Preparation and Evaluation of the Prolonged Release Properties of Nylon Microcapsules

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Abstract □ A method for *in situ* preparation of nylon encapsulated sodium pentobarbital by emulsion polymerization is reported. This was followed by work-up of the microcapsules by one of two processes: (*a*) spray drying and (*b*) vacuum drying. However, somewhat different properties were noted when the free-flowing spray-dried substance was compared to that which had been vacuum dried. Nylon capsules produced in these manners containing sodium pentobarbital exhibited a considerable reduction in dissolution rates relative to the instantaneously soluble barbiturates when examined in distilled water, 0.1 *M* phosphate buffer, pH = 6.75, and 0.1 *N* HCl. When the microcapsular material was tableted, the release rate of the sodium pentobarbital was seen to be inversely proportional to tablet hardness.

Keyphrases □ Nylon microcapsules—release rate, preparation □ Sodium pentobarbital—microcapsule preparation, polymerization □ Release rate—sodium pentobarbital nylon microcapsules □ UV spectrophotometry—analysis

As a method of protecting or prolonging the release of drugs, microencapsulation has intrigued pharmaceutical scientists (1–3) for several years. The first patented use of microcapsules was made by Green and Schleicher (4, 5) to prepare "carbonless carbonpaper." They made use of a gelatin–acacia coacervate system (6) to entrap emulsified oil droplets containing dissolved dyes. In 1967, Luzzi and Gerraughty (2, 7) developed a method for the evaluation of drug-containing capsules prepared *via* complex coacervation.

Miller and Anderson (8) were granted a U. S. patent for the manufacture of microcapsules using "hydrophobic film-forming polymeric wall materials dispersed in a liquid manufacturing vehicle." This patent claims as "an unsuspected virtue ... the encapsulation of aspirin" in ethylcellulose microcapsules. The authors state that aspirin was encapsulatable since it was wetable by cyclohexane. A further, and most interesting, statement made in this patent is that the thickness of the microcapsule wall can be controlled by changing the relative quantity of shell-forming material.

Chang *et al.* (9) prepared semipermeable nylon-shell microcapsules containing an erythrocyte hemolysate and, later (10), published information concerning the use of this type of microcapsule in an extracorporeal shunt system. In this system, the authors assert that capsules prepared in such a manner will allow passage of plasma through the capsule wall, thus allowing contact with the encapsulated material.

The findings, by the above authors, indicate that encapsulation is possible by several systems. There is, however, little indication of work done on encapsulation and evaluation of pharmaceuticals, especially with nylon as the encapsulating medium. In this respect, then, this investigation was designed to encapsulate a drug in a nylon membrane and to evaluate the resultant capsular material as it may pertain to pharmaceutical dosage forms.

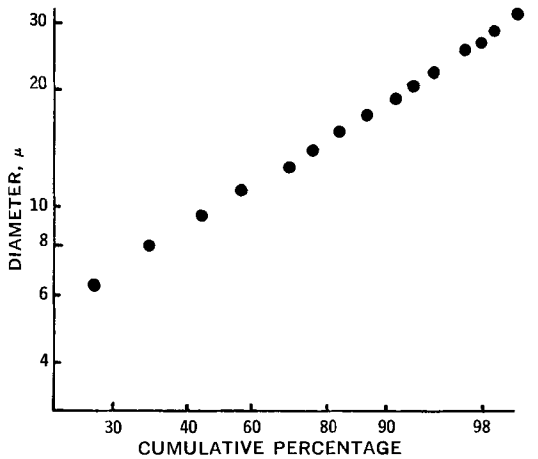

Figure 1—*Log-probability plot of a typical sample of spray-dried microcapsular material. The cumulative percentage is plotted on the X or probability axis. Distribution was determined using a Coulter Counter model B equipped with model M converter.*

EXPERIMENTAL

Preparation of Nylon Microcapsules—The method of Chang *et al.* (9), with certain modifications, was used to prepare nylon microcapsules containing sodium pentobarbital. The basic solutions included: (*a*) mixed solvent system consisting of 1 part by volume chloroform (reagent grade) and 4 parts by volume cyclohexane (reagent grade); (*b*) 0.16% sebacyl chloride (Eastman Organic Chemicals) in part of the above mixed solvent system; (*c*) 1% commercial emulsifier[1] also in part of the mixed solvent; (*d*) an aqueous solution of 2% methylcellulose[2] (50 cps.), and (*e*) an aqueous solution consisting of 2% sodium pentobarbital and 6.75% of 1,6-hexamethylenediamine (Eastman Organic Chemicals).

