Chapter III

Results

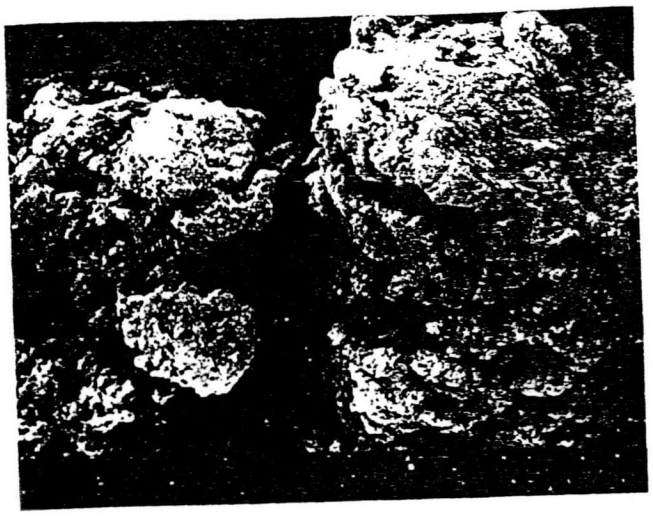
1. Fluidized-Bed Coating Conditions

Methods and conditions for granule coating (Top spray method and Wurster method) were preliminary investigated. Theophylline granule containing Avicel PH101® as filler was selected for coating with ethylcellulose coating solution for this investigating study. The surface of uncoated granules was shown in Figure 7a and 7b.

Top spray coating: Figure 8a, 9a and 10a shows the surface of granule coated using top spray method. Imperfections are seen at both low and high magnifications.

Bottom-spray coating: The bottom spray, which makes use of the Wurster coater, appeared to provide a smooth, continuous film of polymer, as shown in fegure 8b, 9b and 10b.

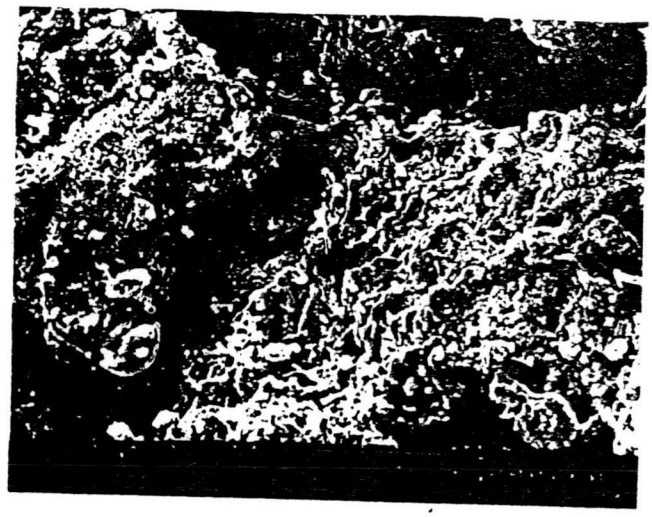
According to SEM examination, Bottom spray coating or Wurster method was used for these studies because it was quite efficient in apply the coating solution to the surface of granules to produce the satisfactory coating. The conditions which were used for coating



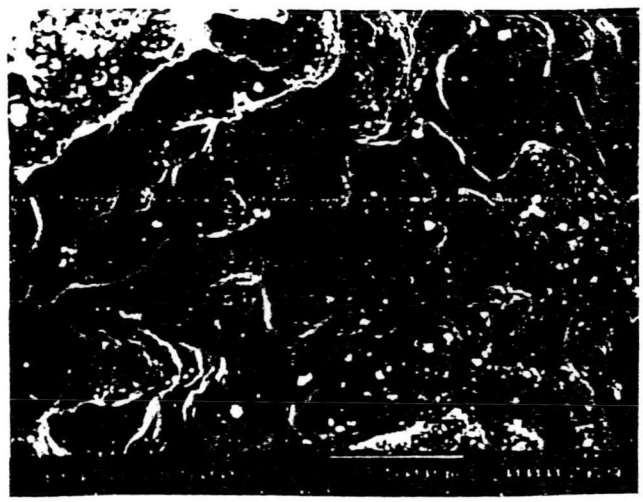
A

B

Figure 7 Uncoated theophylline granules at magnification of 75x(A) and 500x(B)



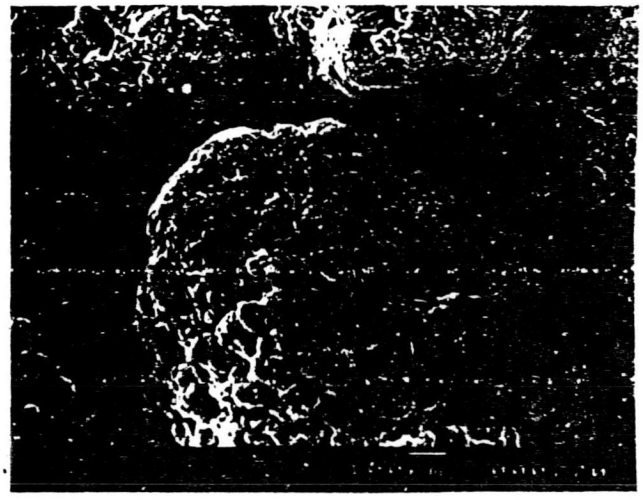
A



B

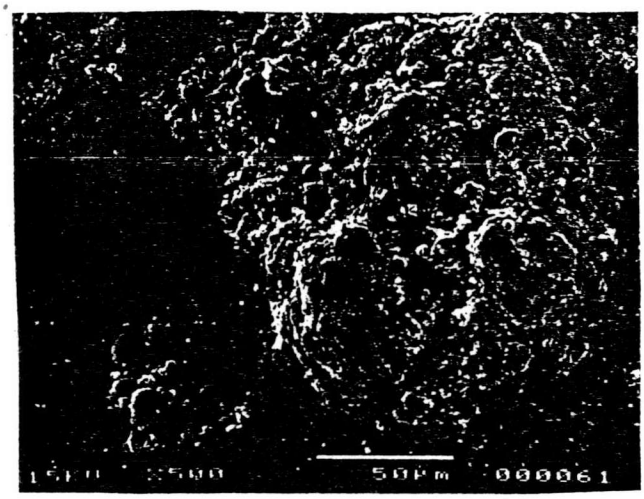
Figure 8 The photomicrographs of 10% coated granules at magnification 500x. The granules in Figure A. were coated using a top spray fluid-bed, the granules in Figure B. were coated using the Wurster coating system.

A



B

Figure 9 The photomicrographs of 20% coated granules at magnification 75x. The granules in Figure A. were coated using a top spray fluid-bed, the granules in Figure B. were coated using the Wurster coating system.



A

B

Figure 10 The photomicrographs of 20% coated granules at magnification 500x. The granules in Figure A. were coated using a top spray fluid-bed, the granules in Figure B. were coated using the Wurster coating system.

granules were summarized in Table 8.

Theophylline granules containing different diluent* (* Avicel PH101®, corn starch, Emcompress®, lactose) were coated with 3 levels (10%, 15%, 20%) of ethylcellulose. The levels of coating were calculated on the basis of ethylcellulose content of coating solution used. Each formulation was determined drug content in coated graules, the results were presented in Table 9. The standard deviation shown implied the uniformity of drug distribution in coated granules.

Table 8 The conditions used for coating theophylline granules

Inlet air temperature (°C)	60
Outlet air temperature (°C)	50
Spray pressure (atm)	2
Diameter of spray nozzle (mm)	1

Table 9 The percent of drug content of coated granules containing various diluent

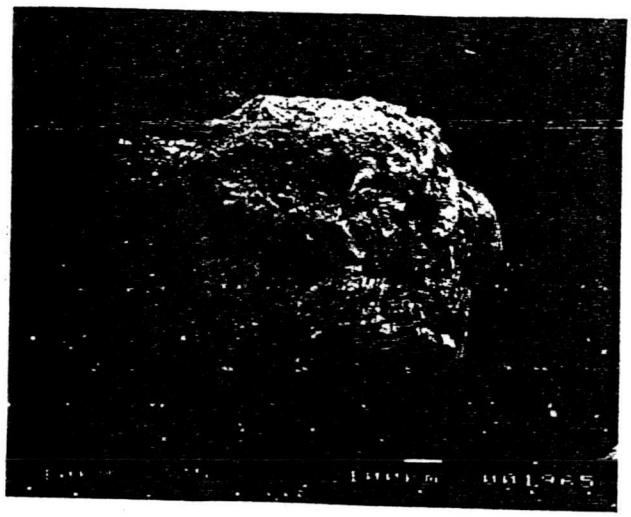
Diluent	%Ethylcellulose coated based on weight of granules		
	% Drug content		
	10%	15%	20%
Avicel PH101®	64.60±0.50	63.20±0.17	60.40±0.29
Corn starch	65.38±0.23	63.84±0.31	61.24±0.11
Emcompress®	67.29±1.17	65.65±1.23	60.78±0.70
Lactose	64.23±0.15	62.93±1.42	60.96±0.47

2. Physical Properties of Coated Granules

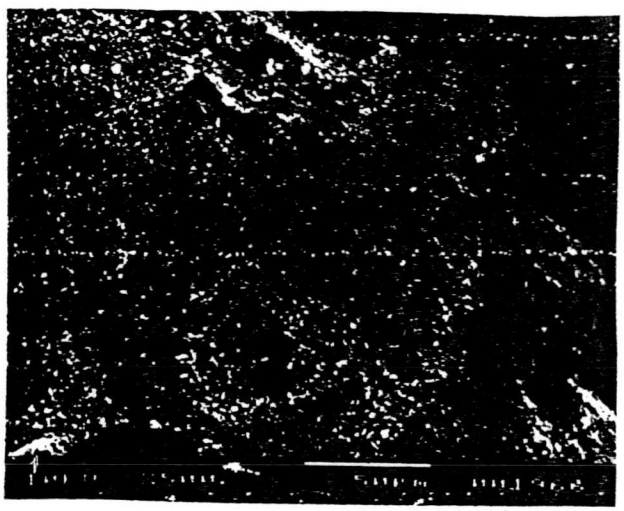
2.1 Morphology of Coated Granules

Theophylline granules (with Avicel PH101®, corn starch, Emcompress® and lactose as filler) coated with varied amout ethylcellulose were examined using scanning electron microscope at different maginfication.

The surface morphology and cross-sections of all formulations are shown in Figure 11-30, Figure 11-15

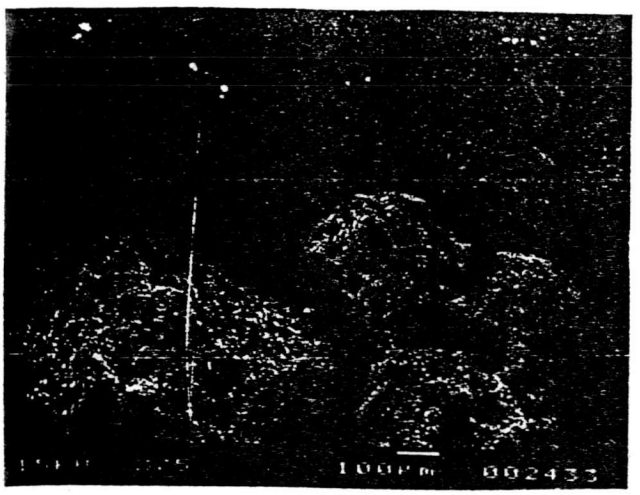


A

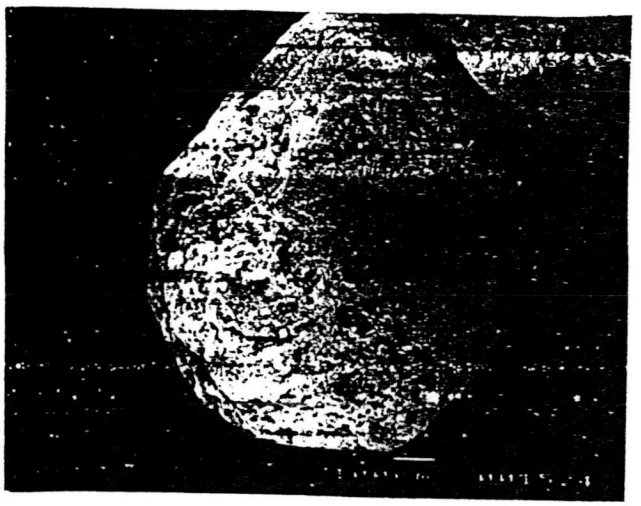


B

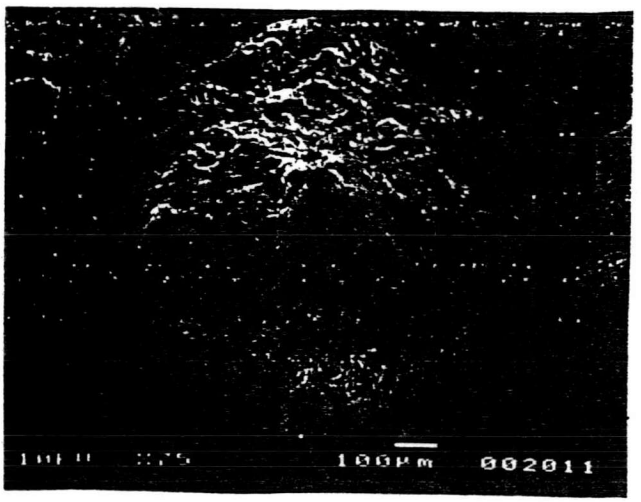
Figure11 The photomicrographs of uncoated Theophylline granules Prepared using Avicel PH101® as filler at magnification 75 x (A) and 500 x (B)



A



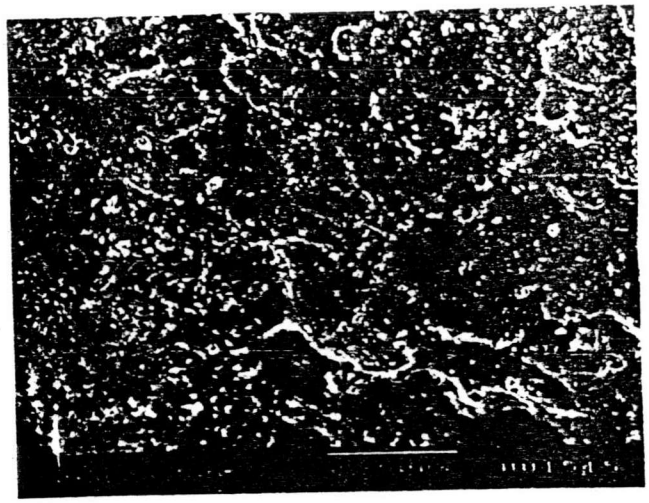
B



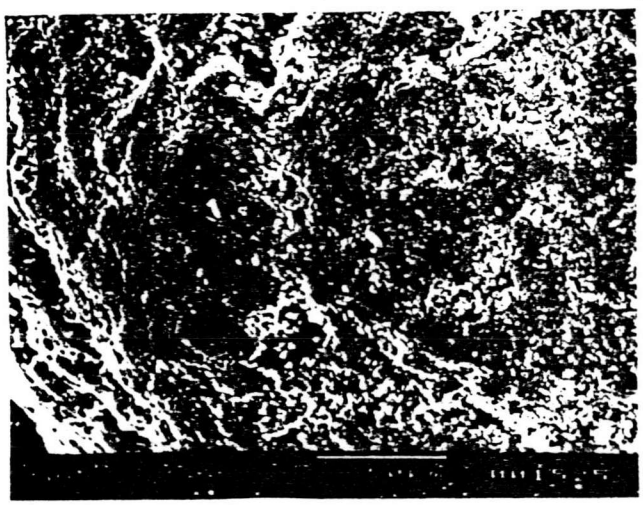
C

Figure 12 The photomicrographs of coated theophylline granules prepared using Avicel PH101® as filler at magnification 75x.

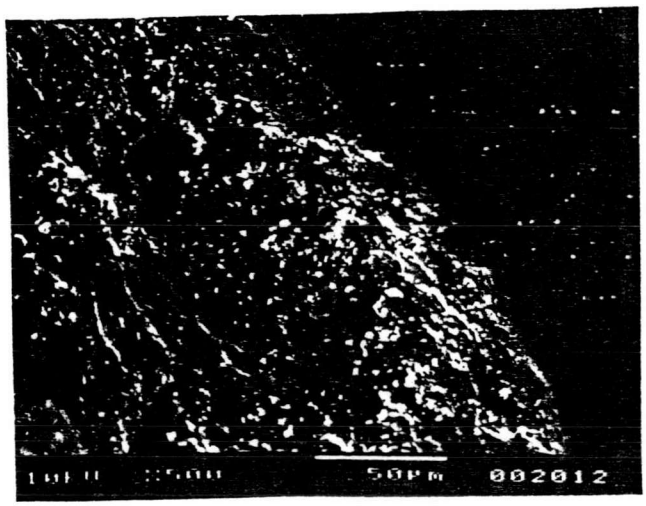
(A= 10%coated, B= 15%coated, C= 20%coated)



A



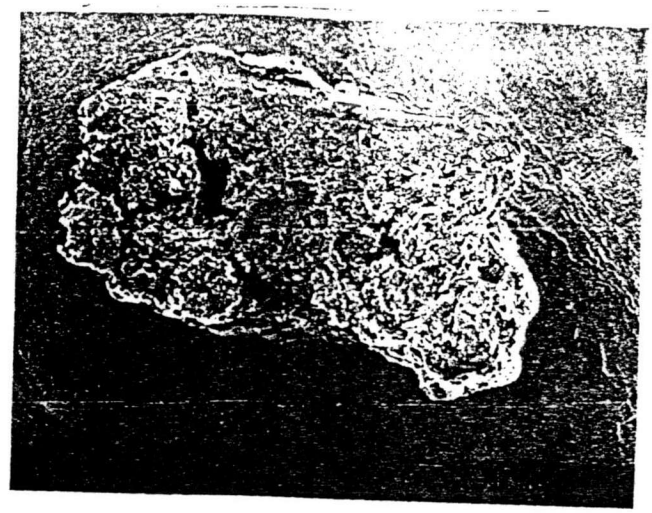
B



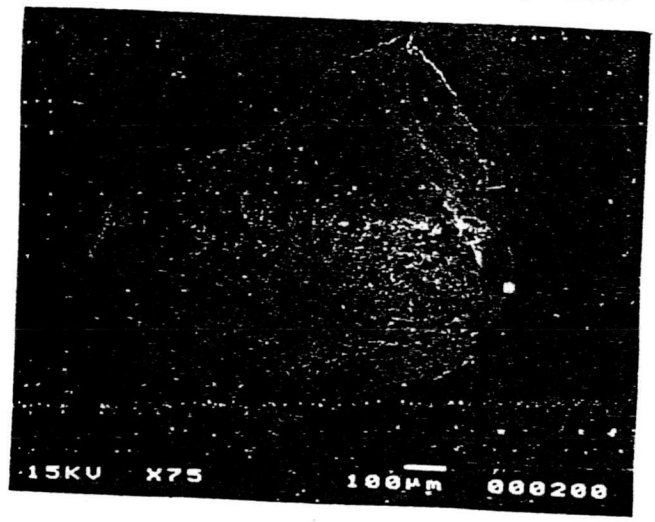
C

Figure 13 The photomicrographs of coated theophylline granules prepared using Avicel PH101® as filler at magnification 500x.

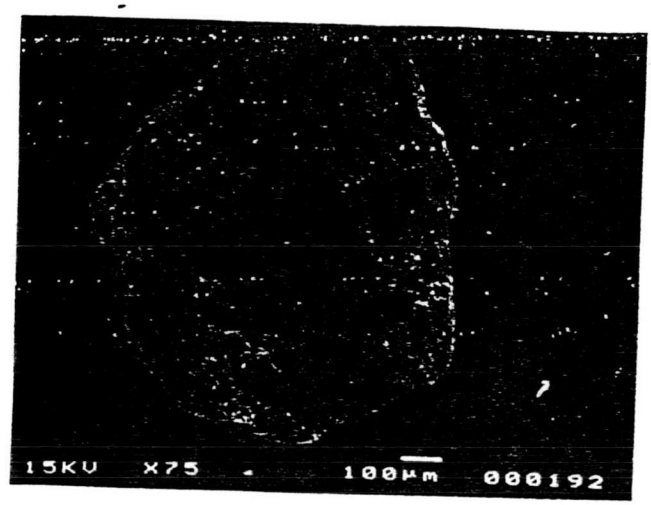
(A =10% coated, B=15% coated, C=20% coated)



A

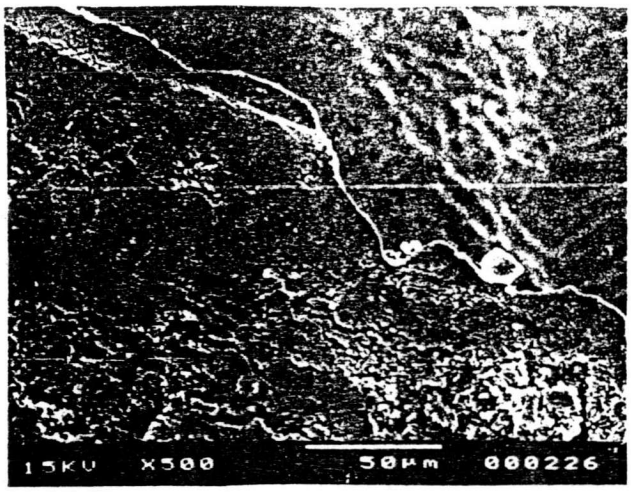


B

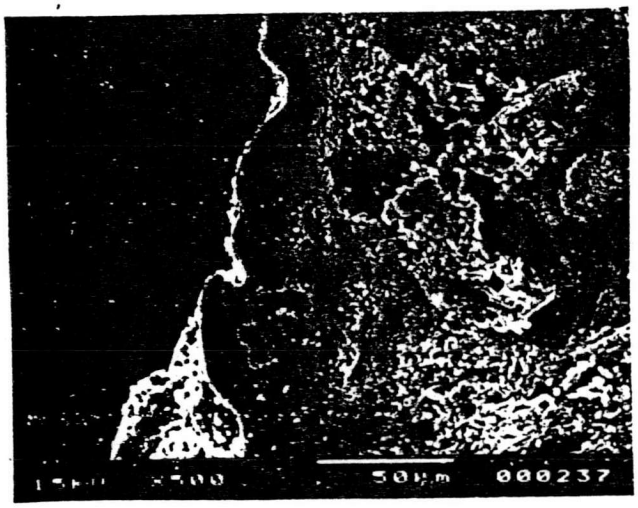


C

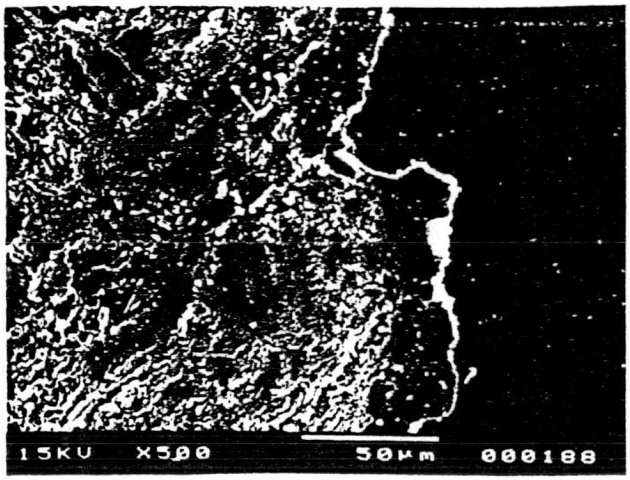
Figure 14 The photomicrographs of coated theophylline granules prepared using Avicel PH101® as filler at magnification 75x (Cross Section: A =10% coated, B =15% coated, C =20% coated)



A



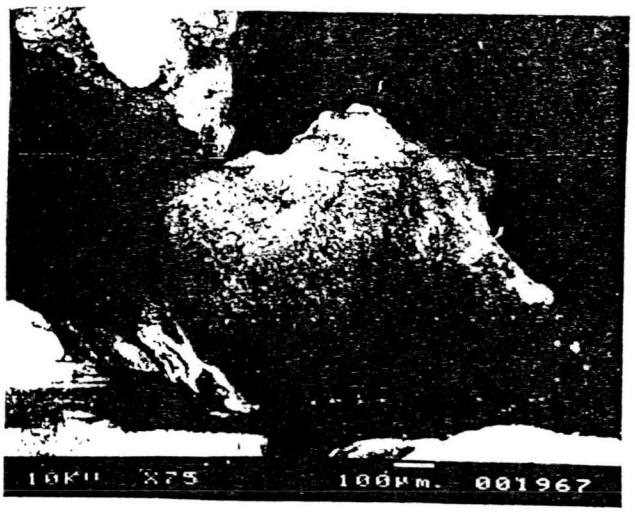
B



C

Figure 15 The photomicrographs of coated theophylline granules prepared using Avicel PH101® as filler at magnification 500x

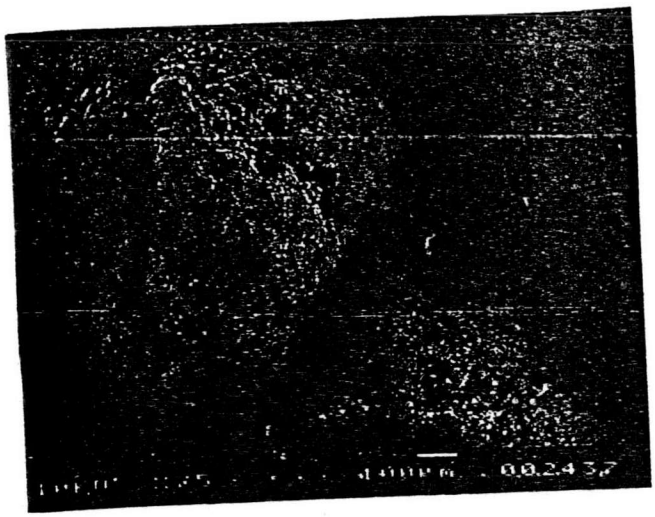
(Cross Section: A =10% coated, B =15% coated, C =20% coated)



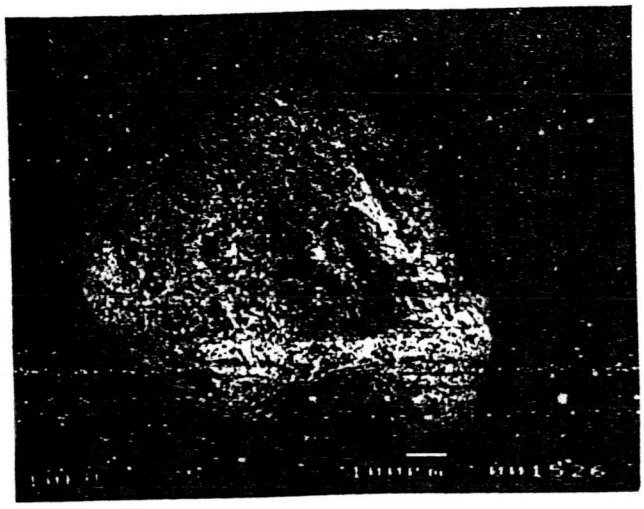
A

B

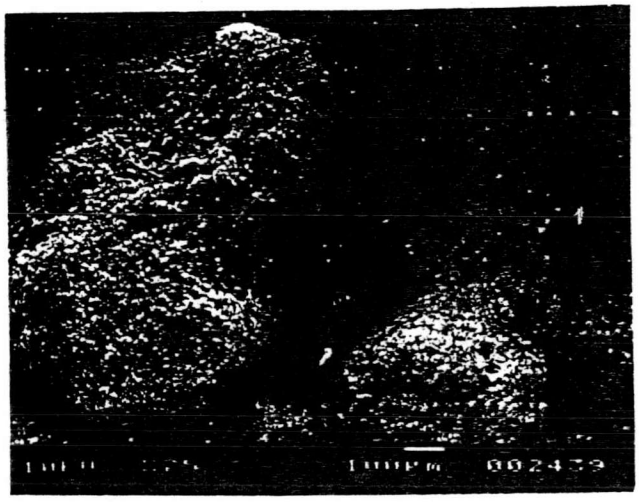
Figure16 The photomicrographs of uncoated theophylline granules prepared using corn starch as filler at magnification 75 x (A) and 500 x (B)



A



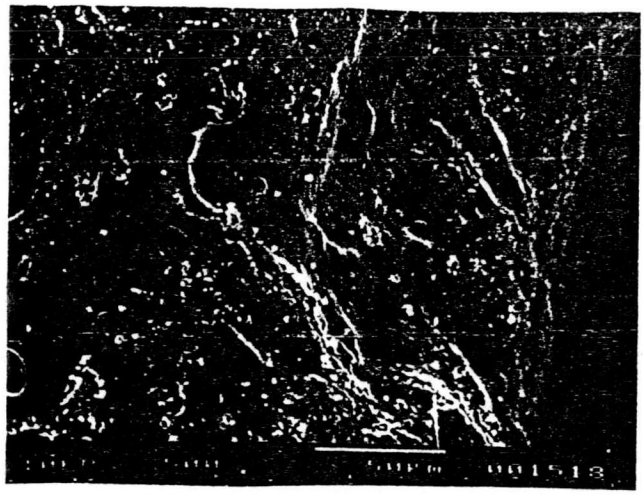
B



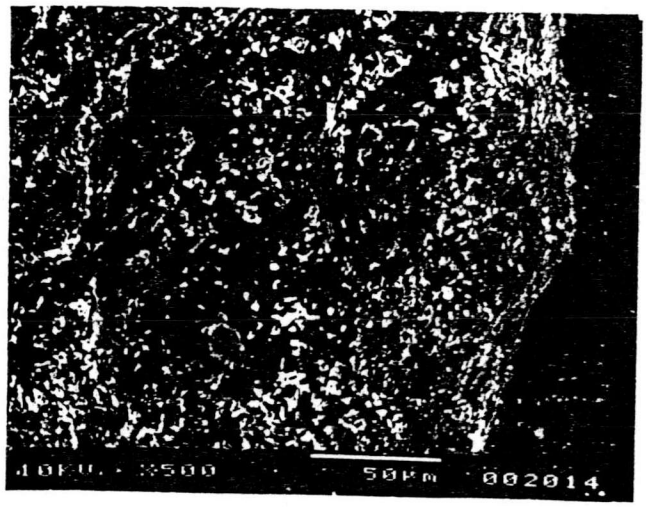
C

Figure 17 The photomicrographs of coated theophylline granules prepared using corn starch as filler at magnification 75X

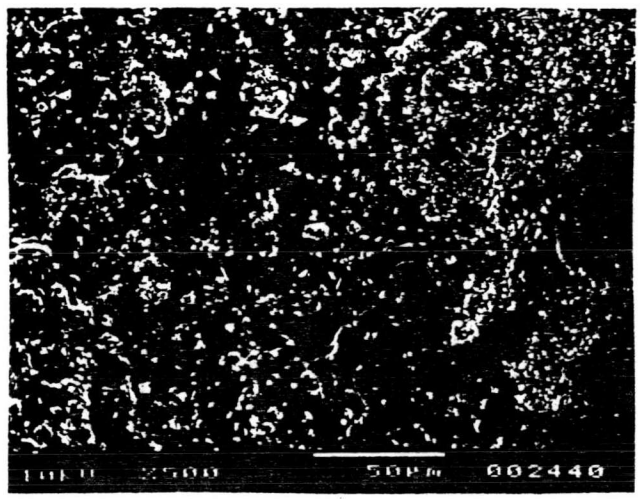
(A= 10%coated, B=15%coated, C= 20%coated)



A



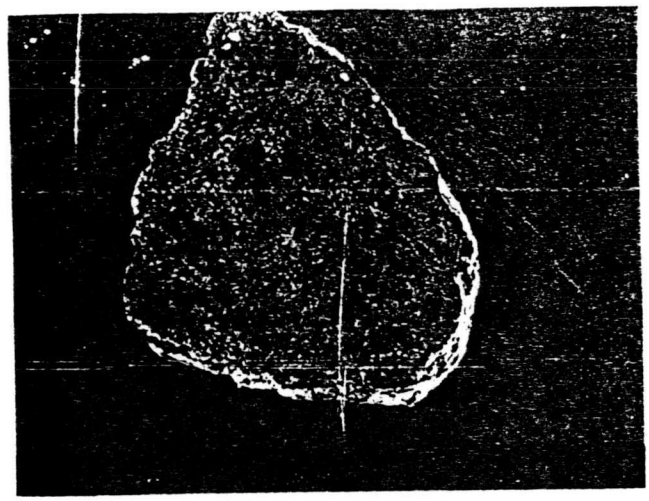
B



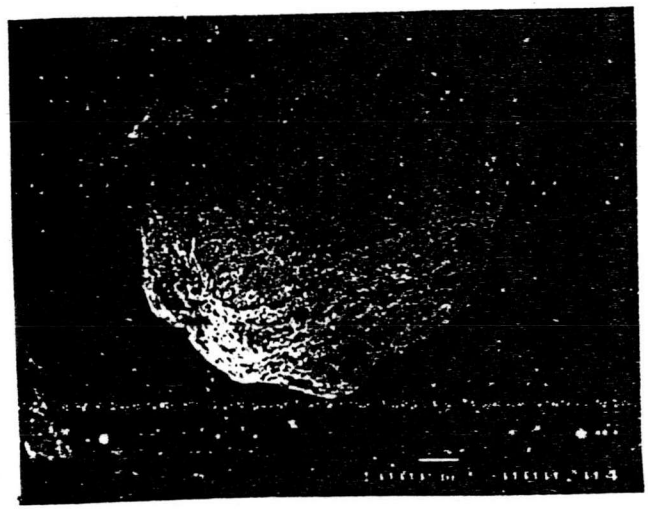
C

Figure18 The photomicrographs of coated theophylline granules prepared using corn starch as filler at magnification 500x.

