Chapter III

Results

I. Film Coating Formulations.

Water-soluble Film Formers.

All the film coating formulations obtained were viscous liquids, but different in physical appearance. CS film coating formulations were yellowish and clear. HPMC film coating formulations were colorless and clear, while both MC and HPC film coating formulations were colorless and turbid, with a lesser extent to HPC.

The rheological properties of these film coating formulations at various concentrations were investigated. The representative flow curves, rheograms, obtained by plotting the rate of shear against the shearing stress from the data in Table 31-50 (Appendix B), are presented in Figure 7-10.

All four film formers behaved in similar characteristics; as increasing in concentration of the polymer in the film coating formulations, the more inclined curves were obtained. The rheograms of CS and MC film coating formulations were drastically affected by the concentration variation, which had a lesser and very little effect on the rheograms of HPMC and HPC film coating formulations, respectively.

Since the viscosity of the coating formulations can affect the degree of atomization, one of the spray variables that should be controlled in the pan-spray film coating process (Seitz,

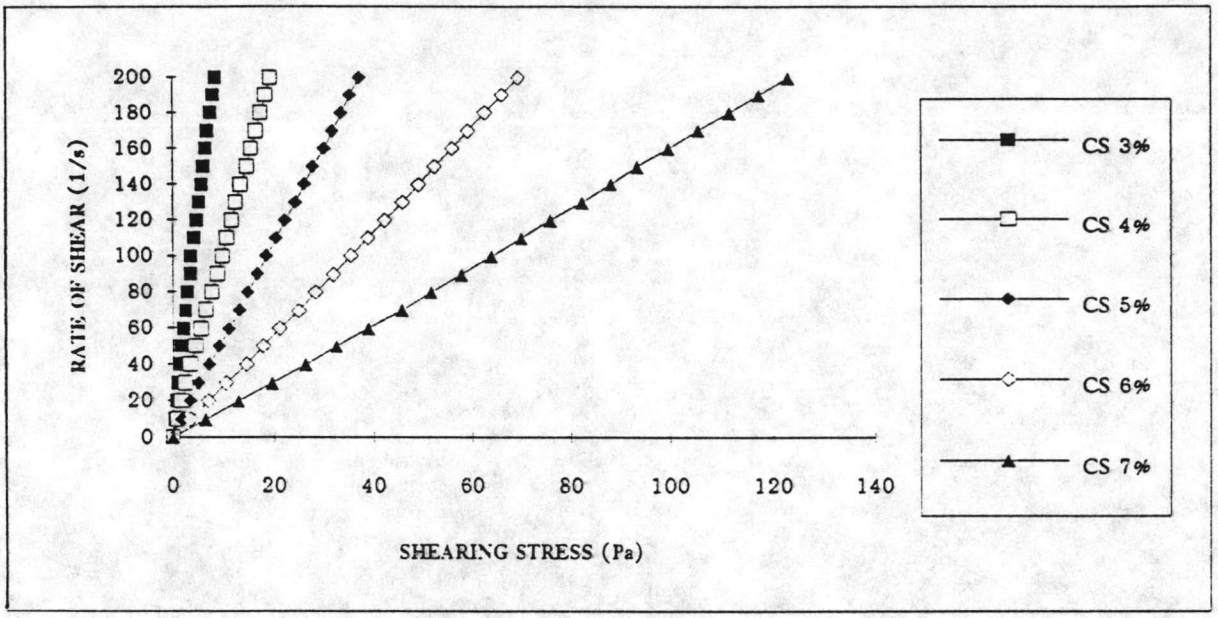


Figure 7 Rheograms of chitosan film coating formulations, at various concentrations

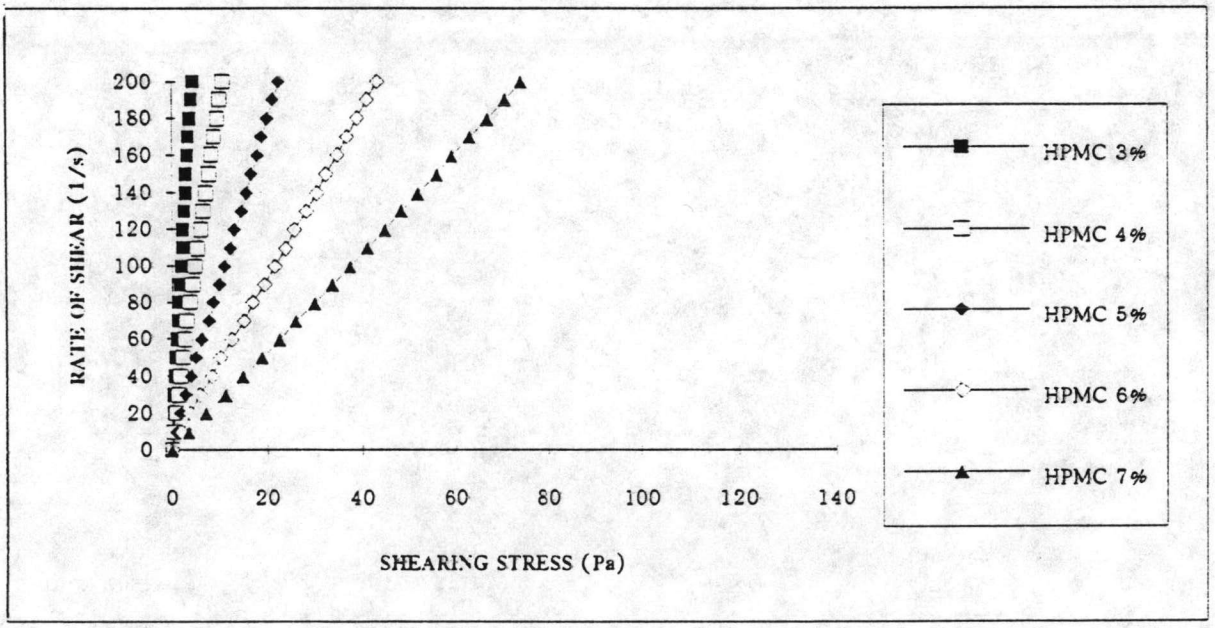


Figure 8 Rheograms of hydroxypropyl methylcellulose film coating formulations, at various concentrations

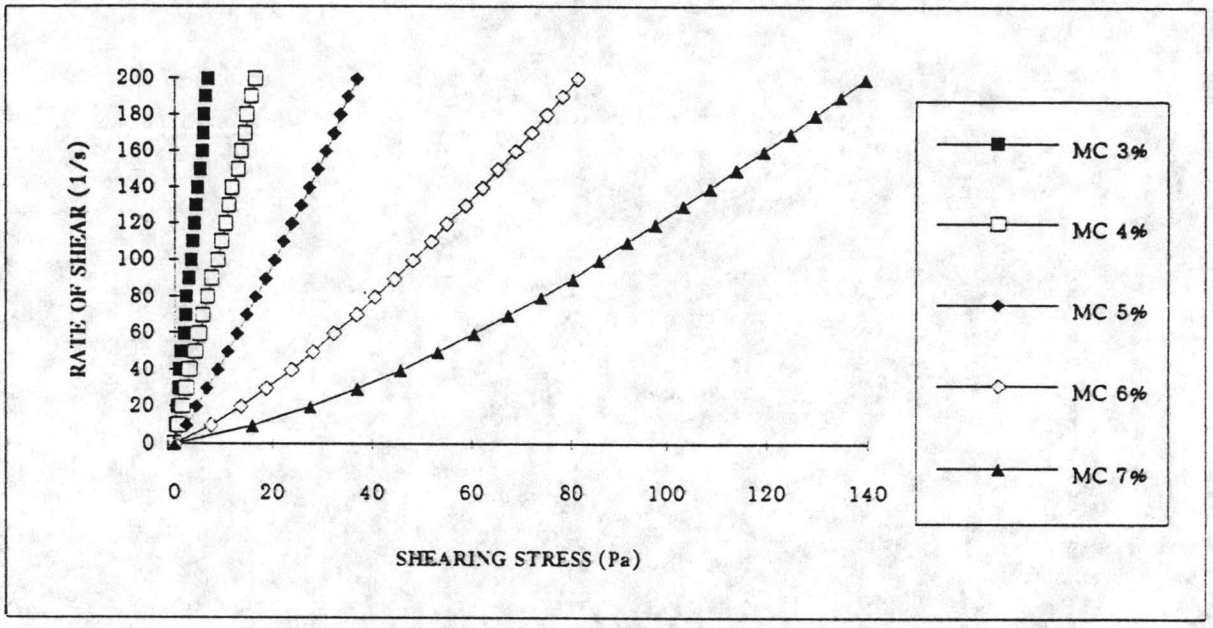


Figure 9 Rheograms of methylcellulose film coating formulations, at various concentrations

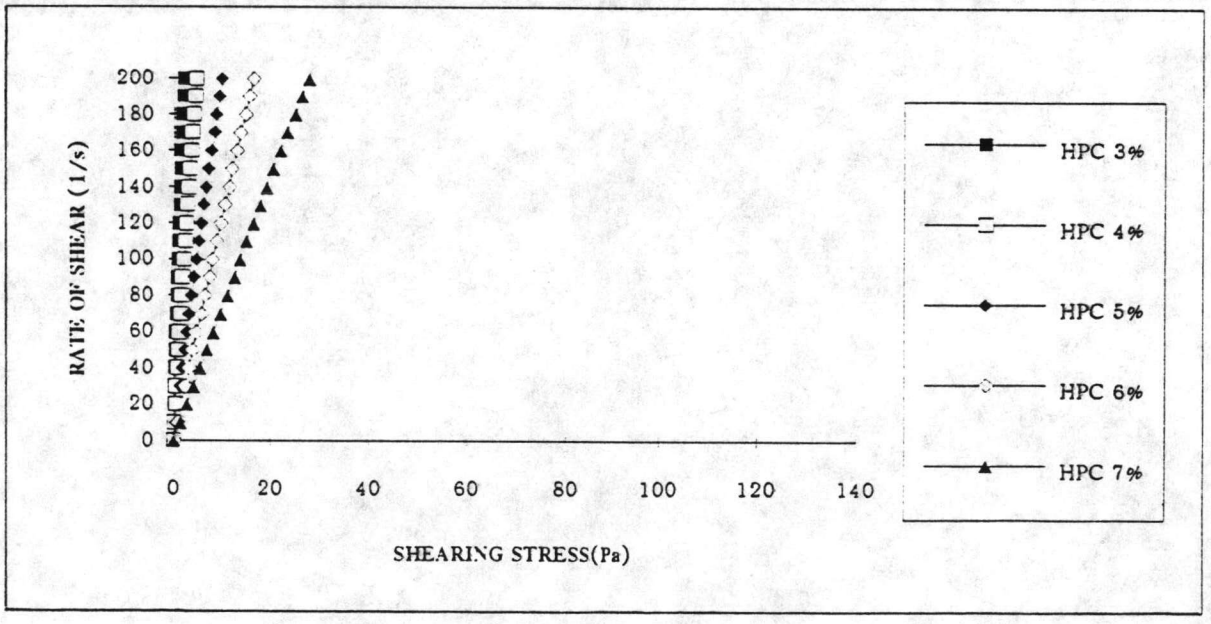


Figure 10 Rheograms of hydroxypropyl cellulose film coating formulations, at various concentrations

Mehta and Yeager, 1986). To control the fluid viscosity, the viscosity coefficient at each concentration of all the film coating formulations had to be first determined. Method of the viscosity coefficient determination and all data obtained are presented in Table 51-54 (Appendix B). Mean and standard deviation of both the concentration and the viscosity coefficient of all the film coating formulations are presented in Table 4-7.

The viscosity coefficient against the concentration plots of all the film coating formulations were found to be almost the semilog linear relationships, as demonstrated in Figure 11. These relationships followed the equations;

$$y = 0.3149\ x - 2.3269 \qquad (1),$$

$$y = 0.3223\ x - 2.6642 \qquad (2),$$

$$y = 0.5812\ x - 3.3602 \qquad (3),$$

$$y = 0.2747\ x - 2.8179 \qquad (4),$$

where y represented log the viscosity coefficient and x represented the concentration (% w/w) of the polymer in the film coating formulations, with correlation coefficient of 0.9983, 0.9977, 0.9952, and 0.9760 for CS, HPMC, MC, and HPC, respectively.

From Figure 11, it was noticed that those relationships of CS, HPMC, and HPC were similar trend and parallel to each other, followed the x coefficient and the intercept in equation (1), (2), and (4) ; whereas that of MC film coating formulations rose straight up more precipitously than the others.

Table 4 Viscosity Coefficient at Various Concentrations of Chitosan Film Coating Formulations.

Concentration (% w/w)	Viscosity Coefficient
2.99 (0.006)*	0.039 (0.001)
4.03 (0.005)	0.090 (0.005)
5.01 (0.015)	0.179 (0.010)
5.95 (0.083)	0.373 (0.039)
7.02 (0.016)	0.728 (0.042)

* Standard Deviation

Table 5 Viscosity Coefficient at Various Concentrations of Hydroxypropyl Methylcellulose Film Coating Formulations

Concentration (% w/w)	Viscosity Coefficient
3.03 (0.024)*	0.020 (0.001)
4.00 (0.019)	0.042 (0.002)
5.01 (0.008)	0.097 (0.006)
6.04 (0.042)	0.195 (0.010)
7.02 (0.022)	0.375 (0.012)

* Standard Deviation

Table 6 Viscosity Coefficient at Various Concentrations of Methylcellulose Film Coating Formulations.

Concentration (% w/w)	Viscosity Coefficient
3.08 (0.090)*	0.031 (0.002)
3.97 (0.035)	0.084 (0.005)
4.98 (0.077)	0.274 (0.044)
6.05 (0.040)	1.432 (0.324)
6.99 (0.053)	5.638 (1.195)

* Standard Deviation

Table 7 Viscosity Coefficient at Various Concentrations of Hydroxypropyl Cellulose Film Coating Formulations.

Concentration (% w/w)	Viscosity Coefficient
3.01 (0.011)*	0.011 (0.000)
4.01 (0.031)	0.020 (0.002)
5.04 (0.022)	0.045 (0.004)
6.02 (0.024)	0.076 (0.001)
7.01 (0.019)	0.135 (0.009)

* Standard Deviation

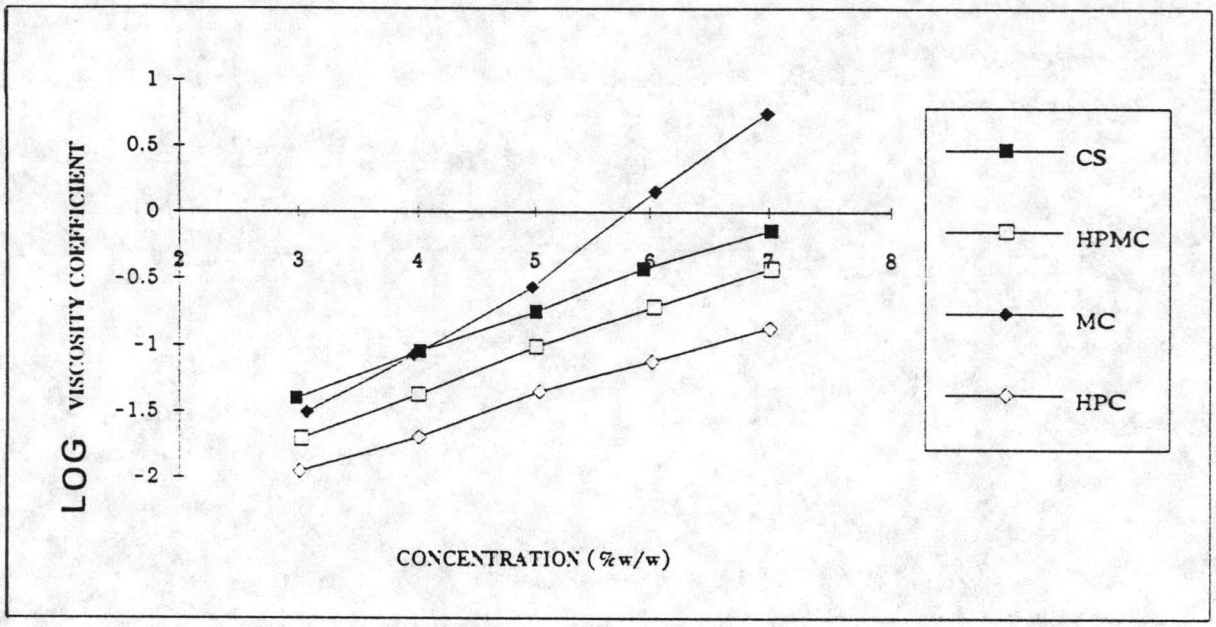


Figure 11 Viscosity coefficient concentration relationship of various water-soluble film formers

The viscosity coefficient of 5% w/w HPMC film coating formulations which was equal to 0.0894 (extrapolated from the relationship in Figure 11), was used as the reference. The concentration of other film formers providing the same viscosity coefficient were further calculated from the least squared equations (1), (3), and (4). The results are presented in Table 8. These concentrations of the polymer in the film coating formulations were used in further steps throughout this investigation.

Water-insoluble Film Formers.

CT pseudolatex aqueous dispersion was prepared by solvent change and self-dispersible technique, whereas EC pseudolatex aqueous dispersion was used as a commercial available product. The CT pseudolatex product obtained was a brownish, "flocculated-like" dispersion. It was demonstrated in comparison with the EC pseudolatex which appeared as an off-white, opaque liquid dispersion in Figure 12.

The solids content of the CT pseudolatex was determined and presented in Table 9. The result was much less than that of the EC pseudolatex which is equal to 25% (Moore, 1989). The average particle size of both products was also measured. The particle size calculated were ranged from 0.94 μm to 10.23 μm. The results presented in Table 10 indicated that the dispersed particles of the CT pseudolatex were larger in both size and size distribution than those of the EC product. These, therefore, resulted in short sedimentation time of the CT product as demonstrated in Figure 13, in comparison with that of the EC product, the particles of which were smaller in size and size distribution. However, the "flocculated-like" particles

Table 8 Concentration of Other Film Formers Providing the Same Viscosity Coefficient as 5% w/w Hydroxypropyl Methylcellulose Film Coating Formulations.

