DISSOLUTION OF SUPPOSITORIES III: EFFECT OF INSOLUBLE POLYVINYLPYRROLIDONE ON ACETAMINOPHEN RELEASE

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Abstract

Previously reported studies from this laboratory have demonstrated the usefulness of a new apparatus for suppository dissolution study. Acetaminophen suppositories gave slow release and it was posited that addition of a disintegrating agent commonly used in tablet manufacture would increase this release rate. To test the hypothesis, four PEG blends were used as bases as in the previous studies. Each contained 320 mg acetaminophen and 1%, 5%, or 10% of insoluble polyvinylpyrrolidone (Polyplasdone XL^{R}). One thousand milliliters of phosphate buffer, pH 8.0 to approximate rectal pH was employed as the dissolution media and maintained at 37.5°. A constant agitation rate of 25 and 50 rpm was used. Acetaminophen was assayed

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spectrophotometrically at 243 nm. Comparative dissolution profiles at the various agitation rates and with the concentrations of polyvinylpyrrolidone were developed. Addition of insoluble polyvinylpyrrolidone increased the dissolution rate constant and dissolution half-times at the two agitation rates. While the disintegration aid increased release, this release was not linear with respect to disintegrating agent concentration.

Release of acetaminophen from suppositories and the bioavailability of acetaminophen from suppository bases have not received much study. Feldman reported that the rate of bioavailability of suppositories was extremely variable and might not produce a clinically noted response (1). Maron and Ickes, however, reported that acetaminophen suppositories were clinically as effective an antipyretic as were tablets (2).

Pagay, et al. studied the influence of the vehicle on the bioavailability of acetaminophen suppositories using a modified beaker method with a media of pH 7.0 and an agitation of 25 rpm (3). These researchers correlated the dielectric constant of the base to acetaminophen bioavailability. Commercial suppositories were not discussed.

A recent report by Palmieri (4) discussed release of acetaminophen from laboratory prepared PEG bases

and commercially available suppositories. Dissolution half-times for laboratory prepared suppositories at 50 rpm ranged from 8 minutes for Base A to 22 minutes for Base D. The commercially available acetaminophen suppositories had a dissolution half-time of 90 minutes at 50 rpm. Because of these apparently slow release rates, it was posited that addition of a disintegrating agent would increase the release of acetaminophen from the polyethylene glycol base suppositores. Polyplasdone XL^{R}, (5) a crosslinked insoluble homopolymer of n-vinyl-2-pyrrolidone was used in an attempt to increase the release rate.

Experimental

I. Preparation of Suppositories

Four basic formulas were used:

Base A	PEG 1000	96%
	PEG 4000	4%
	Acetaminophen	320 mg
Base B	PEG 1540	75%
	PEG 4000	25%
	Acetaminophen	320 mg
Base C	PEG 1540	70%
	PEG 6000	30%
	Acetaminophen	320 mg
Base D	PEG 6000	50%
	PEG 1540	50%
	Acetaminophen	320 mg

Polyplasdone XL^{R} was employed in concentrations of 1%, 5%, and 10% 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 (6) 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 hollow spindle-stirrer apparatus was used to control the stirring rate at 25 rpm and 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 243 nm for dissolved acetaminophen. PEG bases exhibited no absorption at that wavelength. Polyplasdone XL^{R} also exhibited no absorption at this wavelength. Acetaminophen obeyed Lambert-Beer's Law at 243 nm, the wavelength of maximum absorption for the drug.

Results and Discussion

Dissolution rate profiles were obtained as explained in the Experimental Section. Table I is the

Table 1

Base A Dissolution at 25 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	3	4	5	5
3	11	14	14	23
5	21	22	22	35
10	31	39	41	44
20	66	71	74	90
30	73	85	75	98
45	85	86	88	99

average of 5 assays

* = percentage of polyplasdone

dissolution data for Base A at 25 rpm and is illustrated in Figure I. The incorporation of insoluble polyvinylpyrrolidone increased the dissolution rate in direct relationship to the concentration of the disintegrating agent although the increase was not linear with respect to disintegrating agent concentration. Table 2 and Figure 2 contain the data for Base A release at 50 rpm with 0, 1%, 5%, and 10% Polyplasdone XL^{R}. As with the 25 rpm data, a concentration increase in the disintegrating agent increased the dissolution rate, but not linearly.

