# Evaluation of Polymeric Materials III

## *In Vitro* and *In Vivo* Testing of Granules Coated with the *n*-Butyl Half Ester of Poly(Methyl Vinyl Ether)/Maleic Anhydride

By ROBERT JAY NESSEL*, H. GEORGE DEKAY, and GILBERT S. BANKER

**A sustained-action dosage form was developed in which film coated granules designed for independent distribution in the stomach were compressed into tablets for subsequent release in an intact condition upon disintegration of the tablet. The polymeric coating developed contained the *n*-butyl half ester of poly(methyl vinyl ether)/maleic anhydride, diethylphthalate, sorbitan monooleate, and precipitated calcium carbonate. The polymeric coating was applied to medicinally active granules of *d*-amphetamine sulfate which were assayed by *in vitro* and *in vivo* methods for drug release. The administration of the coated granules to a series of rats produced a statistically significant duration of action of 11.5 hours as compared to 7 hours for the uncoated granules. The coated granules were tableted utilizing polyethylene glycol 6000 as the matrix. The tablets of coated granules continued to produce increased motor activity in the test animals after 12 hours, while the tablets of uncoated granules showed no increased activity after 7.5 hours.**

MANY INVESTIGATORS (1, 2) have studied various chemical and physical methods of controlling drug release from solid dosage forms intended for oral administration. One of the most prominent physical methods of achieving this goal has been the use of coatings.

In the last decade, a large number of products has been introduced that are designed to provide a prolonged duration of drug action. One of the most prominent of these consists of encapsulated coated pellets or beads. In the coating of these pellets mixtures of various fatty materials and/or waxes have been the most widely used materials, however, various synthetic polymers (3, 4) have also been used as coatings in the preparation of sustained-release dosage forms.

The tableted sustained-release products have been compressed ion-exchange resins, or drug-wax or drug-resin fusion products or similar mixtures. Coated particles designed for sustained release are conventionally placed in hard gelatin capsules. The virtual absence of coated particles designed for sustained release and placed in tablet form, with the dosage form designed to release the granules in the stomach, may be due to inadequately plasticized films, the use of less pliable films (cellulosics), the lack of a suitably elastic tablet matrix, or a combination of these factors.

The preparation of coated pellets in a tablet dosage form would be advantageous over the conventional encapsulated form from the standpoints of expense, patient convenience, accuracy of dosage, and ease of manufacture. This investigation was undertaken to study the feasibility of preparing a sustained-release dosage form in which coated particles designed for independent distribution in the stomach would be compressed in tablet form for subsequent intact release upon tablet disintegration.

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## EXPERIMENTAL

**Polyvinylpyrrolidone-d-Amphetamine Sulfate Dialysis.**—Polyvinylpyrrolidone[1] was selected as the granulation binding agent because it produces very hard granules. This characteristic is necessary in the formation and coating of granules by the pan method, and was considered vital to the objectives of the study.

Since polyvinylpyrrolidone has been reported to interact with a variety of medicinals (5), it was necessary to determine if any such interaction occurred with *d*-amphetamine sulfate and if the polymer interfered with the assay procedure.

Twenty milliliters of a $3.5 \times 10^{-4}$ *M* solution of polyvinylpyrrolidone was accurately pipeted into bags prepared from Nojax Visking casing. The bags were placed in bottles containing 70 ml. of a $5 \times 10^{-3}$ *M* solution of *d*-amphetamine sulfate. Four such bottles were prepared, tightly sealed, and rotated end over end at 41 r.p.m. in a water bath maintained at 37 ± 2°. Two bottles were removed after 24 hours and the others after 48 hours. Control bottles were similarly prepared by (*a*) substituting distilled water for the polyvinylpyrrolidone, and (*b*) replacing the drug solution with distilled water. These samples served to determine drug-membrane binding and polymer permeability of the membrane. The assay for drug content was conducted using the baseline technique, as described by Royal (6), on the internal and the external solutions. The Bausch & Lomb spec-

[1] Antara Chemicals, Division of General Aniline and Film Corp., New York, N. Y.

tronic 505 recording spectrophotometer[2] was used to obtain the data on the polyvinylpyrrolidone–distilled water samples. The assay for drug content was conducted on the Beckman DU model 2400 spectrophotometer.[3]

**Preparation of Granules.**—The granulation used for the coating procedure was

| | |
|---|---|
| *d*-Amphetamine Sulfate | 3% |
| Lactose | 92% |
| Polyvinylpyrrolidone K-30 | 5% |
| Ethyl Alcohol 75% | *q.s.* |

The dry ingredients (3 Kg.) were mixed and granulated with the alcohol. The mass was passed through a 20-mesh screen by hand and the resulting wet granules were placed in a standard 12-inch stainless steel coating pan revolving at 36 r.p.m. The granules were allowed to rotate until they were rounded and the granule surfaces smoothed, after which an infrared lamp was directed into the revolving pan for drying. The dried granules were sized and those passing through a 20-mesh but not a 30-mesh screen were selected for coating.