Film Formers	Concentration (% w/w)
Chitosan	4.06
Hydroxypropyl Methylcellulose	5.00
Methylcellulose	3.98
Hydroxypropyl Cellulose	6.44

Table 9 Solids Content of Chitin Aqueous Dispersions.

Test No.	Solids Content (% w/w)
1	4.22
2	4.65
3	4.44
Mean (SD)*	4.44 (0.215)

* Standrad Deviation

Table 10 Mean particle Size of Dispersed Phase in Chitin and Ethylcellulsoe Aqueous Dispersions.

Film Formers	Mean Particle Size* (SD)**
Chitin	6.037 (2.284)
Ethylcellulose	1.930 (1.873)

* Volume statistics calculated from 0.94 μm to 10.23 μm.

** Standard Deviation

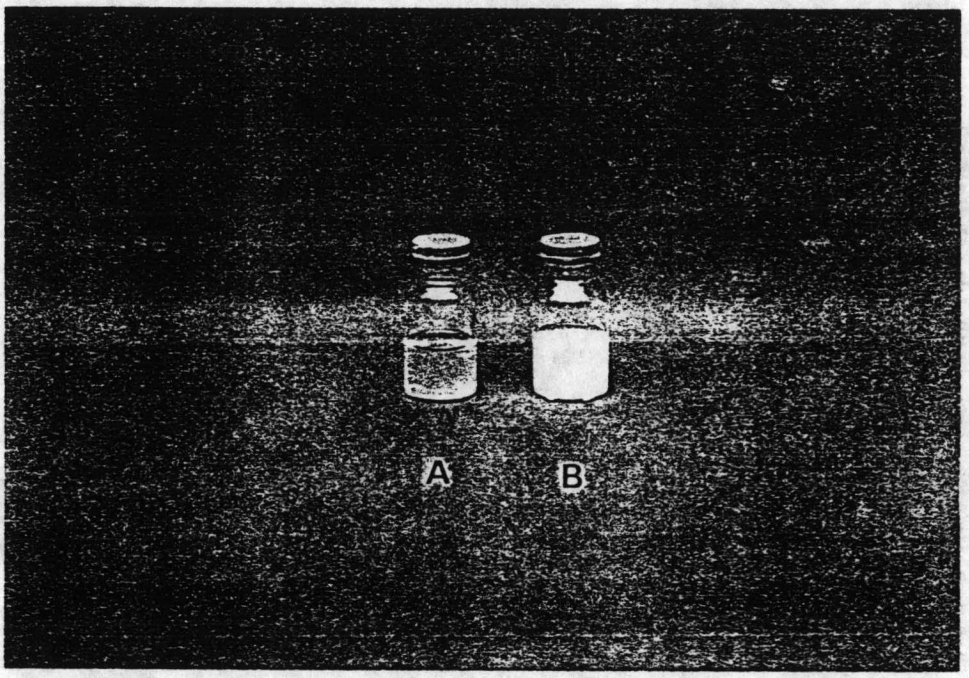


Figure 12 Chitin (A) and ethylcellulose (B) aqueous dispersions

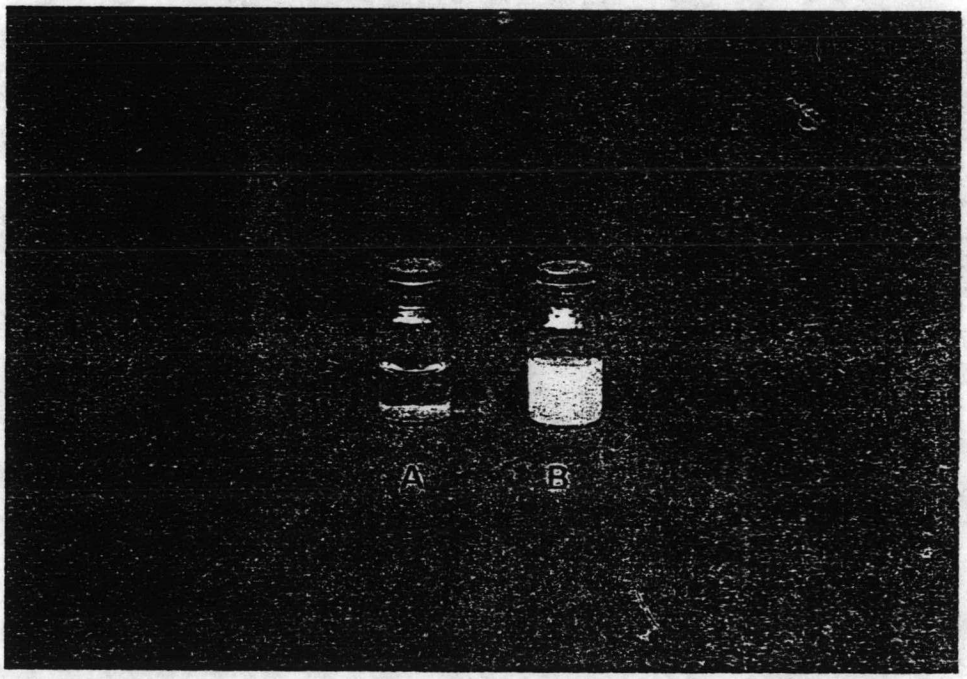


Figure 13 Chitin (A) and ethylcellulose (B) aqueous dispersions after 3 hours standing

of the CT dispersion positively resulted in easily redispersible property of the product only by gently shaking.

The combinations between the film coating formulations of selected water-soluble film formers and those of water-insoluble film formers were studied in their compatability. The combinations of CT versus CS, CT versus HPMC, and EC versus HPMC could be mixed thoroughly in all proportions without any precipitation. Whereas the precipitation was instantly occurred in all proportions and all dilutions when either CS film coating formulations or EC film coating formulations was added to each other.

II. Tablet Evaluations.

Tablets Coated with Film Coating Formulations Containing One Film Former.

The tablets coated with various film coating formulations containing one film former were designated based on the name of the polymer and the desired coating level deposited on the tablets, as presented in Table 11. These designations were used throughout the present investigation. The tablet properties of propranolol HCl core tablets before being coated with the film coating formulations containing the same film former, derived from the data in Table 55-60 (Apperndix C), are presented in Table 12-17.

The average weight, the tablet hardness, and the disintegration time of all core tablet batches were acceptably ranged from 0.26 to 0.28 gm, 9 to 12 kp., and 4 to 10 minutes, respectively. These properties of different batches were not significantly different.

Table 11 Designations for Tablets Coated with Film Coating Formulations Containing One Film Former.

Film Formers	Coating Level (% Increased Weight)			
	3	5	10	15
Chitosan	-	CS 5	CS 10	CS 15
Hydroxypropyl Methylcellulose	-	HPMC 5	HPMC 10	HPMC 15
Methylcellulose	-	MC 5	MC 10	MC 15
Hydroxypropyl Cellulose	-	HPC 5	HPC 10	HPC 15
Chitin	-	CT 5	CT 10	-
Ethylcellulose	EC 3	EC 5	EC 10	-

Table 12 Properties of Propranolol HCl Core Tablets before Being Coated with Chitosan Film Coating Formulations.

Properties	Mean (SD)*		
	CS 5	CS 10	CS 15
1. Weight (gm.)	0.2621(0.007)	0.2707(0.008)	0.2623(0.005)
2. Hardness (kp.)	10.13 (0.706)	9.77 (1.167)	9.23 (1.327)
3. Disintegration time (min.sec)	5.59 (1.02)	5.56 (1.31)	5.59 (1.02)
4. Uniformity of Dosage Units (%)	99.25 (1.76)	99.81 (2.64)	99.25 (1.76)
5. Labeled Content (%)	98.48 (0.57)	101.18 (0.94)	98.48 (0.57)

* Standard Deviation

Table 13 Properties of Propranolol HCl Core Tablets before Being Coated with Hydroxypropyl Methylcellulose Film Coating Formulations.

Properties	Mean (SD)*		
	HPMC 5	HPMC 10	HPMC 15
1. Weight (gm.)	0.2782(0.009)	0.2686(0.008)	0.2722(0.011)
2. Hardness (kp.)	10.52 (1.201)	9.64 (0.789)	10.22 (1.220)
3. Disintegration time (min.sec)	6.57 (0.43)	6.29 (0.52)	9.45 (0.37)
4. Uniformity of Dosage Units (%)	106.72(1.82)	96.82 (2.42)	97.99 (1.69)
5. Labeled Content (%)	106.25(0.21)	95.88 (1.78)	100.94(0.27)

* Standard Deviation

Table 14 Properties of Propranolol HCl Core Tablets before Being Coated with Methylcellulose Film Coating Formulations.

Properties	Mean (SD)*		
	MC 5	MC 10	MC 15
1. Weight (gm.)	0.2688(0.008)	0.2678(0.008)	0.2668(0.007)
2. Hardness (kp.)	11.20 (2.132)	10.09 (1.371)	10.42 (0.970)
3. Disintegration time (min.sec)	4.23 (0.59)	5.56 (1.31)	5.56 (1.31)
4. Uniformity of Dosage Units (%)	97.91 (3.55)	99.81 (2.64)	99.81 (2.64)
5. Labeled Content (%)	99.87 (0.52)	101.18 (0.94)	101.18(0.94)

* Standard Deviation

Table 15 Properties of Propranolol HCl Core Tablets before Being Coated with Hydroxypropyl Cellulose Film Coating Formulations.

Properties	Mean (SD)*		
	HPC 5	HPC 10	HPC 15
1. Weight (gm.)	0.2794(0.006)	0.2606(0.005)	0.2720(0.004)
2. Hardness (kp.)	10.83 (1.059)	9.14 (0.948)	11.48 (0.438)
3. Disintegration time (min.sec)	6.57 (0.43)	5.59 (1.02)	8.17 (0.21)
4. Uniformity of Dosage Units (%)	106.72(1.82)	99.25 (1.76)	101.43(2.06)
5. Labeled Content (%)	106.25(0.21)	98.48 (0.57)	103.29(1.49)

* Standard Deviation

Table 16 Properties of Propranolol HCl Core Tablets before Being Coated with Chitin Film Coating Formulations.

Properties	Mean (SD)*	
	CT 5	CT 10
1. Weight (gm.)	0.2697 (0.006)	0.2728 (0.004)
2. Hardness (kp.)	10.28 (1.363)	11.16 (1.342)
3. Disintegration time (min.sec)	10.15 (0.40)	10.15 (0.40)
4. Uniformity of Dosage Units (%)	99.95 (1.66)	99.95 (1.66)
5. Labeled Content (%)	97.72 (0.64)	97.72 (0.64)

* Standard Deviation

Table 17 Properties of Propranolol HCl Core Tablets before Being Coated with Ethylcellulose Film Coating Formulations.

Properties	Mean (SD)*		
	EC 3	EC 5	EC 10
1. Weight (gm.)	0.2640(0.010)	0.2667(0.006)	0.2625(0.009)
2. Hardness (kp.)	9.59 (1.270)	12.15 (1.889)	11.67 (2.011)
3. Disintegration time (min.sec)	4.23 (0.59)	6.00 (0.55)	9.45 (0.37)
4. Uniformity of Dosage Units (%)	97.91 (3.55)	99.05 (1.91)	97.99 (1.69)
5. Labeled Content (%)	99.87 (0.52)	99.29 (1.45)	100.94(0.27)

* Standard Deviation

The uniformity of dosage units and the percent of labeled content in the same batch were correlated to each other and these properties of every batch were within the range of about 95-106%, which followed the USP standard.

Cumulative percent amount of the drug released as a function of time of the core tablets before being coated with the same film coating formulations from the data in Table 62-67 (Appendix C), are illustrated in Figure 14-19. The core tablets of every batch were completely dissolved in the acid stage solution within about 30 minutes and all profiles seemed to be the same.

The surface topography of the core tablet, observed by the scanning electron microscopy, is demonstrated in Figure 20. The compressed structure of drug containing granules and other added additives was clearly depicted.

The CS film coating formulations produced very much tackiness, resulting in the tablet aggregation during the coating process. The possibility of the film rupturing was present and this could have a detrimental effect on the tablet properties. To overcome such the problem, the spraying rate was adjusted downward or even if the spraying pattern was changed to be intermittent ; consequently, these could lead to much greater process time. The HPC film coating formulations could sometimes produce the tackiness problem, but to a lesser extent. On the other hand, the HPMC, the MC, and the EC film coating formulations appeared to have no tackiness problem. For the CT film coating formulations which were applied to the core tablets by dip coating, they would gradually and slowly deposit on the tablet surface. As a result, this coating technique was also a very much time consuming process.

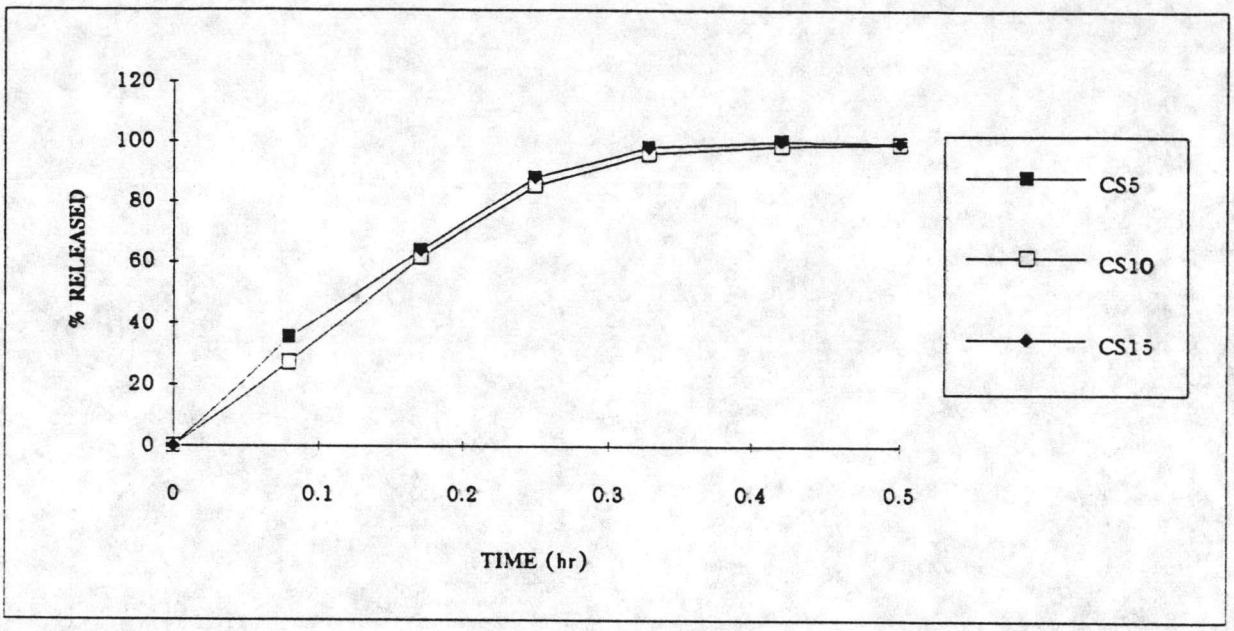


Figure 14 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with chitosan film coating formulations

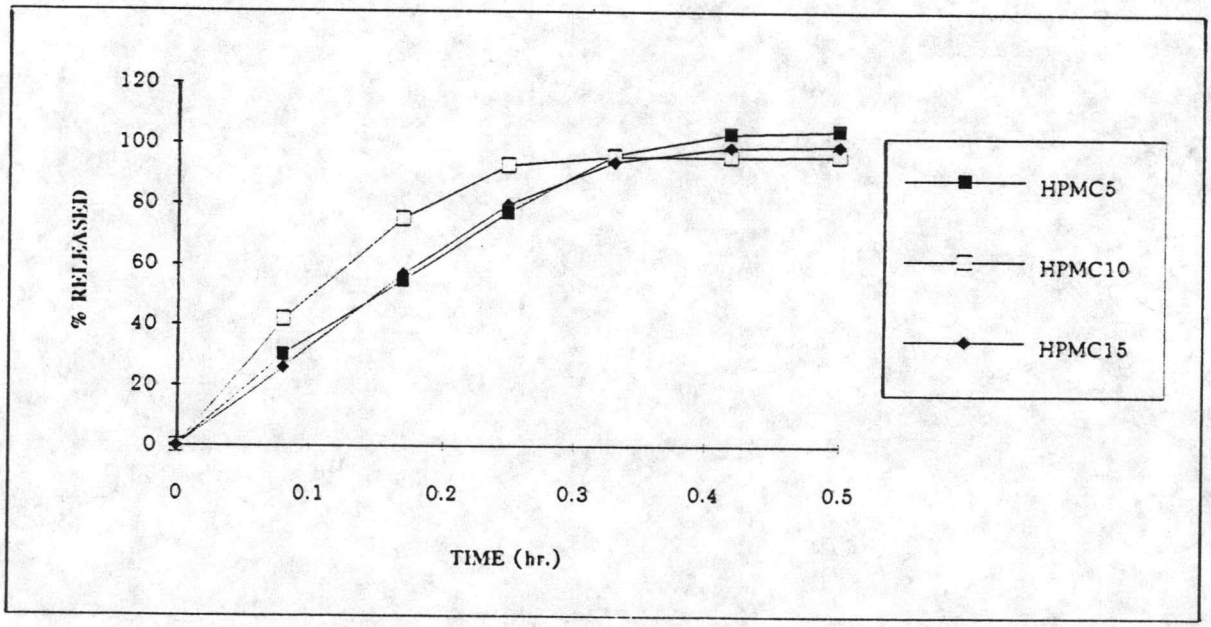


Figure 15 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with hydroxypropyl methylcellulose film coating formulations

