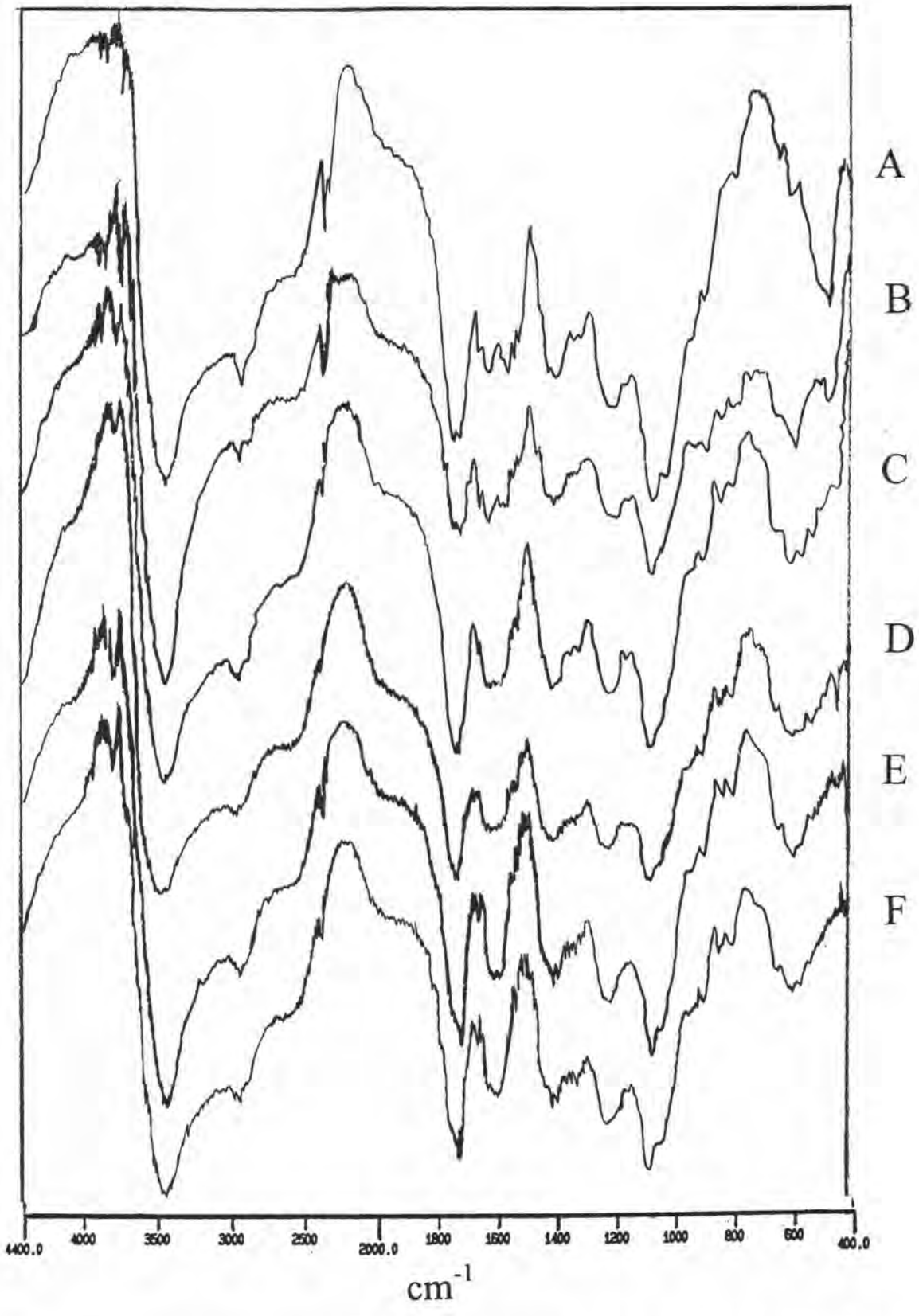


Figure 199 FT-IR spectra of chitosan citrate cast films plasticized with propylene glycol (A) 5% (CC P5); (B) 25% (CC P25); (C) 45% (CC P45); chitosan citrate cast film plasticized with propylene glycol 25% and colored with brilliant blue (D) 0.2% (CC P25 B0.2), (E) 0.5% (CC P25 B0.5) and (F) 1.0% (CC P25 B1).

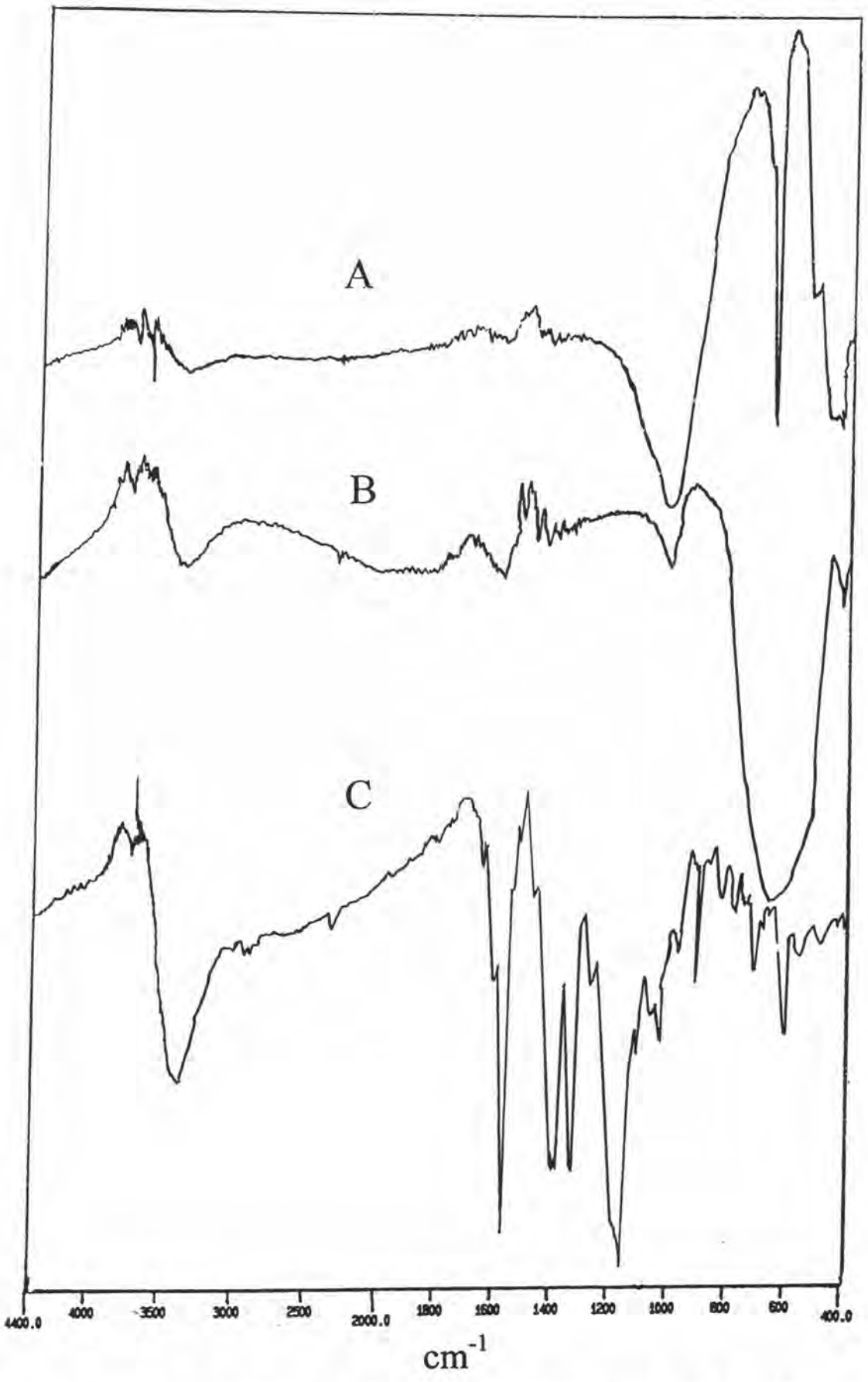


Figure 200 FT-IR spectra of (A) talcum; (B) titanium dioxide and (C) brilliant blue.

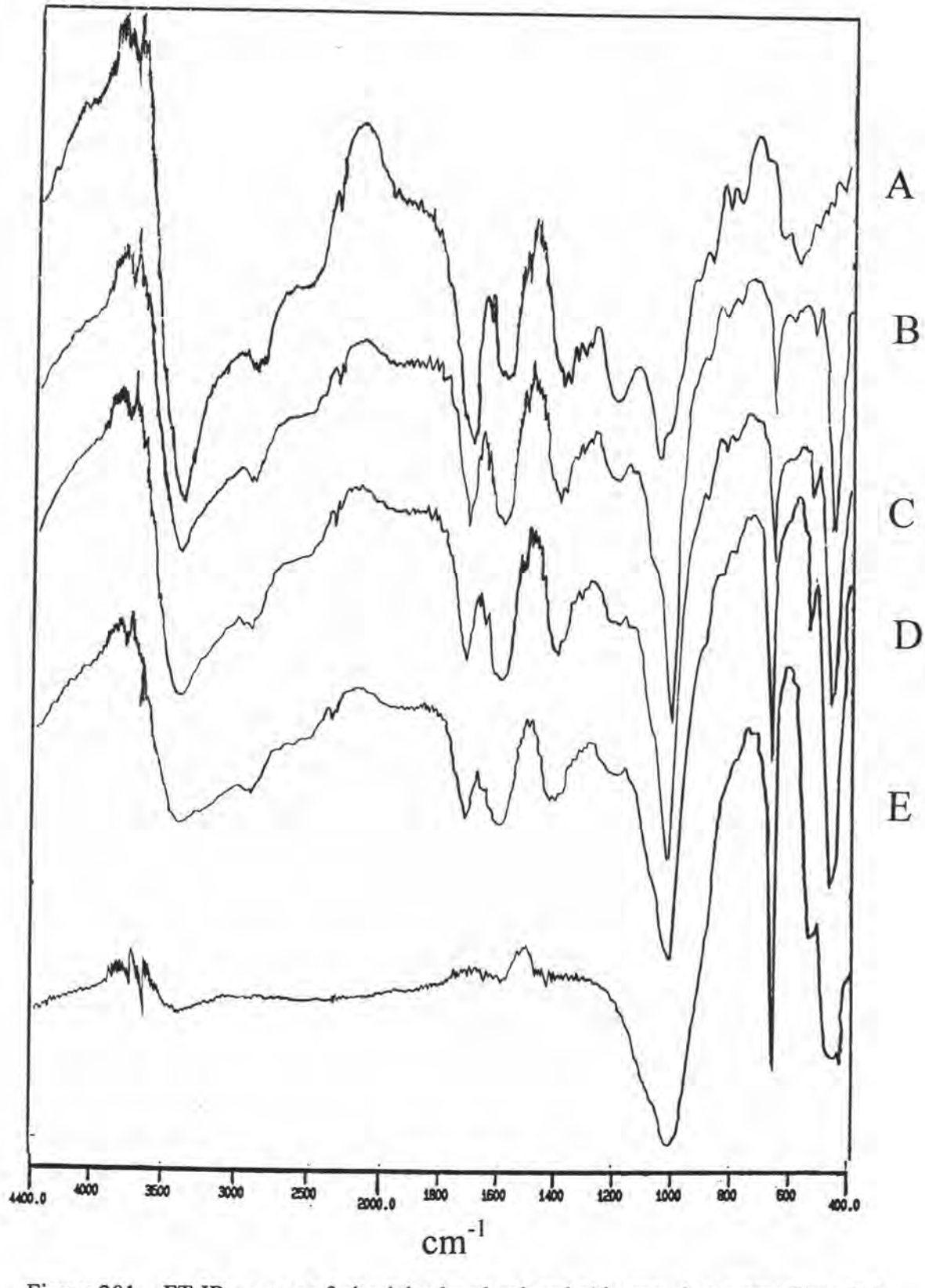


Figure 201 FT-IR spectra of plasticized and colored chitosan citrate cast films (A) unpigmented; pigmented with talcum (B) 15% (CC P25 B0.5 Ta15); (C) 30% (CC P25 B0.5 Ta30); (D) 45% (CC P25 B0.5 Ta45) and talcum.

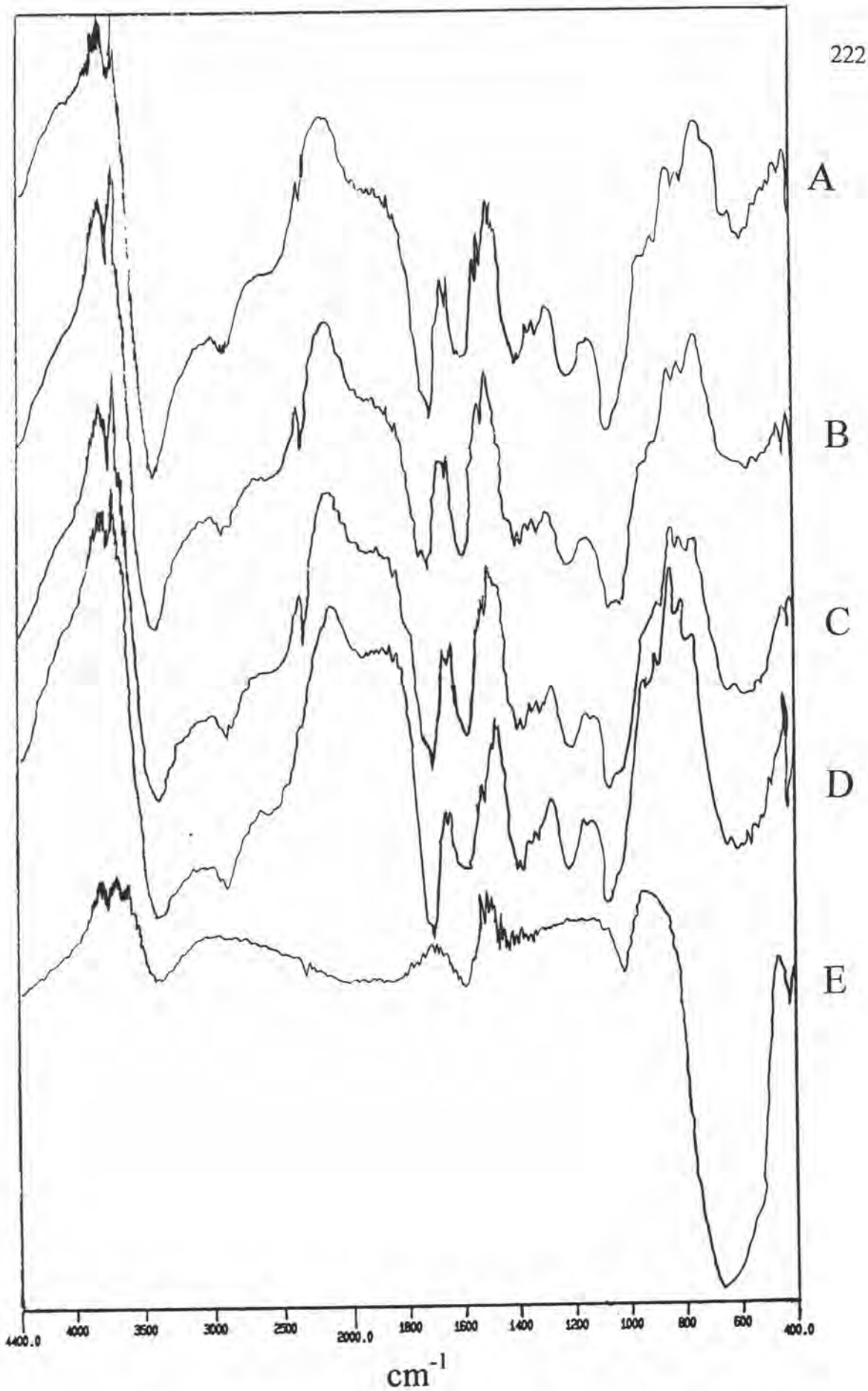


Figure 202 FT-IR spectra of plasticized and colored chitosan citrate cast films (A) unpigmented; pigmented with titanium dioxide (B) 15% (CC P25 B0.5 Ti15); (C) 30% (CC P25 B0.5 Ti30); (D) 45% (CC P25 B0.5 Ti45) and titanium dioxide.

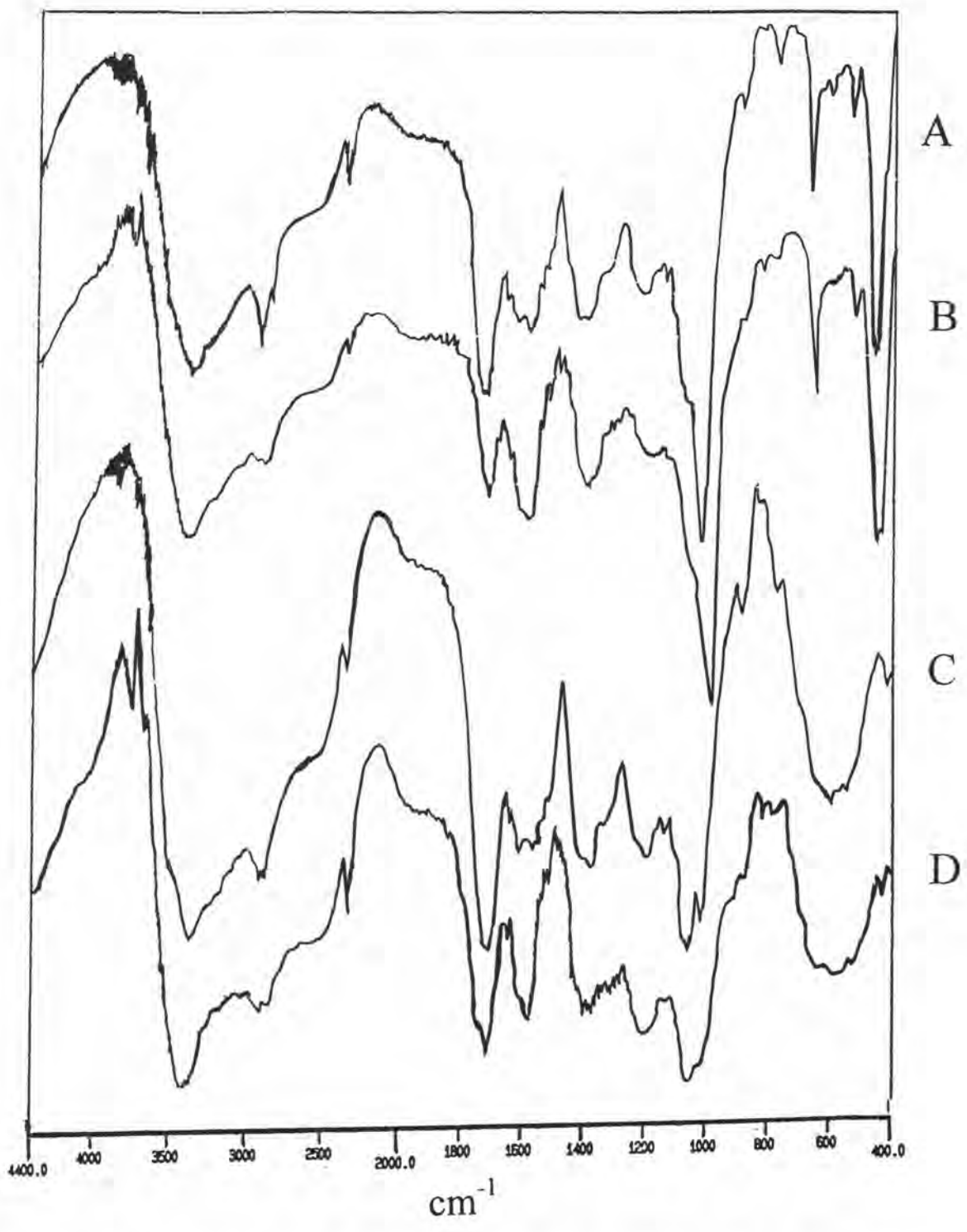


Figure 203 FT-IR spectra of plasticized and colored chitosan citrate cast films pigmented with (A) talcum 30% (CC P25 B0.5 Ta30); (C) titanium dioxide 30% (CC P25 B0.5 Ti30); these films peeled off from coated tablet (B) (CC P25 B0.5 Ta30) and (D) (CC P25 B0.5 Ti30).

The longer duration of moist heat treatment, the sharper of shoulder peak of C=O stretching was found in chitosan film containing magnesium stearate 45% as depicted in Figure *206*. This evidence was also seen in film containing castor oil or castor oil and urea as shown in Figure *207*. The IR spectra of cast films exhibited the same pattern as those of film peeled off from coated tablets as presented in Figure *208*

FT-IR spectroscopy was also utilized to in-depth clarify the effect of magnesium stearate on chitosan acetate film. It was found that when increasing the incubating temperature up to 52°C, magnesium stearate powder in dilute acetic acid suddenly agglomerated to be larger particles. This evidence was not detected when deionized water was used as immersion fluid.

FT-IR spectra of these obtained magnesium stearate after suspended in deionized water and dilute acetic acid are presented in Figure *209*. No peak shift was appeared in spectra of magnesium stearate dispersed in deionized water at room temperature or at 60°C. Whereas all spectra of magnesium stearate dispersed in dilute acetic acid showed the new dominant peak at about 1703 cm^{-1} and other new peak corresponding to the FT-IR spectrum of stearic acid. This alteration was more evidently occurred when the dispersion in dilute acetic acid incubated at higher temperature. The alteration was greater when using the incubating temperature of 60°C than of 40°C and room temperature respectively.

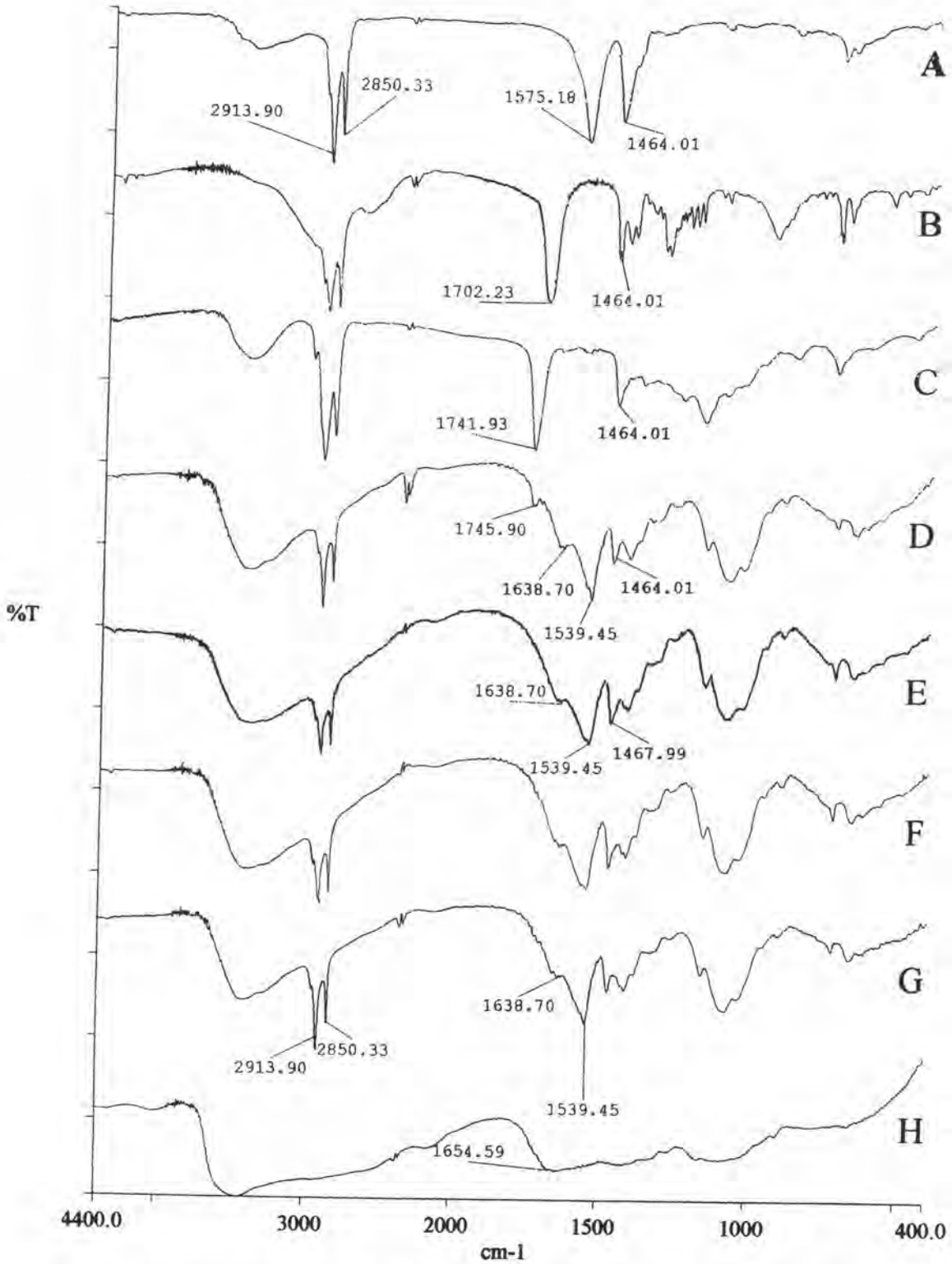


Figure 204 FT-IR spectra of magnesium stearate (A); stearic acid (B); castor oil (C); CA M45 Cas15 (D); CA M75 (E); CA M60 (F); CA M45 (G) and chitosan (H).