**Coating Procedure.**—In the preparation of a coated granulation, 150 Gm. of 20/30-mesh granules was placed in a 6-inch copper coating pan.[4] Coating solutions containing 5% w/v of the *n*-butyl and isobutyl half esters and the 2-ethylhexyl partial ester of PVM/MA [poly(methyl vinyl ether)/maleic acid], one or the other, and 1% w/v of sorbitan monooleate plasticizer in the acetone-alcohol solvent system, were separately applied to the granules. Application was achieved by spraying the various solutions on the moving bed of granules, with a No. 15 DeVilbiss[5] atomizer. Coating was continued until 10% polymer, based on granulation weight, was applied. The acrylic/methacrylic copolymer was similarly applied, but due to its high molecular weight and high viscosity could be applied in a solution concentration of only 1%, and was thus added as a coating at a lower level; 1% polymer to granulation weight.

In addition to coating the granules with the polymer films described above, the granules were also coated with a combination of polymer material and dusting powder. In this study the coating procedure involved spraying 150 Gm. of 3% *d*-amphetamine sulfate granules, as previously described, with Fully Plasticized Coating Solution (No. 1)

| | |
|---|---|
| *n*-Butyl Half Ester of PVM/MA | 5% |
| Sorbitan Monooleate | 3% |
| Diethylphthalate | 1.5% |
| Acetone | |
| Ethyl Acetate | aa *q.s.* 100% |

A sufficient quantity of solution was sprayed on the moving granule bed to completely wet the granules to the point that they began to adhere to each other. One of the three dusting powders (talc, magnesium stearate, or precipitated calcium carbonate) was then applied in a quantity sufficient to restore free bed movement. An infrared lamp was used to thoroughly dry the coating before repeating the cycle. Each dusting powder was used with the coating solution at a 5% and at a 10% level of polymer to uncoated granulation starting weight (150 and 300 ml. of coating solution). In coating with the dusting powder, the coating solution containing the highest concentration of sorbitan monooleate and phthalate plasticizer which would produce an intact film was used, in order that the final film containing a high level of dispersed solid would retain some degree of flexibility.

**In Vitro Assay and Sampling Procedure.**—The assay procedure of Royal (6) was modified in the case of the coated granules, due to polymer and plasticizer interference. The modification entailed the use of carbon tetrachloride as a selective solvent for the plasticizer and an ion-exchange resin, Amberlite IRC-50,[6] to separate the polymer and the drug.

Approximately 1.0 Gm. of coated granules was accurately weighed and placed in a 90-ml. bottle to which was added 60 ml. of simulated gastric fluid. The bottle was tightly sealed and rotated at 41 r.p.m. in a water bath maintained at 37 ± 2°. Samples of the test solution were periodically withdrawn and replaced with other test solutions as shown in Table I.

TABLE I.—SAMPLING TIME AND FLUID REPLACEMENT FOR *In Vitro* ASSAY

| Time, hr. | Sample Withdrawn, ml. | Replacement Fluid | ml. | pH of Test Solution |
|---|---|---|---|---|
| 0.0 | .. | ... | .. | 1.2 |
| 0.5 | 20 | Gastric | 20 | 1.2 |
| 1.5 | 30 | Intestinal | 30 | 2.4 |
| 2.5 | 40 | Intestinal | 40 | 6.8 |
| 4.5 | 30 | Intestinal | 29 | ... |
| | | NaOH T.S. | 1 | 7.6 |
| 6.5 | 30 | Intestinal | 29 | ... |
| | | NaOH T.S. | 1 | 7.6 |
| 8.0 | 30 | ... | .. | ... |