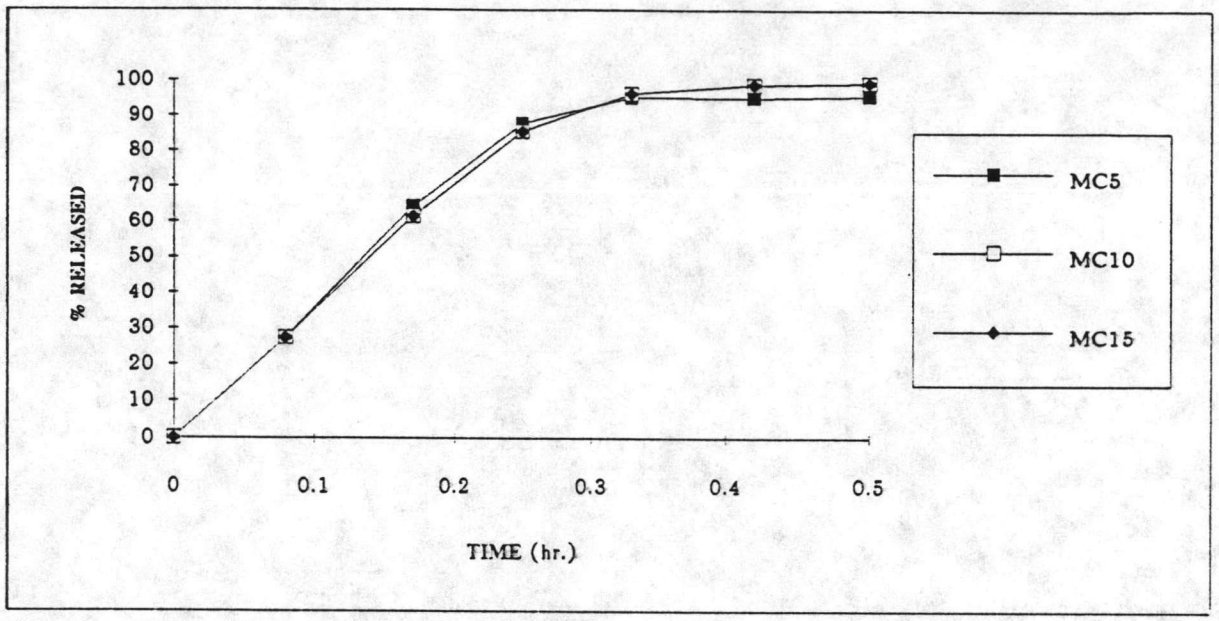


Figure 16 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with methylcellulose film coating formulations

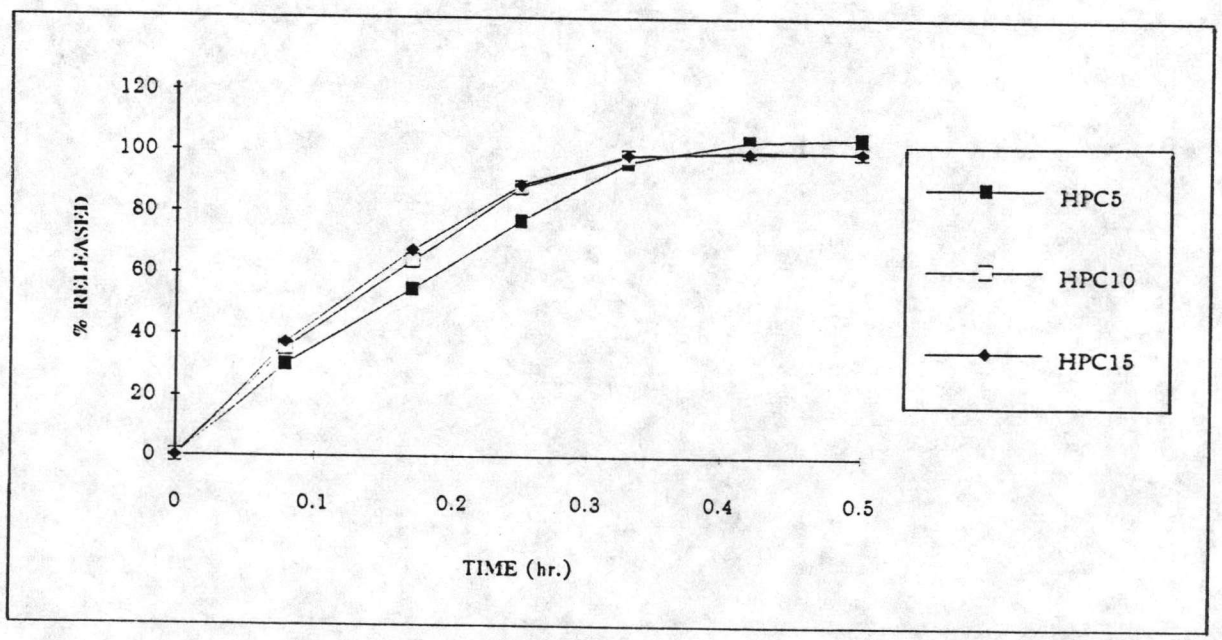


Figure 17 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with hydroxypropyl cellulose film coating formulations

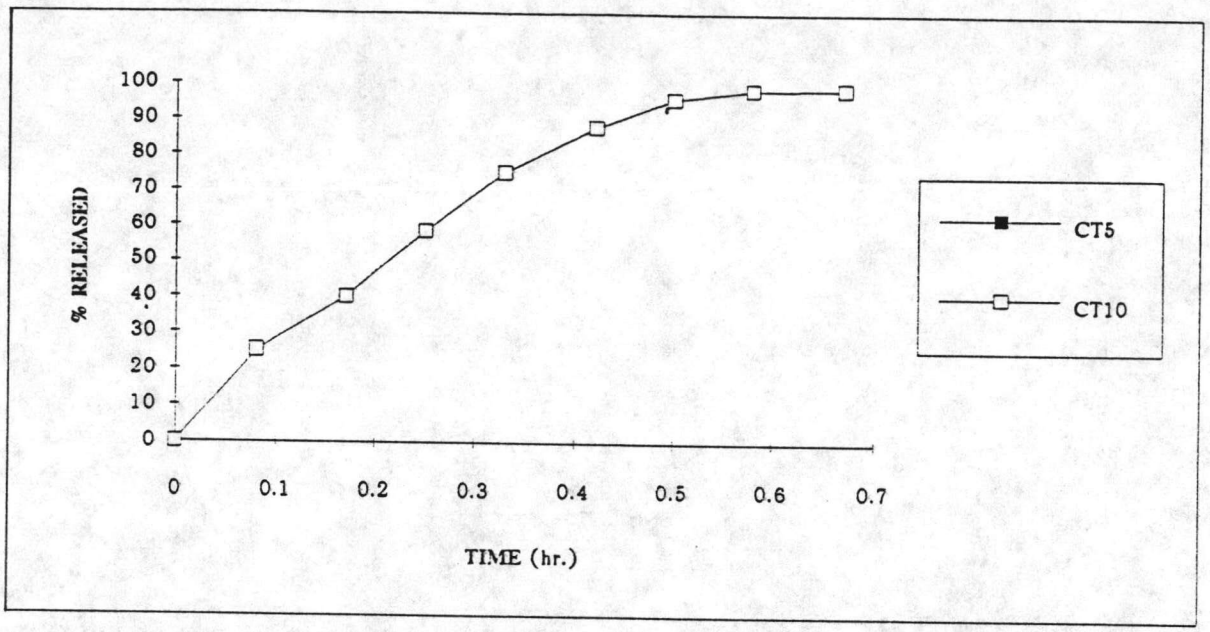


Figure 18 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with chitin film coating formulations

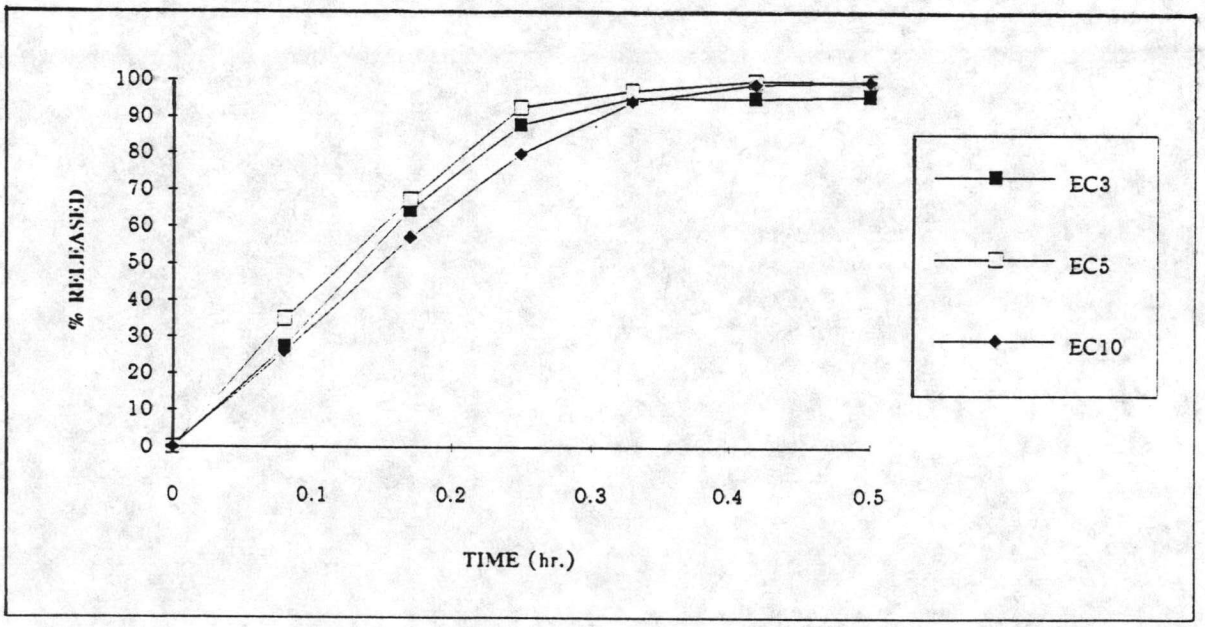
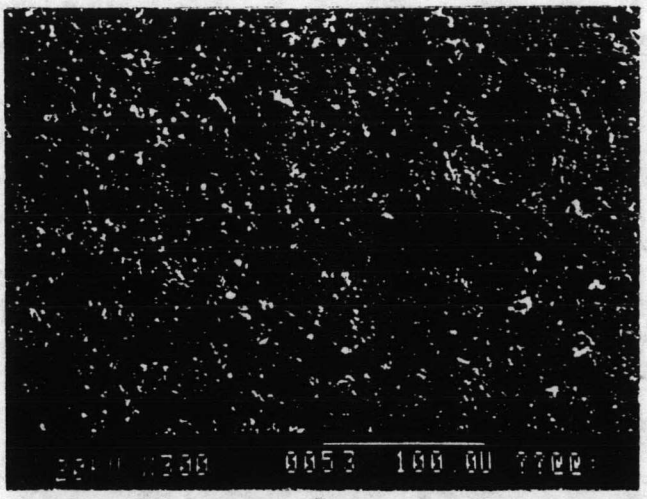
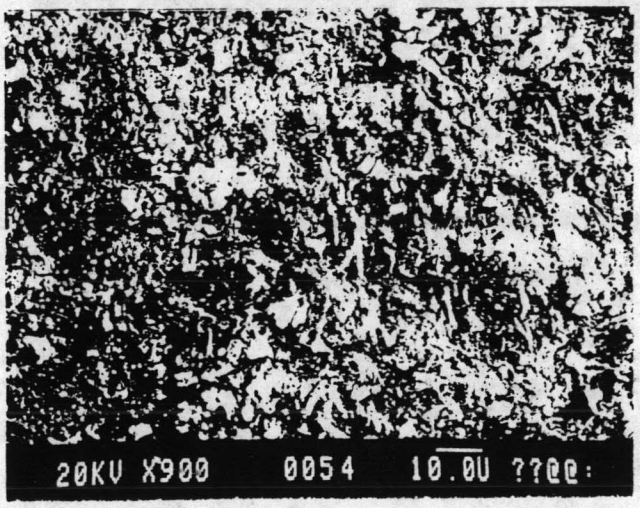


Figure 19 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with ethylcellulose film coating formulations



A



B

Figure 20 Photomicrographs of propranolol HCl core tablets at magnification of 300x (A); and (B) 900x

The appearance of all the film coated tablets obtained were consistent with the appearance of their original film coating formulations. The CS film coated tablets were smooth, yellowish and stickiness in nature, whereas the water-soluble cellulose derived coated tablets were smooth, white and glossy. The tablets coated with coating dispersions were opaque and rough in nature. The CT coated tablets were brownish whereas the EC coated tablets were white. Some of the film coated tablets are also demonstrated in Figure 21-22.

The propranolol HCl tablet properties after coating with the film coating formulations containing one film former, calculated from the data in Table 69-74 (Appendix C), are presented in Table 18-23. All the tablet properties investigated were markedly changed in different manners, depended on the type of film formers. The properties of tablets coated with water-soluble film formers and with water-insoluble film formers were thus separately described.

After coating, the propranolol HCl tablets coated with water-soluble film formers were harder and had the longer disintegration time. The tablet hardness and the disintegration time increased with increasing the coating level, which related to the increased weight as the coating deposited. Mean and standard deviation of the tablet hardness of some formulations could not be calculated because some obtained values exceeded the maximum limit of the apparatus. Based on both parameters at the same coating level, the coated tablets could be ordered as followed : CS < HPC < HPMC ~ MC.

Cumulative percent amount of the drug released as a function of time of the coated tablets, from the data in Table 76-79 (Appendix C), are illustrated in Figure 23-26. Although, all the

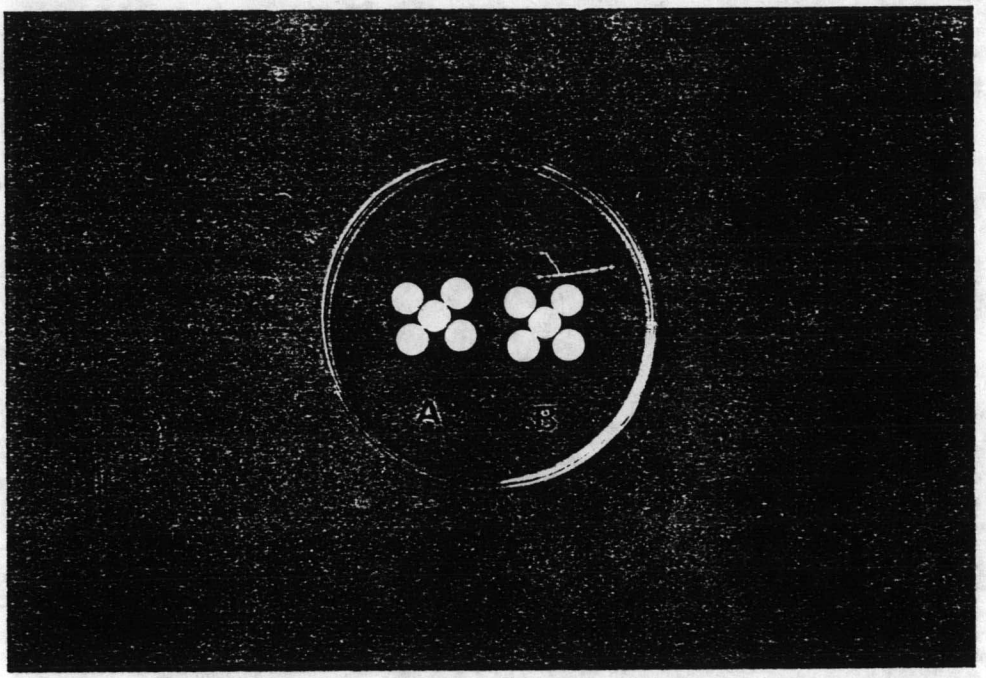


Figure 21 Chitosan (A) and hydroxypropyl methylcellulose (B) coated tablets

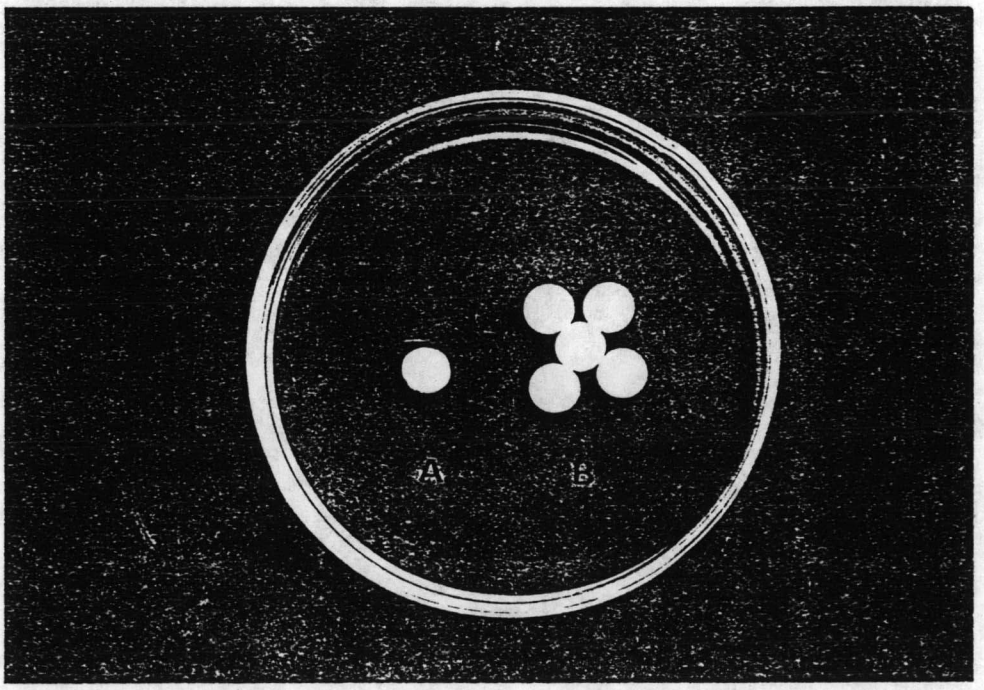


Figure 22 Chitin (A) and ethylcellulose (B) coated tablets

Table 18 Properties of Propranolol HCl Tablets Coated with Chitosan Film Coating Formulations.

Properties	Mean (SD)*		
	CS 5	CS 10	CS 15
1. Weight (gm.)	0.2783(0.006)	0.2996(0.006)	0.3015(0.008)
Increased Weight(%)	6.18	10.70	14.93
2. Hardness (kp.)	13.28 (1.963)	15.99 (1.840)	-**
3. Disintegration time (min.sec)	9.20 (0.48)	9.55 (0.48)	10.23 (0.48)

* Standard Deviation

** some data exceeded the maximum limit of the apparatus

Table 19 Properties of Propranolol HCl Tablets Coated with Hydroxypropyl Methylcellulose Film Coating Formulations.