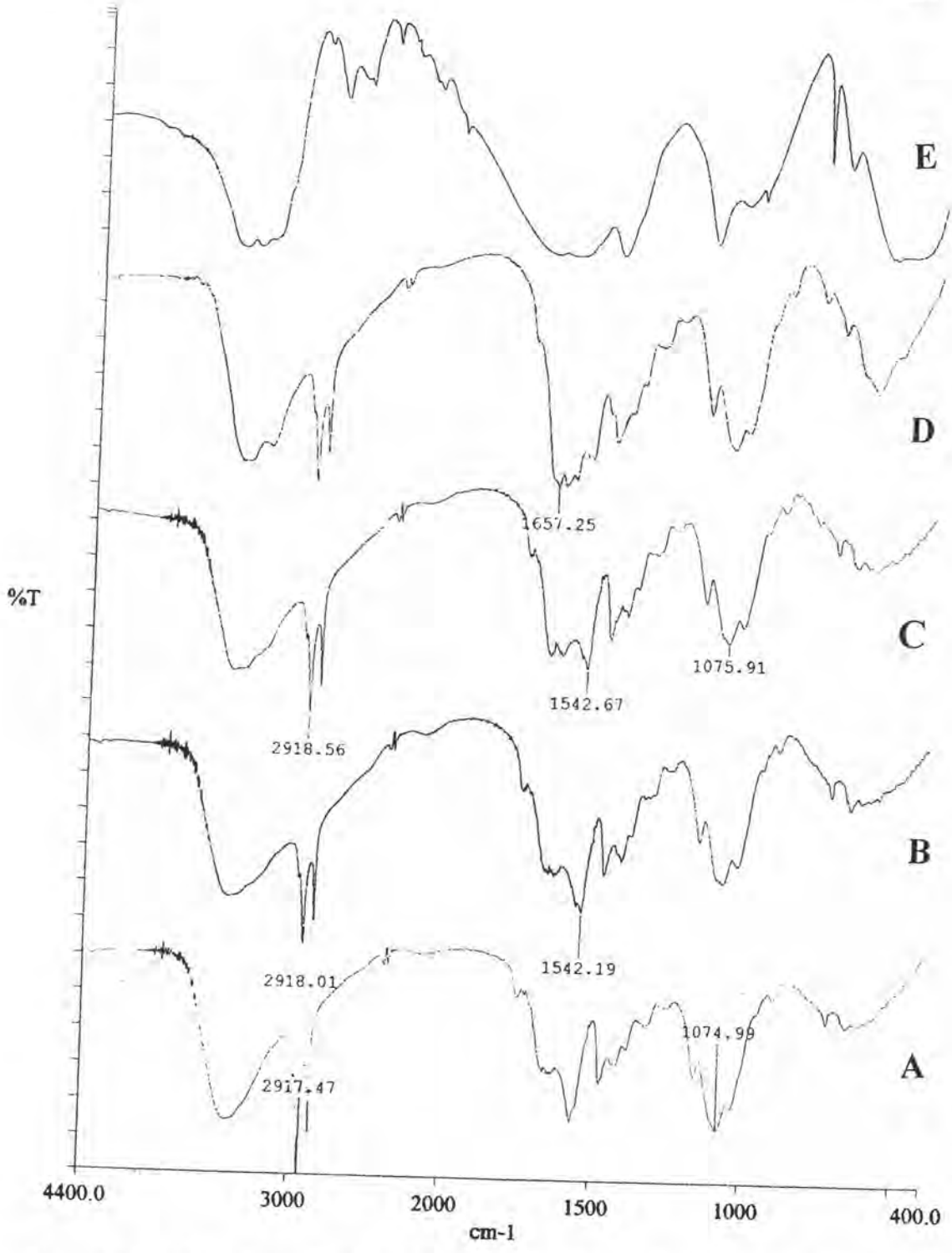


Figure 205 FT-IR spectra of CA M45 Cas15 U5 (A); CA M45 Cas15 U15; (B); CA M45 Cas15 U30 (C); CA M45 Cas15 U45 (D) and urea (E);

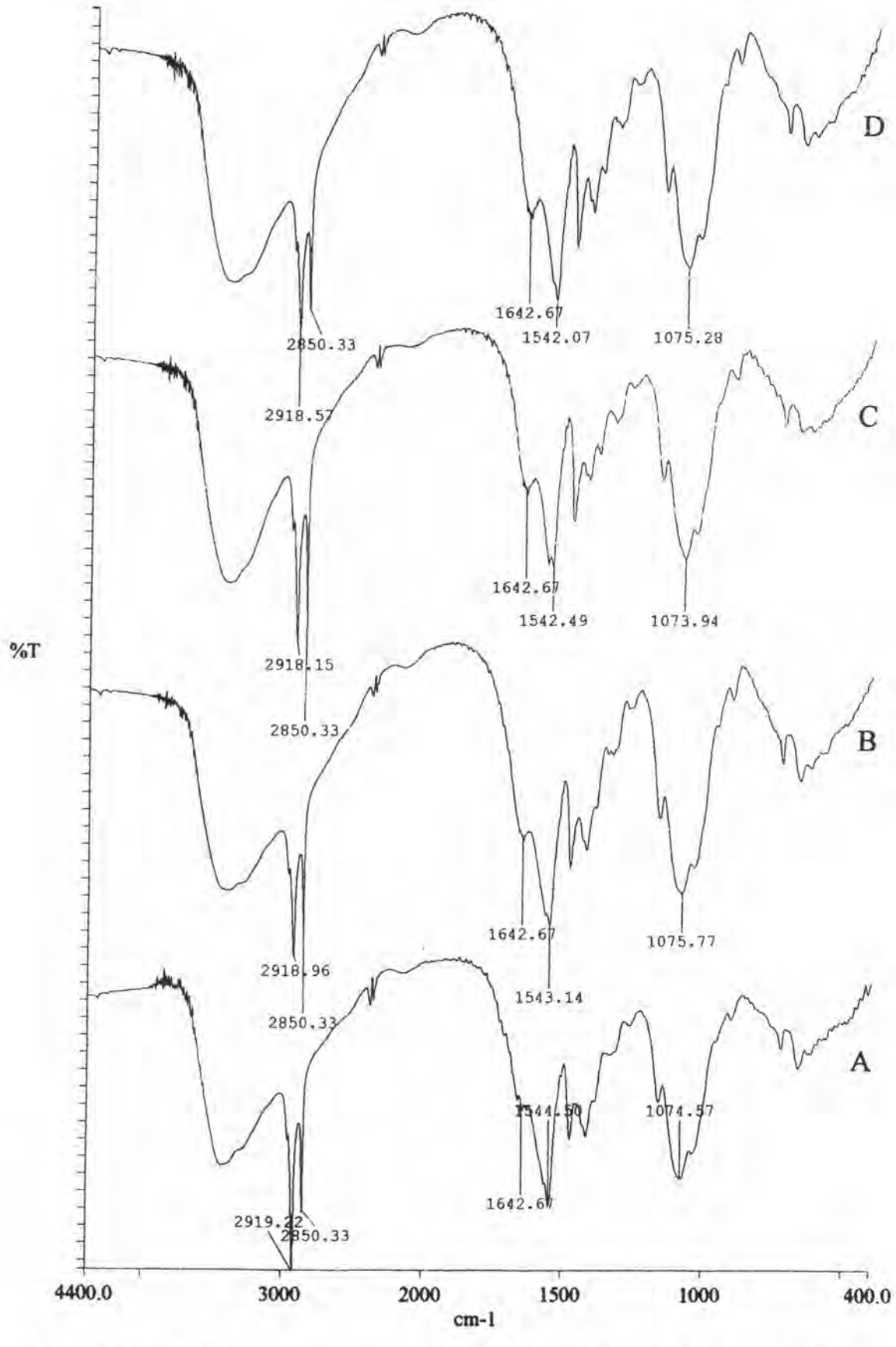


Figure 206 FT-IR spectra of untreated CA M45 (A); CA M45 after moist heat treatment at 60°C for 24 hrs (B); 72 hrs (C) and 120 hrs (D).

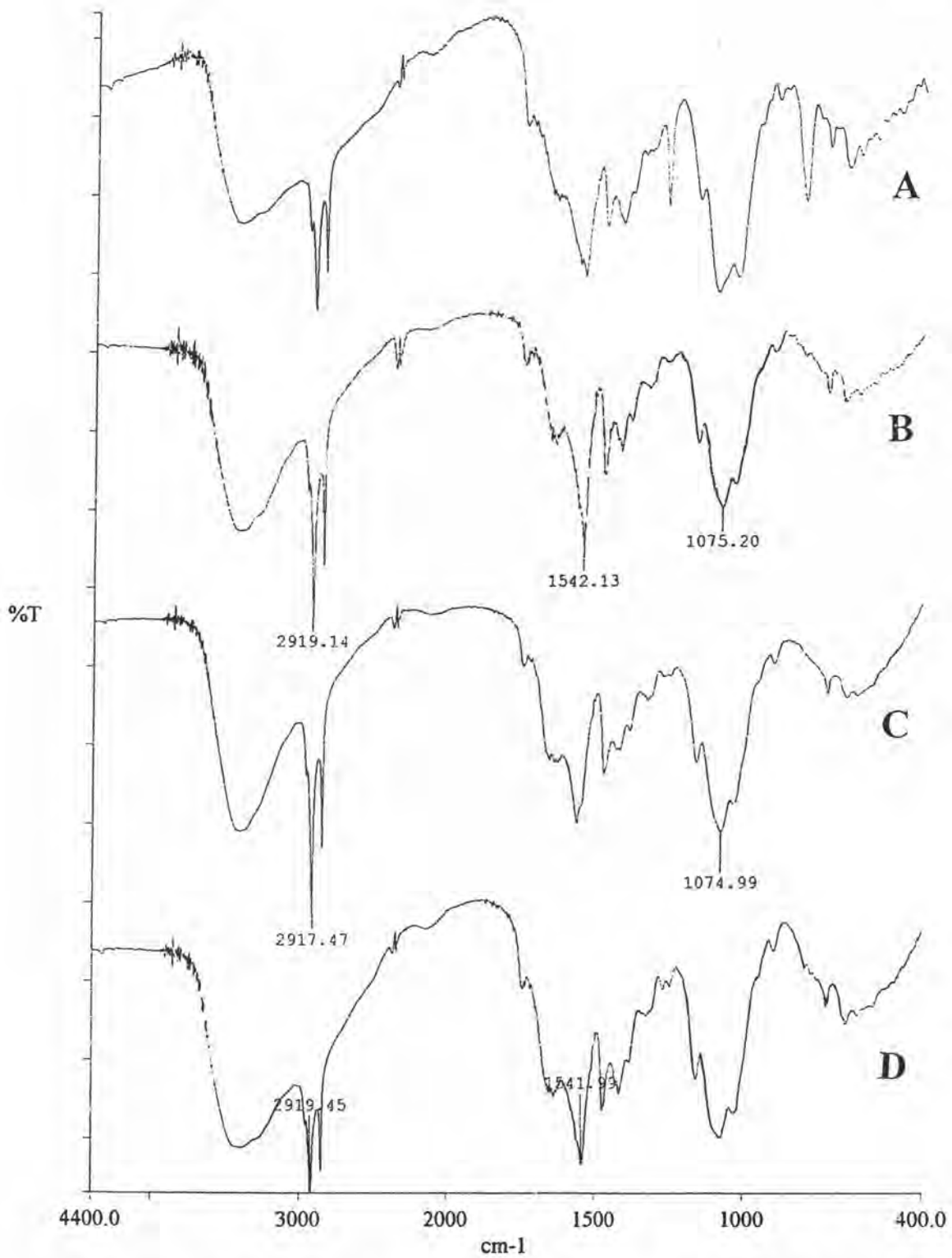


Figure 207 FT-IR spectra of untreated CA M45 Cas15 (A); CA M45 Cas15 after moist heat treatment at 60°C for 24 hrs (B); untreated CA M45 Cas15 U5 (C) and CA M45 Cas15 U5 after moist heat treatment at 60°C for 24 hrs (D).

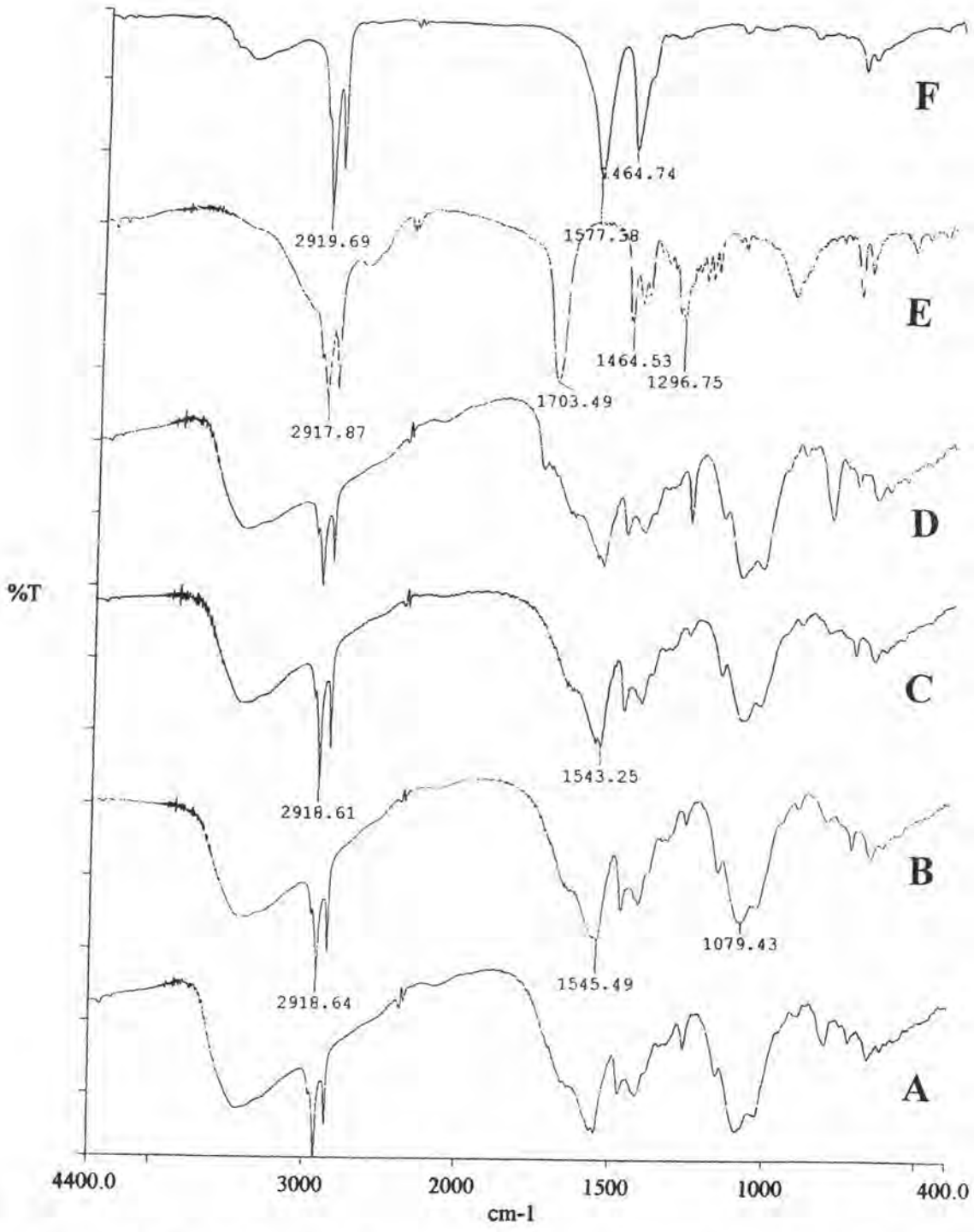


Figure 208 FT-IR spectra of magnesium stearate (A); stearic acid (B); free film of CA M45 Cas15 (C); CA M75 (D); CA M60 (E) and CA M45 (F).

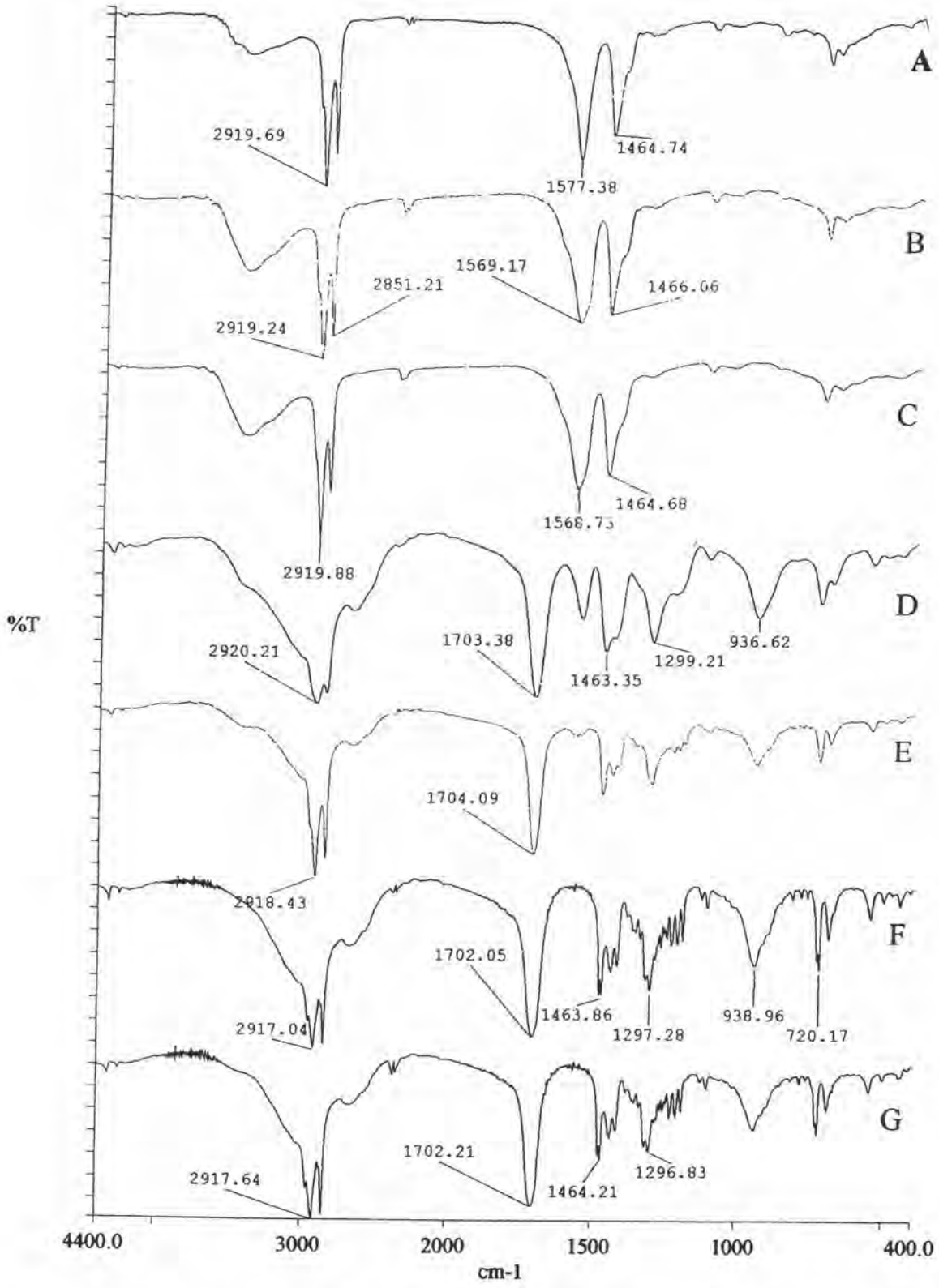


Figure 209 FT-IR spectra of untreated magnesium stearate (A); magnesium stearate after dispersion in deionized water at room temperature (B); at 60°C (C); after dispersion in dilute acetic acid at room temperature (D) ; at 40°C (E); at 60°C (F) and stearic acid (G).

12. 2 Powder X-ray diffraction

The powder X-ray diffraction patterns of unplasticized and plasticized chitosan citrate and malate films are illustrated in Figure *210.* An incorporation of glycerin and propylene glycol could enhance the amorphous form of chitosan citrate and malate films. Although PEG 6000 had relatively high intense diffraction peaks, the chitosan citrate film added this substance exhibited more amorphous pattern. An addition of brilliant blue increased the peak intensity in diffractogram of chitosan citrate (plasticized with propylene glycol) as illustrated in Figure *211.*

The X-ray diffraction patterns of talcum and titanium dioxide utilized in this study are illustrated in Figures *212*A and B respectively. The peak position in X-ray powder pattern of talcum found at 9.4°2θ ,19.4°2θ, 28.6°2θ, 36.2°2θ and other minor peaks. This characteristic came from the conformation of this material that composed of a brucite (MgO) sheet between silicon-oxygen layers (Nawman et al.1994).

TiO_2 is classified into three polymorphic forms, anatase, brookite and rutile. The rutile and anatase polymorphs are commonly encountered. Powder X-ray diffraction can be used to practically differentiate between the polymorphs of TiO_2 (Brittain,1994). The material utilized in this study was in rutile phase. The dominant scattering peaks of TiO_2, rutile phase, appeared at 27.3°, 36.2°, 39.2°,41.1° and 43.9°2θ which were corresponding to the data in Table 3 reported by Brittain (1994).

An increased amount of pigments (talc and TiO_2) provided the higher intense of diffraction peak of these pigments in cast films. The dominant peaks of pigments were also appeared and not shifted in diffraction pattern of film peeled off from coated tablets as depicted in Figures *213* and *214.*

Magnesium stearate used in this study was dihydrate form which exhibited diffractogram most likely to that described by Ertel and Carstensen (1988 a). The dominant peaks were detected at 5.3, 21.8 and 23.5°2θ. The X-ray diffractograms of chitosan acetate film and those after incorporation of magnesium stearate are illustrated in Figure *215.* These films were peeled off from tablets before testing. The more enhancement amount of magnesium stearate, the intensity of dominant peak of this material especially at about 5°2θ was more increased as depicted in Figure *215.* The peak at 23.5°2θ was more sharper as the amount of magnesium stearate loading was more increased. The dominant peaks of magnesium stearate were also appeared and not shifted in diffraction pattern of cast films as depicted in Figures *216.* This film incorporated with castor oil was also found the above peak characteristic as shown in Figure *217.*

The sharper dominant peaks of urea were seen after incorporation of urea in the film, especially, at concentration of 45% w/w as shown in Figure *218.* Moist heat treatment did not obviously alter diffraction pattern of the films as illustrated in Figure *219.*

Powder X-ray diffractograms of magnesium stearate powders after immersion in deionized water and dilute acetic acid for 45 minutes (washed with

deionized water and air dried before measurement) were presented in Figures *220* and *221*.

Magnesium stearate which was suspended in deionized water at room temperature and 60°C exhibited the dominant peaks at 5.3 and 21.8°2θ and minor peak and shoulder peaks at 8.9 and 23.5°2θ respectively, which were similar in position to untreated magnesium stearate. Whereas, after immersion in dilute acetic at room temperature, there were the new peak at 6.6°2θ and 11.2°2θ, and the peak at 5.3°2θ was regressed, and the peak at 23.5°2θ was separated from the peak at 21.8°2θ. These evidences were more dominant as the temperature of immersion fluid was increased. In addition, the peak at 5.3°2θ was disappeared after immersion in dilute acetic acid at 40°C and 60°C. Therefore, the diffraction pattern of magnesium stearate after dispersion in dilute acetic acid was similar in position to stearic acid as shown in Figure *221*.

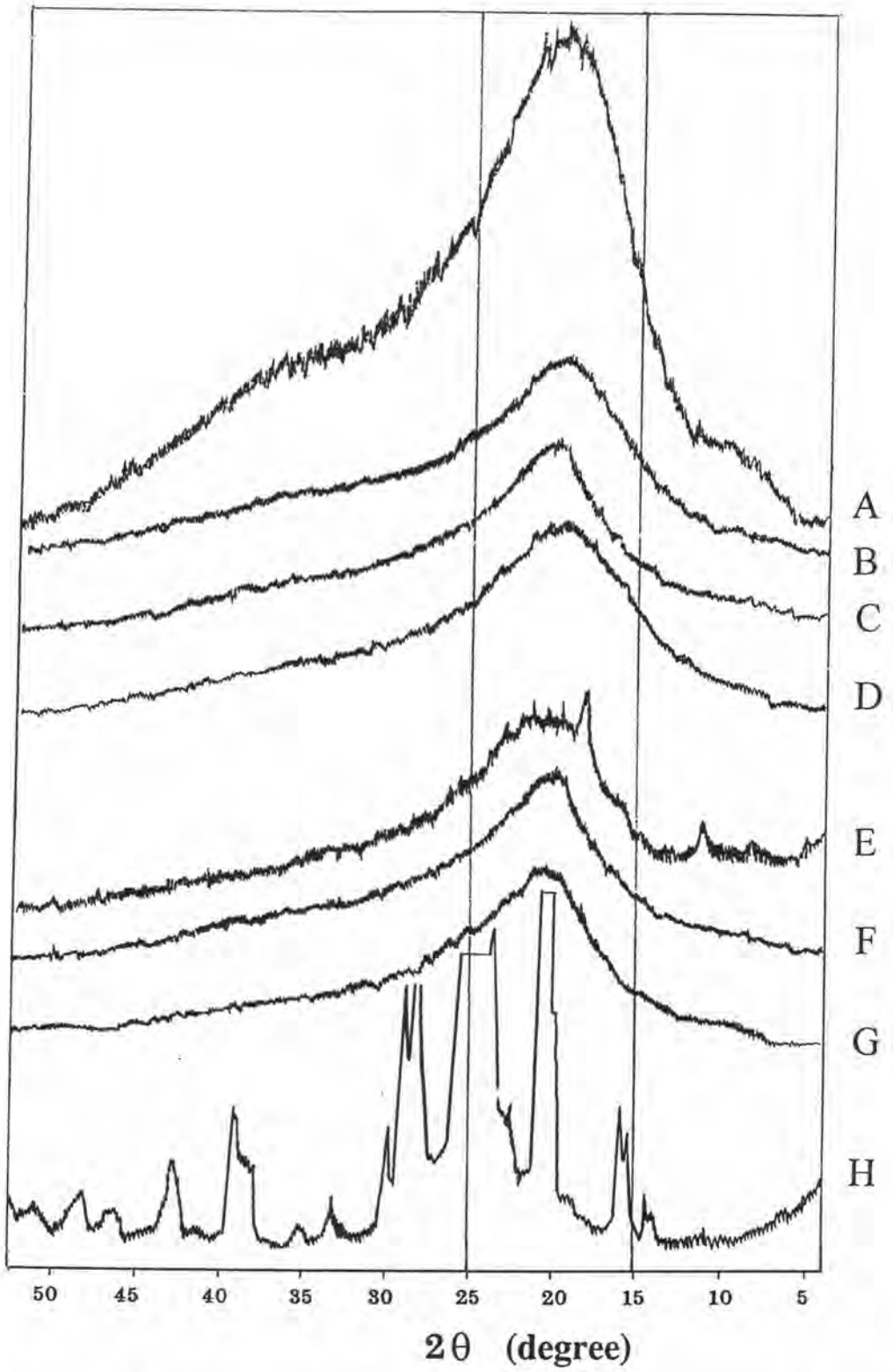


Figure 210 X-ray diffractograms of unplasticized and plasticized chitosan citrate cast films (A) CC; (B) CC G25; (C) CC P25; (D) CC E25; unplasticized and plasticized chitosan malate films (E) CM; (F) CM G25; (G) CM P25 and (H) PEG 6000.

