Influences of Matrixes on Nylon-Encapsulated Pharmaceuticals

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Abstract □ The preparation and properties of nylon microcapsules containing three different matrixes (formalized gelatin, calcium alginate, and calcium sulfate) are described. Microcapsules containing each matrix were dense and free flowing and could be made of very small diameter by controlling the stirring speed during nylon formation. The preparation of microcapsules containing calcium alginate employed freeze-drying procedures. Lyophilization was not necessary with the formalized gelatin and calcium sulfate systems. Various representative drugs (anionic, cationic, nonionic, quaternary, and amphoteric compounds) were used in the formulation studies. The effects of pH, matrix, and encapsulated species on retention of drug in the microcapsules are described. In addition, the surface morphology of the microcapsules was examined using scanning electron microscopy.

Keyphrases □ Nylon microcapsules—preparation and properties, various matrixes and drugs, effects of pH, matrix, and encapsulated species on retention of drug during formulation □ Matrix, microcapsules—formalized gelatin, calcium alginate, and calcium sulfate, influence of matrixes on properties of nylon-encapsulated pharmaceuticals □ Microencapsulation—symposium, influence of matrixes on properties of nylon-encapsulated pharmaceuticals

The preparation of dense, free flowing, drug-containing microcapsules can improve certain physical characteristics of formulations such as compressibility and flow. In addition, the microencapsulation process has been utilized to modify drug release, to improve drug stability, and to permit the mixing and storage of reactive or incompatible materials (1). The types of wall materials and preparation methods of microcapsules were reviewed extensively by Madan (2). Microcapsules can range in diameter from nanometers to millimeters, depending on the material to be encapsulated and the ultimate product use. Microcapsules for oral preparations have been prepared with nonbiodegradable membranes including nylon (3–6), ethylcellulose (7–9), cellulose acetate phthalate (10), polystyrene, and cellulose nitrate (11). *dl*-Polylactic acid (12) and albumin (13–16) have been employed as membranes for biodegradable microcapsules for injectable preparations.

BACKGROUND

Nylon is a polyamide formed from the reaction of a diamine and a diacid halide. Since several different types of nylon can be formed by altering the carbon chain length or configuration in the amine or diacid and since each alteration may change the permeability of the resultant film, nylons seem to offer an excellent array of possibilities for the microencapsulation of pharmaceuticals (17). However, the application of nylon to microcapsules has generally been limited to the encapsulation of large molecules such as proteins and enzymes. For example, Chang and coworkers (18–20) formulated and used encapsulated enzymes to treat enzyme deficiencies. The microencapsulated enzymes are immobilized and are prevented from leaking out of the capsule, thereby preventing hypersensitivity or other immunological reactions. However, the enzymes can act on small molecule substrates, which can dialyze across the semipermeable nylon membrane (21). Pharmaceuticals that have been encapsulated in nylon include pentobarbital sodium (3, 6), phenothiazines (4), and sulfathiazole sodium (5, 22).

The present investigators (5, 22) employed a nylon membrane to encapsulate sulfathiazole sodium as a soluble model compound. The encapsulation essentially combined the nylon microencapsulation technique of Chang *et al.* (19) with the gelatin micropellet method of Tanaka *et al.* (23). The resulting microcapsules consisted of drug embedded in a core of formalized gelatin surrounded by a nylon membrane. Microcapsules containing a solid matrix within the nylon membrane are easily separable by light trituration, following the drying step. In contrast, drug-containing capsules with no matrix tend to stick together, and levigation procedures to separate the capsules often damage the microcapsules. In addition, matrix-containing particles are dense and gritty and do not adhere together. These capsules have excellent flow properties and can be made of very small diameter by controlling the stirring speed during nylon formation.

In the present study, several different pharmaceuticals were encapsulated using the nylon technique. In addition to formalized gelatin, two other matrixes, calcium sulfate hemihydrate and calcium alginate, were investigated. The efficiency of the process with respect to the drug content inside the microcapsules was measured by assaying the dried microcapsules and the external organic medium employed. The surface morphology of the resulting microcapsules was examined by scanning electron microscopy.