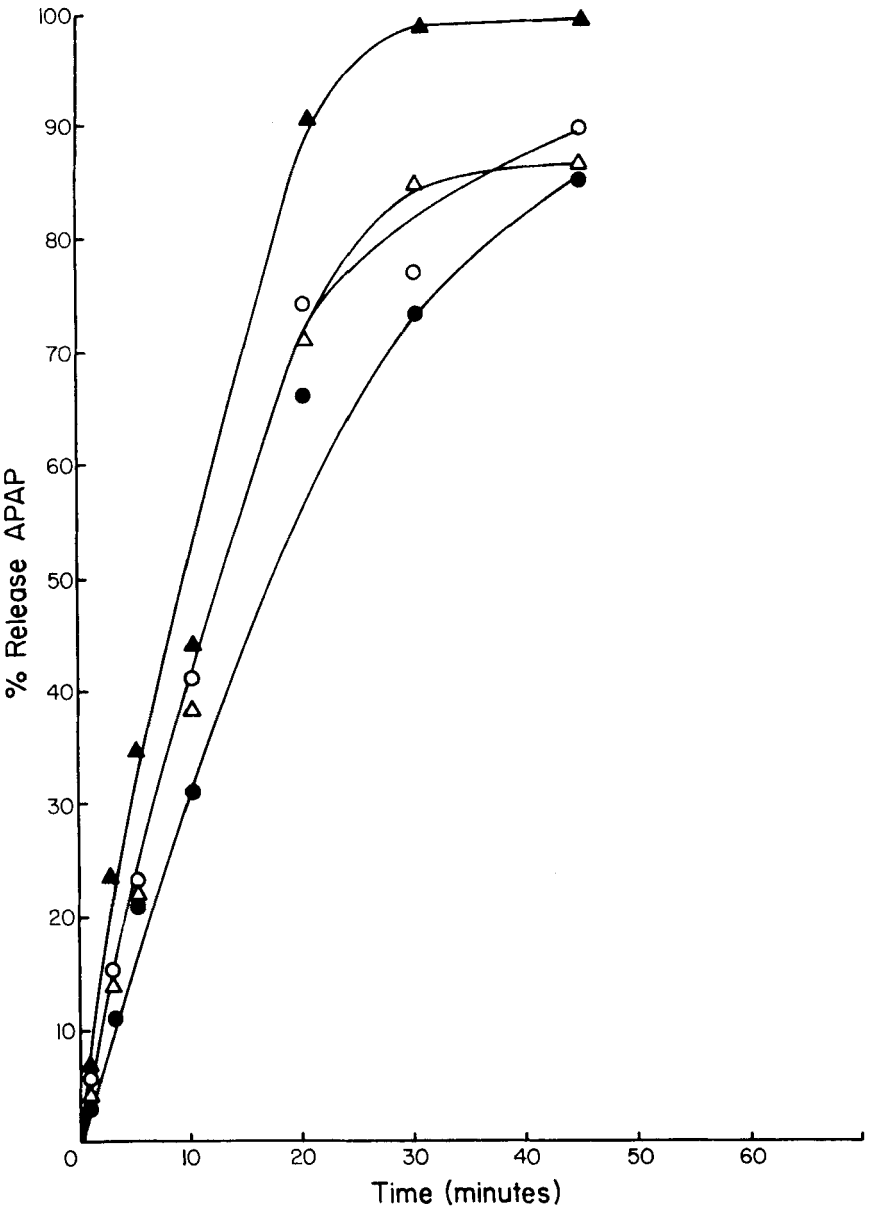

Figure 1: Base A Dissolution at 25 rpm

Key:

- ● 0% polyplasdone
- △ 1% polyplasdone
- ○ 5% polyplasdone
- ▲ 10% polyplasdone

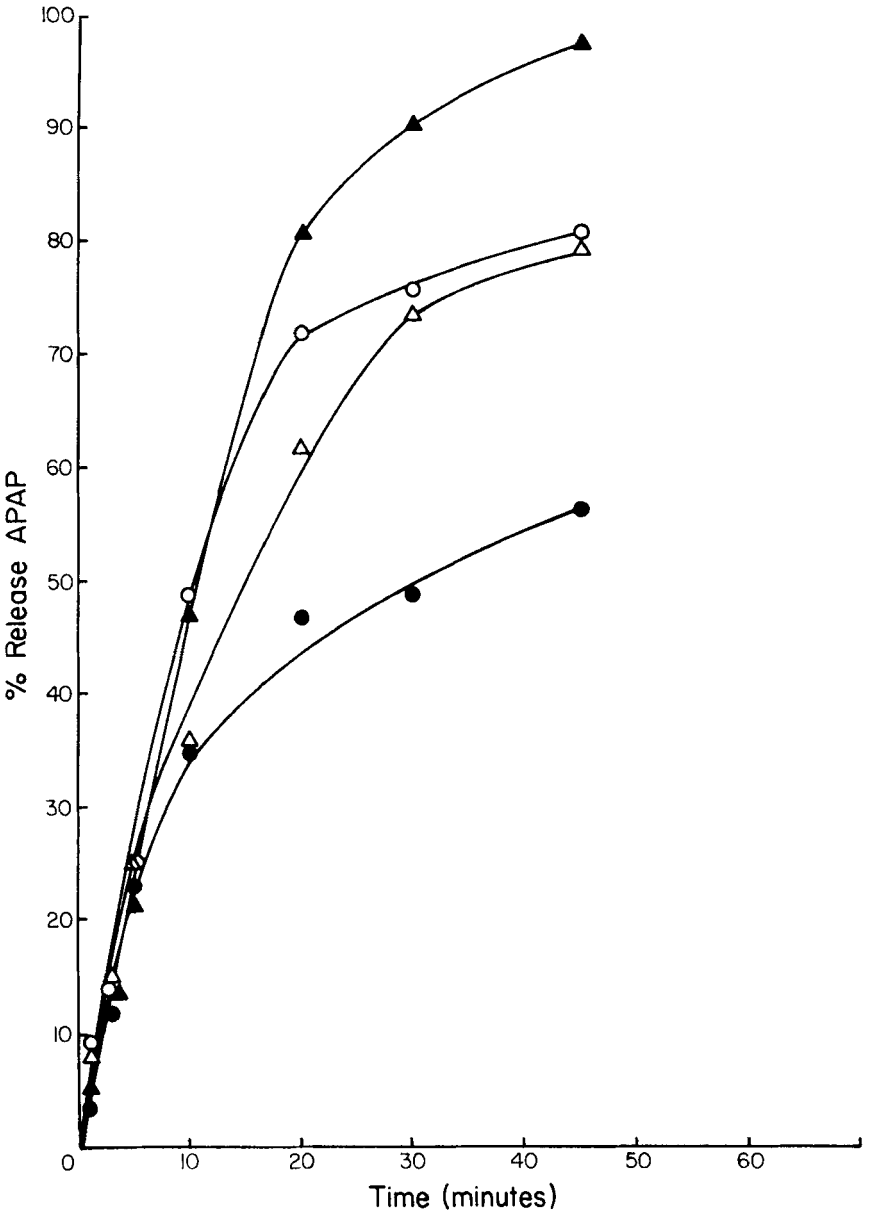

Figure 2: Base A Dissolution at 50 rpm

Key:

- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polyplasdone

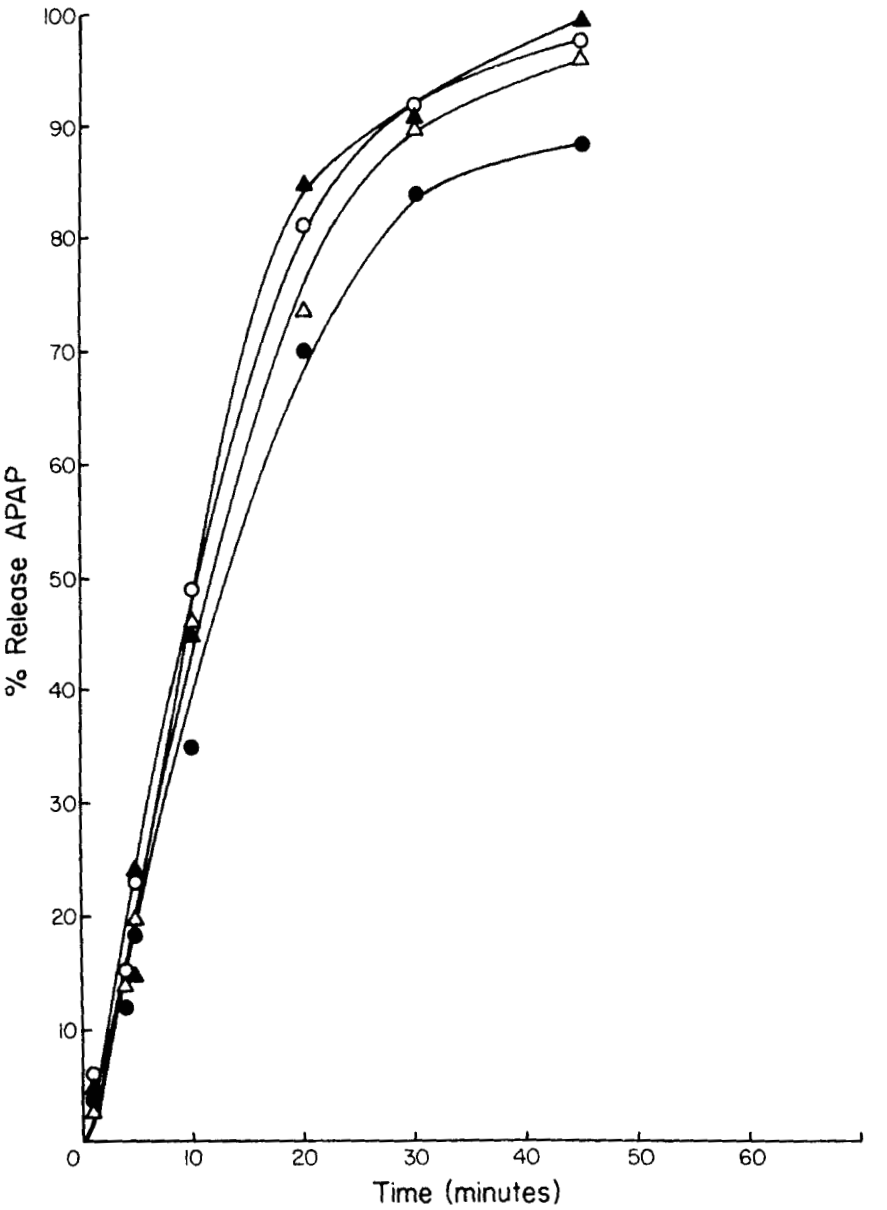

Figure 3: Base B Dissolution at 25 rpm

Key:
- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polyplasdone

Table 2

Base A Dissolution at 50 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	3	8	8	6
3	12	15	14	14
5	23	25	25	22
10	35	36	49	47
20	47	63	73	81
30	49	74	74	90
45	56	78	78	96

average of 5 assays

* = percentage of polyplasdone

Table 3

Base B Dissolution at 25 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	4	4	6	6
3	12	14	15	14
5	18	20	23	23
10	35	46	48	45
20	70	74	81	85
30	84	90	91	91
45	88	96	96	99

average of 5 assays

* = percentage of polyplasdone

Dissolution of Base B (Figures 2 and 3 and Tables 2 and 3) was not affected as much by the addition of the insoluble polyvinylpyrrolidone and, in fact at 50 rpm there was no significant dissolution rate increase. Base C (Figures 5, 6, and Tables 5, 6) had a more rapid dissolution when the disintegrant was added but increasing the amount of the additive did not have a significant bearing on the dissolution rate. Base D (Figures 7, 8 and Tables 7, 8) exhibited much faster dissolution when the disintegrating agent was added. The data at 25 rpm best illustrates the relationship between disintegrating agent concentration and the resultant dissolution rate profiles.

Insoluble PVP then, increased the release rate of acetaminophen from Bases A, C, and D but not Base B. It should also be noted that in all of the experiments the total release of acetaminophen was greater when using polyvinylpyrrolidone. Since the disintegrant quickens the breakup of the suppository it is expected to hasten the dissolution rate. The reason that the total amount of drug in solution is greater is unexplained and further research is necessary before an absolute conclusion can be reached. However, it is posited that if the experiments were carried out for a longer period of time, the total release might be equal. It can be stated that the amount released