A 10-ml. aliquot of each sample which was withdrawn after the time intervals shown in the table was pipeted into a separator containing 10 ml. of carbon tetrachloride, and the mixture was agitated until equilibrium was obtained. The aqueous layer was then quantitatively transferred to an ion-exchange column and allowed to filter at the rate of 1 ml. per minute. To each of the 10-ml. aliquots removed from the samples withdrawn after 0.5, 1.5, 2.5, and 4.5 hours, sodium hydroxide test solution was added to neutralize the acid present and thus prevent premature elution of the drug. The column was then washed with approximately 30 ml. of distilled water. Elution of the drug was carried out using 0.5 *N* sulfuric acid and the eluate was collected in a 50 ml. volumetric flask at the rate of 1 ml. per minute. The acid was passed through the column until the eluate measured 50 ml. Each solution was then assayed for drug content on the Beckman DU model 2400 spectrophotometer.

**In Vivo Assay of Granules.**—The method used in the determination of the *in vivo* release data involved the use of the Williamson activity cage[7] to measure increased spontaneous motor activity.

Female Holtzman rats were used throughout the study. Their initial weight in each case was between 150 and 175 Gm. In all cases, the rats were fasted 18 to 24 hours prior to dosing and were precondi-

[2] Bausch & Lomb Optical Co., Rochester, N. Y.
[3] Beckman Instrument Co., Fullerton, Calif.
[4] Arthur Colton Co., Detroit, Mich.
[5] The DeVilbiss Co., Somerset, Pa.
[6] Rohm & Haas Co., Philadelphia, Pa.
[7] Williamson Development Co., Inc., West Concord, Mass.

TABLE II.—TWENTY-FOUR HOUR DIALYSIS STUDY OF POLYVINYLPYRROLIDONE AND *d*-AMPHETAMINE SULFATE

| Solution Inside Permeable Sac | Solution Outside Permeable Sac | Sample Assayed | Drug Concn., mg./ml. |
|---|---|---|---|
| PVP[a] solution | Drug | Inside sac | 1.5 |
| PVP solution | Drug | Outside sac | 1.4 |
| Water (control) | Drug | Inside sac | 1.5 |
| Water (control) | Drug | Outside sac | 1.5 |

[a] Polyvinylpyrrolidone.

tioned 30 minutes to acquaint the animal with the cage. In all portions of this study, three groups of animals were used simultaneously. One group served as controls, one received uncoated granules of the drug, and the third group received coated *d*-amphetamine sulfate granules. Ten animals were employed in each group. All doses were administered by stomach tube as 5 ml. suspensions in 5% hydroxypropyl methyl cellulose[8] solution. The control animals each received 5 ml. of the suspension vehicle.

Each dose was calculated on the basis of 10 mg. of drug per kilogram of body weight, taking into consideration the weight of the coating. Five milliliters of the suspension vehicle was poured into the barrel of a 5 ml. hypodermic syringe, to which was attached a No. 10 French catheter by means of a collar. The granules were added to the barrel and mixed with the suspension vehicle. The catheter was then forced down the esophagus of the preconditioned rat into the stomach, and the suspension was introduced with the aid of the syringe plunger. The animals were placed in the Williamson activity cages, the room darkened, and the recorder started. The door to the test room was closed and other steps were taken to reduce external animal stimulation due to noise. The test period lasted 12 hours, at which time the total number of responses in each successive half-hour period was determined. For each run of the activity cages at least one animal received coated granules, one received uncoated material, and one (the control) received the vehicle only. According to this method, any condition resulting in external stimulation of the animals would affect all three test groups and would thus have a minimal effect on the end results. As stated above, ten animals received coated granules, ten received uncoated granules, and ten served to provide the control activity line.

The hydroxypropyl methyl cellulose suspension vehicle for the coated and uncoated granules, was selected from a series of suspension vehicles studied, and was virtually the only vehicle of the group which did not appear to affect (retard) the absorption of the drug studied. The vehicles studied included solutions or dispersions of starch, Methocel 4000,[8] sodium carboxymethylcellulose,[9] and Cab-O-Sil,[10] as well as Tween 80,[11] and corn oil.

The *in vivo* assay procedure utilized the granulation coated with 10% w/w of *n*-butyl half ester of PVM/MA [poly(methyl vinyl ether)/maleic acid, low molecular weight grade], plasticized with sorbitan monooleate 60% and diethylphthalate 33% based on polymer weight, and using precipitated calcium carbonate as the dusting powder. A series of ten trials was conducted and the responses per half-hour interval were averaged. Statistical analysis was accomplished using the Student Newman Kuels test as described by Winer (7).

