

SUSTAINED RELEASE
From Coated Ion Exchange Resins

by

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A substantial amount of work has been published concerning the use of ion exchange resins for sustained release of active materials. Applications have included adsorption of drugs with basic nitrogen groups (1), spray drying of drug resin complexes in the presence of dissolved polymers (2), and coating of resin complexes with waxes (3), enteric films (4), and cellulosic films (5,6). All of these steps had the effect of retarding release and/or masking a bitter taste. Ironically, ion exchange resins can also be used to ensure rapid release of some drugs by acting as a tablet disintegrants (7). Factors which control release rate are particle size of the resin, degree of crosslinking, and the chemistry of the resin, degree of crosslinking, and the chemistry of the resin and drug complex (8). The first two influence the rate of diffusion of the active through the resin particles. The third exerts control by altering the ion exchange equilibrium between the resin complex and the electrolytes in the body fluids.

Although it has been demonstrated that the release of actives can be retarded by forming drug resin complexes, the need to further retard the release of certain drugs is demonstrated in figure 1. It can be observed that while chloropheneramine releases from its resin complex (CPA RC) quite slowly, the release of phenylpropanolamine from its resin complex (PPA RC) is much more rapid with 70% of the drug released within 30 minutes. In order to prepare a sustained release form of phenylpropanolamine it was necessary that something other than simple formation of the resin complex be done.

When addressing this problem the Pennwalt Corporation of Rochester, NY asked us to assist them in developing a coated resin complex with sustained release properties. I wish to thank Drs. Raghunathan and Hinsvark and coworkers at Pennwalt Pharmaceutical for permission to discuss the results of this work. I refer those interested to papers these gentlemen presented at the 14th International Symposium on Microencapsulation, March, 1979 in Miami, FL. Papers presented at this symposium will be published in the Fall of 1979 in the Journal of Pharmaceutical Science.

The resin drug complex is prepared by slurring Amberlite® IR-120 or Amberlite® XE-69, hydrogen form, in a water solution of phenylpropanolamine base or any other drug in its basic form. After the drug complex had formed the complex was washed free of any unreacted drug with deionized water and dried in a fluid bed drier at 60 degrees C. The dried resin complex was screened, the Amberlite® XE-69 through a 60 U.S. mesh sieve and the Amberlite® IR-120 through a 10 U.S. mesh sieve. A drug loading of about 33% phenylpropanolamine by weight was obtained with either resin.

Prior to exploring the use of coatings applied as a separate step Pennwalt investigated spray drying the resin complex suspended in a solution of ethylcellulose (9). This process had virtually no effect on the release rate of the active.

We used fluid bed coating techniques (10-13) to apply a film of ethylcellulose 50 dps, plasticized with Durkex 500, a refined vegetable oil. It was found that the ion exchange resin particles could be readily coated by this method, but that simply coating the particles did not provide the complete answer. It was observed that the resin particles, which are a gel type material, swell greatly when placed in water and shrink when redried. This swelling results in rupture of the ethylcellulose film when the coated particles are rewetted, destroying any sustained release effects due to the film. In spite of this it can be observed in figures 2 and 3 that the coating did retard the release of the active from both Amberlite® IR-120 and XE-69 resins (line 1 vs. line 2).

Several efforts were made to coat the particles in the wet swollen state, however these were unsatisfactory due to the poor flow properties of the wet resin and the loss of water in processing. It was determined that impregnation of the swollen particles with certain agents prevented them from shrinking upon drying, thus minimizing any swelling when rewetted. Polyethylene glycol 4000 was selected as having the desired properties. PEG 4000 alone did retard the water uptake of the resin complexes, however the combination of PEG 4000 followed by an ethylcellulose overcoat had a greater effect. Water uptake times are indicative of the rate of diffusion of water into the resin complex and thus correlate with diffusion of the active out of the complex. Water absorption times were measured by contacting 5 grams of resin with 4 mls. of water and measuring the time in seconds for the water to be absorbed (9).