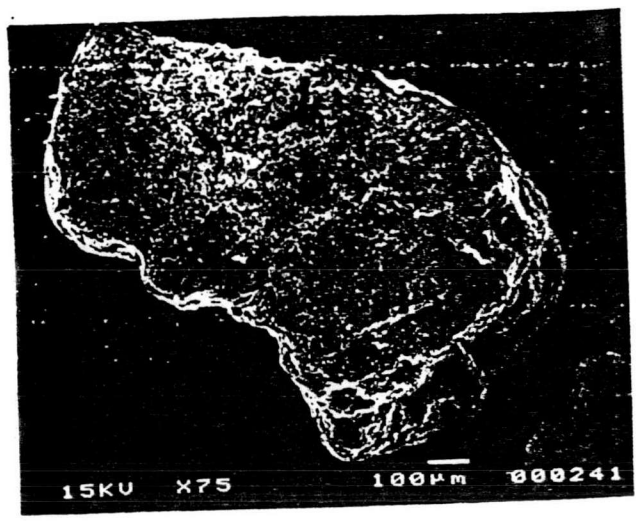
(A =10% coated, B =15% coated, C =20% coated)



A



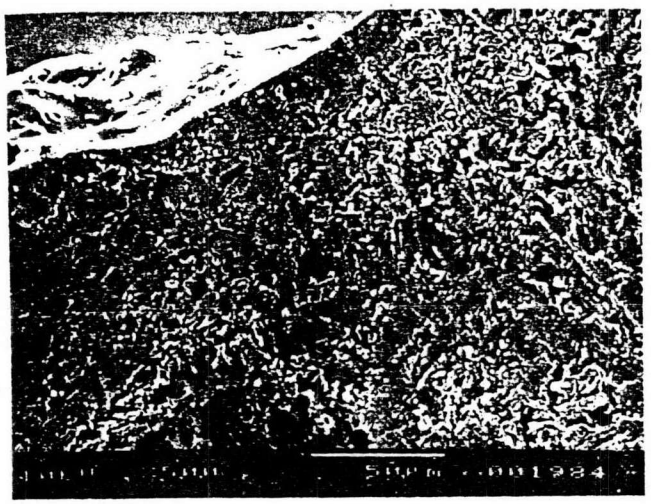
B



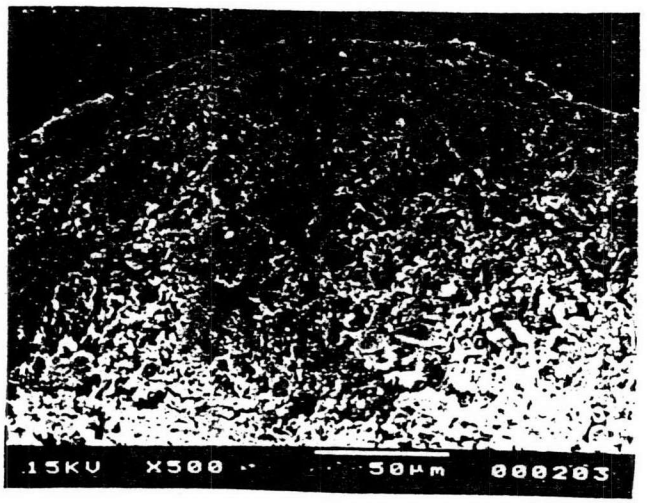
C

Figure 19 The photomicrographs of coated theophylline granules prepared using corn starch as filler at magnification 75x

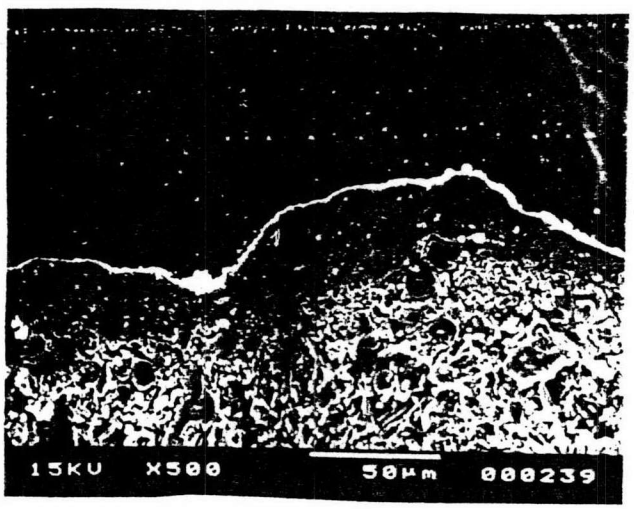
(Cross Section: A =10% coated, B =15% coated, C =20% coated)



A



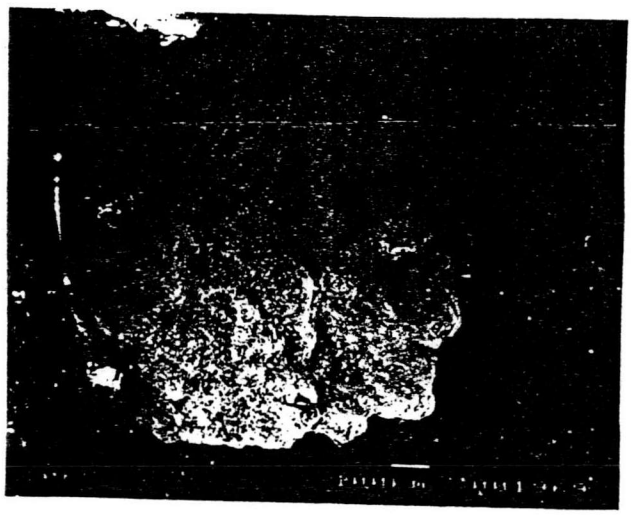
B



C

Figure 20 The photomicrographs of coated Theophylline granules prepared using corn starch as filler at magnification 500x

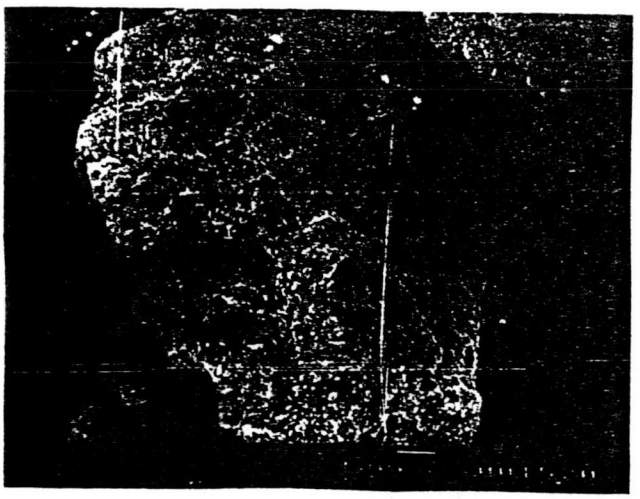
(Cross Section: A =10% coated, B =15% coated, C =20% coated)



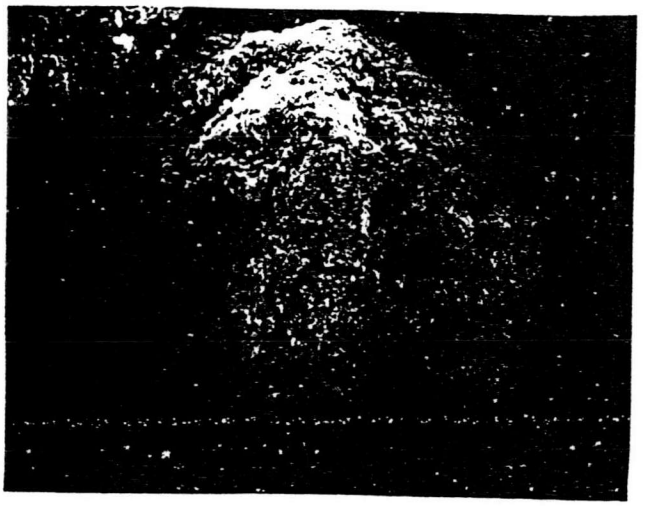
A

B

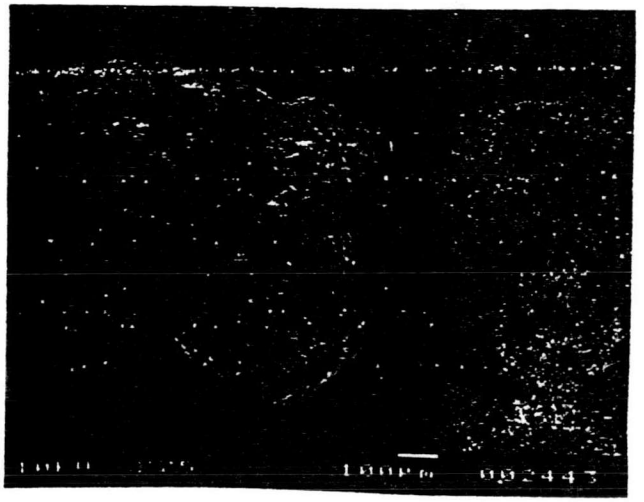
Figure21 The photomicrographs of uncoated theophylline granules Prepared using Emcompress® as filler at magnification 75x(A) and 500x(B)



A



B

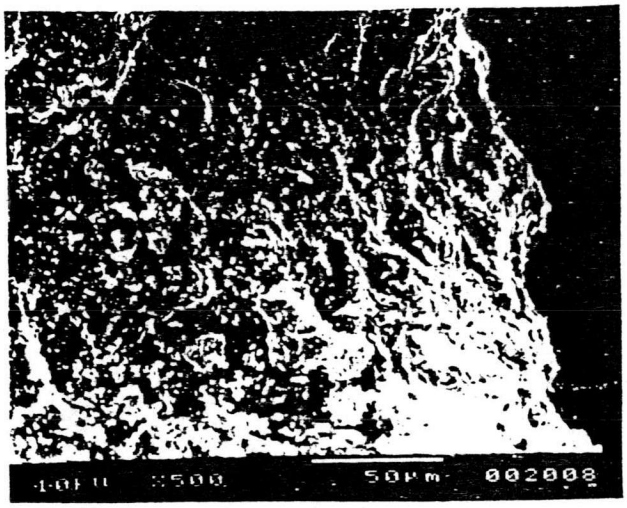


C

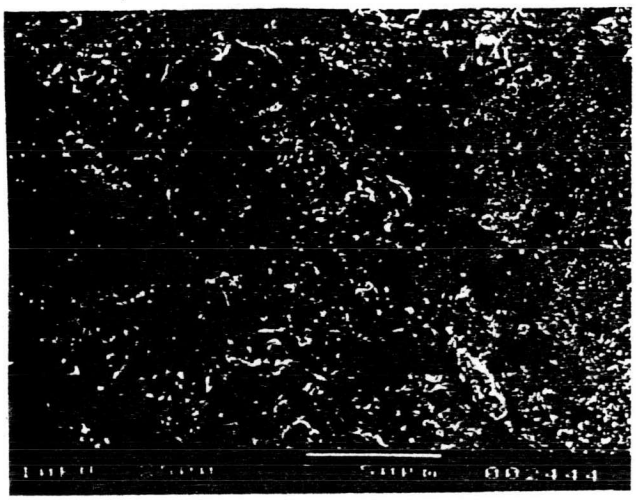
Figure 22 The photomicrographs of coated theophylline granules Prepared using Emcompress® as filler at magnification 75x.

(A= 10%coated, B= 15%coated, C=20%coated)

A



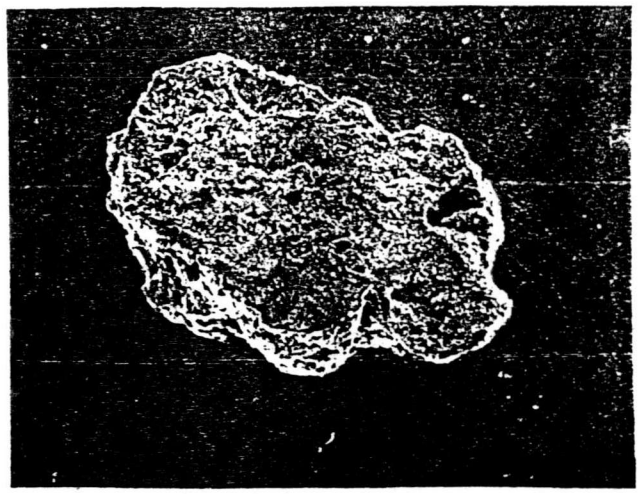
B



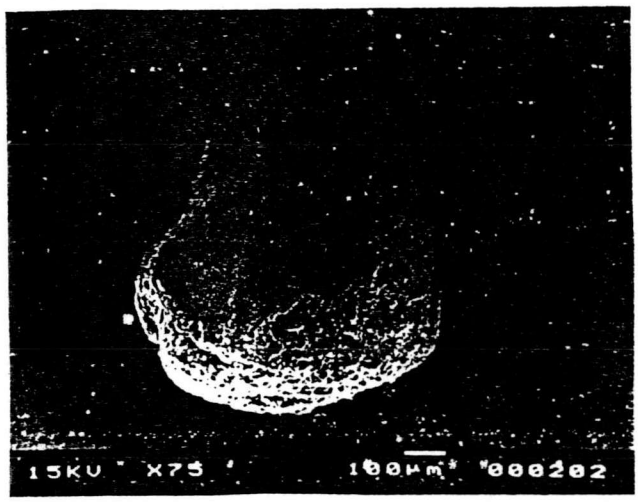
C

Figure 23 The photomicrographs of coated Theophylline granules prepared using EMcompress as filler at magnification 500x.

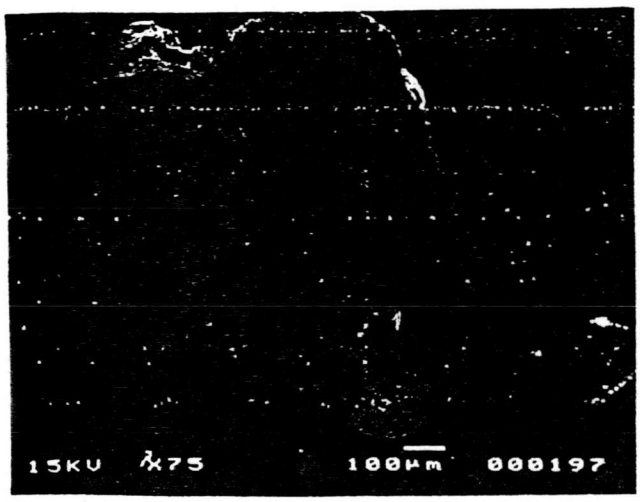
(A =10% coated, B =15% coated, C =20% coated)



A



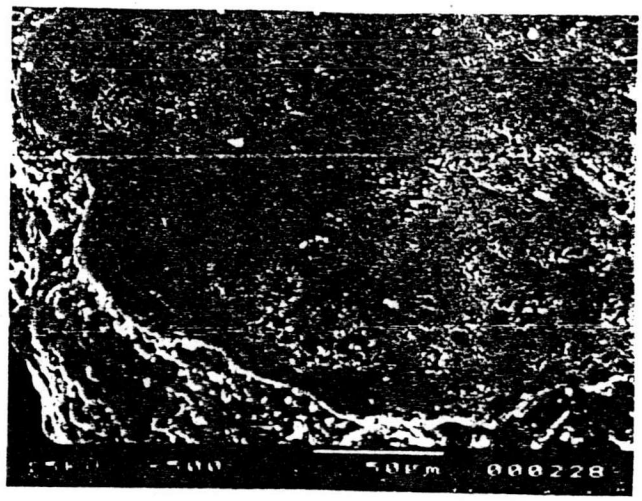
B



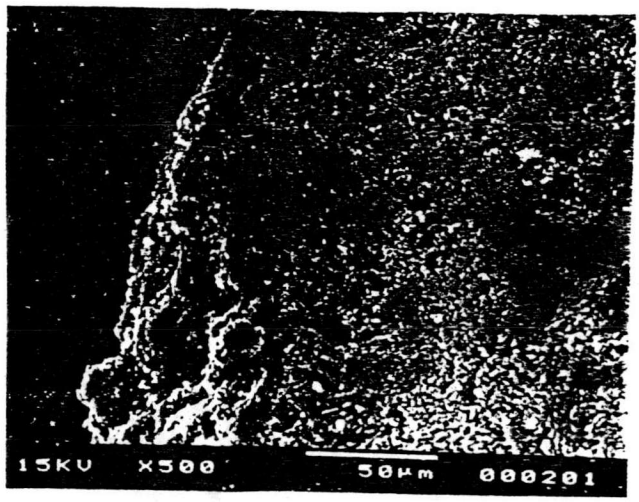
C

Figure24 The photomicrographs of coated Theophylline granules prepared using Emcompress® as filler at magnification 75x

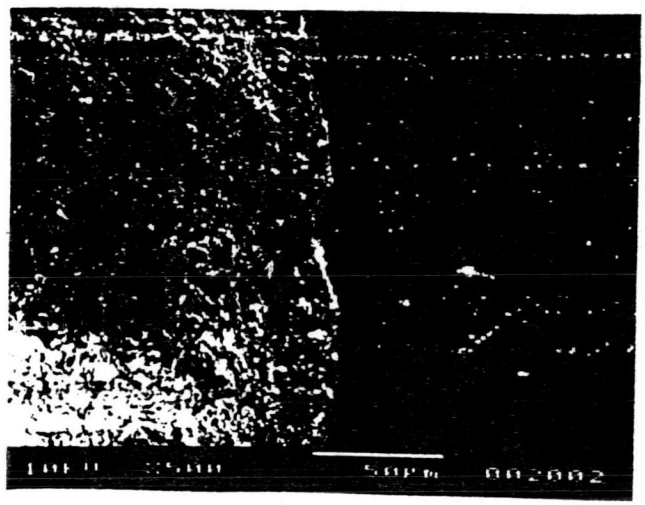
(Crorss Section :A =10%coated, B =15% coated, C =20% coated)



A



B

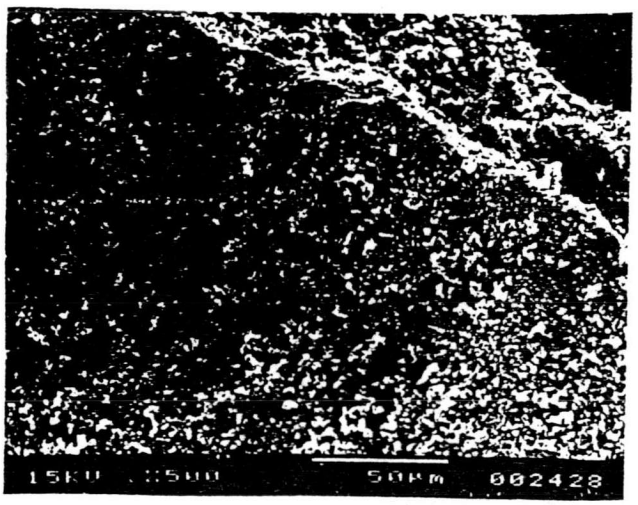


C

Figure25 The photomicrographs of coated theophylline granules prepared using Emcompress® as filler at magnification 500x

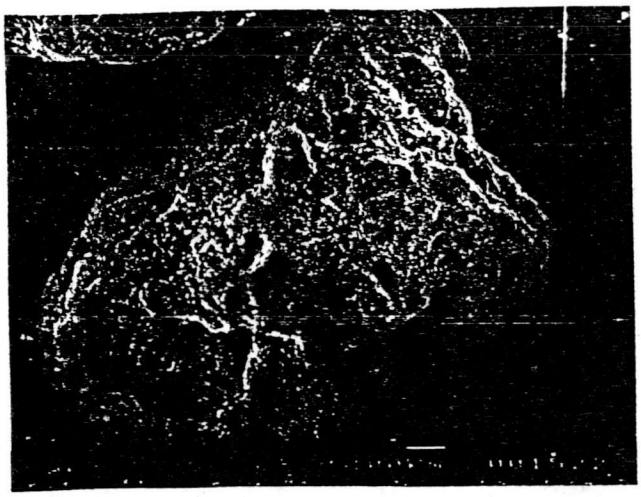
(Crorss Section:A =10%coated, B =15% coated, C =20% coated)

A

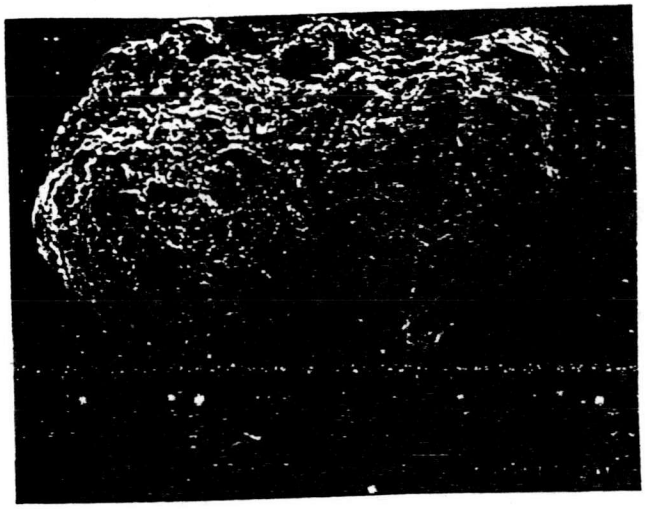


B

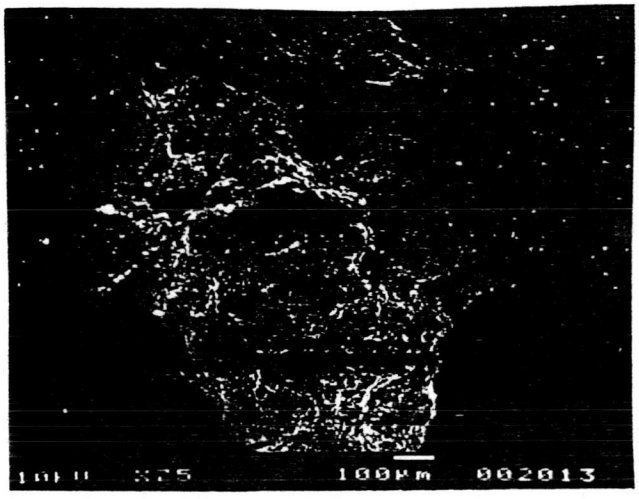
Figure26 The photomicrographs of uncoated theophylline granules prepared using lactose as filler at magnification 75x(A) and 500x(B)



A



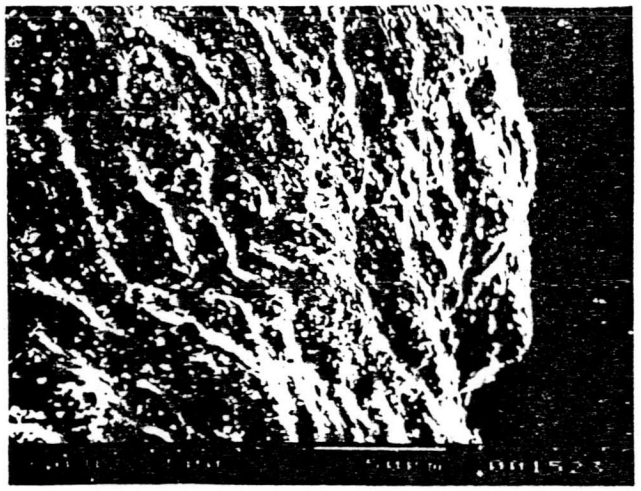
B



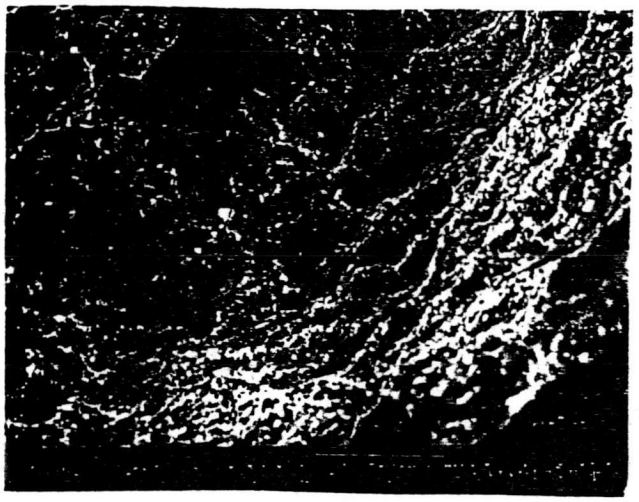
C

Figure 27 The photomicrographs of coated theophylline granules Prepared using lactose as filler at magnification 75x.

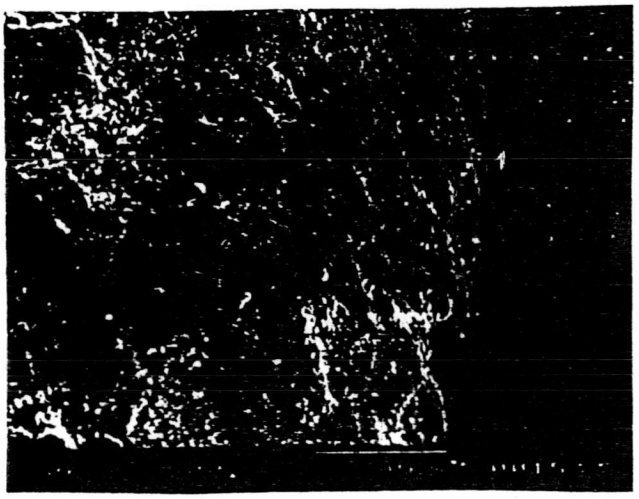
(A =10%coated, B =15%coated, C= 20%coated)



A



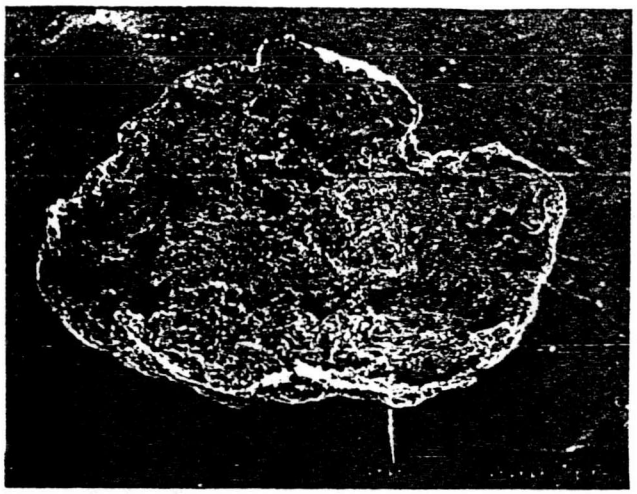
B



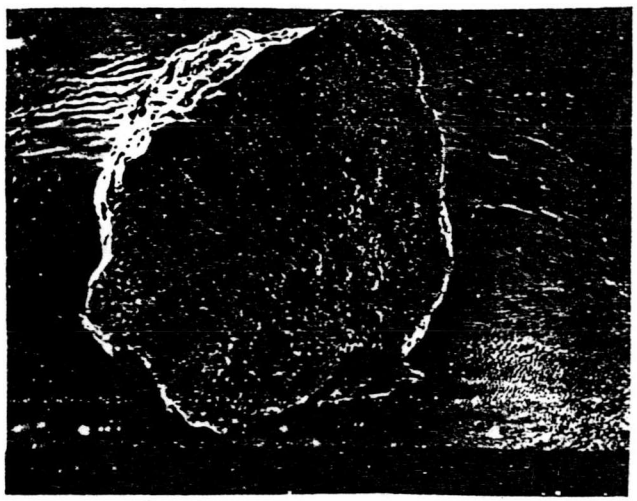
C

Figure 28 The photomicrographs of coated theophylline granules prepared using lactose as filler at magnification 500x.

