CHAPTER 3

RESULTS

Standard Curve

The concentration v.s. absorbance of indomethacin in dissolution medium in Table 14, showed a linear relationship with the correlation coefficient = 0.9995. The standard curve of indomethacin after regression analysis was illustrated in Figure 7.

Table 14 : Absorbance of Indomethacin in 1:4 Phosphate Buffer pH 7.2 : Deaerated Water Determined at 318 nm

Concentration (µg / ml)	Absorbance*
0	0.000
10	0.198
15	0.294
20	0.399
25	0.487
30	0.584
35	0.684
40	0.775

* Average of two determinations

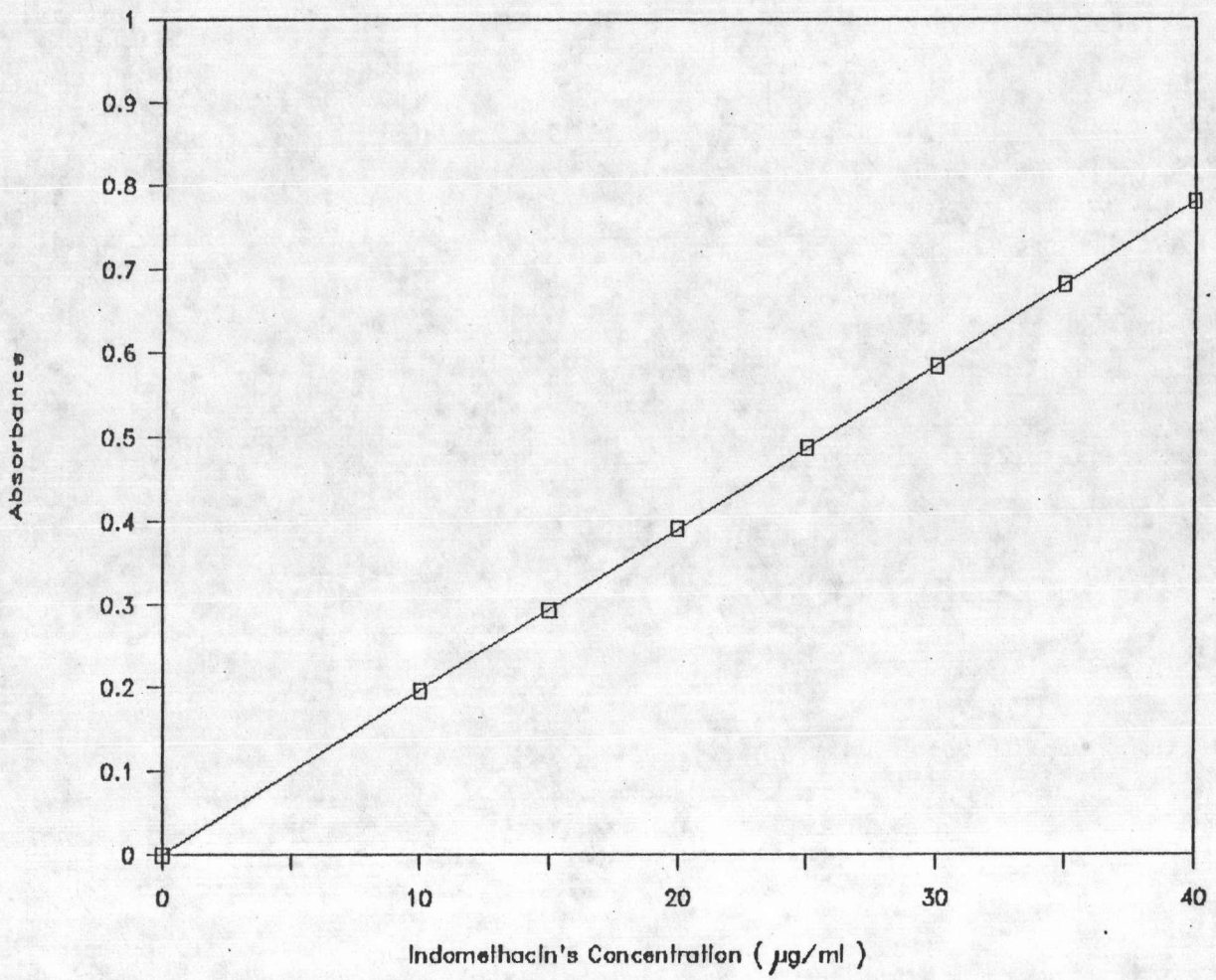


Figure 7 : Standard Curve of Indomethacin in 1:4 Phosphate Buffer pH 7.2 : Deaerated Water Determine at 318 nm.

Granulating and Tableting

Different types of hydrophilic celluloses provided different results in granulation process. Methocel E (5, 15LV) and A 15LV produced easy seiving wet masses at every concentration studied. Sticky mass occurred from both grades of Methocel K after spraying with water led to difficulty in processing. Low concentrations of Methcel A 4C and A 4M of 5 and 10% was easier in seiving through a screen than high concentrations of 15 and 20%. Therefore, three groups of hydrophilic celluloses used in this investigation could be classified by ranking from the most confortable in wet granulating process to the least as follows

1. Methocel E 5, E 15LV, A 15LV, 5-10% of A 4C and A 4M
2. 15-20% of Methocel A 4C and A 4M
3. Methocel K 4M and K 100M

Hydrophobic cellulose polymers, ethylcellulose and HPMCP exhibited an easy seiving wet mass. Higher concentration of ethylcellulose was slightly difficulty in seiving and more difficulty was observed from HPMCP. Formulations containing Methocel K 4M, K 100M and 20% A 4M gave hard dried granules.

Granules of all formulations, except of formulation containing ethylcellulose, were easy to compress and eject from the die. Those produced from ethylcellulose were slightly adhered to the surface of punch and die or container, so difficulty in compression and ejection process was observed.

Thickness, Hardness and Disintegration Time Studies.

Thickness, hardness and disintegration time of tablets from formulations containing single polymer were presented in Tables 15-19. Increase in the amount of polymer produced thicker

Table 15: Thickness(a),Hardness(b) and Disintegration Time(c) of Tablets Containing Methocel A

% of Polymer	Compressional pressure (lb)					
	500			1000		
	a (mm)	b (kg)	c (min)	a (mm)	b (kg)	c (min)
A 4C						
5.0	2.36	4.8	58	2.27	6.2	70
	(0.02)*	(0.3)	(2)	(0.03)	(0.2)	(2)
10.0	2.48	5.6	43	2.43	7.1	58
	(0.04)	(0.3)	(1)	(0.03)	(0.1)	(2)
15.0	2.53	6.3	18	2.49	7.7	31
	(0.04)	(0.4)	(2)	(0.03)	(0.3)	(3)
20.0	2.69	6.1	6	2.62	7.3	11
	(0.03)	(0.2)	(1)	(0.03)	(0.2)	(2)
A 4M						
5.0	2.41	7.2	51	2.36	8.6	72
	(0.02)	(0.1)	(5)	(0.03)	(0.4)	(2)
10.0	2.49	7.7	31	2.44	8.9	65
	(0.03)	(0.4)	(1)	(0.03)	(0.4)	(5)
15.0	2.59	6.2	7	2.52	7.9	13
	(0.03)	(0.2)	(1)	(0.02)	(0.4)	(1)
20.0	2.70	7.1	14	2.65	8.4	16
	(0.02)	(0.1)	(1)	(0.02)	(0.4)	(2)
A 15LV						
1.0	2.27	4.6	>2 hr	2.20	5.1	>2 hr
	(0.02)	(0.5)		(0.02)	(0.4)	
5.0	2.38	6.7	84	2.32	8.1	>2 hr
	(0.16)	(0.3)	(9)	(0.01)	(0.4)	
7.5	2.46	7.5	83	2.39	9.4	111
	(0.01)	(0.2)	(9)	(0.02)	(0.8)	(7)
10.0	2.45	7.3	35	2.41	9.4	46
	(0.02)	(0.3)	(2)	(0.03)	(0.4)	(1)
15.0	2.61	7.1	27	2.55	9.4	31
	(0.02)	(0.4)	(6)	(0.02)	(0.5)	(4)
20.0	2.70	7.6	40	2.62	9.4	39
	(0.02)	(0.6)	(6)	(0.02)	(0.5)	(7)

* (SD)

Table 16: Thickness(a),Hardness(b) and Disintegration Time(c) of Tablets Containing Methocel E

% of Polymer	Compressional pressure (lb)					
	500			1000		
	a (mm)	b (kg)	c (min)	a (mm)	b (kg)	c (min)
E 5						
1.0	2.23 (0.03)*	3.8 (0.4)	>2 hr	2.16 (0.04)	5.6 (0.5)	>2 hr
5.0	2.40 (0.02)	6.5 (0.4)	127 (10)	2.35 (0.02)	8.5 (0.4)	>2 hr
7.5	2.45 (0.02)	7.7 (0.4)	58 (3)	2.36 (0.02)	8.7 (0.7)	63 (7)
10.0	2.55 (0.02)	7.2 (0.3)	39 (5)	2.47 (0.01)	9.1 (0.5)	47 (4)
15.0	2.66 (0.02)	8.2 (0.2)	62 (14)	2.53 (0.02)	9.2 (0.3)	70 (13)
20.0	2.73 (0.06)	8.0 (0.2)	51 (10)	2.62 (0.02)	10.1 (0.3)	56 (13)
E 15LV						
1.0	2.24 (0.02)	4.2 (0.6)	>2 hr	2.21 (0.02)	5.6 (0.6)	>2 hr
5.0	2.39 (0.03)	6.4 (0.4)	90 (8)	2.33 (0.02)	8.3 (0.8)	105 (10)
7.5	2.47 (0.02)	6.6 (0.3)	57 (2)	2.41 (0.02)	8.5 (0.7)	62 (3)
10.0	2.52 (0.02)	7.3 (0.8)	78 (11)	2.44 (0.02)	10.0 (0.2)	86 (7)
15.0	2.62 (0.02)	7.7 (0.3)	88 (10)	2.56 (0.01)	9.3 (0.1)	103 (10)
20.0	2.74 (0.02)	7.9 (0.1)	118 (7)	2.67 (0.02)	9.6 (0.4)	126 (6)

* (SD)

Table 17: Thickness(a),Hardness(b) and Disintegration Time(c) of Tablets Containing Methocel K 4M and K 100M

