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DISSOLUTION OF SUPPOSITORIES V: INFLUENCE OF AGING ON ASPIRIN RELEASE FROM POLYETHYLENEGLYCOL SUPPOSITORIES WITH AND WITHOUT CROSPOVIDONE

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ABSTRACT

This report details the effect of aging on release of aspirin from four PEG blends containing crospovidone as a disintegrant in concentrations of 0, 0.5, 1 and 5%. It has been reported in the literature that release from suppository formulations is often altered upon aging. In this experiment, suppositories containing 350 mg aspirin were dissolved in 1,000 mls of pH 8.0 dissolution fluid, at 37.5° with an agitation rate of 50 rpm. Suppositories were designated as fresh (less than 10 days old), 4 months old and 6 months old. Aspirin was assayed at 265 nm. Dissolution profiles as well as dissolution half-times were reported. Aging had little effect on Base A and Base B. However, Base C exhibited an ambiguous effect in that the dissolution half-times were inconsistent. Base D exhibited a dramatic change in release upon aging in that the dissolution half-times increased from 23 minutes to 55 minutes with 1/2%

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crospovidone. It is hypothesized that Base D stabilized when larger amounts of crospovidone are used although the exact mechanism of this stabilization is unknown.

INTRODUCTION

Published reports have described a suppository dissolution test apparatus as well as the use of crospovidone to increase the rate of release of aspirin and acetaminophen from polyethyleneglycol based suppositories.[1,2,3,4] These reports have documented release rate changes for both aspirin and acetaminophen for freshly made (i.e. less than 10 days old) suppositories. In all instances crospovidone increased the release rate of the drugs. This preliminary study report discusses how aging affects the usefullness of povidone on increasing the release.

PROCEDURE

I. Preparation of Suppositories

Four basic formulas were used:

Base A	PEG 1000	96%
	PEG 4000	4%
	Aspirin	350 mg
Base B	PEG 1000	75%
	PEG 4000	25%
	Aspirin	350 mg
Base C	PEG 1540	70%
	PEG 6000	30%
	Aspirin	350 mg
Base D	PEG 6000	50%
	PEG 1540	50%
	Aspirin	350 mg

Polyplasdone XL^{R} (crospovidone) was employed in concentrations of 0.5%, 1%, and 5% w/w.

The suppositories were prepared by fusion using a standard Armstrong 12 cavity aluminum alloy suppository mold.

II. Dissolution Procedure

A suppository was positioned upright in the basket for suppository dissolution testing, previously described[2] and placed in a USP vessel containing 1000 mls of phosphate buffer pH 8.0 dissolution media to approximate the rectal pH. A Hanson dissolution drive control and hallow spindle-stirrer apparatus was used to control the stirring rate at 50 rpm. A constant temperature water bath was maintained at 37.5°.

Samples were withdrawn with a pipette fitted with glass wool plug to insure that undissolved drug was not withdrawn. An equivalent amount of fresh buffer was added to the flask after each withdrawal. After appropriate dilution the samples were assayed spectrophotmetrically at 265 nm for dissolved aspirin. The various PEG bases exhibited no absorption at this wavelength. Aspirin obeyed Lambert-Beer's Law at 265 nm, the wavelength of maximum absorption for the drug.

Suppositories were stored at room temperature until used at the pre-selected time, fresh (i.e. less than 2 weeks old), 4 months and 6 months.

RESULTS

Tables 1, 2, 3, 4 report the dissolution for the 4 bases with 0, 1/2, 1 and 5% povidone for fresh, 4 month and 6 month suppositories.

TABLE 1

Base A Dissolution

Time (minutes)	% Release Aspirin 0%*			1/2%*			1%*			5%*		
	0	4	6	0	4	6	0	4	6	0	4	6
1	5	5.5	8	4	5	5	5	4	2	5	3	4
3	10	15	16	12	16	14	16	18	14	11	13	15
5	18	23	26	30	30	30	33	31	24	17	21	26
10	50	42	51	49	54	60	60	55	48	41	48	53
20	68	76	77	78	88	79	88	84	78	76	78	81
30	73	81	80	80	88	79	92	84	78	87	81	89

average of 5 assays

• = percentage of crospovidone

0, 4, 6 indicate age of suppository in months

TABLE 2

Base B Dissolution

Time (minutes)	% Release Aspirin 0%*			1/2%*			1%*			5%*		
	0	4	6	0	4	6	0	4	6	0	4	6
1	1	3	8	1	6	3	5	5	3	0	7	2
3	8	12	15	11	14	13	14	14	12	8	12	7
5	15	21	25	19	24	22	25	22	20	21	22	15
10	33	43	48	40	51	45	49	44	45	41	39	44
20	64	75	75	75	90	75	89	75	77	78	75	62
30	75	78	95	79	100	95	95	76	82	93	95	83

average of 5 assays

• = percentage of crospovidone

0, 4, 6 indicate age of suppository in months

TABLE 3

Base C Dissolution

Time (minutes)	% Release Aspirin 0%*			1/2%*			1%*			5%*		
	0	4	6	0	4	6	0	4	6	0	4	6
1	3	2	2	3	1.5	1	3	1	1	2	1	1.5
3	7	7	5	8	7	7	7	5	5	8	7	6
5	12	13	10	13	13	13	14	12	12	13	12	13
10	27	26	25	28	29	27	26	30	27	34	27	26
20	49	52	50	55	59	57	45	61	56	53	50	56
30	68	72	70	75	75	77	73	77	76	72	71	79
45	78	83	80	96	83	77	89	78	90	96	85	81
60	78	95	81	98	94	77		85	90	90	91	81

average of 5 assays

* = percentage of crospovidone

0,4, 6 indicate age of suppository in months

As seen from Table 1, aging had an insignificant, only slight effect on aspirin release for Base A. This is as expected, since addition of crospovidone also had only a negligible effect. Table 5 summarizes the dissolution half-times, that is the time for 50% to dissolve, for Base A. Here too, little effect of aging is apparent.