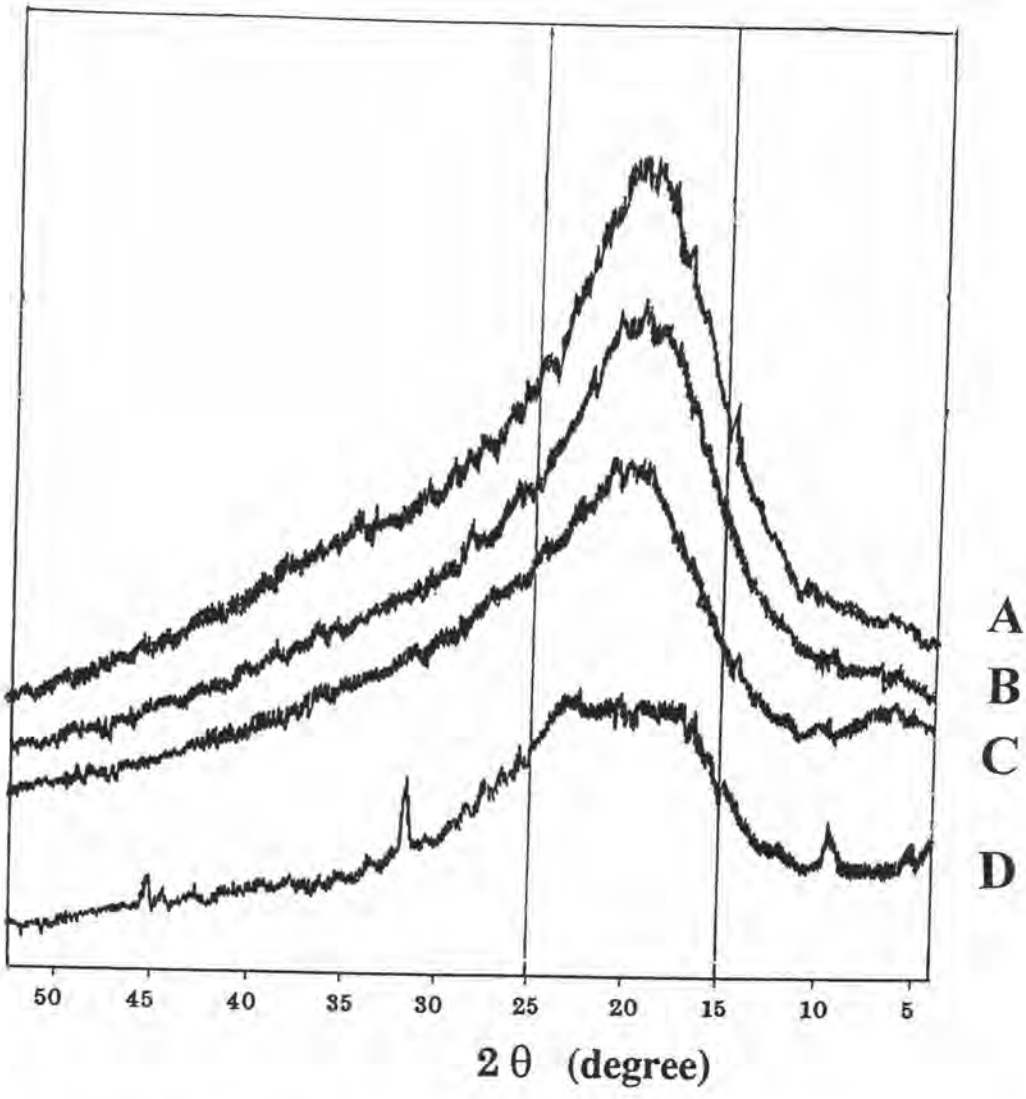


Figure 211 X-ray diffractograms of plasticized chitosan citrate cast films colored with brilliant blue (A) 0.2% (CC P25 B0.5); (B) 0.5% (CC P25 B0.5); (C) 1.0% (CC P25 B1) and (D) brilliant blue.

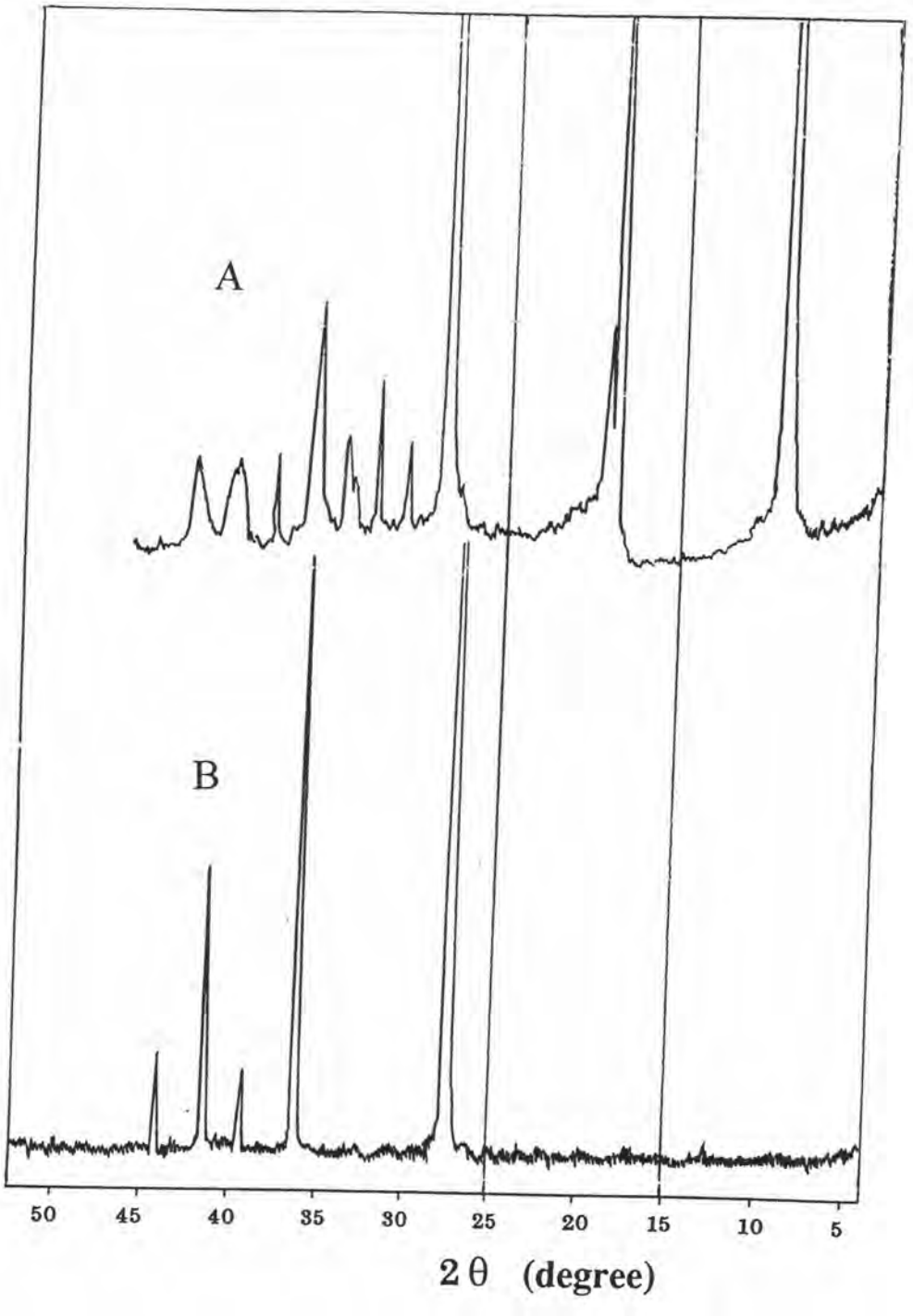


Figure 212 X-ray diffractograms of (A) talcum and (B) titanium dioxide.

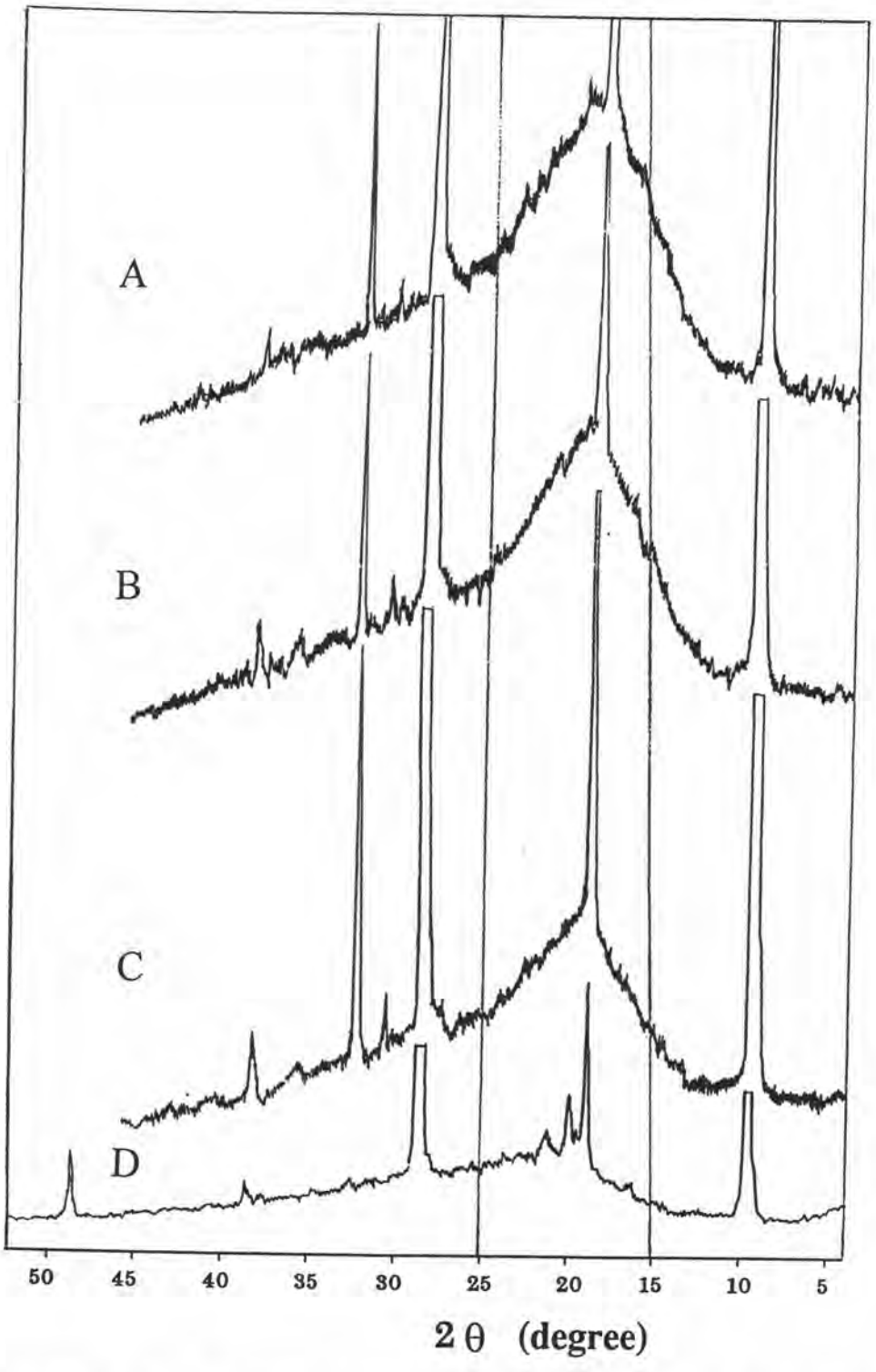


Figure 213 X-ray diffractograms of plasticized and colored chitosan citrate cast films pigmented with talcum (A) 15% (CC P25 Ta15); (B) 30% (CC P25 Ta30); (C) 45% (CC P25 Ta45); and (D) CC P25 Ta30 film peeled off from coated tablet.

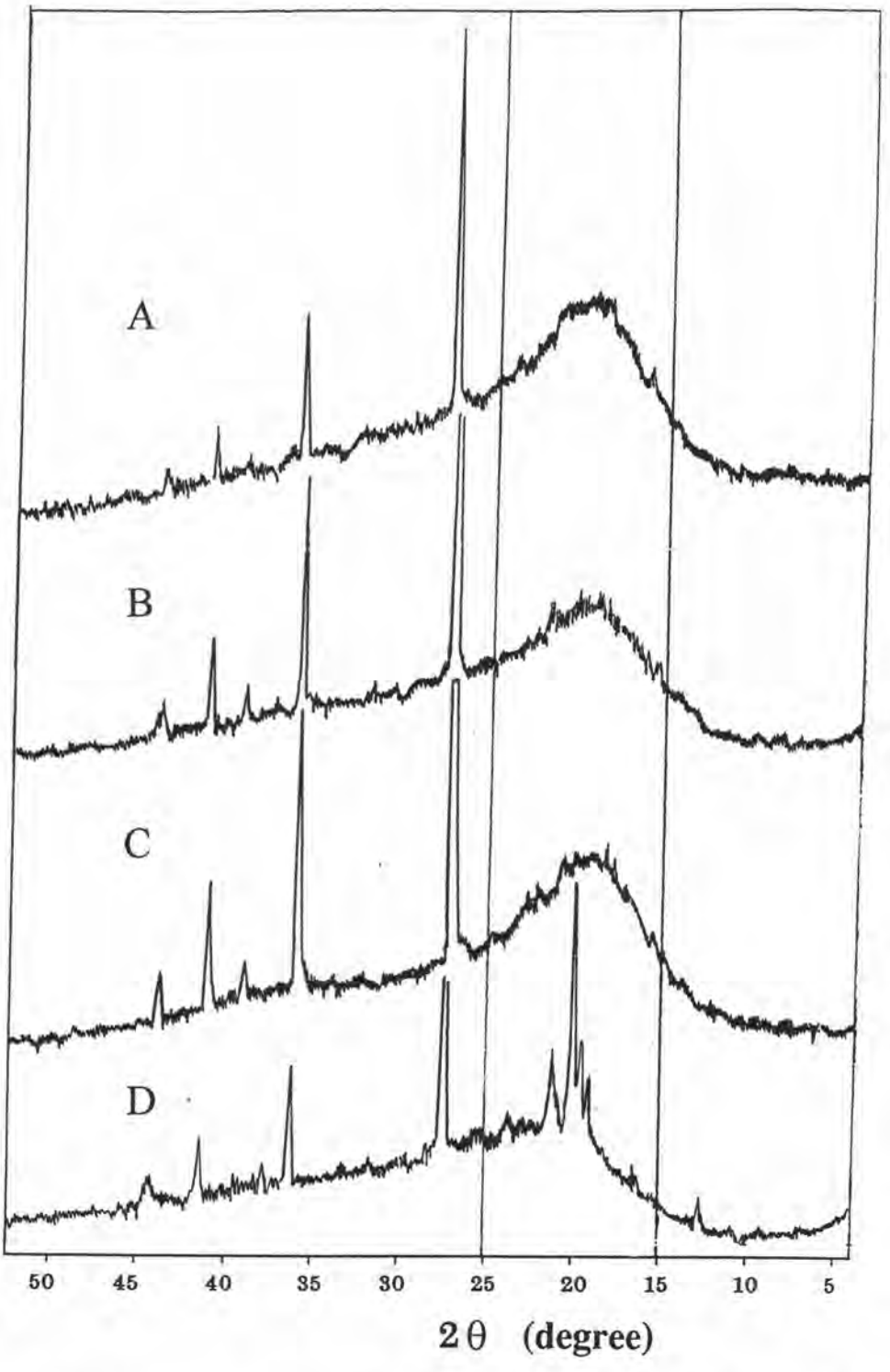


Figure 214 X-ray diffractograms of plasticized and colored chitosan citrate cast films pigmented with titanium dioxide (A) 15% (CCP25 TI15); (B) 30% (CC P25 Ti30); (C) 45% (CC P25 Ti45); and (D) CC P25 Ti30 film peeled off from coated tablet.

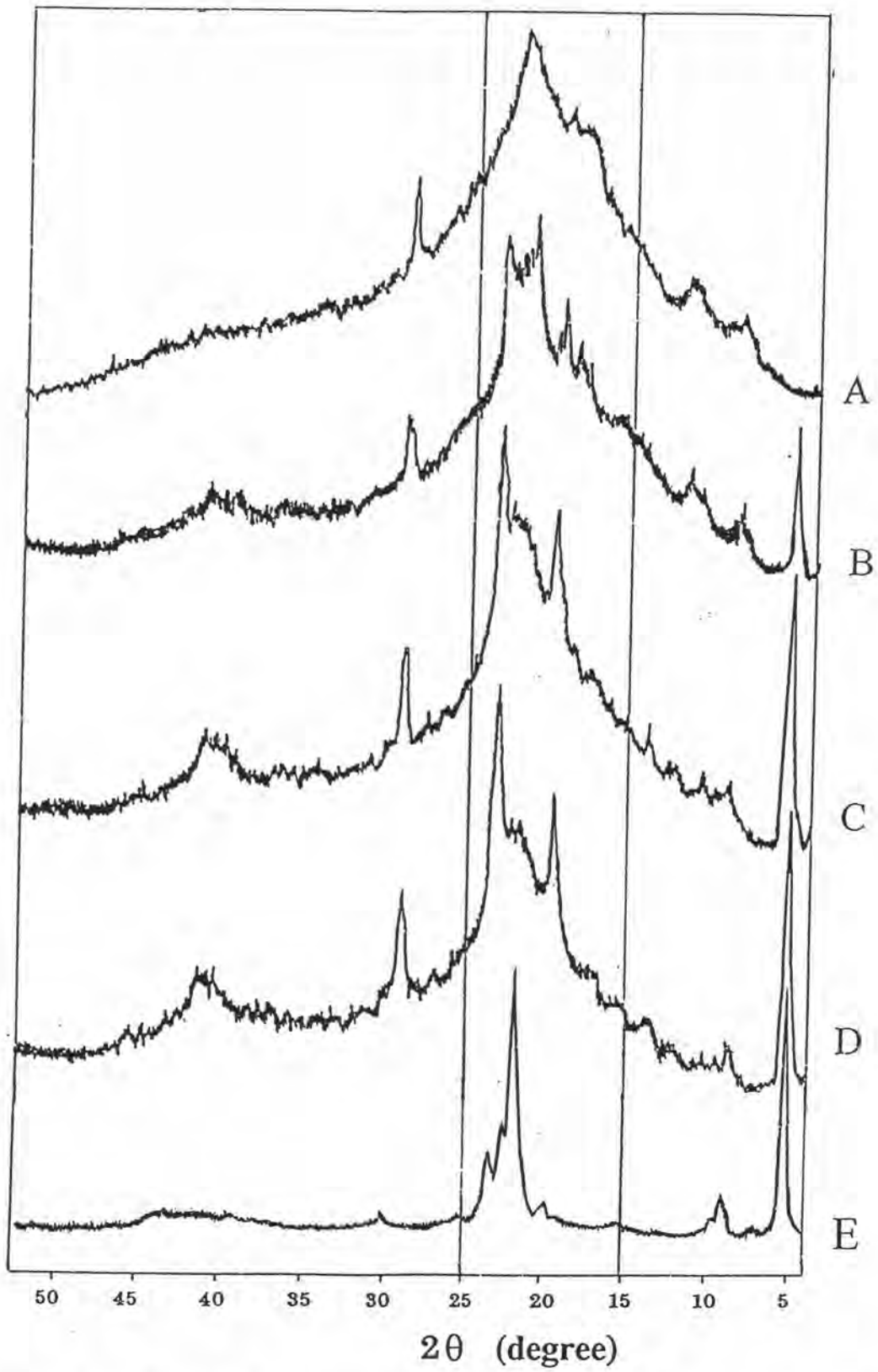


Figure 215 X-ray diffractograms of film peeled off from coated tablets (A) chitosan acetate film; chitosan acetate film containing magnesium stearate (B) 45% (CA M45); (C) 60% (CA M60); (D) 75% (CA M75) and (E) magnesium stearate.

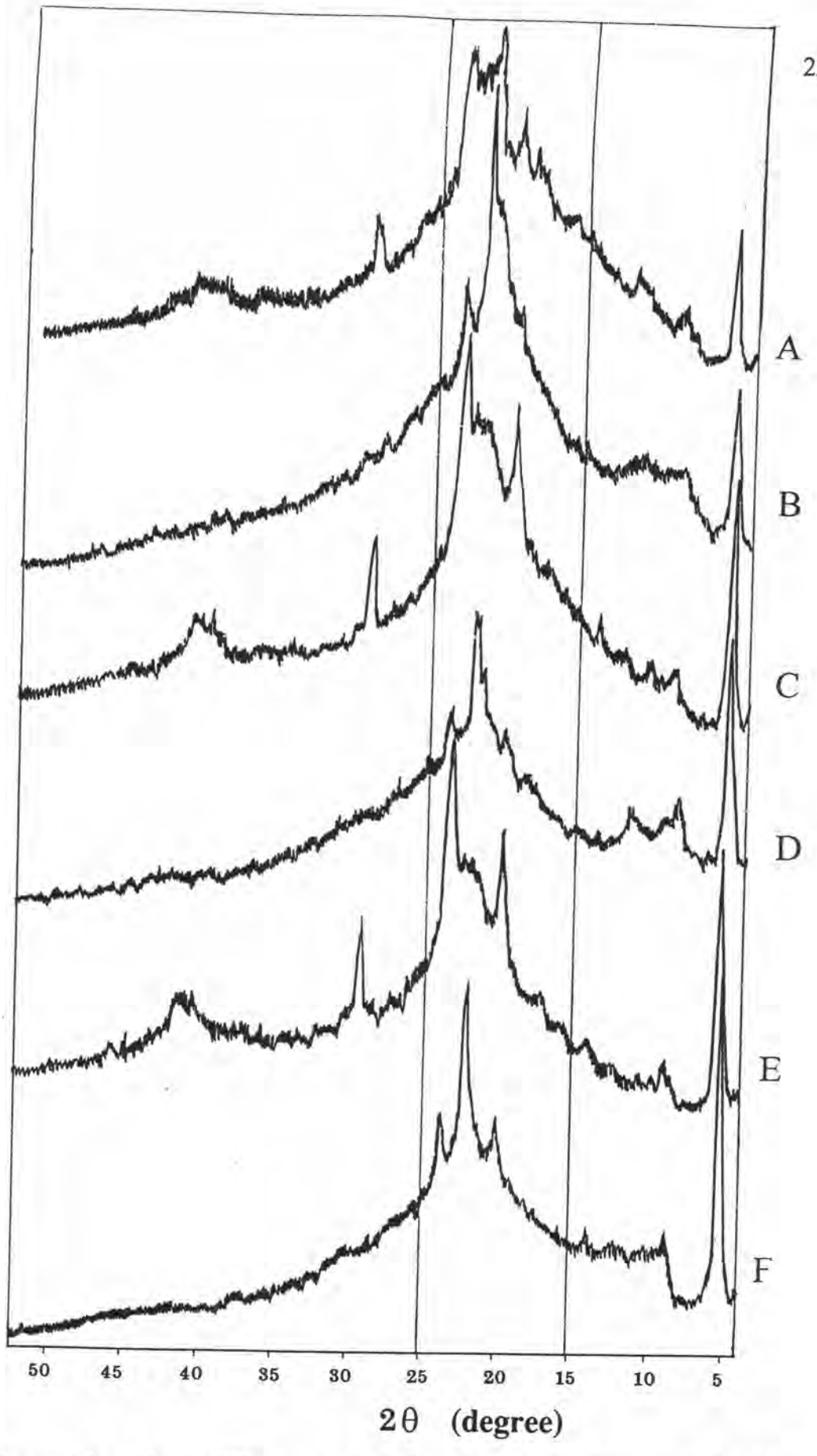


Figure 216 X-ray diffractograms of film peeled off from coated tablets: chitosan acetate film containing magnesium stearate (A) 45% (CA M45); (C) 60% (CA M60); (E) 75% (CA M75) and chitosan acetate cast films containing magnesium stearate (B) 45% (CA M45); (D) 60% (CA M60); (F) 75% (CA M75).