Polymer (%)	Compressional pressure (lb)					
	500			1000		
	a (mm)	b (kg)	c (min)	a (mm)	b (kg)	c (min)
K 4M (5.0)	2.42 (0.01)*	6.8 (0.6)	>2 hr	2.37 (0.01)	8.7 (0.7)	>2 hr
K 4M (10.0)	2.52 (0.01)	7.5 (0.8)	>2 hr	2.43 (0.01)	9.2 (0.4)	>2 hr
K 100M (3.0)	2.34 (0.01)	6.2 (0.2)	>2 hr	2.27 (0.01)	7.3 (0.8)	>2 hr

* (SD)

Table 18: Thickness(a),Hardness(b) and Disintegration Time(c) of Tablets Containing Ethylcellulose (10 cps)

% of Polymer	Compressional pressure (lb)					
	500			1000		
	a (mm)	b (kg)	c (min)	a (mm)	b (kg)	c (min)
5.0	2.39 (0.02)*	6.2 (0.5)	>2 hr	2.33 (0.02)	7.0 (0.4)	>2 hr
10.0	2.49 (0.03)	7.3 (0.6)	>2 hr	2.42 (0.02)	8.8 (0.6)	>2 hr
15.0	2.62 (0.02)	7.8 (0.4)	>2 hr	2.54 (0.02)	9.5 (0.3)	>2 hr
20.0	2.72 (0.02)	7.2 (0.9)	>2 hr	2.64 (0.01)	9.5 (0.3)	>2 hr

* (SD)

Table 19: Thickness(a),Hardness(b) and Disintegration Time(c) of Tablets Containing HPMCP HP-50

% of Polymer	Compressional pressure (lb)					
	500			1000		
	a (mm)	b (kg)	c (min)	a (mm)	b (kg)	c (min)
1.0	2.26 (0.01)*	3.0 (0.5)	>2 hr	2.22 (0.01)	4.8 (0.4)	>2 hr
3.0	2.35 (0.02)	4.8 (0.4)	>2 hr	2.23 (0.02)	6.0 (0.6)	>2 hr
5.0	2.41 (0.03)	6.6 (0.4)	>2 hr	2.33 (0.01)	8.1 (0.8)	>2 hr
7.0	2.48 (0.01)	7.6 (0.7)	>2 hr	2.41 (0.01)	8.0 (0.7)	>2 hr

* (SD)

tablet. Higher compressional pressure increased hardness and disintegration time but decreased thickness. The average value of thickness increase was 0.068 mm with a standard deviation of 0.02 mm when compressional pressure increased from 500 to 1,000 lb. Tablets containing 1% of hydrophilic celluloses as well as every level of Methocel K and hydrophobic celluloses showed more than 2 hours of disintegration time. Those parameters from combined formulations were also presented in Table 20. The hardness of combination 1* was 0.9 kg less than combination 1, which was correlated to the lower disintegration time.

Dissolution Studies

The amount of drug release at any time interval of tablets containing single polymer, combined polymers, and Indocid-R capsules were illustrated in Figures 8-18, respectively.

1. Hydrophilic Celluloses

Methocel A 15LV

The release of drug from tablets containing all levels of Methocel A 15LV was not affected by compressional pressure as shown in Figures 8 (a,b). However, the influence of amount was exhibited. More amount of polymer gave higher amount of drug release. Methocel A 15LV of 1% and 5% released the same amount of drug during the first four hours, then the release rate were different. The former released more drug to the maximum of 25% at the 12th hour while the latter released only 16%. In addition, polymer of 10% and 15% gave the same release profile with a maximum drug release of 75%. Only formulation of 20% polymer gave complete drug release in 12 hours. The release patterns of tablets containing 10% polymer or more seemed to be similar, the initially rapid release of drug in the first two hours followed by slower release uptil 12 hours was observed.

Table 20 : Thickness(a),Hardness(b) and Disintegration Time(c) of Tablets in Combined Formulations.

Formula	a (mm)	b (kg)	c (min)
Combination 1	2.48	9.3	62
	(0.03)★	(0.6)	(2)
Combination 2	3.55	9.0	71
	(0.03)	(0.3)	(3)
Combination 3	2.40	9.4	59
	(0.02)	(0.4)	(3)
Combination 1* [1]	2.50	8.4	58
	(0.02)	(0.6)	(4)

[1] Tablets of this formulation were compressed with tableting machine.

★ (SD)

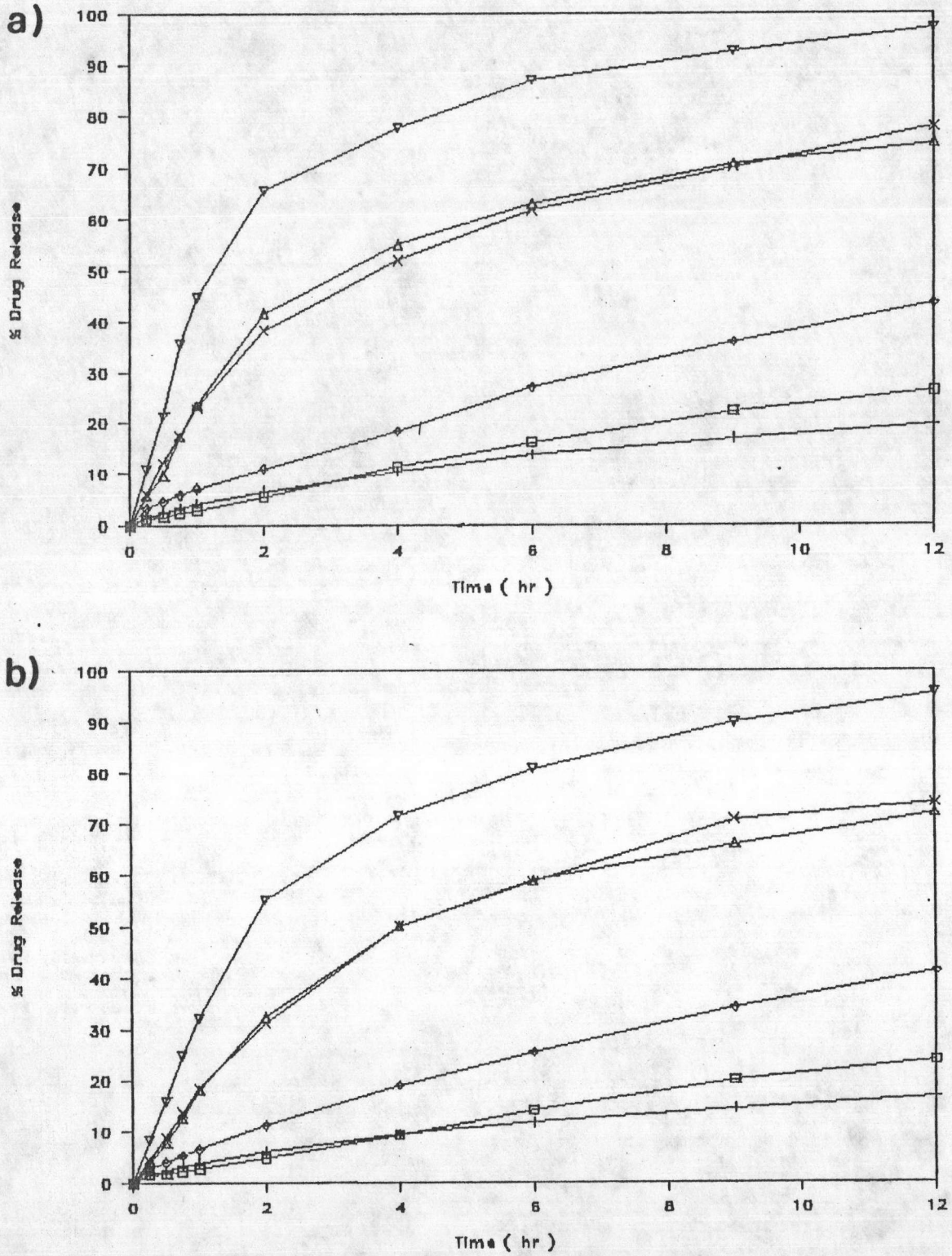


Figure 8 : Release Profiles of Indomethacin from Tablet Containing Various Concentrations of Methocel A 15LV (□—□ 1%, +—+ 5%, ◇—◇ 7.5%, △—△ 10%, ×—× 15%, ▽—▽ 20%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

Methocel A 4C

Figures 9 (a,b) indicated that the amount of indomethacin released from tablets was increased as the amount of Methocel A 4C increased. From tablets of 15% and 20% polymer, the drug was rapidly released during the first hour and the rate was slow down uptil 100% drug release occurred. Both left some small pieces of gelatinous matrices after 12 hours. Compressional pressure seemed to affect the release pattern at lower amount of Methocel A 4C (5% and 10%) where higher pressure retarded the drug release, this effect was more prominent in tablets containing 10% polymer.

Methocel A 4M

Dissolution profiles of tablets containing Methocel A 4M in Figures 10 (a,b) showed that higher concentration of polymer increased the amount of indomethacin release. Tablets containing 5% polymer showed a linear dissolution profile with the drug release of 20%. Non-linear release pattern was observed in tablets containing higher amount of polymer. Rapid release of drug occurred during the initial hours followed by a slow release. Small sponge-like pieces were found after experiment. Compressional pressure did not affect the pattern of drug release except in the formulation containing 10% polymer where high pressure decreased the drug release. Nevertheless, high compressional pressure gave more steady drug release. The maximum amount of drug released from 500 and 1,000 lb compressed tablets of 10% polymer after 12 hours were 70 and 50%, respectively.