Table 2 shows the data for Base B release while Table 6 shows the corresponding dissolution half-times. Interestingly the half-times were increased upon aging for all Base B formulations

TABLE 4

Base D Dissolution

Time (minutes)	% Release Aspirin											
	0%*			1/2%*			1%*			5%*		
	0	4	6	0	4	6	0	4	6	0	4	6
1	2	1.5	0	2	2	0	2	2	1.5	2	1	1
3	6	2.5	1.5	7	6	2	5	6	6	6	6	4
5	9	6	3	12	10	7	14	12	14	9	12	12
10	23	13	6	21	23	15	20	25	31	21	23	25
20	46	23	16	44	46	36	45	49	51	46	47	50
30	63	32	23	64	74	55	61	72	70	67	68	69
45	87	37	33	88	95	76	87	78	78	89	86	80
60	91	39	37	93	95	91	91	78	78	96	86	83

average of 5 assays

* = percentage of crospovidone

0, 4, 6 indicate age of suppository in months

TABLE 5

Dissolution Half-times for Base A

Age of Suppository (in months)	% Povidone			
	0%	1/2%	1%	5%
0	10	10	8	12
4	13	11	9	13
6	9	8	11	13

TABLE 6

Dissolution Half-times for Base B

Age of Suppository (in months)	% Povidone 0%	1/2%	1%	5%
0	15.5	13	10	12
4	18	9	12	12
6	18	11	12	13

except the 1/2% povidone formulation. Release from aged suppositories was also delayed in the formulation without the disintegrant.

TABLE 7

Dissolution Half-times for Base C

Age of Suppository (in months)	% Povidone 0%	1/2%	1%	5%
0	21	14	22	18
4	18	15	18	20
6	20	15	19	17

TABLE 8

Dissolution Half-times for Base D

Age of Suppository (in months)	% Povidone 0%	1/2%	1%	5%
0	22.5	22.5	23	22.5
4	>60	24	21	21
6	>60	55	19	20

Table 3 and Table 7 summarizes the Base C data. Here, as in Base A, the changes were very small, within experimental error. However, the release half-times were slightly slower for aged suppositories.

Table 4 and Table 8 illustrate the most dramatic changes, those with Base D. Aging affected all of the formulations but most dramatically the formulations with 0 to 1/2% crospovidone. Increases in the t_{50} were especially evident in these two formulas while there was insignificant change in the suppositories with 1 and 5% povidone.

It is posited that the 1% and 5% formulations may, in fact be stabilized due to the povidone while the 1/2% povidone does not stabilize the system.

The effect of aging for each individual base is illustrated in Figures 1 through 16. The effect of aging is exhibited by

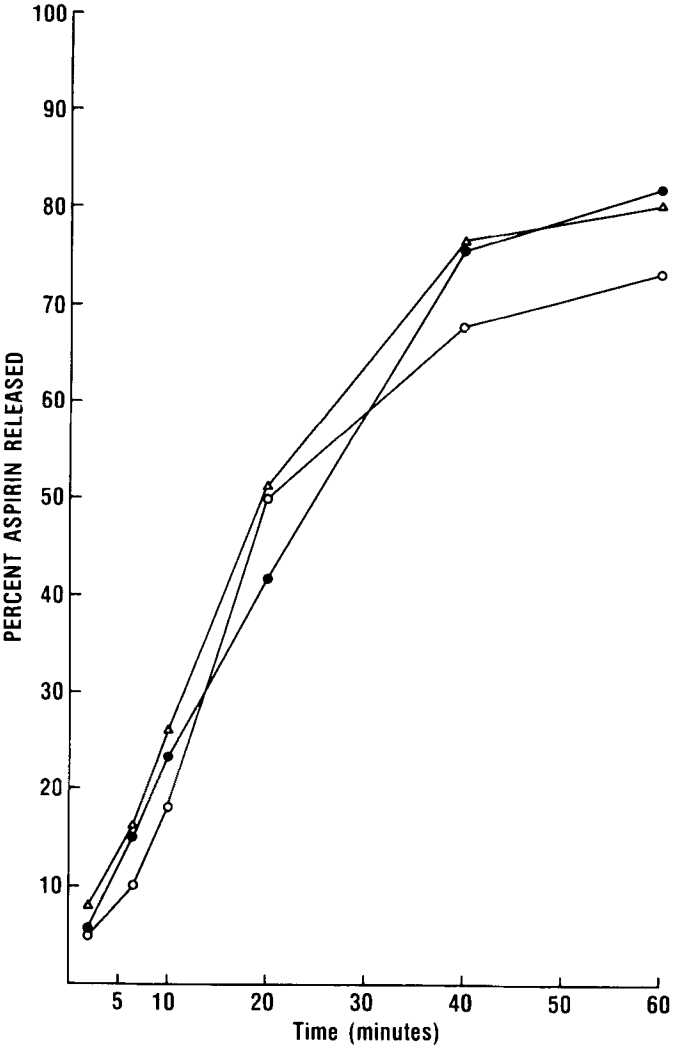

FIGURE 1 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE A, 0% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