The procedure for the preparation of the product consisted of slowly adding at low speed[3] a mixture of equal volumes (25 ml.) of the methylcellulose and sodium pentobarbital–hexamethylenediamine solutions, then adding 165 ml. of the mixed solvent–surfactant solution, and blending for approximately 30 sec. at low speed. Sebacyl chloride solution (165 ml.) was added and blended at high speed for 10 sec. and then for 1 min. at low speed to complete the nylon-producing reaction. The capsules were allowed to settle and the supernatant was removed.

Spray-Drying Process—A Nerco-Niro portable spray dryer equipped with a special nozzle adapter atomizing assembly (Nichols Engineering and Research Corp.), a Zero-Max Sigma-motor assembly, and a vacuum exhaust system attached to the dryer were used to effect drying.

In order to prepare the mixture for the spray-drying process, approximately 15 ml. of chloroform was added to the slurry remaining after decantation. The resultant dilution was constantly agitated while liquid remained in the feed flask in order to maintain a uni-

[1] Brij 52 (HLB 5.3), Atlas Chemical Industries, Wilmington, Del.
[2] Methocel HG, The Dow Chemical Co., Midland, Mich.
[3] Waring blender, deluxe model two speed, Waring Products Co., Winstead, Conn.

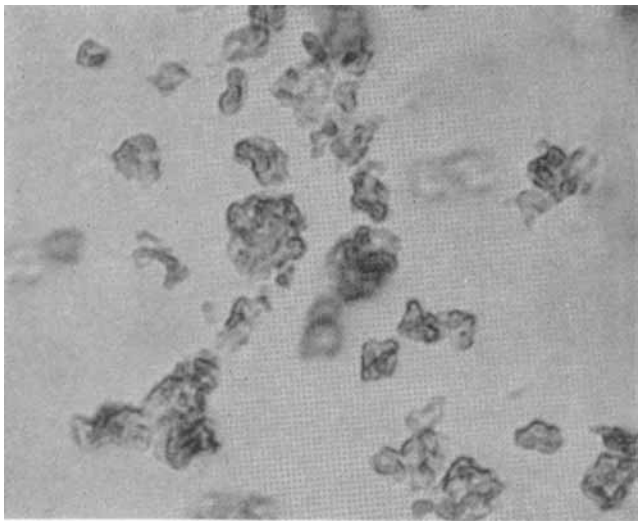

Figure 2—*A photomicrograph of dried microcapsular material (× 512).*

form flow of solids to the spray dryer. The internal temperature of the dryer was maintained at 125° throughout the drying process.

The collected powder was placed in a vacuum oven at 35° for 10–12 hr. to remove residual solvent and moisture. The resultant free-flowing powder containing 7.6% sodium pentobarbital was divided into several lots. One portion was examined as the free-flowing powder and the other portions were tableted so as to yield a range of tablet hardnesses prior to examination. Tablets were prepared by power compression on a single punch tableting machine (Stokes model E). Five hundred to one thousand tablets of each hardness were prepared with care taken to maintain a hardness variation of approximately ±0.5. Hardness was measured on a model B, Strong Cobb Arner tablet hardness tester.

Flash Evaporation Process—The wet slurry consisting of the microcapsule material and the vehicle which remained after decantation (along with the chloroform) was placed into a flash evaporator at 35° for 24 hr. The resultant dry material containing 7.6% sodium pentobarbital was held together loosely and was not dense.

Assay Methods—A Cary model 14 recording spectrophotometer was used to determine the concentration of sodium pentobarbital in each case. The wavelength of maximum absorption was found at 240 mμ, and all measurements were made at this wavelength while employing appropriate blanks. The same basic procedure was used to detect solubilized sodium pentobarbital regardless of the form of the drug being tested.

The following is the assay procedure used to study dissolution. A 200-mg. sample of free-flowing microcapsular powder or a 200-mg. tablet was placed in a 150-ml. beaker and 100 ml. of liquid (0.1 *N* HCl, 0.1 *M* KH_2PO_4–KOH buffer, pH 6.75, ionic strength 0.2, or distilled water) was added and the mixture stirred at a constant rate of 6 r.p.m., using a Bodine electric speed reducing motor (Bodine Electric Co.). The temperature was maintained at 37° and the beaker covered with aluminum foil. One-milliliter filtered samples were removed at the time intervals indicated in the various figures and appropriate dilutions were made employing 0.1 *N* NH_4OH.