Properties	Mean (SD)*		
	HPMC 5	HPMC 10	HPMC 15
1. Weight (gm.)	0.2930(0.006)	0.2962(0.007)	0.3119(0.008)
Increased Weight(%)	5.35	10.30	14.60
2. Hardness (kp.)	>20	>20	>20
3. Disintegration time (min.sec)	9.39 (1.04)	14.02 (0.44)	21.29 (1.26)

* Standard Deviation

Table 20 Properties of Propranolol HCl Tablets Coated with Methylcellulose Film Coating Formulations.

Properties	Mean (SD)*		
	MC 5	MC 10	MC 15
1. Weight (gm.)	0.2818(0.007)	0.2919(0.006)	0.3054(0.007)
Increased Weight(%)	4.84	9.00	14.44
2. Hardness (kp.)	>20	>20	>20
3. Disintegration time (min.sec)	10.33 (1.48)	15.25 (1.58)	19.08 (2.11)

* Standard Deviation

Table 21 Properties of Propranolol HCl Tablets Coated with Hydroxypropyl Cellulose Film Coating Formulations.

Properties	Mean (SD)*		
	HPC 5	HPC 10	HPC 15
1. Weight (gm.)	0.2940(0.005)	0.2843(0.008)	0.3138(0.003)
Increased Weight(%)	5.23	9.09	15.36
2. Hardness (kp.)	15.75 (2.329)	-**	>20
3. Disintegration time (min.sec)	11.20 (2.08)	14.02 (1.59)	22.14 (1.52)

* Standard Deviation

** some data exceeded the maximum limit of the apparatus

Table 22 Properties of Propranolol HCl Tablets Coated with Chitin Film Coating Formulations.

Properties	Mean (SD)*	
	CT 5	CT 10
1. Weight (gm.)	0.2852(0.006)	0.3028(0.007)
Increased Weight(%)	5.76	11.01
2. Hardness (kp.)	-**	>20
3. Disintegration time (min.sec)	9.00 (0.06)	14.36 (2.27)

* Standard Deviation

** some data exceeded the maximum limit of the apparatus

Table 23 Properties of Propranolol HCl Tablets Coated with Ethylcellulose Film Coating Formulations.

Properties	Mean (SD)*		
	EC 3	EC 5	EC 10
1. Weight (gm.)	0.2719(0.007)	0.2802(0.006)	0.2907(0.004)
Increased Weight(%)	3.01	5.05	10.72
2. Hardness (kp.)	-**	-	13.75(1.851)
3. Disintegration time (min.sec)	37.33 (4.51)	-***	> 2 hr.

* Standard Deviation

** some data exceeded the maximum limit of the apparatus

*** some data were greater than 2 hr.

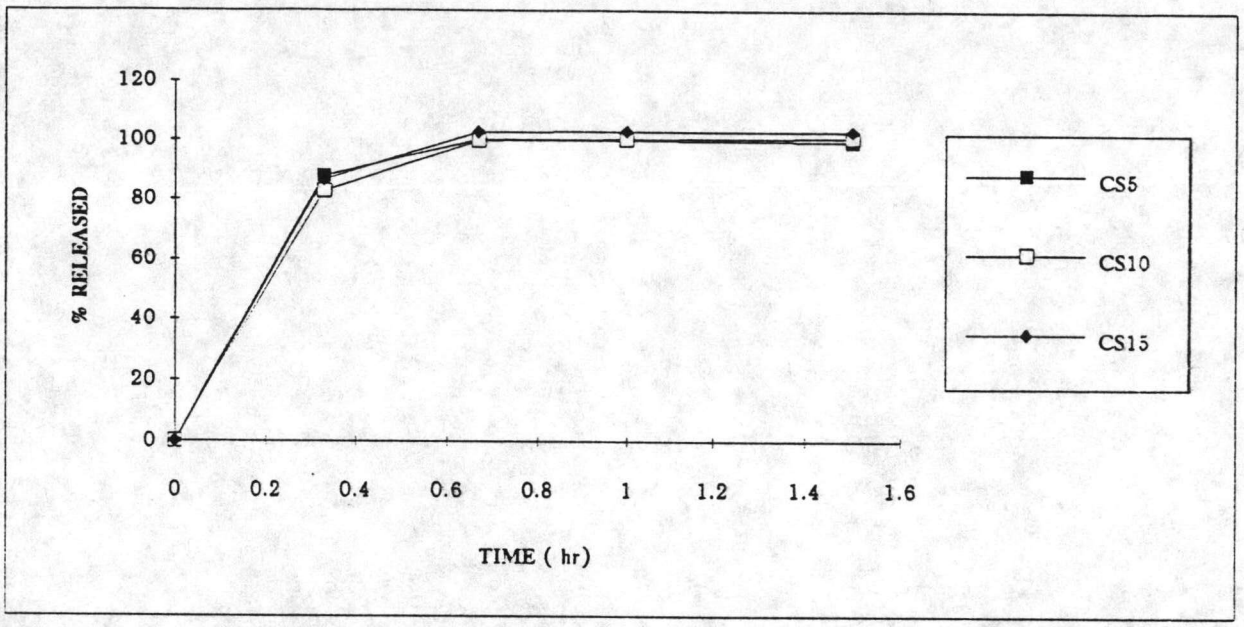


Figure 23 Cumulative percent amount of the drug released from propranolol HCl tablets coated with chitosan film coating formulations

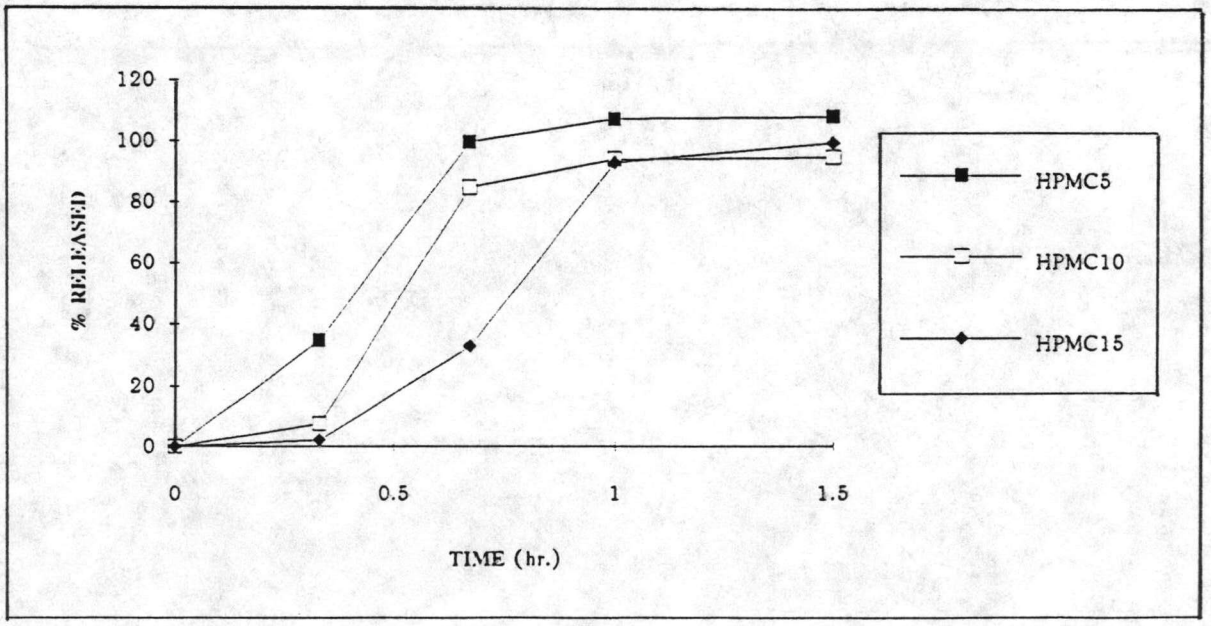


Figure 24 Cumulative percent amount of the drug released from propranolol HCl tablets coated with hydroxypropyl methylcellulose film coating formulations

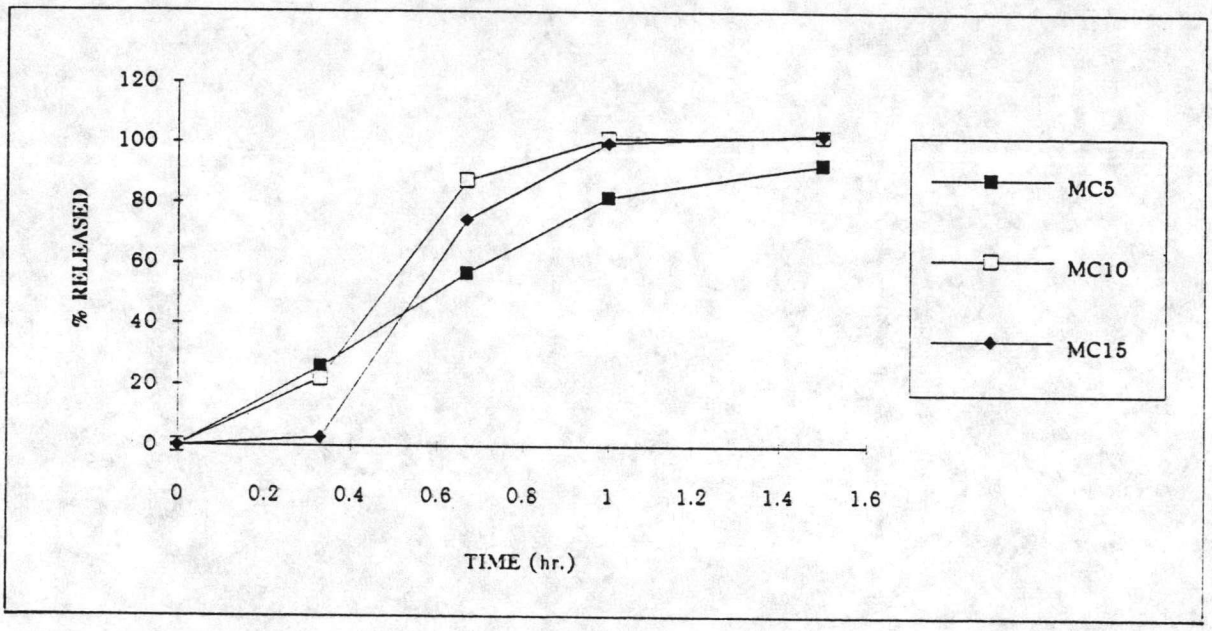


Figure 25 Cumulative percent amount of the drug released from propranolol HCl tablets coated with methylcellulose film coating formulations

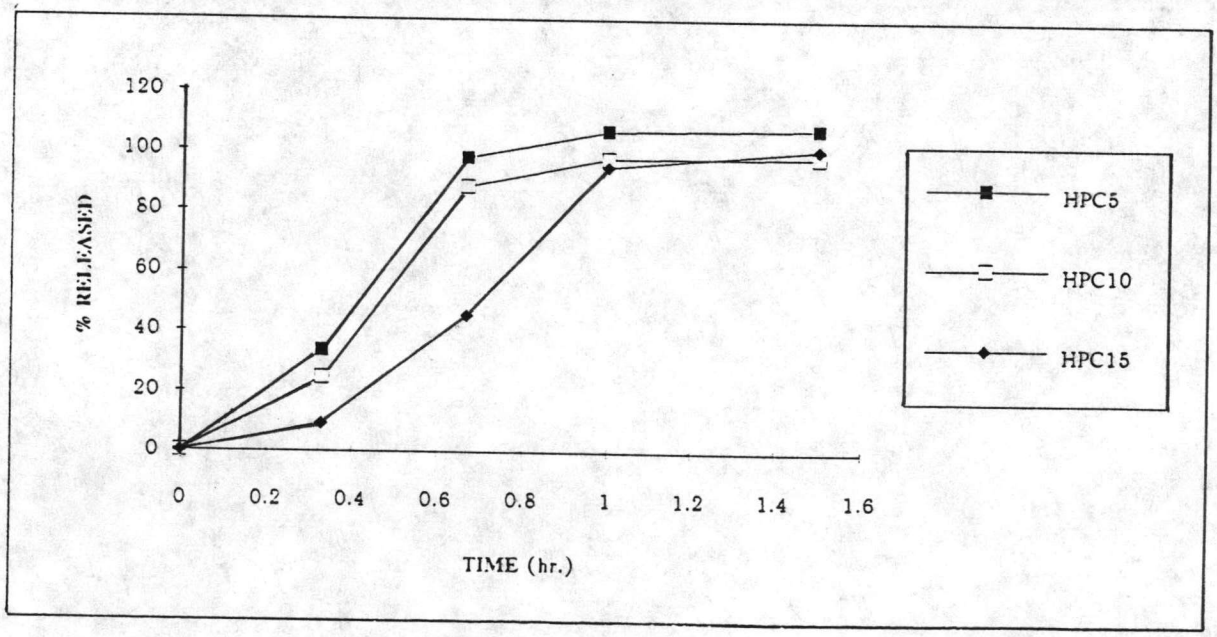
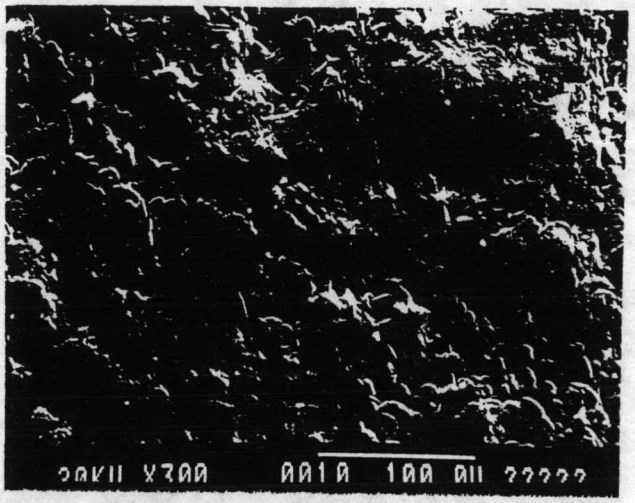


Figure 26 Cumulative percent amount of the drug released from propranolol HCl tablets coated with hydroxypropyl cellulose film coating formulations

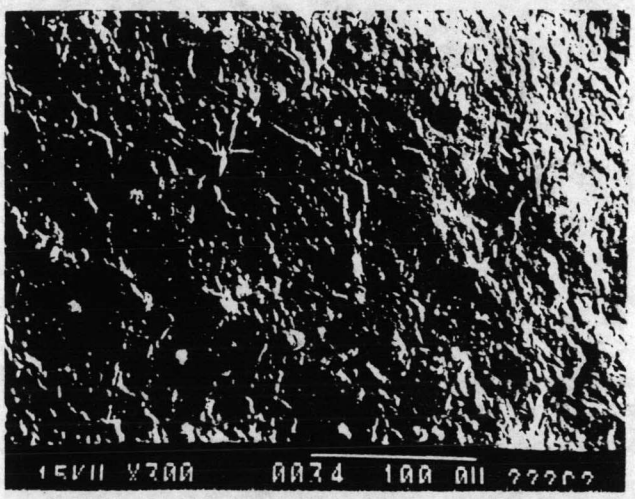
coated tablets had slower drug release, when compared with the corresponded core tablets, they were still readily dissolved in the acid stage solution within one and a half hour. The drug release was found to follow the coating level, as increasing the coating level the slower release was obtained. However, the coating level was found to unaffect the drug release from the CS coated tablets, whereas it strongly influenced the drug release from the cellulose coated tablets. At the same coating level, the tablets could be ordered as followed : CS < HPMC ~ MC ~ HPC.

The tablet surface after coating of the tablets was examined by scanning electron microscopy as shown in Figure 27-28. The coating could be characterized by many layers of thin film deposited one after another on the tablet surface. As the coating level was increased, the CS coated tablet surface was decreased in the degree of smoothness. When compared with the HPMC coated tablet surface, their degree of smoothness were comparable, but the CS tablet surface was more wrinkled. The HPC coated tablet surface seemed to have the highest degree of smoothness as well as the highest degree of wrinkle, which was clearly viewed at higher magnification. The MC tablet surface seemed to have the lowest degree of smoothness. It was also noted that the CS tablet surface could not be examined at higher magnification of 900x.

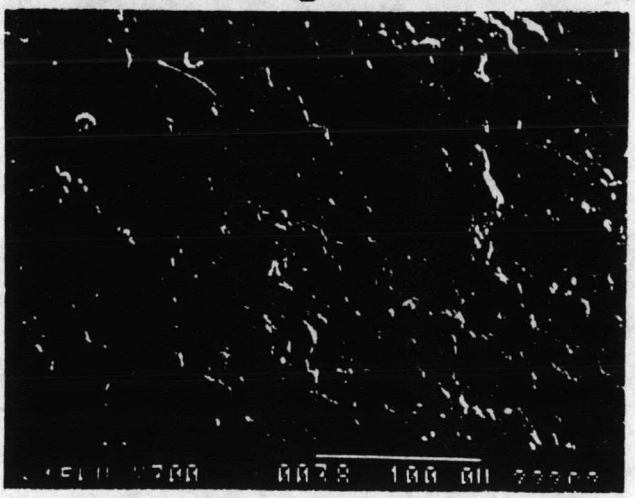
For tablets coated with water-insoluble film formers, they tended to be harder and have the longer disintegration time, compared with the corresponded core tablets. However, the disintegration time of the CT coated tablets at the coating level of 5% increased weight was slightly decreased from 10.15 to 9.00 (min.sec), after coating.