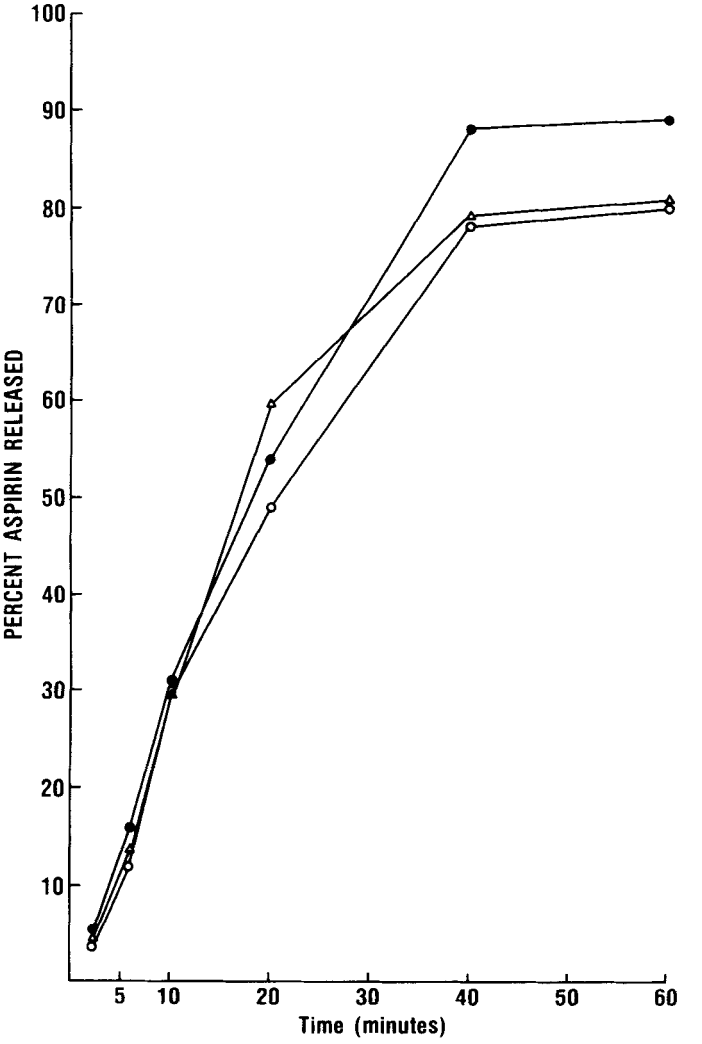

FIGURE 2 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE A, ½% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

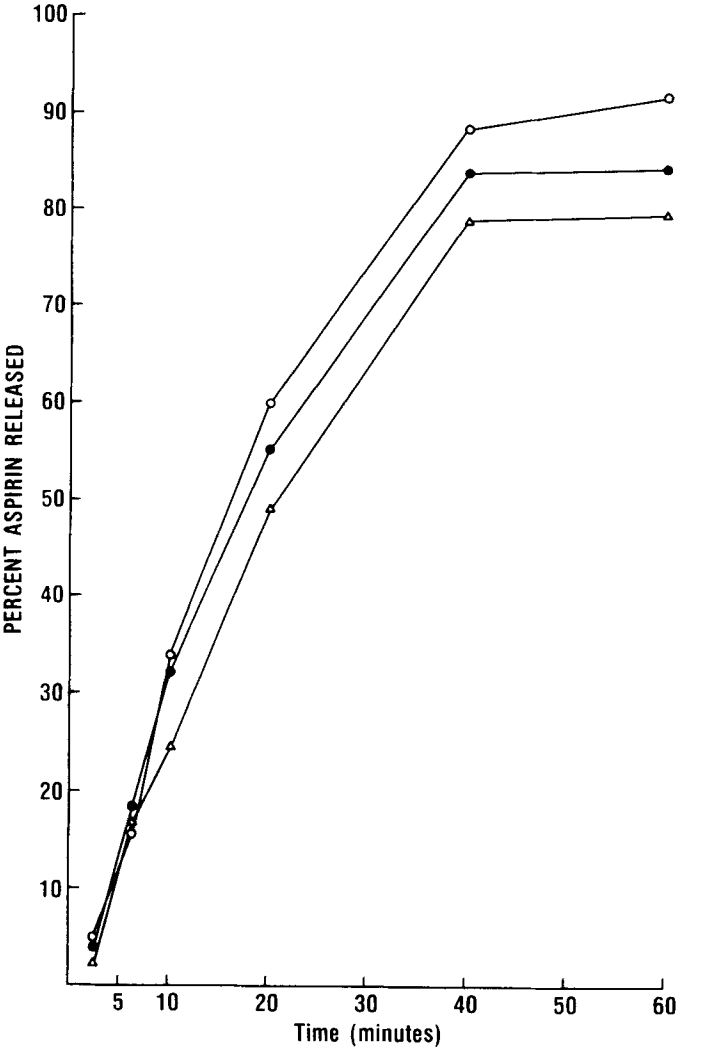

FIGURE 3 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE A, 1% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

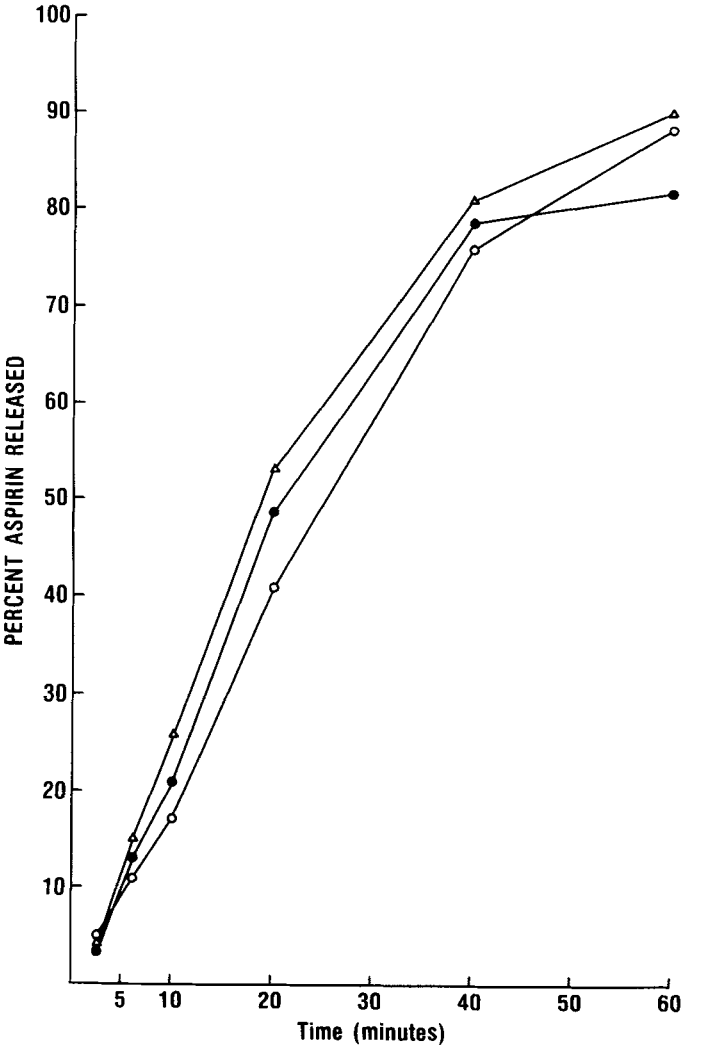

FIGURE 4 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE A, 5% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