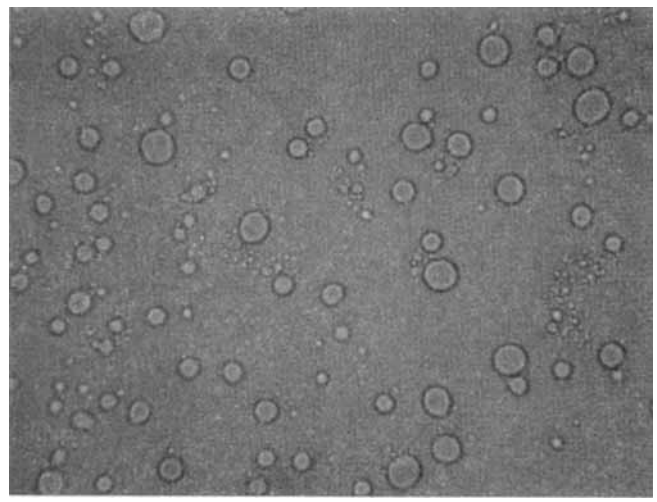

Figure 3—*A photomicrograph of nylon microcapsules in liquid medium before drying (× 400).*

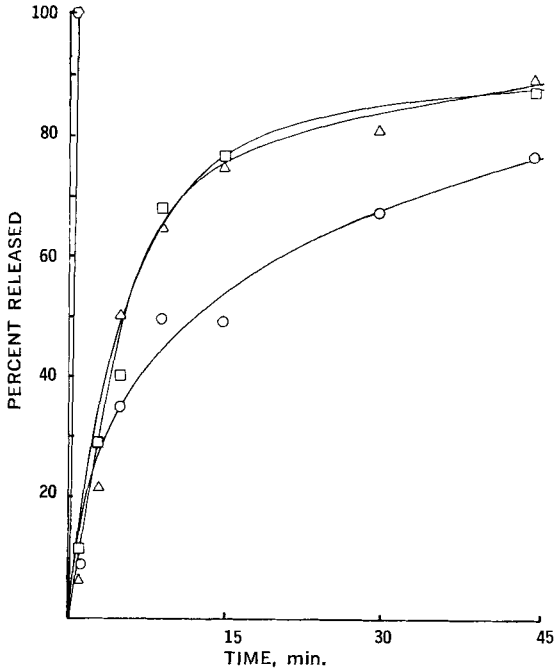

Figure 4—*Release rate of sodium pentobarbital from microcapsules prepared via evaporation and suspended in various aqueous media. Key: ○, in 0.1 N HCl; □, in H_2O; △, in 0.1 M PO_4; and ⬡, nonencapsulated sodium pentobarbital.*

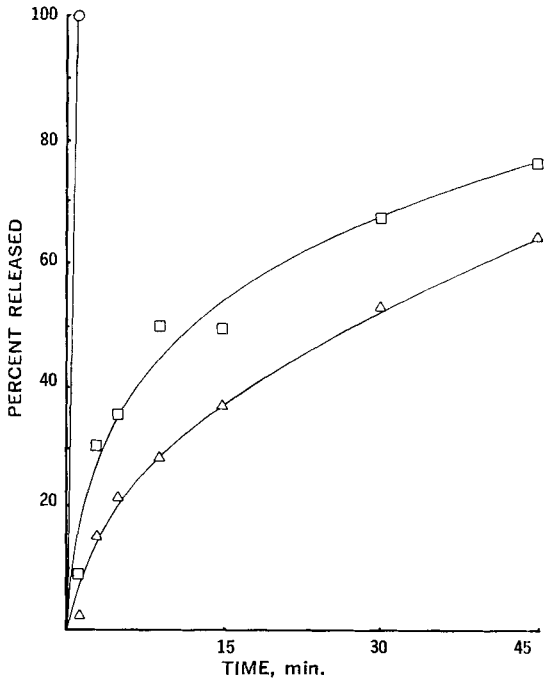

Figure 5—*A comparison of the release rate of sodium pentobarbital from microcapsules prepared by evaporation and by spray drying to 0.1 N HCl. Key: □, evaporation process; △, spray dried; and ○, nonencapsulated sodium pentobarbital.*

Table I—Rates[a] (K) of Dissolution for Tablets of Various Hardness in Three Liquid Media

Tablet Hardness	Liquid Medium	K hr.$^{-1}$	Time Measured, hr.
8	0.1 M HCl	5.01	9.0
8	0.1 M PO_4	4.12	9.0
8	H_2O	3.81	9.0
5	0.1 M HCl	7.13	8.0
5	0.1 M PO_4	4.28	8.0
5	H_2O	5.54	9.0
2	0.1 M HCl	14.37	1.5
2	0.1 M PO_4	15.22	3.0

[a] First-order rates are used for comparative analysis of results. The order of release cannot be established by the data presented in this study although there appears to be a trend toward first order.