Methocel E 5

Figures 11 (a,b) illustrated the release patterns of indomethacin from tablets containing various concentrations of Methocel E 5. They indicated that more amount of polymer caused larger amount as well as the rate of drug release. Compressional

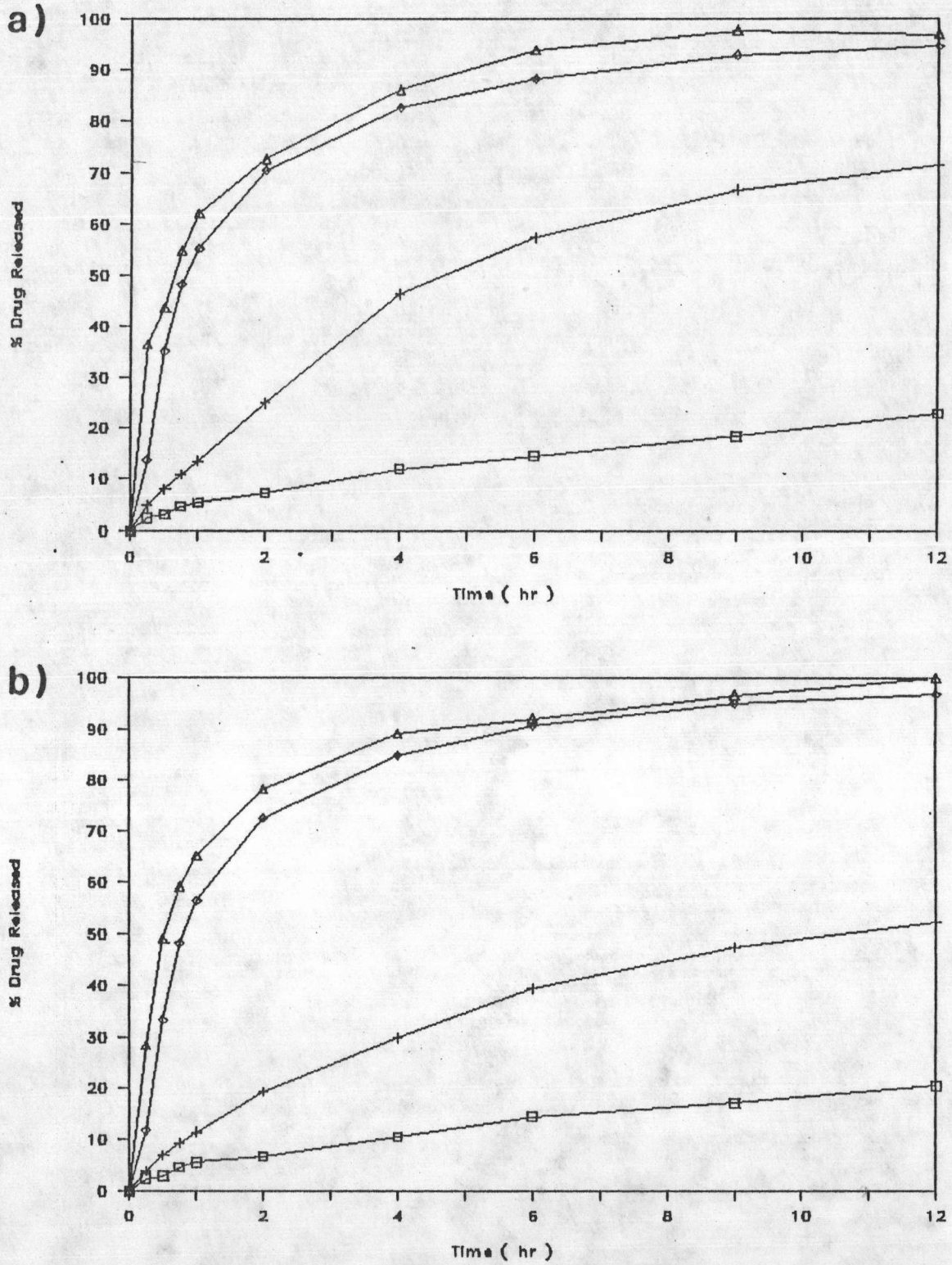


Figure 9 : Release Profiles of Indomethacin from Tablet Containing Various Concentrations of Methocel A 4C (□——□ 5%, +——+ 10%, ◇——◇ 15%, △——△ 20%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

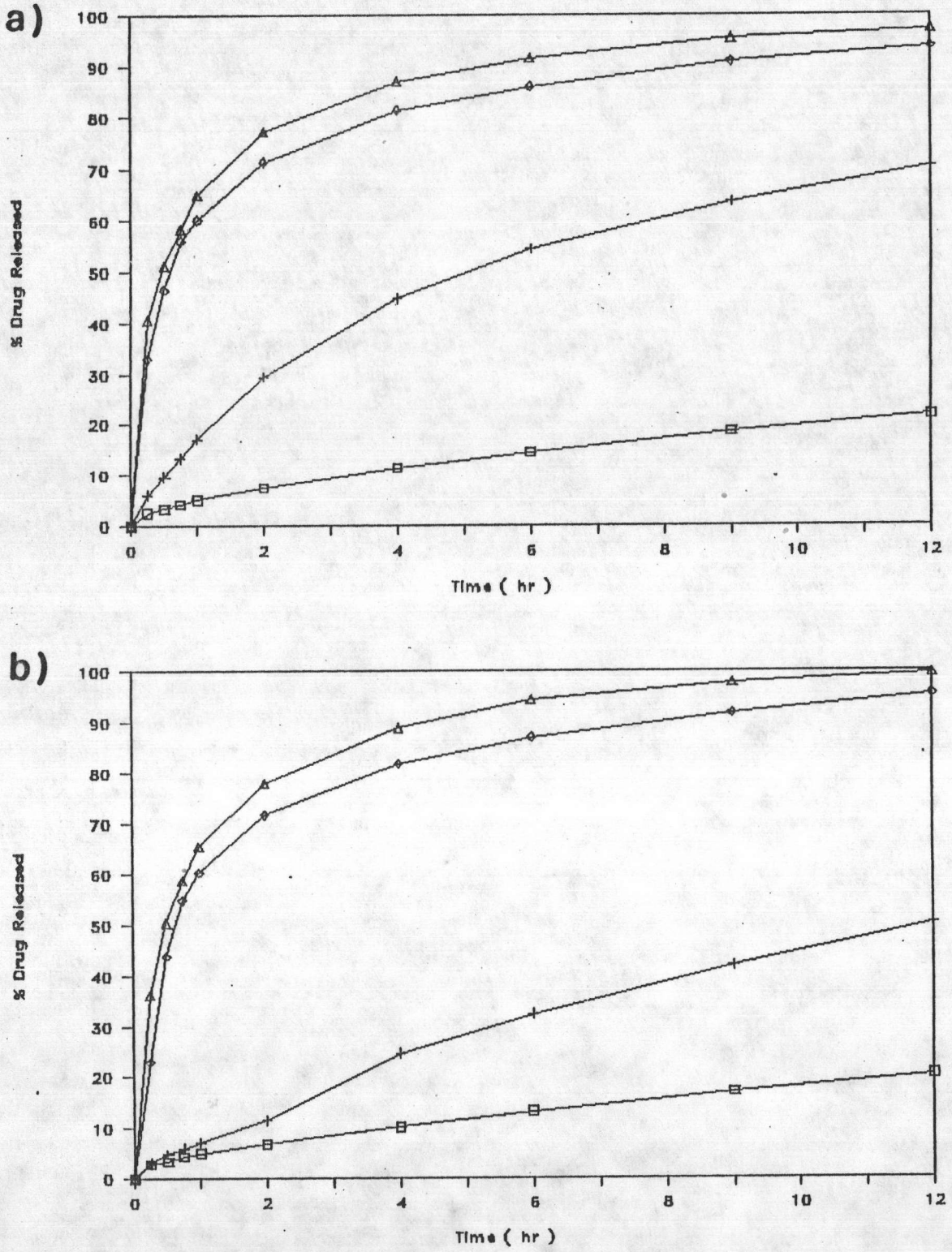


Figure 10: Release Profiles of Indomethacin from Tablet Containing Various Concentrations of Methocel A 4M (□——□ 5%, +——+ 10%, ◇——◇ 15%, △——△ 20%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

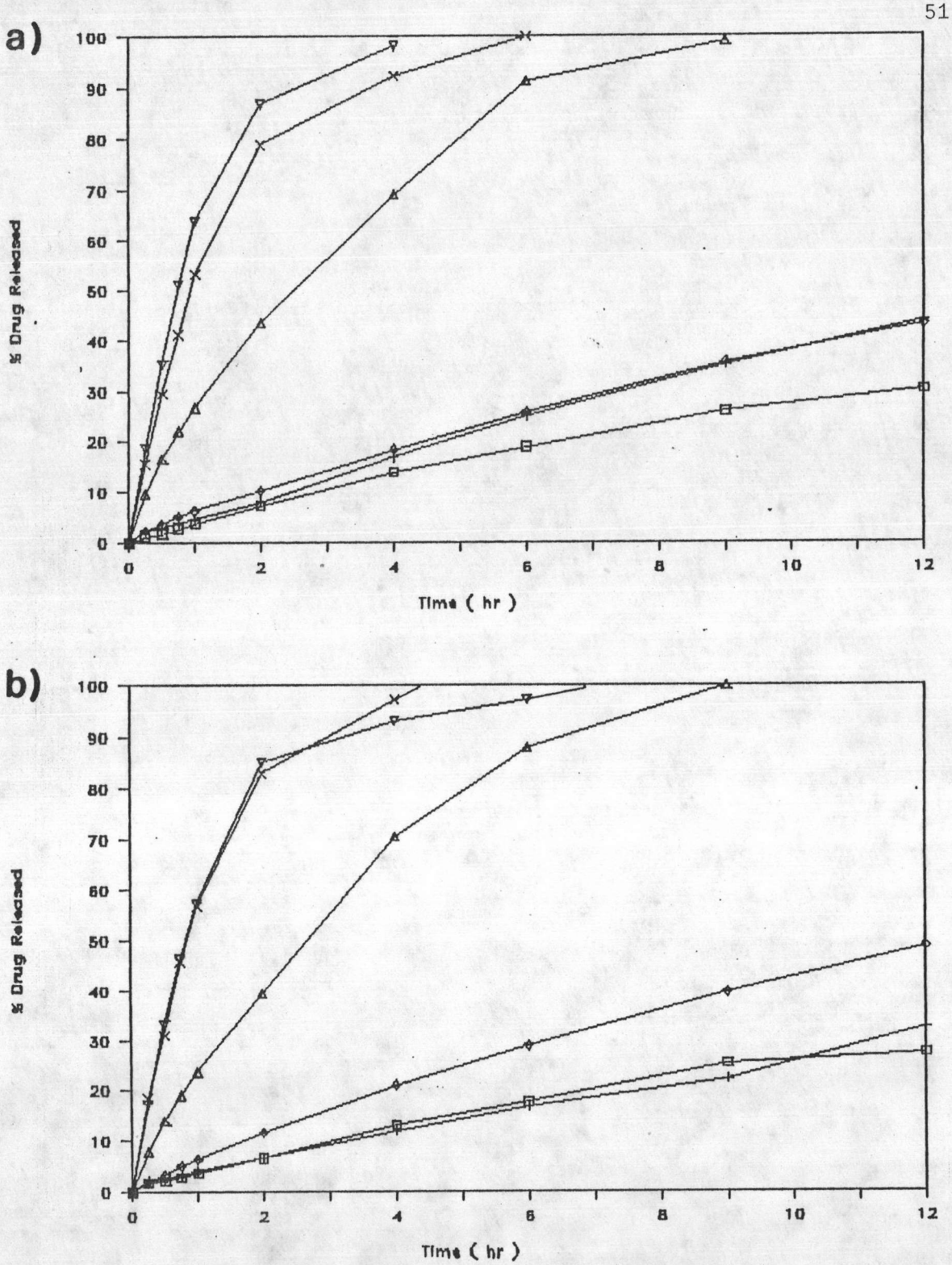


Figure 11 : Release Profiles of Indomethacin from Tablet Containing Various Concentrations of Methocel E 5 (□—□ 1%, +—+ 5%, ◇—◇ 7.5%, △—△ 10%, ×—× 15%, ▽—▽ 20%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

pressure affected release pattern of tablets containing 5 and 15% polymer where higher pressure seemed to decrease release rate. Complete drug release from tablets containing 7.5, 10 and 15 as well as 20% polymer occurred in 9, 6 and 4 hours, respectively.