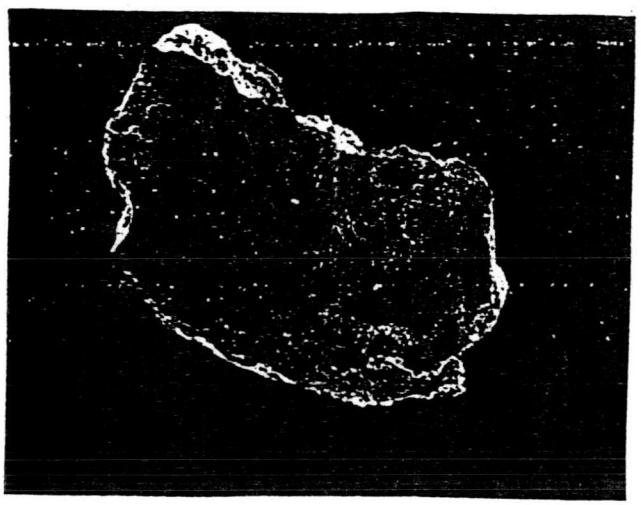
(A =10% coated, B =15% coated, C =20% coated)



A



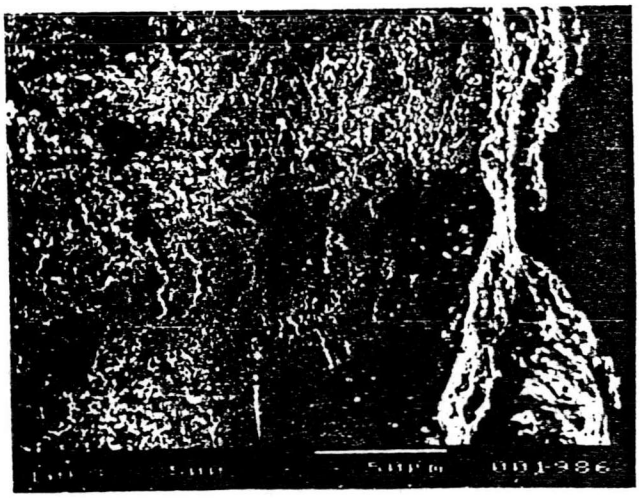
B



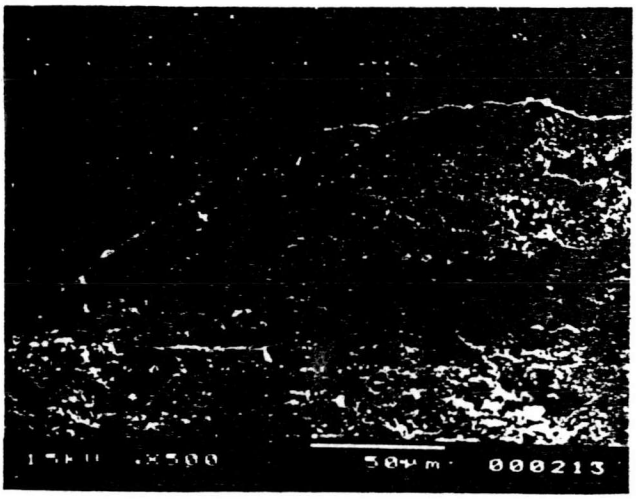
C

Figure 29 The photomicrographs of coated theophylline granules prepared using lactose as filler at magnification 75x

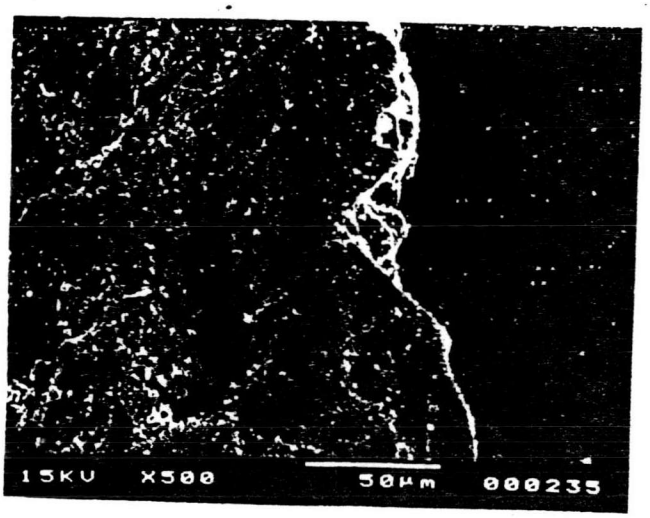
(Crorss Section: A =10%coated, B =15% coated, C =20% coated)



A



B



C

Figure 30 The photomicrographs of coated theophylline granules prepared using lactose as filler at magnification 500x

(Crorss Section:A =10%coated, B =15% coated, C =20% coated)

were coated granules containing Avicel PH101® as filler, Figure 16-20 were coated granules containing corn starch as filler, Figure 21-25 were coated granules containing Emcompress® as filler and Figure 26-30 were coated granules containing lactose as filler. The photomicrographs showed granules were coated with uniform film and the film thickness increased with the increasing the amount of ethylcellulose coated on the granules.

2.2.1 Dissolution Profiles of Uncoated Granules

The release profiles of uncoated granules were studied by basket and paddle method in 0.1N Hcl and phosphate buffer pH 6.8 could be plotted between the percentage amount of drug release against time. The dissolution data of each formulation was described in Table 17-18 (Appendix).

A. Influence of Dissolution Apparatus on the Release Profiles of Uncoated Granules

The dissolution test of uncoated granules of theophylline containing various fillers were carried out in 0.1N Hcl by either the basket or paddle method, both of which are official in USP XXI and are refered to as USP method I (basket method) and II (paddle method). All release data at various sampling times are

expressed as the percentage of amount of drug release againts time which are tabulated in Table 18 (Appendix).

The plot illustrated comparable release profiles for the paddle and the basket method were shown graphically in Figure 31. However, the release profiles of theophylline from granules, irrespective of filler type showed higher release profiles using basket method than paddle method. The flotation of granules in medium was observed when using paddle method so that these result would be due to the better exposure of the total surface area of granules to the dissolution medium by the rotating basket. Finally, the USP method I (Basket method) was selected to study the drug release from uncoated and coated granules.

B. Influence of Filler Exipients on the Dissolution Profiles of Uncoated Granules

The filler excipients or diluents investigated included microcrystalline cellulose (Avicel PH101®),corn starch,dibasic calcium phosphate (Emcompress®) and lactose. The dissolution data of theophylline from the granules containing 75% theophylline anhydrous and 25% filler studied by basket method in 0.1N Hcl and phosphate buffer pH 6.8 are tabulated in Table 17,18 (Appendix) and are shown graphically in Figure 32A and 32B.

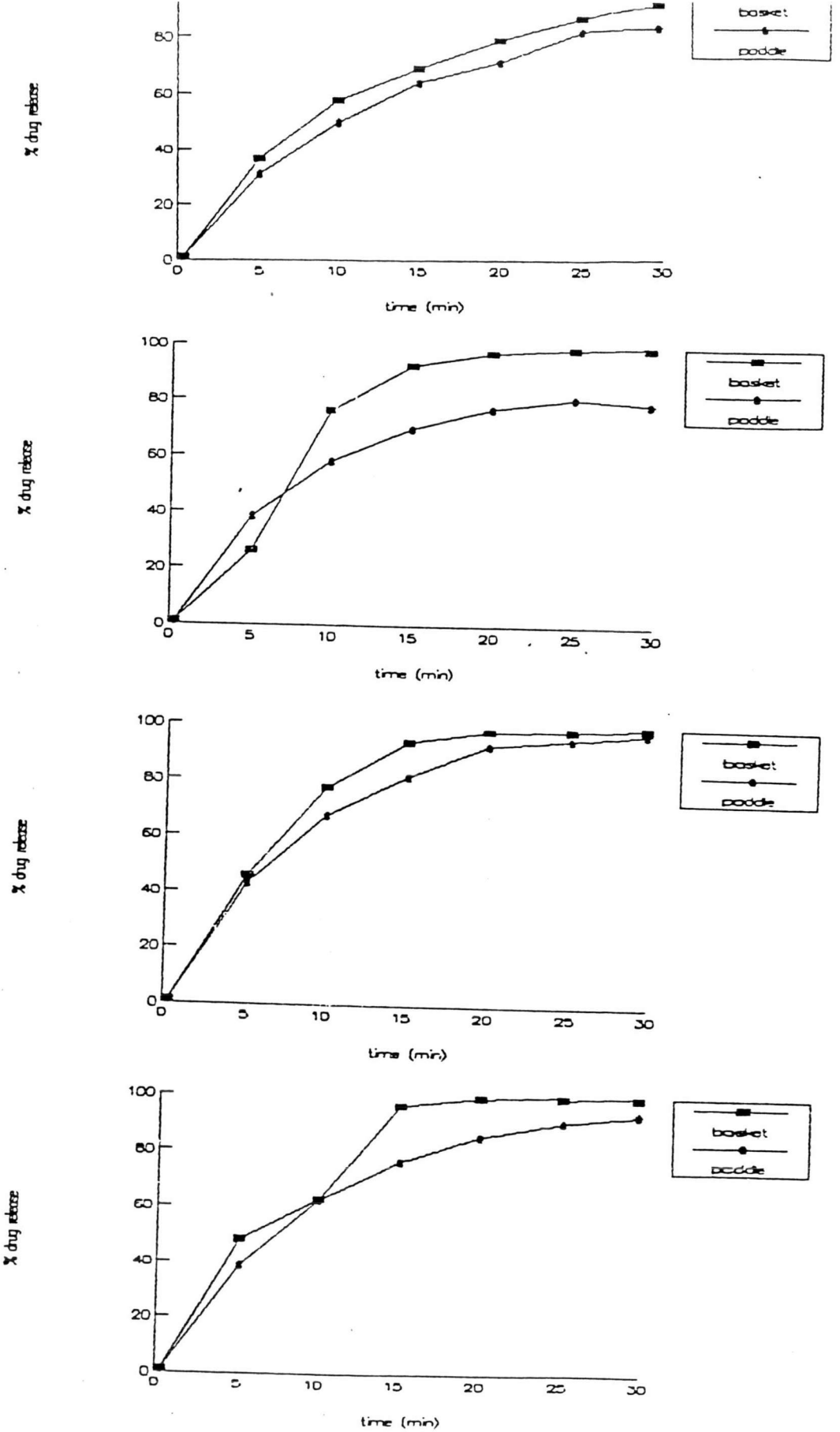


Figure 31 Influence of dissolution apparatus on theophylline release profiles from uncoated granules containing various fillers in 0.1N Hcl A: Avicel PH 101® B: corn starch, c: Emcompress®, D: lactose

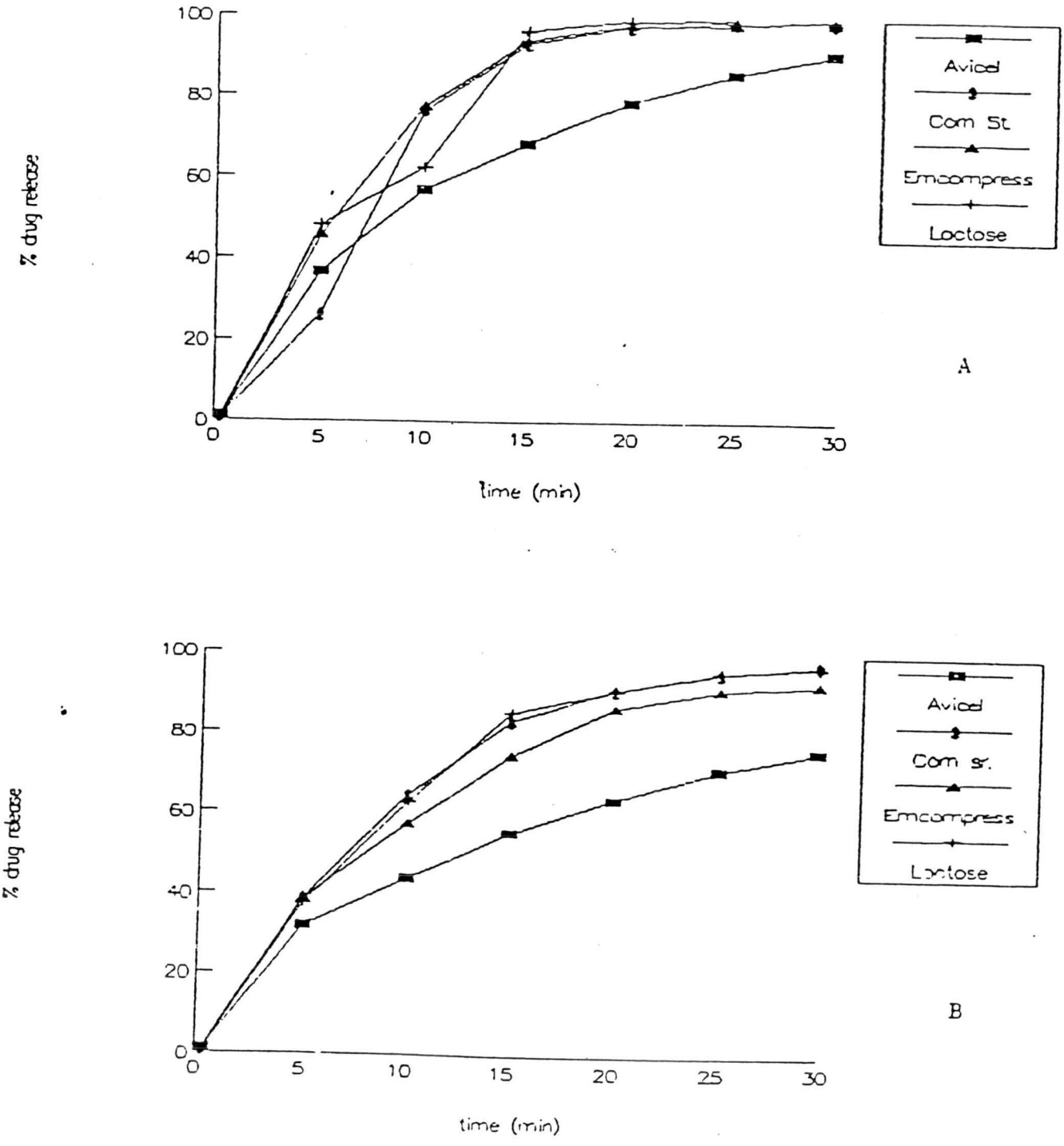


Figure 32 Influence of various fillers on the theophylline release profiles from uncoated graunles studied by basket method.

A: in o.1N Hcl B:in phosphate buffer pH6.8

Each point represents the average value obtained from three samples at the given sampling time. The obtained result,from uncoated granules containing corn starch, Emcompress®, lactose as filler studied by basket method in 0.1N Hcl (FIG 32A), more than 90% release in 15 minute but Avicel PH101® showed only 68% release. Hence, the uncoated granule containing Avicel PH101® as filler gave the slowest release profile.

The influence of fillers on drug release from uncoated granules were also studied in phosphate buffer pH 6.8 by basket method (FIG 32B). The drug release profiles in buffer pH 6.8 were lower than the studies in acid medium but the obtained results were similar. The uncoated granules containing Avicel PH101® as filler also gave the slowest release profile.

2.2.2 Dissolution Profiles of Coated Granules.

Drug release from granule containing theophylline and various fillers (Avicel PH101®, corn starch, Emcompress®, lactose) coated with 3 level (10%, 15%,20%) of ethylcellulose were studied by USP apparatus I (basket method) in PH change method. The amount of drug release against time are tabulated in Table 19-22 (Appendix).

A. Influence of Coating Level on the Drug Release Profile of Coated Granules.

The uncoated theophylline granules shown more than 90% release in half hour. Initially, ethyl cellulose was aplied to the granules. The dissolution profiles of theophylline granules containing various fillers and coated with 10, 15, 20% ethylcellulose are shown in Figure 33. The lowest drug release profiles were obtained when 20% ethylcellulose was used as a coating level, 15% coated granule release the drug at slightly higher profiles and the highest release profiles were observed with 10% coated. These results agreed with those obtained from SEM photomicrographs of coated granules which increasing the amount of ethylcellulose coated were increasing the film thickness and the release of drugs would be retarded.

B. Influence of Filler Excipients on the Dissolution Profiles of Coated Granules.

Several filler excipients(Avicel PH101®,corn starch,Emcompress®,lactose) were evaluated for there influence on release profiles of the same level of ethylcellulose coated granules. The comparative release profiles for various fillers at the same coating level were shown graphically in Figure 34. Figure 34a shows release profiles of granules containing Avicel PH101®, corn starch, Emcompress®, lactose as filler excepient at

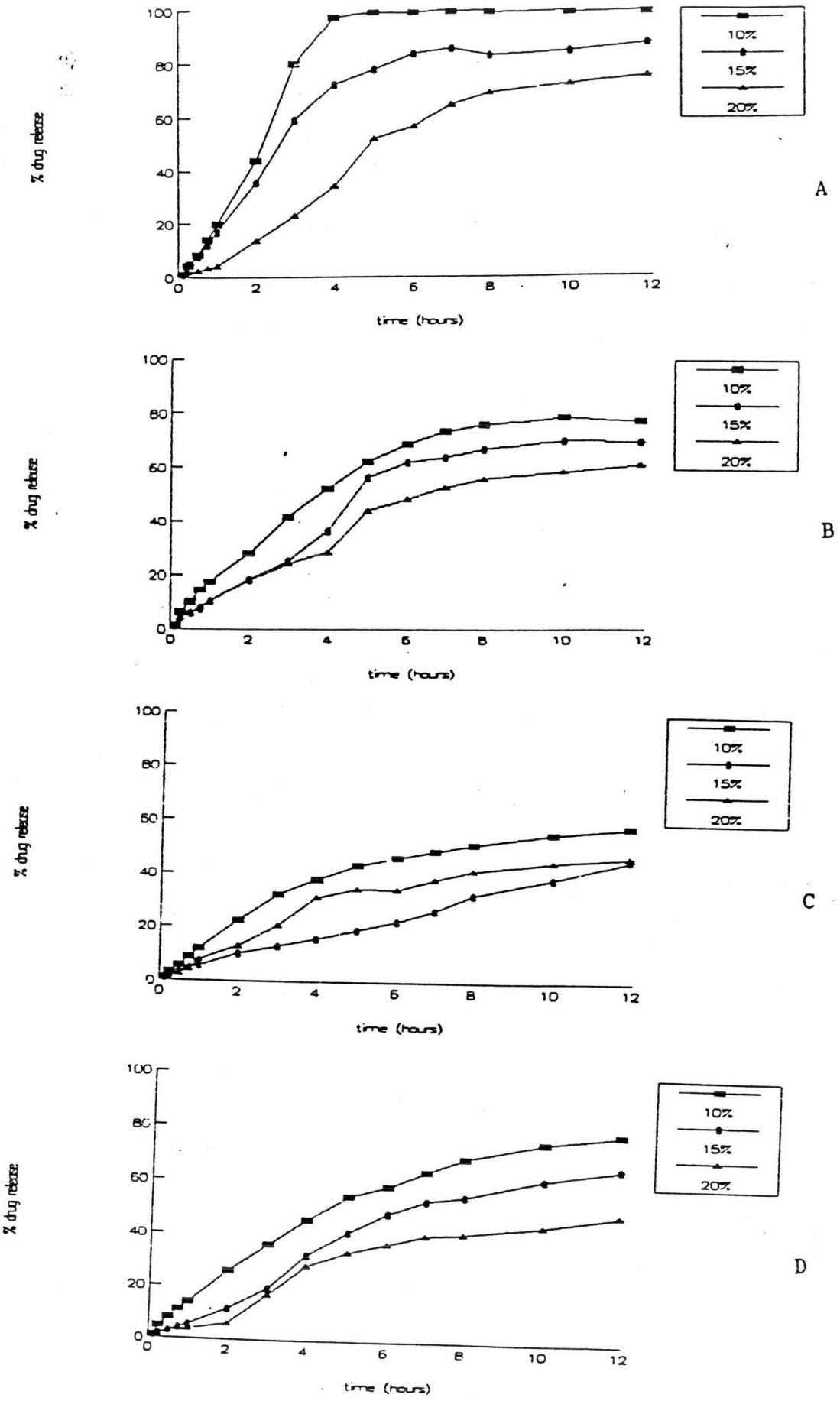


Figure 33 Influence of coating level on theophylline release profiles from coated granules containing various fillers; A: Avicel PH101^{R} B: corn starch C: Emcompress^{R} D: lactose

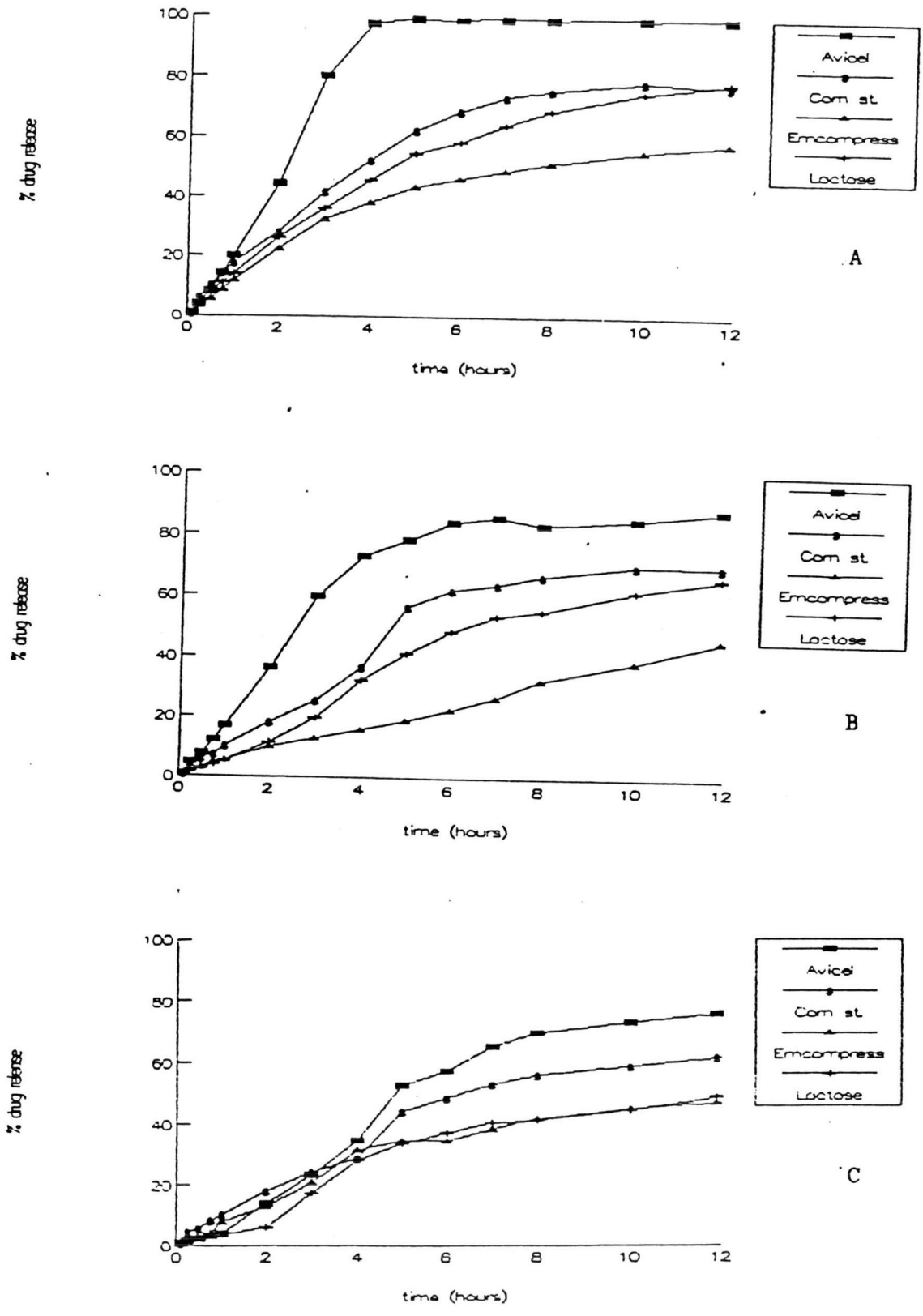


Figure 34 Influence of fillers in granules on Theophylline release from coated granules; A: 10% coated granules B: 15% coated granules C: 20% coated granules

10% coated level, Figure 34b for 15% coated level and Figure 34c for 20% coated level.

The release profiles were compared, For 10% and 15% coated granules the release were found to be the highest from granules containing Avicel PH101®. Release profiles of drug from granules containing corn starch was the second, lactose was the third and the lowest was Emcompress®. In 20% coated granules (FIG. 34C), at first 4 hours release of drug from coated granules containing various fillers were not very different and the lowest was the release profile from granules containing lactose as filler. After that, as same as the other level of coating, the release from Avicel PH101® was hightest and the second was corn starch. Dissolution profile of Emcompress® and lactose were quite equal. These results were contrary to the result obtained from uncoated granules which Avicel PH101® gave least drug release.

3. Physical Properties of Tablets Prepared from Coated Granules

3.1 Thickness, Hardness and Disintegration Time of Tablets

Thickness, hardness and disintegration time of tablets prepared from coated granules were presented in Table 10-13.

TABLE 10. Thickness , Hardness and Disintegration Time of Experimental Tablet Prepared from Coated Granules Containing Avicel PH101® as Filler

Formulations	Thickness(mm) +SD	Hardness(Kp) +SD	DT*
10%A1	5.12±0.25	8.61±1.21	1.50±0.06
10%A2	5.07±0.26	9.21±1.42	3.20±0.57
10%A3	5.01±0.33	12.32±1.42	2.65±0.29
10%A4	4.89±0.35	11.78±1.56	4.47±0.89
10%A5	4.86±0.35	15.24±1.02	2.23±0.45
10%A6	4.80±0.42	16.56±1.29	20.06±1.22
15%A1	5.34±0.21	7.89±0.57	1.46±0.29
15%A2	5.13±0.36	8.21±1.34	4.15±0.79
15%A3	5.20±0.28	10.92±1.21	3.10±0.51
15%A4	5.01±0.41	11.22±1.29	6.22±0.85
15%A5	5.15±0.16	16.25±1.56	3.89±0.19
15%A6	5.01±0.41	18.95±1.56	30.02±2.01
20%A1	5.55±0.25	9.22±0.77	2.89±0.55
20%A2	5.42±0.12	9.67±0.68	3.28±0.72
20%A3	5.31±0.16	12.59±1.02	2.86±0.55
20%A4	5.21±0.31	12.98±1.21	6.15±0.87
20%A5	5.20±0.35	17.16±1.35	3.27±0.47
20%A6	5.16±0.41	18.56±1.46	23.26±1.02

*Disintegration time(min)

TABLE 11. Thickness, Hardness and Disintegration Time of Experimental Tablet Prepared from Coated Granules Containing Corn Starch as Filler

Formulations	Thickness(mm) +SD	Hardness(Kp) +SD	DT*
10%C1	5.01±0.11	6.79±1.18	2.02±0.22
10%C2	4.85±0.25	7.11±0.75	2.79±1.12
10%C3	4.87±0.42	10.88±1.32	2.15±0.42
10%C4	4.70±0.27	11.78±1.56	6.71±1.57
10%C5	4.75±0.29	15.96±1.97	3.12±0.87
10%C6	4.67±0.15	18.56±2.31	33.39±2.21
15%C1	5.11±0.35	7.29±1.18	1.09±0.77
15%C2	4.71±0.16	7.59±1.17	4.12±1.27
15%C3	5.02±0.31	12.15±1.27	3.27±0.19
15%C4	4.65±0.25	12.86±1.38	12.17±1.87
15%C5	4.83±0.24	16.78±1.31	4.77±0.33
15%C6	4.59±0.31	17.59±1.47	23.56±1.27
20%C1	4.95±0.35	7.89±1.27	0.93±0.89
20%C2	5.23±0.21	7.78±0.88	3.77±0.78
20%C3	4.81±0.21	12.67±1.32	1.79±0.76
20%C4	5.01±0.33	13.29±1.26	10.27±1.88
20%C5	4.83±0.41	17.59±2.10	5.19±0.85
20%C6	5.02±0.41	17.87±1.27	38.21±2.13

*Disintegration time(min)

TABLE 12. Thickness, Hardness and Disintegration Time of Experimental Tablet Prepared from Coated Granules Containing Emcompress® as Filler

Formulations	Thickness(mm) +SD	Hardness(Kp) +SD	DT*
10%E1	4.79±0.28	6.32±1.29	1.59±0.23
10%E2	4.68±0.27	7.12±0.73	5.59±1.65
10%E3	4.56±0.21	12.15±1.33	2.56±0.78
10%E4	4.45±0.31	13.59±0.85	18.29±2.56
10%E5	4.41±0.32	16.29±1.25	5.12±0.25
10%E6	4.39±0.23	17.21±1.21	40.56±3.25
15%E1	4.82±0.25	7.11±0.59	2.02±0.57
15%E2	4.69±0.33	8.33±0.75	4.59±1.20
15%E3	4.80±0.41	12.69±0.98	2.13±0.49
15%E4	4.82±0.21	13.33±1.23	12.16±2.45
15%E5	4.65±0.23	17.21±1.21	6.03±0.52
15%E6	4.88±0.17	19.22±1.42	41.25±3.21
20%E1	5.52±0.16	7.59±1.12	1.49±0.32
20%E2	5.31±0.22	7.32±1.21	4.32±1.02
20%E3	5.43±0.32	13.15±0.58	2.20±0.59
20%E4	5.16±0.21	14.22±0.97	20.63±3.01
20%E5	5.16±0.45	19.12±1.05	5.45±0.34
20%E6	5.03±0.31	19.28±1.45	45.51±2.63

*Disintegration time(min)

TABLE 13. Thickness, Hardness and Disintegration Time of Experimental Tablet Prepared from Coated Granules Containing Lactose as Filler

Formulations	Thickness(mm) +SD	Hardness(Kp) +SD	DT*
10%L1	5.08±0.32	8.21±1.26	2.01±0.79
10%L2	4.91±0.25	8.98±0.79	4.21±1.24
10%L3	4.87±0.45	13.16±1.37	2.17±0.42
10%L4	4.73±0.16	14.19±1.21	15.12±2.15
10%L5	4.79±0.11	16.55±1.32	3.03±0.78
10%L6	4.65±0.42	17.76±1.33	30.21±1.66
15%L1	5.12±0.25	9.01±1.26	1.55±0.26
15%L2	4.93±0.39	9.24±1.26	5.16±1.89
15%L3	4.97±0.36	12.41±1.31	3.84±0.91
15%L4	4.79±0.21	14.55±1.37	12.21±2.96
15%L5	4.92±0.31	17.21±1.12	5.79±0.66
15%L6	4.73±0.15	18.19±1.31	35.12±2.18
20%L1	5.43±0.59	8.16±0.76	1.03±0.34
20%L2	5.24±0.32	8.91±1.03	5.67±1.32
20%L3	5.21±0.43	11.25±1.27	2.75±0.25
20%L4	5.20±0.41	12.34±1.51	19.21±1.52
20%L5	5.18±0.33	16.13±1.46	4.15±0.56
20%L6	5.03±0.15	17.16±1.13	36.29±2.19

*Disintegration time(min)

From the obtained data thickness of the tablets increased when increasing level of coating at fixed compressional force. But increasing the compressional force on the tablet decreased tablets thickness. At the same level of coating, tablets prepared from granules containing Emcompress® as filler seemed to give the lowest thickness, the hightest thickness was observed for tablets prepared from granules containing Avicel PH101® as filler (Formulation 20%A1). Average value of hardness increased when compressional force was increased and increasing level of coating the hardness was found to be slightly increased. Disintegration times of tablets containing Explotab® as disintegrant were faster than tablets without Explotab® and less SD were observed. At the same level of coating tablets containing Emcompress® as granular filler gave the highest disintegration time. With increasing level of coating ,disintegration time was slightly increased.

3.2 Dissolution Profiles of Theophylline Tablets

Drug release from tablets containing various percent of ethylcellulose coated granules (10, 15, 20%), various type of fillers in granules (Avicel PH101®, corn starch, Emcompress®, lactose), various applied compressional force (500, 1000, 1500 lbs) and containing Explotab® as disintegrant or without Explotab® were

studied by USP paddle method in pH change method. The amount of drug release againsts time are presented in Table 23-26(Appendix).

3.2.1 Influence of Coating Level on the Dissolution Profiles of Theophylline Tablets

In order to investigate this effect, the percent release of theophylline from tablet prepared from granules containing various fillers which coated by different percent levels of ethylcellulose and compressed to tablet at the same compressing force were compared. They are shown graphically in Figure 35-42.

Figure 35-38 show the cumulative percent release of theophylline from tablets prepared form coated granule containing various fillers with Explotab® as tablet disintegrant. Figure 39-42 show cumulative percent release of theophylline from tablets prepared from coated granules containing various fillers without disitegrant. Almost of them showed amount of drug release decreased when increased percent ethylcellulose coated (10%>15%>20%).