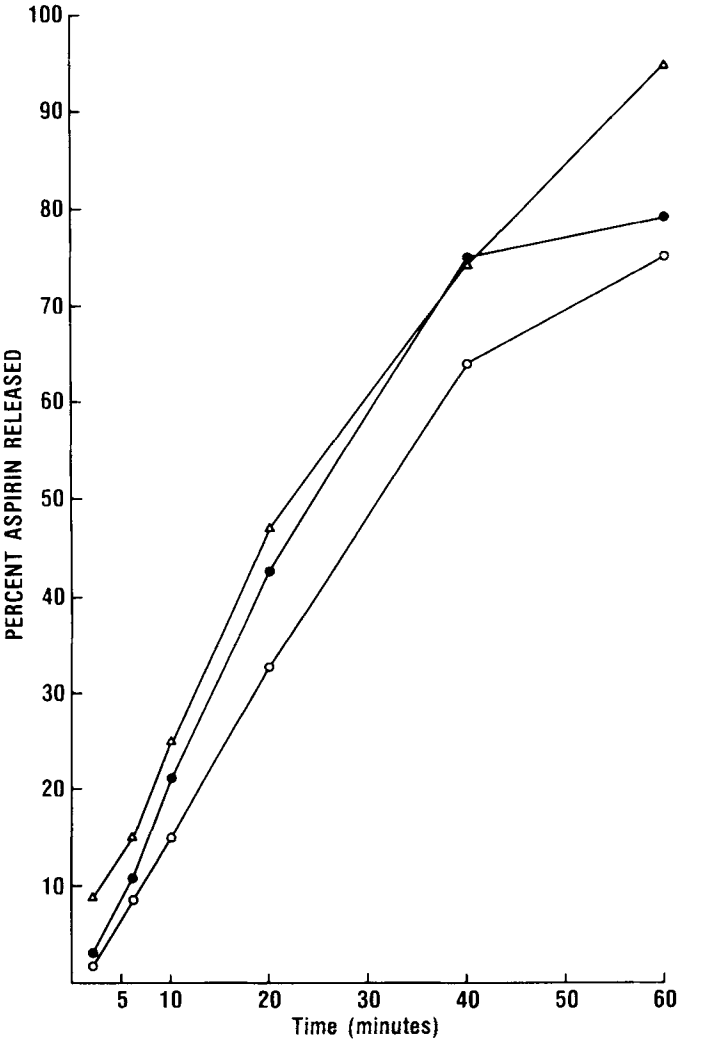

FIGURE 5 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE B, 0% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

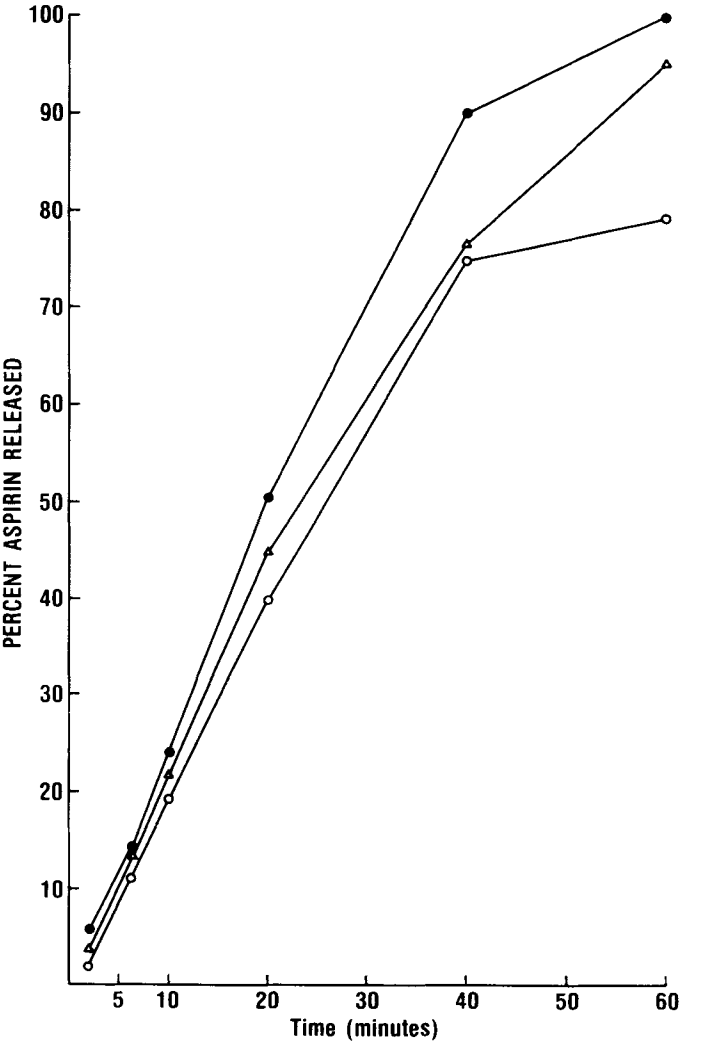

FIGURE 6 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE B, ½% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