Methocel E 15LV

Compressional pressure did not affect the release pattern of tablets containing Methocel E 15LV as shown in Figures 12 (a,b). Straight release was observed when the concentration of polymer was 1%. The more amount of polymer presented in tablets, the more amount of indomethacin released. Nevertheless, polymer in concentration of 10% or more gave the same release rate. Tablets containing 7.5 and 10-20% polymer completely released the drug at the 9th and 4th hour, respectively while those containing 1% and 5% showed a maximum drug release of 25 and 58% after 12 hours.

Methocel K 4M

Drug release patterns of tablets containing Methocel K 4M were illustrated in Figures 13 (a,b). The effect of concentration was the same as the results obtained by the aforementioned polymers. Increasing the amount of polymer in the formulation increased the amount of drug release from tablets of both compressional pressures. Complete drug release from tablets containing 5% and 10% polymer occurred in 6 and 9 hours, respectively. Again, compressional pressure did not affect the release patterns.

Methocel K 100M

Figure 14 showed that there was no effect of compressional pressure on the release profiles of indomethacin from tablets containing 3% Methocel K 100M. Complete drug release was seen on the 9th hour of experiment.

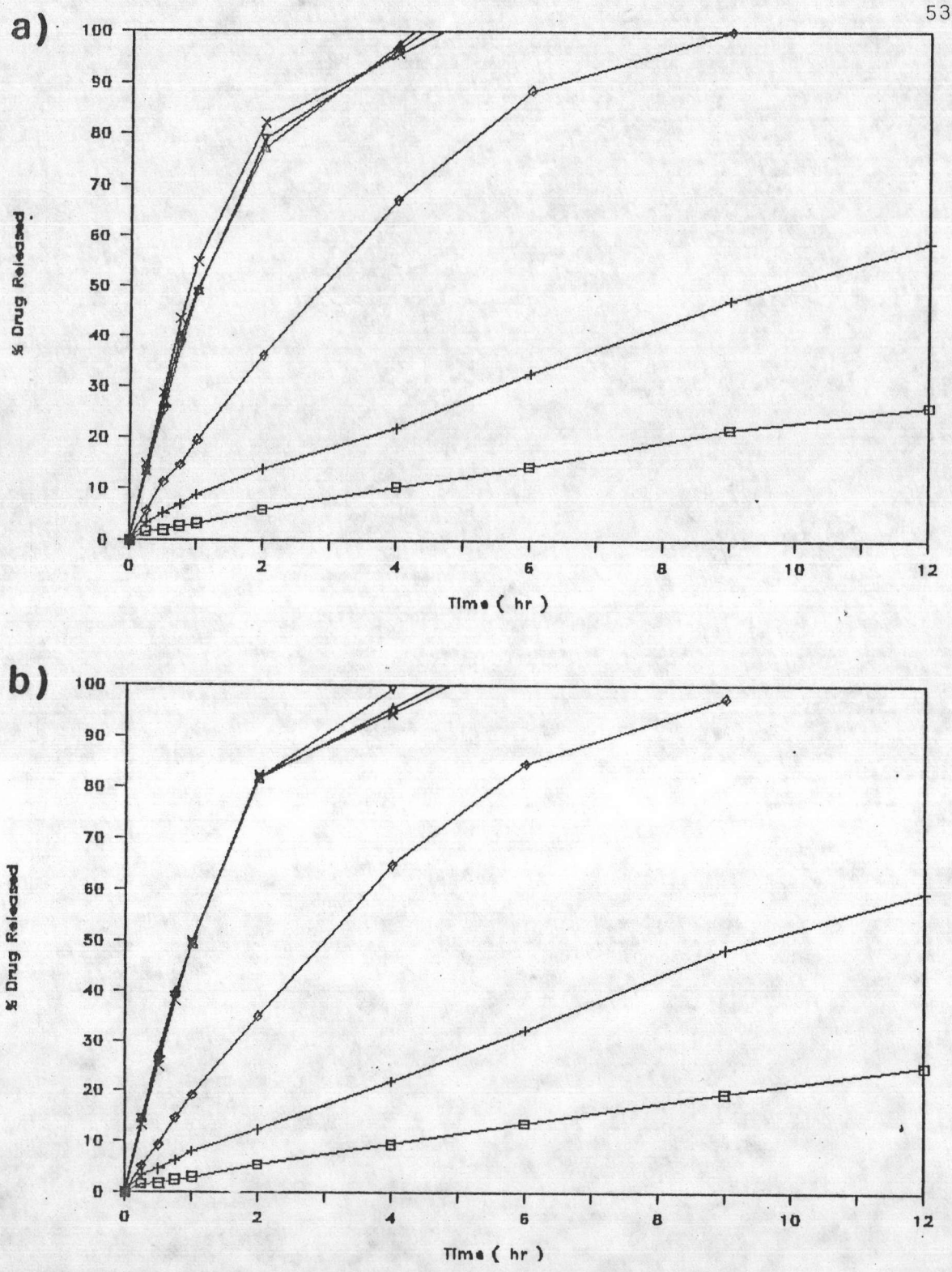
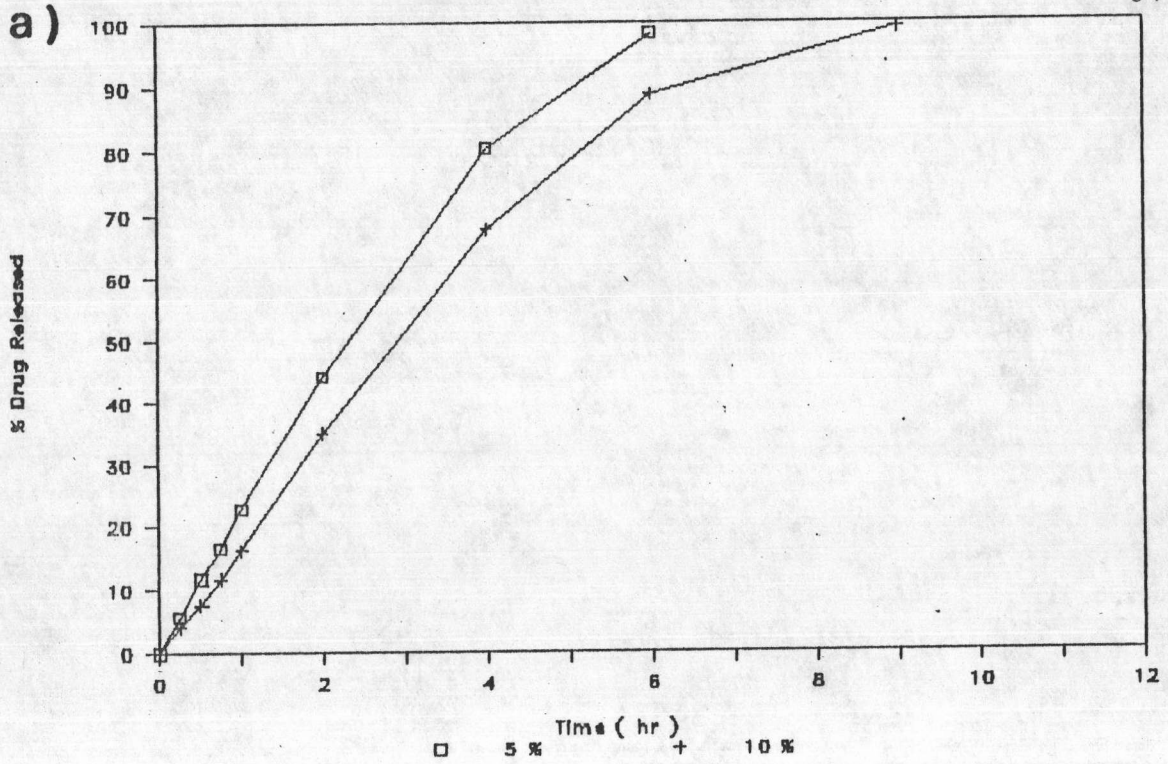


Figure 12: Release Profiles of Indomethacin from Tablet Containing Various Concentrations of Methocel E 15LV (□—□ 1%, +—+ 5%, ◇—◇ 7.5%, △—△ 10%, ×—× 15%, ▽—▽ 20%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb



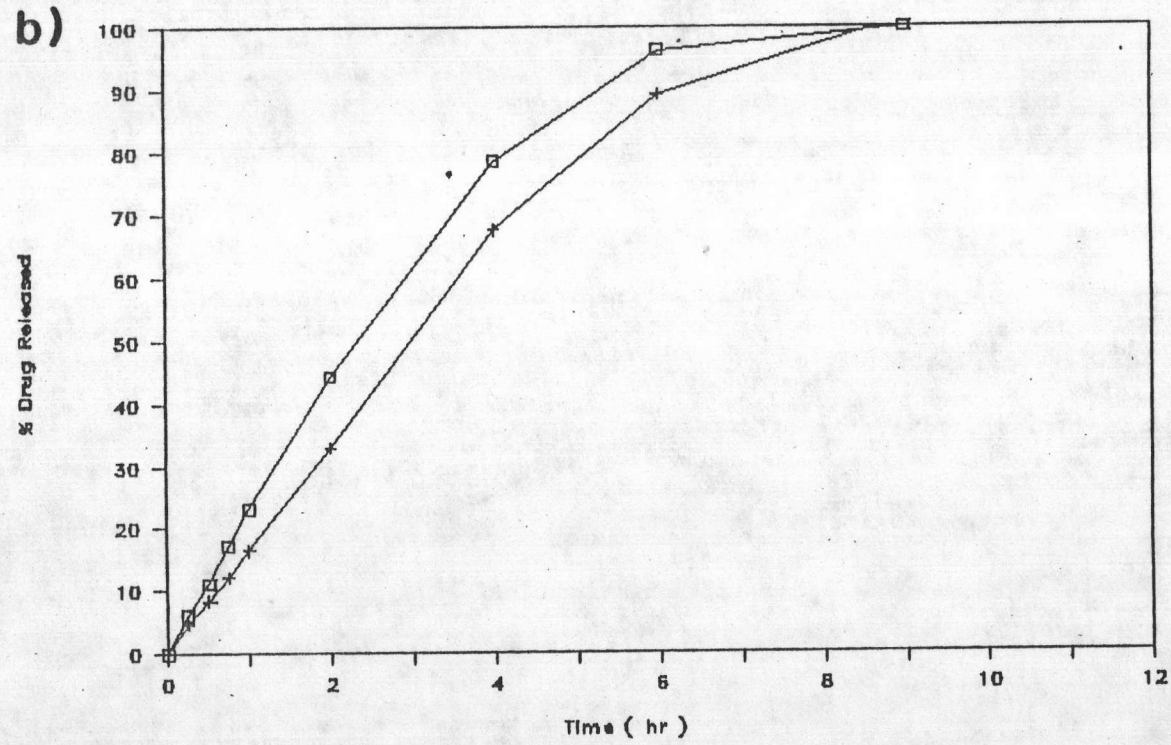


Figure 13: Release Profiles of Indomethacin from Tablet Containing Various Concentrations of Methocel K 4M (+——+ 5%, □——□ 10%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

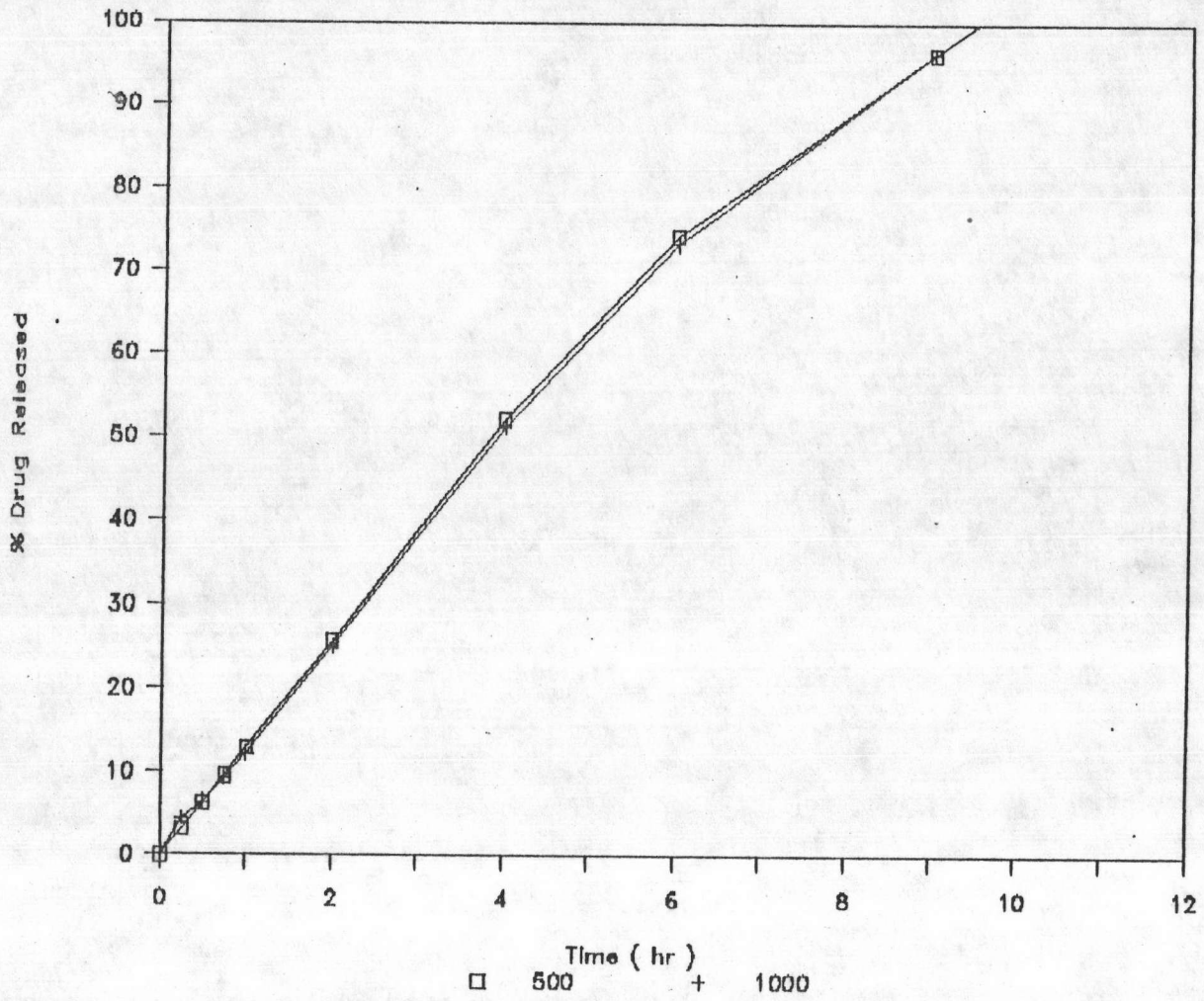


Figure 14: Release Profiles of Indomethacin from Tablets Containing 3% of Methocel K 100M Compressed at 500 lb and 1,000 lb.

2. Hydrophobic Celluloses

Ethylcellulose

Figures 15(a,b) showed that linear release profile were obtained from tablets containing ethylcellulose. All formulations exhibited the same release rate as well as the maximum drug release of 15%. Compressional pressure did not affect the drug release.

HPMCP

Slightly increase in the amount of indomethacin released occurred when increasing the amount of HPMCP as shown in Figures 16 (a,b). Tablets containing 5% and 7% HPMCP exhibited the same release rate during the first six hours then the latter showed more drug release uptil 12 hours. Maximum amount of drug release from tablets containing 1% and 7% HPMCP were 25% and 40%, respectively while from those containing 3% and 5% was 32%.

3. Blank

Indomethacin itself could be compressed and the pattern of drug release from tablets is shown in Figure 17. The maximum amount of drug release was 28%. A constant release rate was observed.

4. Indocid-R Capsules

From Figure 18, linear release pattern with fast release of drug occurred in the initial hours then the rate was slow down until the drug was completely release at the 9th hour. Fifty percent of indomethacin released from this dosage form in 1.5 hours. Small, plastic-like pieces were found after the test.

5. Combined Formulations

The release profiles of indomethacin from three combined formulations and Indocid-R were comparatively illustrated in Figure 18. Mixture of Methcel E 15LV 7.5% and HPMCP 1%

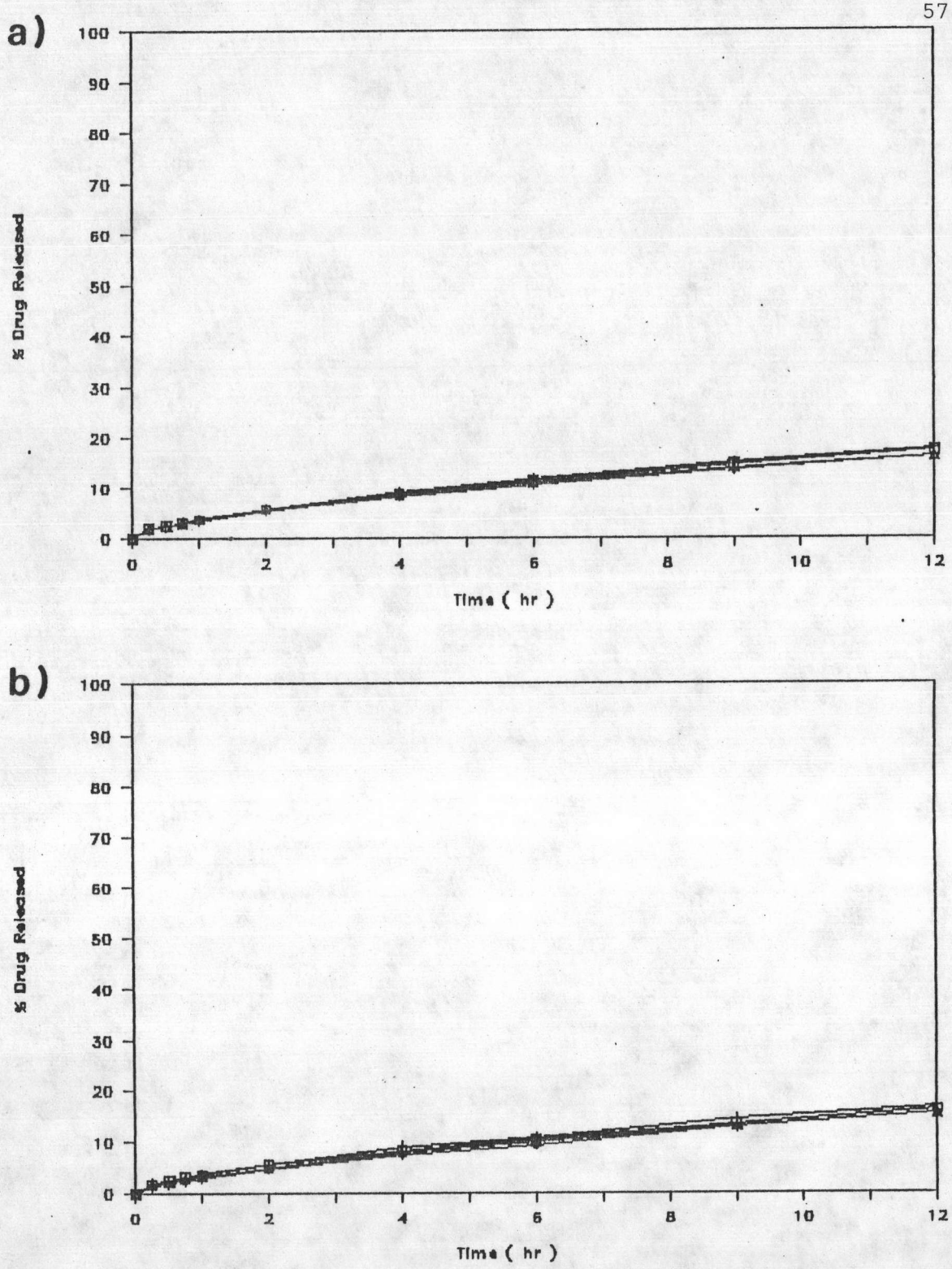


Figure 15: Release Profiles of Indomethacin from Tablets Containing Various Concentration of Ethylcellulose 10 cps (□—□ 5%, +—+ 10%, ◊—◊ 15%, Δ—Δ 20%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