These results agreed with the results obtained in coated granules studied. However, some dissolution profiles, for example;15% coated granules gave release profile close to 10% or 20% coated granules such as in tablet containing corn starch as filler in

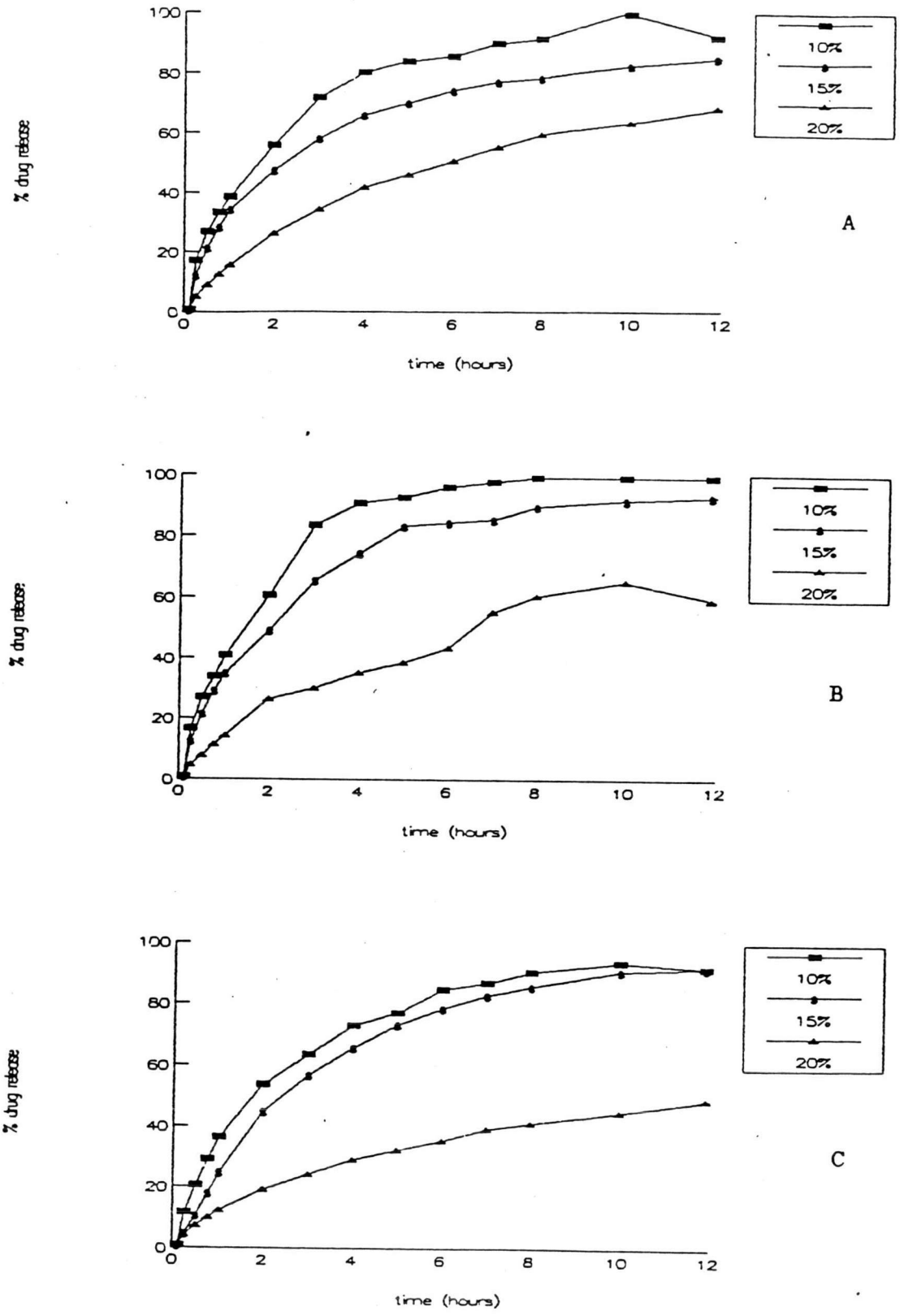


Figure 35 Influence of coating levels of granules on theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing Avicel PH101® as filler);

A: Compressed at 500lbs, B: Compressed at 1000 lbs, C: Compressed at 1500 lbs

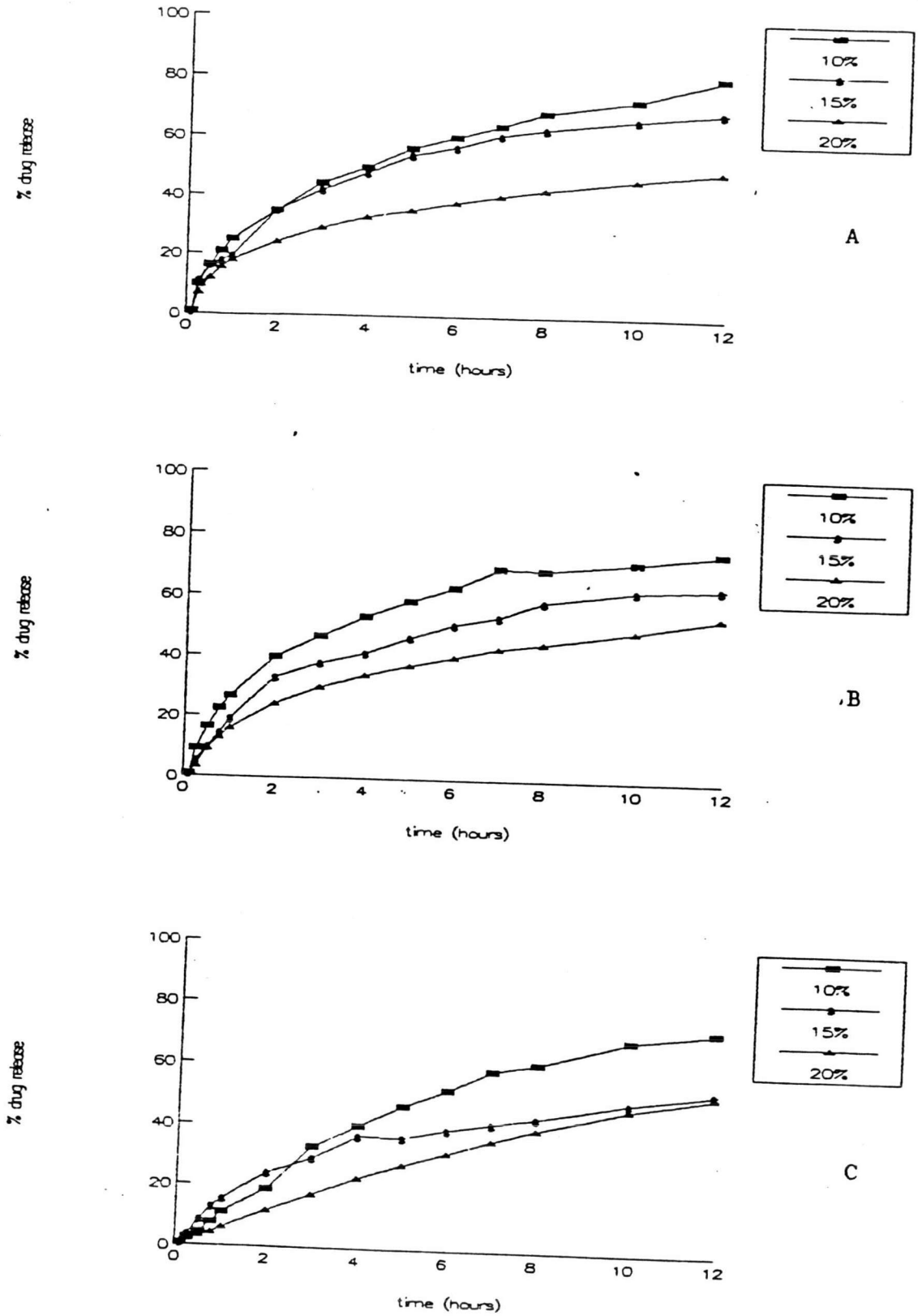


Figure 36 Influence of coating levels of granules on theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing corn starch as filler);

A: Compressed at 500lbs, B: Compressed at 1000lbs,

C: Compressed at 1500 lbs.

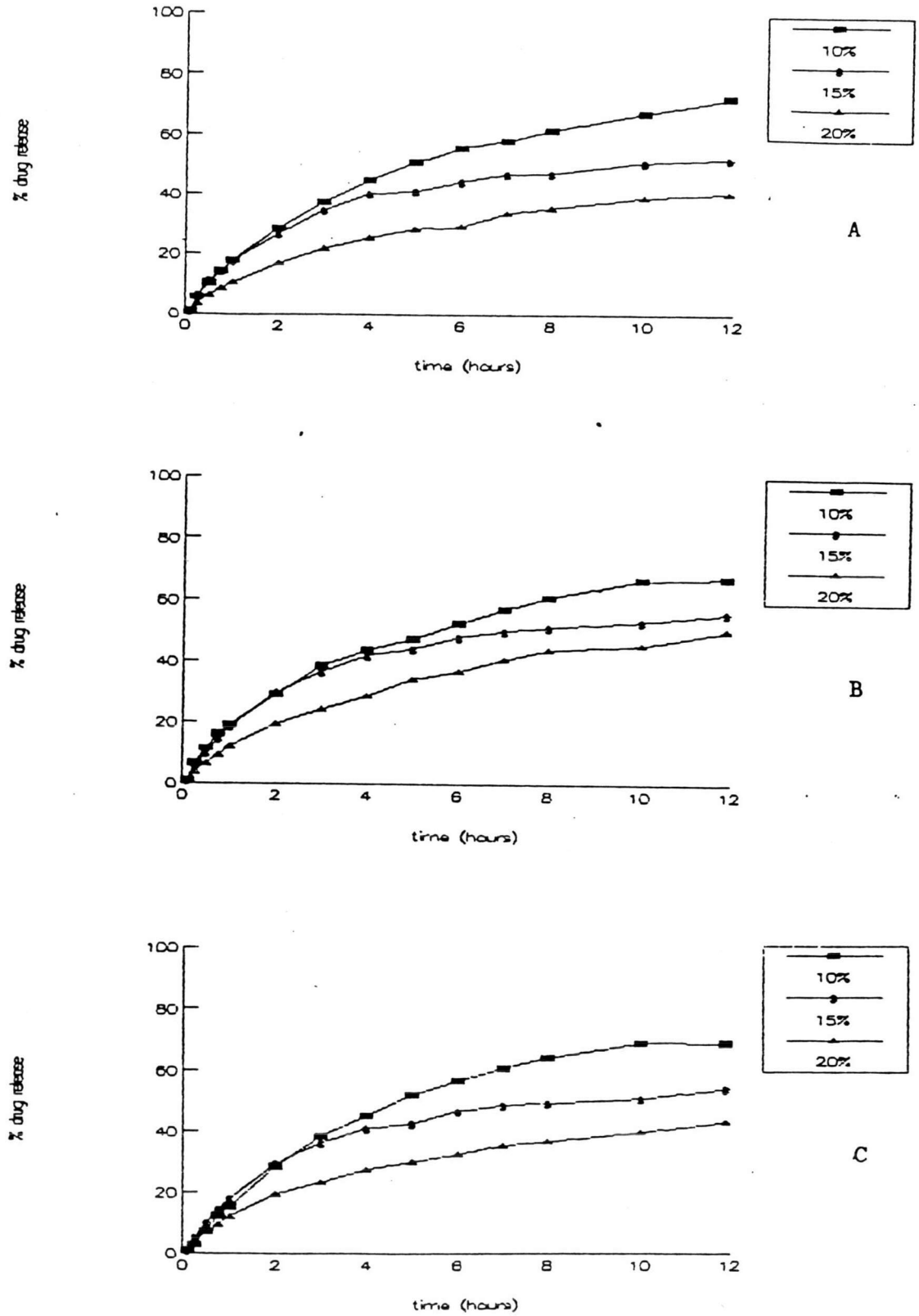


Figure 37 Influence of coating levels of granules on theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing Emcompress® as filler);

A: Compressed at 500lbs, B: Compressed at 1000lbs,

C: Compressed at 1500 lbs

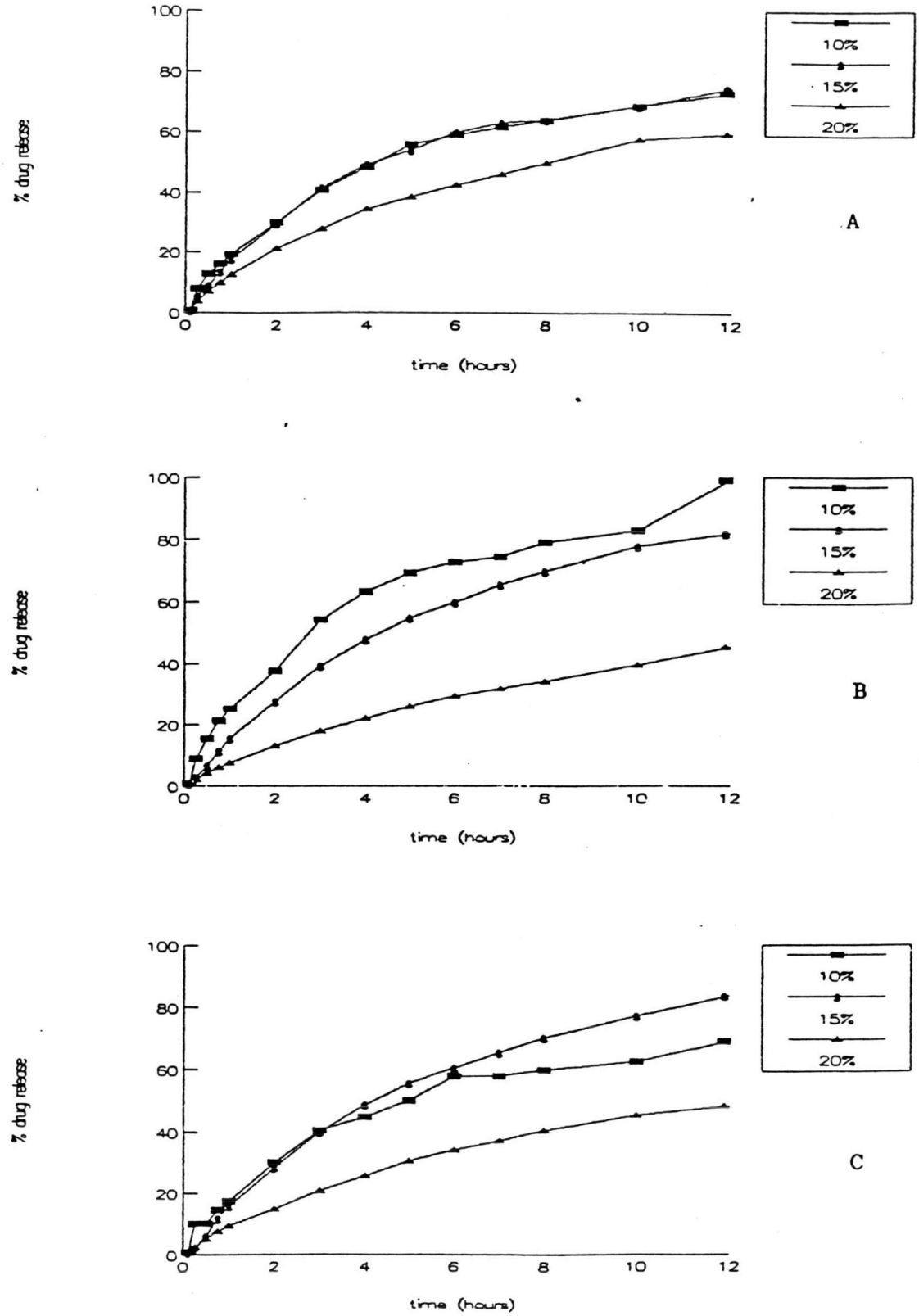


Figure 38 Influence of coating levels of granules on theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing lactose as filler); A: Compressed at 500lbs, B: Compressed at 1000lbs, C: Compressed at 1500lbs.

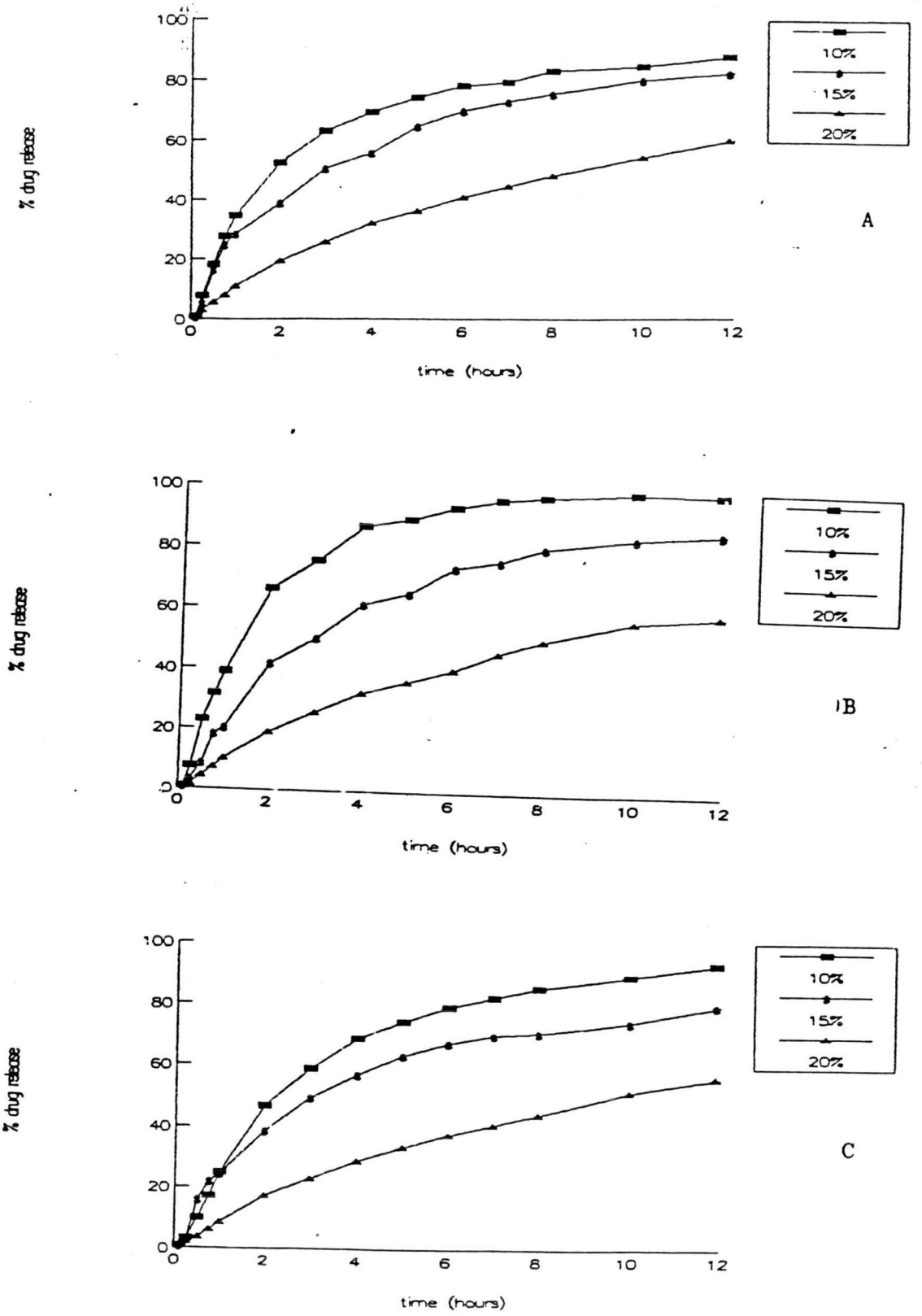


Figure 39 Influence of coating levels of granules on theophylline releaseprofilesfrom tablet without disintegrant (granules containing Avicel PH101^{R} as filler); A: Compressed at 500 lbs, B: Compressed at 1000 lbs, C: Compressed at 1500 lbs)

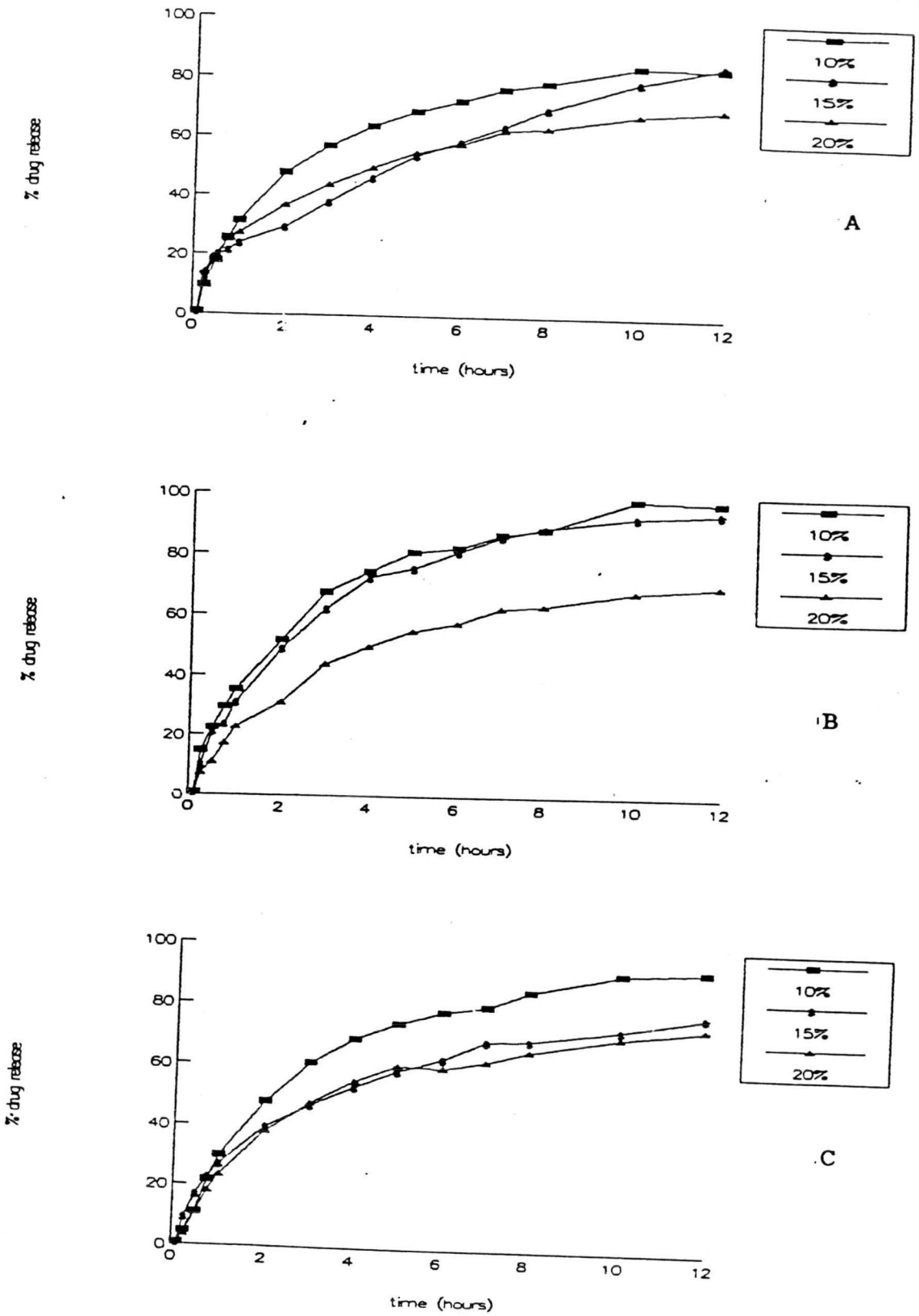


Figure 40 Influence of coating levels of granules on theophylline release profiles from tablet without disintegrant (granules containing corn starch as filler);
A: Compressed at 500 lbs, B: Compressed at 1000 lbs,
C: Compressed at 1500 lbs)

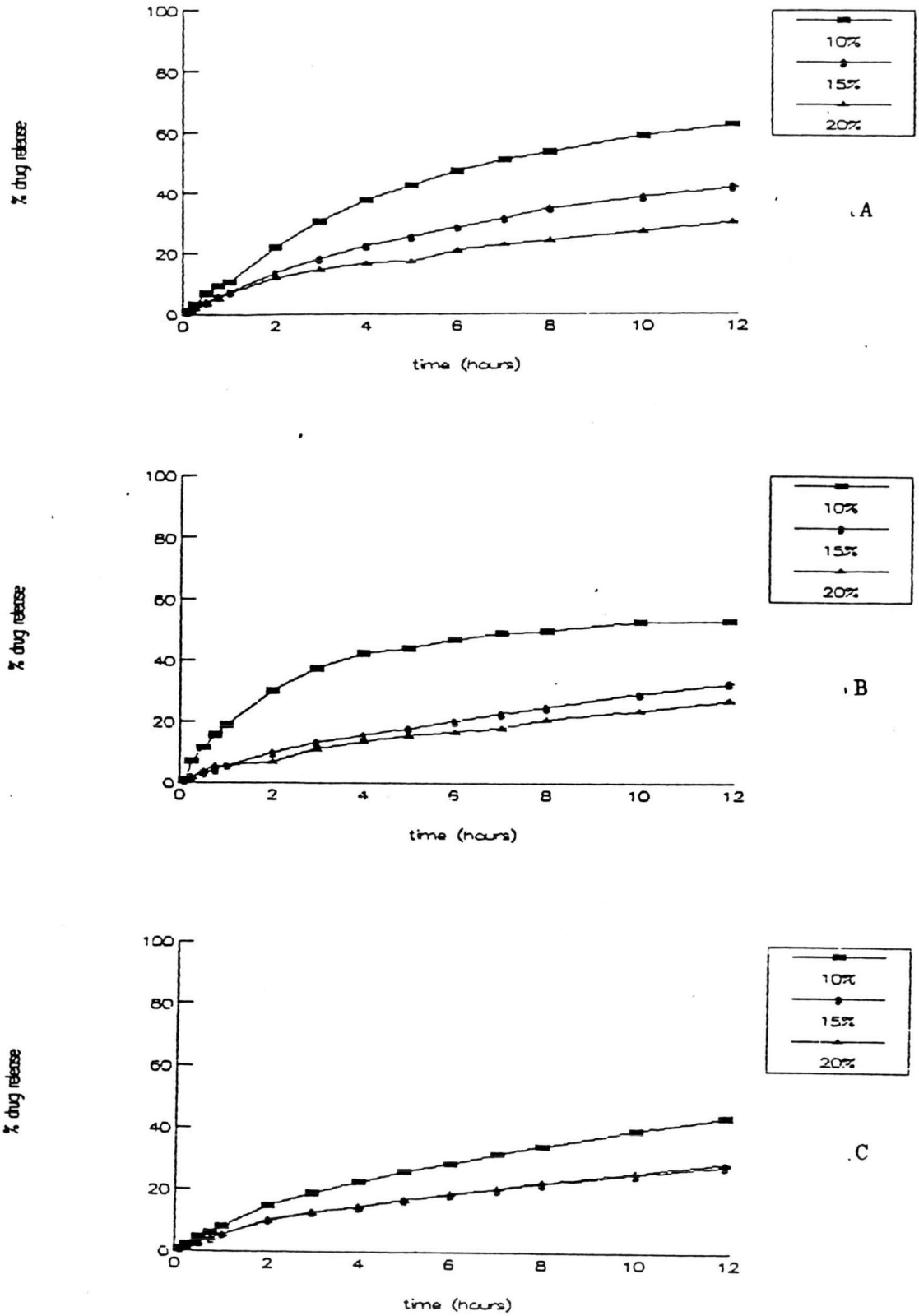


Figure 41 Influence of coating levels of granules on theophylline release profiles from tablet without disintegrant (granules containing Emcompress® as filler); A: Compressed at 500 lbs, B: Compressed at 1000 lbs, C: Compressed at 1500 lbs)

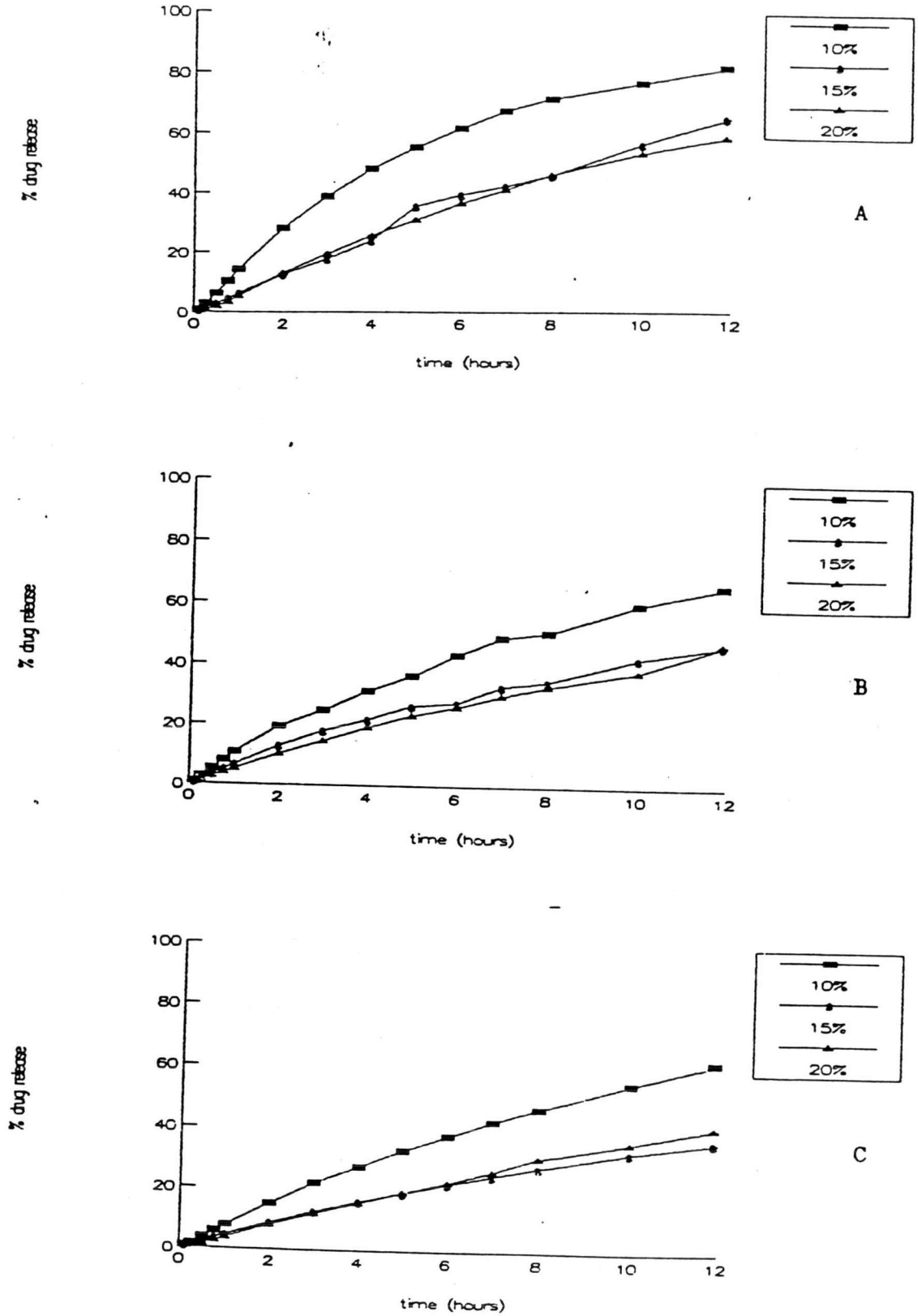


Figure 42 Influence of coating levels of granules on theophylline release profiles from tablet without disintegrant (granules containing lactose as filler);
A: Compressed at 500 lbs, B: Compressed at 1000 lbs,
C: Compressed at 1500 lbs)

granules (Compresed at 1000, 1500 lbs. and without disintegrant) shown in Figure 40B and 40C. The release profile of 15% coated granule was closed to 10% coated granule release profiles when the tablets were compressed at 1000 lbs. but closed to 20% coated granules release profile when compressed at 1500 lbs. Figures 41, 42 show release profiles of tablets containing coated granules with Emcompress® and lactose as granular fillers. At all level of compressional force, it is seen that the release profiles of 15% coated granules were closed to 20% coated granules. These would indicate that not only the coating level or film thickness which affected the release but there were other factors which influenced the release profiles of drug from tablet and seemed difficult to predict such as compressional force.