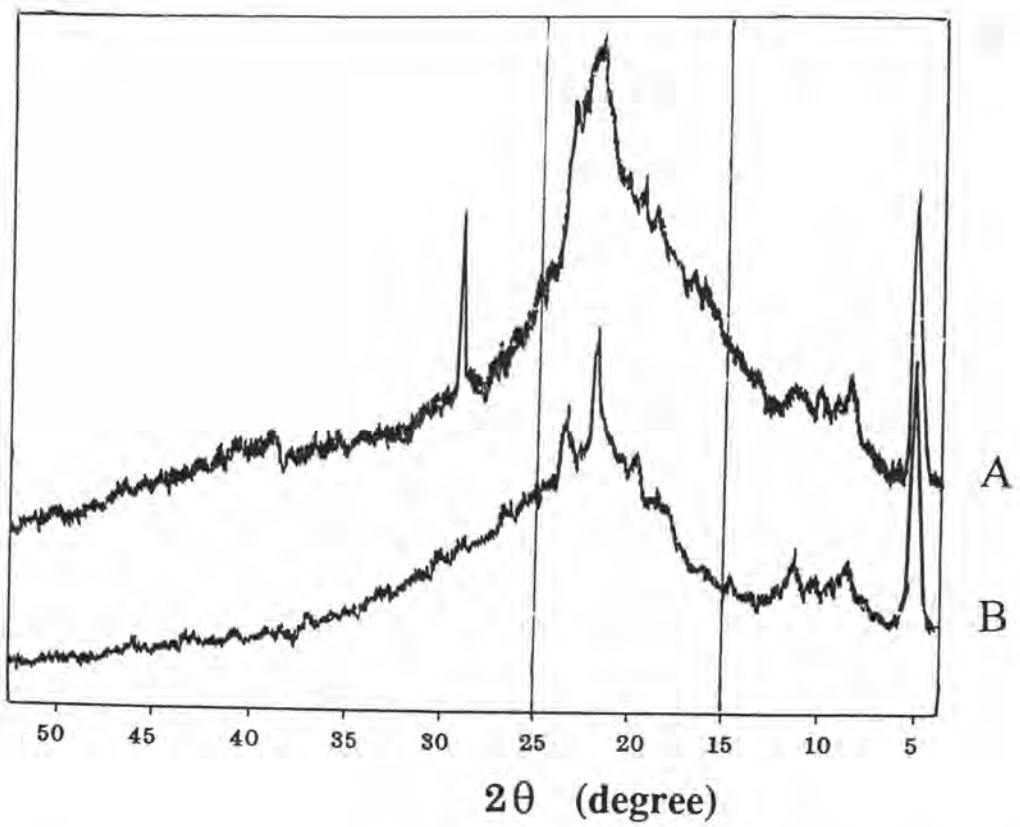


Figure 217 X-ray diffractograms of film peeled off from coated tablets: chitosan acetate film containing magnesium stearate 45% and castor oil 15% (CA M45 Cas15) (A) peeled off from coated tablet and (B) cast film.

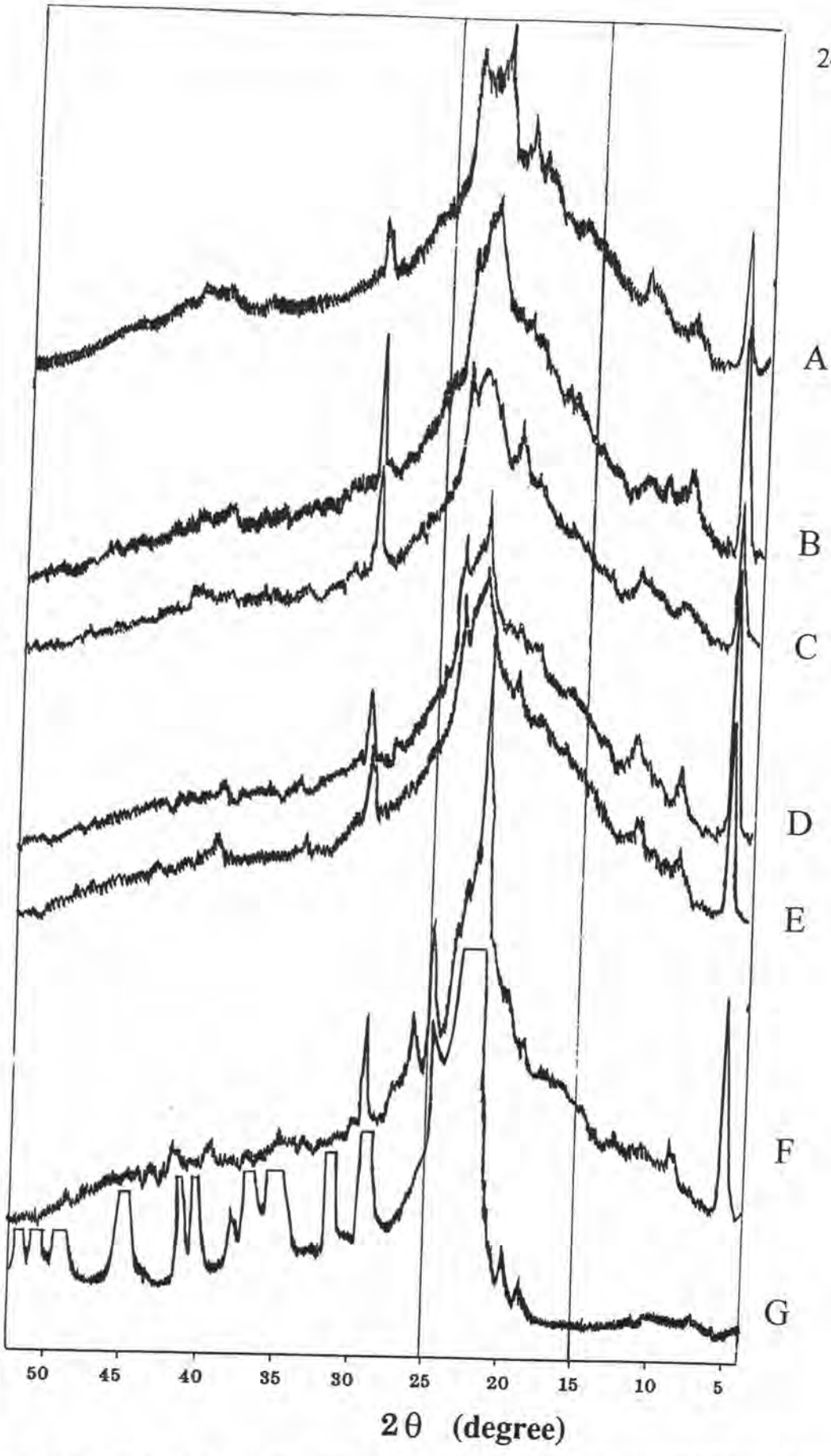


Figure 218 X-ray diffractograms of film peeled off from coated tablets (A) chitosan acetate film containing magnesium stearate 45% (CA M45); (B) chitosan acetate film containing magnesium stearate 45% and castor oil 15% (CA M45 Cas15); chitosan acetate film containing magnesium stearate 45%, castor oil 15% and urea (C) 5% (CA M45 Cas15 U5); (D) 15% (CA M45 Cas15 U15); (E) 30% (CA M45 Cas15 U30); (F) 45% (CA M45 Cas15 U45) and (G) urea.

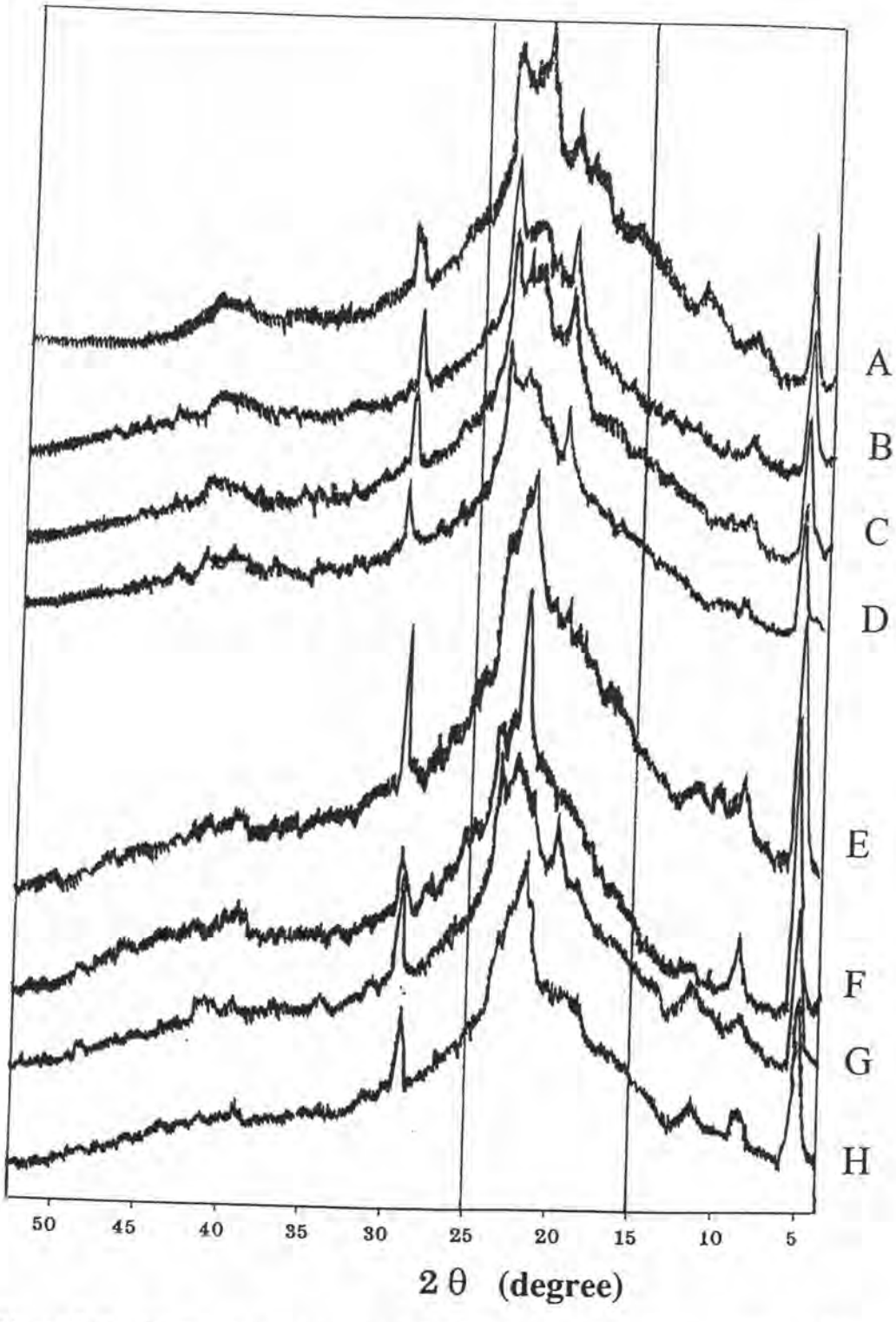


Figure 219 X-ray diffractograms of film peeled off from coated tablets: chitosan acetate film containing magnesium stearate 45% (CA M45) (A) freshly prepared; after exposed to moist heat at 60°C for (B) 24 hrs.; (C) 72 hrs.; (D) 120 hrs.; chitosan acetate film containing magnesium stearate 45% and castor oil 15% (CA M45 Cas15); (E) freshly prepared; (F) after exposed to moist heat at 60 °C for 24 hrs.; chitosan acetate film containing magnesium stearate 45%, castor oil 15% and urea 5% (CA M45 Cas15 U5) (G) freshly prepared and (H) after exposed to moist heat at 60°C for 24 hrs.

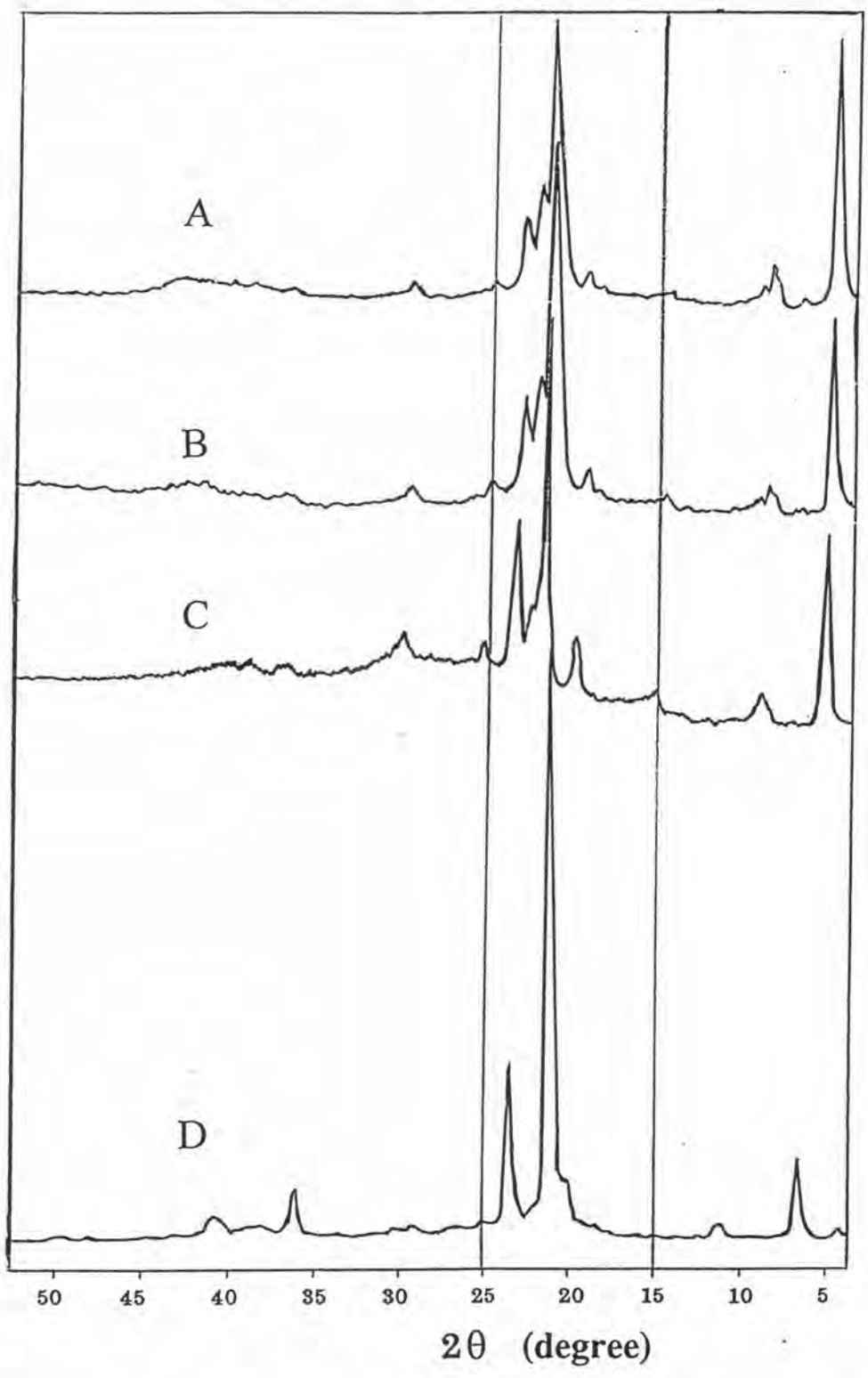


Figure 220 X-ray diffractograms of magnesium stearate (A) untreated; after dispersed in deionized water for 45 min at (B) room temperature; (C) 60°C and (D) untreated stearic acid.

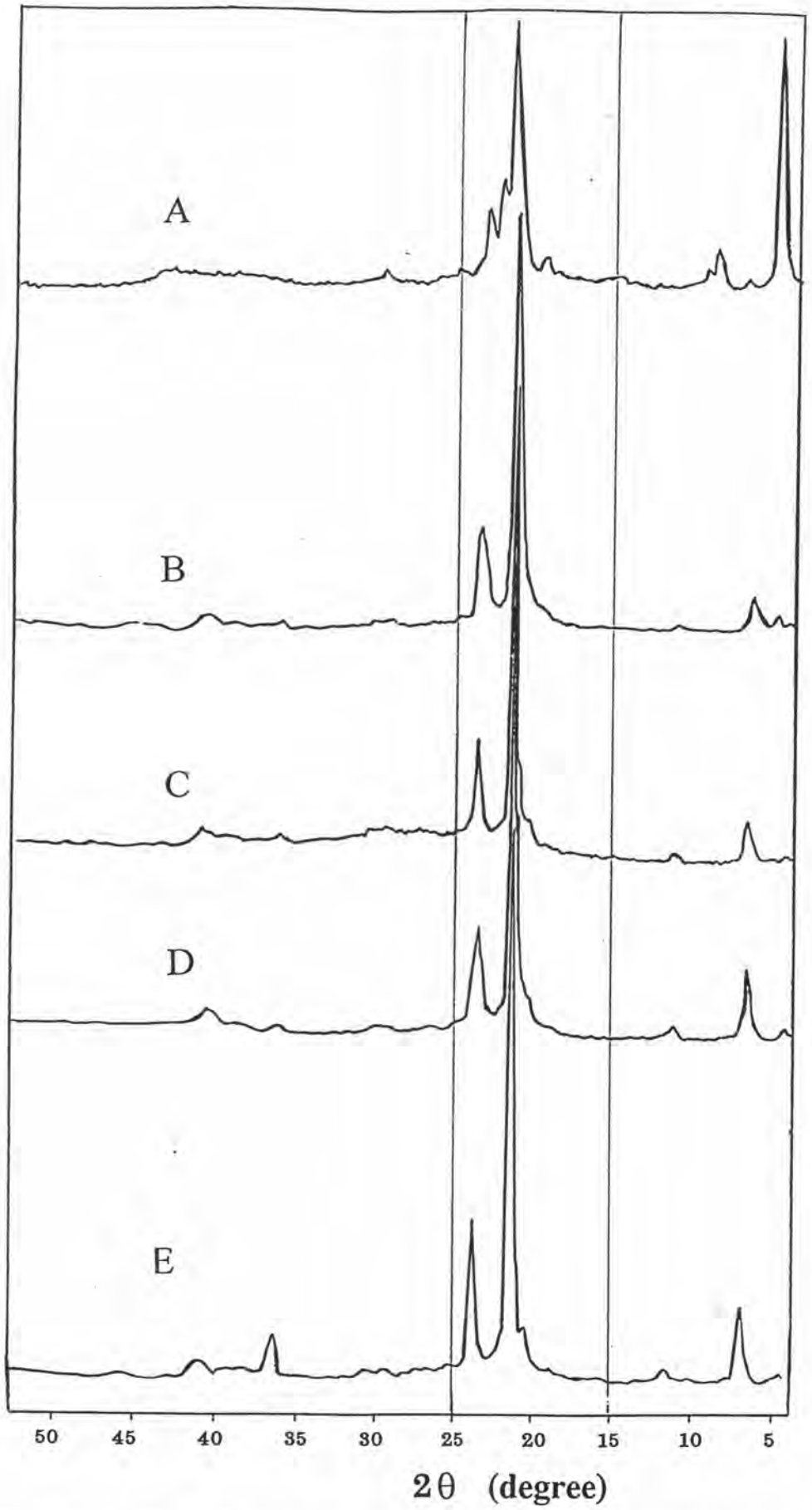


Figure 221 X-ray diffractograms of magnesium stearate (A) untreated; after dispersed in dilute acetic acid for 45 min at (B) room temperature; (C) 40°C and (D) 60°C and (E) untreated stearic acid.

12. 3 Differential Scanning Calorimetry (DSC) Studies

The endothermic and exothermic peaks from DSC curve of brilliant blue powder, plasticized chitosan citrate film and plasticized chitosan citrate film colored with brilliant blue 0.5%w/w of chitosan are illustrated in Figure *222*. The endothermic peak appearing nearly to 100°C of brilliant blue powder was associated with the loss of water and the exothermic peak at 291°C should be the degradation temperature of this dye. The plasticized chitosan citrate film exhibited the endothermic peak at 175.5°C which related to the melting point of this mixture and the degradation temperature appeared at 354.0°C respectively. The endothermic and exothermic peaks of colored film appeared at 175.16°C and 352.16°C respectively which occurred nearly to those of non-colored film. There was no evidence of new peak or significant peak shift in the thermogram of colored film. It was also found that the peak of brilliant blue did not appear in this film, thus the brilliant blue incorporated at 0.5% could be miscible with plasticized chitosan citrate film.

An incorporation of pigment (talcum and titanium dioxide) at concentration of 25% w/w in plasticized and colored chitosan citrate film did not alter the DSC thermogram as shown in Figure *222*, this evidence indicated that both talcum and titanium dioxide did not change the thermal properties of plasticized and colored chitosan citrate film.

DSC thermograms of chitosan acetate films containing different additives are presented in Figure *223*. DSC analyses of chitosan acetate film containing magnesium stearate at concentration of 45% w/w showed that there was no endothermic peak of magnesium stearate but the new endothermic peak was appeared at 83.3°C. This characteristic was also seen in film containing magnesium stearate combined with castor oil, and film containing magnesium stearate, castor oil and urea.

The endothermic peaks of magnesium stearate appeared at 92.20 and 114.31°C as depicted in Figure *224* which associated with the loss of bound water and the melting of the crystal. DSC curves associated with thermal events of magnesium stearate after dispersion in deionized water and dilute acetic acid at different temperature are illustrated in Figure 224 and peak temperature and enthalpy from DSC curves are summarized in Table *16*. The major endothermic peaks of untreated magnesium stearate were appeared at 92.20°C and 114.31°C with the enthalpy of 56.19 and 86.03 J/g respectively. The shoulder endothermic peak at 67.46°C was also detected. The powder of magnesium stearate dispersed in deionized water, when dried, exhibited the endothermic peaks and enthalpy which were similar to untreated magnesium stearate. Whereas the values of enthalpy of this material after dispersed in this medium at 60°C were changed and the shoulder peak was more dominant and slightly shifted to 78.06°C. After dispersion magnesium stearate in dilute acetic acid at room temperature, the alteration of endothermic peak temperature was found as depicted in Figure *225*. The new sharp endothermic peak was obviously detected at 60.8°C and minor peak was found at 72.64°C. The noticeable decrease in minor peak was appeared after dispersion magnesium stearate in dilute acetic acid at 40°C. Furthermore the minor peak was disappeared after dispersed at 60°C. The sharp peak occurred at about 60°C in DSC curves of magnesium stearate after dispersion in dilute acetic acid was occurred at the same endothermic temperature of that found in DSC curve of stearic acid. Considerably, it was found that the enthalpy values of the sharp peak of acid treated magnesium stearate at 40°C and 60 °C were nearly to that of stearic acid.

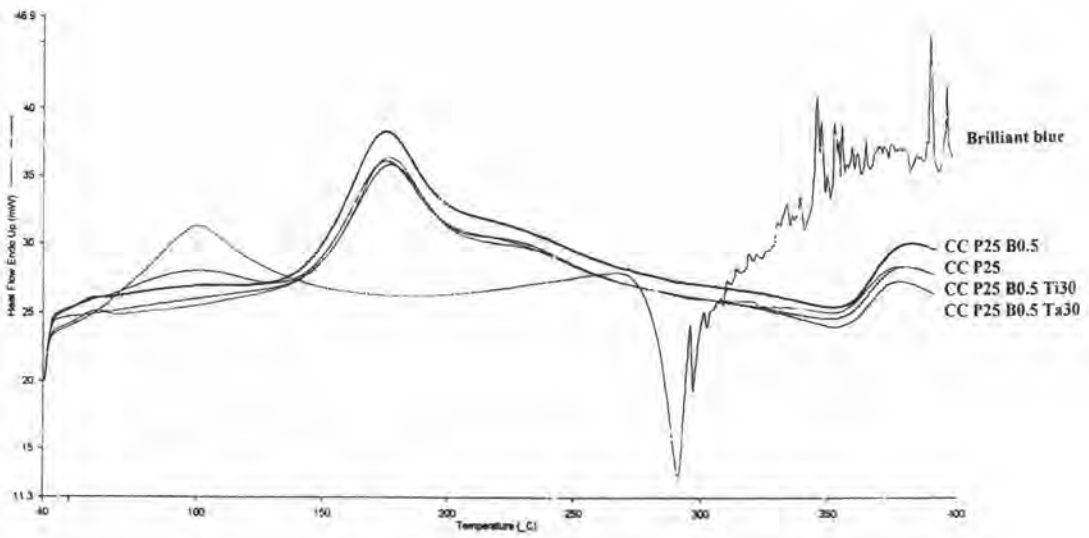


Figure 222 DSC thermograms of brilliant blue, chitosan citrate film plasticized with propylene glycol 25% (CC P25); chitosan citrate film plasticized with propylene glycol 25% and colored with brilliant blue 0.5% (CC P25 B0.5); chitosan citrate film plasticized with propylene glycol 25% and colored with brilliant blue 0.5% and pigmented with talcum 30% (CC P25 B0.5 Ta30) and titanium dioxide 30% (CC P25 B0.5 Ti30).

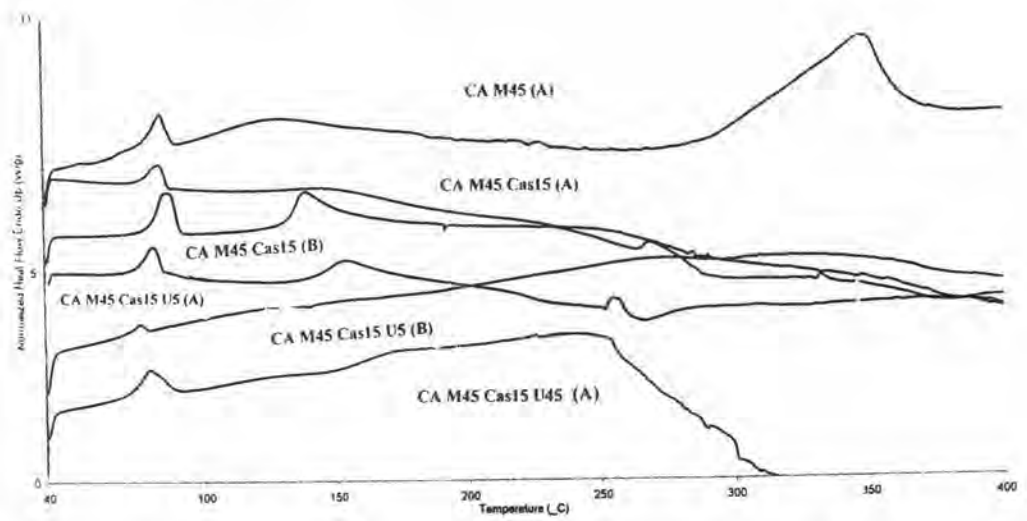


Figure 223 DSC thermograms of film peeled off from coated tablets; chitosan acetate film containing magnesium stearate 45% (CA M45); chitosan acetate film containing magnesium stearate 45% and castor oil 15% (CA M45 Cas15), chitosan acetate film containing magnesium stearate 45%, castor oil 15% and urea 5% (CA M45 Cas15 U5); chitosan acetate film containing magnesium stearate 45%, castor oil 15% and urea 45% (CA M45 Cas15 U45) (A) freshly prepared and (B) after exposed to moist heat at 60°C for 24 hrs.