**Preparation of Tablets.**—The formulas for the tablets were

TABLETS OF COATED GRANULES

| | |
|---|---|
| Polyethylene Glycol 6000[12] (20-mesh flakes) | 90 mg. |
| Coated Granules | 40 mg./tablet |

TABLETS OF UNCOATED GRANULES

| | |
|---|---|
| Polyethylene Glycol 6000 (20-mesh flakes) | 90 mg. |
| Lactose | 18 mg. |
| Uncoated Granules | 22 mg./tablet |

CONTROL TABLETS

| | |
|---|---|
| Polyethylene Glycol 6000 (20-mesh flakes) | 90 mg. |
| Lactose | 40 mg. |

Tablets were designed to contain the correct drug dose (10 mg./Kg.) for each rat according to weight. The quantity of each ingredient per tablet was weighed separately, mixed, and transferred to a 1/4-inch die for compression by hand on a single punch tablet machine, to a hardness of 5 to 7 Kg.

**In Vivo Assay of Tablets.**—Administration of the tablets to the test animals was accomplished by surgical procedure. Female rats were fasted as previously described and were then anesthetized. An incision was made in the area of the greater curvature in the cardiac region of the stomach, and three tablets of one of the three series were introduced into the stomach. The incision was then sutured and the animals were transferred to activity cages. Three groups of animals were used as before (one group for tablets containing coated drug granules, one for uncoated granules, and one for the control tablets), but in this case only three or four animals were used per group. Statistical analysis of the results was conducted in the same manner as that used for the granules.

## RESULTS AND DISCUSSION

**Polyvinylpyrrolidone-d-Amphetamine Sulfate Dialysis.**—Prior to the preparation of the *d*-amphetamine sulfate granulation, it was necessary to determine the existence or extent of drug-polymer granulating agent interaction. The results of the dialysis study relating to this portion of the work are shown in Table II. Other dialysis samples which were run for 48 hours demonstrated the same results as those shown in the table, *i.e.*, free and equilibrated drug exchange across the membrane indicating no significant polymer drug binding.

**Drug Release from Coated Granules.**—The *in vitro* release rates of the 3% *d*-amphetamine sulfate granulation coated with 10% w/w polymer are given in Table III. Only 1% w/w of acrylic/methacrylic copolymer coating was used as previously discussed. The rapid release rates found for these coated granules was at first regarded as surprising, but on more careful analysis was concluded to be the result of inadequate coating.

[8] Methocel 60HG, 50 cps., Dow Chemical Co., Midland, Mich.
[9] CMC-7HG, Hercules Powder Co., Wilmington, Del.
[10] Cabot Corp., Boston, Mass.
[11] Atlas Chemical Co., Wilmington, Del.
[12] Carbowax, Union Carbide and Carbon Co., New York, N. Y.

TABLE III.—RELEASE OF *d*-AMPHETAMINE SULFATE FROM COATED GRANULES

| Polymer Coating | % w/w of Polymer Coating | % Release with Time ½ Hr. | 1½ Hr. |
|---|---|---|---|
| PVM/MA 2-ethylhexyl ester | 10 | 84 | 100 |
| PVM/MA *n*-butyl half ester | 10 | 82 | 100 |
| PVM/MA isobutyl half ester | 10 | 85 | 100 |
| Acrylic/methacrylic copolymer | 1 | 96 | 100 |

One gram of uncoated 20/30-mesh drug granulation was found to contain about 1750 granules. Since the rounded granules passed a No. 20 U. S. Sieve Series standard sieve and were retained on a No. 30 sieve, the mean diameter of the granules might be taken as the mean open dimension of these sieves, or 0.72 mm., as a sieve analysis approximation. The surface of 1750 such particles if they were true spheres, would be 28.2 cm.$^2$. Since many of the "rounded" granules were observed to be elongated the actual surface was probably considerably larger than this. If a thin film such as the 0.003-inch dry film which was the thinnest studied in the permeability study, was applied to completely coat 1 Gm. of granulation, 0.214 cm.$^3$ of polymer would be required (28.2 cm.$^2$ area × 0.0076 cm. thickness). This corresponds to 0.278 Gm. of polymer film material needed to coat 1 Gm. of granulation (the film density was 1.30 Gm./cm.$^3$). In other words if the granules had been truly spherical, nearly 30% of polymer composition would be required, based on the weight of the uncoated granulation, to produce a thin drug impermeable film about the granules. Since the granules were not truly smooth surfaced and spherical, the actual percentage of polymer coat material needed to produce the necessary protective film, might be closer to 50 to 100% of the granulation weight being coated at a 20/30-mesh uncoated particle size range.