EXPERIMENTAL

Materials—The following were used: chloroform[1], cyclohexane[1], gelatin USP[1], formalin[1] (formaldehyde solution USP, 37%), 1,6-hexamethylenediamine[2], sebacyl chloride[2], caffeine[2], theobromine[2], sulfathiazole sodium[3], methantheline bromide[4], benzalkonium chloride[5], phenytoin[6], diphenhydramine hydrochloride[6], diazepam[7], theophylline[8], morphine sulfate[9], sodium alginate[10], and calcium sulfate hemihydrate[11].

Preparation of Microcapsules—Nylon-coated microcapsules containing matrixes of formalized gelatin, calcium sulfate, and calcium alginate were prepared. The microcapsules were formulated to contain a matrix-to-drug ratio of 2:1. The content of matrix chosen represents the amount needed to provide a workable viscosity of the aqueous phase during microcapsule preparation.

For the preparation of formalin-treated nylon gelatin microcapsules, 30 ml of aqueous 0.4 *M* hexamethylenediamine solution was added to an equal aqueous volume containing 5 g of gelatin and 2.5 g of drug. This solution was emulsified in 300 ml of an organic phase (cyclohexane–chloroform, 4:1) using a suitable mixer[12]. A nylon membrane was formed at the interface of the emulsified droplets by the slow addition of 1.2 ml of sebacyl chloride in 300 ml of the organic phase. The reaction vessel then was cooled to 5° in an ice bath. Next, 10 ml of 37% formalin was added to harden the gelatin matrix, and the reaction vessel was maintained at 5° for 12 hr. The microcapsules then were separated from the organic phase and dried at 37° to constant weight.

Nylon microcapsules containing a calcium sulfate matrix were prepared similarly. Initially, 7.5 ml of the hexamethylenediamine solution was added to 10 g of calcium sulfate hemihydrate and 5 g of drug. The addition of 3.5 ml of water to this mixture resulted in 20 ml of thick suspen-

[1] Fisher Scientific Co., Fair Lawn, N.J.
[2] Eastman, Rochester, N.Y.
[3] Mallinckrodt, St. Louis, Mo.
[4] Searle and Co., San Juan, Puerto Rico.
[5] Winthrop Laboratories, New York, N.Y.
[6] Parke-Davis and Co., Detroit, Mich.
[7] Hoffmann-La Roche, Nutley, N.J.
[8] Knoll Pharmaceuticals, New York, N.Y.
[9] Merck & Co., Rahway, N.J.
[10] Kelcosol, Kelco Co., Chicago, Ill.
[11] Plaster of Paris.
[12] Eppenbach.

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Table I—Partitioning of Drug between Microcapsules and the Organic Phase [a]

Drug	Formalized Gelatin	Calcium Sulfate	Calcium Alginate
Sulfathiazole sodium	>99:1	>99:1	≥99:1
Sodium salicylate	≥99:1	≥99:1	≥99:1
Methantheline bromide	—[b]	—[b]	—[b]
Benzalkonium chloride	—[b]	—[b]	—[b]
Phenytoin	>99:1	>99:1	≥99:1
Diazepam	90:10	75:25	88:12
Caffeine	75:25	66:34	75:25
Theophylline	69:31 (>99:1)[c]	—[b]	≥99:1
Theobromine	>99:1	>99:1	>99:1
Diphenhydramine hydrochloride	56:44	41:59	40:60
Morphine sulfate	85:15	96:4	95:5

[a] Expressed as the ratio of percent drug found in microcapsules to percent drug found in the organic phase. The amounts of drug originally formulated into microcapsules containing matrixes of formalized gelatin, calcium sulfate, and calcium alginate were 2.5, 5, and 1.25 g, respectively. [b] Microcapsules did not form. [c] Absence of formalin.

sion, and this suspension was emulsified in 300 ml of organic phase. The addition of 0.3 ml of sebacyl chloride contained in 300 ml of organic phase resulted in the formation of nylon-coated microcapsules. The capsules were allowed to stand at room temperature for 12 hr and then were separated from the organic phase. The microcapsules were allowed to dry undisturbed at 30° for 1 week.

To prepare nylon microcapsules containing a matrix of calcium alginate, 30 ml of the hexamethylenediamine solution was added initially to 30 ml of an aqueous solution containing 2.5 g of sodium alginate and 1.25 g of drug. This aqueous mixture then was emulsified in 300 ml of the organic phase. Nylon was formed by the slow addition of 1.2 ml of sebacyl chloride contained in 300 ml of organic phase. Calcium alginate was formed by the addition of 5 ml of saturated calcium chloride solution to the reaction mixture. Following the removal of 90% of the organic phase, the slurry of microcapsules was frozen using dry ice–acetone. Lyophilization for 2 days followed. The microcapsules then were stored at room temperature in a desiccator. Lyophilization prevented the microcapsules from sticking together during drying. The calcium alginate matrix should only be used for calcium-compatible drugs.