<u>RESIN COMPLEX</u>	<u>ABSORP. (SEC)</u>
XE-69 PPA RC, untreated, uncoated	36
XE-69 PPA RC, treated w/PEG 4000	1149
XE-69 PPA RC, treated w/PEG, coated	1800+

Line 3 in figures 2 and 3 indicates the retardation of release of phenylpropanolamine for IR-120 and XE-69 resin complexes after treating with PEG 4000 and overcoating with ethylcellulose. Notice that there is a difference in both time scale and coating level between figures 2 and 3. XE-69 is a small particle form IR-120.

The effect of coating level can be observed in figure 4 which shows the release of a different drug, d-methorphan, from XE-69 with no coating and two different levels of coating. This is further demonstrated in figure 5 which shows the release of PPA RC when coated with three different levels of ethylcellulose. As expected, the release is slower when heavier coatings are used.

For practical reasons it is necessary to control the particle size not only of the starting ion exchange resin but also of the treated coated product. This is particularly true when oral suspensions are to be the final product form. Screen data for both the coated and uncoated PPA RC are as follows (10):

U.S. Std. Sieve Size	Uncoated PPA RC	Coated PPA RC
+14 mesh	0.3%	0.3%
-40/+80	10.0%	15.1%
-80/+140	30.6%	42.4%
-140/+200	38.1%	27.0%

-200

20.9%

15.3%

The d_{50} for the uncoated and coated forms are 90 micrometers and 123 micrometers respectively.

Figure 6 compares the release of PPA from coated PPA RC mixture with the release from fully formulated capsules and a suspension. It can be seen that there is good correlation between the curves.

Hinsvark, et. al. (14) present data which shows that, when administered at 12 hour intervals the experimental dosage form produced comparable plasma minima demonstrating equivalent efficacy, and a prolonged time at peak when compared with the conventional dosage form administered at 6 hour intervals.

For further information concerning the development of this product contact COATING PLACE, INC.