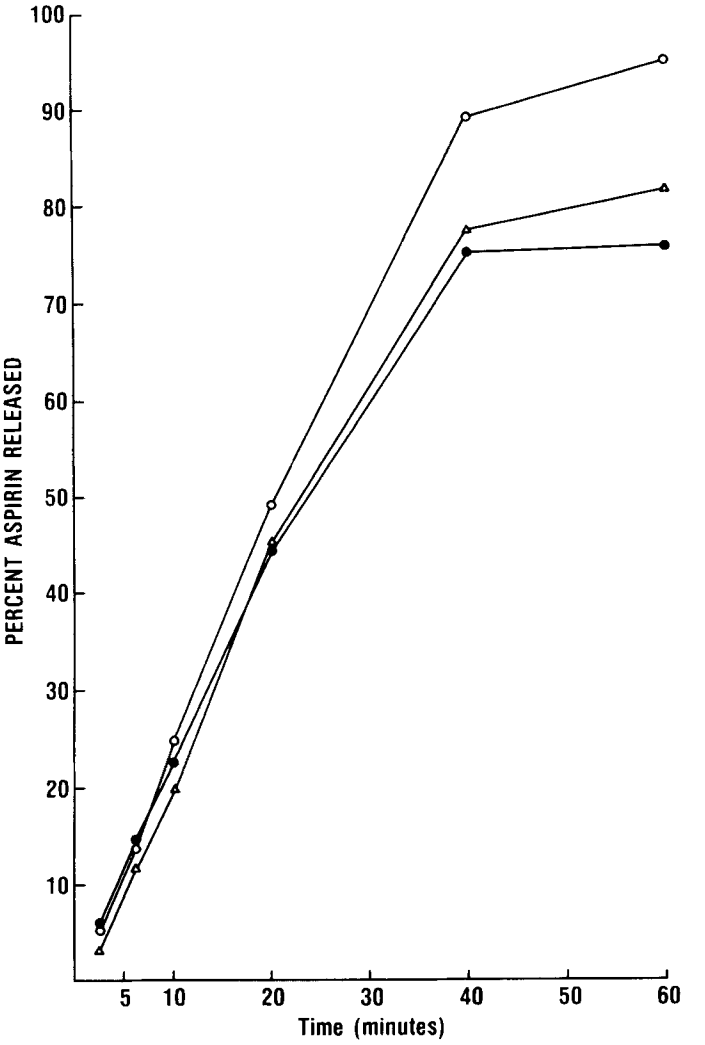

FIGURE 7 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE B, 1% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

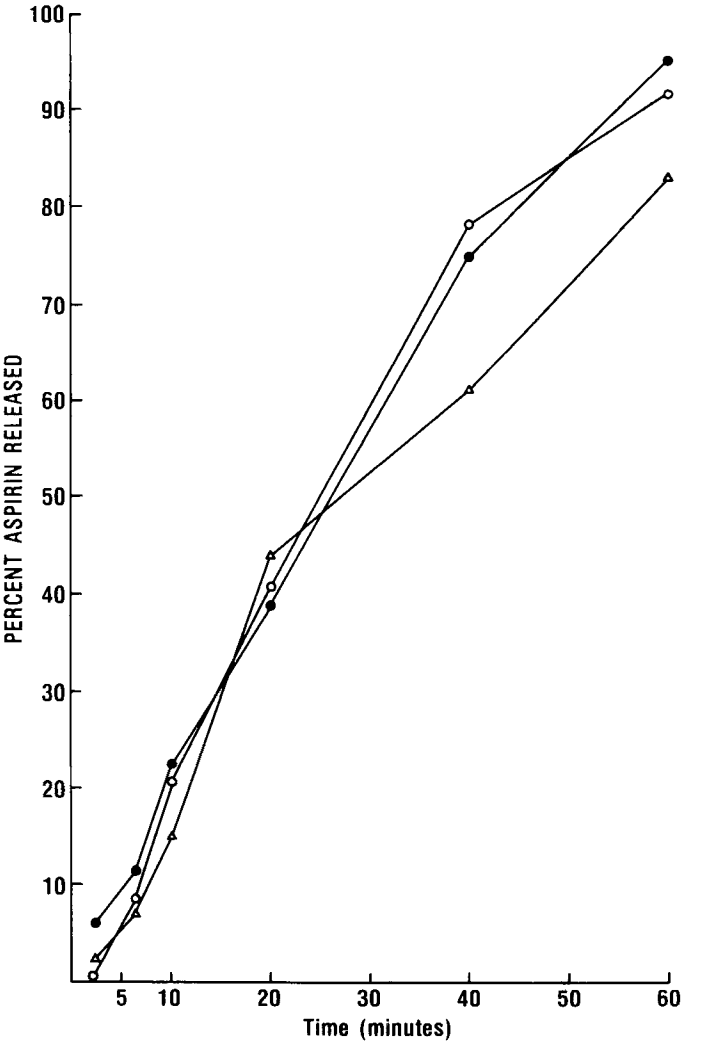

FIGURE 8 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE B, 5% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

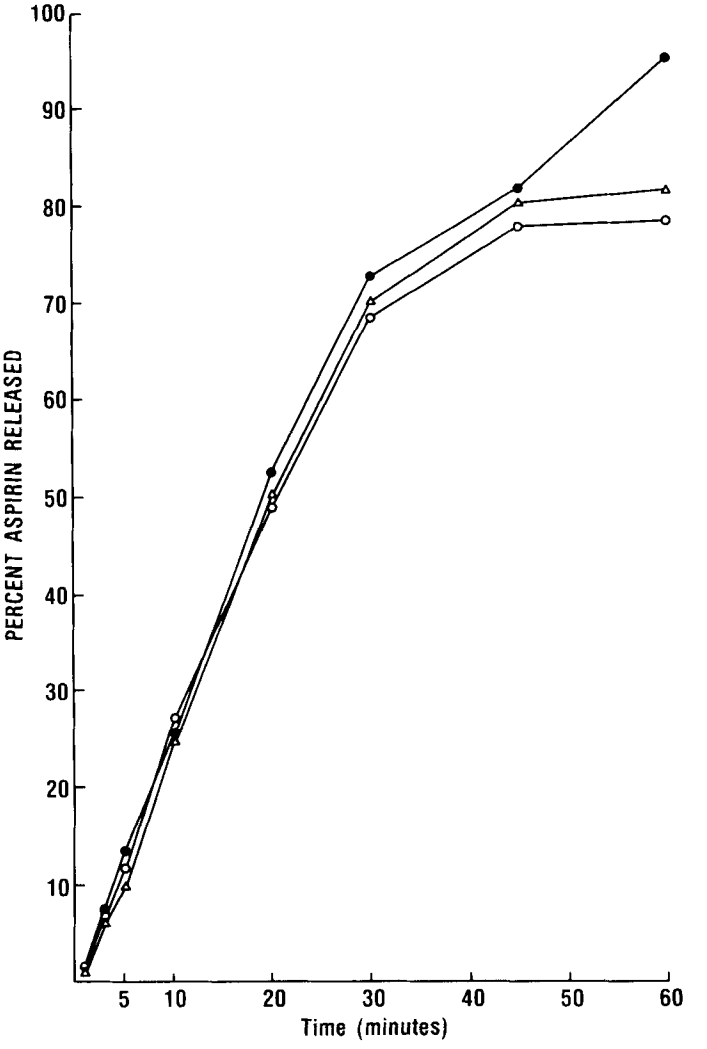

FIGURE 9 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE C, 0% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