**Selection of a Filler-Coating Dusting Powder.**—Since the application of more than 10% w/w of polymer film composition could not be conveniently or economically applied to the granules, various dusting powders were studied as coating adjuvants in order to increase effective coat thickness without having to resort to long coating times and high polymer concentrations in the dosage form. The materials used as dusting powders included two agents which are substantially insoluble in the pH environment of the alimentary canal—talc and magnesium stearate—and one material, precipitated calcium carbonate, which is reactive and soluble in the acid environment of the stomach.

Eight granulations were coated with the aid of the three dusting powders and the average amount of each coating constituent per gram was calculated (Table IV). Utilizing the extraction procedure for the removal of the plasticizer from solution, each granulation was assayed with time and pH change to determine the drug release rate (Table V).

In reference to Table V it will be noted that the granulations coated with the aid of magnesium stearate as a dusting powder, showed some promise as prolonged-action coatings as the concentration of dusting powder was increased. However the low density of the material resulted in more than doubling the granule size when 0.20 Gm. of magnesium stearate was added to the uncoated granule weighing 0.40 Gm. The coatings containing magnesium stearate were also friable.

The granulations coated with the aid of talc preliminarily released the drug *in vitro* even at the higher dusting powder concentrations.

Precipitated, calcium carbonate even though it was the only dusting powder used which was not inert in the test solutions, most effectively prolonged drug release *in vitro*, of the three dusting powders used. More recent work with other polymers, as well as the data reported by Wagner (4), suggests that each polymeric coating must be separately considered to determine the best dusting powder filler. It might be hypothesized that the various polymer film surfaces vary in their affinity for the various dusting powders, and that this affinity is an important consideration in this type of dosage form development.

TABLE IV.—AVERAGE AMOUNT OF COATING CONSTITUENT APPLIED TO EACH GRANULE[a]

| Coating Number | Polymer,[b] mg. | Diethylphthalate, mg. | Magnesium Stearate, mg. | Precipitated Calcium Carbonate, mg. | Talc, mg. |
|---|---|---|---|---|---|
| 1 | 0.0284 | 0.0085 | ... | ... | ... |
| 2 | 0.0568 | 0.0171 | ... | ... | ... |
| 3 | 0.0284 | 0.0085 | ... | ... | 0.185 |
| 4 | 0.0568 | 0.0171 | ... | ... | 0.368 |
| 5 | 0.0284 | 0.0085 | 0.1014 | ... | ... |
| 6 | 0.0568 | 0.0171 | 0.2041 | ... | ... |
| 7 | 0.0284 | 0.0085 | ... | 0.2230 | ... |
| 8 | 0.0568 | 0.0171 | ... | 0.3860 | ... |

[a] Calculation: 0.402 Gm. of uncoated granules = 707 granules on the average; therefore, 150 Gm. = 263.806 granules. Thus, (total quantity of material added/263.806) = quantity/granule. [b] *n*-Butyl half ester of PVM/MA.

TABLE V.—*In Vitro* ASSAY OF PER CENT DRUG RELEASE FROM GRANULES COATED WITH THE DIFFERENT DUSTING POWDERS

| Coating Number[a] | Per Cent Release After (Hr.) 0.5 | 1.5 | 2.5 | 4.5 | 6.5 | 8 |
|---|---|---|---|---|---|---|
| 1 | 69.48 | 1.56 | 0.00 | Dissolved | ... | ... |
| 2 | 44.41 | 24.67 | 0.49 | Dissolved | ... | ... |
| 3 | 64.34 | 3.28 | 0.00 | Dissolved | ... | ... |
| 4 | 60.96 | 7.54 | 0.00 | Dissolved | ... | ... |
| 7 | 48.16 | 16.05 | 0.00 | 5.55 | Dissolved | ... |
| 8 | 25.69 | 35.60 | 0.00 | 0.00 | 9.91 | Dissolved |

[a] Constituents listed in Table IV.