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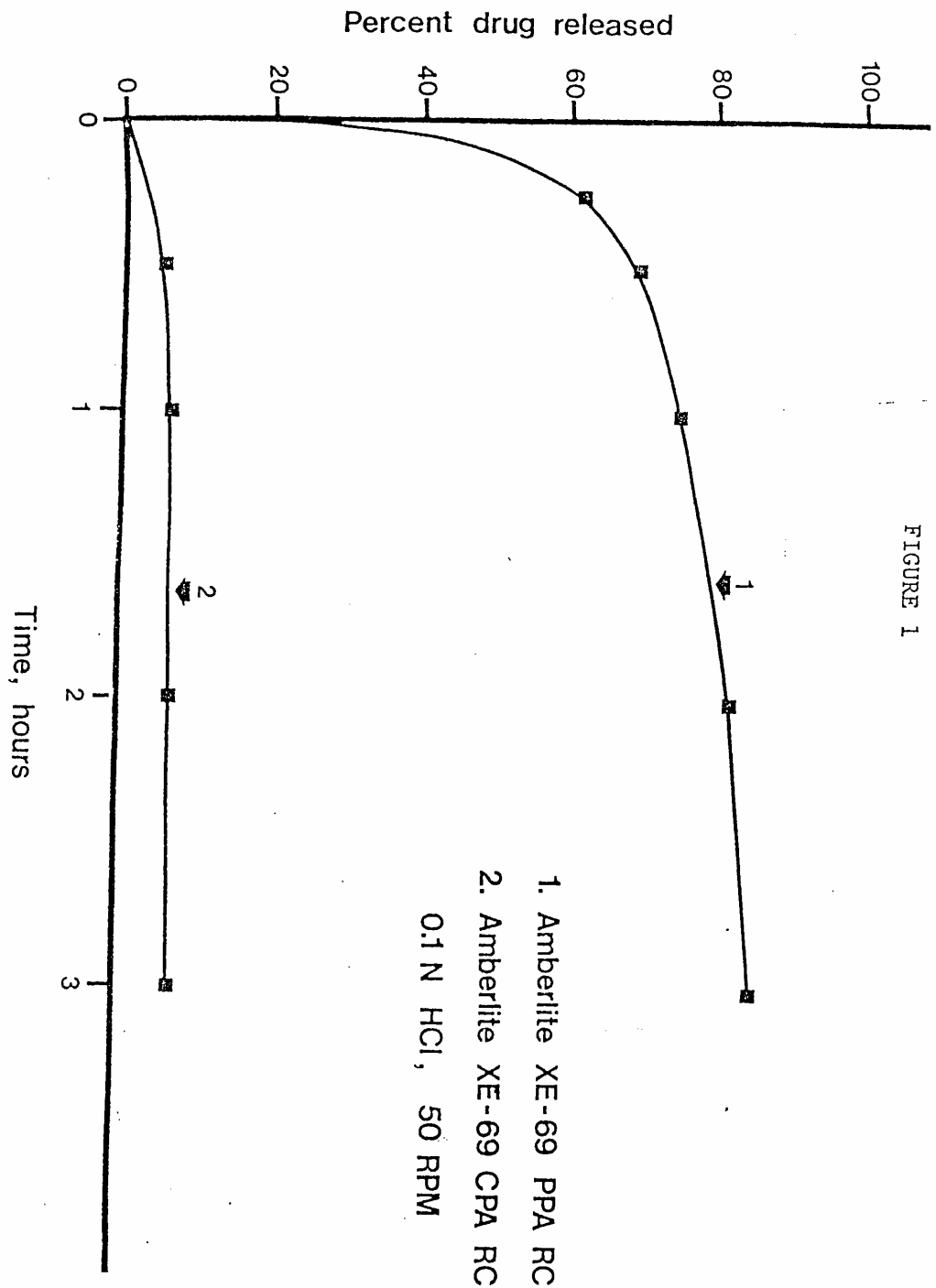
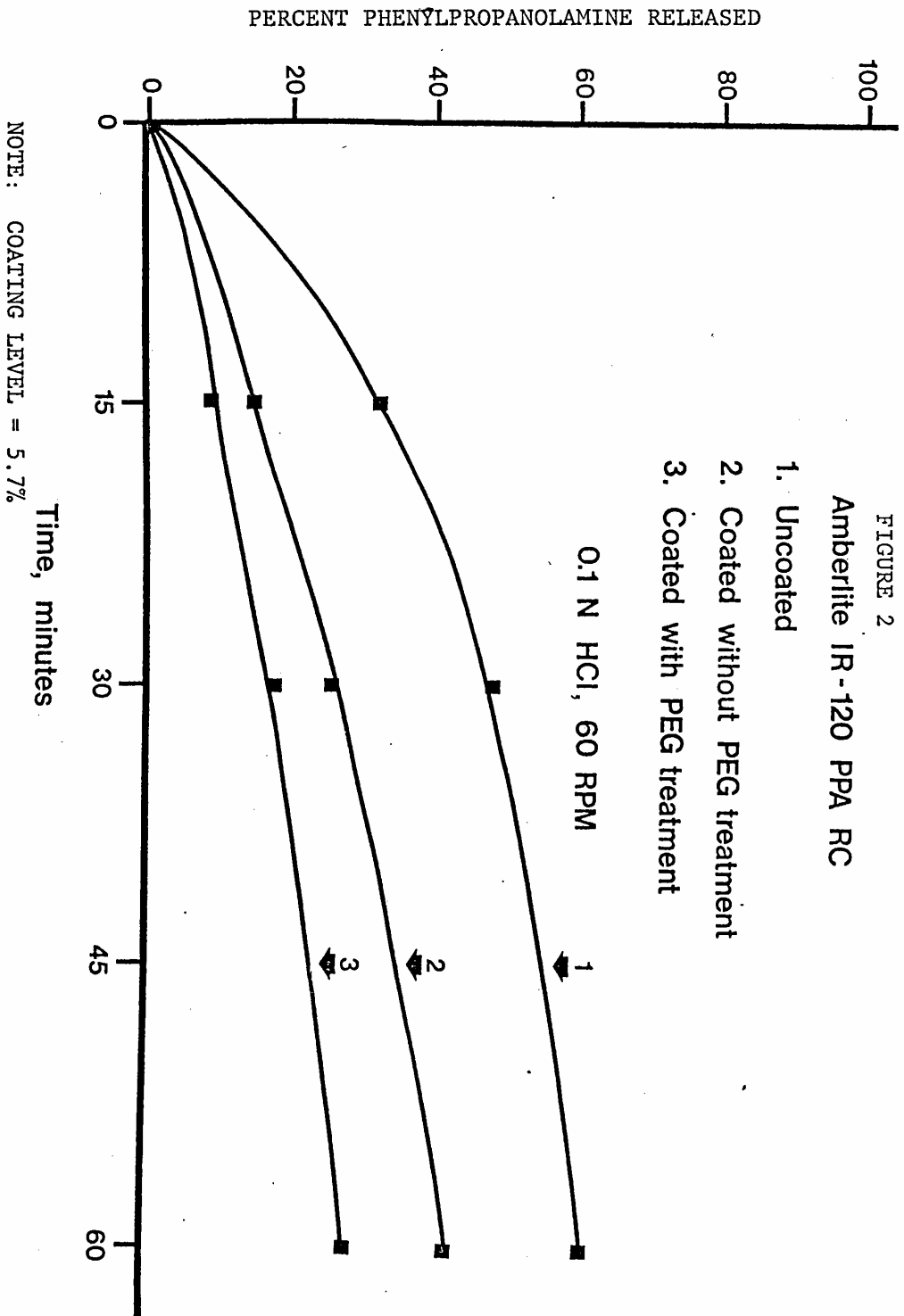