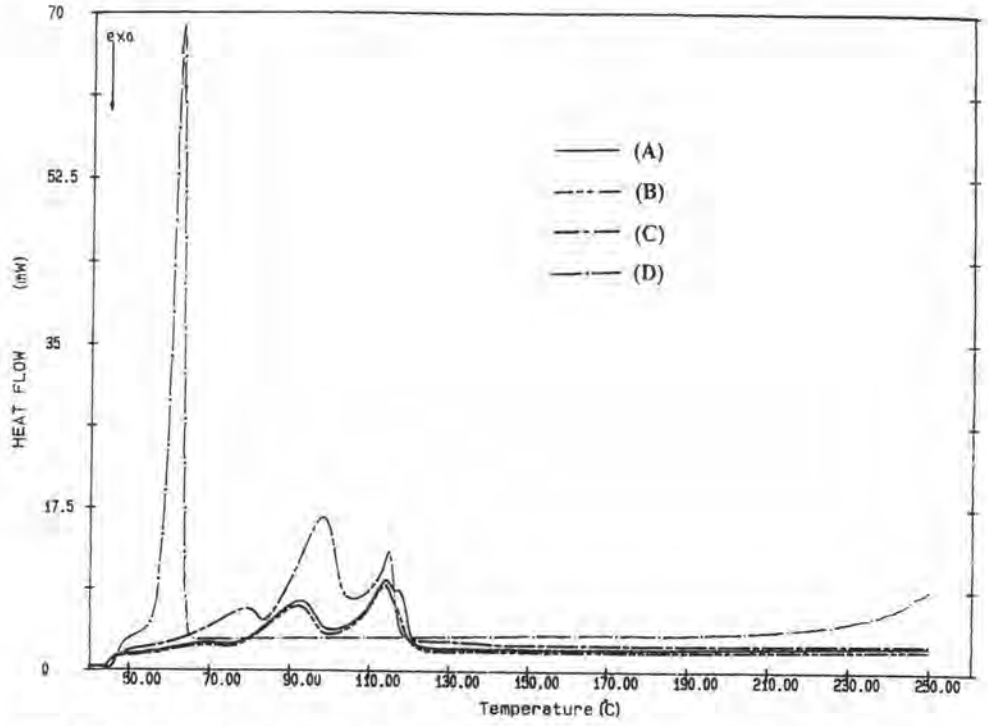


Figure 224 DSC thermograms of magnesium stearate (A) untreated; after dispersed in deionized water for 45 minutes at (B) room temperature; (C) 60°C and (D) untreated stearic acid.

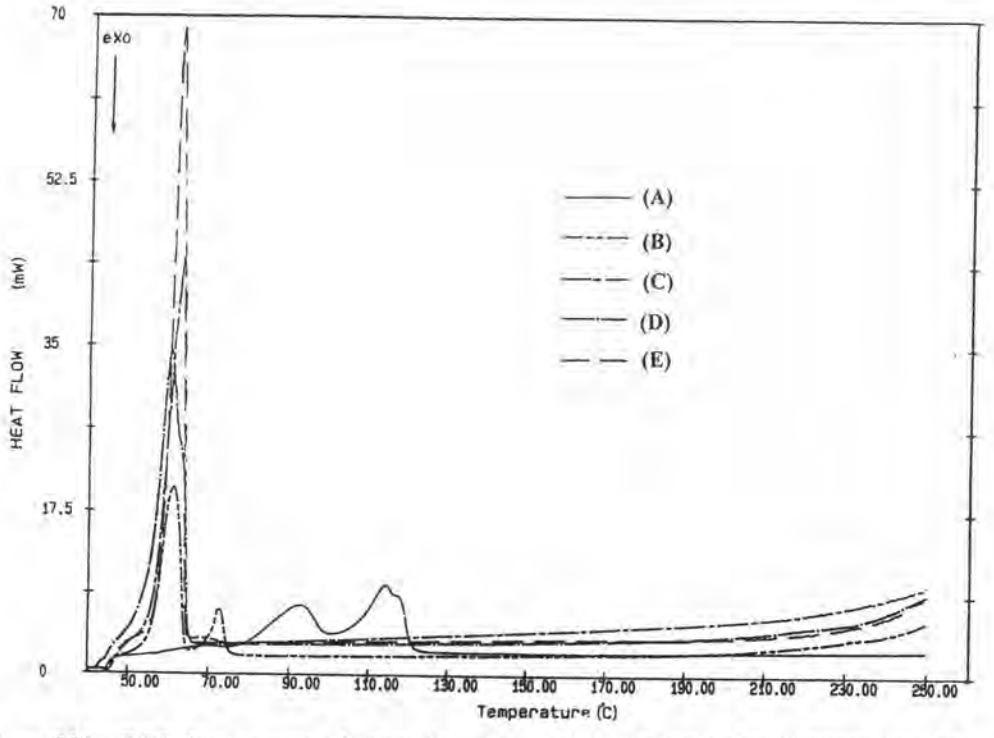


Figure 225 DSC thermograms of magnesium stearate (A) untreated; after dispersed in dilute acetic acid for 45 minutes at (B) room temperature; (C) 40°C and (D) 60°C and (E) untreated stearic acid.

Table 16 Peak temperature and enthapy of endothermic peak from DSC curves of untreated and treated magnesium stearate and untreated stearic acid

Sample	Endothermic Peak	
	Peak Temperature (°C)	Enthalpy(J/g)
Mg stearate	92.20 114.31	56.19 86.03
Mg stearate after dispersion in water at RT	91.70 113.98	59.10 82.84
Mg stearate after dispersion in water at 60°C	97.88 114.93	97.18 29.67
Mg stearate after dispersion in dilute acetic acid at RT	60.80 72.64	155.44 28.75
Mg stearate after dispersion in dilute acetic acid at 40°C	62.87	190.80
Mg stearate after dispersion in dilute acetic at 60°C	60.04	182.15
Stearic acid	62.28	188.61

Part III

Release Model Development and Curve Fitting

1. Release Model Development

The original mathematic form of diffusion theory was declared as Fick's first law (Burnette, 1987). The rate of transfer of diffusant per unit area of section or the mass flux (J) was given by Fick's first law of one dimensional diffusion as:

$$J = (dQ/dt)(1/A) = -D\,(dC/dx) \qquad \text{.....(Eq. 19)}$$

This is based on the hypothesis that the rate of transfer of diffusant through unit area of a section which is normal to the direction of transport is proportional to the concentration gradient. A is the surface area, D is called the diffusivity or diffusion coefficient, dQ/dt is the mass transfer rate and dC/dx is the gradient of concentration, C, of the diffusant along the x-axis of diffusion. x is a position coordinate measured perpendicularly to the surface to which the diffusion flow has been refered (Jost, 1960; Flynn et al., 1974; Crank, 1975)

The model of drug release and the schematic representation of diffusion from a reservoir across aqueous soluble chitosan film are developed and presented in Figures *226* and *227*.

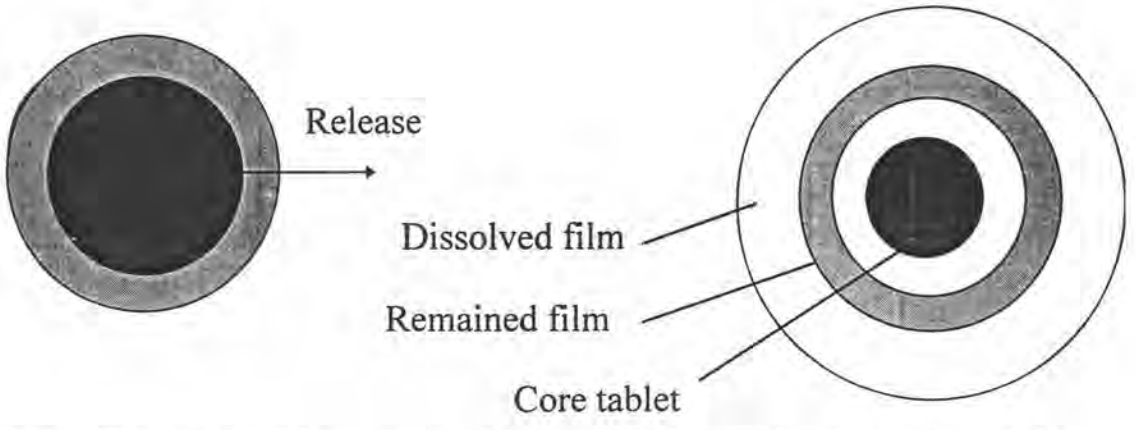


Figure 226 The model of drug release from a reservoir coated with aqueous soluble chitosan film.

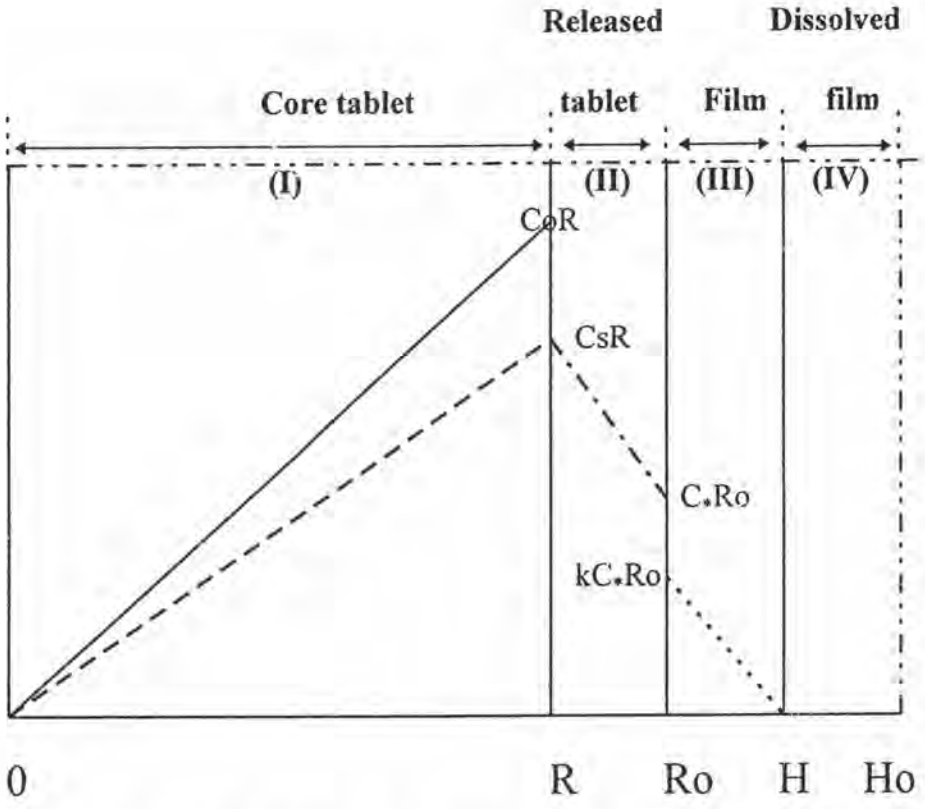


Figure 227 The model of drug release and schematic representation of diffusion from a reservoir across a membrane

where
I is the area of the undissolved core tablet
II is the area of released tablet
III is the area of undissolved film
IV is the area of dissolved film
C_0 is the concentration of drug in core tablet
C_S is the saturated concentration of drug
C*is the concentration of drug in film
k is the partition coefficient
R_0 is the radius of core tablet
R is the radius of undissolved core tablet
H_0 is the radius of coated tablet
H is the radius of dissolved film coated tablet

When the diffusion is radial, the diffusion equation for a constant diffusion coefficient takes the form

$$\partial C/\partial t = D[\partial^2 C/\partial r^2 + 2\partial C/r\partial r] \quad \text{.....(Eq. 20)}$$

It can simplify the mathematical treatment for solving the partial differential equation for drug diffusion by employing the equivalent plate transformation method suggested by Carslaw and Jaeger (1959) and Kwok et al. (1991). Upon putting the function U = C.r, the above equation is reduced to

$$\partial U/\partial t = D\partial^2 U/\partial r^2 \quad \text{.....(Eq. 21)}$$

where U is the equivalent-plate concentration.

Since this is the equation for linear flow in one dimension, the solutions of in any problems of mass transport in radial flow in a sphere can be deduced immediately from those of the corresponding linear problems following the analogies presented by Crank (1975). In condition of steady state when the concentration of diffusant does not depend on time and the concentration of substance depends on position the equation is

$$\frac{d}{dr}\left(r^2 \frac{dC}{dr}\right) = 0 \quad \text{.....(Eq. 22)}$$

of which the general solution is $C = X + Y/r$ .....(Eq. 23)

$$rC = Xr + Y \quad \text{.....(Eq. 24)}$$

where X and Y are constants to be determined from the boundary conditions. The boundary condition expresses the concentration of diffusant on the surface (Crank, 1975).

Therefore, diffusion in a sphere at steady state takes the form:

$$rC = Xr+Y \quad \text{.....(Eq. 25)}$$

The concentration of drug in different position can be determined as:

(I) $0<r<R$; $rC = rCo$ and $C_{(I)} = Co$ .....(Eq. 26)

(II) $R<r<Ro$; $rC = RC_s - \frac{RCs-RoC^*}{Ro-R}(r-R)$ .....(Eq. 27)

$$rC = \frac{RCs(Ro-R) + R(RCs-RoC^*)}{Ro-R} - \frac{RCs-RoC^*}{Ro-R}.\ r \quad \text{(Eq. 28)}$$

$$C_{(II)} = \frac{RRo(Cs-C^*)}{(Ro-R)r} - \frac{RCs-RoC^*}{Ro-R} \quad \text{.....(Eq. 29)}$$

(III) $Ro<r<H$; $rC = kC^*Ro - \frac{kC^*Ro}{H-Ro}(r-Ro)$ .....(Eq. 30)

$$rC = \frac{kC^*Ro(H-Ro) + kC^*(Ro)^2}{H-Ro} - \frac{kC^*Ro}{H-Ro}.r \quad \text{.....(Eq. 31)}$$

$$C_{(III)} = \frac{kC^*RoH}{(H-Ro)r} - \frac{kC^*Ro}{H-Ro} \quad \text{.....(Eq. 32)}$$

From $Q = \text{Mass}_{\text{initial}} - \text{Mass}_{\text{undissolved}}$ .....(Eq. 33)

$$Q = V_O \rho - V\rho \quad \text{.....(Eq. 34)}$$

$$Q = (4\pi/3)(Ro)^3 .\rho - (4\pi/3)(R)^3.\rho \quad \text{.....(Eq. 35)}$$

$$(4\pi/3)(R)^3.\rho = Q_0 - Q \quad \text{.....(Eq. 36)}$$

$$R = \{ (3/4\pi\rho)(Q_0 - Q)\}^{1/3} \quad \text{.....(Eq. 37)}$$

From the Fick's first law : $dQ/dt = AD (dC/dx)$
The release rate (dQ/dt) is then expressed mathematically as

$$dQ/dt = 4\pi(H)^2.Df.(dC_{III}/dr)_{r=H} = 4\pi(Ro)^2.(dC_{III}/dr)_{r=Ro} \quad \text{(Eq. 38)}$$

Boundary Condition

$$4\pi(Ro)^2.D.(dC_{II}/dr)_{r=Ro} = 4\pi(Ro)^2.Df.(dC_{III}/dr)_{r=Ro} \quad \text{.....(Eq. 39)}$$

$$dC_{II}/dr = \frac{RRo(Cs-C^*)}{(Ro-R)} (-1/(r)^2) \quad \text{.....(Eq. 40)}$$

$$dC_{III}/dr = \frac{kC^*RoH}{(H-Ro)} (-1/(r)^2) \quad \text{.....(Eq. 41)}$$

$$D.R.Ro(Cs-C^*)/(Ro-R) = Df.k.C^*Ro.H/(H-Ro) \quad \text{.....(Eq. 42)}$$
$$D.R.Cs/(Ro-R) = (Df.k.H.C^*)/(H-Ro) + (D.R.C^*)/(Ro-R) \quad \text{(Eq. 43)}$$
$$D.R.Cs/(Ro-R) = \{(Df.k.H)/(H-Ro) + (D.R)/(Ro-R)\}.C^* \quad \text{(Eq. 44)}$$

$$C^* = \frac{(H-Ro).D.R.Cs}{(Ro-R).Df.k.H + (H-Ro).D.R} \quad \text{.....(Eq. 45)}$$

$$dQ/dt = 4\pi H^2.Df.\frac{k.C^*.Ro.H.}{(H-Ro)} (1/H^2) \quad \text{.....(Eq. 46)}$$

$$dQ/dt = \frac{(4\pi.Df.\ k.Ro.H)}{(H-Ro)} . \frac{(H-Ro).D.R.Cs}{\{(Ro-R).Df.k.H + (H-Ro).D.R\}} \quad \text{.....(Eq. 47)}$$

$$dQ/dt = \frac{4\pi.Df.\ k.Ro.H.\ D.R.Cs}{(Ro-R).Df.k.H + (H-Ro).D.R} \quad \text{.....(Eq. 48)}$$

$$dQ/dt = \frac{4\pi.Df.k.Ro.H.Cs}{\{(Ro/R)-1\}.\frac{Df.k.H}{D} + (H-Ro)} \quad \text{.....(Eq. 49)}$$

$$\text{From } (Ro/R)-1 = \frac{((3/4\pi).Q_0)^{1/3}}{\{(3/4\pi).(Q_0-Q)\}^{1/3}} - 1 \quad \text{.....(Eq. 50)}$$

$$= \frac{Q_0^{1/3} - (Q_0-Q)^{1/3}}{(Q_0-Q)^{1/3}} = \frac{1-(1-(Q/Q_0))^{1/3}}{(1-(Q/Q_0))^{1/3}} \quad \text{.....(Eq. 51)}$$

$$dQ/dt = \frac{4\pi.k.Df.Ro.Cs}{(Df.k/D).[(1-(1-(Q/Q_0))^{1/3}/(1-(Q/Q_0)^{1/3}]+[((Ho-Ro)-at)/Ho]} \quad \text{.....(Eq. 52)}$$

$$dQ/dt = \frac{4\pi.k.Df.Ro.Ho.Cs}{(Df.k.Ho/D).[(1-(1-(Q/Q_0))^{1/3}/(1-(Q/Q_0)^{1/3}]+(Ho-Ro)-at} \quad \text{.....(Eq. 53)}$$

$$dQ/dt = \frac{4\pi.D.Ro.Cs}{[((1-(1-(Q/Q_0))^{1/3}/(1-(Q/Q_0)^{1/3})]+[(D.(Ho-Ro))/Df.k.Ho]-(Da.t/Df.k.Ho)} \quad \text{.....(Eq. 54)}$$

$$dQ/dt = \frac{C}{A - Bt + \{\frac{1-(1-(Q/Q_0))\}^{1/3}}{1-(Q/Q_0)^{1/3}}} \quad \text{.....(Eq. 55)}$$

Upon putting the lag time (Tl), the equation is expressed as

$$dQ/dt = C/\left\{A - B(t-Tl) + \left\{\frac{1-(1-(Q/Q_0))^{1/3}}{(1-(Q/Q_0))^{1/3}}\right\}\right\} \quad \text{.....KGT1 (Eq. 56)}$$

A = D(Ho-Ro)/Df.k.Ho
B = (D.a)/Df.k.Ho
C = 4πDRoCs

where r is the radius measured from the center of coated tablet, Df is the diffusion constant of drug in the coating film, D is the difffusion constant of the drug in the space between the undissolved core tablet and the film coat, Vo is the initial volume of core tablet, V is the volume of undissolved core tablet, a is the decrease rate of film thickness, Tl is the lag time, Q is the drug released and Q_0 is the total amount of drug in dosage form. The sink condition was assumed at H.

The applicability of the developed physical model to the prediction of experimental results depended on the validity of the assumption within the model. These assumptions are suggested as following.

It was assumed that coated tablet consisted of encapsulated drug in core material and a coat which was the rate-limiting element in the release process. The model

was developed based on a composite sphere assumption for the simplifying mathematical process. The assumption of steady state was necessary as well as the boundary layer. The shrinking sphere core without existent change in the shape was assumed. It was reasonable to assume that there was the drug diffusion in a sphere device. Drug release from coated tablet was a mass transport process involving diffusion of drug from a region of high to low concentration. Two transfer processes occurred in the coated tablet. The one concerned with the penetration of liquid through the polymer to dissolve of drug and then allowed the other transfer of drug into the polymer out of the coated tablet. Both transfer process were controlled by transient diffusion, and were connected with each other. The lag time corresponding to the initial phase where coated tablet was introduced into dissolution fluid, permeating fluid penetrated through the film coat and dissolved the encapsulated drug was separately accounted. The model was applied as the drug in the core had been dissolved by the penetrating medium as mentioned by Christensen, et al. (1980, 1982). Additionally, this physical model included the assumption that there was the drug concentration potential gradient between the remained core surface and somewhere in the space between undissolved core tablet and the film coat. To ascertain which relationship of curve fitting of individual release profile and different release kinetic was applicable, the coefficient of determination was intentionally used as the principle criteria for evaluation. The coefficient of determination was a measure of the fraction of the total variance accounted for by the applying model and was more appropriate than either correlation or R-squared to indicate the goodness-of-fit. The core tablet behaved as contracting sphere during the drug release process with the drug-depleted zones providing as a diffusive barrier. The drug concentration in dissolution medium was assumed to be uniform at all times due to effective stirring. It did not consider the initial swelling of coated tablets and release of drug when coated tablets were exposed to dissolution medium and thereby this was accounted by the inclusion of lag time in equation corresponding to the duration of this phase. Since there were no data available to calculated the initial phase kinetics, it is necessary to rely on experimental evidence for a reasonable assessment of lag time. This initial phase was the duration of water penetration through the film coat and dissolved the drug in the core. The developed physical model was applied from the time when the drug in the core was dissolved by the penetrating water.

The initial thickness of film coat is Ho-Ro and gets thinner and thinner with time. The time interval, $T = A/B = (Ho-Ro)/a$, the thickness becomes zero, that is, the film has dissolved completely and only the core tablet is remained to release thereafter. Thus this equation is good for $t < A/B$. Therefore during $t > A/B$; it should be applied cube root equation for the drug release from only remained core tablet. So when $t > A/B$ this study selects $dQ/dt = K (Q_0-Q)^{(2/3)}$ which is the differentiated form of the cube-root equation (Wagner and Pernarowski, 1971), describes the drug release from the core tablet.

The application of this physical developed model is depended on the time. It will be good for $(0< t< (A/B))$ and it has to use the cube-root equation for $t > (A/B)$. The combined equation of above two equations is obtained as

$$dQ/dt = C/\left\{A - B(t-Tl) + \left\{\frac{1-(1-(Q/Q_0))^{1/3}}{(1-(Q/Q_0))^{1/3}}\right\}\right\} + K(1-(Q/Q_0))^{2/3} \quad \text{..KGT2 (Eq. 57)}$$

The total time for film dissolution (Tf) can be calculated from [(A/B) + lag time]. Thus the film dissolution rate could be calculated from film thickness/Tf (μm/min).

In case of insoluble film, it can simply set a = 0 or B = 0. In case of the barrier changing to the insoluble film, then (a) or (B) in equation KGT1 is set as a function of time (t), (a) or (b) decreasing with time.

In case (a=0), the original equation (KGT1) can be integrated to give:

$$(3/2).\{Q_0-(Q_0)^{1/3}.(Q_0-Q)^{2/3}\} + (A-1).Q = C.(t-Tl) \quad \text{.....KGT3 (Eq. 58)}$$

As the polymer swells, a frame of reference is fixed with respect to the original device, in order to simplicity calculations (Crank, 1975). This equation provides the time course of drug release, it cannot express the release rate by a simple parameter. Thus the release rate for this case is then expressed mathematically by the below equation.

$$dQ/dt = C/ ((1- (Q/Q_0))^{-1/3}+(A-1)) \quad \text{.....(Eq. 59)}$$

2. Curve Fitting and Comparison of Goodness-of-Fit

The determination of the suitable mathematical model was required to explain the drug release characteristics, therefore, an analysis of dissolution profiles was performed to elucidate which model would be best fitted by the experimental release data. Coefficient of determination from nonlinear regression was employed as statistical parameter to indicate the goodness of curve fitting.

2.1 Fast Release

The coefficient of determination from curve fitting of drug release from fast release preparation and different equations are shown in Tables *353-359* in Appendix D. The estimate parameters and informative parameters from curve fitting with KGT2 are shown in Tables *353-415* in Appendix D. In case of drug release from core tablets and tablets coated with chitosan citrate film at different coating levels in dilute HCl solution and phosphate buffer pH 6.8, the coefficient of determinations from curve fitting with cube root, first order, Higuchi's, KGT2 and Weibull equations were obtained as tabulated in Tables *353* and *358* in Appendix D. The highest coefficient of determination was obtained from curve fitting between KGT2 equation and drug release profiles of core tablet both using of acid fluid (0.9977 ± 0.0010) and basic fluid (0.9979 ± 0.0010) as dissolution medium as presented in Table *17* and *18*. Curve fitting with Weibull equation also provided high value of coefficient of determination which was greater than that from curve fitting with cube root equation.

A comparative evaluation of coefficient of determination values showed that the best fit model for release profiles of chitosan citrate film coated tablets both in acid and basic medium appeared to be KGT2 equation as presented in Table *17* and *18*, with the except of those from curve fitting of release profiles of tablets coated with this film at coating level of 12%. The high values of coefficient of determination indicated that this model yielded satisfactory fits. The graphical representation of the fitting results of fraction of drug released vs time in dilute HCl solution of tablets coated with chitosan citrate films at coating level of 6 and 12% based on polymeric salt to KGT2 equation is presented in Figure *228* . For drug release from tablet coated with this film at coating level of 12% in acid medium, the Weibull model provided the coefficient of determination slightly greater than KGT2 model, while in basic medium the high values of this statistical parameter were obtained from curve fitting with KGT2 and Weibull models.