3.2.2 Influence of Various Fillers in Coated Granules on the Dissolution Profiles of Theophylline Tablets

Four filler excipients (Avicel PH101®, corn stach, Emcompress®, lactose) were evaluated for their influence on release profiles of theophylline tablets. The dissolution profiles in pH change medium are shown in Figure 43-48. These profiles demonstrate a dramatic influence of the filler excipients on the drug release characteristics from the tablet. Drug release was almost highest from tablet containing micorcrystalline cellulose

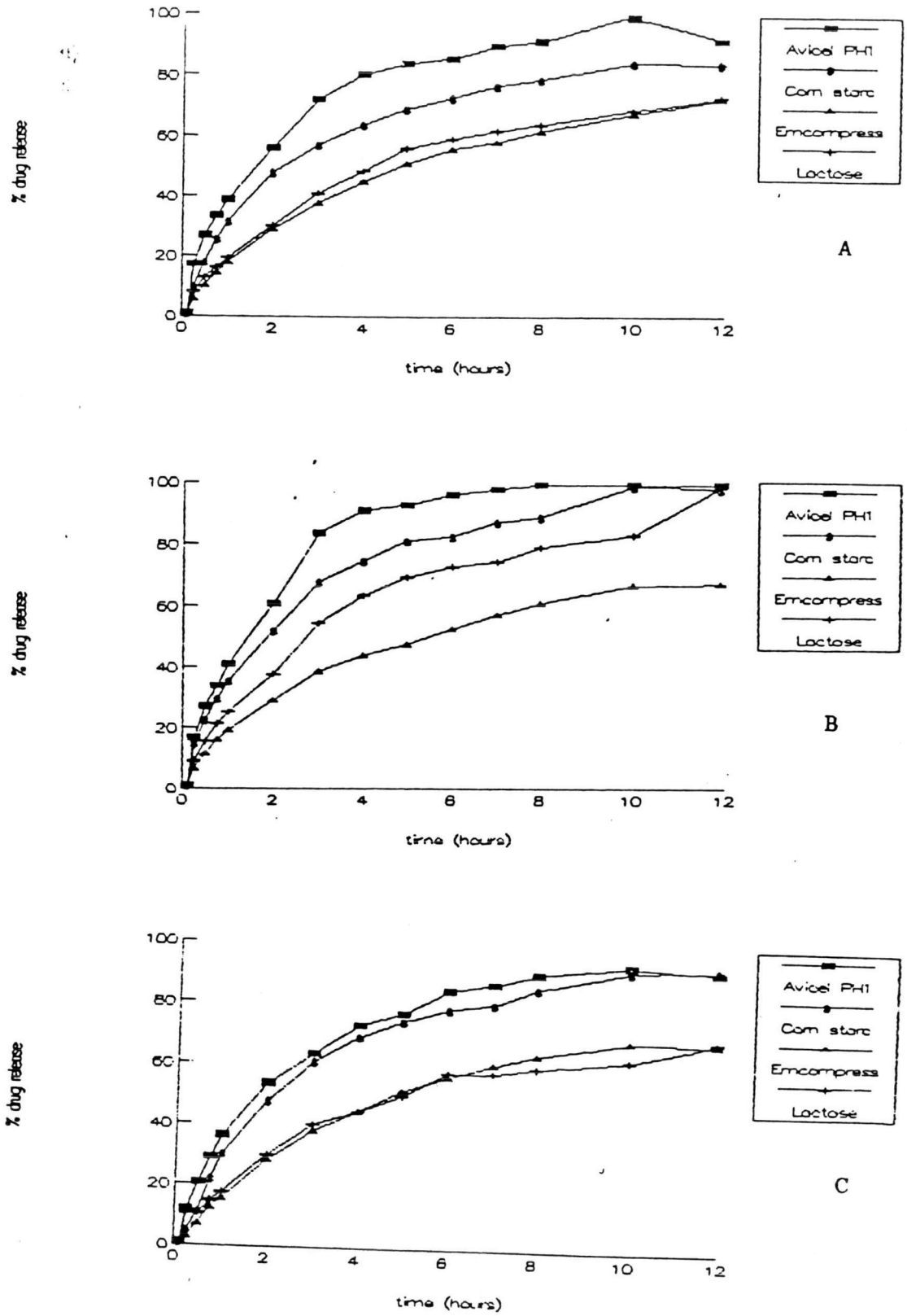


Figure 43 Influence of filler in 10% coated granules on the theophylline release profiles from tablets containing Explotab® as disintegrant;
A: Compressed at 500lbs, B: Compressed at 1000lbs, C: Compressed at 1500lbs)

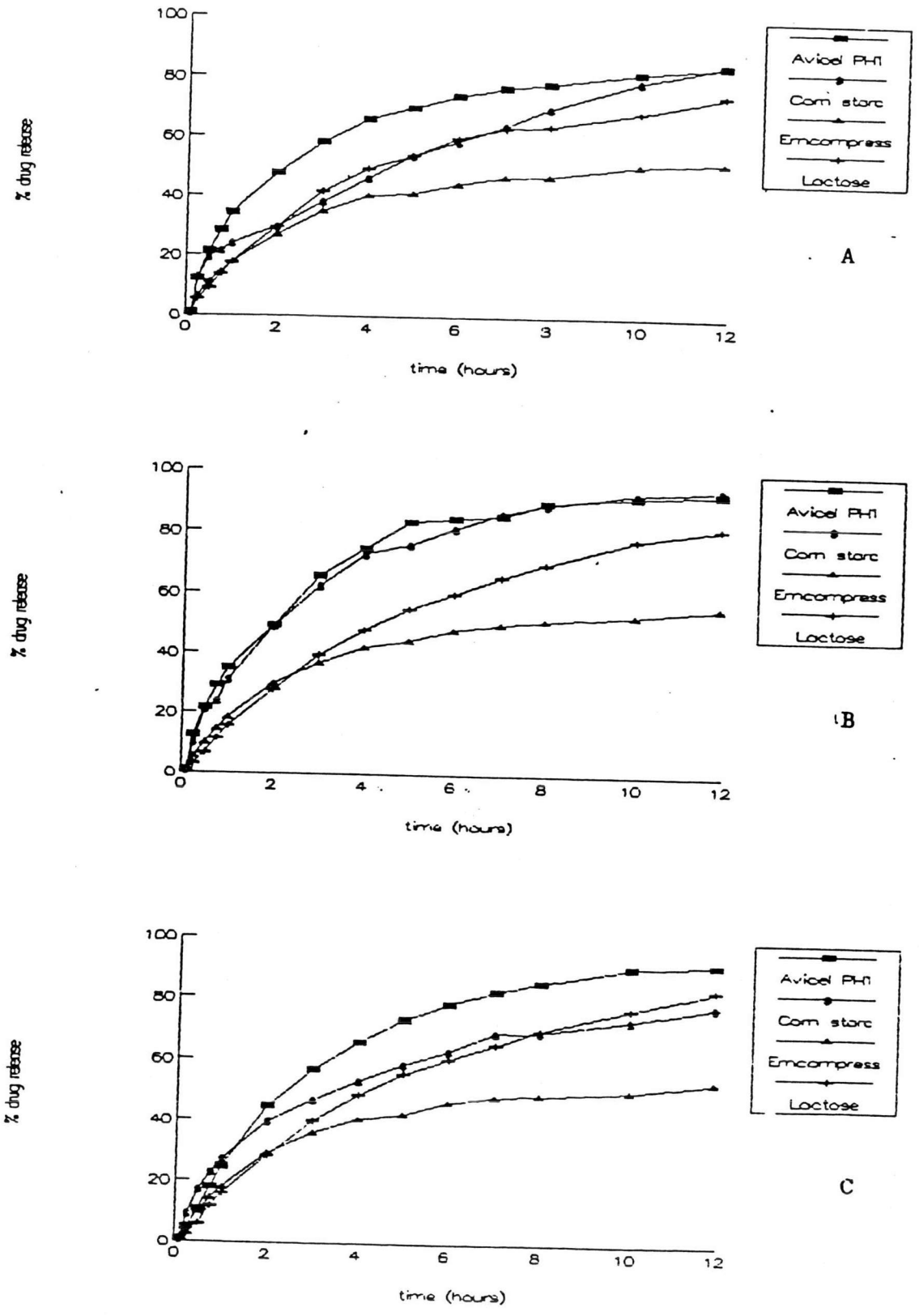


Figure 44 Influence of filler in 15% coated granules on the theophylline release profiles from tablets containing Explotab® as disintegrant;
A: Compressed at 500lbs, B: Compressed at 1000lbs,
C: Compressed at 1500lbs)

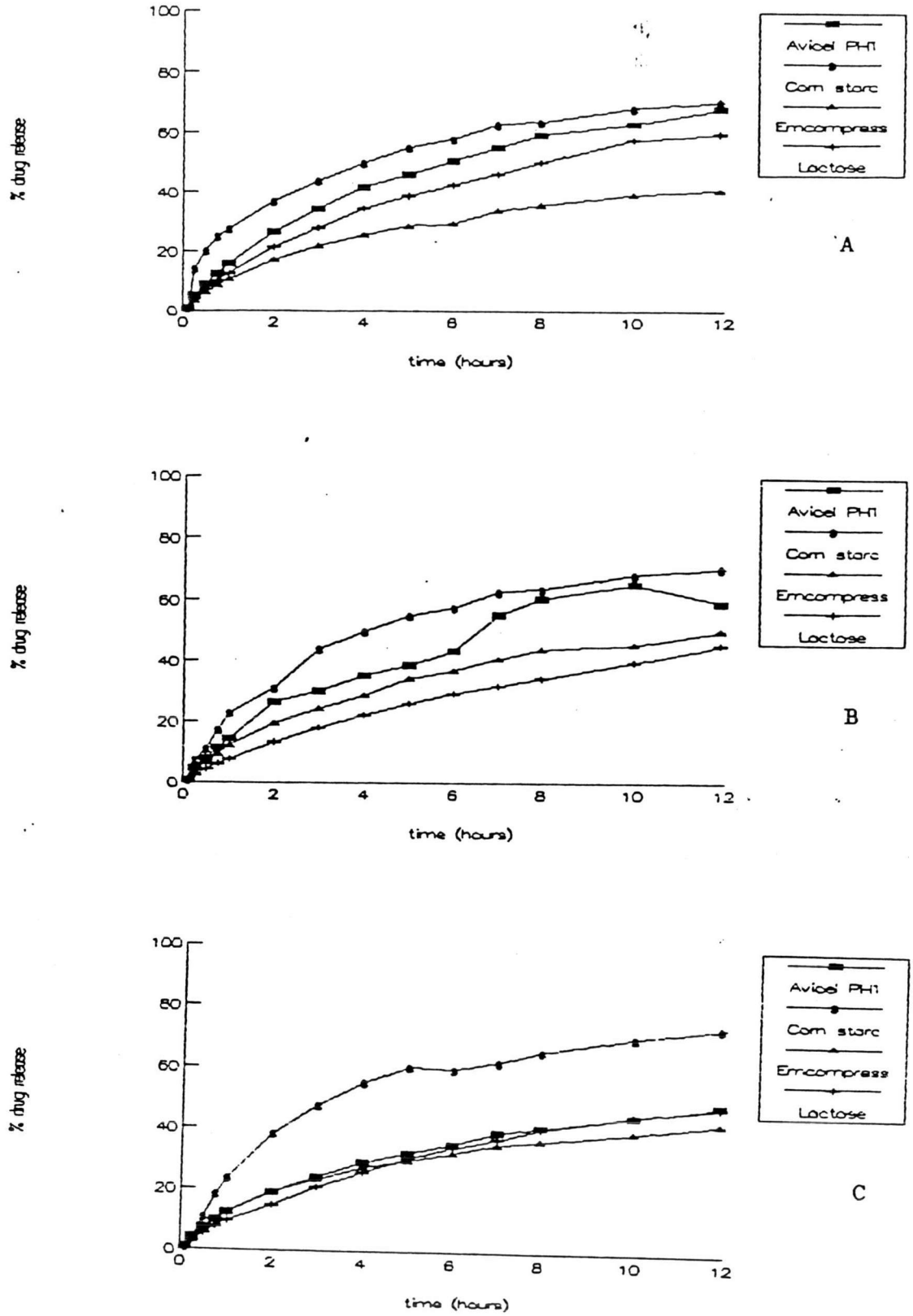


Figure 45 Influence of filler in 20% coated granules on the theophylline release profiles from tablets containing Explotab® as disintegrant;
A: Compressed at 500lbs, B: Compressed at 1000lbs,
C: Compressed at 1500lbs)

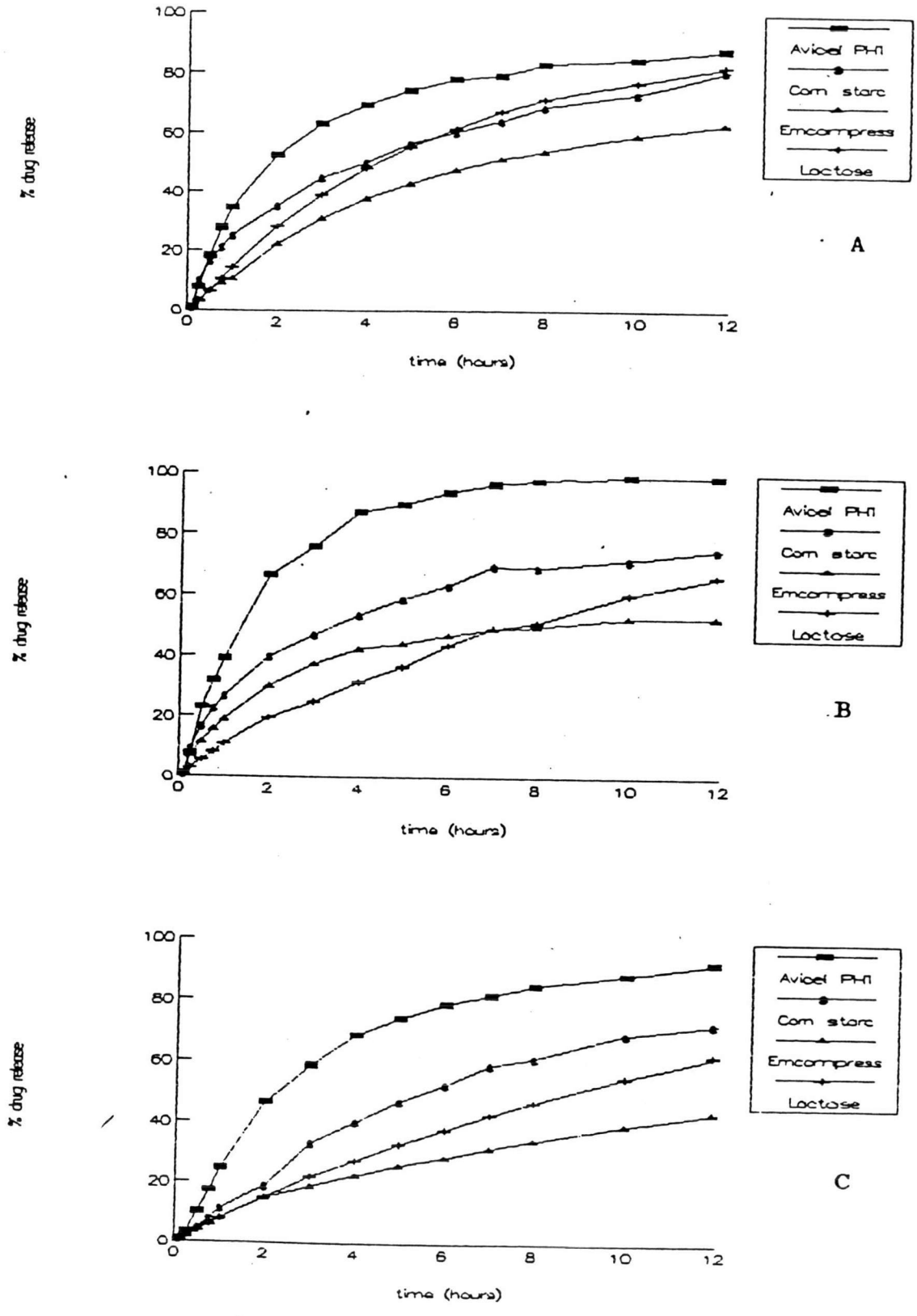


Figure 46 Influence of filler in 10% coated granules on the theophylline release profiles from tablets without disintegrant;

A: Compressed at 500lbs, B: Compressed at 1000lbs, C: Compressed at 1500lbs.

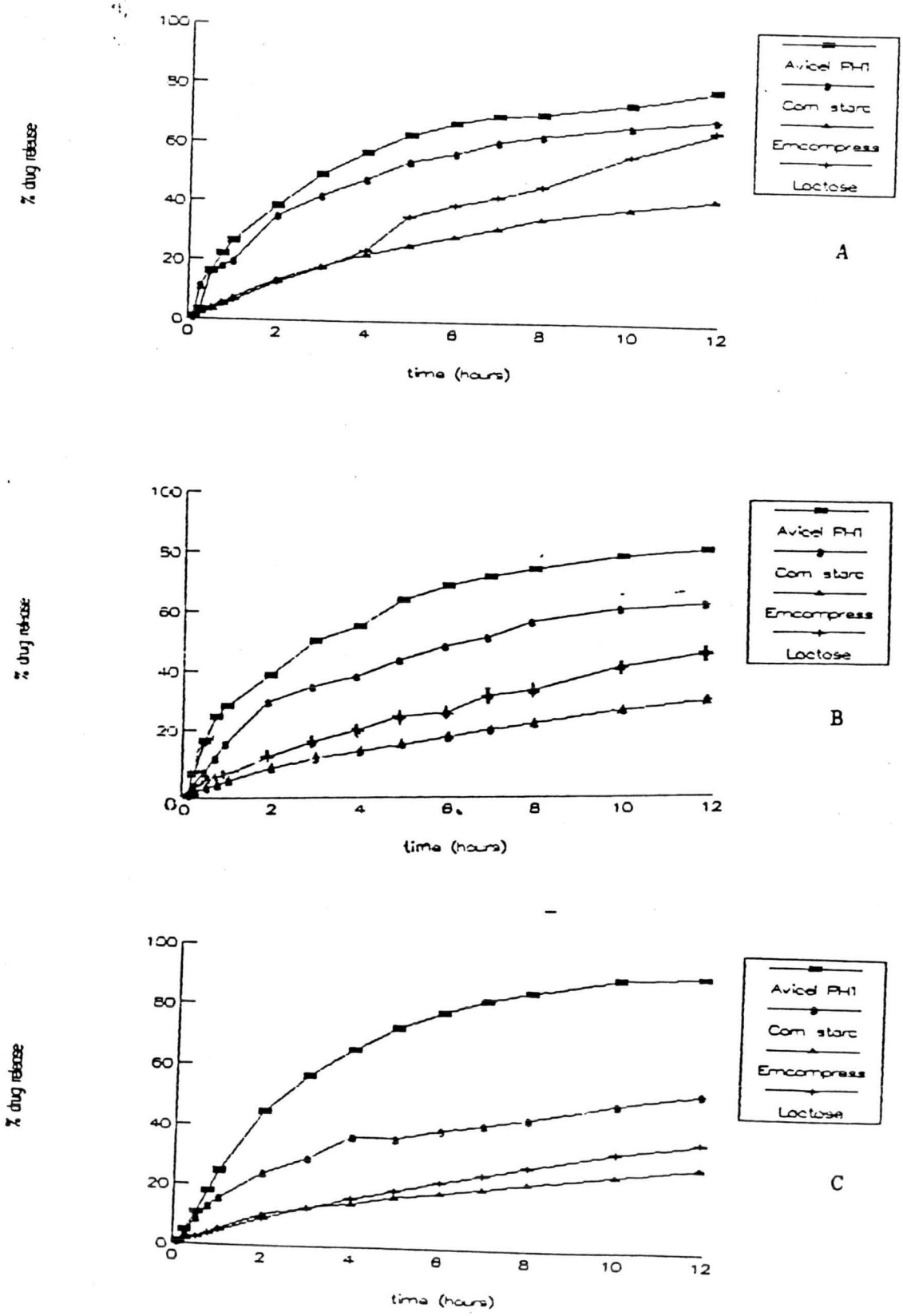


Figure 47 Influence of filler in 15% coated granules on the theophylline release profiles from tablets without disintegrant;

A: Compressed at 500lbs, B: Compressed at 1000lbs, C: Compressed at 1500lbs)

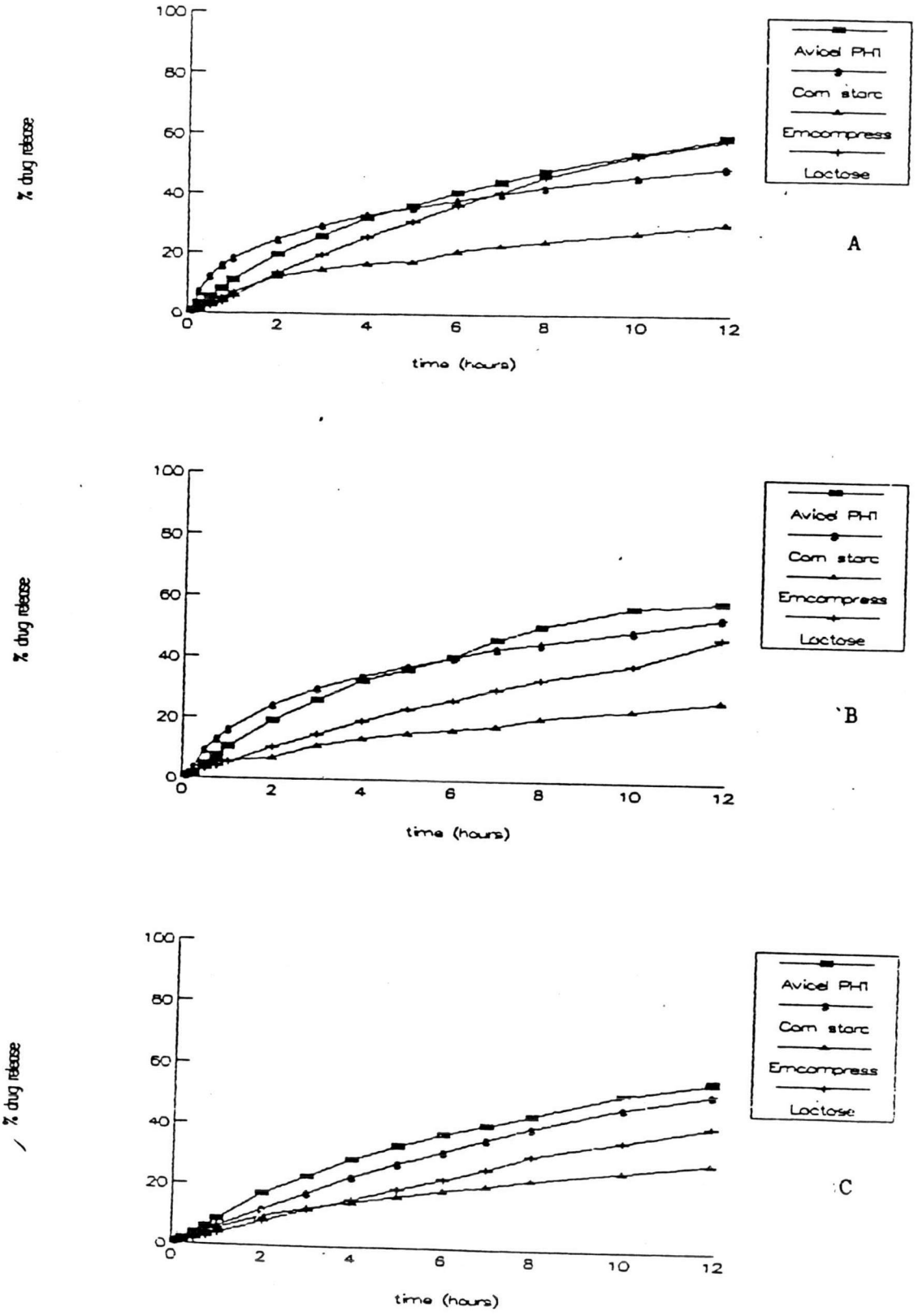


Figure 48 Influence of filler in 20% coated granules on the theophylline release profiles from tablets without disintegrant;

A: Compressed at 500lbs, B: Compressed at 1000lbs, C: Compressed at 1500lbs)

(Avicel PH101®). Tablet containing Emcompress® (dibasic-calcium phosphate) released the smallest amount of drug during 12 hrs period while tablets containing the other fillers, released drug at intermediate amount. This results were similar to the study of the effect of fillers in coated granules.

3.2.3 Influence of Explotab® on the Dissolution Profile of Theophylline Tablets

The investigation of the effect of the disintegrant (Explotab®) was carried out. Tablets prepared by direct compression using Avicel PH101® as direct compression excipient, talcum and magnesium stearate as lubicants. Tablets containing Explotab® and without Explotab® were prepared in each case. The results of the tablets prepared from granules coated with the same level of ethylcellulose and compressional force were compared and shown graphically in Figure 49-60.

From the profiles, they showed that release rates were increased when using Explotab® as disintergrant and the obtained SD(standard deviation of mean) from tablets containing Explotab® were less than from tablets without Explotab®.

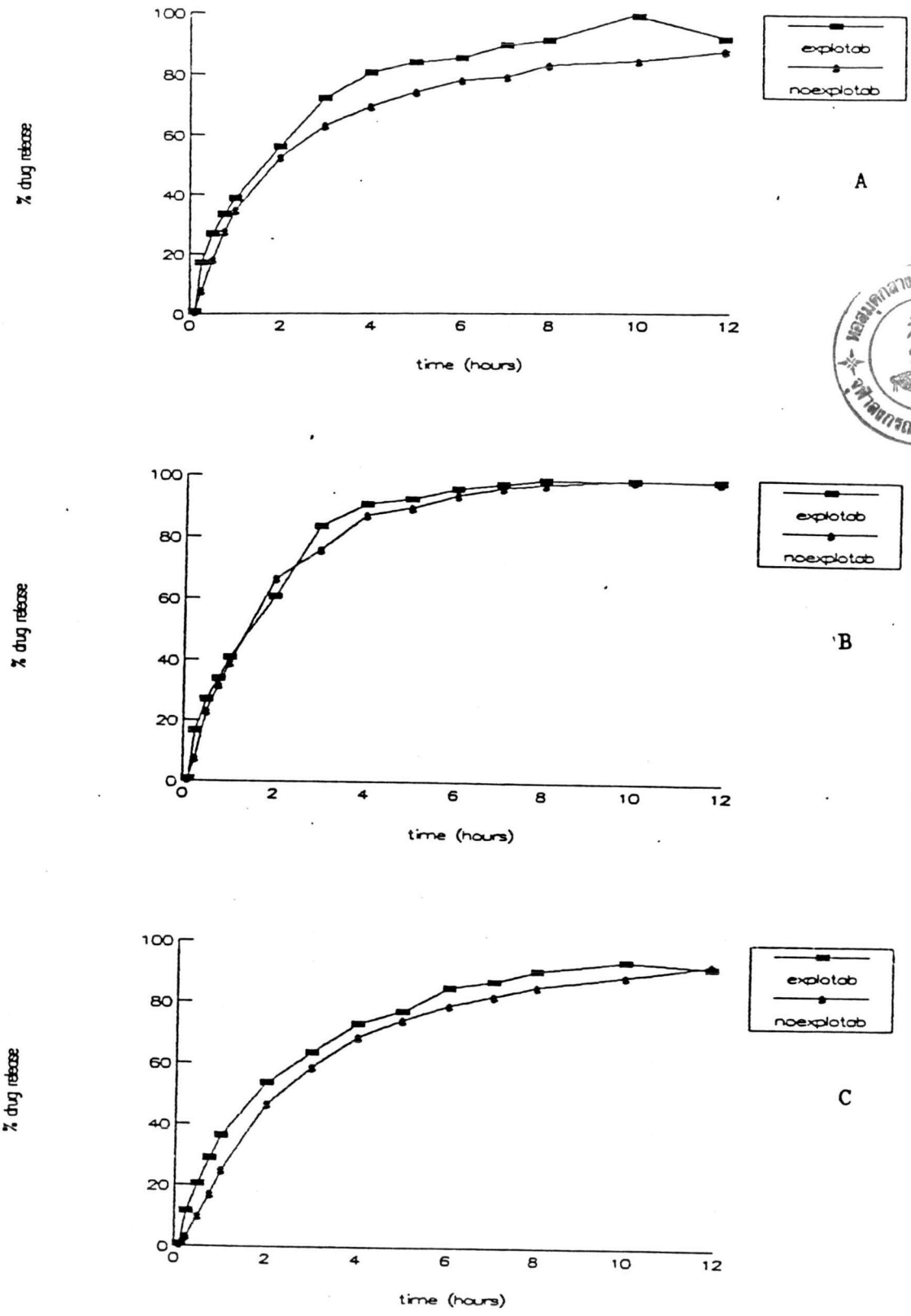


Figure 49 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 10% coated granules with Avicel PH101^{R} as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