FIGURE 1



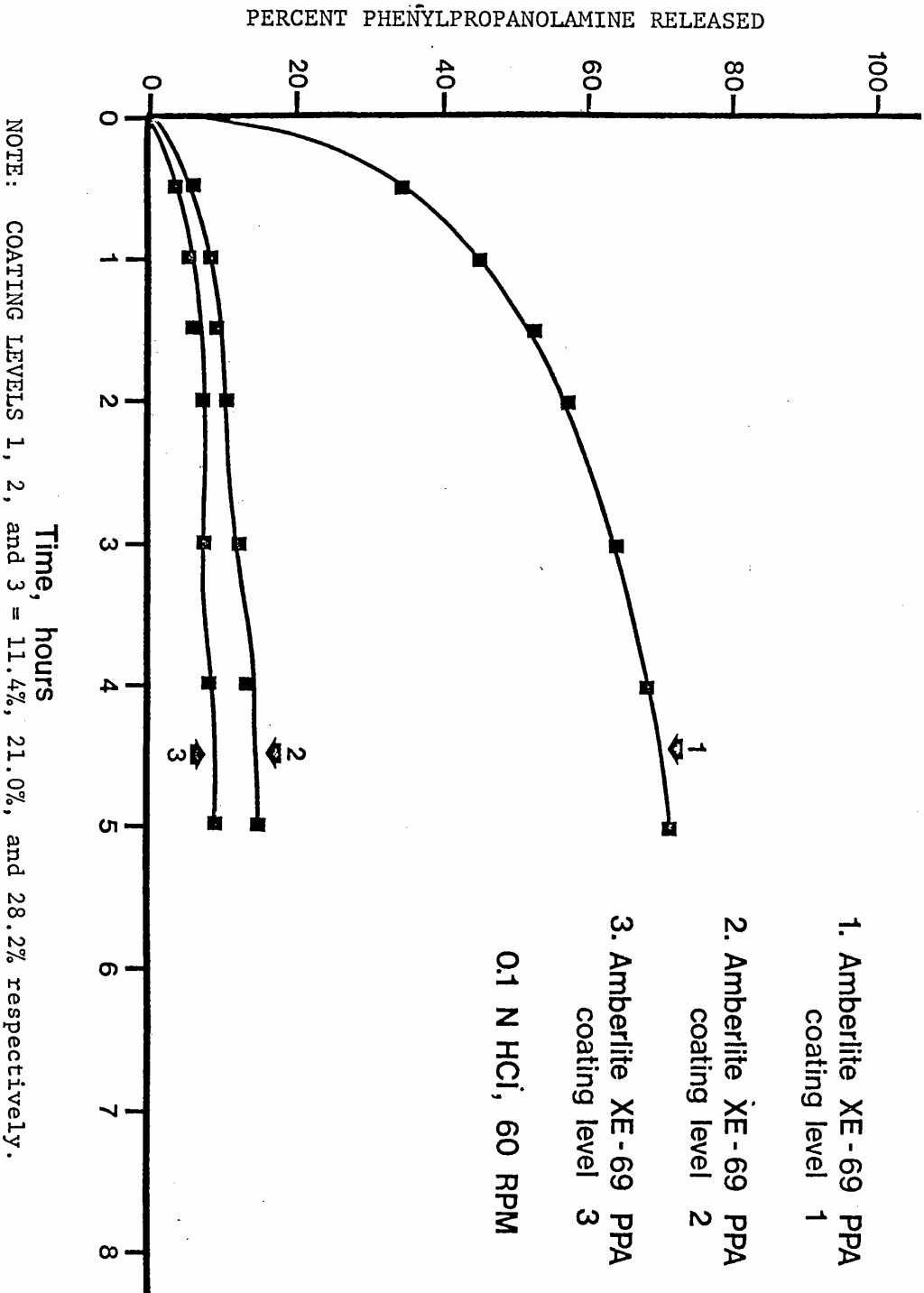