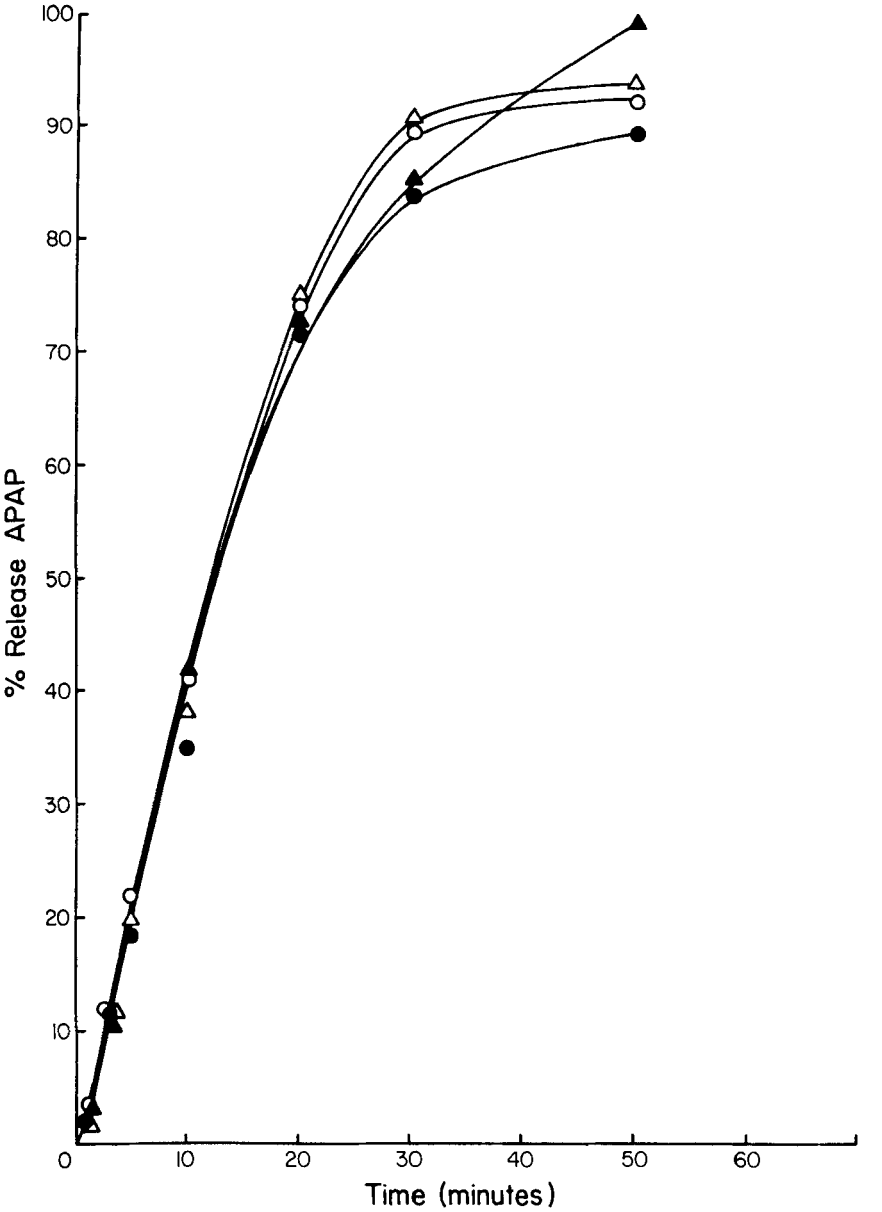

Figure 4: Base B Dissolution at 50 rpm

Key:
- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polylpasdone

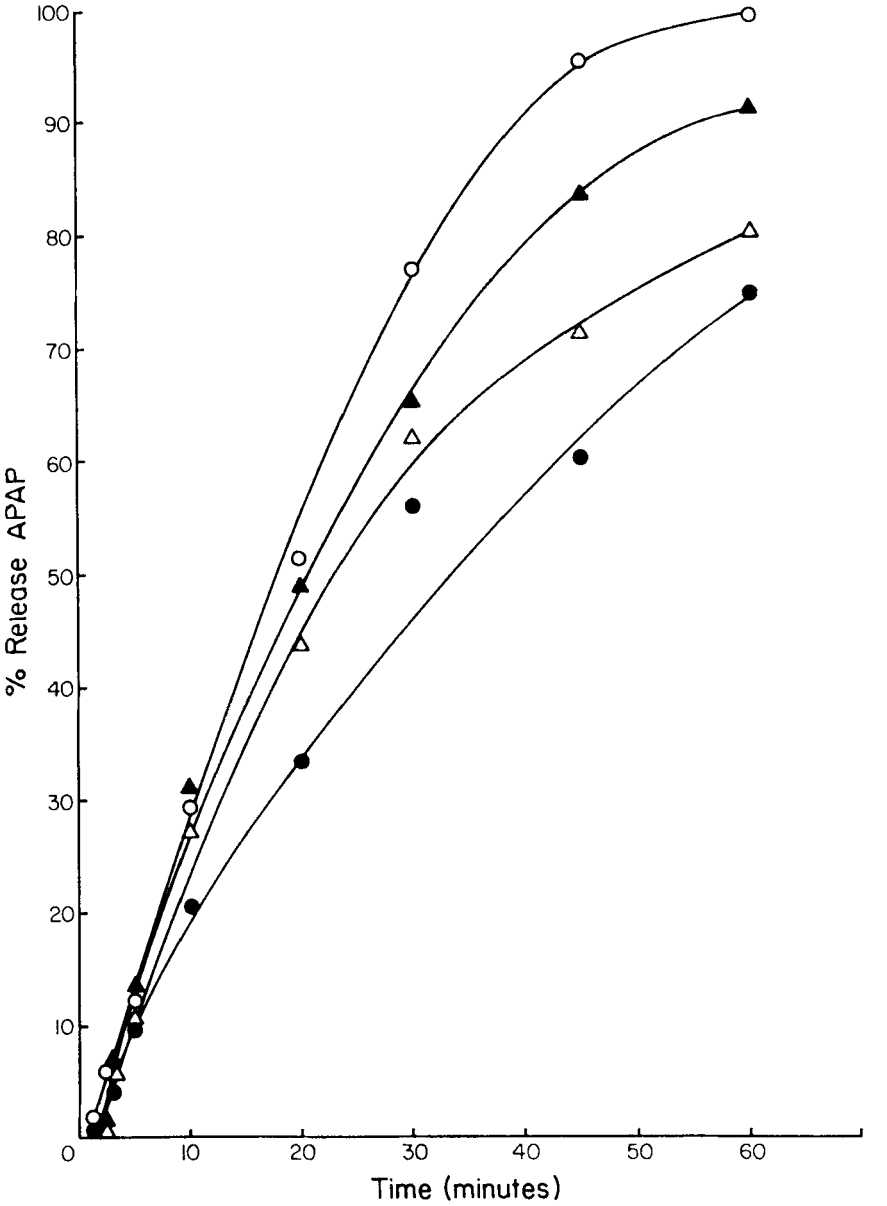

Figure 5: Base C Dissolution at 25 rpm

Key:
- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polyplasdone

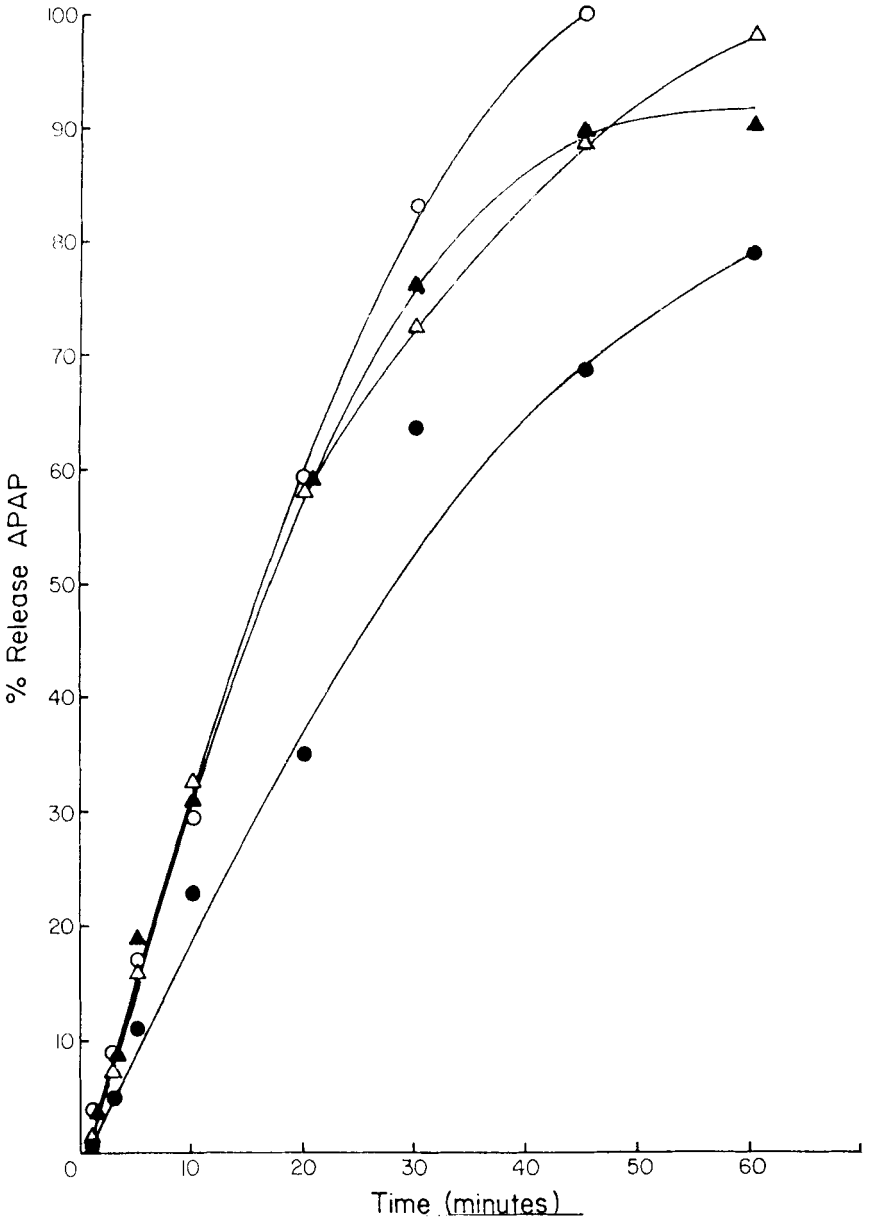

Figure 6: Base C Dissolution at 50 rpm

Key:
- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polylpasdone

Table 4

Base B Dissolution at 50 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	3	3	4	4
3	12	12	12	11
5	18	20	22	23
10	35	38	41	42
20	72	75	74	73
30	84	91	89	85
45	89	93	92	99

average of 5 assays

* = percentage of polylasdone

Table 5

Base C Dissolution at 25 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	1	1	1	2
3	4	6	6	7
5	10	10	12	13
10	21	27	29	31
20	33	44	52	49
30	56	63	77	65
45	60	71	95	83

average of 5 assays

* = percentage of polyplasdone

Table 6

Base C Dissolution at 50 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	1	2	3	3
3	5	8	9	9
5	11	17	17	19
10	23	33	29	33
20	35	57	59	58
30	64	72	83	76
45	68	88	99	89
60	78	98	--	90

average 5 assays

* = percentage of polyplasdone

at 45 minutes is greater when insoluble polyvinylpyrrolidone is employed.

The time for fifty-percent of the drug to be released (t_{50}) is most often correlated closely with relative absorption and as such, often relates to bioavailability (7). The t_{50} indicates a central tendency of the dissolution data and eliminates the need to attempt a kinetic interpretation of the data. Table 9 shows the dissolution t_{50}'s for Base A with the various concentrations of disintegrating agent. The 50 rpm data is the most dramatic, exhibiting a