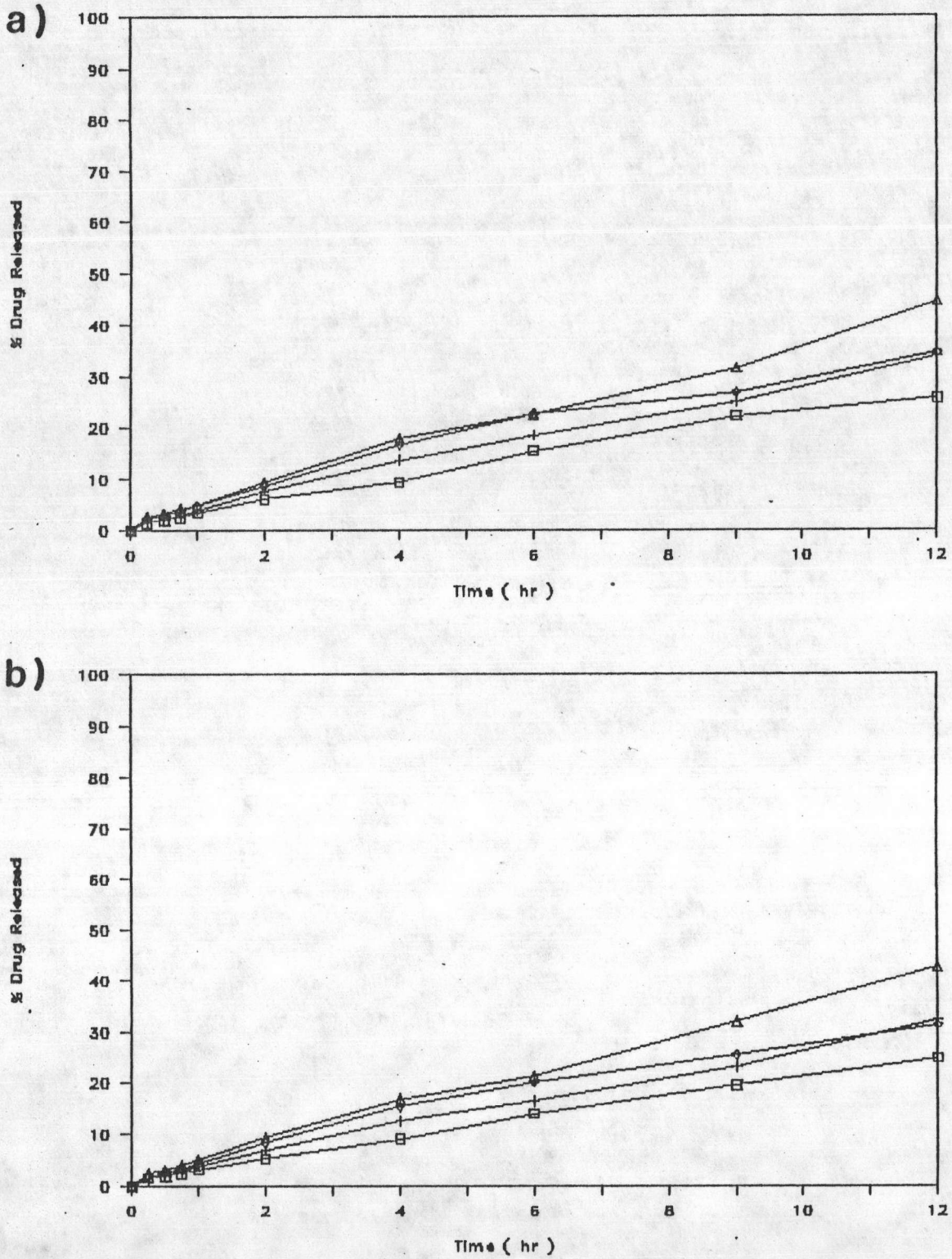


Figure 16: Release Profiles of Indomethacin from Tablets Containing Various Concentration of HPMCP HP-50 (□—□ 1%, +——+ 3%, ◇——◇ 5%, △——△ 7%)

a) Compressional Pressure = 500 lb

b) Compressional Pressure = 1,000 lb

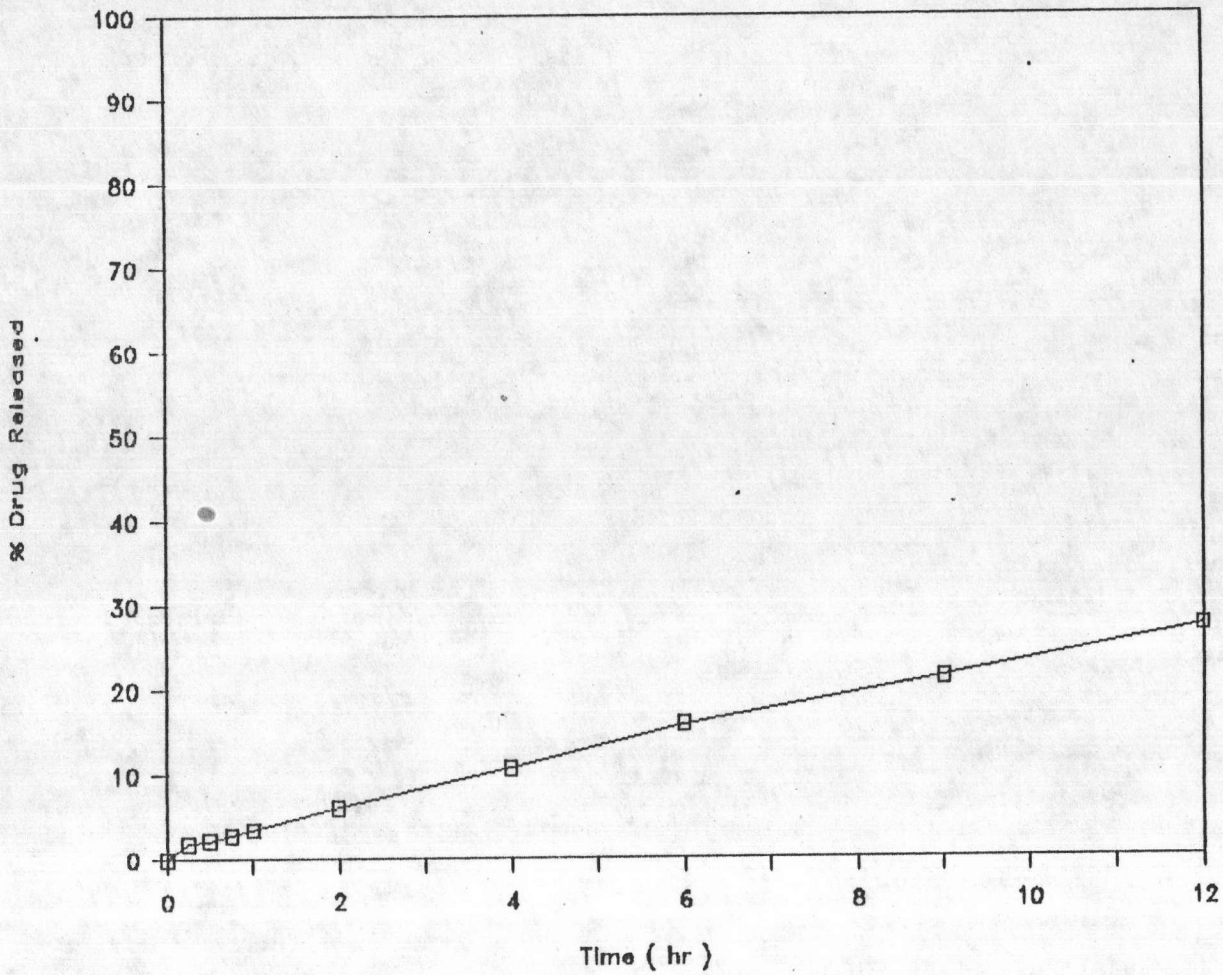


Figure 17 : Release Profile of Indomethacin from Tablet Produced without any Polymer (Compressional Pressure = 1000 lb).