Electron Scanning Microscopy—The microcapsules were coated under an argon atmosphere with ~200 Å of gold–palladium using a cold sputter module in a high-vacuum evaporator equipped with an omnirotary stage. Samples were examined with a scanning electron microscope[13] using 20,000–30,000 kv.

Analysis of Microcapsules and Organic Phase—The amount of drug remaining in the microcapsules after formulation was determined by extracting the particles in an aqueous pH-adjusted medium for 12 hr. To determine the amount of drug that had partitioned into the organic phase during formulation, 100-ml volumes of this phase were evaporated to dryness and reconstituted with an aqueous medium of the appropriate pH to facilitate rapid drug dissolution. The drug concentration in both the microcapsules and the organic phase was determined spectrophotometrically at the wavelength of maximal absorbance for each drug.

RESULTS AND DISCUSSION

The inclusion of hard matrixes such as formalized gelatin, calcium sulfate, and calcium alginate inside nylon coatings resulted in the formation of dense, free flowing, spherical microcapsules. In all cases, >95% of the finished solid product was present as intact microcapsules. Nylon microcapsules containing these matrixes were formulated with anionic, cationic, quaternary, amphoteric, and nonionic compounds to determine the versatility of this process (Table I).

The nylon membrane is formed *in situ* by interfacial polymerization. Morgan and Kwolek (24) showed that nylon, like most water-insensitive polymers, forms and grows on the organic solvent side of the interface. These workers found that the strongest nylon membrane was formed when the ratio of amide to diacid was approximately 1.8:1. However, the excess of diamine in the aqueous phase resulted in an alkaline pH inside the microcapsule after the nylon membrane was formed. Studies with the formalized gelatin matrix containing phenolphthalein showed that the pH was >9 prior to the addition of formalin. The addition of 10 ml of formalin to microcapsules containing phenol red in a gelatin matrix

[13] Model 1000, Advanced Metals Research, Burlington, Mass.

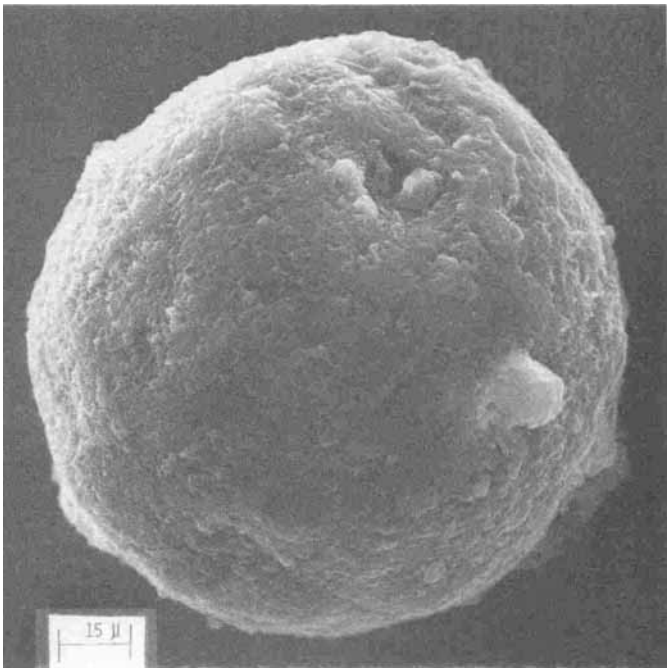

Figure 1—*Scanning electron micrograph of a formalin-treated nylon gelatin microcapsule containing morphine sulfate.*

resulted in a slightly acidic pH inside the microcapsule. Since formalin was not added to nylon capsules containing calcium sulfate and calcium alginate, the pH of the microcapsule remained alkaline due to the excess quantities of the amine and the calcium salt.

For several drugs, the pH inside the microcapsule influenced the ionic character of the encapsulated drug. To determine the extent of partitioning into the organic phase, the microcapsules and organic phase were assayed for drug content; the ratio of drug in the capsule to the amount of drug partitioned into the organic phase at equilibrium is shown in Table I. Equilibrium conditions were established rapidly with all of the drugs studied. As expected with anionic drugs, little sulfathiazole sodium and sodium salicylate appeared in the organic phase.