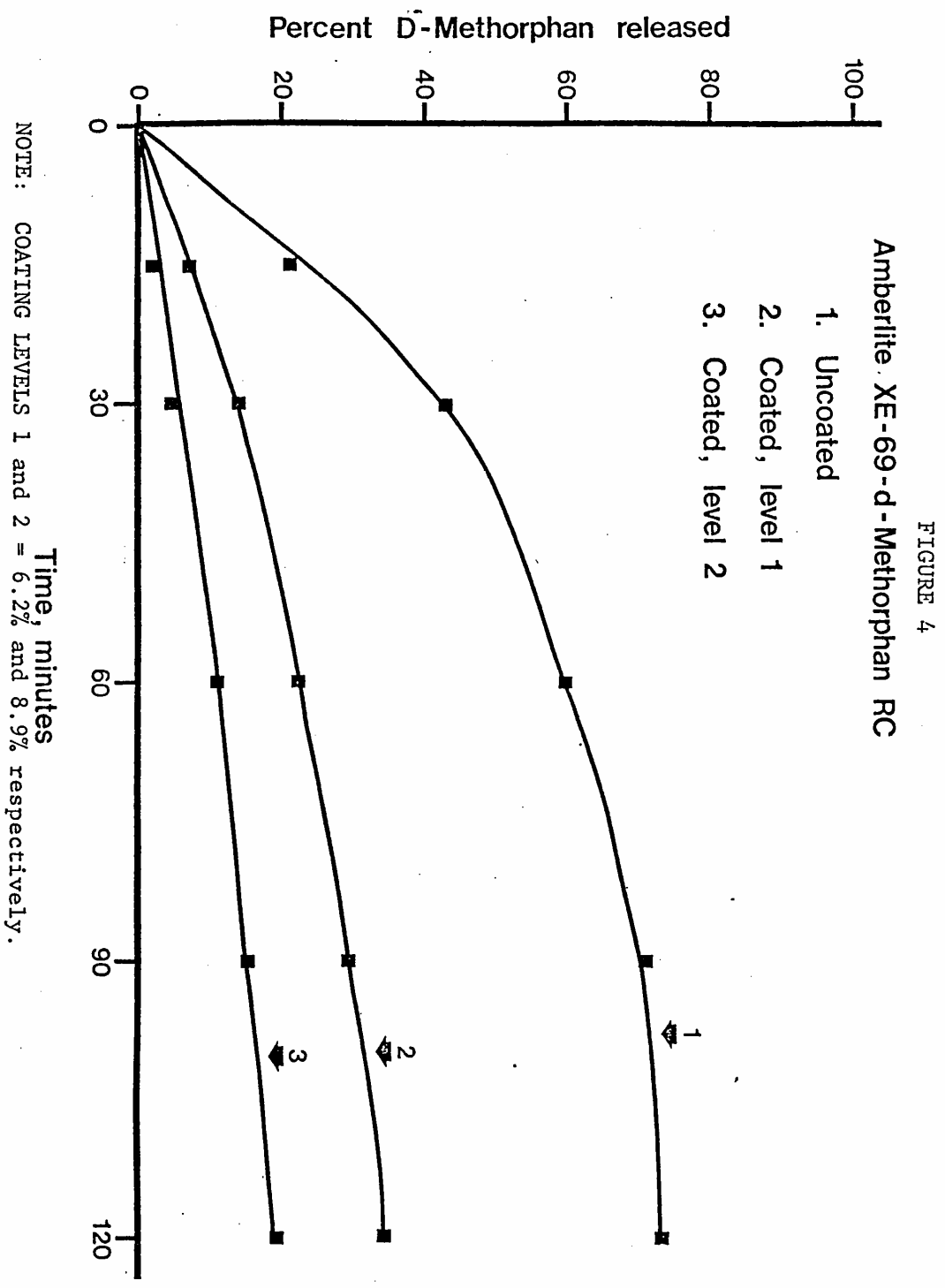