A



B



C

Figure 27 Photomicrographs of propranolol HCl tablets coated with chitosan film coating formulations at magnification of 300x: at the coating level of 5% (A); 10% (B); and 15% (C) increased weight

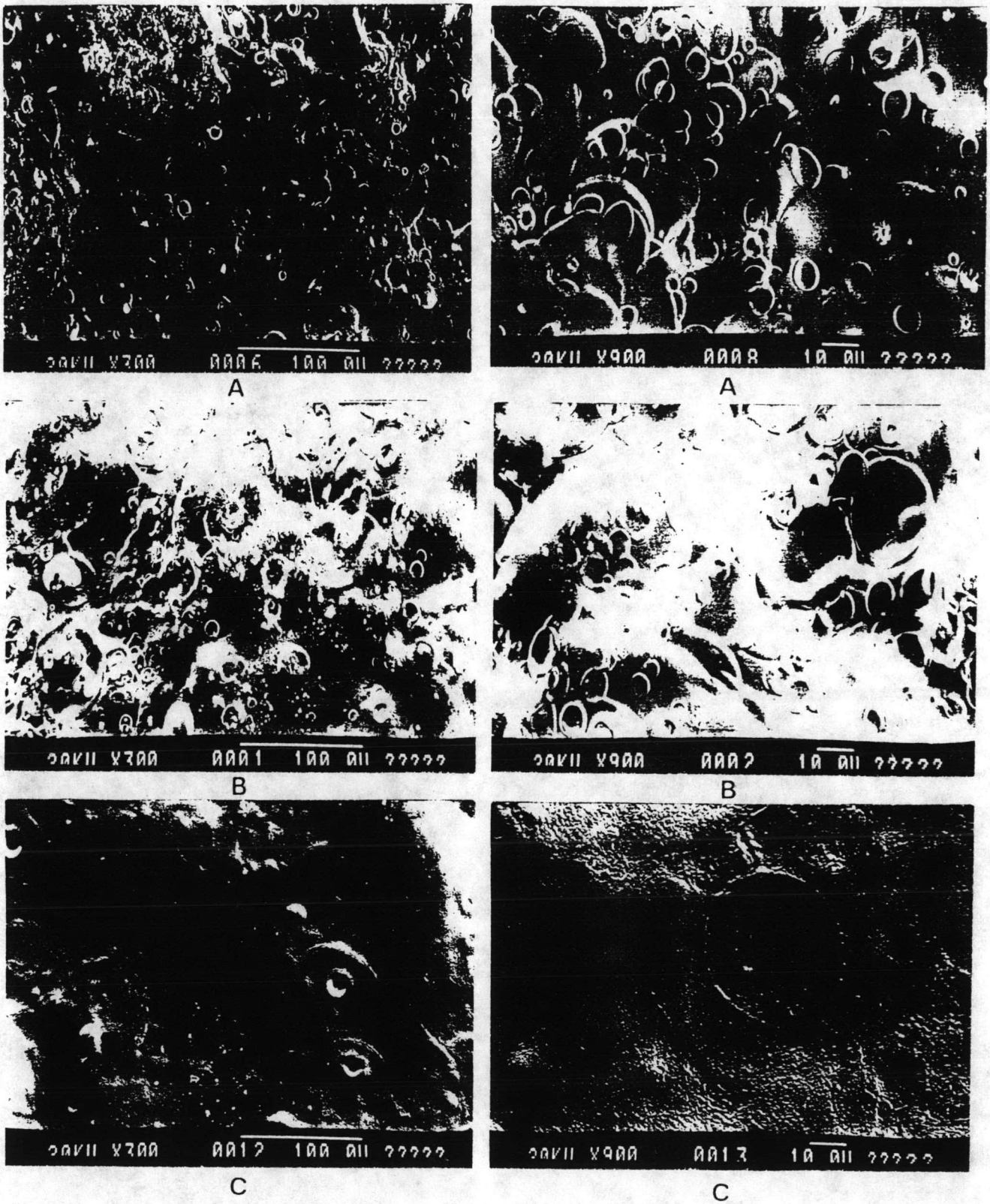


Figure 28 Photomicrographs of propranolol HCl tablets coated with HPMC (A); MC (B); and HPC (C) film coating formulations at magnification of 300x and 900x

The hardness of the CT coated tablets increased with increasing the coating level. The coating level also affected the hardness of the EC coated tablets but this effect was unpredictable. Since the hardness of the EC coated tablets at the coating level of 3% and 5% increased weight were comparable whereas that at the coating level of 10% increased weight seemed to be lower. However, the hardness of both CT and EC coated tablets were still comparable. If mean and standard deviation of the tablet hardness could not be calculated, the reason was the same as previously described.

The disintegration time of the CT and the EC coated tablets increased as the coating level was increased, but the EC coated tablets had much longer disintegration time than the CT coated tablets. With similar reason to the tablet hardness calculation, mean and standard deviation of the disintegration time could not be calculated if some values obtained were greater than 2 hours.

Cumulative percent amount of the drug released as a function of time of the CT and the EC coated tablets, from the data in Table 80-81 (Appendix C), is illustrated in Figure 29-30. When compared with the corresponded core tablets, the drug release was much slower, with a much higher extent to the EC coated tablets.

The drug release from the CT coated tablets was slightly slower with increasing the coating level from 5% to 10% increased weight. It was complete within 5 and 10 hours for the tablets at the coating level of 5% and 10% increased weight, respectively. It was also noticed that the drug release was complete at the maximum amount of the drug released about 90%. The drug release from the EC coated

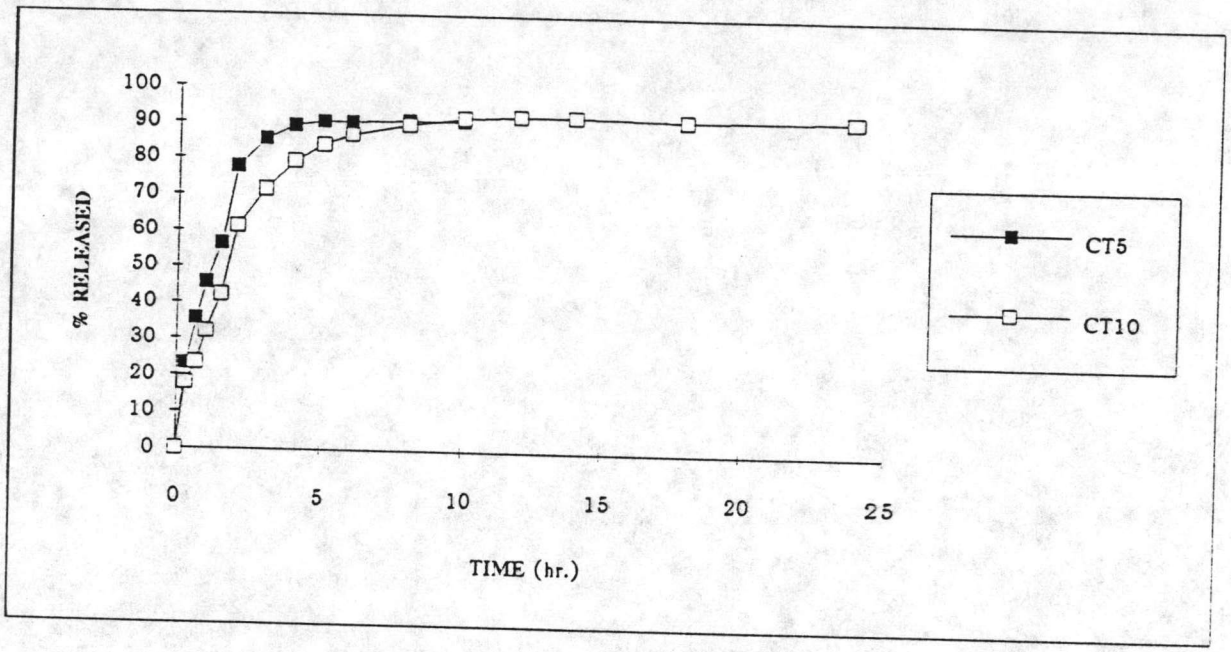


Figure 29 Cumulative percent amount of the drug released from propranolol HCl tablets coated with chitin film coating formulations

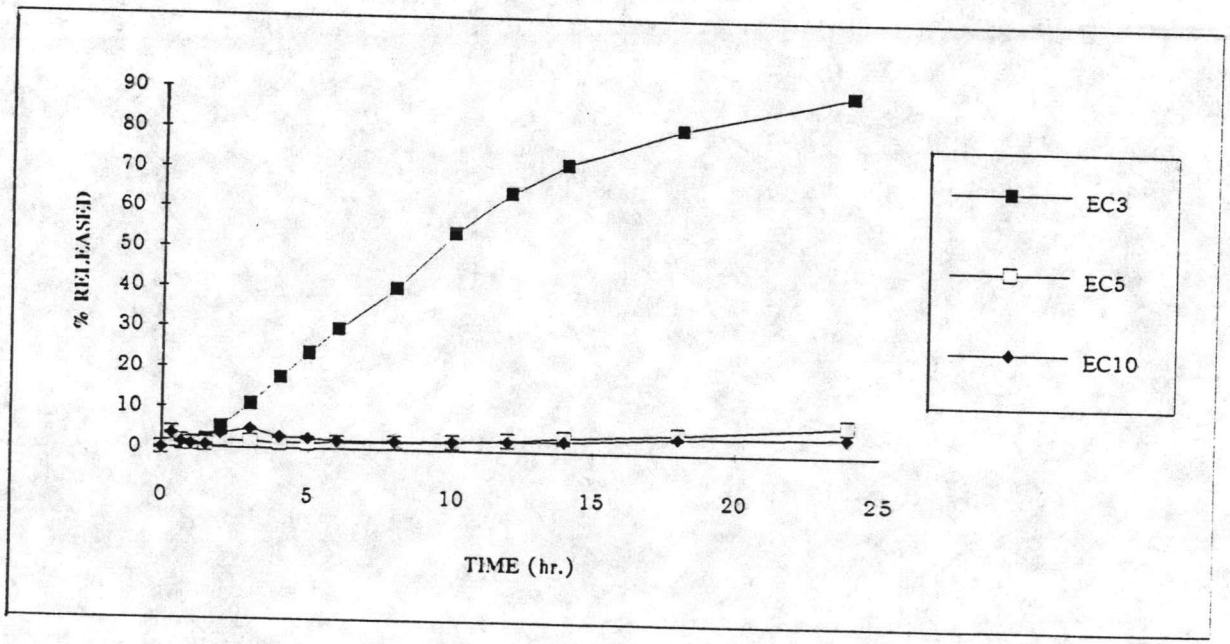


Figure 30 Cumulative percent amount of the drug released from propranolol HCl tablets coated with ethylcellulose film coating formulations

tablets was markedly decreased and slightly decreased when the coating level was increased from 3% to 5%, and to 10% increased weight, respectively. All of 3 coating levels could maintain the drug release throughout the time course of 24 hours. It was clearly seen that the drug release from the EC coated tablets was much slower than that from the CT coated tablets at all coating levels.

The surface topography of the CT and the EC coated tablets at the coating level of both 5% and 10% increased weight is demonstrated in Figure 31-32. The porous structure as well as the degree of smoothness of the tablet surface were obviously presented. As the coating level was increased, the CT tablet surface looked denser whereas the EC tablet surface looked alike. In comparison, the CT tablet surface was more rough and porous than the EC tablet surface. Furthermore, the EC coating deposited was clearly more characterized by many layers of the film deposited one after another on the tablet surface than the CT coating.

Since both the CT and the EC coated tablets remained intact after the time course of drug release, their surface topography was also examined as illustrated in Figure 33-34. After the drug release test, the CT tablet surface was found to be looser and characterized with the macroporous structure, while the EC tablet surface was found to be almost unchanged and characterized with a little of microporous structure, compared with those before being subjected to the drug release test. With the higher coating level, the CT tablet surface was denser, whereas the EC tablet surface was still alike.

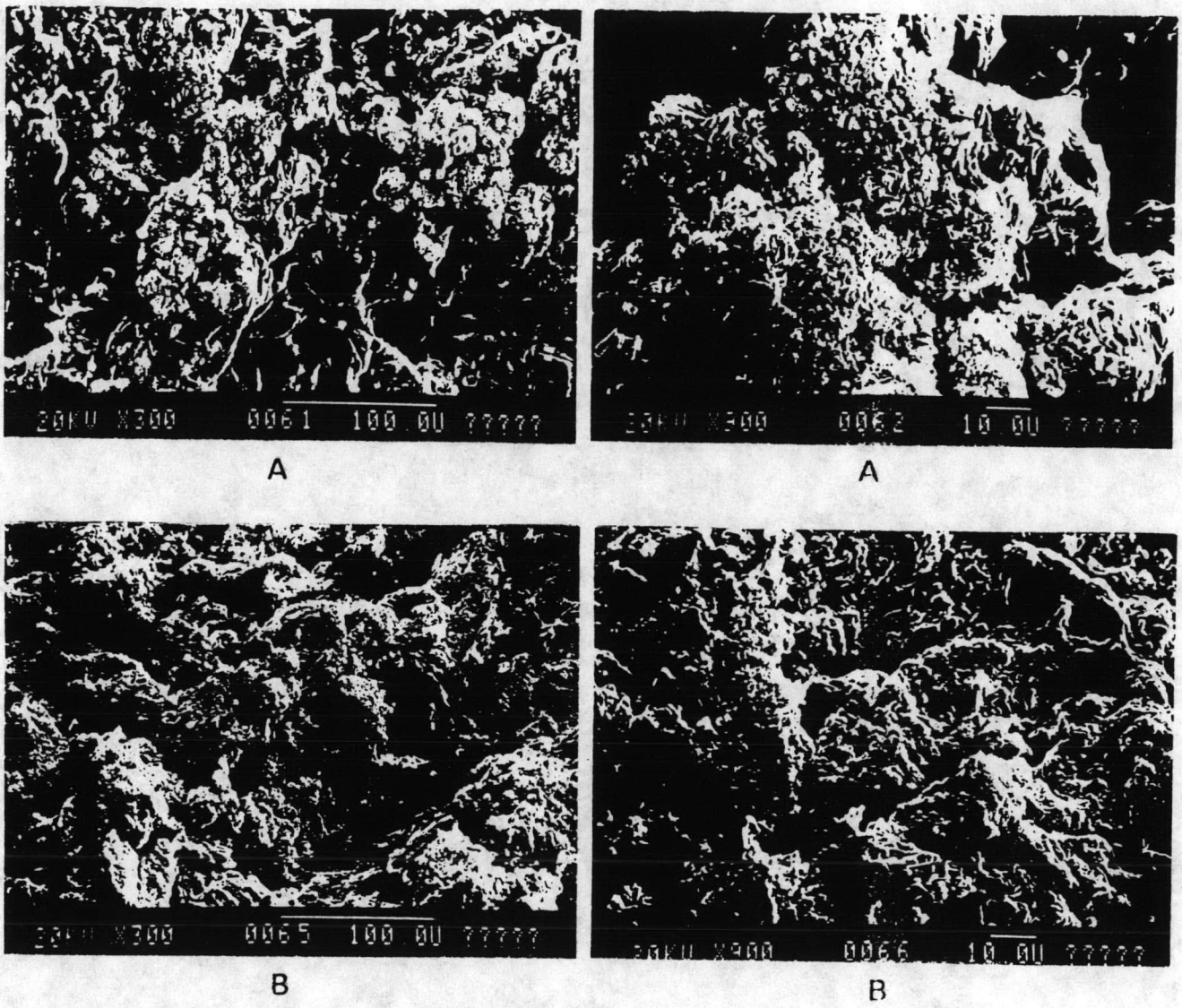


Figure 31 Photomicrographs of propranolol HCl tablets coated with chitin film coating formulations at magnification of 300x and 900x: at the coating level of 5% (A); and 10% (B) increased weight

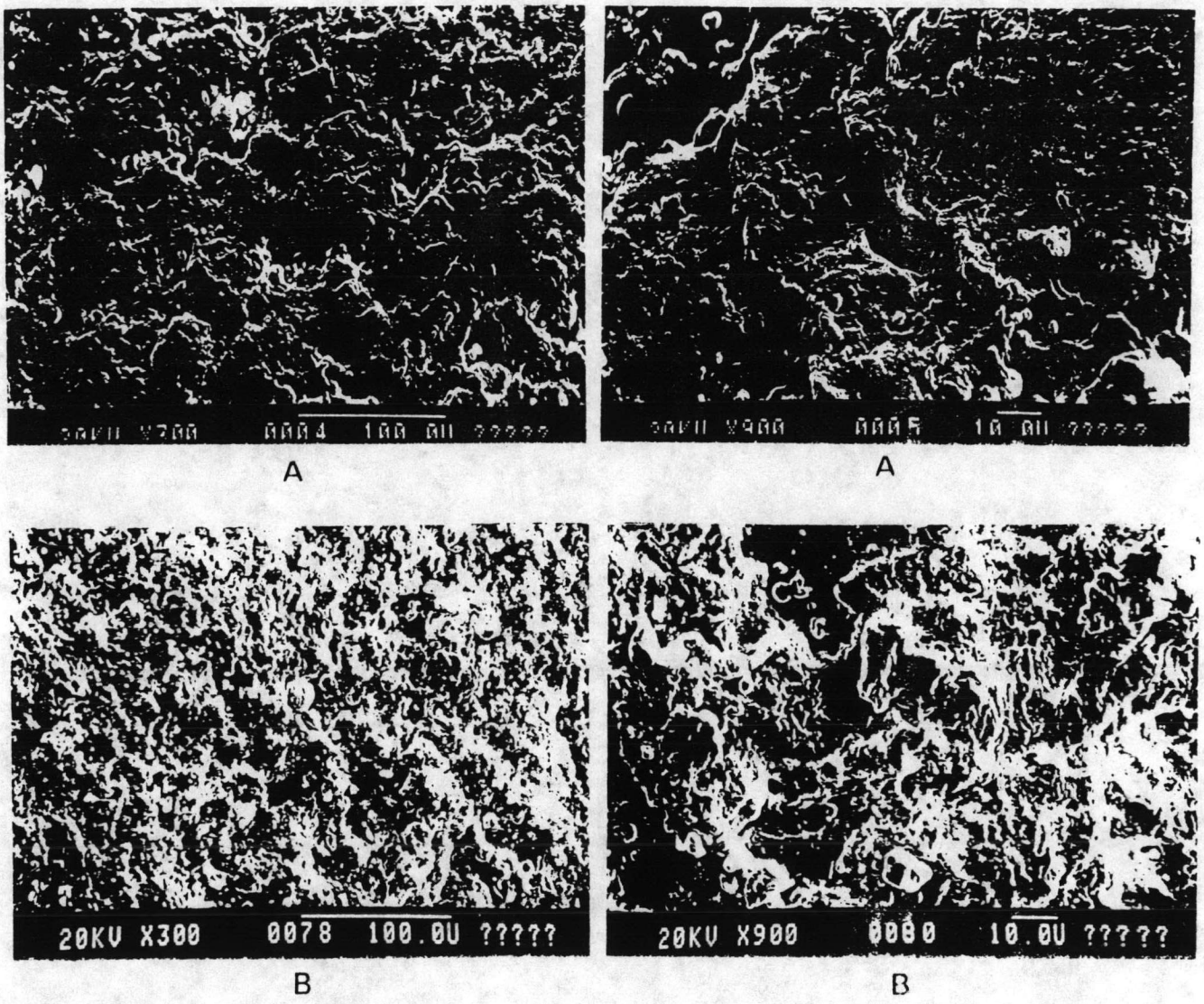


Figure 32 Photomicrographs of propranolol HCl tablets coated with ethylcellulose film coating formulations at magnification of 300x and 900x: at the coating level of 5% (A); and 10% (B) increased weight