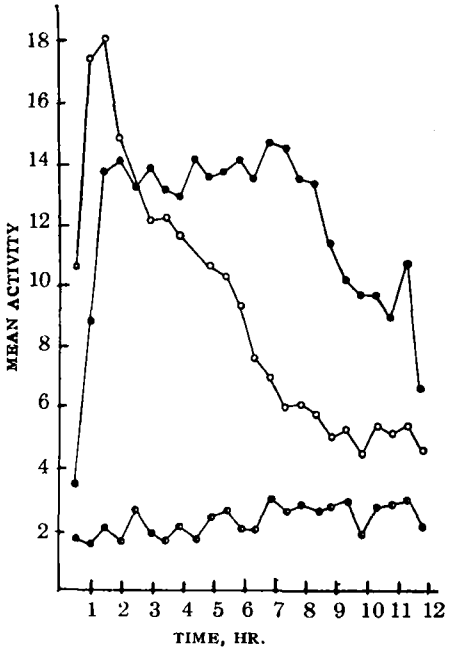


Fig. 1.—*In vivo* comparison of coated and uncoated granules. Key: ● coated, O uncoated, ◐ control.

**In Vivo Activity of Coated Granules.**—The *in vivo* activity of the coated granules was determined using the 3% *d*-amphetamine sulfate granulation coated with 10% of PVM/MA *n*-butyl half ester applied from the fully plasticized coating solution (No. 1), with the aid of the calcium carbonate dusting powder (101.8 Gm. of powder/150 Gm. of uncoated granulation). The coated granules were then administered to the test animals as previously described. The *in vivo* results of administering the coated granules, the uncoated granules, and the control material are presented in Fig. 1. Each line in Fig. 1 represents the average results from the responses of ten animals, with the data being averaged and plotted at half-hour intervals.

The results of the Newman Kuels significance tests showed that the uncoated granules had an immediate onset of action (within the first half-hour), and that the duration of action lasted until the seventh hour. At this time there was no significant difference between the control and the uncoated granules (2 × 3). The coated granules caused a significant response within 1 hour after administration and provided a duration of significant therapeutic response lasting 11.5 hours. This is an increase in duration of activity of the coated granules over the uncoated material of 4.5 hours. In addition to the longer duration of activity the coated granules eliminated the high response peak in the first hour. This was statistically shown by the significant difference between the coated and uncoated granules during that time period.

**Tableting of Coated Granules.**—Polyethylene glycols with and without starch or lactose were evaluated as tablet matrices for the coated granules. The major criterion for the selection of the tablet matrix was the prevention of rupture of the granule coating upon compression.

The tablets were prepared by mixing various ratios of polyethylene glycol 6000, 9000, and 20,000 and coated granules. The results of the disintegration tests on the tablets prepared with different polyethylene glycols showed that the addition of starch and lactose had no effect on the disintegration time as compared to that of tablets using polyethylene glycol alone. During the compression of the coated granules the pressure was adjusted to produce tablets of a hardness of 5 to 7 Kg., so as to maintain a disintegration time of 15 to 20 minutes and prevent rupture of the granule coating. Disintegration time increased considerably and the coating ruptured when the hardness of the tablets was 9 Kg. or higher. Analysis of the disintegrated tablets for ruptured granules showed that polyethylene glycol 6000, 20-mesh flakes, was the best matrix.

As a result of the tableting investigation, a maximum of approximately 30% coated granules was found to produce the most satisfactory tablets. Concentrations of coated granules exceeding this resulted in ruptured coatings due to an inadequate amount of "cushioning" material. Granules with ruptured coatings were identified by their ability to float, upon tablet disintegration, as compared to the denser intact granules. The floating granules were found to be empty shells. The pattern of granule release upon tablet disintegration is shown in Fig. 2.

Figure 3 shows the time-response curves for each group of tablets. The onset of action of the tablets containing coated granules occurred 2 to 3 hours after administration, which was considerably slower than the onset of the coated granules. This is due to the fact that the tablets must disintegrate before the granules are released. Although the disintegration time *in vitro* was between 15 and 20 minutes, this time period was probably considerably longer *in vivo* due to the smaller volume of fluid present in the animal's stomach. In the formulation of a complete product, it would thus be desirable to combine coated granules with some uncoated granules in order to provide the initial dose.

The release of the *d*-amphetamine from the uncoated granules compares favorably to the release obtained from tablets of the same granules. Significant reponses were obtained from the tablets for 7.5 hours as compared to 7 hours for the independent granules. Tablets of the coated granules continued to show increased activity after 12 hours, while the independent granules showed no increased activity after 11.5 hours.