The lag times estimated from curve fitting with KGT2 were longer as the amount of film coat was increased especially in case of drug release undertaken in phosphate buffer. The Tf representing the film dissolution time of drug release in acid medium was not markedly different while it had a tendency to increase in the case of drug release in basic medium as the coating level was enhanced. The dissolution rate of chitosan citrate film from coated tablets in acid medium was increased when the coating level was increased as shown in Table *23*. Whereas in basic medium the film dissolution rate was likely to be decreased as coating level was greater than 6% as shown in Table *24*. The release rates (K) of drug from remaining core tablet are presented in Tables *23* and *24*. A comparative evaluation showed that the drug release rates of remaining core tablet after film completely dissolved of all coated tablets were less than that of core tablet both in acid and alkaline dissolution fluids which were 0.3215 ± 0.0814 and 0.2974 ± 0.0272 respectively. An enhancement of coating level resulted in the decrease of release rate of drug in basic medium, but it could not see this tendency of drug release rate in acid medium. By comparison, the drug release rates in acid medium was higher than those in basic medium.

The experimental release data of tablet coated with chitosan malate film in acid medium could be fitted successfully with KGT2 model providing high values of coefficient of determination (0.9962 ± 0.0017 to 0.9987 ± 0.0010) as shown in Table *19*. The graphical representation of the fitting results of fraction of drug released vs time in dilute HCl solution of tablets coated with chitosan malate films at coating level of 6 and 12% based on polymeric salt to KGT2 equation is presented in Figure *228*. The lag time and film dissolution time had a tendency to increase as coating level was increased and they were also longer than those of tablets coated with chitosan citrate film as presented in Table *25*. The dissolution rate of chitosan malate film from coated tablets increased as the coating level was enhanced. However the rate was slower than that of chitosan citrate film with the except at coating level of 1%. As the coating level was increased, the release rate of drug from remaining core tablet was decreased as shown in Table *25*.

The drug release profiles of tablets coated with unplasticized and plasticized chitosan citrate or chitosan malate films at coating level of 3% w/w based on polymer could successfully fitted with KGT2 equation providing high coefficient of determination (0.9917 ± 0.0081 to 0.9977 ± 0.0019) as shown in Table *20*. Tf of these film

Table 17 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with chitosan citrate film at different coating level based on chitosan salt in dilute HCl acid and different equations (n=6)

	Coefficient of Determination				
Coating Level (%	Cube Root	First Order	Higuchi's	KGT2	Weibull
0	0.9798±0.0210	0.9588±0.0168	0.5557±0.1572	0.9977±0.0010	0.9826±0.1930
1	0.9938±0.0051	0.9663±0.0103	0.7413±0.0862	0.9970±0.0027	0.9921±0.0033
3	0.9859±0.0047	0.9670±0.0082	0.7184±0.0558	0.9984±0.0018	0.9962±0.0028
6	0.9885±0.0069	0.9477±0.0129	0.6671±0.1032	0.9988±0.0012	0.9970±0.0009
9	0.9883±0.0135	0.9432±0.0131	0.7489±0.0361	0.9972±0.0021	0.9959±0.0043
12	0.9891±0.0070	0.9466±0.0168	0.7807±0.0883	0.9970±0.0019	0.9974±0.0018

Table 18 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with chitosan citrate film at different coating level based on chitosan salt in phosphate buffer pH 6.8 and different equations (n=6)

	Coefficient of Determination				
Coating Level (%	Cube Root	First Order	Higuchi's	KGT2	Weibull
0	0.9841±0.0073	0.9757±0.0078	0.4734±0.1554	0.9979±0.0010	0.9938±0.0017
1	0.9868±0.0088	0.9652±0.0132	0.7386±0.0818	0.9927±0.0046	0.9769±0.0089
3	0.9834±0.0212	0.9731±0.0108	0.8323±0.0226	0.9951±0.0039	0.9722±0.0222
6	0.9533±0.0810	0.9852±0.0148	0.9313±0.0338	0.9909±0.0042	0.9821±0.0139
9	0.9859±0.0084	0.9659±0.0225	0.8812±0.0281	0.9917±0.0059	0.9882±0.0074
12	0.9857±0.0151	0.9636±0.0281	0.8851±0.0716	0.9907±0.0089	0.9907±0.0093

Table 19 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with chitosan malate and chitosan acetate films at different coating level based on chitosan salt in dilute HCl acid and KGT2 (n=6)

Coating Level (%)	Coefficient of Determination	
	CM	CA
1	0.9987±0.0010	0.9937±0.0045
3	0.9985±0.0013	0.9977±0.0019
6	0.9973±0.0018	0.9955±0.0053
9	0.9962±0.0017	0.9980±0.0011
12	0.9979±0.0006	0.9854±0.0093
15	-	0.9857±0.0083

Table 20 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with unplasticized and plasticized chitosan citrate and chitosan malate films at coating level of 3%w/w based on chitosan based on chitosan in dilute HCl acid and KGT2 (n=6)

Coated Tablet	Coefficient of Determination
	In Dilute HCl Solution
CC	0.9972±0.0024
CC G25	0.9917±0.0081
CC P25	0.9977±0.0011
CM	0.9930±0.0107
CM G25	0.9962±0.0027
CM P25	0.9977±0.0019

Table 21 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with chitosan citrate films at coating level of 3% w/w based on chitosan in dilute HCl acid and phosphate buffer pH 6.8and KGT2 (n=6)

Coated Tablet	Coefficient of Determination	
	In Dilute HCl Solution	In Phosphate Buffer
CC P25 G0.5	0.9923±0.0142	0.9955±0.0023
CC P25 B0.5	0.9945±0.0018	0.9953±0.0024
CC P25 B0.5 Ta15	0.9988±0.0008	0.9924±0.0037
CC P25 B0.5 Ta30	0.9989±0.0009	0.9934±0.0058
CC P25 B0.5 Ta45	0.9966±0.0042	0.9974±0.0023
CC P25 B0.5 Ti15	0.9970±0.0016	0.9923±0.0041
CC P25 B0.5 Ti30	0.9969±0.0024	0.9953±0.0017
CC P25 B0.5 Ti45	0.9980±0.0009	0.9955±0.0044

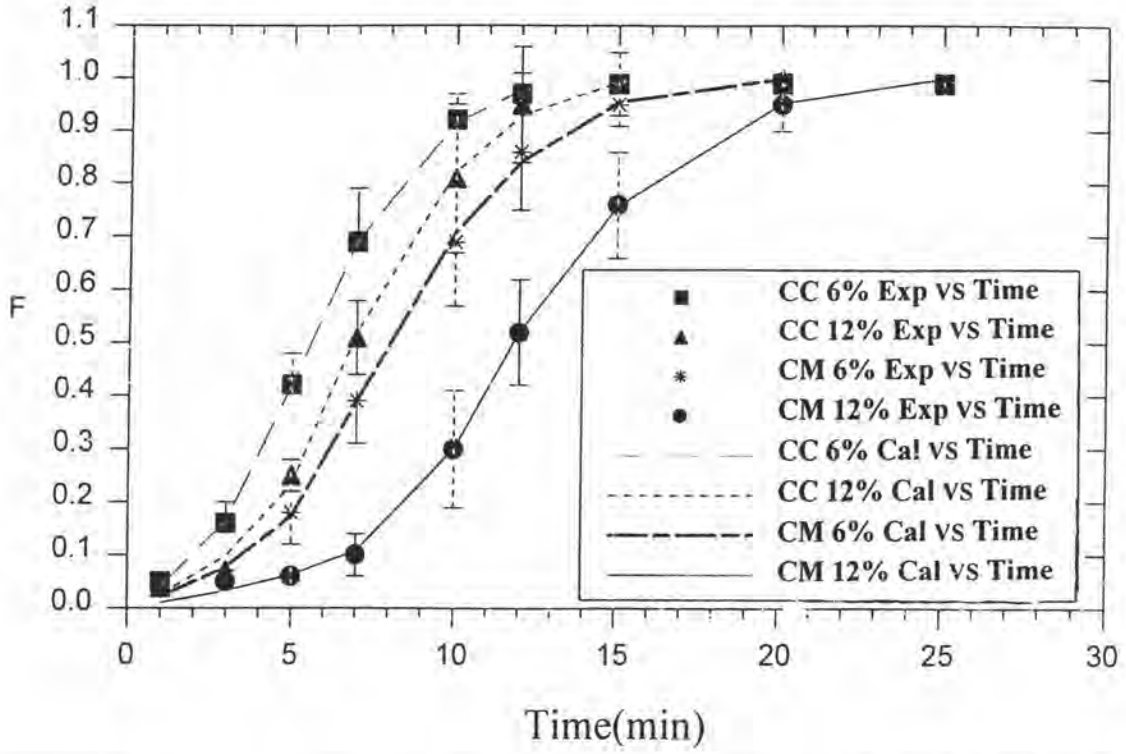


Figure 228 Graphical representation of the fitting results of fraction of drug released vs time in dilute HCl solution of tablets coated with chitosan citrate and chitosan malate films at different coating level based on polymeric salt to KGT2 equation.

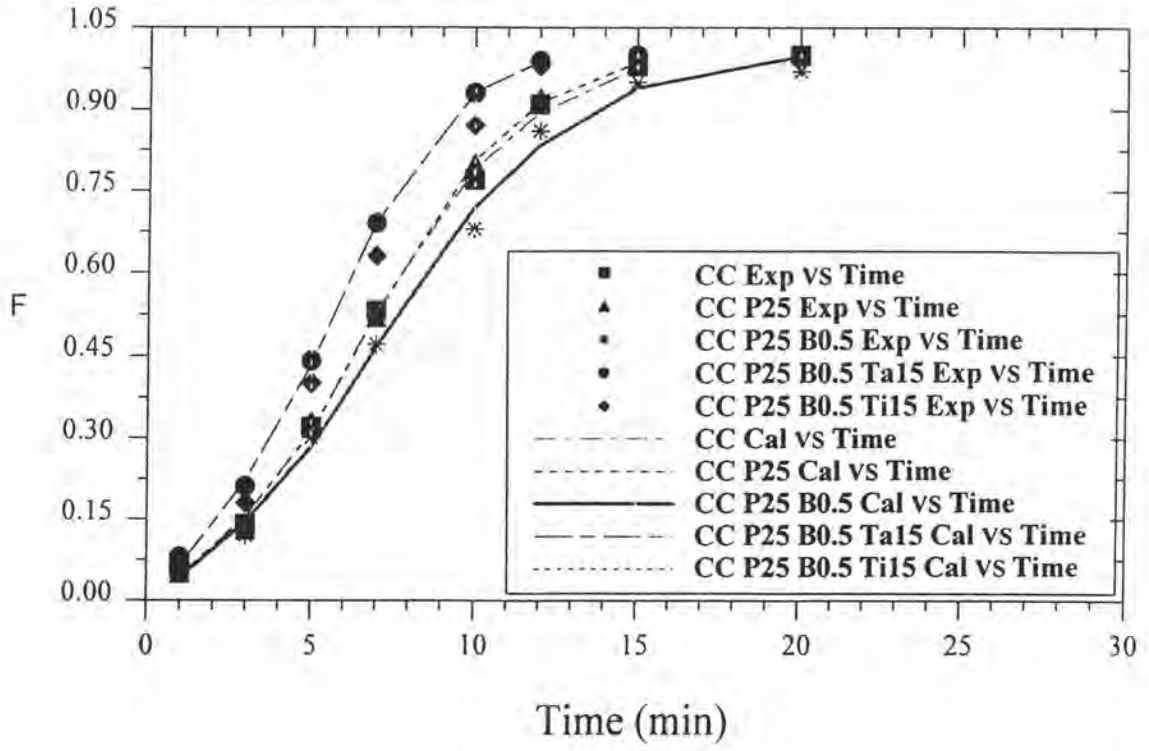


Figure 229 Graphical representation of the fitting results of fraction of drug released vs time in dilute HCl solution of tablets coated with chitosan citrate films containing different additives at coating level of 3% w/w based on chitosan to KGT2 equation.

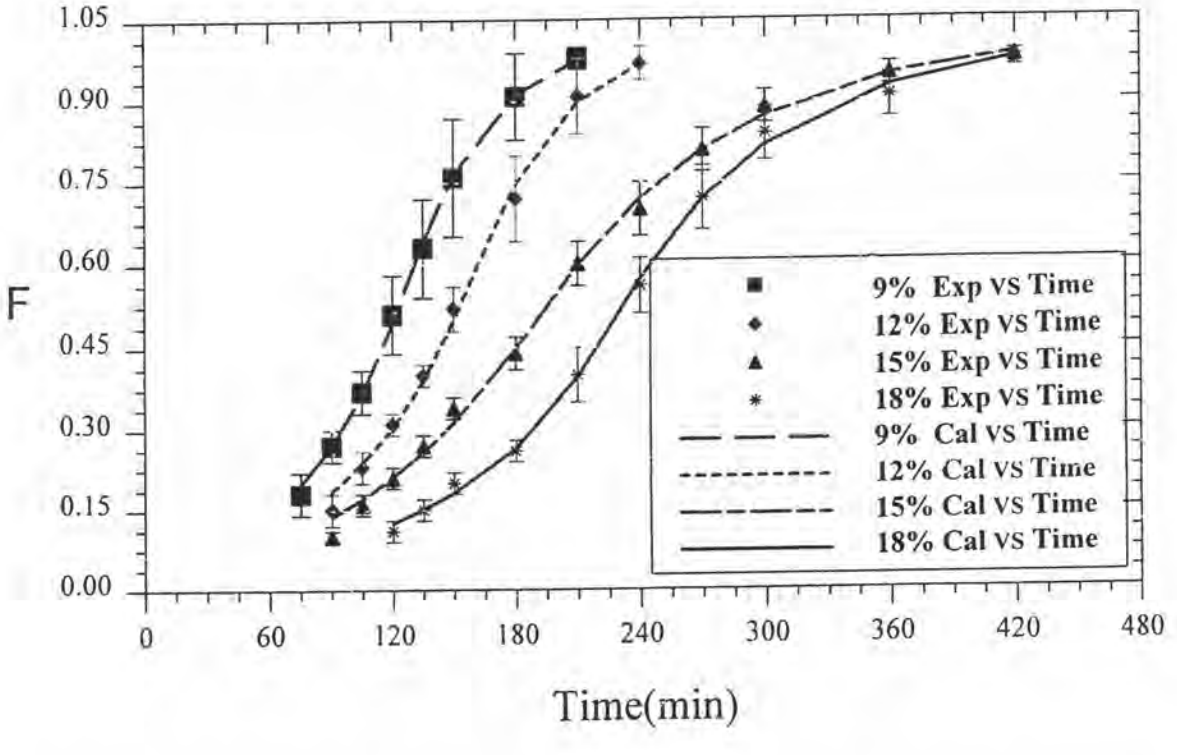


Figure 230 Graphical representation of the fitting results of fraction of drug released vs time in HCl buffer pH 1.2 of tablets coated with CA M45 Cas15 film at different coating level based on chitosan to KGT2 equation.

Table 23 Estimate parameters from curve fitting between drug release from tablet coated with chitosan citrate film at different coating level based on chitosan salt in dilute HCl acid and KGT2 (n=6)

Coating Level (%)	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
1	0.00±0.00	7.50±2.04	0.58±0.20	7.2302±0.5803	0.2794±0.0951
3	0.85±0.38	4.67±1.29	3.55±1.03	3.8511±0.6665	0.2284±0.0376
6	1.37±0.35	4.77±0.78	8.77±1.29	1.9932±0.5671	0.2215±0.0706
9	1.95±0.90	5.67±0.83	10.49±1.39	3.6098±1.0443	0.1973±0.0228
12	2.21±0.12	6.07±0.78	12.07±1.89	1.9558±0.6273	0.1670±0.0287

Table 24 Estimate parameters from curve fitting between drug release from tablet coated with chitosan citrate film at different coating level based on chitosan salt in phosphate buffer pH 6.8 and KGT2 (n=6)

Coating Level (%)	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
1	1.07±1.43	3.29±1.11	1.32±0.38	1.4114+0.7700	0.2028+0.0529
3	1.01±2.46	3.82±0.52	4.12±0.59	0.6541+0.3018	0.1702+0.0261
6	5.65±0.60	6.08±0.59	6.80±0.64	0.8325+0.3275	0.0916+0.0265
9	7.01±0.59	9.39±0.76	6.26±0.49	0.2403+0.0986	0.0904+0.0221
12	8.57±2.07	12.23±1.56	5.97±0.75	0.3310+0.2669	0.0786+0.0087

Table 25 Estimate parameters from curve fitting between drug release from tablet coated with chitosan malate film at different coating level based on chitosan salt in dilute HCl acid and KGT2 (n=6)

Coating Level (%)	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
1	0.00±0.00	4.27±0.32	1.19±0.07	1.4955±0.4070	0.2794±0.0951
3	0.03±0.01	6.50±1.17	2.68±0.45	2.9600±0.6305	0.2284±0.0376
6	1.45±0.22	7.20±1.56	5.05±1.02	2.1131±0.3911	0.2215±0.0706
9	2.36±0.12	7.50±1.28	6.88±1.06	2.1766±0.7803	0.1973±0.0228
12	3.90±0.24	9.97±0.89	6.92±0.61	1.5521±0.5907	0.1670±0.0287

Table 26 Estimate parameters from curve fitting between drug release from tablet coated with chitosan unplasticized and plasticized citrate film at coating level of 3%w/w based on chitosan in dilute HCl acid and KGT2 (n=6)

Coated Tablet	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
CC	1.20±0.00	8.52±2.32	4.31±1.16	4.0971±1.5664	0.2626±0.904
CC G25	1.31±0.01	9.28±1.78	5.47±1.53	3.1770±1.2443	0.2252±0.0780
CC P25	0.85±0.06	7.08±1.63	5.64±1.24	3.4210±1.3496	0.2419±0.0704
CM	0.48±0.13	6.03±0.60	5.94±0.65	2.9896±1.0822	0.2186±0.0705
CM G25	0.56±0.00	8.33±1.85	5.01±1.11	2.4453±0.3907	0.1751±0.0363
CM P25	0.56±0.13	7.71±1.43	4.99±0.85	2.7448±1.1154	0.1742±0.0358

Table 27 Estimate parameters from curve fitting between drug release from tablet coated with chitosan colored and pigmented citrate film at coating level of 3%w/w based on chitosan in dilute HCl acid and KGT2 (n=6)

Coated Tablet	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
CC P25 G0.5	0.21±0.10	8.38±1.66	5.74±1.15	2.3823±0.9907	0.2452±0.0800
CC P25 B0.5	0.12±0.13	6.90±1.65	6.34±1.29	2.0388±0.6184	0.1686±0.0287
CC P25 B0.5 Ta15	0.63±0.08	6.96±1.46	5.31±1.22	5.2077±1.4748	0.2972±0.0455
CC P25 B0.5 Ta30	0.56±0.00	6.14±2.22	6.23±2.16	4.3196±1.9564	0.2813±0.0663
CC P25 B0.5 Ta45	0.44±0.12	5.31±0.46	9.00±0.73	5.5936±0.6169	0.3416±0.0778
CC P25 B0.5 Ti15	0.64±0.18	8.00±2.28	6.34±2.18	5.2844±1.4519	0.3329±0.1014
CC P25 B0.5 Ti30	0.57±0.02	7.24±0.91	7.42±0.97	5.8844±1.6206	0.2806±0.0308
CC P25 B0.5 Ti45	0.56±0.00	7.44±1.43	7.11±1.21	5.1147±1.1372	0.2854±0.0519

Table 28 Estimate parameters from curve fitting between drug release from tablet coated with chitosan colored and pigmented citrate film at coating level of 3%w/w based on chitosan in phosphate buffer pH 6.8 and KGT2 (n=6)

Coated Tablet	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
CC	3.95±0.99	8.90±1.43	3.96±0.64	0.2189±0.0788	0.0841±0.0142
CC P25	5.58±2.44	10.42±1.29	3.74±0.45	0.0947±0.0448	0.0544±0.0066
CC P25 G0.5	6.38±1.35	7.49±1.29	6.41±1.44	0.3277±0.1840	0.0958±0.0018
CC P25 B0.5	6.60±0.49	7.45±0.55	5.66±0.40	0.0632±0.0671	0.1996±0.2865
CC P25 B0.5 Ta15	5.79±2.51	13.54±3.31	2.76±0.68	0.1835±0.1352	0.0646±0.0192
CC P25 B0.5 Ta30	5.17±1.22	10.51±2.84	3.50±0.98	0.2810±0.1023	0.0590±0.0166
CC P25 B0.5 Ta45	2.51±1.03	5.69±0.72	8.46±1.06	0.2862±0.1049	0.1185±0.0269
CC P25 B0.5 Ti15	9.98±3.08	12.90±3.21	3.85±1.01	0.0913±0.0464	0.0385±0.0056
CC P25 B0.5 Ti30	9.14±0.98	12.45±2.04	4.36±0.75	0.0979±0.0331	0.0406±0.0055
CC P25 B0.5 Ti45	8.19±3.58	13.77±3.65	3.98±1.06	0.0712±0.0320	0.0376±0.0055

Table 29 Estimate parameters from curve fitting between drug release from tablet coated with chitosan acetate film at different coating level based on chitosan in dilute HCl acid and KGT2 (n=6)

Coating Level (%)	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+2)	K
1	0.00±0.00	2.15±0.82	4.62±2.02	0.2995±0.1391	0.0523±0.0084
3	0.00±0.00	2.48±0.61	7.45±1.86	0.5632±0.1710	0.0512±0.0119
6	1.33±0.58	5.14±1.72	6.87±2.31	0.3088±0.1720	0.0409±0.0061
9	6.29±0.29	7.25±0.69	6.87±0.58	1.1705±0.1661	0.0379±0.0051
12	7.19±0.80	9.11±1.65	7.59±1.23	0.6518±0.6894	0.0303±0.0057
15	13.04±1.65	13.04±1.65	4.55±0.98	0.0635±0.0621	0.0308±0.0062

Table 30 Estimate parameters from curve fitting between drug release from tablet coated with CA M45 Cas15 film at different coating level based on chitosan in HCl buffer pH 1.2 and KGT2 (n=6)

Coating Level (%)	Tl (min)	Tf (min)	Film Dissolusion Rate(mcm/min)	C Value (E+3)	K(E+3)
9	65.85±8.23	119.46±19.3	1.0167±0.1528	1.8323±0.6700	19.4700±5.5149
12	64.24±2.76	138.29±2.58	1.1037±0.1015	1.5231±0.1243	15.3986±3.9719
15	67.37±1.79	146.36±4.22	1.1418±0.0332	1.0682±0.0538	6.9438±0.7882
18	95.39±2.73	192.59±4.47	1.2545±0.0288	0.9804±0.0947	8.4259±1.5510

coated tablets was about 8 minutes and the lag time was very short as presented in Table 26. The film dissolution rate was about 5 μm/min. The drug release rate from remaining core tablets of tablets coated with unplasticized and plasticized chitosan malate films was less than that of remaining core tablets of tablets coated with unplasticized and plasticized chitosan citrate films. After incorporation of water soluble dyes or pigments in chitosan citrate film plasticized with 25% propylene glycol, the release profiles from release test in acid medium of tablet coated with these films could provide high coefficient of determination after curve fitting with KGT2 model (0.9923±0.0142 to 0.9989±0.0009) as shown in Table *21*. Graphical representation of the fitting results of fraction of drug released vs time in dilute HCl solution of tablets coated with chitosan citrate films containing different additives at coating level of 3% w/w based on chitosan to KGT2 equation is depicted in Figure *229*. Lag time of drug release from these coated tablets was very short. Tf of tablet coated with film colored with green FS was longer than that of tablet coated with film colored with brilliant blue as presented in Table *27*. The film dissolution rate of tablet coated with film colored with green FS was less than that of tablet coated with film colored with brilliant blue. The more addition of talcum, the shorter was the Tf. Tf values of tablet coated with film pigmented with talcum was less than that of unplasticized or plasticized film coated tablets and shorter than that of tablets coated with film pigmented with titanium dioxide. The film dissolution rate of tablets coated with chitosan film pigmented with talcum was increased as the amount of this pigment was increased. The highest film dissolution rate was obtained after incorporation of talcum at amount of 45%. The drug release rate of remaining core tablet of pigmented film coated tablets was greater than that of unpigmented film coated tablets. However this release rate of tablets coated with film colored with green FS was greater than that of tablet coated with film colored with brilliant blue.

The high values of coefficient of determination (0.9923±0.0041 to 0.9974±0.0023) pointed out that the release data from the dissolution test in phosphate buffer could fit well with KGT2 model as shown in Table *21*. Tl and Tf of tablet coated with film pigmented with talcum had a tendency to decrease as the amount of pigment was increased as presented in Table *28*. Tl and Tf of tablet coated with film pigmented with titanium dioxide was rather longer than those of the others. The film dissolution rate of tablets coated with film pigmented with talcum 45% was very high and that of tablet coated with film colored with green FS was higher than that of tablet coated with film colored with brilliant blue. The drug release rate of remaining core tablets of tablets coated with fim colored with green FS was less than that of tablet coated with film colored with brilliant blue. Whereas the release rate of remaining core tablet of tablet coated with film pigmented with titanium dioxide was less than that of the others. By comparison, the C value of abovementioned drug release in basic medium was noticeable less than that of drug release in acid medium.

In case of dissolution test in acid dissolution medium, the drug release profiles of tablets coated with chitosan acetate film at different coating level could fit with KGT2 model providing high coefficient of determination (0.9854±0.0093 to 0.9980±0.0011) as shown in Table *19*. Tl and Tf were gradually longer as the amount of film coat was increased as shown in Table *29*. The film dissolution rate was slightly greater than that of chitosan malate film coated tablets as shown in Table *29*. The drug release rate from remaining core tablet had a tendency to gradually decrease as the

amount of film coat was increased and was markedly less than that of tablets coated with chitosan citrate and chitosan malate films.