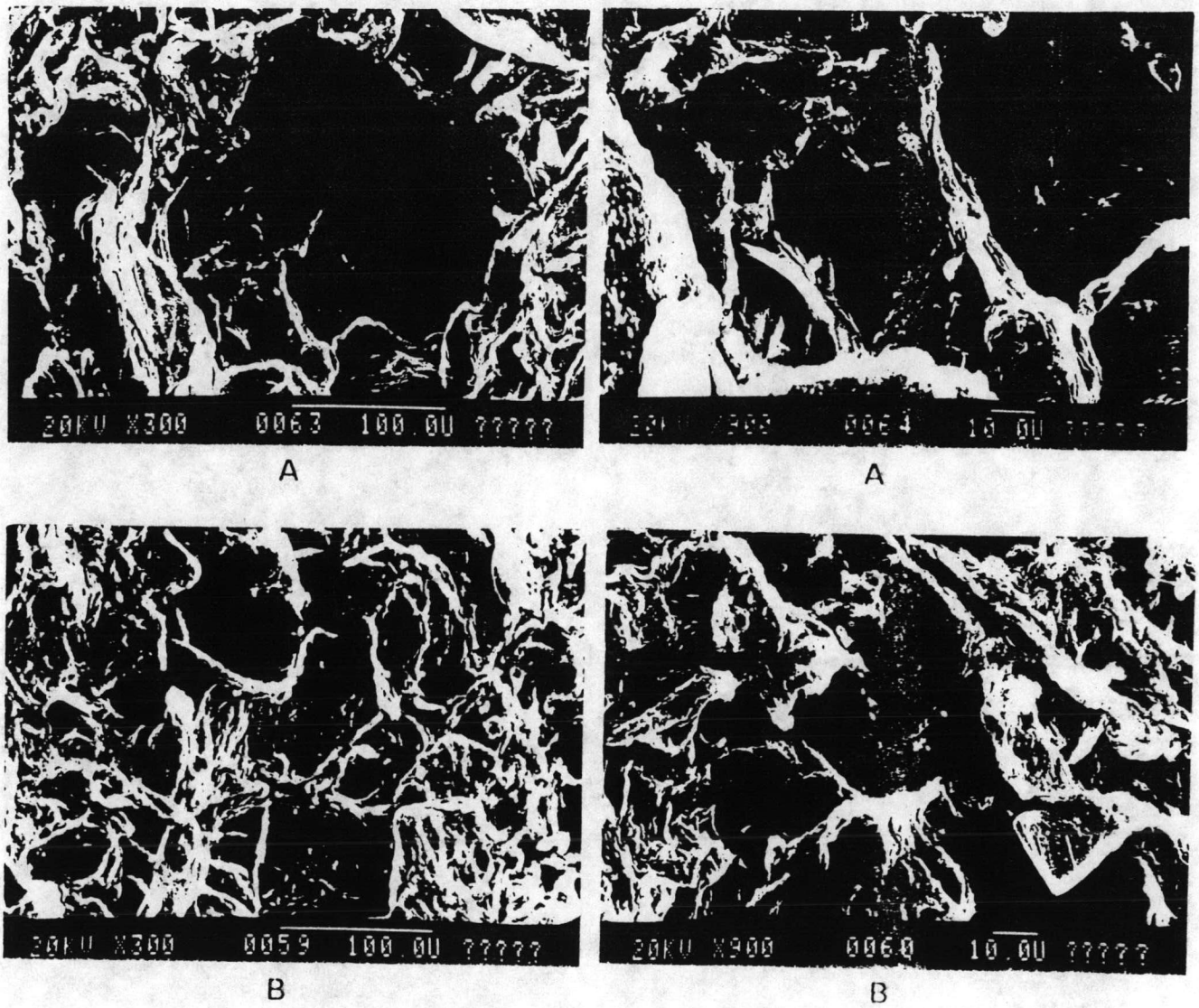


Figure 33 Photomicrographs of propranolol HCl tablets coated with chitin film coating formulations after drug release test at magnification of 300x and 900x: at the coating level of 5% (A); and 10% (B) increased weight

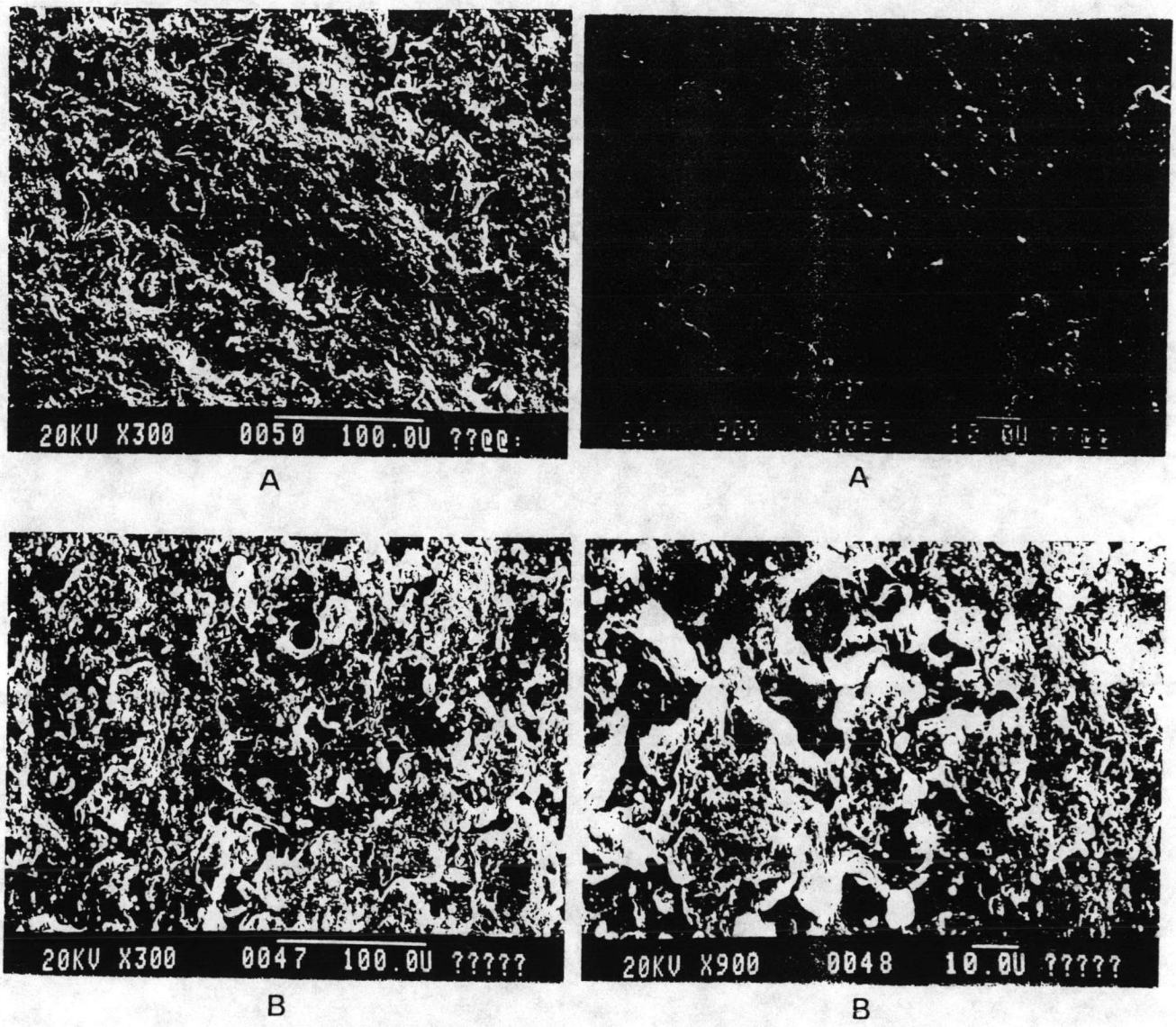


Figure 34 Photomicrographs of propranolol HCl tablets coated with ethylcellulose film coating formulations after drug release test at magnification of 300x and 900x: at the coating level of 5% (A); and 10% (B) increased weight

Tablets Coated with Film Coating Formulations Containing Combined Film Formers.

Since CT coated tablets could not maintain the drug release throughout time course of the test at any coating level. The film coating formulations containing the combination of CT and other water-soluble film formers could not help improve the sustained drug release characteristic and were thus not studied in this step. Whereas the EC coated tablets at the coating level of 5% increased weight was the least coating level that could consistently maintain the drug release throughout time course of the test. Therefore, the film coating formulations containing the combination of EC and HPMC at various ratios were selected to coat the core tablets at the fixed coating level of 5% increased weight in this step. All the coated tablets were designated based on the name and the ratio of both polymers. The first letter "E" represented the film former EC and the second letter "H" represented the film former HPMC. The first two and the last two digits represented the proportion of EC and HPMC in the combination, respectively. For example, the designation "EH 4060" meaned the tablets coated with EC and HPMC in the ratio of 40 : 60 at the coating level of 5% increased weight.

Mean and standard deviation of the tablet properties of the propranolol HCl core tablets before being coated with the film coating formulations containing the combination of EC and HPMC, calculated from the data in Table 61, are presented in Table 24. The average weight, the tablet hardness, the disintegration time, the uniformity of dosage units and the percent labeled content were in the same range as those of the core tablets before being coated with film coating formulations containing one film former.

Table 24 Properties of Propranolol HCl Core Tablets before Being Coated with Combination of Ethylcellulose and Hydroxypropyl Methylcellulose Film Coating Formulations.

Properties	Mean (SD)*							
	EH 4060	EH 5050	EH 6040	EH 8020	EH 8218	EH 8515	EH 8713	EH 9010
1.Weight (gm.)	0.2668 (0.007)	0.2624 (0.005)	0.2614 (0.005)	0.2757 (0.004)	0.2721 (0.004)	0.2831 (0.005)	0.2807 (0.006)	0.2788 (0.008)
2.Hardness (kp.)	10.31 (0.960)	10.69 (1.096)	11.08 (0.953)	11.09 (1.349)	10.75 (1.020)	10.49 (1.543)	11.48 (1.739)	12.24 (1.514)
3.Disintegration Time (min.sec)	9.04 (0.41)	8.04 (1.07)	8.17 (0.21)	10.58 (0.52)	10.15 (0.40)	8.11 (0.56)	8.11 (0.56)	9.04 (0.41)
4.Uniformity of Dosage Units (%)	99.84 (3.30)	99.55 (1.66)	101.43 (2.06)	102.55 (1.40)	99.95 (1.66)	104.06 (2.73)	104.06 (2.73)	99.84 (3.30)
5.Labeled Content (%)	103.89 (0.64)	101.10 (0.40)	103.29 (1.49)	98.19 (2.94)	97.72 (0.64)	104.79 (1.28)	104.79 (1.28)	103.89 (0.64)

* Standard Deviation

Cumulative percent amount of the drug released as a function of time from the core tablets as presented in Table 68 (Appendix C), are illustrated in Figure 35. Again, all of the core tablets were completely dissolved in the acid stage solution within about 30 minutes. However, there were two profiles different from others; the core tablets before being coated with the formulations EH 6040 had the faster release profile and those with the formulations EH 8020 had the slower release profile, compared with others.

During coating, none of the film coating formulations was found to generate any problem, particularly the tackiness. The propranolol HCl tablet properties after coating with the formulations containing various ratios of the polymers, calculated from the data in Table 75, are presented in table 25. The tablet hardness and the disintegration time of the coated tablets were increased when compared with those of the corresponded core tablets. The polymer ratio in the combined film coating formulations seemed to affect the tablet hardness but the effect was unpredictable. However, the disintegration time of the coated tablets was found to be increased with increasing the EC proportion in the combined film coating formulations.

Cumulative percent amount of the drug released as a function of time of the coated tablets from the data in Table 82 (Appendix C), are illustrated in Figure 36. After coating, all of the coated tablets had slower drug release characteristics when compared with the corresponded core tablets, but in different manners depended on the polymer ratio in the film coating formulations. The formulations EH 4060, EH 5050, and EH 6040 were found to ineffectively maintain the drug release throughout time course of the test. They were completely dissolved in the acid stage solution within one and a half hour.

Table 25 Properties of Propranolol HCl Tablets Coated with Combination of Ethylcellulose and Hydroxypropyl Methylcellulose Film Coating Formulations.

Properties	Mean (SD)*							
	EH 4060	EH 5050	EH 6040	EH 8020	EH 8218	EH 8515	EH 8713	EH 9010
1.Weight (gm.)	0.2818	0.2736	0.2772	0.2882	0.2842	0.2985	0.2941	0.2920
	(0.011)	(0.003)	(0.006)	(0.003)	(0.003)	(0.006)	(0.008)	(0.008)
Increased Weight (%)	5.65	4.23	6.06	4.53	4.46	5.44	4.76	4.73
2.Hardness (kp.)	>20	-**	-	-	-	-	-	-
3.Disintegration	12.30	10.17	13.14	16.22	20.48	24.35	29.26	45.47
Time (min.sec)	(0.38)	(0.50)	(1.10)	(0.42)	(1.20)	(1.45)	(3.01)	(7.28)

* Standard Deviation

** some data exceeded the maximum limit of the apparatus

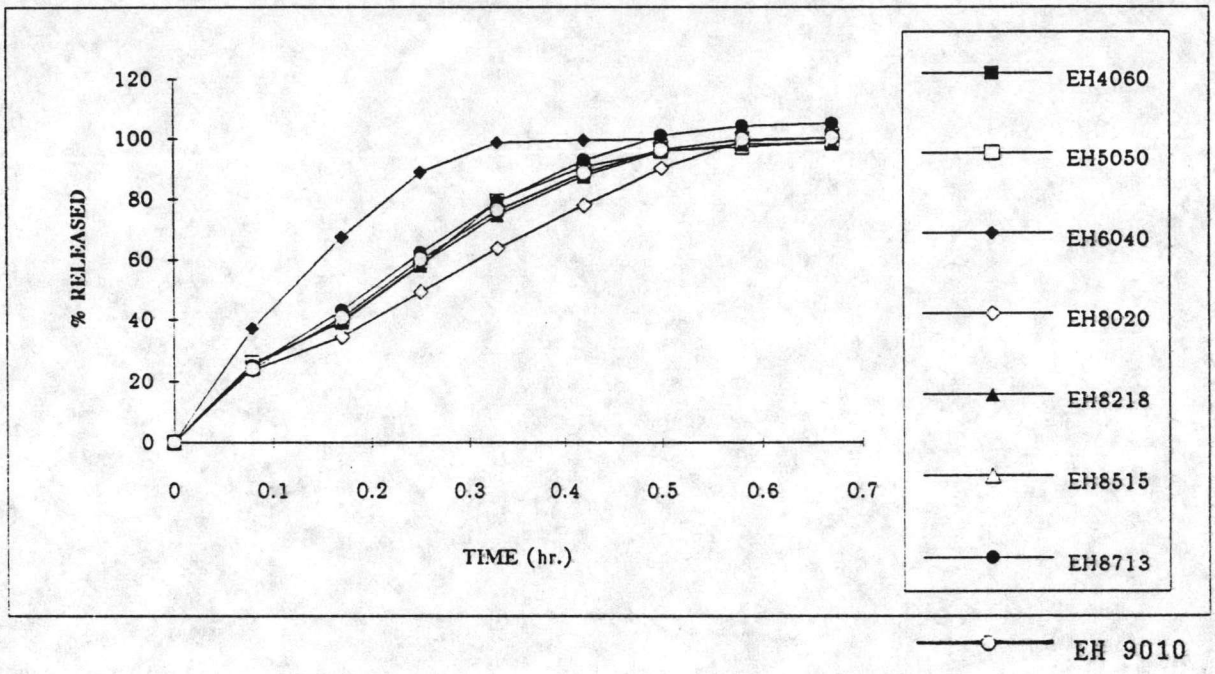


Figure 35 Cumulative percent amount of the drug released from propranolol HCl core tablets before being coated with combination of EC and HPMC film coating formulations

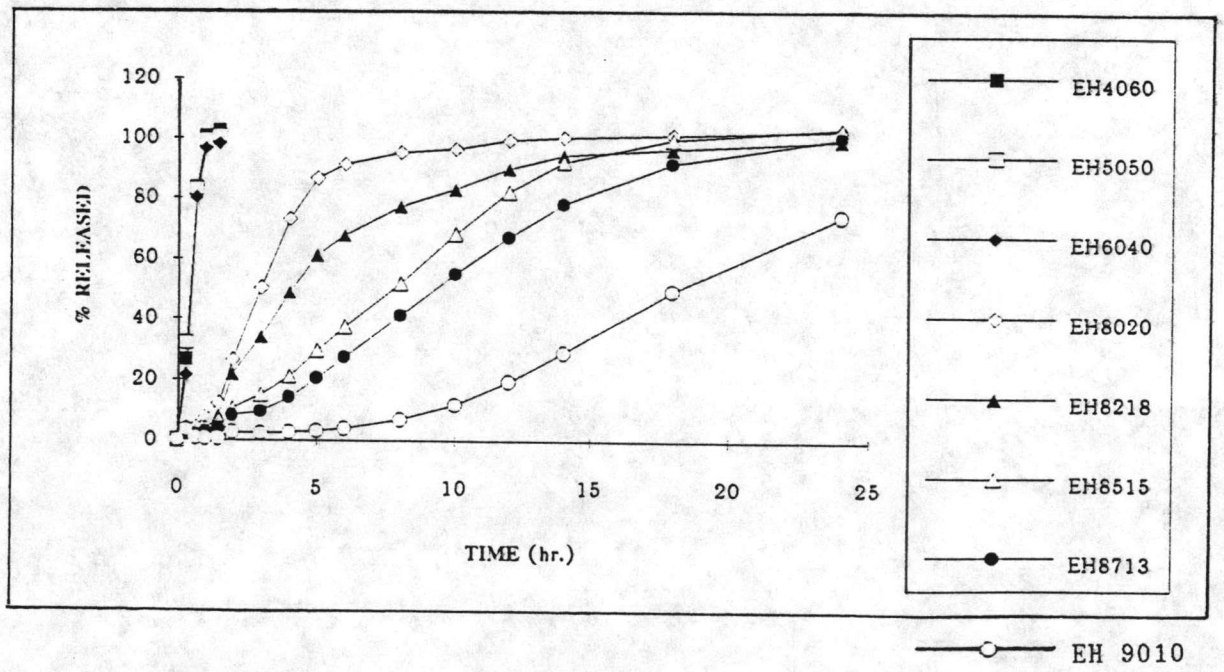


Figure 36 Cumulative percent amount of the drug released from propranolol HCl tablets coated with combination of EC and HPMC film coating formulations

Therefore, the EC proportion was increased as in the formulations EH 8020, EH 8218, EH 8515, EH 8713, and EH 9010. The release profiles of these formulations were characterized by three -phase curves. Phase I, in which the drug gradually and slowly released until the inflection point, was characterized as the lag time phase. In phase II, the drug release was increased and further remained constant till the other inflection point ; it was characterized as the consistent drug release phase. Phase III, in which the drug release was found to reach the maximum amount of the drug released, was characterized as the plateau phase. As the EC proportion in the film coating formulations was increased, the drug release profiles were characterized by the longer lag time phase, the slower consistent drug release phase, and reaching the plateau phase slower, respectively. However, the formulation EH 9010 seemed not to reach the plateau phase within time course of the test.