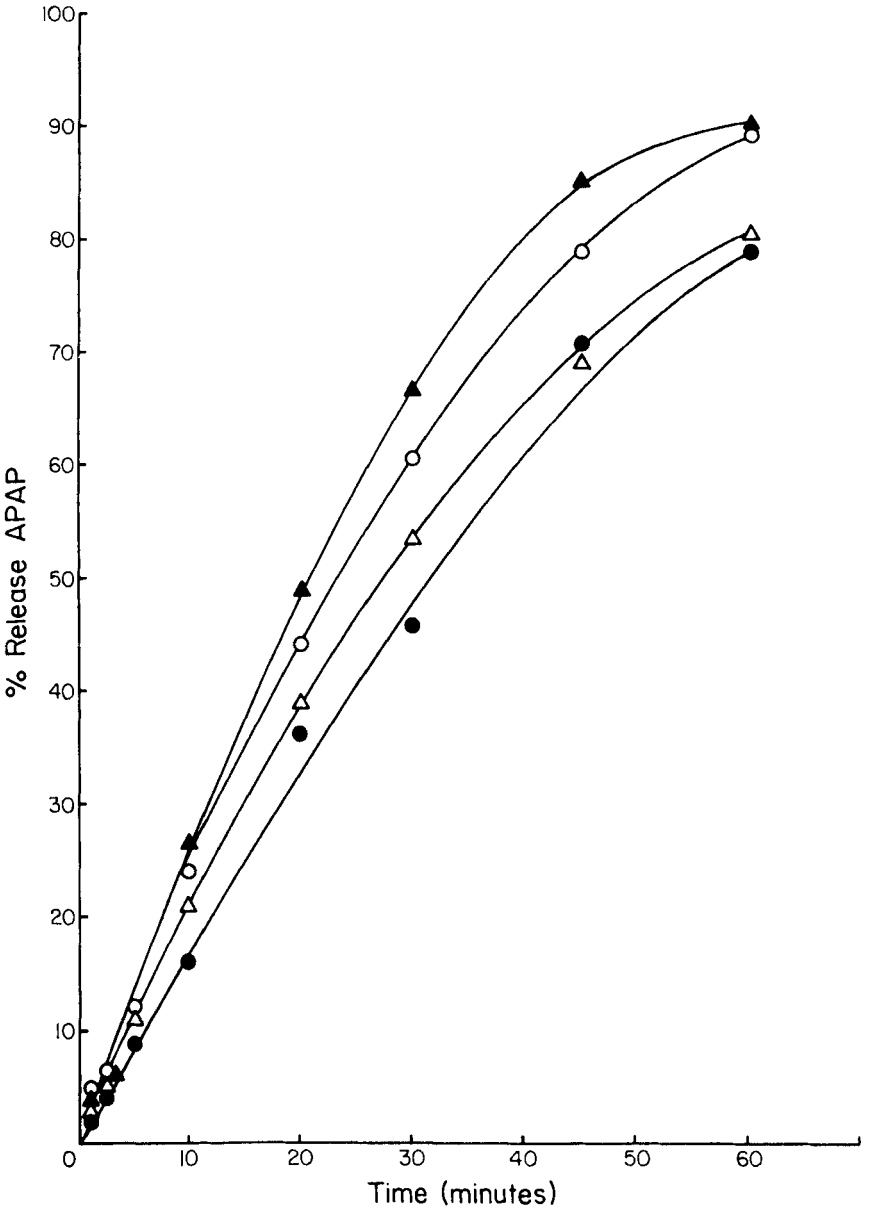

Figure 7: Base D Dissolution at 25 rpm

Key:
- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polyplasdone

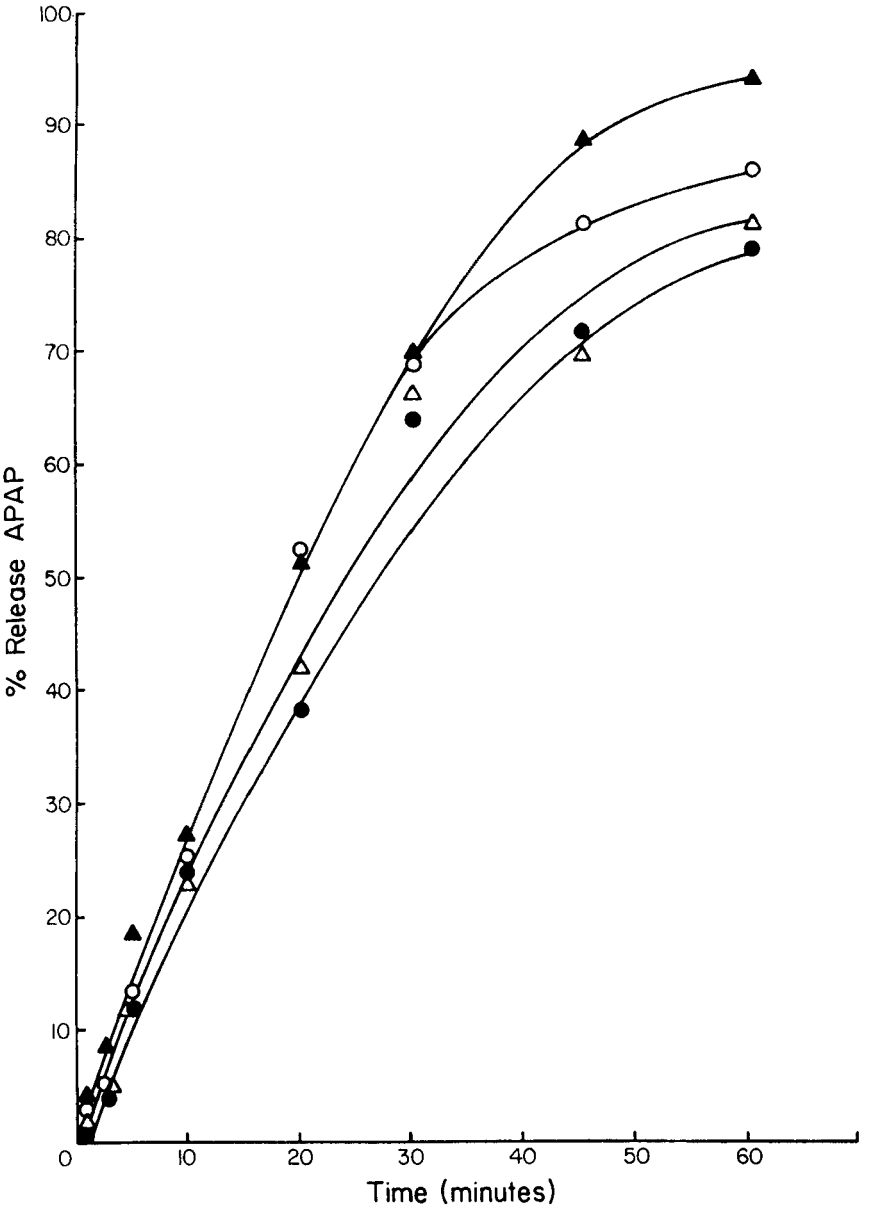

Figure 8: Base D Dissolution at 50 rpm

Key:
- 0% polyplasdone
- 1% polyplasdone
- 5% polyplasdone
- 10% polyplasdone

Table 7

Base D Dissolution at 25 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	2	2	3	3
3	5	6	5	6
5	8	11	11	12
10	17	21	22	26
20	36	39	44	49
30	46	53	60	67
45	71	68	78	85
60	79	80	88	89

average 5 assays

* = percentage of polyplasdone

t_{50} without Polyplasdone XL^{R} of 31 minutes being reduced to 7 minutes with 10% Polyplasdone XL^{R}. Base B, as shown in Table 10 also has a reduced t_{50} with the disintegrating agent although not as a dramatic a reduction as for Base A. This agrees with the previously mentioned data for Base B. With Base C (Table 11) once again the use of a disintegrant significantly decreases the dissolution half-time. Interestingly, the concentration of disintegrant does not greatly affect disolution half-time. As shown in Table 12, Base D dissolution t_{50} is also signifi-

Table 8

Base D Dissolution at 50 rpm

Time (minutes)	% Release APAP 0%*	1%*	5%*	10%*
1	1	2	2	3
3	4	5	5	9
5	12	12	13	18
10	24	23	25	26
20	38	43	53	52
30	64	67	68	69
45	72	69	81	89
60	79	82	86	94

average 5 assays

* = percentage of polyplasdone

Table 9

Dissolution Half-times for Base A

% polyplasdone	25 rpm (min)	50 rpm (min)