FIGURE 3



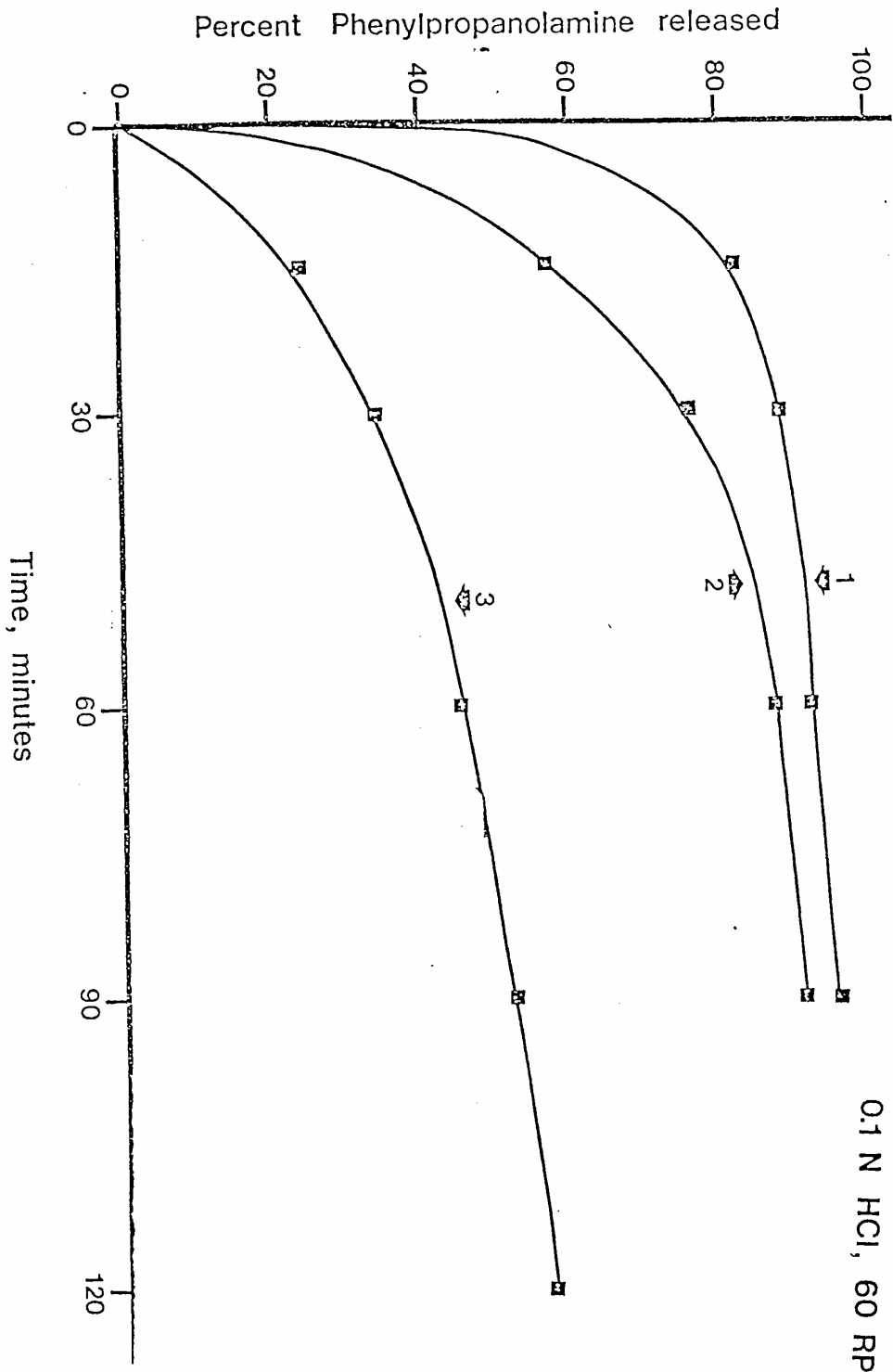


FIGURE 3

- Amberlite XE-69 PPA RC
1. Uncoated
 2. Coated without PEG treatment
 3. Coated with PEG treatment