From all of the studied formulations, the formulation EH 8218 was found to pass the drug release test for Propranolol Hydrochloride Extended-release Capsules USP XXII. Its drug release profile is illustrated in comparison with that of the commercially available product in Figure 37. While the drug release profile of the experimental formulation was characterized by the three-phase curve, the drug release profile of the commercial preparation was initially fast and gradually decreased with time without any lag time. After time course of the test, the experimental formulation released the drug more completely than the commercial preparation.

The tablet surface of all the coated tablets is illustrated in Figure 38. In addition to the characterization by many layers of

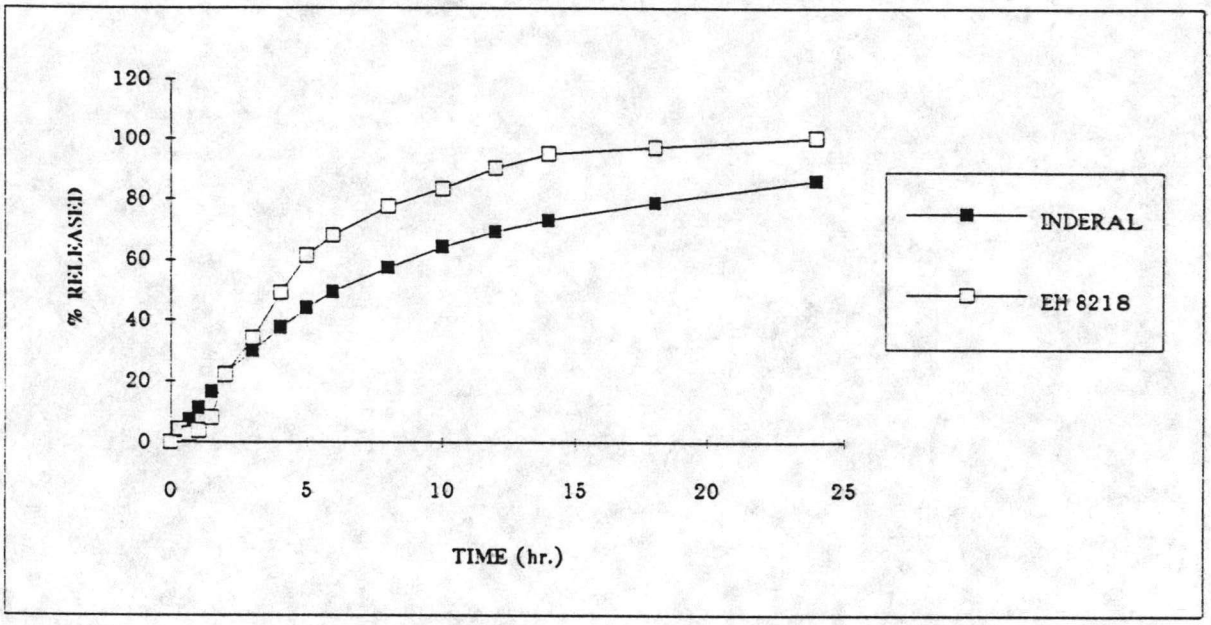


Figure 37 Cumulative percent amount of the drug released from propranolol HCl tablets coated with film coating formulations EH 8218 in comparison with the commercial preparation

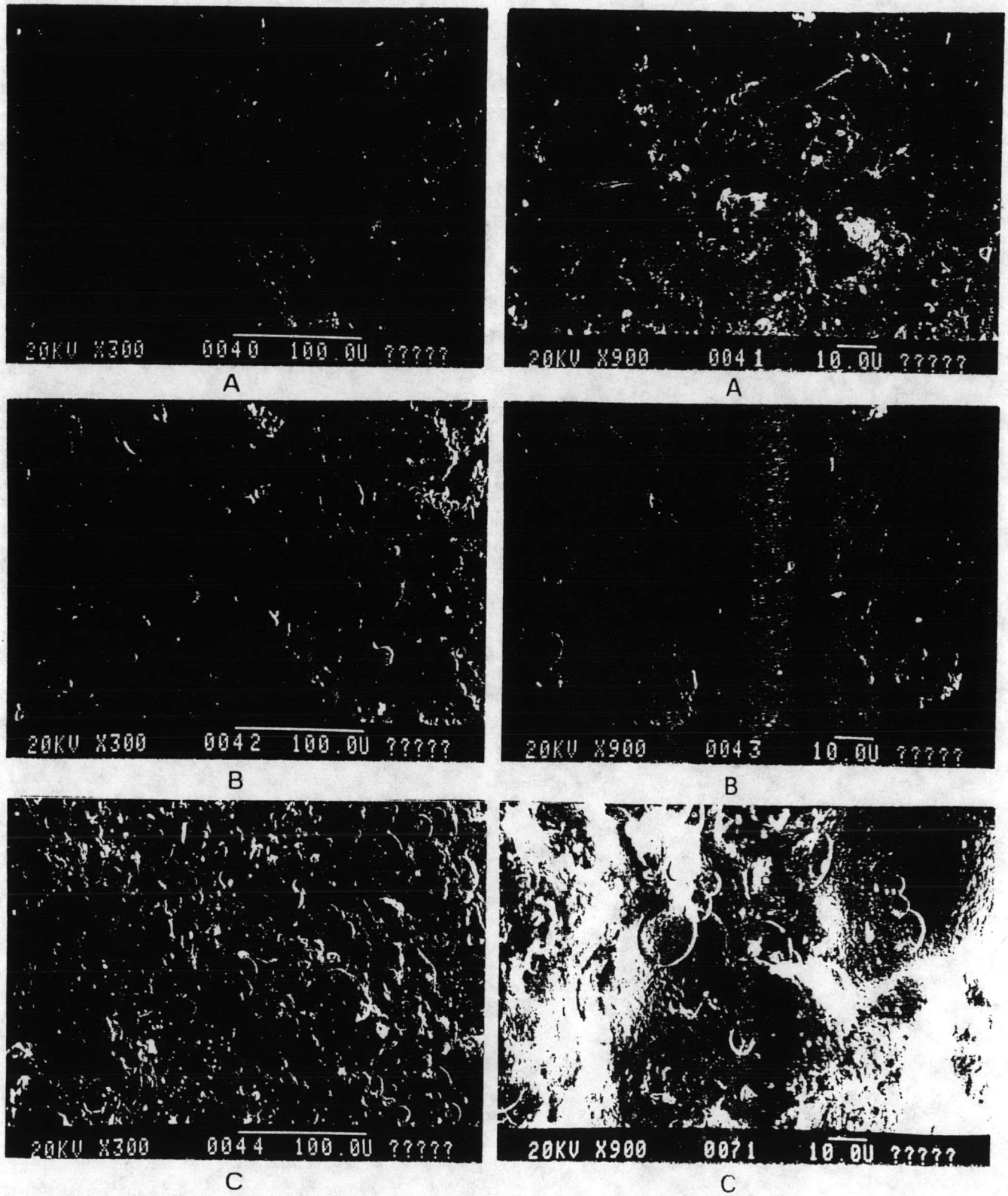


Figure 38 Photomicrographs of propranolol HCl tablets coated with film coating formulations EH 4060 (A); EH 5050 (B); and EH 6040 (C) at magnification of 300x and 900x

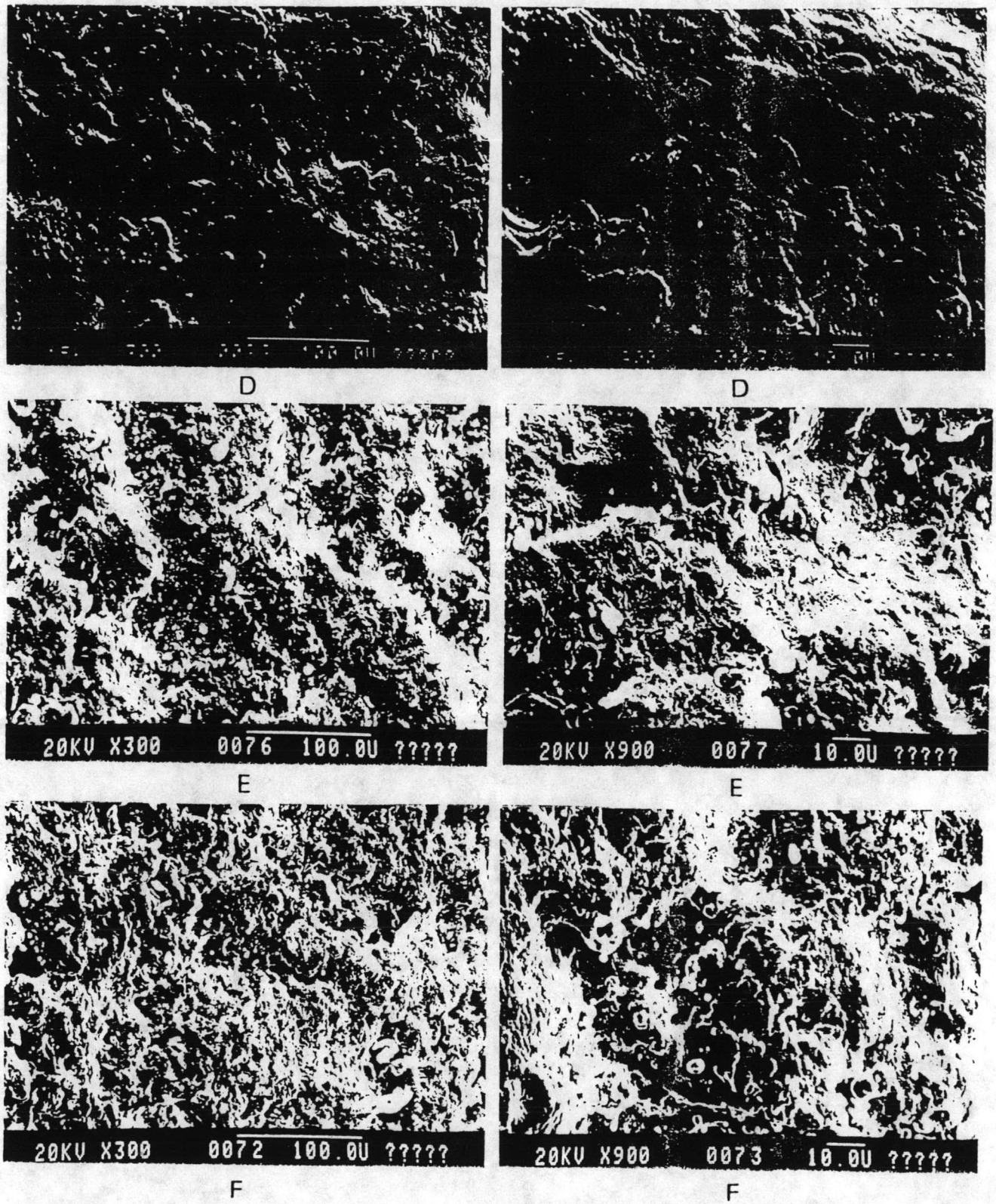


Figure 38 Photomicrographs of propranolol HCl tablets coated with film coating formulations EH 8020 (D); EH 8218 (E); and EH 8515 (F) at magnification of 300x and 900x (cont.)

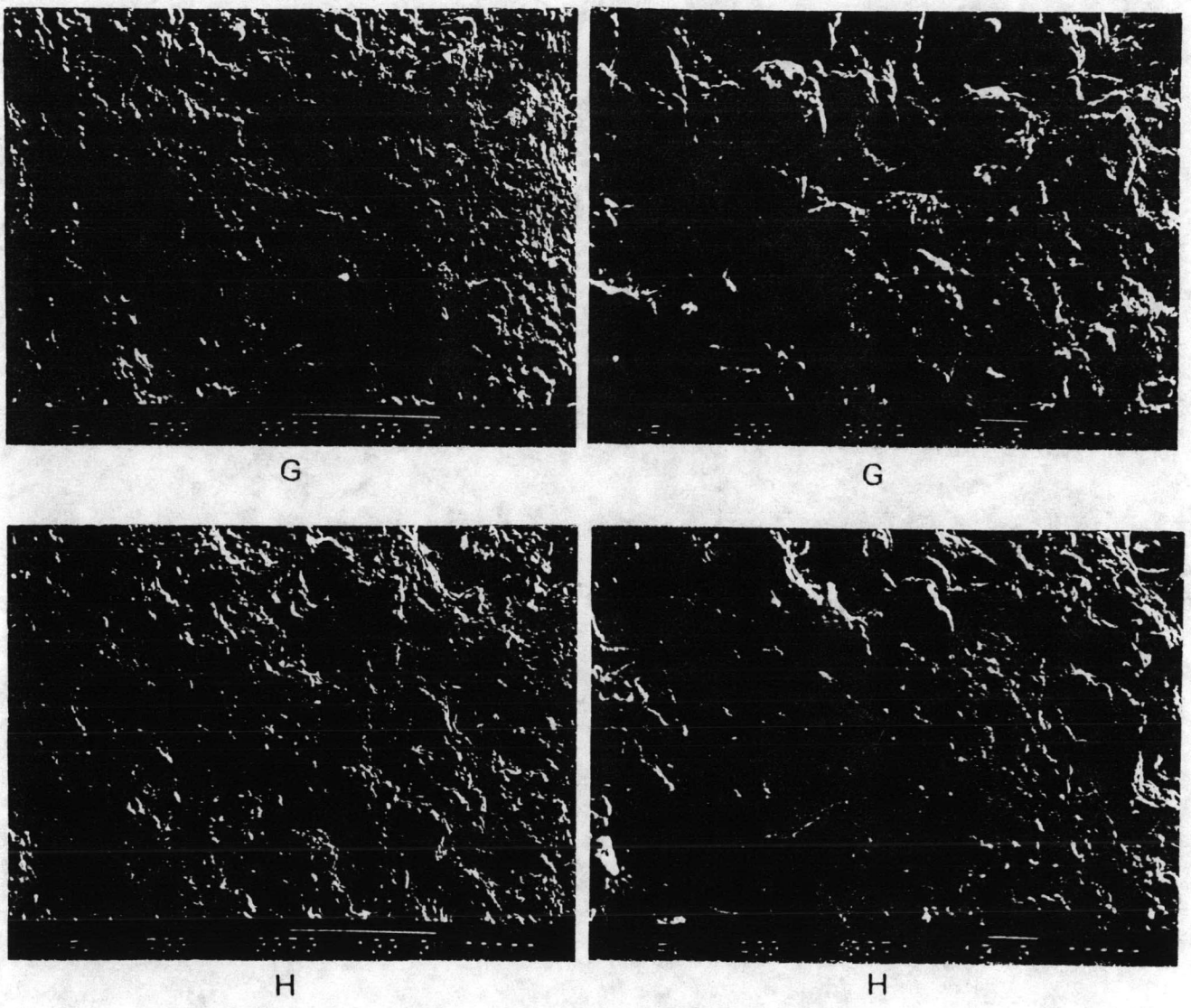


Figure 38 Photomicrographs of propranolol HCl tablets coated with film coating formulations EH 8713 (G); and EH 9010 (H) at magnification of 300x and 900x (cont.)

the coating deposited one after another on the surface, the combined characteristics between EC and HPMC were obviously presented. The degree of smoothness was high at the higher HPMC proportion in the formulations. If the EC proportion presented in the formulations was increased, the degree of smoothness was decreased and the porous structure of the coating could be more clearly observed.

The tablets that could remain intact after time course of the drug release test, were observed in their surface topography and demonstrated in Figrue 39. The porous structure was more obviously observed than that before being subjected to the drug release test. The pores seemed to be smaller as the EC proportion in the formulations was increased.

III Cast Film Evaluations.

All the film coating Formulations that could be cast were evaluated in their physical characteristics, tensile properties, and moisture sorption. In addition, CS cast films were modified with some additives in order to investigate their effects on the film properties and sometimes subsequently forecast the properties of the film coated tablets. These additives included polyethylene glycol 400 (PEG 400) which represented as a plasticizer, and colloidal silicon dioxide (CSD) which represented as an antiadherent or a tackiness reducer. The amount added was equivalent to 20% and 1% w/w based on the polymer weight, for PEG 400 and CSD, respectively.

Physical Characteristics.