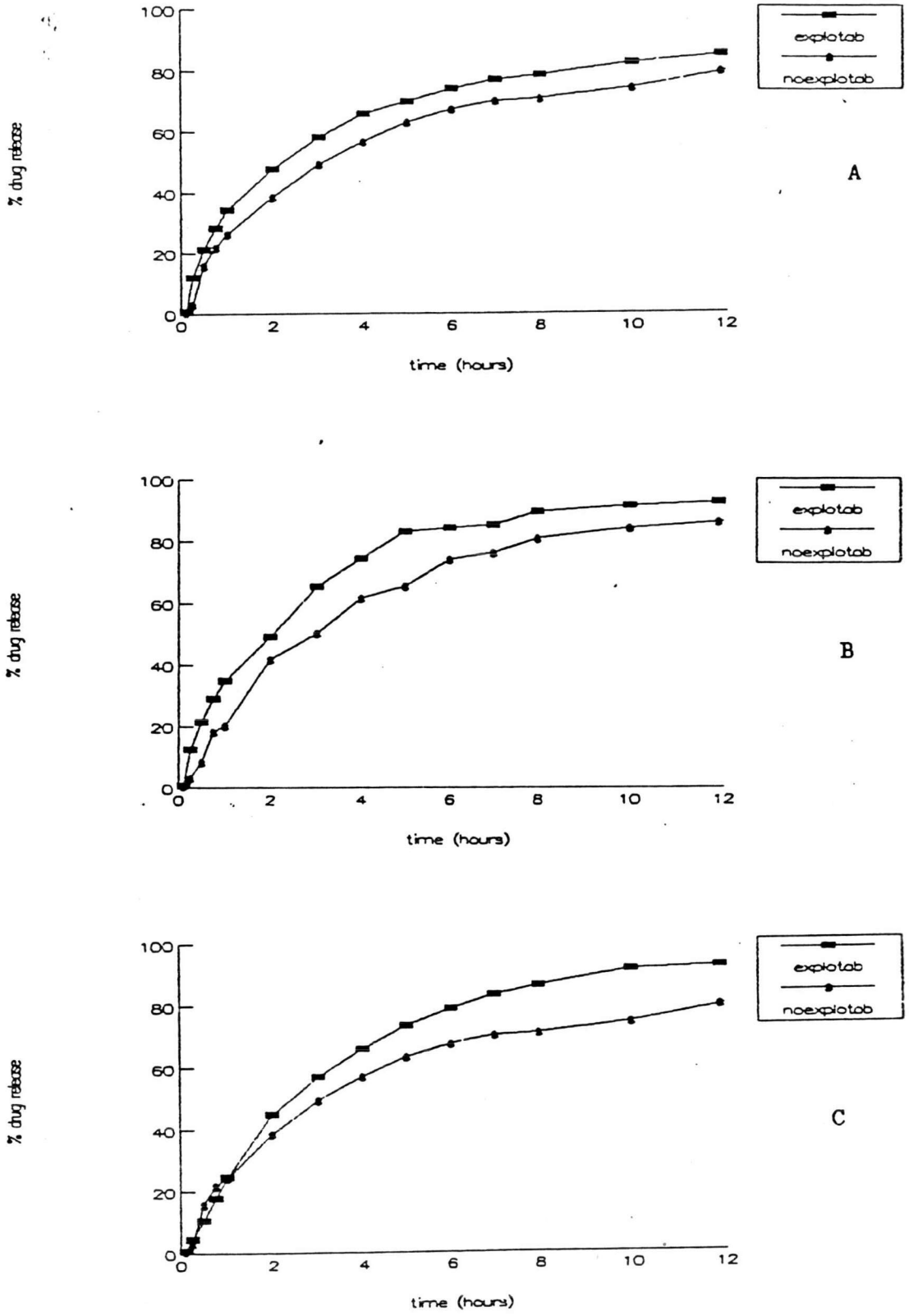


Figure 50 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 15% coated granules with Avicel PH101^{R} as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

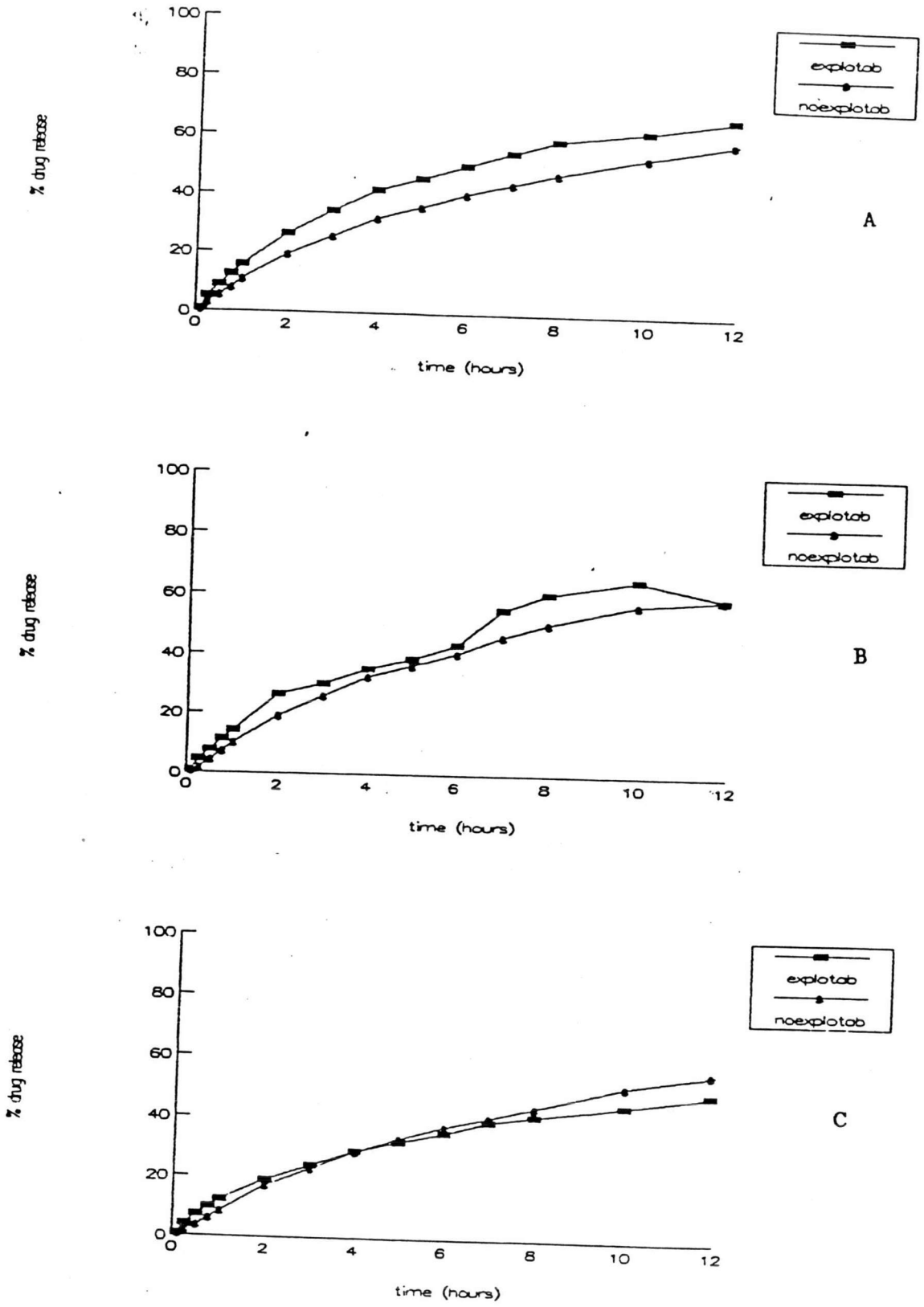


Figure 51 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 20% coated granules with Avicel PH101[R] as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs D: Compressed at 1500 lbs

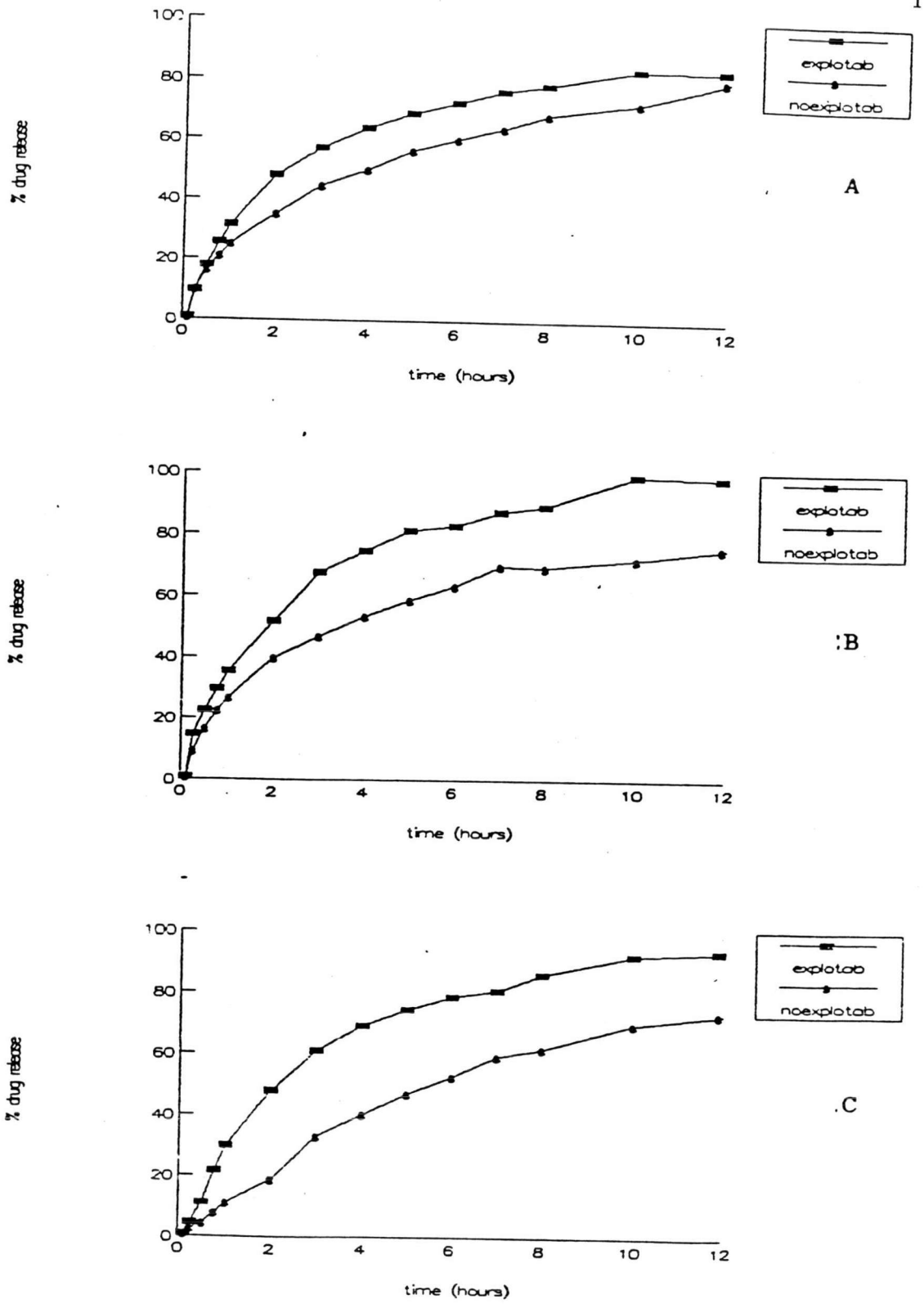


Figure 52 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 10% coated granules with corn starch as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

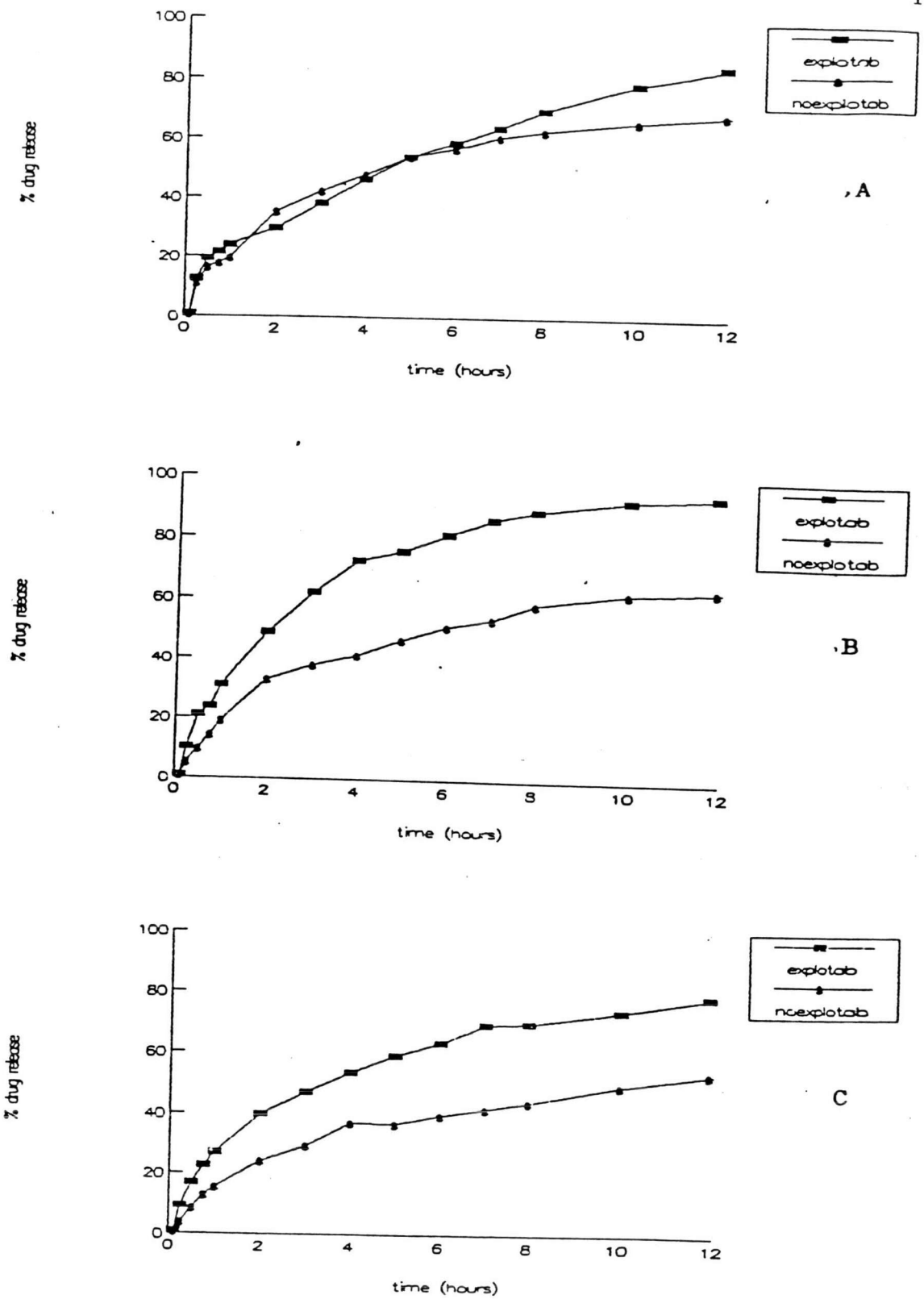


Figure 53 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 15% coated granules with corn starch as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

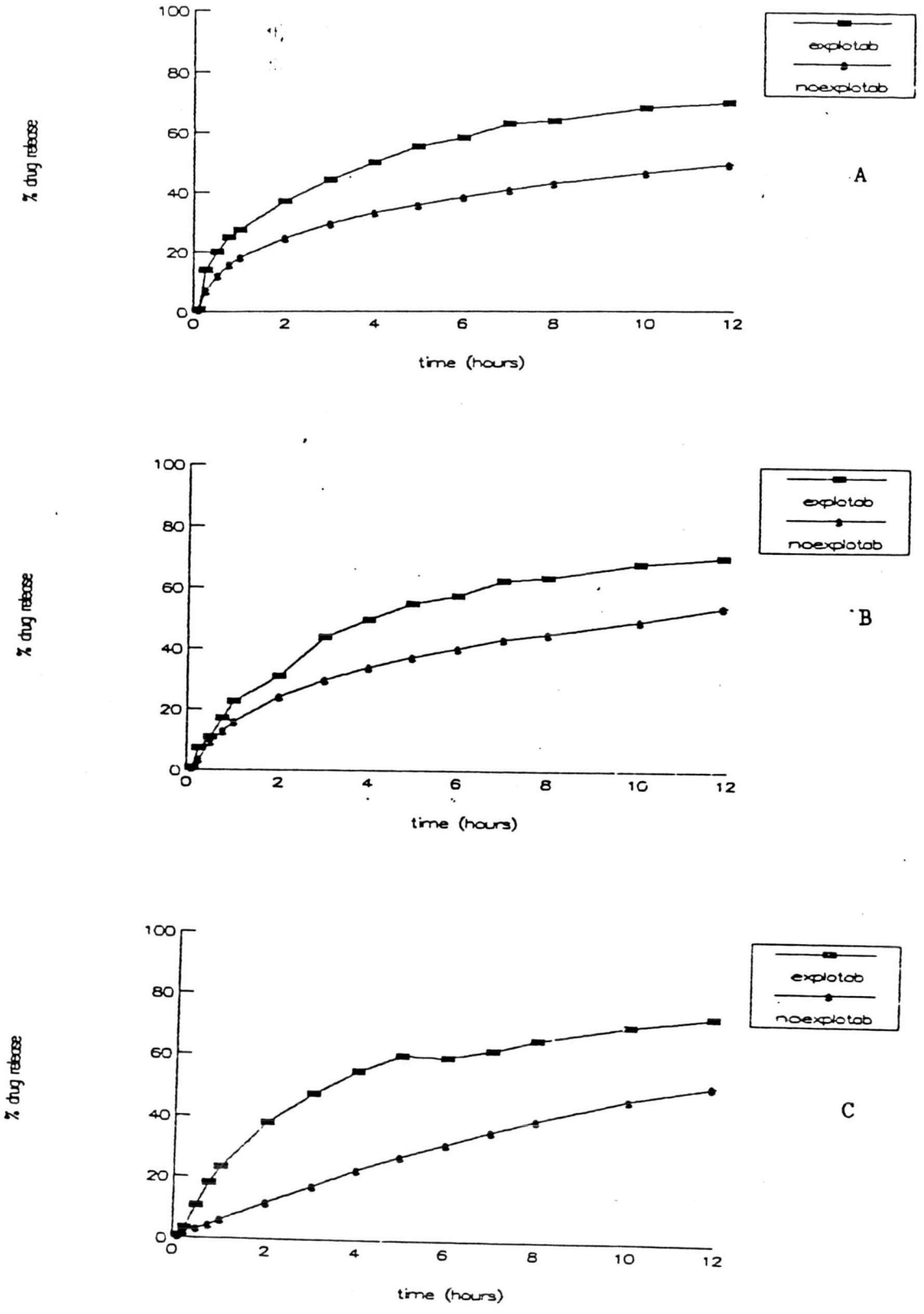


Figure 54 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 20% coated granules with corn starch as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lb

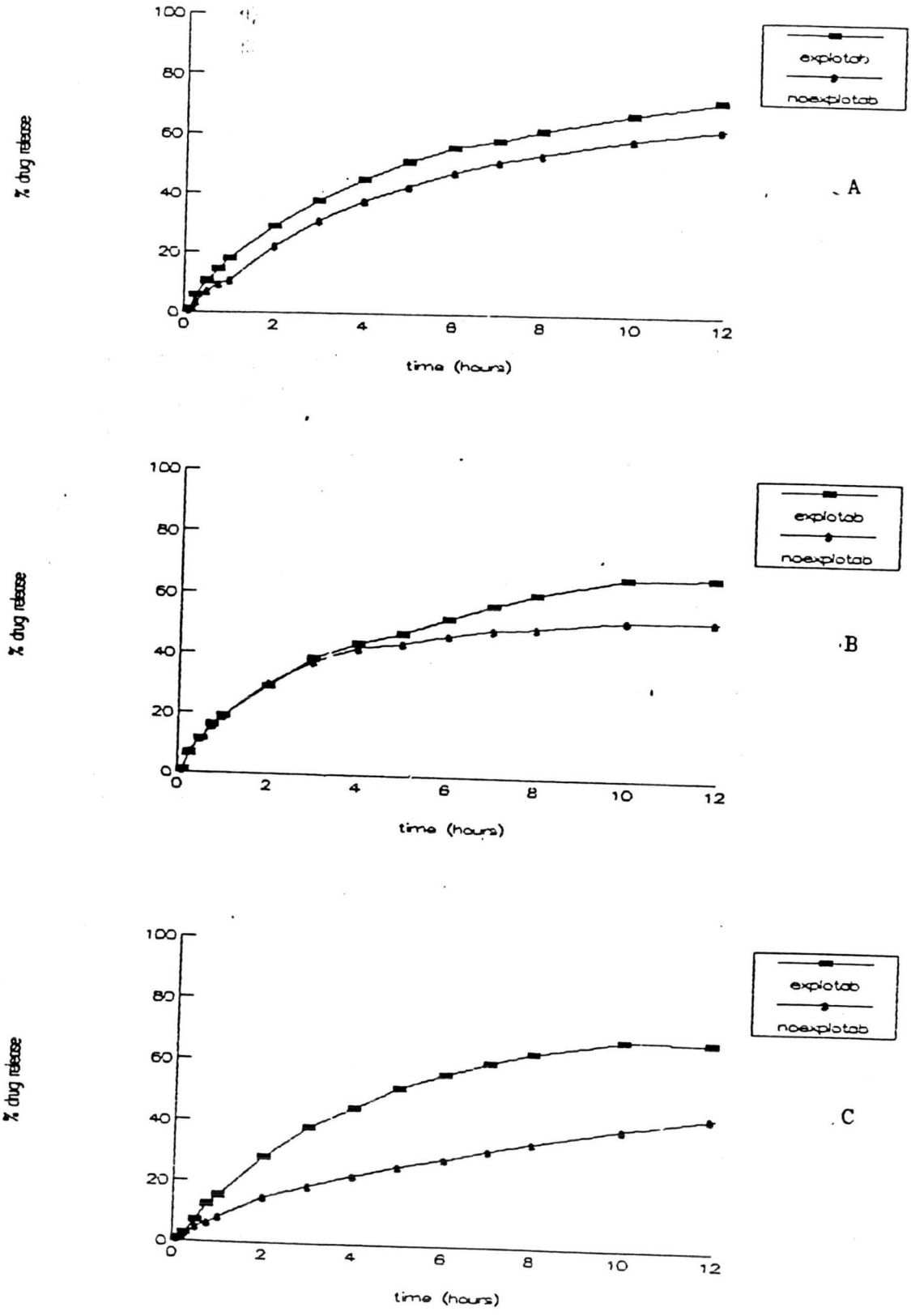


Figure 55 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 10% coated granules with Emcompress® as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

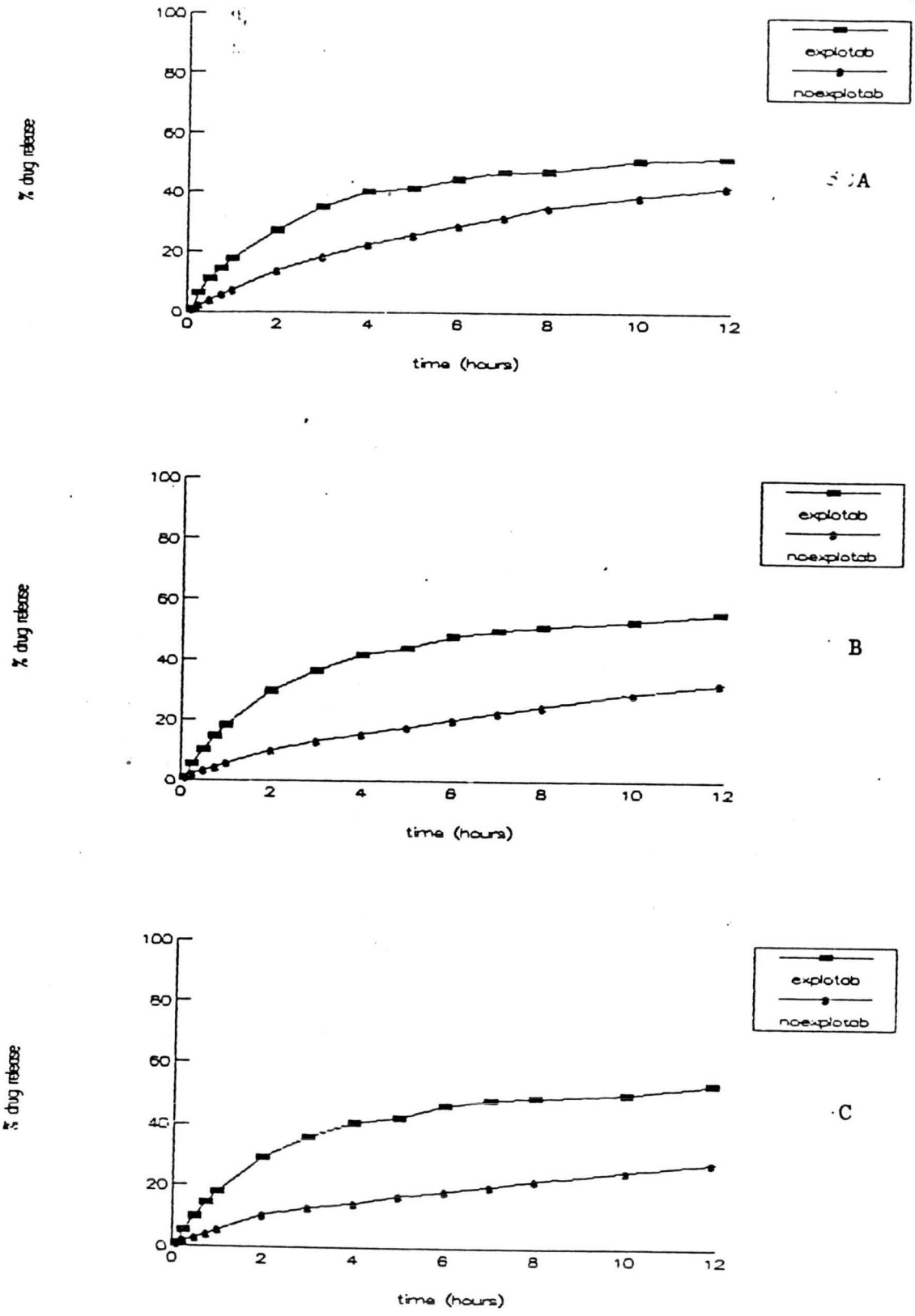


Figure 56 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 15% coated granules with Emcompress® as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

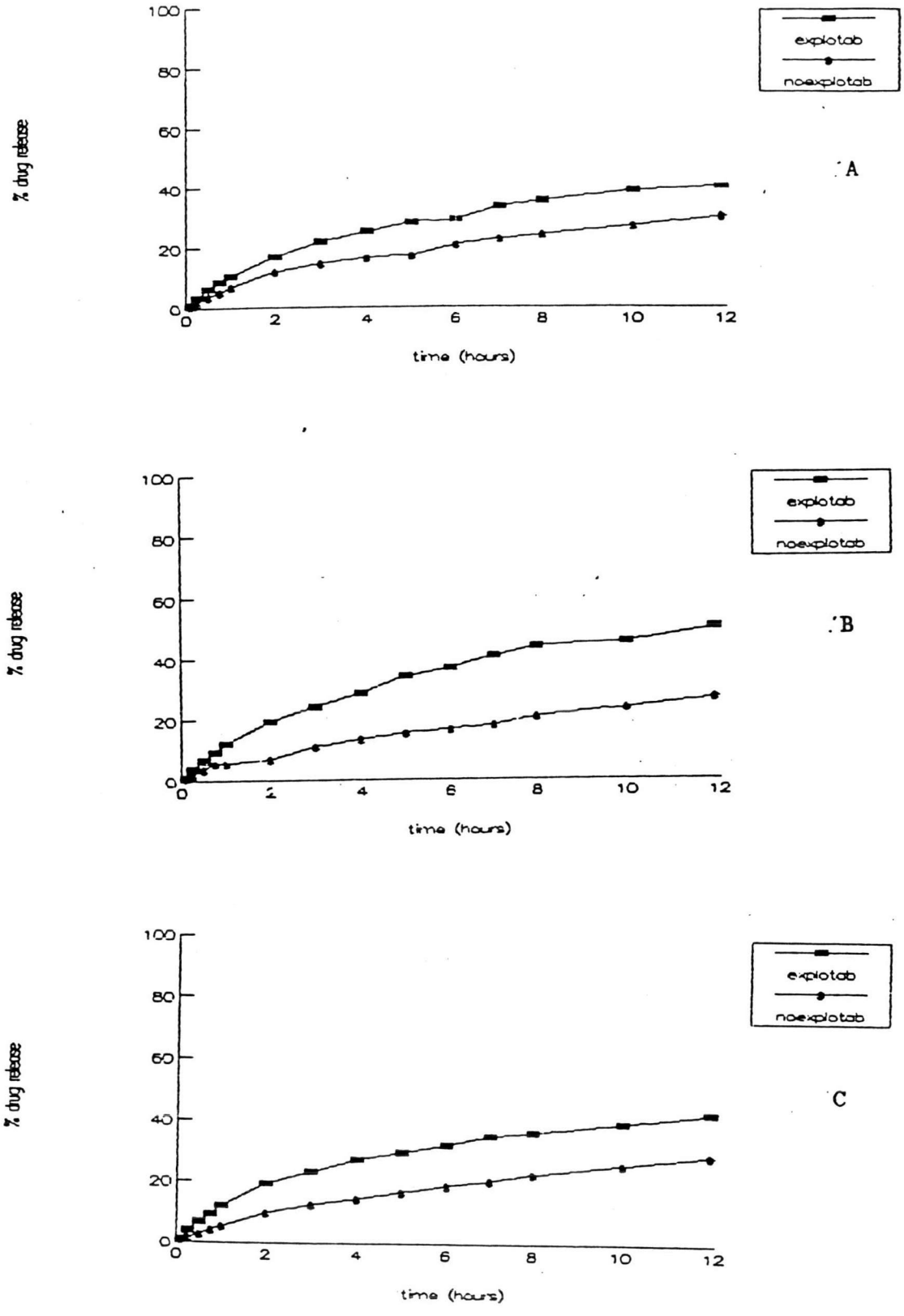


Figure 57 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 20% coated granules with Emcompress® as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500

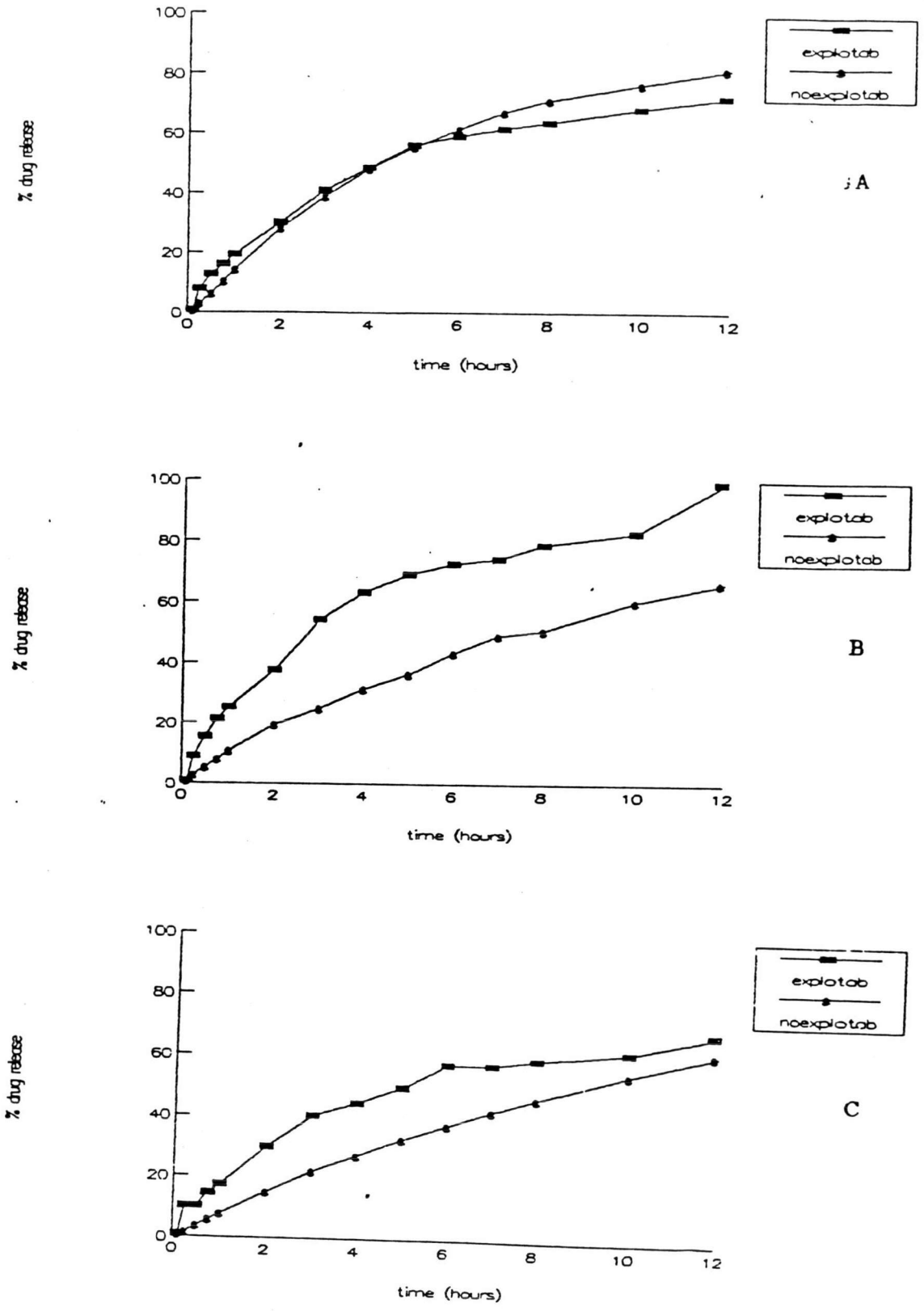


Figure 58 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 10% coated granules with lactose as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