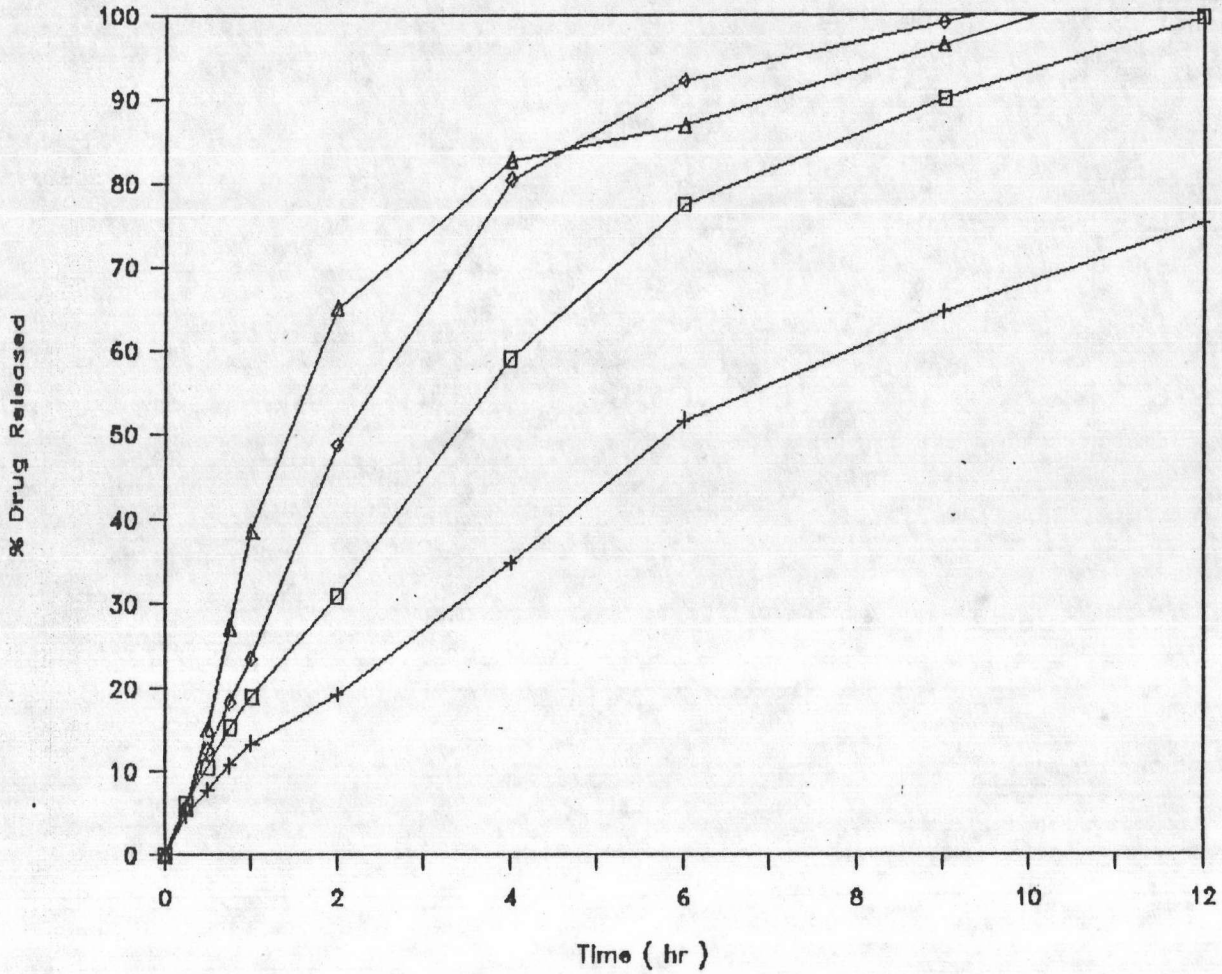


Figure 18 : Release Profile of Indomethacin from Three Combined Formulations(1,000 lb Compressional Pressure) :

□——□ Combination 1, +——+ Combination 2,

◇——◇ Combination 3, △——△ Indocid-R.

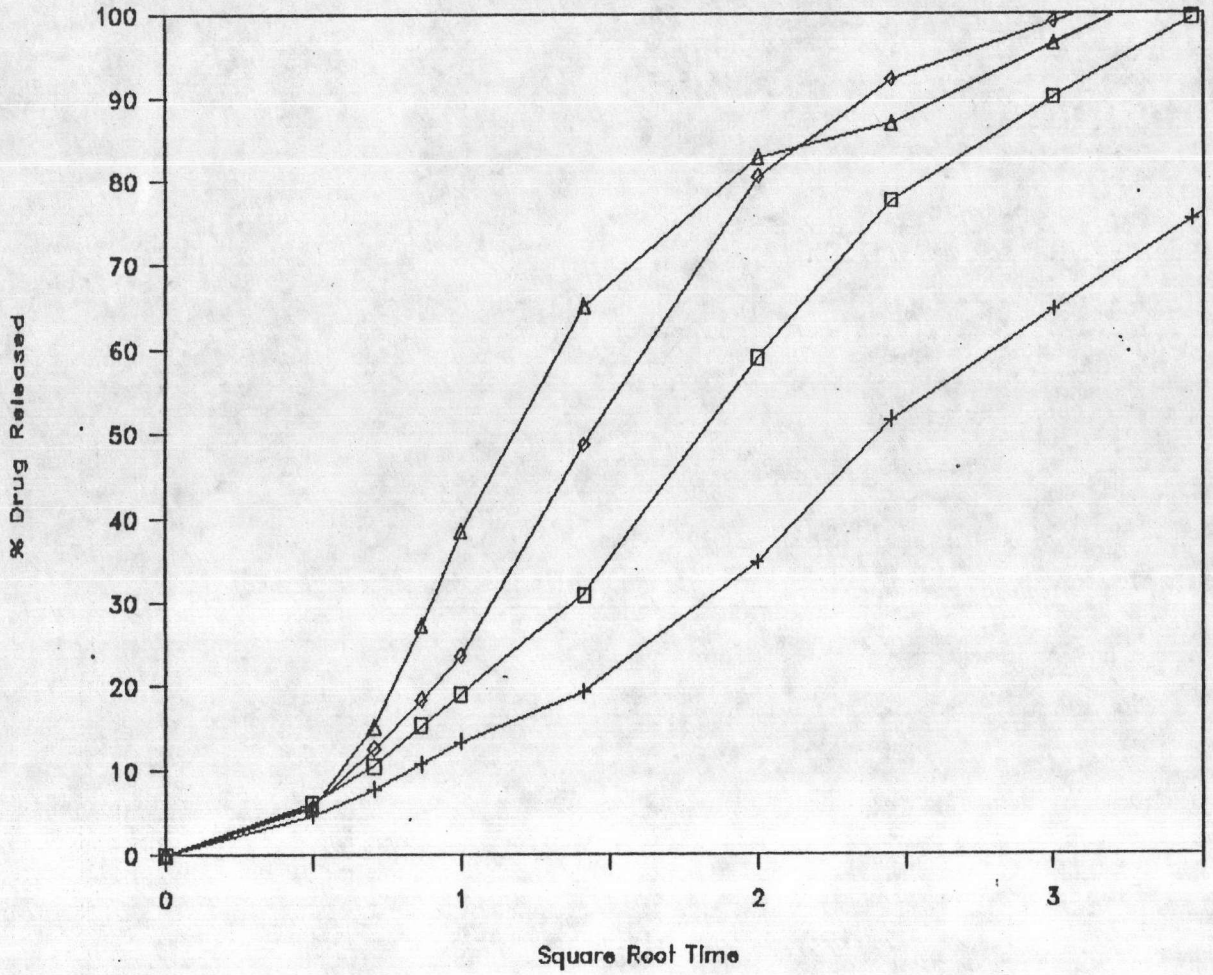


Figure 19 : The Amount of Indomethacin Release v.s. Square Root Time's Plot Compared between three Combinations; □—□ 1, +——+ 2, ◇——◇ 3, and △——△ Indocid-R.

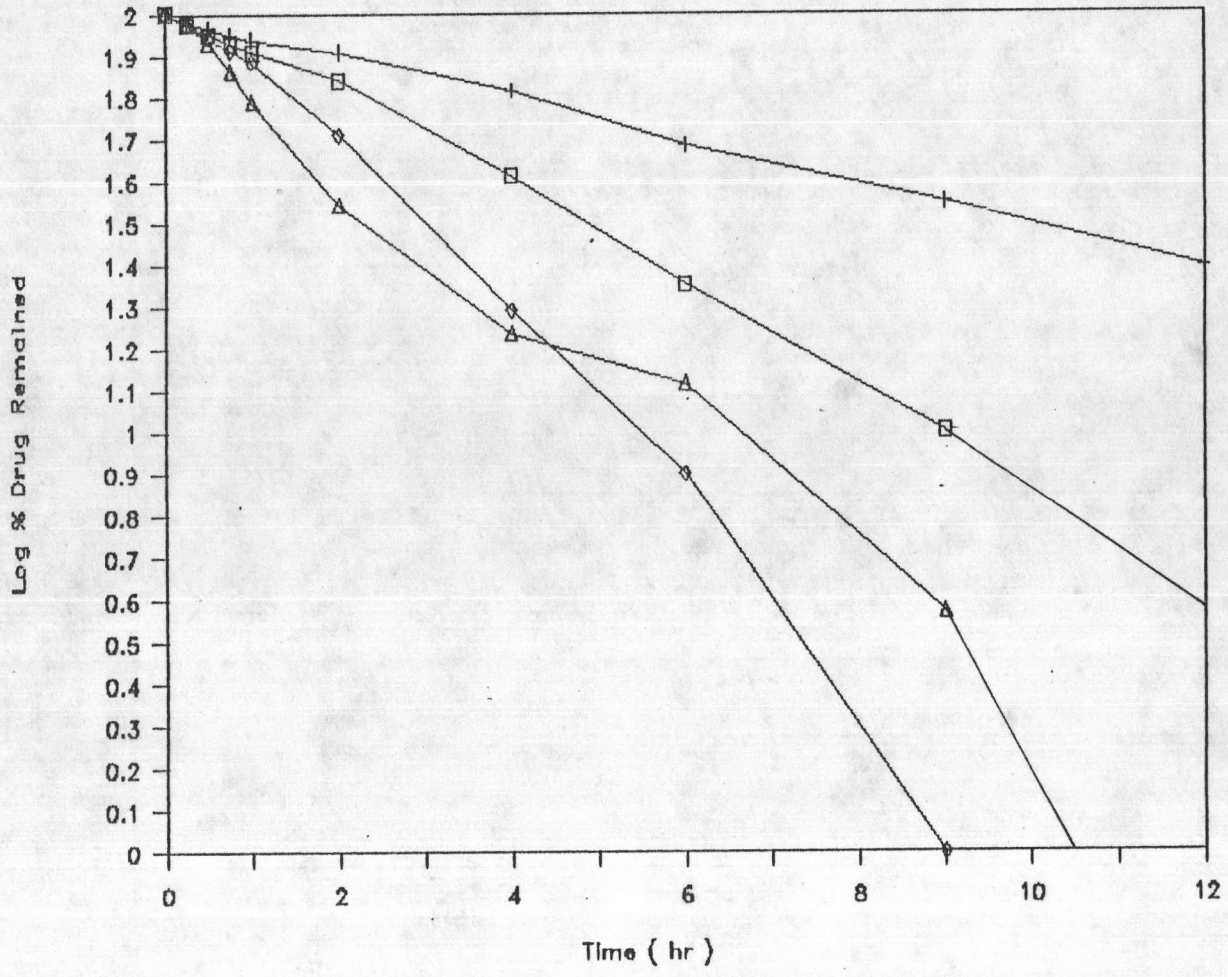


Figure 20 : The First order Plot of Indomethacin Release Compared between three Combinations; □—□ 1, +——+ 2, ◇——◇ 3, and △——△ Indocid-R.