The CS and modified CS film coating formulations yielded yellowish and translucent cast films. They were all sticky in nature

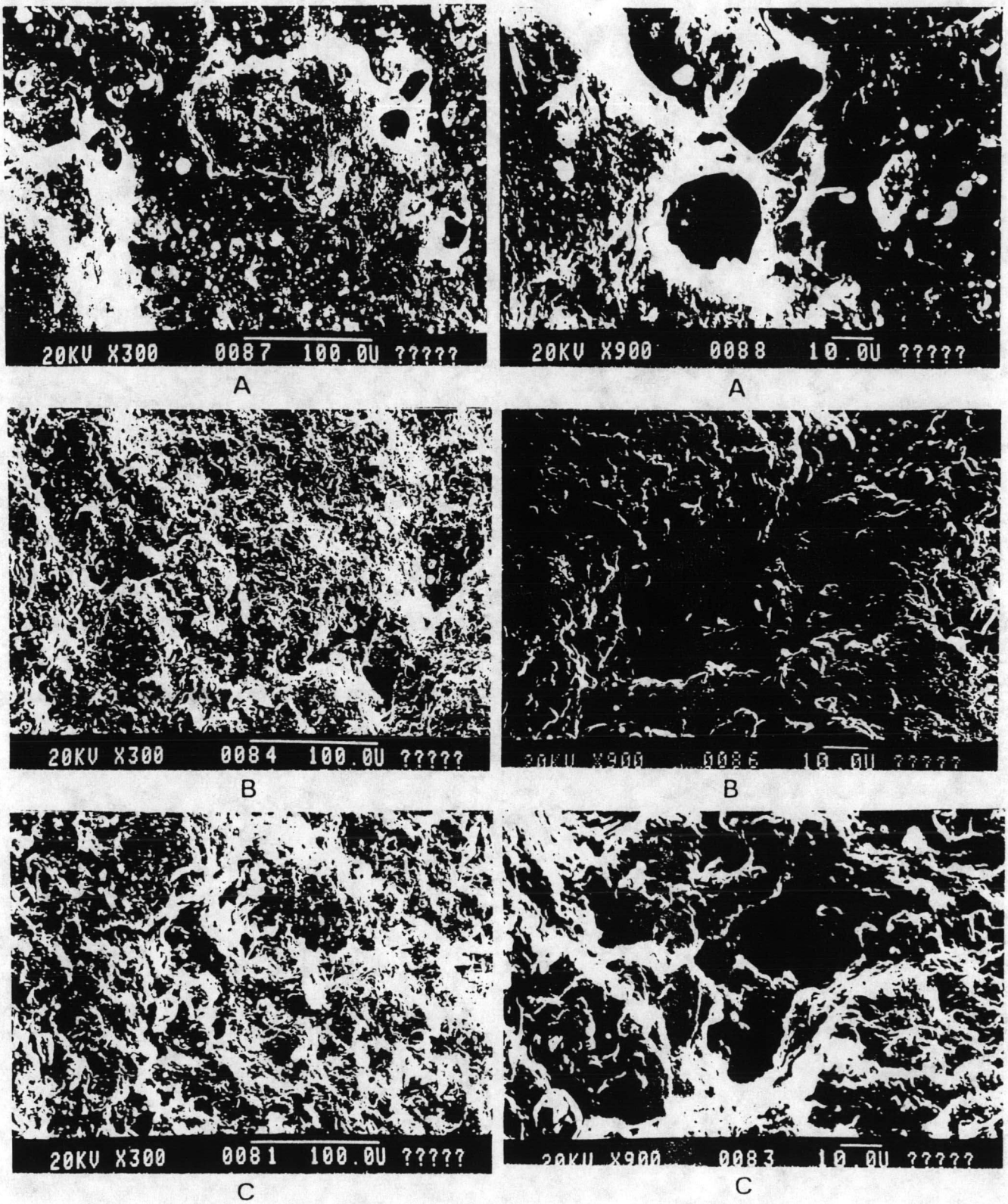


Figure 39 Photomicrographs of propranolol HCl tablets coated with film coating formulations EH 8020 (A); EH 8218 (B); and EH 8515 (C) after drug release test at magnification of 300x and 900x

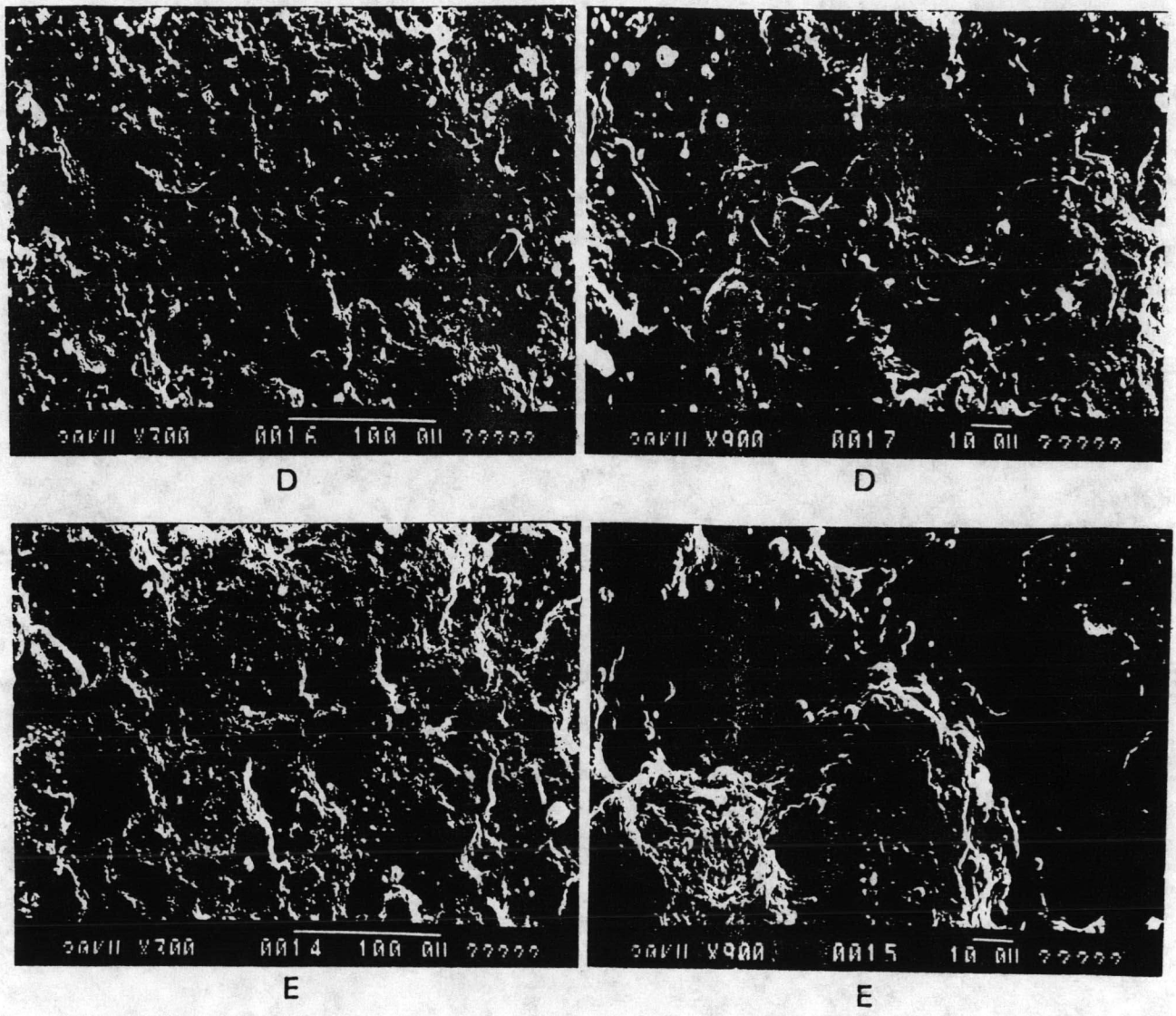


Figure 39 Photomicrographs of propranolol HCl tablets coated with film coating formulations EH 8713 (D); and EH 9010 (E) after drug release test at magnification of 300x and 900x (cont.)

with a lesser extent to turbid CSD-modified CS films, resulting in difficulty to detach from the glass plates even though they were pretreated. For cellulose derived films, HPMC cast films were colorless and transparent whereas MC and HPC cast films were also colorless but translucent, with a lesser extent to HPC films. The film coating formulations EH 5050 yielded white opaque films. These cellulose-composed films all were non-stickiness and easily detachable. Figure 40 also illustrates the physical appearance of CS cast film in comparison with HPMC cast film.

Tensile Properties.

The mean and standard deviation of the parameters included the ultimate tensile strength and the percent elongation at break, were calculated from the data in Table 84-91 (Appendix D) and presented in Table 26.

Based on the obtained ultimate tensile strength, all the cast films could be classified roughly into two groups. The CS and modified CS films had low ultimate tensile strength, compared with the other group, in the almost narrow range of about 0.2-0.7 kg/mm^2. Modification of the CS films with CSD or with both PEG and CSD resulted in increasing the ultimate tensile strength whereas modification with PEG alone resulted in decreasing the ultimate tensile strength. The HPC and EH 5050 films could be classed as the low ultimate tensile strength films, which were equal to 0.663 and 0.951 kg/mm^2, respectively.

The other group, the ultimate tensile strength of which was much greater than that of the former, included the HPMC and the MC

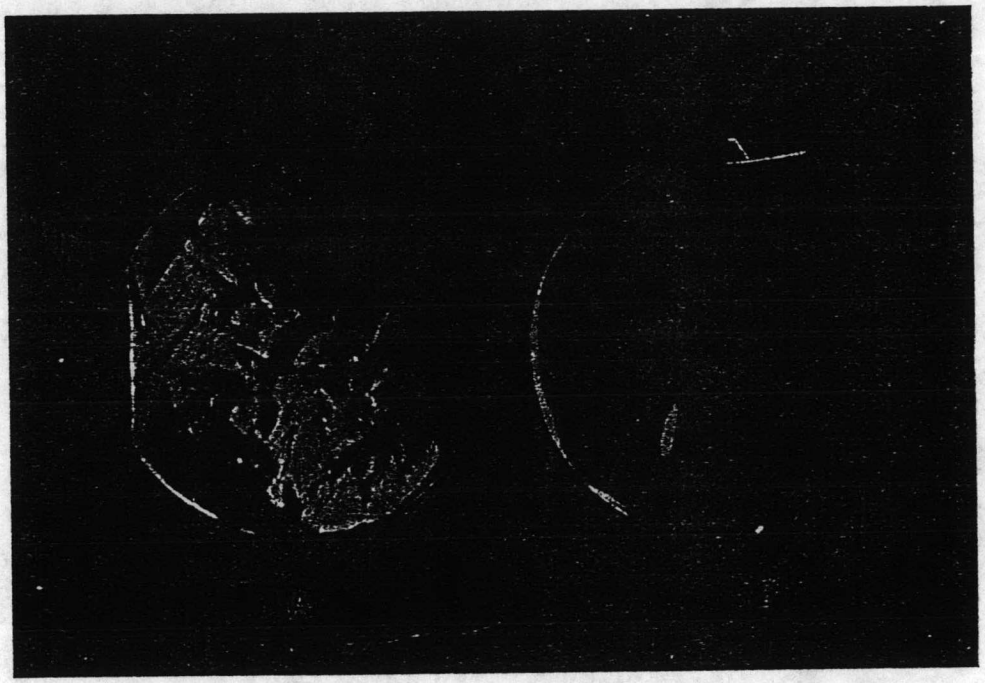


Figure 40 Chitosan (A) and hydroxypropyl methylcellulose (B) cast films

Table 26 Tensile Properties of Various Cast Films.

Cast Films	Ultimate Tensile Strength (kg./ mm^2)	Elongation (%)
CS	0.462 (0.098)***	30.0 (8.9)
CS+20%* PEG 400	0.280 (0.062)	56.0 (8.6)
CS+1% CSD**	0.670 (0.071)	46.0 (8.0)
CS+20% PEG 400 and 1% CSD**	0.678 (0.356)	101.0(23.3)
HPMC	6.235 (0.523)	13.0 (5.1)
MC	5.507 (0.259)	10.0 (3.2)
HPC	0.663 (0.068)	10.0 (3.2)
EH 5050	0.951 (0.079)	5.0 (0.0)

* % w/w of the polymer weight

** Colloidal Silicon Dioxide

*** Standard Deviation

cast films which provided the ultimate tensile strength of about 5-6 kg/mm^2. It was also noticed that incorporation of EC as dispersions into the HPMC films produced the markedly decreasing in the ultimate tensile strength of the HPMC films.

The CS and modified CS films had much higher the percent elongation at break than those of the cellulose containing films. The addition of PEG and/or CSD into the CS films dramatically promoted an increase in the percent elongation at break of the films, with the highest extent to the CS films contained both PEG and CSD, and smaller extent to the PEG- and CSD-modified films, respectively.

The cellulose containing films yielded the lower percent elongation at break in the narrow range of about 5-13%. Again, the addition of EC dispersions into the HPMC films also affected the film property, resulting in decreasing the percent elongation at break.

Moisture Sorption.

Alteration of the film weight represented the moisture sorption ability, after exposure to 76% relative humidity at controlled room temperature of various cast films were determined and illustrated in Figure 41 (based on the data in Table 92, Appendix D).

Almost cast films seemed to reach the equilibrium in moisture sorption within 15 days, except the HPMC and MC films which gradually reached the equilibrium within 60 days. The CS films had the moisture sorption ability evenly as the HPMC films. Incorporation of PEG alone into the CS films slightly increased the moisture sorption ability of the CS films upon storage, whereas the incorporation of both PEG and CSD drastically increased the moisture

sorption ability. On the other hand, the incorporation of CSD alone resulted in decreasing the moisture sorption ability of the CS films after storage. In other cases, MC films, HPC films, and the incorporation of EC dispersion into the HPMC films, as in EH 5050 films yielded the comparable lowest moisture sorption ability.

In cases of ethylcellulose film coating formulations and /or high level content of EC aqueous dispersion containing film coating formulations, they could not be cast to form free films. Even though chitin aqueous dispersions could be cast to form free films, the cast films obtained were too brittle to be prepared as test specimens. Therefore, the films of these film coating formulations were not evaluated. The physical appearance of CT and EC cast films are also illustrated *in situ* in Figure 42.

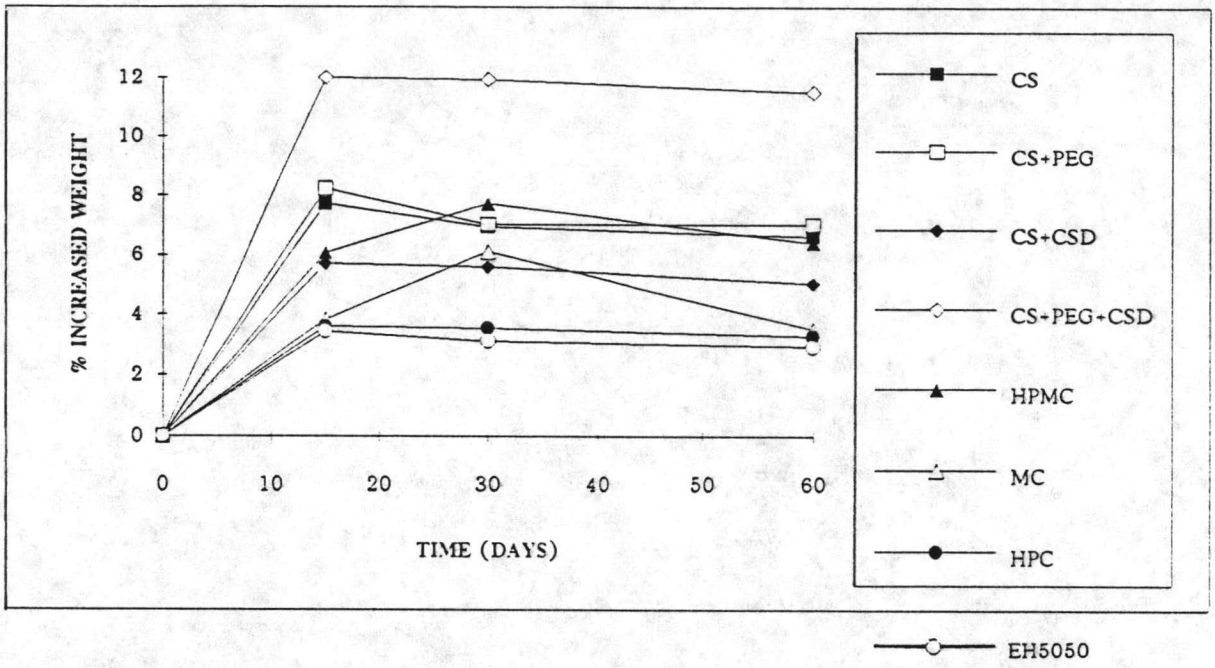


Figure 41 Moisture sorption ability of various cast films

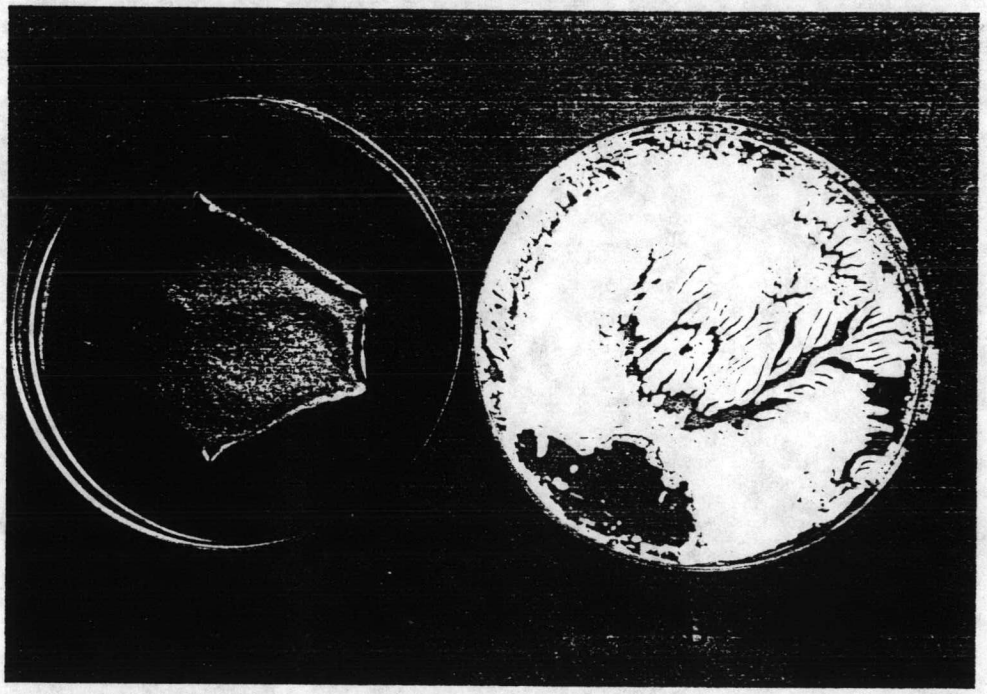


Figure 42 Chitin (A) and ethylcellulose (B) cast films