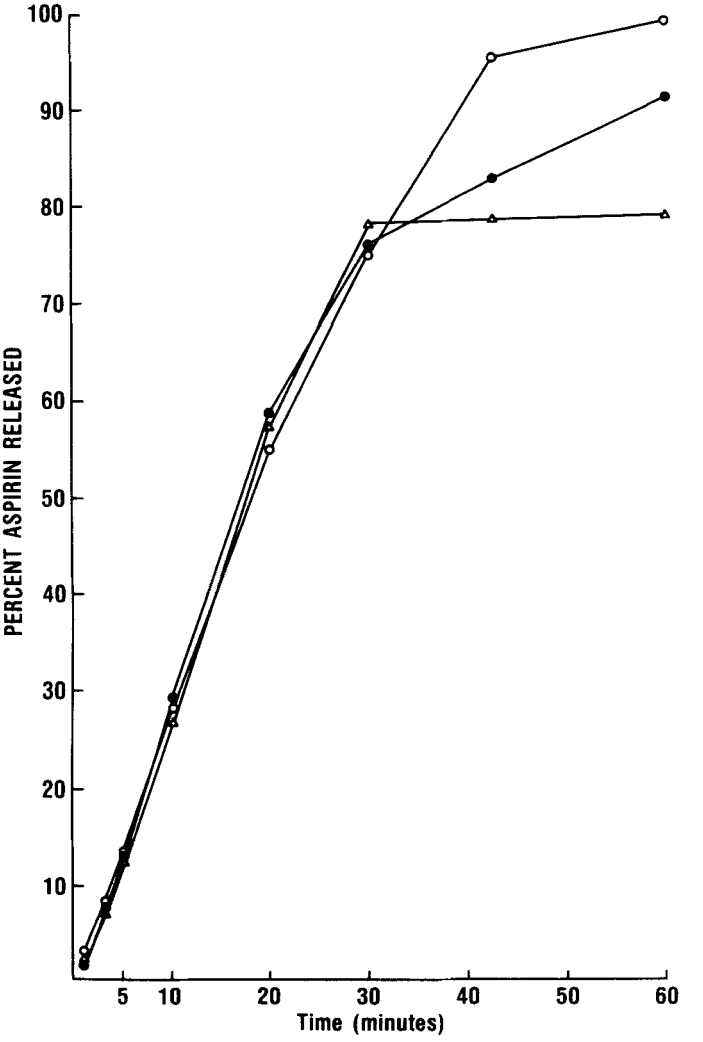

FIGURE 10 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE C, ½% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

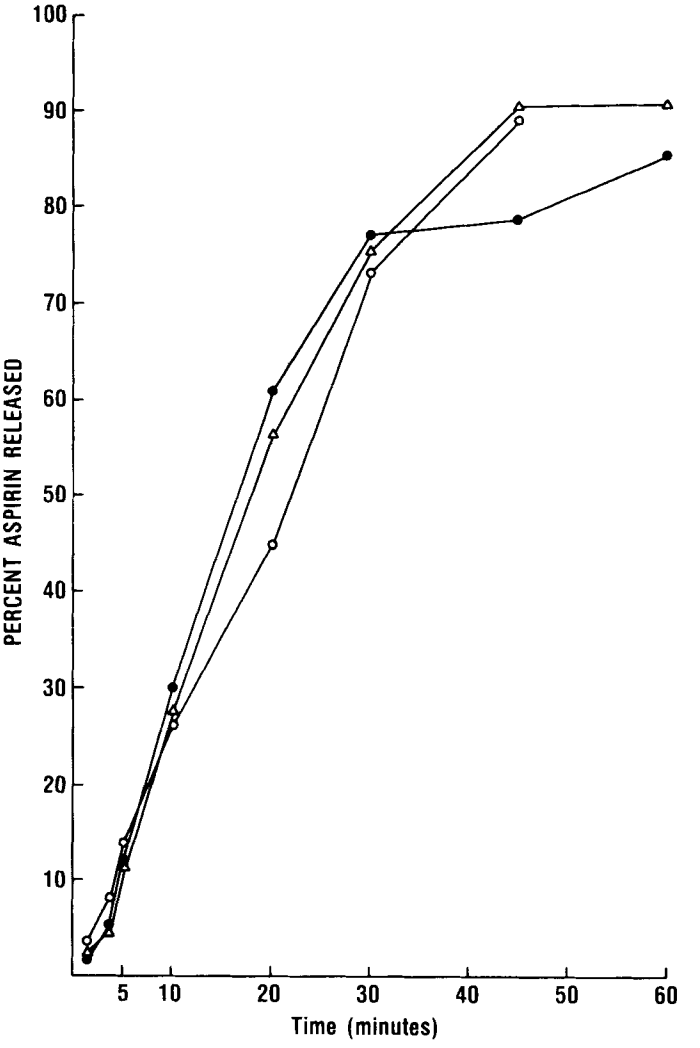

FIGURE 11 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE C, 1% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