In case of drug release profiles of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% at different coating level in HCl buffer pH 1.2. The coefficient of determination from curve fitting with cube root, first order, Higuchi's, KGT2, power law and Weibull equations were obtained as tabulated in Table *22*. A comparative evaluation of coefficient of determination values revealed that the best fit equation for drug release from tablet coated with film at coating level of 9, 15 and 18% was KGT2. Graphical representation of the fitting results of fraction of drug released vs time in HCl buffer pH 1.2 of tablets coated with CA M45 Cas15 film at different coating level based on chitosan to KGT2 equation is illustrated in Figure *230*. At coating level of 12%, curve fitting with KGT2 also provided high coefficient of determination (0.9931±0.0031) but this value was slightly less than that from curve fitting with Power law expression (0.9935±0.0031). The more increase in coating level, the longer was the film dissolution time as shown in Table *30*. The film dissolution rate had a tendency to increase as the coating level was increased as shown in Table *30* . By comparison the film dissolution rate of tablets coated with this film coating formulation was obviously slower than that of chitosan citrate, chitosan malate and chitosan acetate films. The drug release rate of remaining core tablet had a tendency to decrease as the coating level was increased. The C value was notably decreased as coating level was increased and was less than that of drug release from tablets coated with chitosan citrate, chitosan malate and chitosan acetate film.

2.2 Extended Release

The values of coefficient of determination from curve fitting with different equations of core and coated tablets are shown in Tables *416-435* in Appendix D. The highest coefficient of determination was obtained from curve fitting between power law expression and drug release from core tablet both in acid (0.9988±0.0006) and basic (0.9992±0.0008) media as presented in Tables *416* and *417* respectively in Appendix D. Curve fitting with KGT3 also provided the high coefficient of determination both in acid (0.9970±0.0015) and basic (0.9991±0.0004) medium.

The estimate parameters and informative parameters from curve fitting with KGT3 and first order equations are presented in Tables *436-522* in Appendix D. In case of tablets coated with chitosan acetate film containing magnesium stearate 45% after moist heat treatment at 60°C, the best equation to be fitted with most drug release profiles was Weibull equation as shown in Table *31*. Curve fitting with KGT3 also provided high coefficient of determination (0.9877±0.0084 to 0.9970±0.0018) but it was slightly less than that from curve fitting with Weibull equation (0.9920±0.0025 to 0.9981±0.0010).

Curve fitting with KGT3 and Weibull equations of drug release from tablets coated with chitosan acetate film containing talcum 45% treated with moist heat at different time intervals also provided the high value of coefficient of determination. The coefficient of determination of drug release profiles of these coated tablets after moist heat treatment at 45°C by fitting with KGT3 and Weibull equations was 0.9675±0.0407 to 0.9978±0.0016 and 0.9860±0.0082 to 0.9981±0.0008 respectively as shown in Table

Table 31 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 film after moist heat treatment at 60°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination						
	Cube Root	First Order	Higuchi's	KGT3	Power Law	Weibull	Zero Order
24	0.9698±0.0102	0.9873±0.0055	0.9771±0.0134	0.9909±0.0079	0.9830±0.1110	0.9946±0.0047	0.8877±0.0360
48	0.9891±0.0039	0.9936±0.0044	0.9895±0.0039	0.9937±0.0036	0.9906±0.0050	0.9937±0.0045	0.9516±0.0049
72	0.9966±0.0014	0.9923±0.0027	0.9790±0.0069	0.9969±0.0014	0.9964±0.0026	0.9969±0.0010	0.9857±0.0023
120	0.9723±0.0224	0.9845±0.0131	0.9726±0.0037	0.9877±0.0084	0.9858±0.0107	0.9920±0.0025	0.9241±0.0473
168	0.9875±0.0166	0.9906±0.0054	0.9763±0.0117	0.9970±0.0018	0.9934±0.0033	0.9981±0.0010	0.9604±0.0450

Table 32 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA Ta45 film after moist heat treatment at 45°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination						
	Cube Root	First Order	Higuchi's	KGT3	Power Law	Weibull	Zero Order
24	0.9910±0.0079	0.9744±0.0118	0.9647±0.0261	0.9937±0.0049	0.9970±0.0009	0.9943±0.0008	0.9901±0.0052
48	0.9847±0.0060	0.9841±0.0025	0.9611±0.0128	0.9850±0.0046	0.9789±0.0051	0.9876±0.0051	0.9655±0.0148
72	0.9705±0.0357	0.9591±0.0448	0.9128±0.0792	0.9675±0.0407	0.9872±0.0019	0.9860±0.0082	0.9713±0.0052
120	0.9935±0.0035	0.9975±0.0002	0.9761±0.0110	0.9978±0.0016	0.9955±0.0030	0.9981±0.0008	0.9628±0.0127
168	0.9956±0.0019	0.9974±0.0013	0.9753±0.0053	0.9977±0.0010	0.9974±0.0006	0.9975±0.0012	0.9701±0.0068

Tble 33 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA Ta45 film after moist heat treatment at 60°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination						
	Cube Root	First Order	Higuchi's	KGT3	Power Law	Weibull	Zero Order
24	0.9912±0.0065	0.9941±0.0015	0.9836±0.0038	0.9944±0.0016	0.9903±0.0053	0.9952±0.0015	0.9643±0.0203
48	0.9920±0.0045	0.9925±0.0044	0.9843±0.0100	0.9951±0.0009	0.9927±0.0026	0.9961±0.0024	0.9654±0.0246
72	0.9942±0.0047	0.9923±0.0039	0.9573±0.0377	0.9944±0.0048	0.9874±0.0090	0.9939±0.0047	0.9788±0.0081
120	0.9980±0.0008	0.9946±0.0033	0.9732±0.0091	0.9981±0.0006	0.9955±0.0010	0.9990±0.0001	0.9812±0.0038
168	0.9800±0.0271	0.9759±0.0379	0.9517±0.0489	0.9854±0.0226	0.9967±0.0027	0.9929±0.0100	0.9800±0.0135

Table 34 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 Cas15 film after moist heat treatment at 45°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination						
	Cube Root	First Order	Higuchi's	KGT3	Power Law	Weibull	Zero Order
24	0.9967±0.0018	0.9971±0.0002	0.9880±0.0058	0.9977±0.0010	0.9952±0.0029	0.9990±0.0005	0.9699±0.0088
48	0.9893±0.0117	0.9945±0.0039	0.9904±0.0068	0.9959±0.0025	0.9916±0.0052	0.9970±0.0016	0.9515±0.0372
72	0.9789±0.0080	0.9908±0.0055	0.9866±0.0081	0.9945±0.0037	0.9918±0.0022	0.9955±0.0032	0.9245±0.0178
120	0.9576±0.0240	0.9750±0.0092	0.9513±0.0284	0.9806±0.0035	0.9764±0.0091	0.9859±0.0033	0.9235±0.0702
168	0.9791±0.0100	0.9906±0.0014	0.9834±0.0056	0.9944±0.0024	0.9906±0.0012	0.9959±0.0030	0.9270±0.0413

Table 35 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 Cas15 film after moist heat treatment at 60°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination						
	Cube Root	First Order	Higuchi's	KGT3	Power Law	Weibull	Zero Order
24	0.9818±0.0122	0.9925±0.0054	0.9874±0.0054	0.9948±0.0018	0.9775±0.0121	0.9960±0.0005	0.9299±0.0317
48	0.9762±0.0079	0.9899±0.0047	0.9841±0.0123	0.9932±0.0046	0.9846±0.0088	0.9947±0.0032	0.9200±0.0230
72	0.9949±0.0017	0.9949±0.0033	0.9842±0.0054	0.9964±0.0023	0.9882±0.0075	0.9965±0.0031	0.9461±0.0300
120	0.9939±0.0012	0.9940±0.0008	0.9849±0.0051	0.9946±0.0005	0.9944±0.0011	0.9943±0.0005	0.9787±0.0061
168	0.9962±0.0026	0.9953±0.0034	0.9869±0.0060	0.9965±0.0029	0.9960±0.0033	0.9963±0.0028	0.9793±0.0043

32. Whereas those of tablets after moist heat treatment at 60°C by fitting with KGT3 and Weibull equations was 0.9854±0.0226 to 0.9981±0.0006 and 0.9929±0.0100 to 0.9990±0.0001 as presented in Table *33*.

Curve fitting between drug release profiles of tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% after moist heat treatment at 45°C and 60°C, with Weibull equation provided the coefficient of determination (0.9859±0.0033 to 0.9990±0.0005) as shown in Tables *34* and *35* which was greater than from curve fitting with KGT3 (0.9806±0.0035 to 0.9977±0.0010), with the except that the drug release profiles of coated tablets after moist heat treated at 60°C for 120 and 168 hours could be fitted with KGT3 (0.9946±0.00050 and 0.9965±0.0029) greater than Weibull equation (0.9943±0.00060 and 0.9963±0.0028).

A comparative evaluation of coefficient of determination demonstrated that curve fitting with cube root, Higuchi's and zero order equations was less successful due to providing low coefficient of determination value. Theoretically, Weibull expression did not indicate the release mechanism, therefore the next procedure of curve fitting for other release profiles was performed relied on first order, Higuchi's, KGT3 and power law expressions. Due to the widely used of Higuchi's equation, this study also included this expression for comparison the degree of curve fitting with other models too.

Most drug release profiles of tablets coated with chitosan acetate film containing magnesium stearate 60% and 75% after moist heat treatment at 45°C and 60°C for different time intervals could be fitted with KGT3 providing the values of coefficient of determination (0.9718±0.0231 to 0.9948±0.0017 and 0.9652±0.0102 to 0.9968±0.0020 respectively) which were higher than those from curve fitting with first order, Higuchi's and power law expression as presented in Tables *36* and *37*. Whereas curve fitting of release profiles of tablets after moist heat treatment at 45°C and 60°C with Higuchi's equation provided the lowest value of coefficient of determination (0.9506±0.0274 to 0.9885±0.0063 and 0.8829±0.335 to 0.9941±0.0006 respectively).

In case of drug release tested in glucose solutions with different osmolality, the curve fitting with first order, KGT3 and power law expression provided relatively high coefficient of determination value whereas this value was relatively low in curve fitting with Higuchi's and zero order equation as presented in Tables *38* and *39*. However the coefficient of determination value from curve fitting with zero order equation was increased when the osmotic pressure of glucose solution was increased.

The coefficient of determination from curve fitting of drug release profiles of tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5% respectively after moist heat treatment at different %RH at 60°C for 24 hours with release models are shown in Table *40*. Most of release profiles could be best fitted with KGT3 equation which the coefficient of determination from curve fitting was 0.9887±0.0077 to 0.9972±0.0009 and curve fitting with first order and power law expression also provided the high value of coefficient of determination which the values were 0.9844±0.0113 to 0.9952±0.0017 and 0.9825±0.0135 to 0.9969±0.0008 respectively. Whereas curve fitting with Higuchi's and zero order

Table 36 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M60 film after moist heat treatment at 45°C and 60°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination							
	At 45°C 75% RH				At 60°C 75% RH			
	First Order	Higuchi's	KGT3	Power Law	First Order	Higuchi's	KGT3	Power Law
24	0.9722±0.0227	0.9484±0.0537	0.9718±0.0231	0.9854±0.0171	0.9340±0.0137	0.8829±0.0334	0.9652±0.0102	0.9679±0.0036
72	0.9916±0.0031	0.9885±0.0063	0.9948±0.0017	0.9903±0.0045	0.9475±0.0160	0.9189±0.0267	0.9840±0.0088	0.9742±0.0112
120	0.9825±0.0237	0.9728±0.0333	0.9867±0.0156	0.9823±0.0192	0.9941±0.0022	0.9890±0.0006	0.9949±0.0034	0.9897±0.0001

Table 37 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M75 film after moist heat treatment at 45°C and 60°C for different time in pH change system and different equations (n=3)

Duration of Treatment (hrs)	Coefficient of Determination							
	At 45°C 75% RH				At 60°C 75% RH			
	First Order	Higuchi's	KGT3	Power Law	First Order	Higuchi's	KGT3	Power Law
24	0.9772±0.0077	0.9580±0.0340	0.9775±0.0062	0.9646±0.0119	0.9239±0.0130	0.8933±0.0284	0.9766±0.0067	0.9748±0.0125
72	0.9840±0.0142	0.9767±0.0170	0.9905±0.0085	0.9899±0.0043	0.9612±0.0279	0.9604±0.0257	0.9953±0.0050	0.9790±0.0067
120	0.9693±0.0173	0.9506±0.0274	0.9863±0.0044	0.9765±0.0079	0.9958±0.0035	0.9866±0.0075	0.9968±0.0021	0.9949±0.0037

Figure 38 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 film after moist heat treatment at 60°C for 48 hrs. in glucose solutions and different equations (n=3)

Molality (m)	Coefficient of Determination				
	First Order	Higuchi's	KGT3	Power Law	Zero Order
0	0.9498±0.0158	0.9125±0.0324	0.9680±0.0089	0.9533±0.0124	0.7818±0.0467
1.22	0.9964±0.0014	0.9883±0.0030	0.9959±0.0016	0.9936±0.0021	0.9562±0.0119
2.06	0.9985±0.0008	0.9866±0.0030	0.9982±0.0010	0.9956±0.0030	0.9658±0.0088
3.13	0.9976±0.0003	0.9849±0.0121	0.9976±0.0001	0.9991±0.0003	0.9914±0.0075

Table 39 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 Cas15 film after moist heat treatment at 60°C for 24 hrs. in glucose solutions and different equations (n=3)

Molality (m)	Coefficient of Determination				
	First Order	Higuchi's	KGT3	Power Law	Zero Order
0	0.9618±0.0062	0.9279±0.0146	0.9794±0.0062	0.9762±0.0131	0.8313±0.0270
1.22	0.9961±0.0022	0.9917±0.0037	0.9954±0.0023	0.9977±0.0004	0.9826±0.0056
2.06	0.9956±0.0036	0.9796±0.0096	0.9938±0.0085	0.9963±0.0031	0.9879±0.0041
3.13	0.9944±0.0035	0.9739±0.0084	0.9924±0.0051	0.9978±0.0011	0.9973±0.0009

Table 40 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 Cas15 U5 film after moist heat treatment at 60°C for 24 hrs in glucose solutions and different equations (n=6)

%RH	Coefficient of Determination				
	First Order	Higuchi's	KGT3	Power Law	Zero Order
0	0.9844±0.0113	0.9594±0.0292	0.9887±0.0077	0.9825±0.0135	0.9751±0.0187
75	0.9904±0.0069	0.9741±0.0157	0.9953±0.0048	0.9965±0.0036	0.9845±0.0070
85	0.9952±0.0017	0.9831±0.0061	0.9972±0.0009	0.9969±0.0008	0.9765±0.0073
96	0.9920±0.0053	0.9706±0.0160	0.9967±0.0025	0.9954±0.0040	0.9850±0.0061

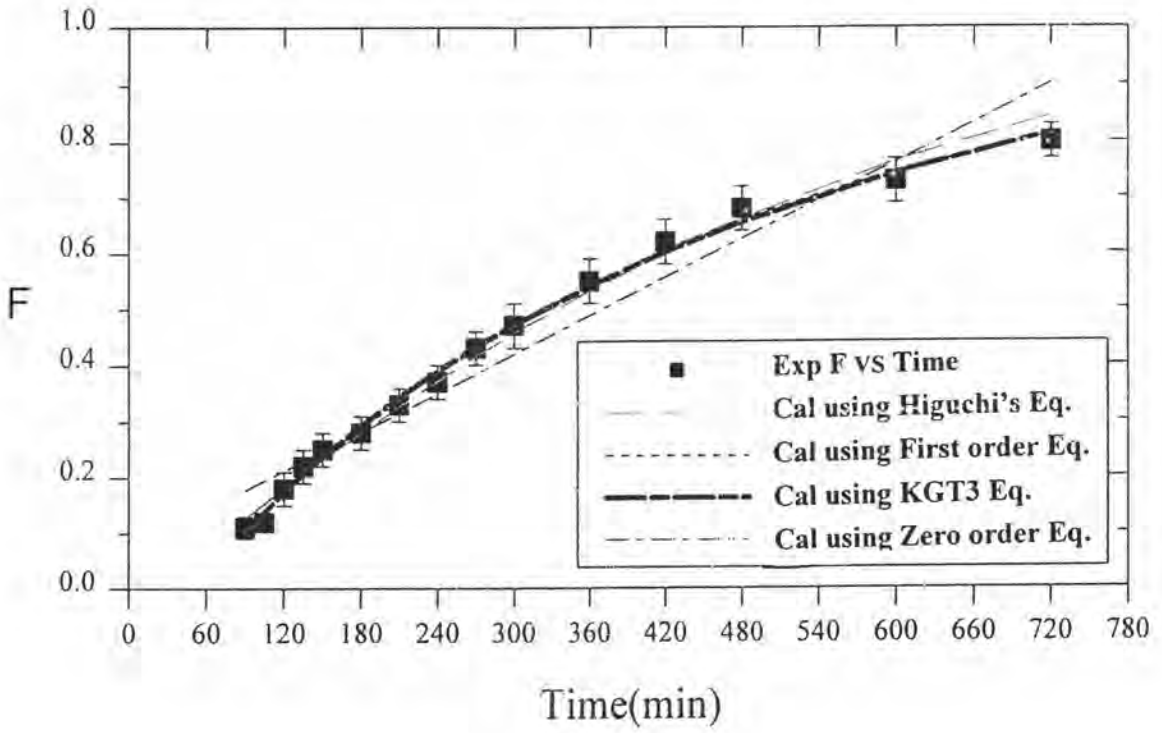


Figure 231 Graphical representation of the fitting results of fraction of drug released vs time in pH change system of tablets coated with CA M45 film at coating level of 15% w/w based on chitosan after moist heat at 60°C for 48 hrs to KGT3 equation.

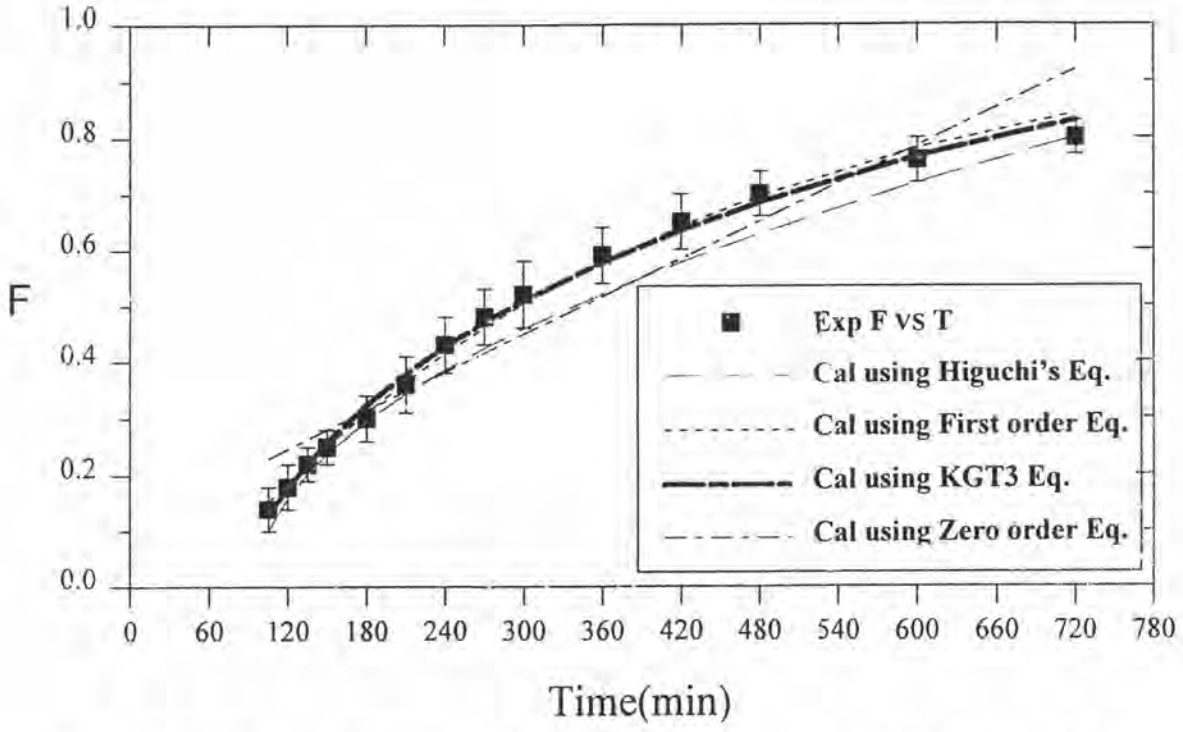


Figure 232 Graphical representation of the fitting results of fraction of drug released vs time in pH change system of tablets coated with CA M45 Cas15 film at coating level of 15% w/w based on chitosan after moist heat at 60°C for 24 hrs to KGT3 equation.

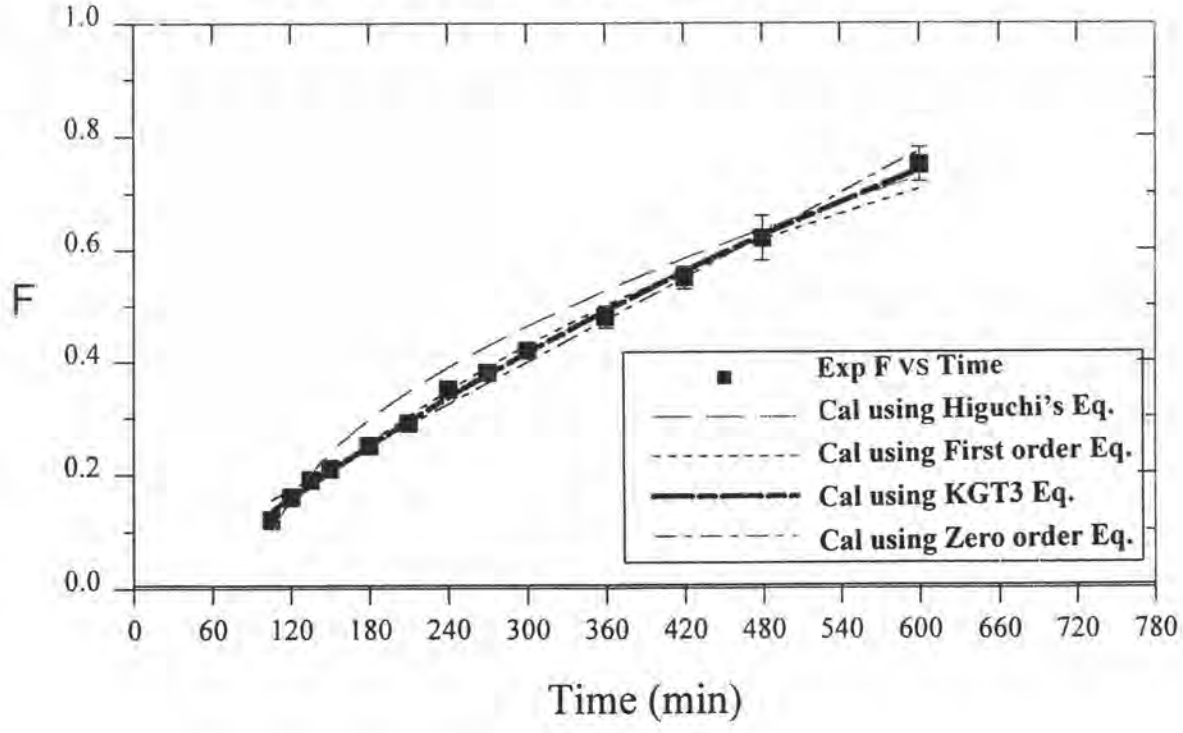


Figure 233 Graphical representation of the fitting results of fraction of drug released vs time in pH change system of tablets coated with CA M45 Cas15 U5 film at coating level of 15% w/w based on chitosan after moist heat at 60°C for 24 hrs to KGT3 equation.

Table 41 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45, CA M45 Cas15 and CA M45 Cas15 U5 films after moist heat treatment at 60°C in HCl buffer pH 1.2 and different equations

Coated Tablet	Coefficient of Determination				
	First Order	Higuchi's	KGT3	Power Law	Zero Order
CA M45[a]	0.9898±0.0023	0.9692±0.0040	0.9971±0.0034	0.9963±0.0036	0.9910±0.0038
CA M45 Cas15[b]	0.9910±0.0034	0.9682±0.0082	0.9973±0.0011	0.9952±0.0015	0.9870±0.0064
CA M45 Cas15 U5[c]	0.9829±0.0059	0.9540±0.0112	0.9984±0.0016	0.9987±0.0015	0.9973±0.0016

[a] After moist heat treatment for 48 hrs (n=3); [b] for 24 hrs (n=3); [c] for 24 hrs (n=6)

Table 42 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45, CA M45 Cas15 and CA M45 Cas15 U5 films after moist heat treatment at 60°C in phosphate buffer pH 6.8 and different equations

Coated Tablet	Coefficient of Determination				
	First Order	Higuchi's	KGT3	Power Law	Zero Order
CA M45[a]	0.9972±0.0014	0.9785±0.0128	0.9966±0.0019	0.9949±0.0040	0.9746±0.0154
CA M45 Cas15[b]	0.9943±0.0043	0.9922±0.0061	0.9980±0.0018	0.9949±0.0023	0.9365±0.0163
CA M45 Cas15 U5[c]	0.9978±0.0006	0.9913±0.0044	0.9980±0.0006	0.9962±0.0014	0.9481±0.0544

[a] After moist heat treatment for 48 hrs (n=3); [b] for 24 hrs (n=3); [c] for 24 hrs (n=6)

Table 43 Comparison of the coefficient of determination from curve fitting between drug release from tablet coated with CA M45 Cas15 and CA M45 Cas15 U5, CA M45 Cas15 HPMC45 films at coating level of 15% in pH change system and different equations

Coated Tablet	Coefficient of Determination				
	First Order	Higuchi's	KGT3	Power Law	Zero Order
CA M45 Cas15	0.9943±0.0026	0.9786±0.0048	0.9937±0.00441	0.9870±0.0081	0.9524±0.0303
CA M45 Cas15 HPMC45	0.9844±0.0084	0.9516±0.0154	0.9968±0.0034	0.9968±0.0015	0.9934±0.0044
CA M45 Cas 15 U5	0.9899±0.0054	0.9692±0.0170	0.9969±0.0022	0.9962±0.0028	0.9855±0.0062

equations had the coefficient of determination values (0.9594±0.0292 to 0.9831±0.0061 and 0.9751±0.0187 to 0.9850±0.0061) respectively less than those from above curve fitting. Graphical representation of the fitting results of fraction of drug released vs time in pH change system of tablets coated with CA M45 film after moist heat at 60°C for 48 hours to KGT3 equation is depicted in Figure *231* and that of CA M45 Cas15 and CA M45 Cas15 U5 films after moist heat at 60°C for 24 hours to KGT3 equation are shown in Figure *232* and *233*.