Sustained action was obtained from these coated granules by two mechanisms. The first involved the random entry of the granules into the intestinal tract. The active constituent was then released by dissolution of the coating at the various pH levels of the intestine due to the small variation in coating

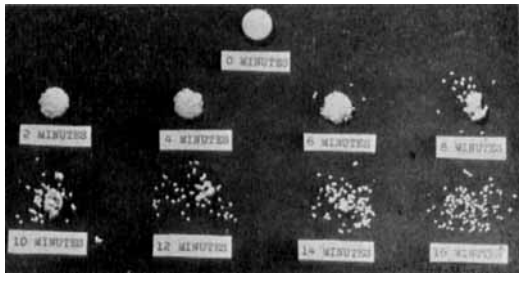

Fig. 2.—Granule release upon tablet disintegration.

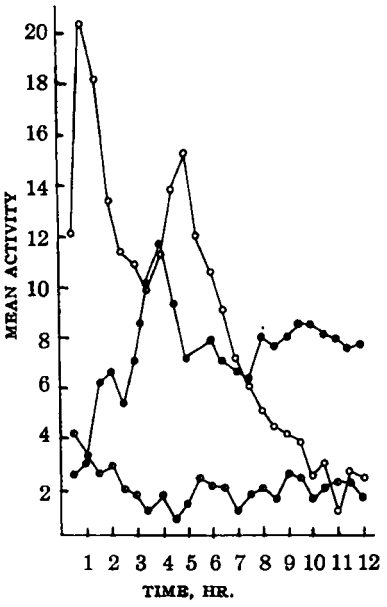


Fig. 3.—*In vivo* comparison of tableted coated and uncoated granules. Key: ● coated, O uncoated, ◐ control.

thickness, which occurs in pan coating. This was shown by the *in vivo* procedure.

An added advantage to this approach to obtaining sustained release is the use of a single coating composition which is applied in one concentration to an entire batch of granules. Therefore the entire coating process is accomplished in one easy operation without additional coatings and mixing of the coated granules.


## SUMMARY

*d*-Amphetamine sulfate granules were successfully coated with a plasticized film of the *n* butyl half ester of PVM/MA 119 using each of three dusting powders: talc, magnesium stearate, and precipitated calcium carbonate. *In vitro* release rates were determined for each coating and the granules coated with the aid of precipitated calcium carbonate produced the most satisfactory results. *In vitro* tests indicated that the coated granules could be recovered intact from compressed tablets.

*In vivo* release rates were determined using the Williamson activity cage to measure spontaneous motor activity. The results obtained showed that the activity of the rats receiving the coated granules was 4.5 hours longer than those receiving uncoated granules.

*In vivo* analysis of tablets prepared by compressing the coated granules in a polyethylene glycol 6000 matrix, showed a continued increase in motor activity after 12 hours, while the tablets containing uncoated granules showed no increase after 7.5 hours.


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# Gas Chromatography of Some Antihistamines

By ALEXANDER MACDONALD, JR., and RONALD T. PFLAUM

**The gas chromatographic behavior of 16 antihistamines was investigated using packed 0.010-in. diameter capillary and 0.065-in. open tubular columns. All packed columns were 6 ft. long, with a low phase to support ratio and were operated at 175°. The liquid phases used were Carbowax 20M, SE-30, XF-1150, and PDEAS. Of the seven solid supports evaluated for use in low loaded columns, only glass beads, Gas Chrom-P, and Chromosorb W-HMDS proved to be satisfactory. The most successful column for the separation of these antihistamines was a 6-ft.–0.08% PDEAS on 120/170 glass-bead column operated at a temperature of 175°. This column provided good separation and symmetrical peaks. Instrument limitations prevented any valid evaluation of the 0.010-in. capillary column and of the 0.065-in. open tubular column for antihistamine separation.**

Gas chromatography has proved to be a valuable tool for the separation and identification of many types of compounds. In pharmaceutical analysis, barbiturates (1–4), sympathomimetic amines (5–7), and tranquilizers (8, 9) have been successfully separated by gas chromatography. Toxicological screening of alkaloids and the above classes using gas chromatographic separation on a single column has been reported by Parker (10). Gas chromatographic data on 14 antihistamines using a 5-ft. × 1/8-in. diameter–2% Carbowax 20M on 10% KOH

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