(combination 3) produced tablets with 100% drug release in 9 hours similar to Indocid-R but different pattern was observed. Drug release from combined formulation between Methocel E 15LV 7.5% and HPMCP 1% (combination 3) was slower in the first four hours and became higher until drug was completely released when compared to release pattern of Indocid-R. Combination 1 and 2 contained the same amount and type of hydrophilic cellulose but those of hydrophobic were different. Combination 1 contained 1% of HPMCP while combination 2 contained 5% of ethylcellulose. It was found that, in the present of equal amount of hydrophilic cellulose, ethylcellulose caused less amount of drug release than HPMCP. The maximum amount of drug release from combination 2 (10% Methocel E 5 and 5% ethylcellulose) was 75%. Only tablets from combination 1 (10% Methocel E 5 and 1% HPMCP) exhibited complete drug release at 12 hours of experiment. The amount of drug released at any time interval of this formulation was in between combination 3 which produced faster drug release and combination 2 which drug release was incomplete.

Of the three combined formulations, combination 1 (10% Methocel E 5 and 1% HPMCP) was selected to be compressed using tableting machine. These tablets were called combination 1*. As shown in Figure 21, both combination 1 and 1* showed a complete drug release at the 12th hour. Both release profiles were comparable.

Release Mechanism Studies

The correlation coefficients of % drug released v.s. time, % drug released v.s. square root of time, and log % drug remained v.s. time of formulations containing single polymer and combined polymers were tabulated in Tables 21 and 22, respectively.

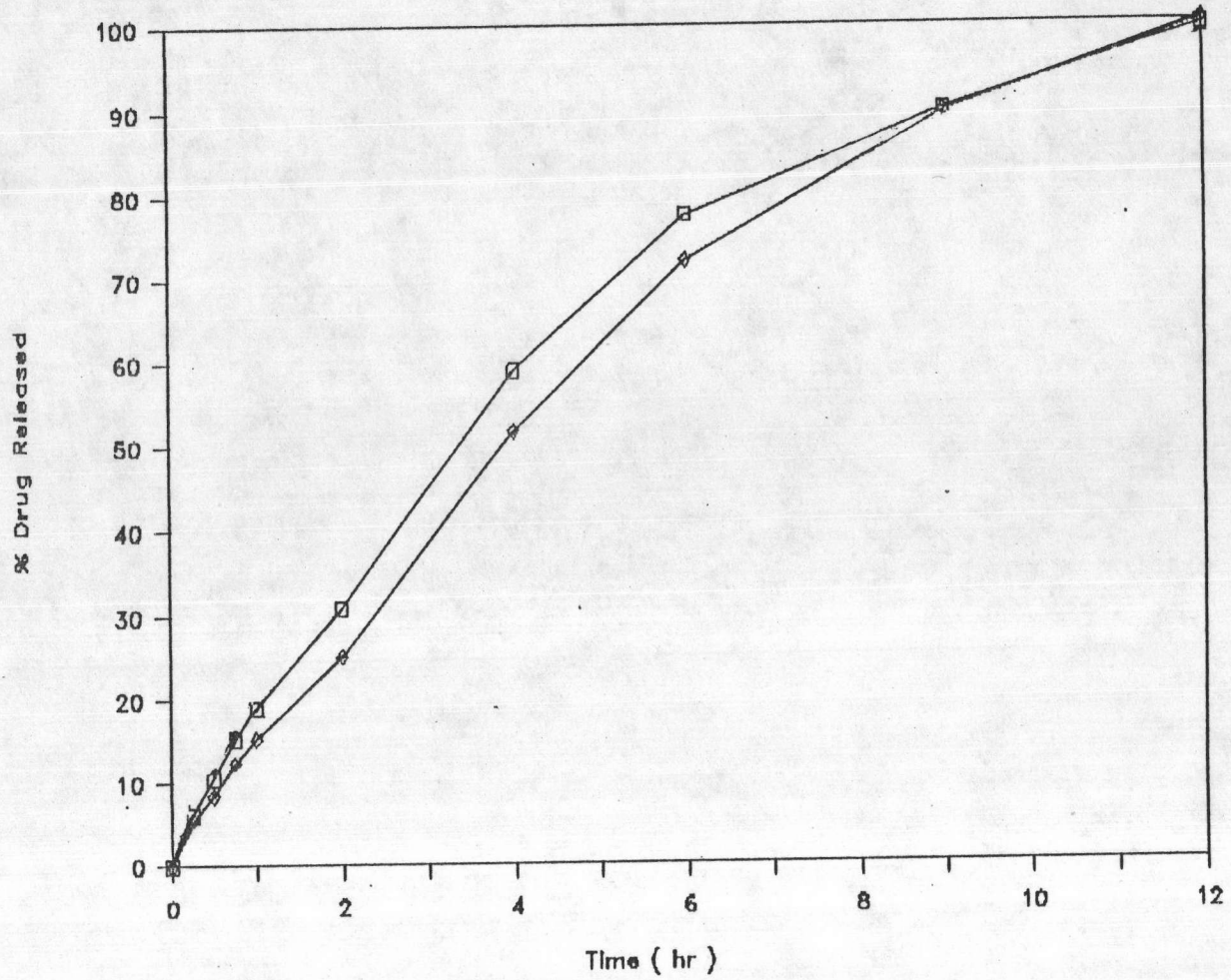


Figure 21 : Comparison of Release Profiles of Indomethacin between □——□ Combination 1 and ◇——◇ 1*

Table 21: Correlation Coefficients of the Relationships between % Drug Released v.s. Time (I), % Drug Released v.s. Square Root Time (II), and Log % Drug Remained v.s. Time (III) (Tablets Containing Single Polymer).

Polymer	%	Compressional Pressure					
		500 lb			1000 lb		
		I	II	III	I	II	III
Methocel A 4C	5.0	0.9661	0.9916	0.9767	0.9537	0.9608	0.9984
	10.0	0.9156	0.9769	0.9716	0.9376	0.9912	0.9720
	15.0	0.6545	0.8605	0.9195	0.6540	0.8581	0.9464
	20.0	0.6292	0.8849	0.9818	0.5910	0.8151	0.9096
Methocel A 4M	5.0	0.9621	0.9954	0.9732	0.9666	0.9930	0.9763
	10.0	0.9141	0.9890	0.9768	0.9789	0.9750	0.9954
	15.0	0.5758	0.8034	0.9378	0.5900	0.8200	0.9800
	20.0	0.6070	0.8277	0.9112	0.6200	0.8400	0.9300
Methocel A 15LV	1.0	0.9875	0.9633	0.9936	0.9921	0.9563	0.9957
	5.0	0.9610	0.9930	0.9710	0.9500	0.9970	0.9600
	7.5	0.8370	0.9740	0.9970	0.9839	0.9800	0.9960
	10.0	0.8370	0.9590	0.9330	0.8800	0.9730	0.9540
	15.0	0.8810	0.9820	0.9710	0.8987	0.9810	0.9680
	20.0	0.7500	0.9200	0.9810	0.8270	0.9592	0.9926
Methocel E 5	1.0	0.9814	0.9713	0.9909	0.9825	0.9692	0.9904
	5.0	0.9960	0.9531	0.9990	0.9932	0.9431	0.9892
	7.5	0.9896	0.9717	0.9986	0.9903	0.9704	0.9996
	10.0	0.9398	0.9792	0.9409	0.9389	0.9794	0.9200
	15.0	0.8024	0.9513	0.8816	0.8311	0.9664	0.9995
	20.0	0.7808	0.9478	0.9994	0.7345	0.9162	0.9670
Methocel E 15LV	1.0	0.9939	0.9594	0.9971	0.9971	0.9555	0.9991
	5.0	0.9951	0.9595	0.9940	0.9965	0.9523	0.9933
	7.5	0.9511	0.9699	0.9464	0.9545	0.9712	0.9648
	10.0	0.8870	0.9742	0.9896	0.8619	0.9626	0.9956
	15.0	0.8357	0.9594	0.9969	0.8553	0.9526	0.9883
	20.0	0.8221	0.9661	0.9970	0.8829	0.9661	0.9723
Methocel K 4M	5.0	0.9470	0.9593	0.9460	0.9554	0.9589	0.9680
	10.0	0.9797	0.9548	0.9263	0.9027	0.9602	0.9248
Methocel K 100M	3.0	0.9887	0.9532	0.9284	0.9909	0.9499	0.9226
Ethylcellulose	5.0	0.9675	0.9922	0.9755	0.9647	0.9949	0.9726
	10.0	0.9674	0.9920	0.9750	0.9622	0.9940	0.9708
	15.0	0.9660	0.9930	0.9740	0.9790	0.9865	0.9845
	20.0	0.9580	0.9960	0.9965	0.9680	0.9930	0.9748
HPMCP	1.0	0.9883	0.9578	0.9923	0.9967	0.9556	0.9987
	3.0	0.9804	0.9614	0.9968	0.9953	0.9526	0.9948
	5.0	0.9743	0.9761	0.9862	0.9757	0.9793	0.9876
	7.0	0.9934	0.9507	0.9834	0.9960	0.9532	0.9944

Table 22: Correlation Coefficients of the Relationships between % Drug Released v.s. Time (I), % Drug Released v.s. Square Root Time (II), and Log % Drug Remained v.s. Time (III) (Combined Formulatioms and Indocid-R).

Formula	Total % of Polymer	I	II	III
Blank	0.0	1.0000	0.9608	0.9984
Combination 1	11.0	0.9340	0.9807	0.9150
Combination 2	15.0	0.9747	0.9786	0.9980
Combination 3	8.5	0.8898	0.9612	0.9859
Indocid-R	-	0.8003	0.9349	0.9808
Combination 1**	11.0	0.9614	0.9751	0.9237

** Tablets of this formulation were compressed with tableting machine