0	18.5	31
1	14.5	16
5	12.5	8.5
10	7.0	7.0

Table 10

Dissolution Half-times for Base B

% polyplasdone	25 rpm (min)	50 rpm (min)
0	15.5	14
1	12	13
5	11	12
10	10	12

Table 11

Dissolution Half-times for Base C

% polyplasdone	25 rpm (min)	50 rpm (min)
0	34	30
1	23	18
5	20.5	16
10	20	18

Table 12

Dissolution Half-times for Base D

% polyplasdone	25 rpm (min)	50 rpm (min)
0	32.5	26.5
1	28	24
5	23	19.5
10	21	19.5

cantly changed with the addition of insoluble polyvinylpyrrolidone, although there is no difference between the 5% and 10% data. This would indicate that there is a maximum dissolution rate regardless of PVP concentration above 5%.

Conclusions

In summary, except for Base B, the insoluble polyvinylpyrrolidone increased the total dissolution, the dissolution rate and the dissolution half-time for the polyethylene glycol base acetaminophen suppositories that were studied. While this data can not yet be correlated to *in vivo* suppository performance, it does indicate that addition of insoluble PVP might lead to increased absorption of acetaminophen from polyethylene glycol suppository bases.

Notes

1. The Polyplasdone XL^{R} was donated by the GAF Corporation, 140 West 51st Street, New York, N.Y. 10020
2. The Basket for Suppository dissolution testing s now available from Hanson Research Corp. 19727 Bahama Street, Northridge, CA 91324; part number 65-700-048

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