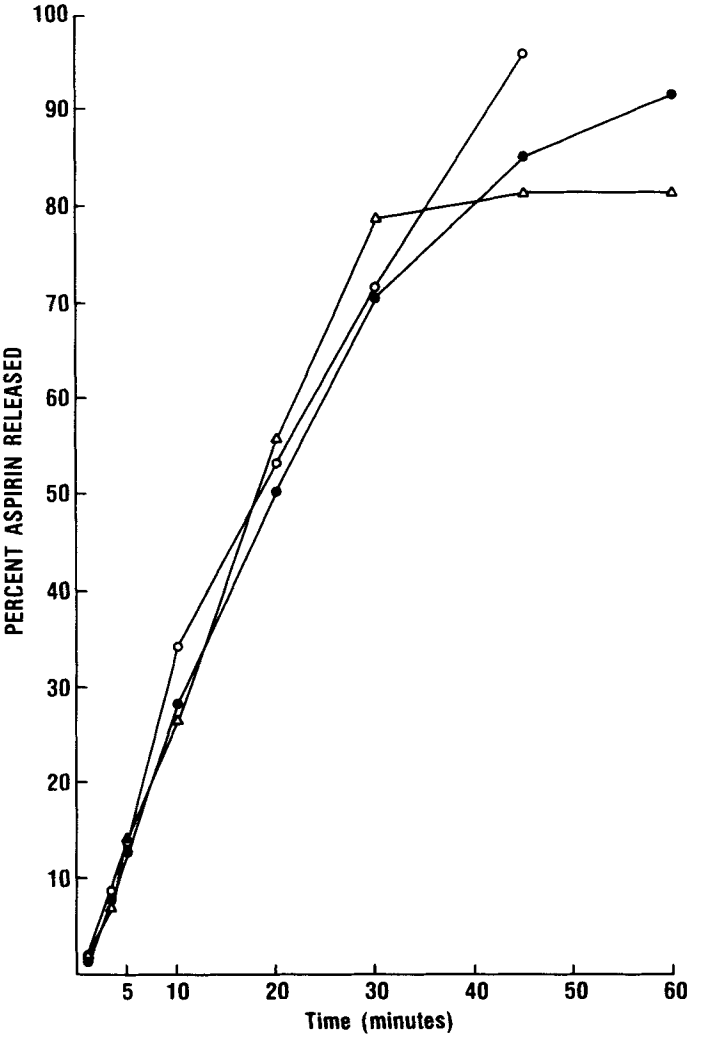

FIGURE 12 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE C, 5% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

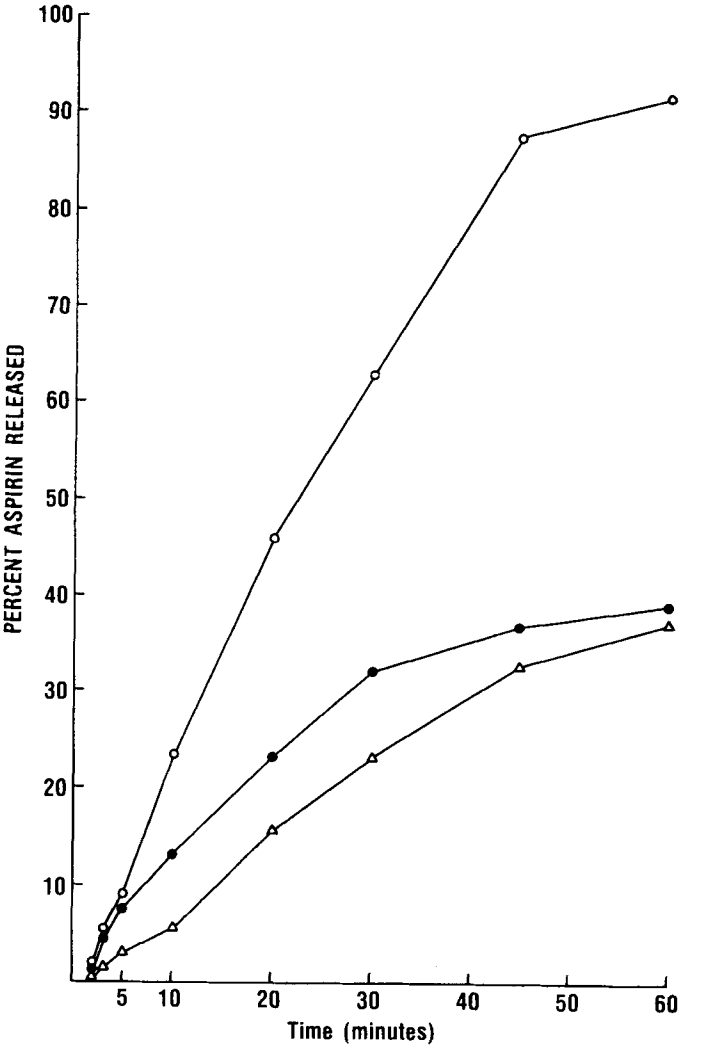

FIGURE 13 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE D, 0% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

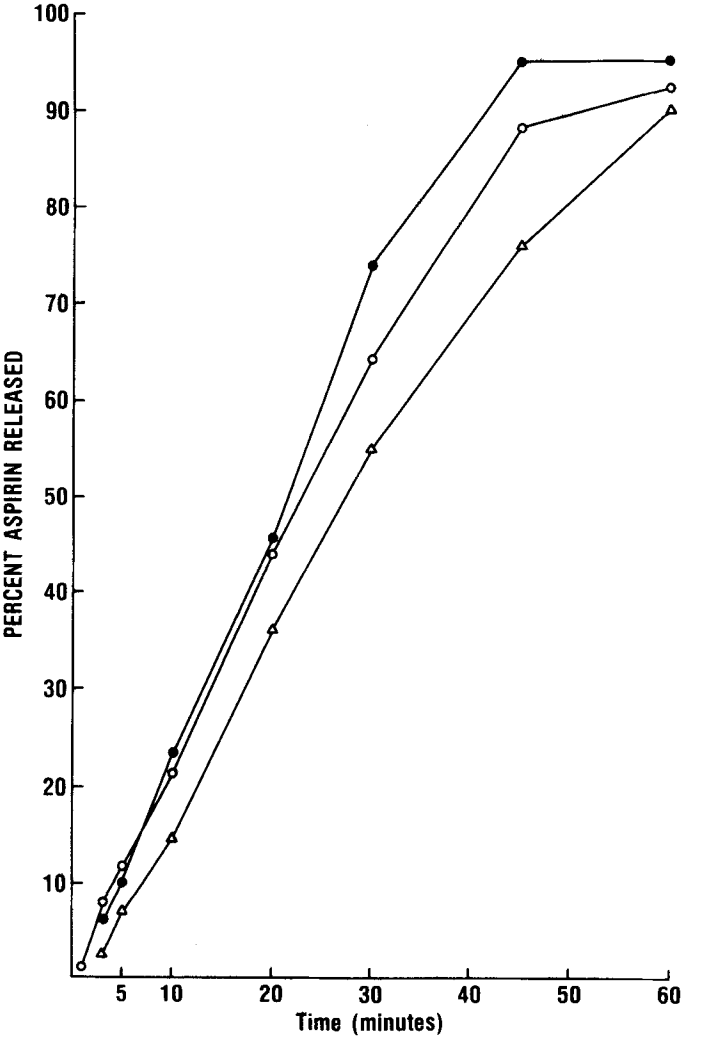

FIGURE 14 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE D, ½% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