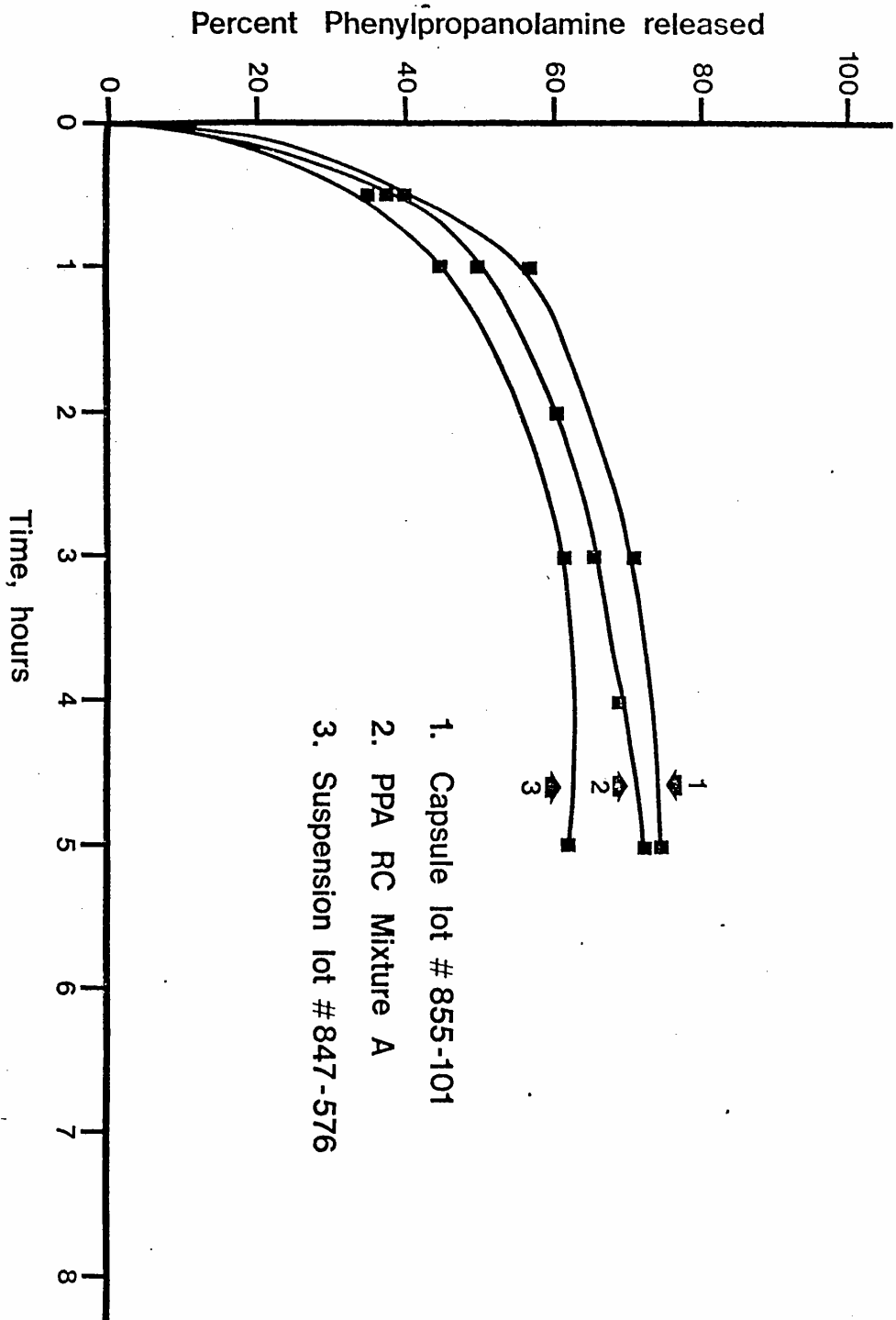


FIGURE 6