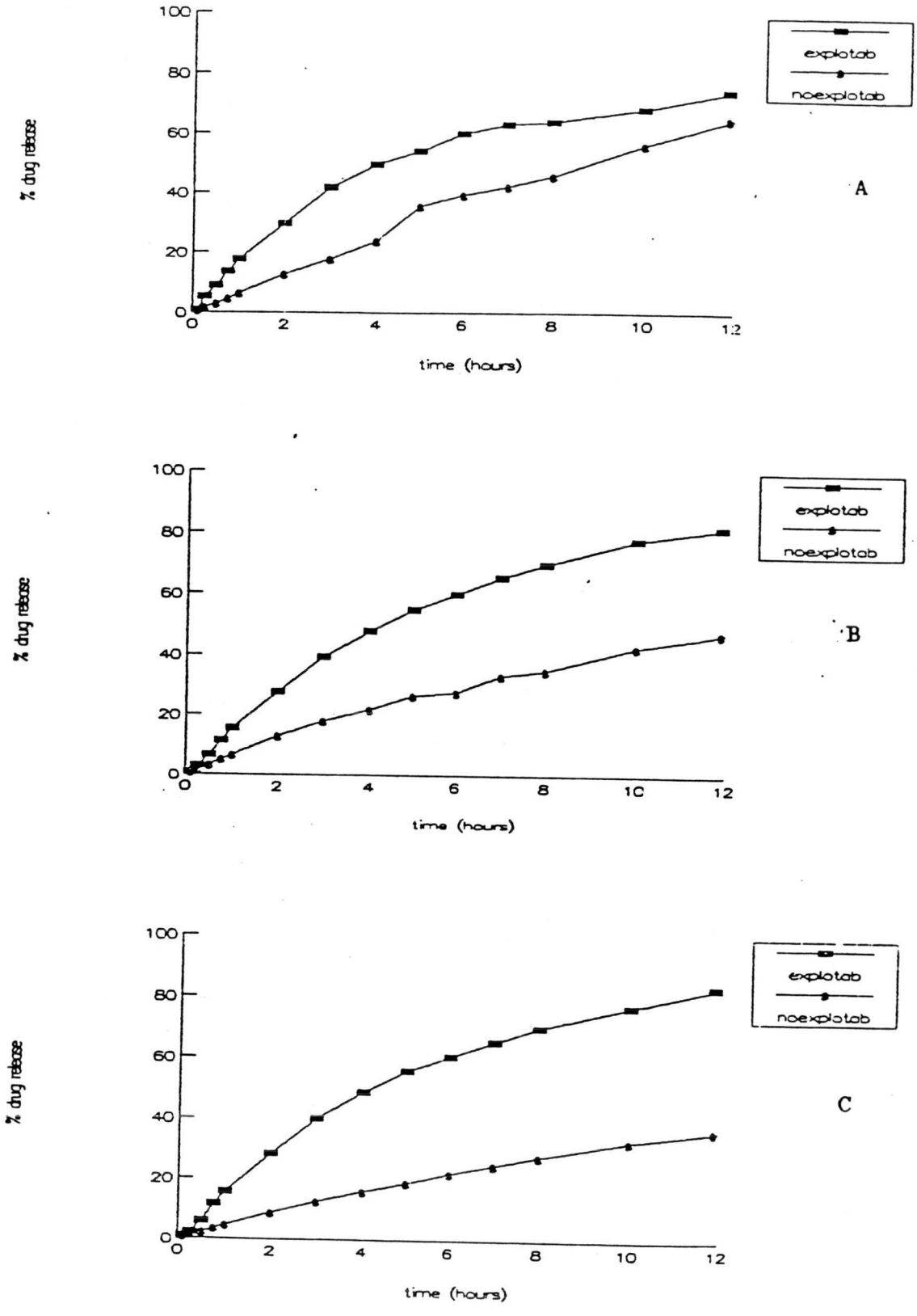


Figure 59 Influence of disintegrant in tablet on Theophylline release profiles from tablet containing 15% coated granules with lactose as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

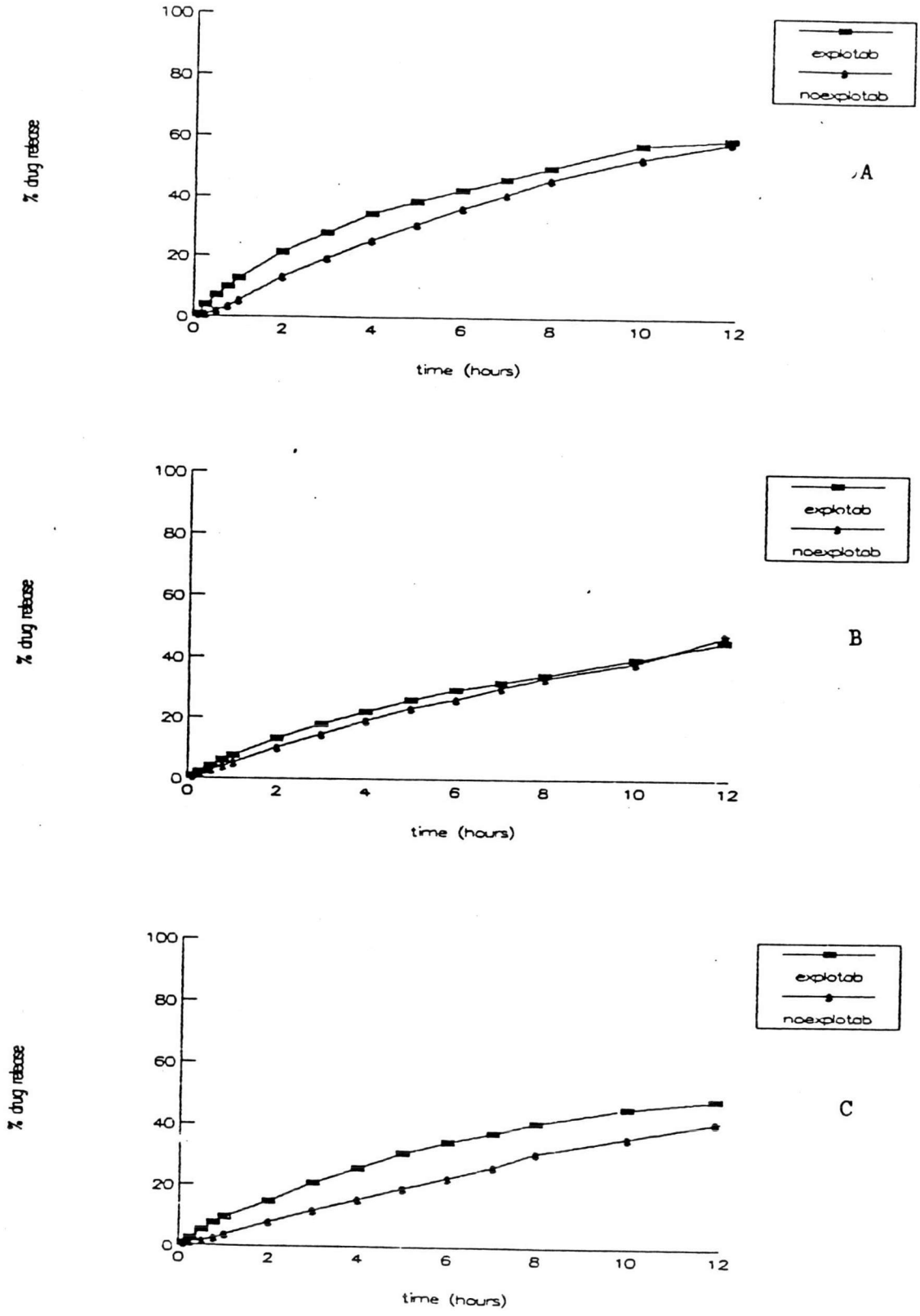


Figure 60 Influence of disintegrant in tablet on theophylline release profiles from tablet containing 20% coated granules with lactose as filler in granules

A: Compressed at 500 lbs

B: Compressed at 1000 lbs C: Compressed at 1500 lbs

3.2.4 Influence of Compressional Force on the Dissolution Profiles of Theophylline Tablets

To investigate the compressional force effect, coated granules were compressed in to tablets by three levels of force (500, 1000, 1500 lbs). The comparative data are shown graphically in Figure 61-68.

The dissolution behavior of tablets prepared from coated granule seemed to be affected by the applied pressure but the relationship between compressional force and dissolution profiles of each coating level of granule was not consistent. For some profiles, it may be possible that the higher compression force (1500/bs) resulted in compaction of granules in tablet, leading to the lower release profile as in Figure 67, 68. But some profiles at higher compression force gave higher release profiles(Fig.65). This may be due to the breakage of the wall of coated granules in tablets. So that the influence of compression force on the dissolution profiles of tablets prepared from coated granules were complicated and unpredictable.

4. Dissolution of Tablets Containing Combined Different Coated Granules

The tablet prepared from combined granules coated with different thickness of film were observed for

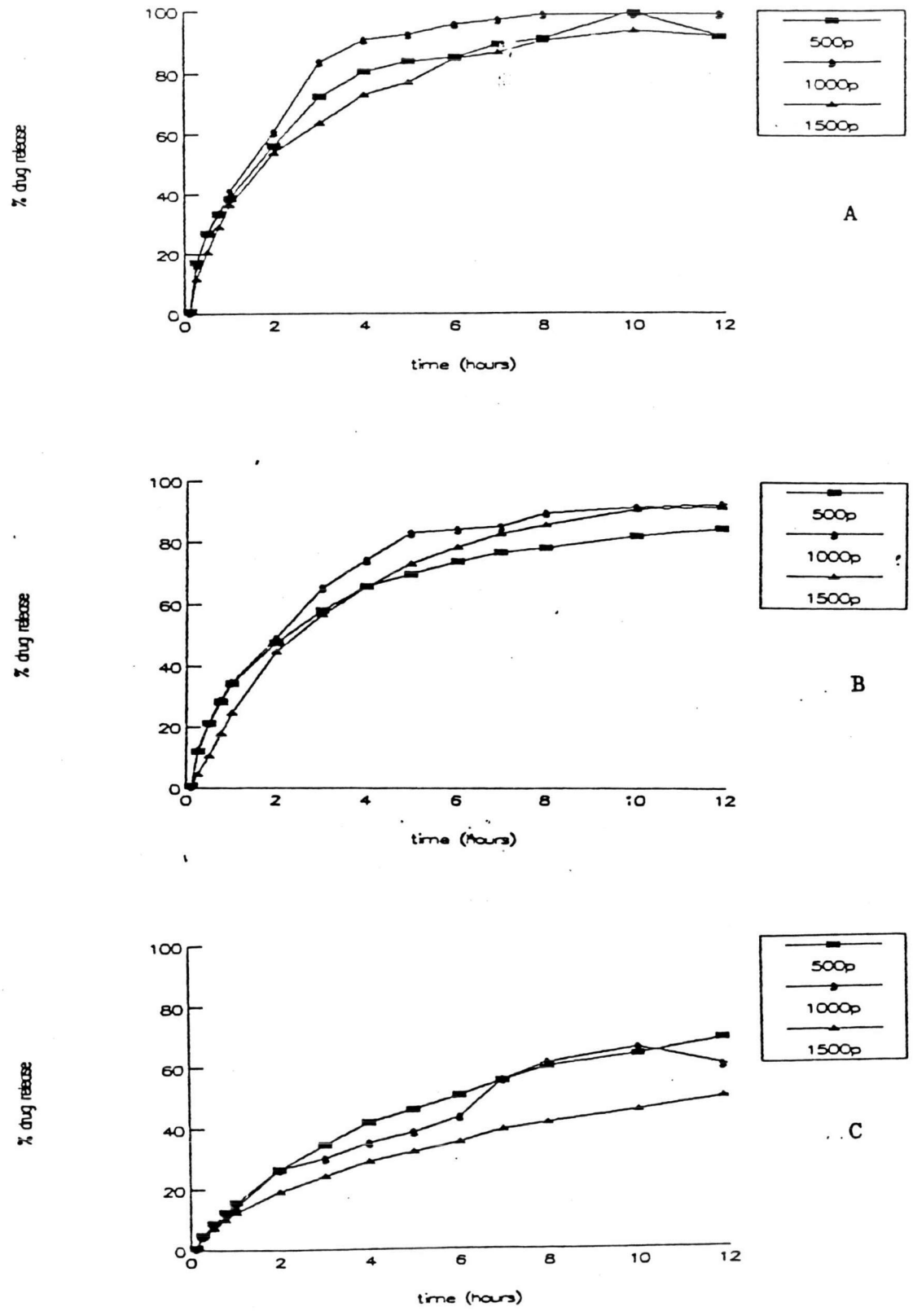


Figure 61 Influence of compressional force of tablet to theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing Avicel PH101® as filler); A: 10% coated granule B: 15% coated Granule C: 20% coated Granule

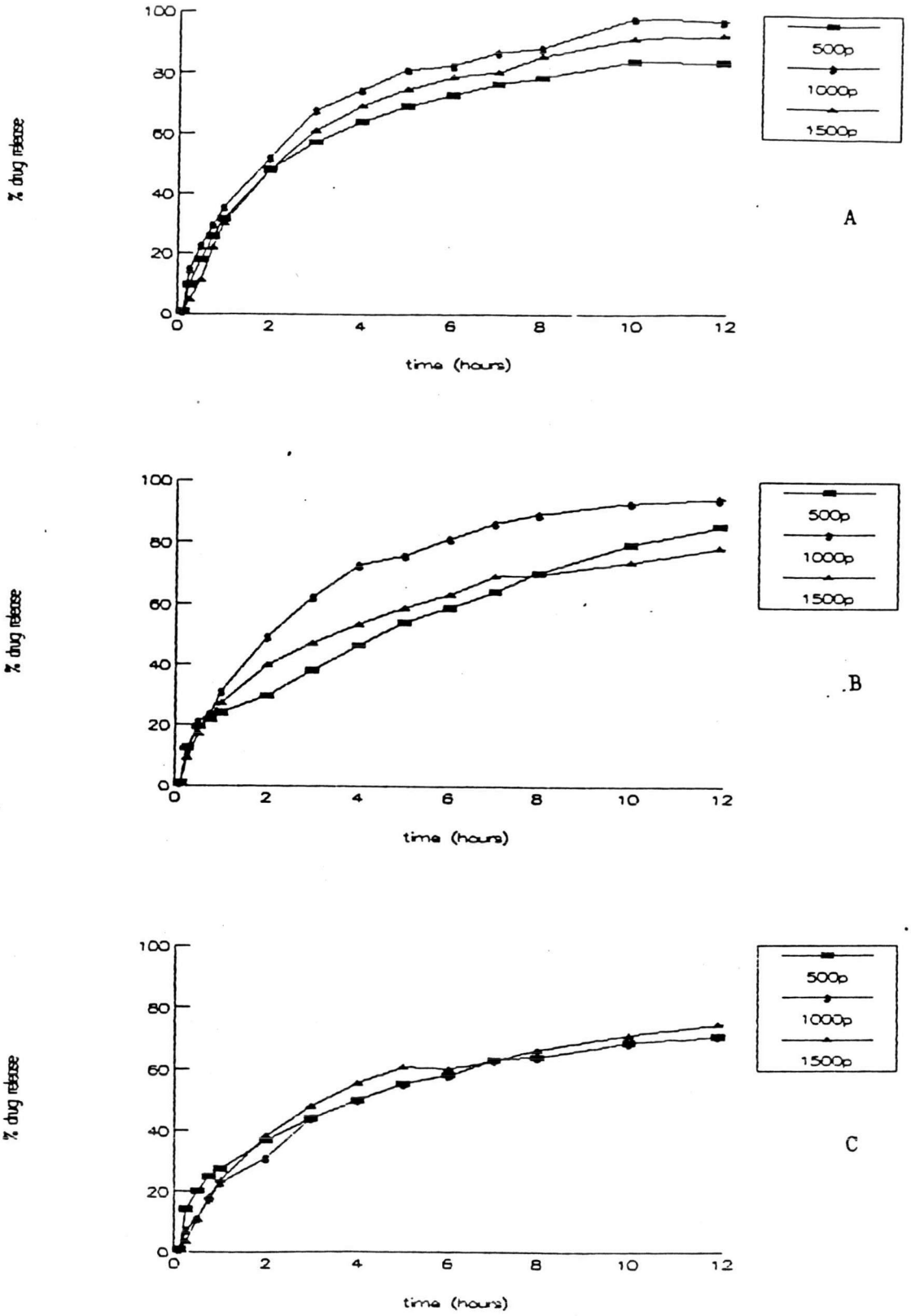


Figure 62 Influence of compressional force of tablet to theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing corn starch as filler); A: 10% coated granules B: 15% coated granules C: 20% coated granules

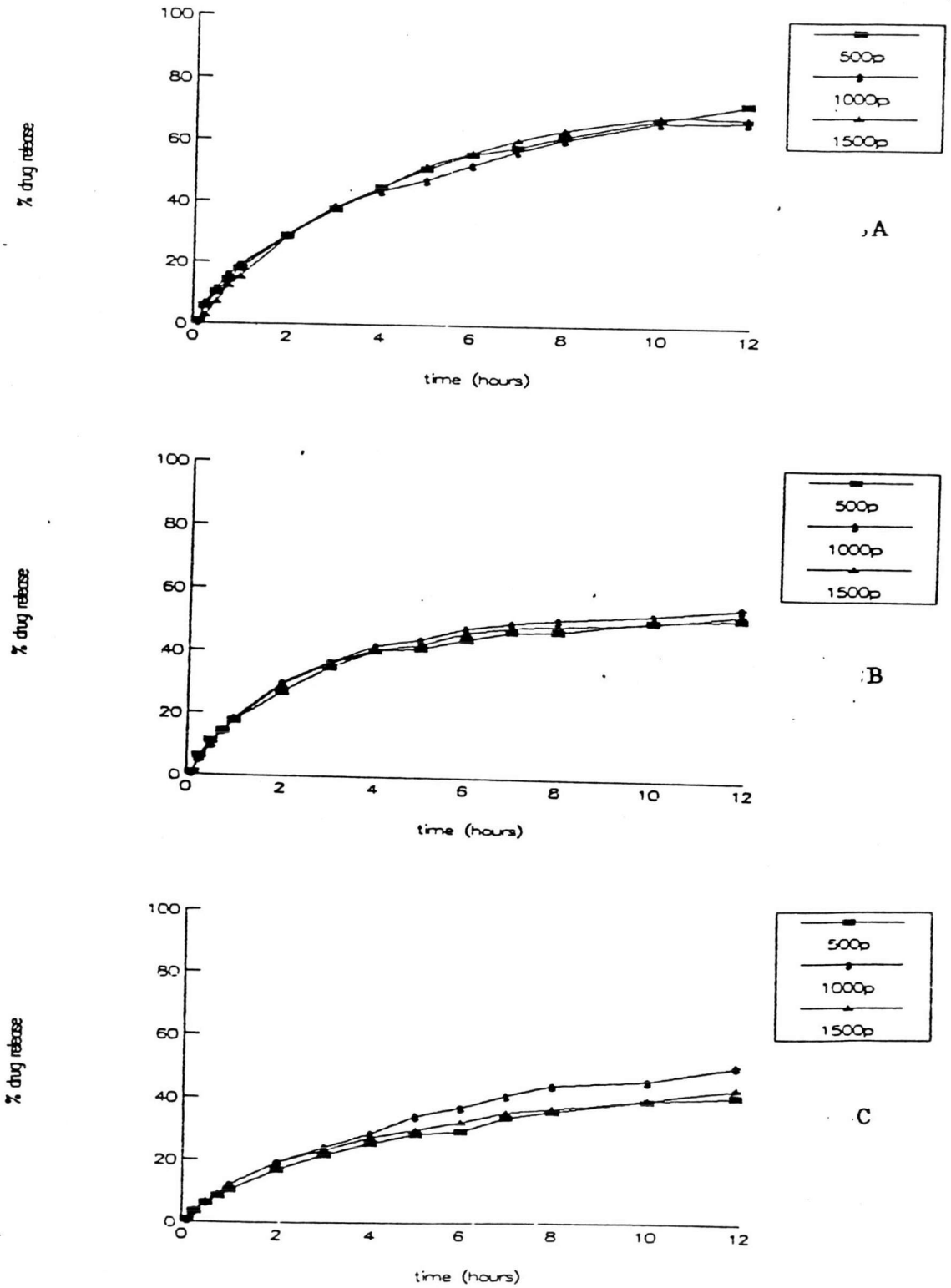
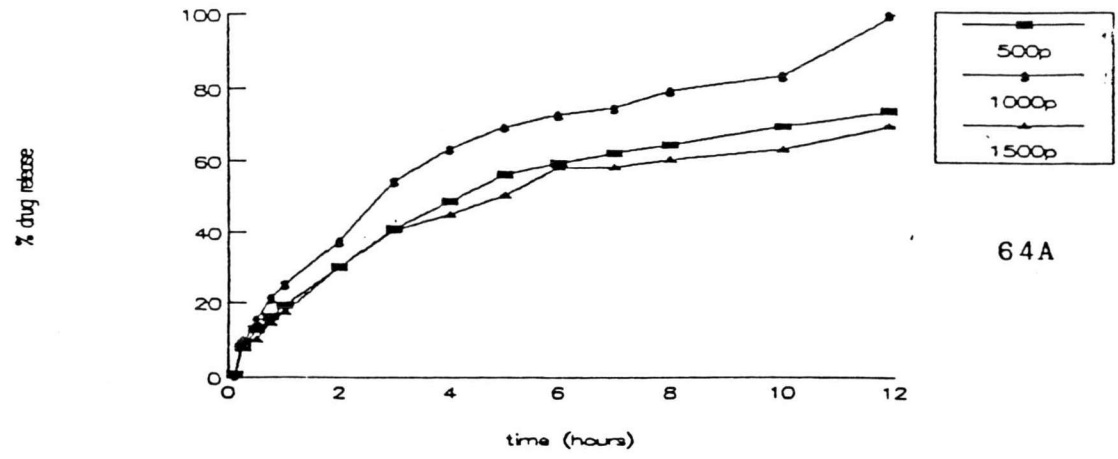
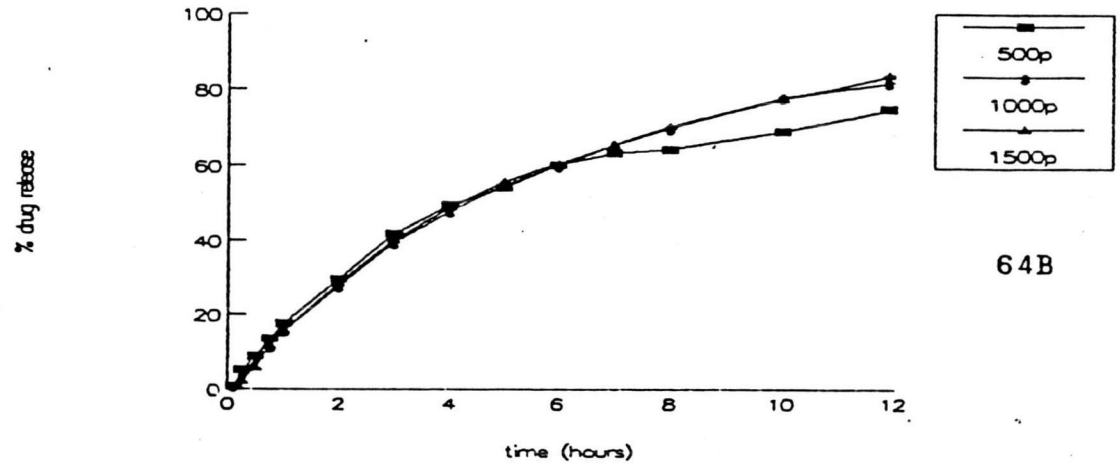


Figure 63 Influence of compressional force of tablet to theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing Emcompress® as filler); A: 10% coated granules B: 15% coated granules C: 20% coated granules





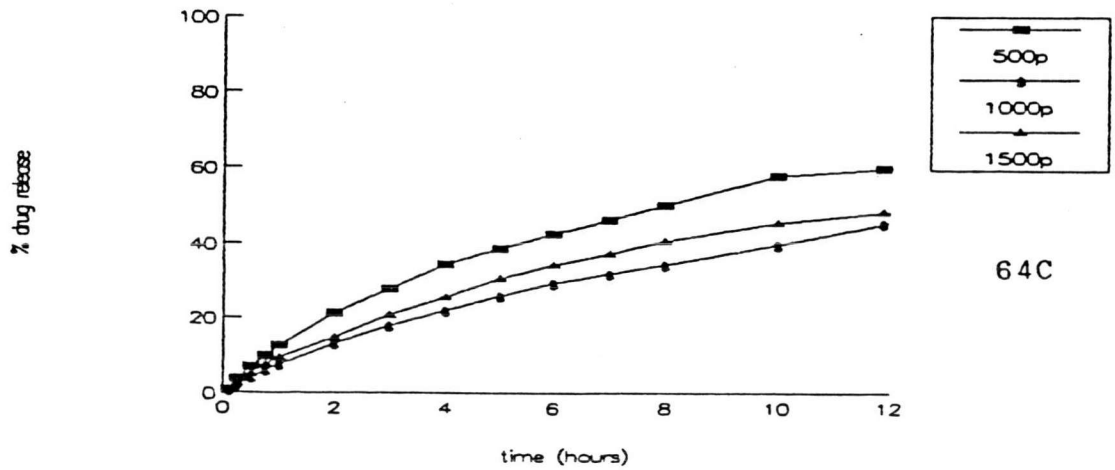


Figure 64 Influence of compressional force of tablet to theophylline release profiles from tablet containing Explotab® as disintegrant (granules containing lactose as filler); A: 10% coated granules B: 15% coated granules C: 20% coated granules

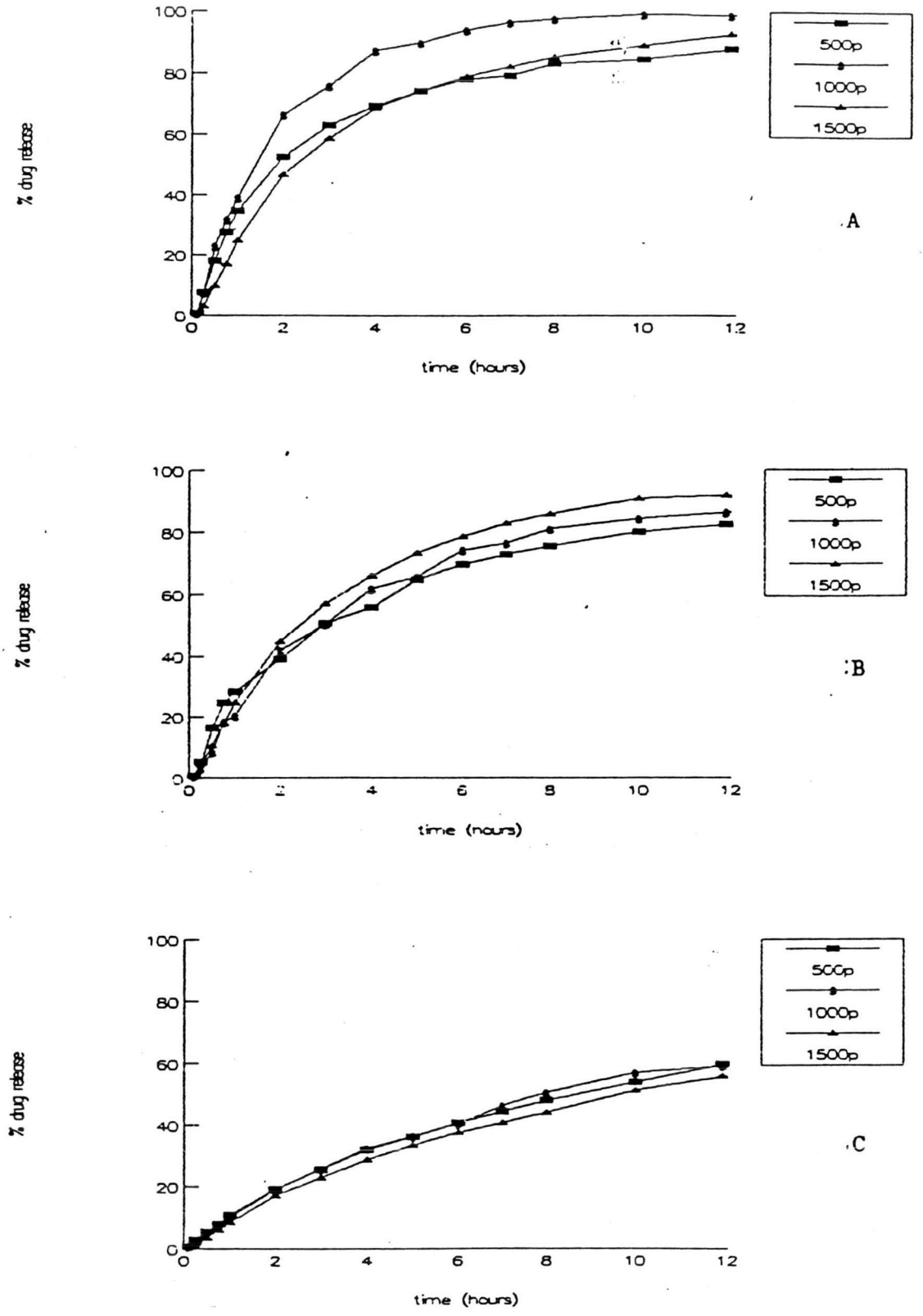
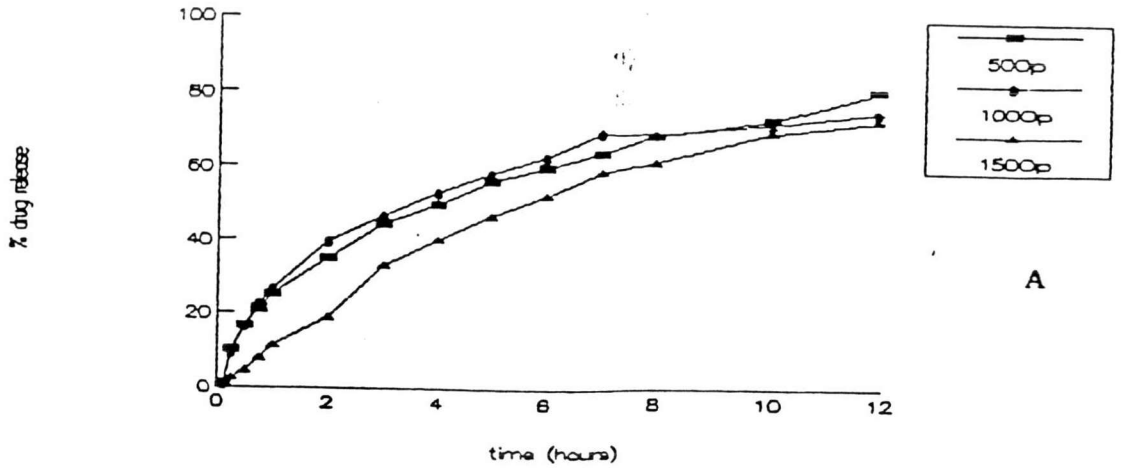
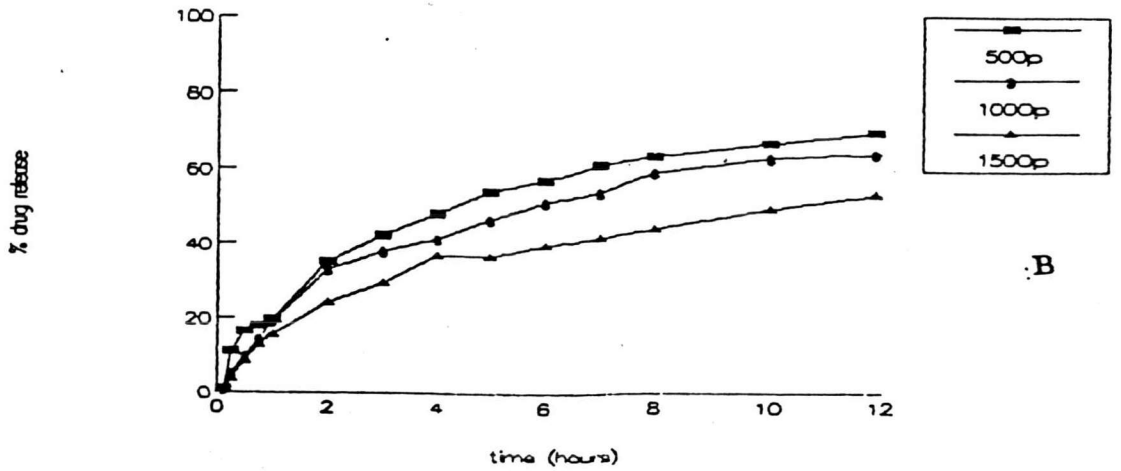