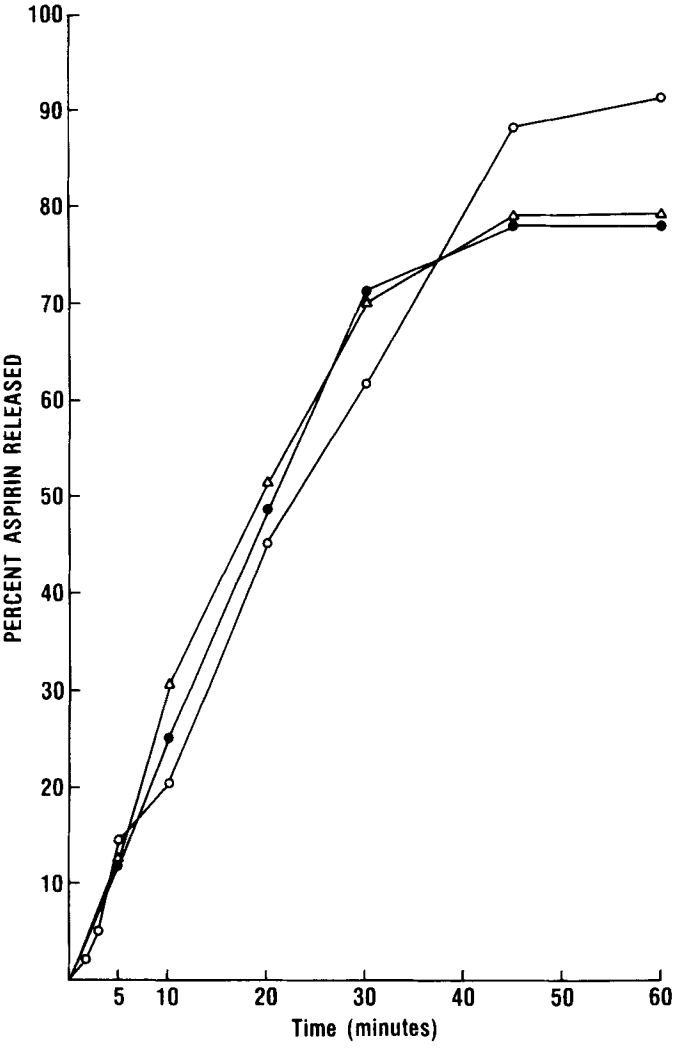

FIGURE 15 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE D, 1% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

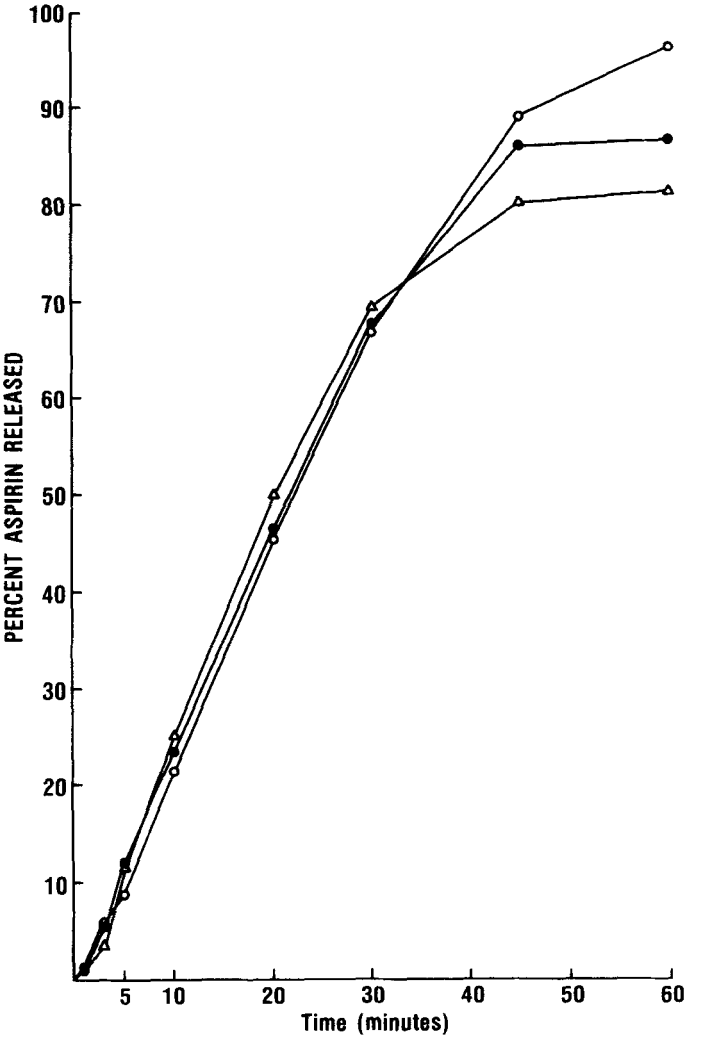

FIGURE 16 PERCENT ASPIRIN RELEASE VERSUS TIME FROM BASE D, 5% CROSPOVIDONE

○ NEW SUPPOSITORIES
● 4 MONTH OLD SUPPOSITORIES
△ 6 MONTH OLD SUPPOSITORIES

graphing dissolution profiles of percent of aspirin released as a function of time. While crospovidone concentration appears to have only a slight effect on release from aged suppositories, note that Figure 13, for suppositories of Base D, with no crospovidone, shows that new suppositories have a much faster release than aged suppositories. When viewed with the other figures, this indicates that suppositories of Base D manufactured with crospovidone are less susceptible to changes in their release patterns with aging than are those prepared without crospovidone. This indicates that the crospovidone may alter the stability of the dose form or influence the interaction between the aspirin and polyethylene glycol. The fact that this did not occur with Base C, most closely related to Base D chemically, is unexplainable at this time.

CONCLUSION

The affect of aging on aspirin release from polyethylene glycol suppositories with crospovidone were studied. Only a slight effect was seen in most bases. Base D stability was significantly increased by use of crospovidone. In formulations where changes of release patterns on aging occur, addition of crospovidone to the suppository base should be studied.

ACKNOWLEDGEMENT

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