Total Concentration—In order to be able to make a comparison of the amount of active ingredient released to that contained, 100 mg. of the microcapsular powder was placed in a blender and 500 ml. of 0.1 N NH_4OH was added. The blender was run for 5 min. at high speed and a clear liquid collected through a 0.45-μ filter. The absorbance was taken and compared to a standard.

Analysis of Data—An IBM 360 model 50 computer was used. The equations were standard and readily available (11).

Particle Size—Determination of particle distribution was carried out by using a Coulter Counter model B equipped with a model M volume converter. A 30-μ aperture tube, 2% sodium chloride, and a ragweed pollen standard (19.5 μ mean diameter) were used in this determination. No attempt was made to separate particles into definite ranges nor were other particle size distributions employed.

RESULTS AND DISCUSSION

Only one particle size range of spray-dried microcapsular material was used in this experiment. Figure 1 is a log-probability plot of the particles which shows that a statistically normal distribution was found. The geometric mean diameter was 10 μ with an arithmetic mean diameter of 12.08 μ. The vacuum-dried material did not, however, show a normal particle distribution, but contained particles as estimated microscopically ranging from about 1.0 to about 100.0 μ with 90% greater than 25.0 μ.

Figure 2 is a photomicrograph[4] of a typical grouping of spray-dried nylon-membraned microcapsules. It can be seen that the particles are not spherical and that, in most cases, several particles are clumped together. Figure 3 is a photograph of nylon-membraned microcapsules before drying. The particles here are generally spherical and clumping is minimal; no coalescence of particles was noted.

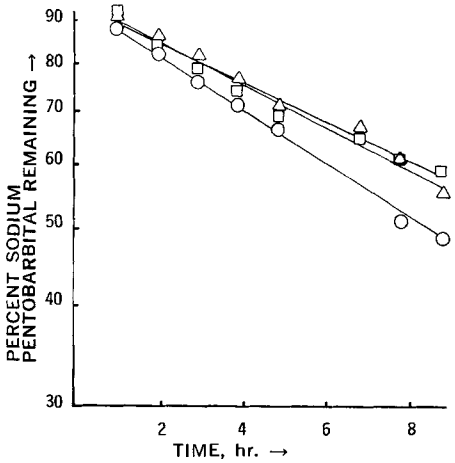

Figure 6—*A comparison of the release relationship of tablets of approximately 8 hardness in three liquid media. Key:* ○, *in 0.1* N *HCl;* △, *in 0.1* M PO_4; *and* □, *in* H_2O.

[4] Photomicrographs were taken using a Leitz Research microscope with Aristophot and Polaroid Land assembly.

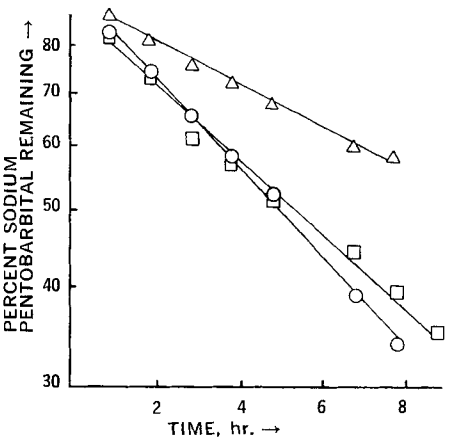

Figure 7—*A comparison of the release relationships of tablets of approximately 5 hardness in three liquid media. Key:* ○, *in 0.1* N *HCl;* △, *in 0.1* M PO_4; *and* □, *in* H_2O.

The dissolution profiles for sodium pentobarbital in a vacuum-dried microcapsular state is shown in Fig. 4. As may be expected, the results of release studies for sodium pentobarbital from the untableted powders showed a tendency to be greater at higher pH values. It may be seen that in a 45-min. period about 13.7 mg. (90%) of the encapsulated sodium pentobarbital was released to the phosphate buffer and the H_2O media while only about 11.4 mg. (75%) was released to the medium containing HCl.