The aforementioned result was also found in case of curve fitting of drug release profiles of tablets coated with chitosan acetate film containing magnesium stearate 45% after moist heat treatment at 60°C for 48 hours, tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% after moist heat treatment at 60°C for 24 hours and tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5% respectively which using acid or basic fluids as dissolution media as shown in Tables *41* and *42* respectively.

In case of drug release test with pH change method, the curve fitting of drug release profiles of freshly prepared tablets coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% and urea or HPMC showed the result similar to that of aforementioned case. Curve fitting with KGT3, first order and power law expression provided high coefficient of determination as shown in Table *43*. Whereas curve fitting with Higuchi's and zero order equation had the values of coefficient of determination less than those from above curve fitting.

A comparative evaluation of C value in KGT3 equation from curve fitting showed that there was a tendency of decreasing this value when duration of moist heat treatment was longer or the temperature of treatment was higher as presented in Figures *234* and *235*.

The C value from curve fitting of drug release profiles of moist heat treated tablets coated with chitosan acetate film containing magnesium stearate 45% was less than that of moist heat treated tablets coated with chitosan acetate film containing talcum 45%. Whereas an addition of castor oil in film containing magnesium stearate also decreased the C value. An increase in amount of magnesium stearate and temperature of moist heat treatment also decreased the C value.

The C value was also more decreased as the molality of glucose solution was increased as presented in Figure *236*. An increase in %RH during moist heat treatment also decreased the C value in KGT3 equation of drug release profiles of tablets coated with chitosan acetate film containing magnesium stearate, castor oil and urea at concentration of 45, 15 and 5% after moist heat treatment at 60°C for 24 hours as shown in Figure *237*.

The C value obtained from curve fitting of drug release in acid medium was obviously higher than that obtained from drug release in basic medium. In case of the drug release test in acid or basic dissolution fluids, C value from curve fitting of profile of tablet coated with chitosan acetate film containing magnesium stearate 45% and

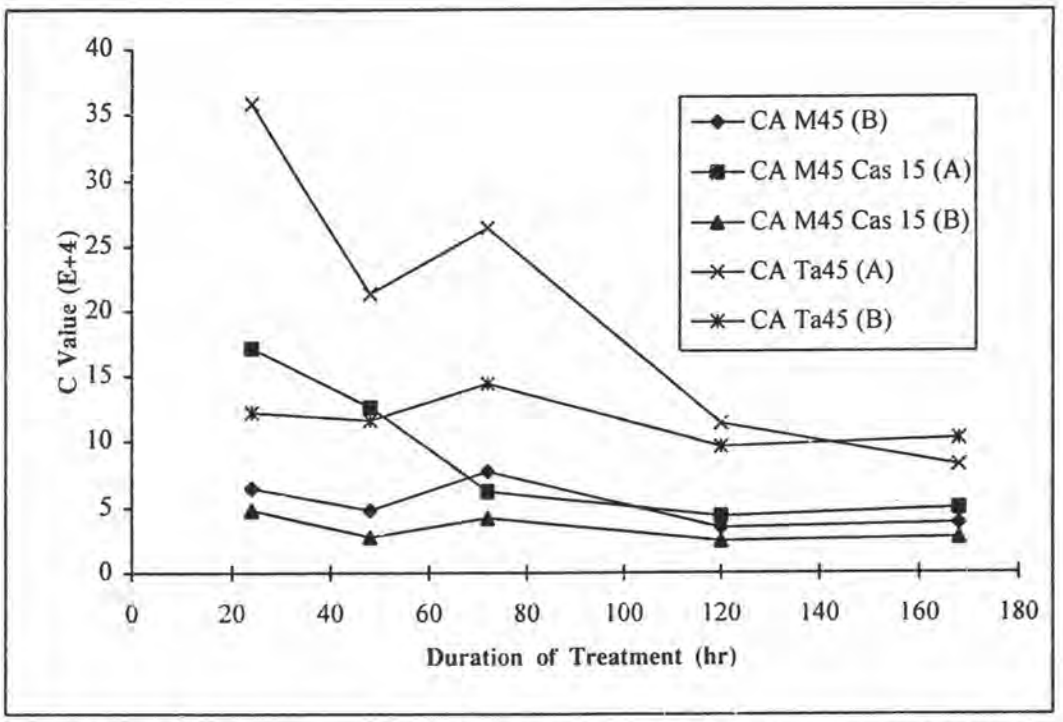


Figure 234 C value from curve fitting with KGT3 equation of drug release of coated tablets after moist heat treatment at 45°C (A) and 60°C (B) for different time interval in pH change system

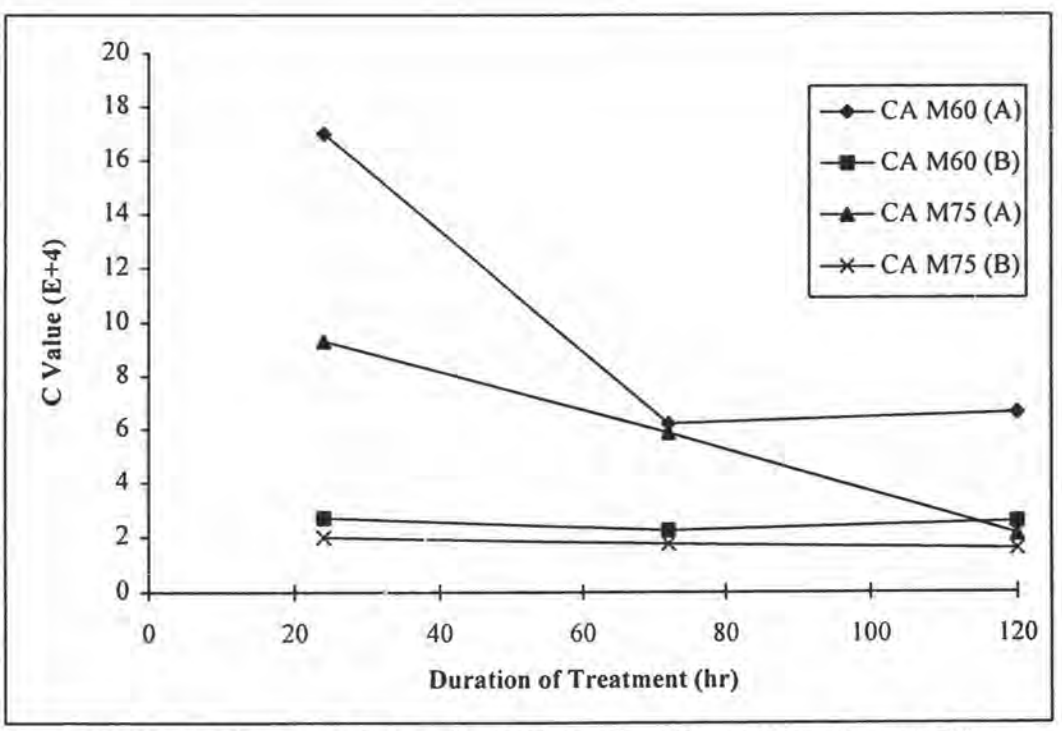


Figure 235 C value from curve fitting with KGT3 equation of drug release of coated tablets coated with CA M60 and CA M75 films at coating level of 15% after moist heat treatment at 45°C (A) and 60°C (B) for different time interval in pH change system

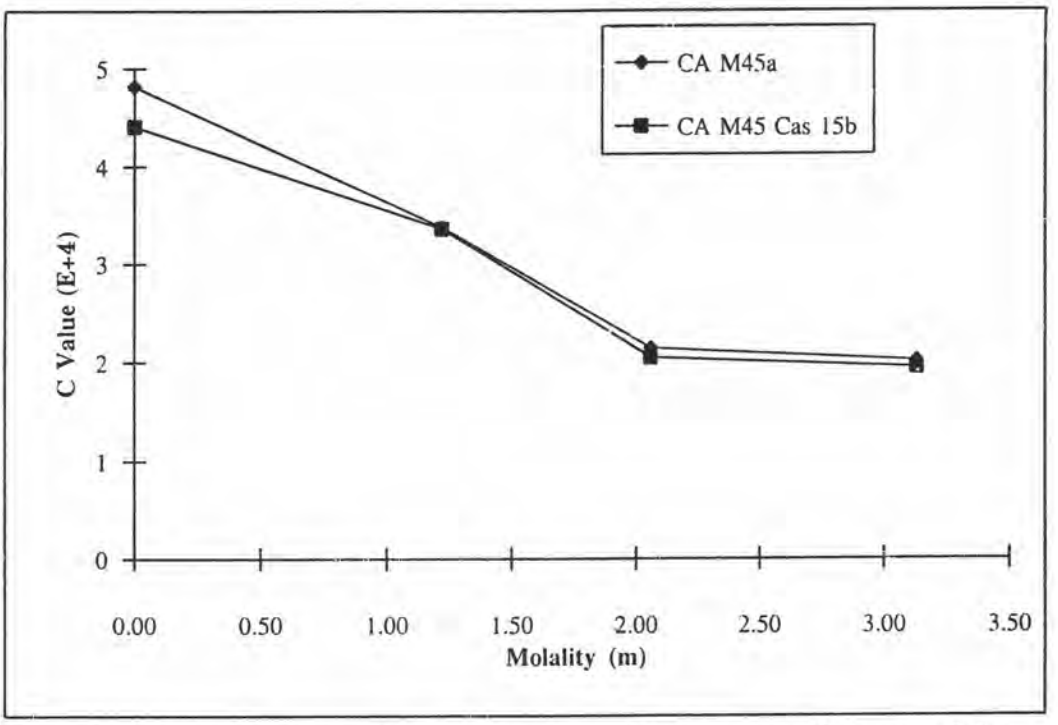


Figure 236 Relationship between C value and molality of glucose solution from curve fitting with KGT3 equation of drug release of tablets coated with CA M45 and CA M45 Cas15 films at coating level of 15% after moist heat treatment at 60°C for 48 hrs (a) and 24 hrs (b) respectively in glucose solution

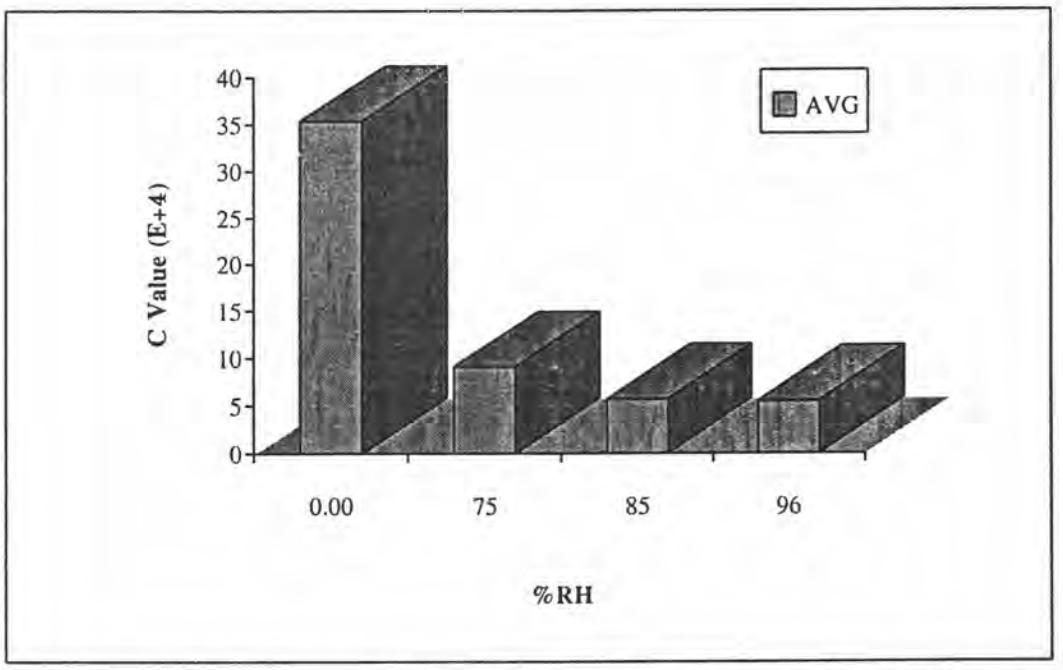


Figure 237 Relationship between %RH and C value from curve fitting with KGT3 of drug release of tablet coated with CA M45 Cas15 U 5 at coating level of 15% after moist heat treatment at 60°C at different %RH in pH change system

Table 44 C value from curve fitting with KGT3 of drug release of tablet coated with CA M45, CA M45 Cas15 and CA M45 Cas15 U5 films after moist heat treatment at 60°C in HCl buffer pH 1.2 and phosphate buffer pH 6.8

Coated Tablet	C Value (e+4)	
	In Acid medium	In Basic Medium
CA M45[a]	22.3700±4.5024	3.9358±0.5803
CA M45 Cas15[b]	20.9254±8.2774	2.2558±0.1217
CA M45 Cas15 U5[b]	29.1266±8.1134	3.0347±0.4789

[a] after moist heat treament at 60°C for 48 hrs (n=3)

[b] after moist heat treament at 60°C for 24 hrs (n=6)

Table 45 C value from curve fitting with KGT3 of drug release of tablet coated with CA M45 Cas15, CA M45 Cas15 HPMC45 and CA M45 Cas15 U5 films at coating level of 15% in pH change system

Coated Tablet	C Value (e+4)
CA M45 CAS15	9.0457±2.5053
CA M45 Cas15 HPMC45	28.6799±8.2883
CA M45 Cas 15 U5	24.2946±6.4738

castor oil 15% after moist heat treatment at 60°C for 24 hours was less than the other two coated tablets as shown in Table *44*.

In case of drug release tested in pH change method, the C value from curve fitting of freshly prepared tablet coated with chitosan acetate film containing magnesium stearate 45% and castor oil 15% was less than that of freshly prepared tablets coated with this film incorporated with urea or HPMC as presented in Table *45*.

The release rate from curve fitting with first order equation and the exponent from curve fitting with power law expression of drug release from different coated tablets are shown in Tables *46-62*. The drug release rate from curve fitting with first order equation of core tablet in basic medium was faster than that of drug release from core tablet in acid medium as shown in Table *46*. A comparative evaluation of release rate from curve fitting with first order showed that there was a tendency of decreasing the release rate when duration of moist heat treatment was longer as shown in Tables 47-55. Release rate of coated tablets which was moist heat treated at 60°C was slower than that of coated tablets moist heat treated at 45°C. By comparison the release rate between Tables 47 and 49, an addition of talcum was less effective to reduce release rate of treated coated tablets than that of magnesium stearate. An incorporation of castor oil into chitosan acetate film containing magnesium stearate 45% markedly reduced the release rate as shown in Tables *54* and *55*. The more increase in osmolality of glucose solutions, the lower was the release rate of selected coated tablets as shown in Tables *56* and *57*. An enhancement of %RH during moist heat treatment also obviously decreased the release rate as shown in Table 58.

The drug release rate of moist heat treated coated tablets in basic dissolution medium was extensively lower than that in acid medium as shown in Tables *59-61*. An addition of urea or HPMC in chitosan acetate film containing magnesium stearate, castor oil and urea enhanced the release rate of tablets coated with these films as shown in Table *62*. By comparison, urea incorporation more effectively enhanced release rate than that of HPMC.

A comparative evaluation of diffusional exponent (n) value from curve fitting with Power law expression revealed that most of drug release of core and coated tablets was anomalous (non-Fickian) transport characteristic since the value of diffusional exponent (n) was between 0.43-0.85 as shown in Tables *46-62*. There was the evidence of increase in exponent as the osmolality of glucose solution was increased as shown in Tables *56* and *57*.

Although the coefficient of determinations from curve fitting with KGT3 of most drug release profiles were greater than those with first order, the t-values calculated from the coefficient of determinations of curve fitting between most of drug release and first order and KGT3 equations did not show statistically significant difference ($p>0.05$) as shown in Tables *63* to *78*.

Table 46 Release rate and exponent from curve fitting with first order and power law equations of drug release from core tablet in HCl buffer pH 1.2 (A) and in phosphate buffer pH 6.8 (B) (n=6)

Tablet	Release Rate from First Order (K)	Exponent from Power Law (n)
A	0.0554±0.0056	0.6979±0.0523
B	0.1338±0.0109	0.8013±0.0451

Table 47 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	4.3413±0.5451	0.4488±0.0245
48	2.4594±0.2825	0.5411±0.0359
72	1.9817±0.0895	0.6929±0.0268
120	1.9146±0.4437	0.5095±0.0653
168	1.3274±0.0686	0.6208±0.1746

Table 48 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA Ta45 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	8.4371±0.4433	0.7850±0.1692
48	7.5230±0.2404	0.6496±0.0607
72	7.3235±0.4894	1.1362±0.7486
120	5.2392±0.5492	0.5574±0.0763
168	3.6746±0.4229	0.5567±0.0394

Table 49 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA Ta45 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	5.1173±0.3524	0.6098±0.0445
48	3.6864±0.3520	0.5863±0.1268
72	3.6867±0.2392	0.5937±0.0899
120	2.7290+0.0508	0.6875±0.0431
168	1.9353±0.6027	1.1260±0.7659

Table 50 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M60 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	8.0742±2.6143	0.8951±0.6632
72	3.9952±0.6005	0.4891±0.0526
120	4.4115±0.3362	0.4671±0.0900

Table 51 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M60 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	2.2142±0.0049	0.3243±0.0279
72	1.8075±0.4368	0.3415±0.0221
120	1.1517±0.0303	0.5156±0.0259

Table 52 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M75 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	5.3750±0.1817	0.4720±0.1232
72	3.9619±0.5259	0.4689±0.0334
120	1.6838±0.2912	0.3857±0.0319

Table 53 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M75 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	1.4243±0.0930	0.3062±0.0416
72	1.1384±0.0964	0.4060±0.0503
120	0.7105±0.0750	0.6257±0.0880

Table 54 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	6.8929±0.1350	0.5928±0.0228
48	5.5042±0.6764	0.5640±0.0933
72	4.0379±0.9945	0.4541±0.0500
120	2.5428±0.1386	0.4475±0.1098
168	2.8906±0.3632	0.4800±0.0883

Table 55 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (n=3)

Time (hr)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
24	2.8562±0.4416	0.6163±0.0482
48	1.8383±0.0672	0.4864±0.0439
72	1.4558±0.2609	0.5633±0.0475
120	0.8988±0.0651	0.6338±0.0471
168	0.9839±0.0674	0.6260±0.0249

Table 56 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 at coating levels of 15% after moist heat treatment at 60°C for 48 hrs in glucose solution with different molality (n=3)

Conc(m)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
0.00	4.2584±0.5693	0.3786±0.0299
1.22	1.7279±0.1522	0.5662±0.0233
2.06	1.0659±0.0914	0.5922±0.0266
3.13	0.6820±0.0357	0.7031±0.1038

Table 57 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 at coating levels of 15% after moist heat treatment at 60°C for 24 hrs in glucose solution with different molality (n=3)

Conc(m)	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
0.00	3.5286±0.7534	0.3437±0.0401
1.22	1.5532±0.0608	0.6126±0.0386
2.06	0.8246±0.0210	0.7062±0.0607
3.13	0.5915±0.0223	0.9555±0.1199

Table 58 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 U5 at coating levels of 15% after moist heat treatment at 60°C for 24 hrs in pH change system (n=3)

%RH	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
0	6.2502±3.1503	0.7364±0.0578
75	2.2574±0.1011	0.6944±0.0773
85	1.9840±0.1886	0.6188±0.0487
96	1.3848±0.1889	0.7063±0.0704

Table 59 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 at coating levels of 15% after moist heat treatment at 60°C for 48 hrs in HCl buffer pH 1.2 (A) and phosphate buffer pH 6.8 (B) (n=3)

Medium	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
A	4.2270±0.3224	0.7598±0.0247
B	1.8539±0.0547	0.6343±0.0650

Table 60 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 at coating levels of 15% after moist heat treatment at 60°C for 48 hrs in HCl buffer pH 1.2 (A) and phosphate buffer pH 6.8 (B) (n=3)

Medium	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
A	4.3080±0.6623	0.7419±0.0645
B	1.4856±0.1798	0.4693±0.0488

Table 61 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 U5 at coating levels of 15% after moist heat treatment at 60°C for 48 hrs in HCl buffer pH 1.2 (A) and phosphate buffer pH 6.8 (B) (n=3)

Medium	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
A	3.4762±0.1571	0.8741±0.0732
B	1.3422±0.0845	0.5764±0.0452

Table 62 Release rate and exponent from curve fitting with first order and power law equations of drug release from tablets coated with CA M45 Cas15 film without or containing different additives at coating levels of 15% in pH change system (n=3)

Coated Tablet	Release Rate from First Order (K)(E+3)	Exponent from Power Law (n)
CA M45 Cas15	3.5911±0.1963	0.6043±0.0729
CA M45 Cas15 HPMC45	4.1812±0.4885	0.8402±0.0959
CA M45 Cas15 U5	6.0084±0.4661	0.6908±0.0846

Table 63 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (data from Table 31) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-0.06367	NS
48	-2.0158	NS
72	-2.6826	NS
120	-0.3554	NS
168	-1.9234	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 64 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA Ta45 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (data from Table 32) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-2.6306	NS
48	-0.3048	NS
72	-0.2414	NS
120	-0.3922	NS
168	-0.3740	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 65 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA Ta45 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (data from Table 33) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-0.1530	NS
48	-1.0004	NS
72	-0.5591	NS
120	-1.838	NS
168	-0.376	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 66 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M60 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (data from Table 36) (unpaired t-test)

Time (hr)	t-value*	Result**
24	0.0196	NS
72	-1.5519	NS
120	-0.2509	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 67 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M60 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (data from Table 36) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-3.1672	S
72	-3.4659	S
120	-0.3572	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 68 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M75 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (data from Table 37) (unpaired t-test)

Time (hr)	t-value*	Result**
24	0.0527	NS
72	-0.6686	NS
120	-1.6527	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 69 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M75 at coating levels of 15% after moist heat treatment at 60°C for different time intervals in pH change system (data from Table 37) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-6.2439	S
72	-2.083	NS
120	-0.403	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 70 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 at coating levels of 15% after moist heat treatment at 45°C for different time intervals in pH change system (data from Table 34) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-1.0114	NS
48	-0.522	NS
72	-0.9771	NS
120	-1.0078	NS
168	-2.332	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 71 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 at coating level of 15% after moist heat treatment at 60°C for different time intervals in pH change system (data from Table 35) (unpaired t-test)

Time (hr)	t-value*	Result**
24	-0.6732	NS
48	-0.8852	NS
72	-0.6404	NS
120	-1.1377	NS
168	-0.4658	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 72 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 at coating level of 15% after moist heat treatment at 60°C for 48 hrs in glucose solution with different molality (data from Table 38) (unpaired t-test)

Conc(m)	t-value*	Result**
0.00	-1.7306	NS
1.22	0.4673	NS
2.06	0.5181	NS
3.13	0.193	NS

*If $t_{0.05}$, df = 4 then critical values of t are ± 2.776; ** S = Significance and NS = Non-significance

Table 73 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 at coating level of 15% after moist heat treatment at 60°C for 48 hrs in glucose solution with different molality (data from Table 39) (unpaired t-test)

Conc(m)	t-value*	Result**
0.00	-3.4994	S
1.22	0.3744	NS
2.06	0.3483	NS
3.13	0.5814	NS

*If $t_{0.05}$, df = 4 then critical values of t are $\pm$ 2.776; ** S = Significance and NS = Non-significance

Table 74 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 U5 at coating levels of 15% after moist heat treatment at 60°C for 24 hrs under different %RH (data from Table 40) (unpaired t-test)

%RH	t-value*	Result**
0	-0.7614	NS
75	-1.4172	NS
85	-2.5863	S
96	-1.9898	NS

*If $t_{0.05}$, df = 10 then critical values of t are $\pm$ 2.228; ** S = Significance and NS = Non-significance

Table 75 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 at coating level of 15% after moist heat treatment at 60°C for 48 hrs in HCl buffer pH 1.2 (A) and phosphate buffer pH 6.8 (B) (data from Tables 41 and 42)(unpaired t-test)

Medium	t-value*	Result**
A	-3.084	S
B	0.4685	NS

*If $t_{0.05}$, df = 4 then critical values of t are $\pm$ 2.776; ** S = Significance and NS = Non-significance

Table 76 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 at coating level of 15% after moist heat treatment at 60°C for 24 hrs in HCl buffer pH 1.2 (A) and phosphate buffer pH 6.8 (B) (data from Tables 41 and 42) (unpaired t-tes

Medium	t-value*	Result**
A	-3.0391	S
B	-1.3684	NS

*If $t_{0.05}$, df = 4 then critical values of t are $\pm$ 2.776; ** S = Significance and NS = Non-significance

Table 77 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 U5 at coating level of 15% after moist heat treatment at 60°C for 24 hrs in HCl buffer pH 1.2 (A) and phosphate buffer pH 6.8 (B) (data from Tables 41 and 42) (unpaired t-test)

Medium	t-value*	Result**
A	-6.167	S
B	-0.5433	NS

*If $t_{0.05}$, df = 10 then critical values of t are $\pm$ 2.228; ** S = Significance and NS = Non-significance

Table 78 t-values calculated between coefficient of determination from curve fitting with first order and KGT3 equations of drug release from tablets coated with CA M45 Cas15 film without or containing different additives at coating levels of 15% in pH change system (data from Table 43) (unpaired t-test)

Coated Tablet	t-value*	Result**
CA M45 Cas15	0.2635	NS
CA M45 Cas15 HPMC45	-3.3735	S
CA M45 Cas15 U5	-2.9497	S

*If $t_{0.05}$, df = 10 then critical values of t are $\pm$ 2.228; ** S = Significance and NS = Non-significance