Figure 65 Influence of compressional force of tablet to theophylline release profiles from tablet without disintegrant (granules containing Avicel PH101® as filler); A: 10% coated granules
B: 15% coated granules C: 20% coated granules





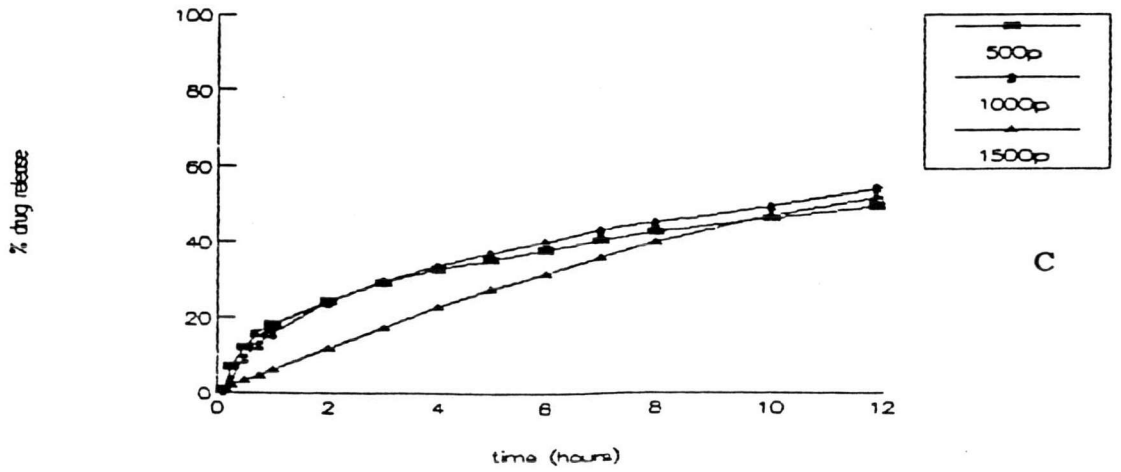


Figure 66 Influence of compressional force of tablet to theophylline release profiles from tablet without disintegrant (granules containing corn starch as filler); A: 10% coated granules B: 15% coated granules C: 20% coated granules

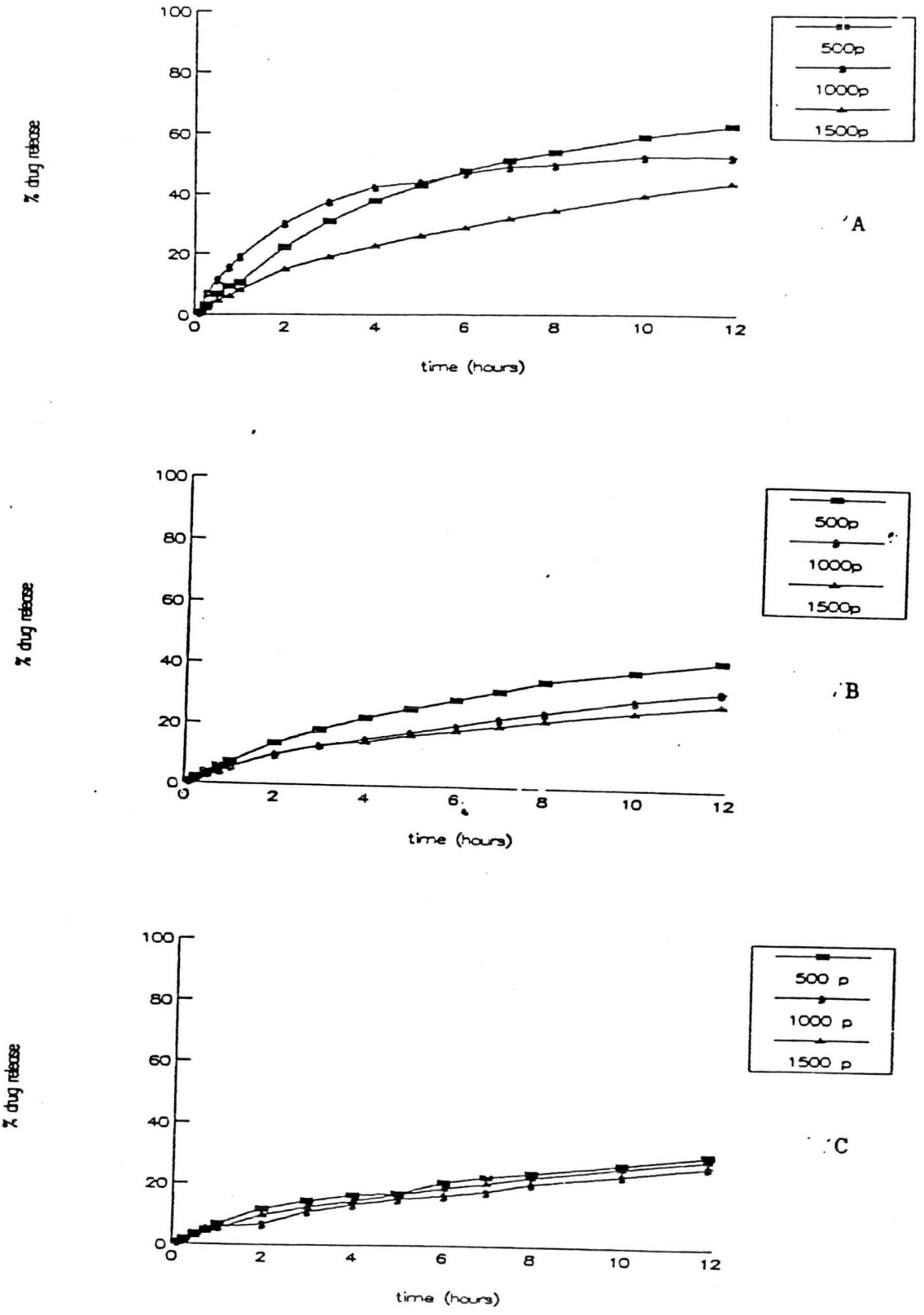


Figure 67 Influence of compressional force of tablet to theophylline release profiles from tablet without disintegrant (granules containing Emcompress® as filler); A: 10% coated granules B: 15% coated granules C: 20% coated granules

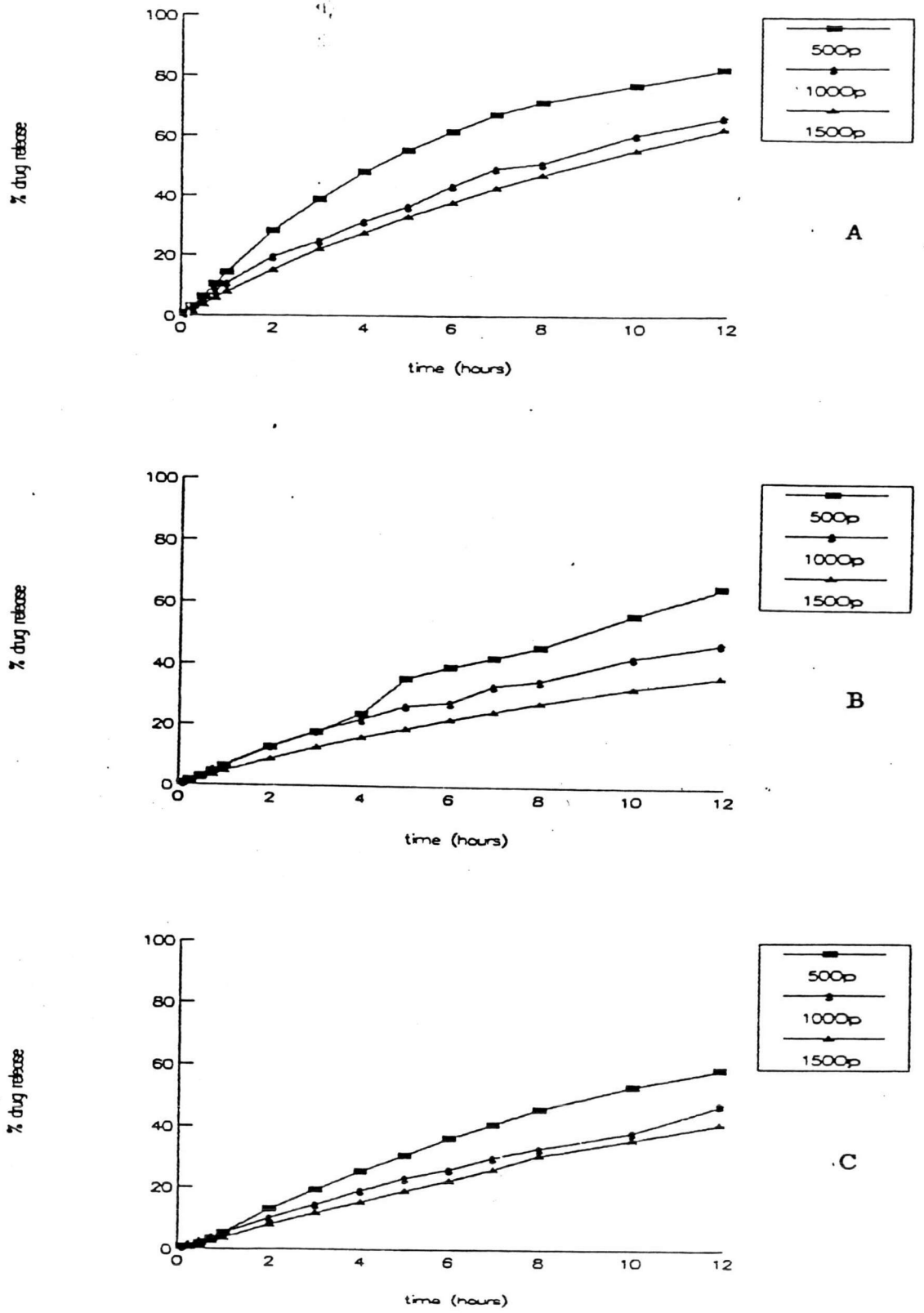


Figure 68 Influence of compressional force of tablet to theophylline release profiles from tablet without disintegrant (granules containing lactose as filler); A: 10% coated granules B: 15% coated granules C: 20% coated granules

their release characteristics. Coated granules containing Avicel PH101® as filler were selected for this study. This was due to the highest release profiles of tablet prepared from 10% coated granules containing Avicel PH10I® as filler

Granules containing Avicel PH101® as filler coated at 10% and 20% were mixed, 50:50 or 70:30, and compressed into tablet with Explotab® and others ingredients as in tablet formulation at compressional force of 500 lbs. Dissolution profiles from these two preparations compared with each coating level were shown graphically in Figure 69-70. As was expected, the dissolution profiles from combined coated granule tablets seem to be lower than 10% coated granules and higher than 20% coated granules.

5. Dissolution Profiles of Selected Formulation Compared with Commercial Products

The satisfactory formulations were selected and compared their dissolution profiles with available commercial products,Theodur® and Neulin®. The selections of formulations were based on : They should gave drug release at 12 hours interval not less than 70%(base on commercial products, Theodur® =72.52%), they should gave uniform release profiles with less standard deviation and the mechanism test was used for this selection.

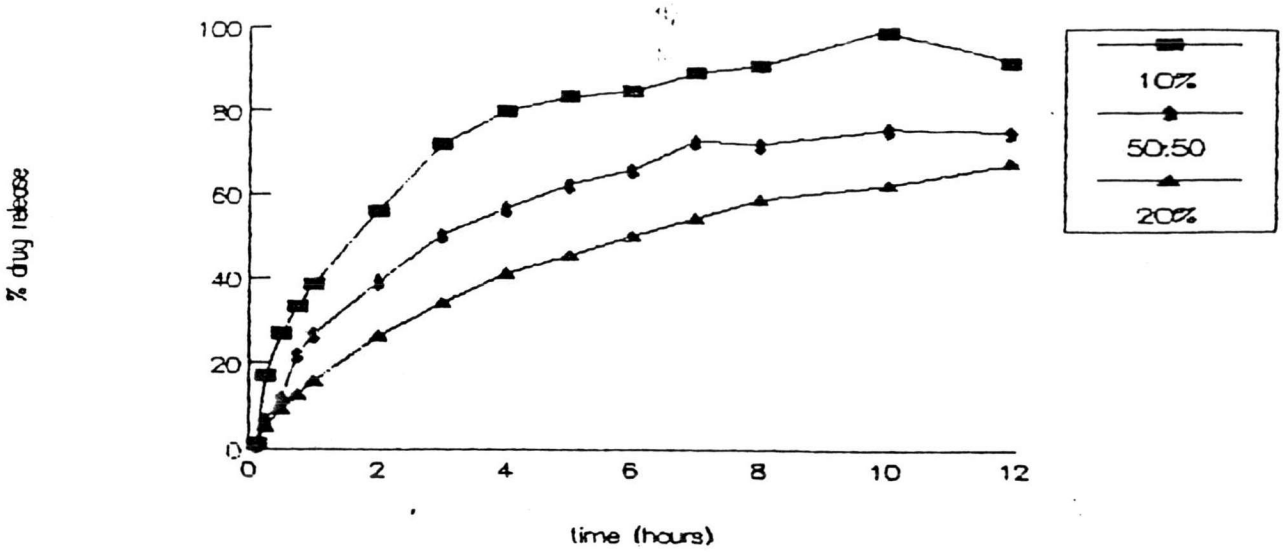


Figure 69 The release profiles of combined ,10%+20%(50:50), coated granules containing Avicel PH 101[R] as filler

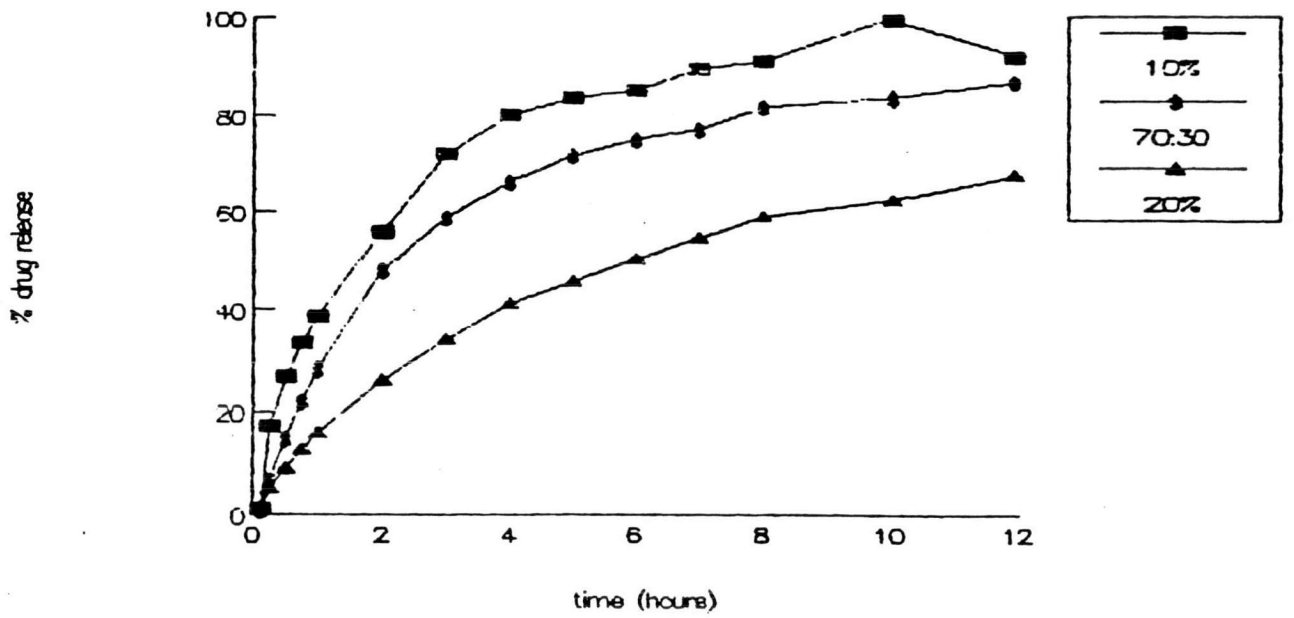


Figure 70 The release profiles of combined ,10%+20%(70:30), coated granules containing Avicel PH 101[R] as filler

Release mechanism is based on equation:

$$\frac{M_t}{M\alpha} = kt^n$$

Where Mt/Mα is the fraction of drug released up to time t.

t is the release time

k is a constant incorporating structural and geometric characteristics of the controlled device

n is the diffusion release exponent indicative of the mechanism of release

The relationship between the diffusional exponent n and the corresponding release mechanism is shown in Table 33 (Appendix). The value of n is 0.43 for Fickian diffusion, when the value of n is >0.43 and <1.00, the release was said to be non Fickian. A value of n = 1 mean the drug release is independent of time or Zero oder release. So a desirable mechanism for the application is leaded to n = 1, which charaterized Zero order release behavior. The release exponents (n) of the selected for mulations, Nuelin® and Theodur® were analyzed by Data Test Computer Program developed by Dr.Poj Kulvanich and Puriwat Leesawat and shown in table 14 .

Table 14 The Values of Release Exponent (n) Following Linear Regression of Selected Formulation Theodur® and Neulin® in pH change method

Formulation	n Release Exponent	Formulation	n Release Exponent
$10\%A_1$	0.52	$20\%C_1$	0.49
$10\%A_3$	0.55	$20\%C_3$	0.58
$10\%A_5$	0.61	$20\%C_5$	0.68
$15\%A_1$	0.56	$10\%E_1$	0.60
$15\%A_3$	0.61	$10\%L_1$	0.65
$15\%A_5$	0.61	$10\%L_3$	0.68
$10\%C_1$	0.58	$15\%L_1$	0.74
$10\%C_3$	0.60	$15\%L_3$	0.77
$10\%C_5$	0.73	$15\%L_5$	0.78
$15\%C_1$	0.51	Nuelin®	0.56
$15\%C_3$	0.67	Theodur®	0.95
$15\%C_5$	0.52		

A lot of formulations were observed but only a single formulation would be selected for furthur study. From drug release mechanism test, formulation 15%L5 was selected because it gave hightest n release exponent (0.78). The release exponents n of Theodur® and Nuelin® were 0.95 and 0.56. These indicated that the release

mechanisms of all formuulations were anomalous transport and the release mechanism of theodur® was nearest to Zero order transport since the value of n approached 1.0.

Figure 71 showed the profile of the selected formulation when compared with two commercial products, Theodur® 300 mg and Nuelin® 250 mg. The percent theophylline release at two hour from theodur® =15.22±0.67, Nuelin® = 27.04 ± 1.75, Experimental formulation = 28.39 ± 1.72. After 12 hours dissolution study, the percent theophylline released highest from the experimental formulation (83.56±3.51), Nuelin® was the second (74.23± 0.59), Theodur® was the third (72.52±0.96).

6. Reproducibility of Coated Granules and Tablets by Fluidized Bed

In order to produce the desired sustained release profiles, uniform and complete ethylcellulose coating must be applied to granules. To study the reproducibility of dissolution profiles of theophylline from theophylline coated granules from batch to batch, three batches of the selected formulation were prepared (formulation 15%L5). Content of drug in batch I = 62.93± 1.42 , batch II = 63.25±0.61 and batch III = 61.59±1.25 Figure 72, which were SEM of these coated granules in cross-section, showed distinct layer of film coating.These

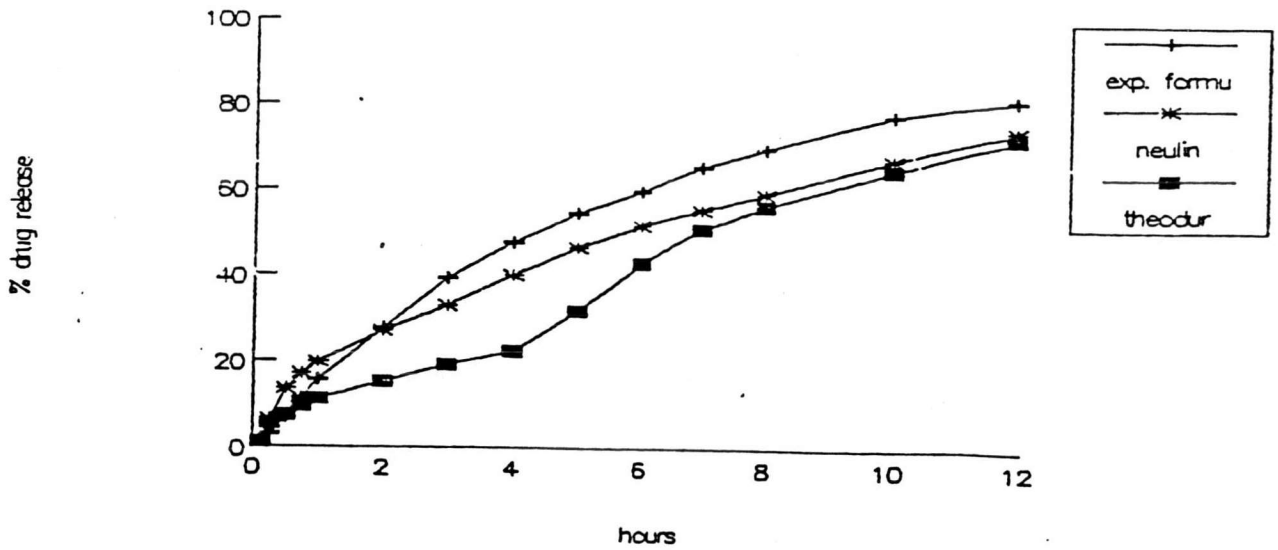
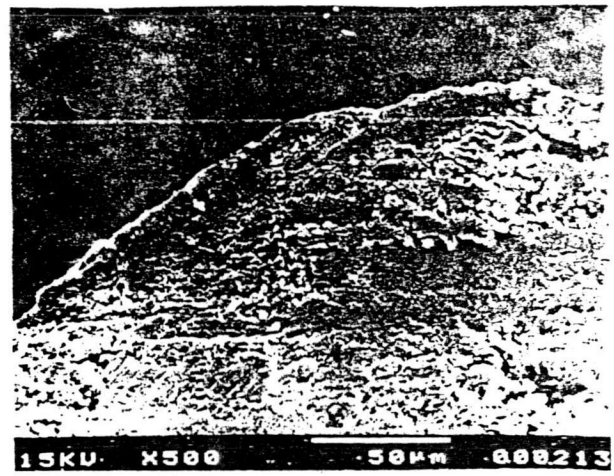
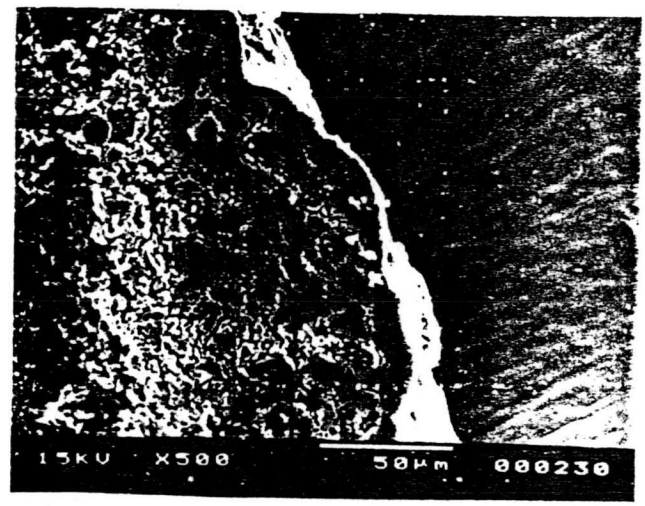


Figure 71 The release profile from the selected formulation compared with Theodur® and Nuelin®

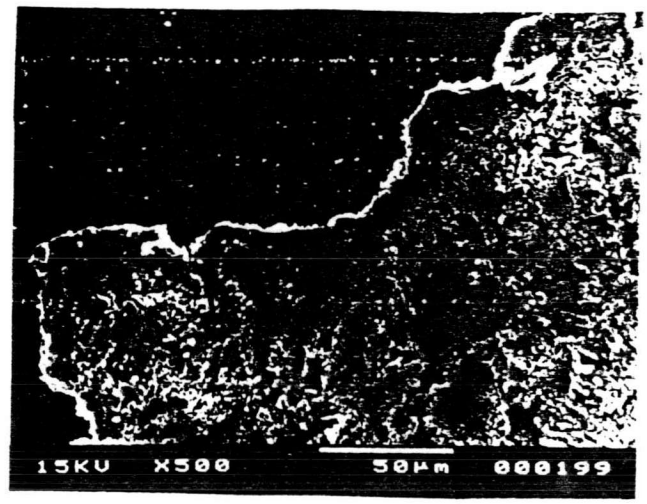
layer of coated granules seem to have similary thickness and dissolution behavior , as shown in Figure 73. The dissolution profiles of granules were found to be reproducible. Tablets were also prepared from each batch of coated granule, and the release profiles were shown in Figure 74.The obtained data showed same pattern of release profiles. This indicated that tablets containing coated granules prepared by fluidized bed were reproducible.



A



B



C

Figure 72 The photomicrographs of 15% coated granules containing lactose as filler from three batches (cross-section)

A: batch I B: batch II C: batch III

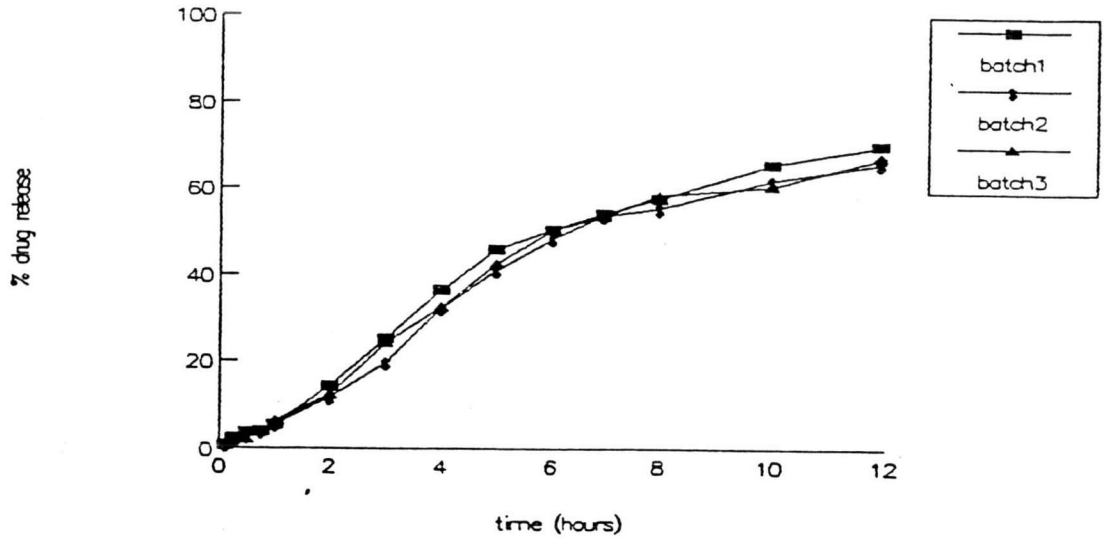


Figure 73 The release profiles from three batches of 15% coated granules containing lactose as filler

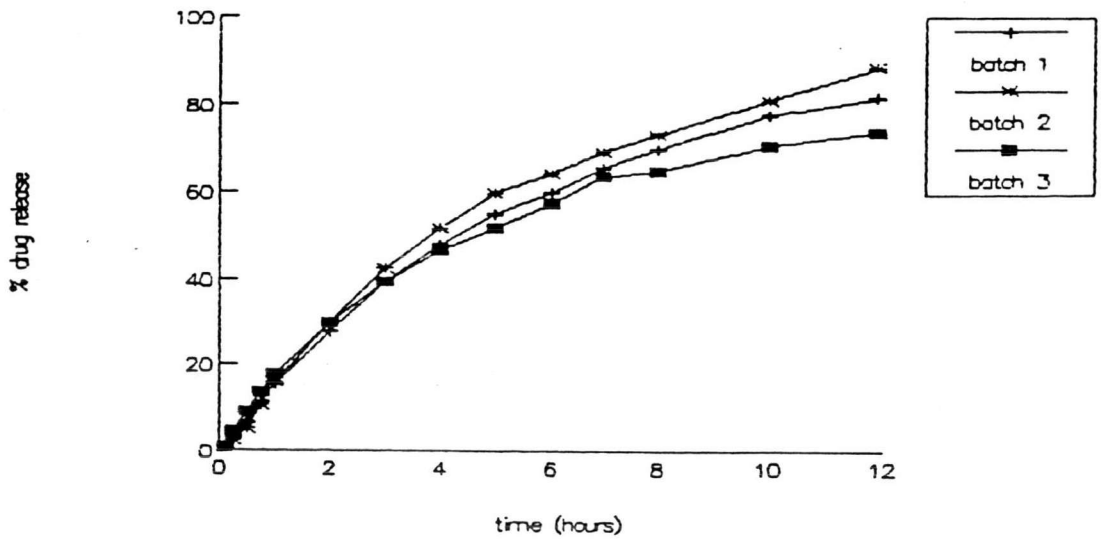


Figure 74 The release profiles from three batches of tablets prepared from 15% coated granules containing lactose as filler