Although dissolution studies for the spray-dried material were carried out in the three media previously mentioned, only those results for HCl are shown (Fig. 5). The release patterns are very similar to those obtained for other media and show that the vacuum-dried microcapsular powder initially releases sodium pentobarbital more quickly than the spray-dried material.

It was thought that since the vacuum-dried material had to be scraped from the collection vessel and then spatulated in order to obtain a powder, that some of the capsules might have been disrupted and that this led to the greater release. The spray-dried material, on the other hand, was free flowing as it was collected. For these reasons, further work was done using only the spray-dried powder.

When the microcapsular material was tableted, without lubricants or other adjuvants, both the disintegration of the tablet and the ability of the liquid medium to wet the tablet seemed to play an

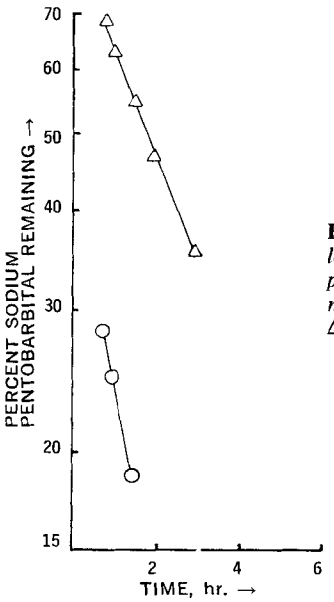

Figure 8—*A comparison of the release relationship of tablets of approximately 2 hardness in two liquid media. Key:* ○, *in 0.1* N *HCl; and* △, *in 0.1* M PO_4.

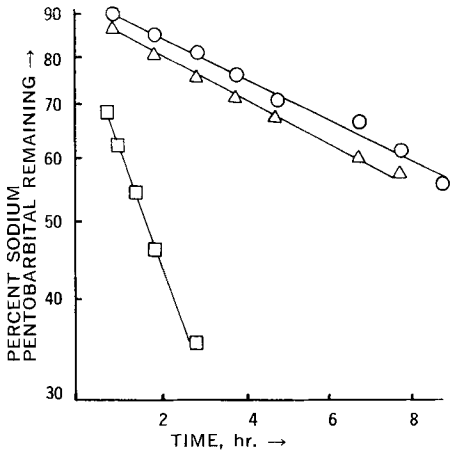

Figure 9—*A comparison of the release relationship of microcapsular tablets of three different hardnesses in 0.1* M PO_4 *liquid media. Key:* ○, *8 hardness;* △, *5 hardness; and* □, *2 hardness.*

important role in release of active ingredient. It was expected that disintegration and/or wetting would not appreciably be affected from liquid to liquid. However, as indicated in Figs. 6–8, there apparently is some disintegrating or wetting action since the release of sodium pentobarbital is slightly more rapid in acid solution; this is contrary to the trend found in Fig. 4.

Figures 6–8 demonstrate the release of sodium pentobarbital from the microcapsules. Although a first-order release is not justified except by the trend of the data, first-order rates are used for purposes of comparison. A comparison of these figures indicates that the differences in rate from one dissolution medium to the other became greater as the hardness of the tablet tested decreased. These differences in rate of release are shown more clearly in Fig. 9. Figure 9 is a comparison of the release rate of tablets of various hardness. It can be seen that the more rapid release rates were found in the softer tablets with the greater difference between tablets of hardness 5 and 2.

Table I is a compilation of slopes and significant data for the release of sodium pentobarbital from tablets of various hardnesses and the several liquid media. The mechanism of release (9, 10) probably involves leeching of the sodium pentobarbital through a network of nylon fibers constituting the microcapsule.

SUMMARY

The studies reported here demonstrate that interphasal polymerization can be used to prepare nylon-membrane microcapsules. It has also been shown that a free-flowing powder can be obtained by spray drying slurries of microcapsules.

When the free-flowing powder was tableted, it was observed that changes in release rate could be controlled by varying hardness. It was also observed that vacuum drying yielded capsule material of different appearance and release characteristics from spray-dried microcapsular material.

Although a statistical evaluation of particle size was carried out, there could be no significance attached to the range found. However, examination of the effect of size of particle on release rate is presently being investigated.

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