Great difficulty was experienced in encapsulating the quaternary drugs, methantheline bromide and benzalkonium chloride, in nylon; in each

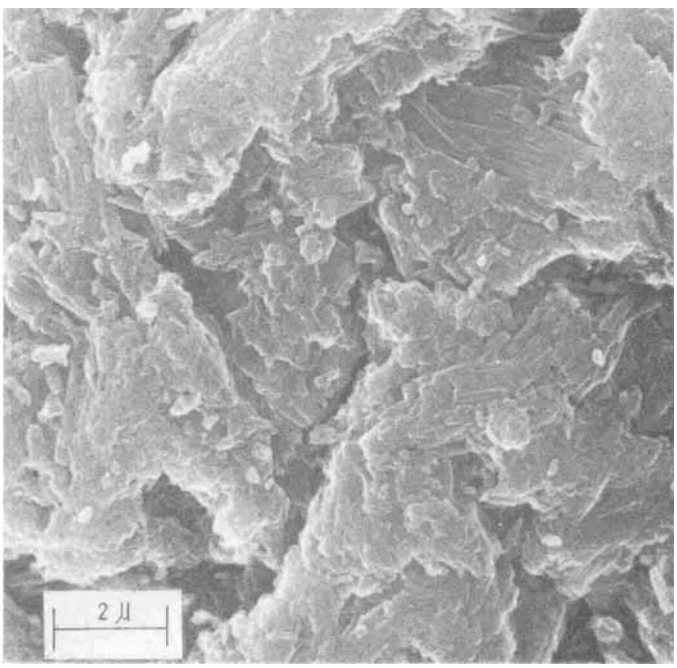

Figure 2—*Scanning electron micrograph of the microcapsule surface in Fig. 1.*

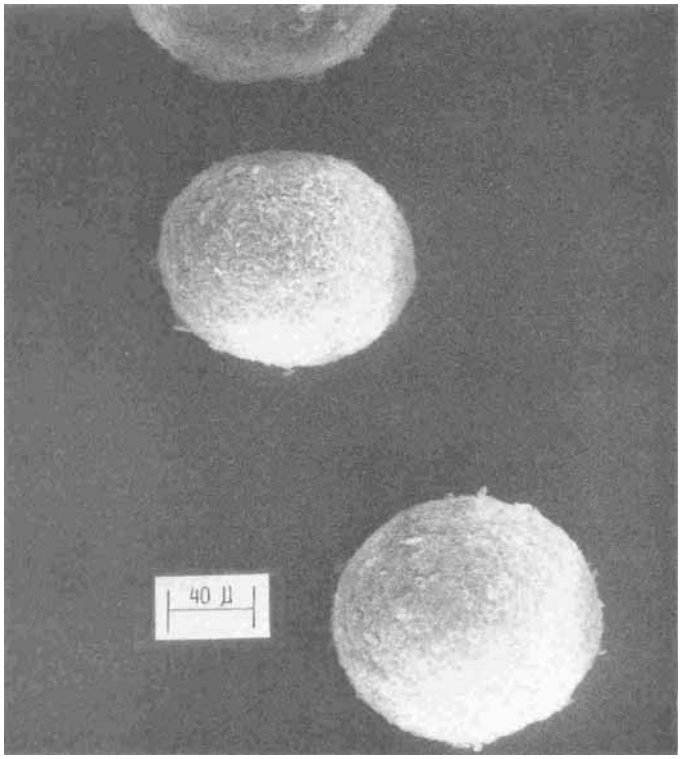

Figure 3—*Scanning electron micrograph of nylon microcapsules containing morphine sulfate in a calcium alginate matrix (lyophilized for 2 days).*

case, microcapsules were not formed. Preliminary studies showed that another quaternary compound, pralidoxime iodide, could be encapsulated in nylon with a formalized gelatin matrix, although the capsules were sticky and difficult to separate. Quaternary compounds apparently interfere with the reaction to form nylon.

Both phenytoin and diazepam formed suspensions in the aqueous phase containing hexamethylenediamine and the matrix components. Phenytoin can form a sodium salt at very high pH, so a small amount of a diamine salt may have formed in the hexamethylenediamine solution.

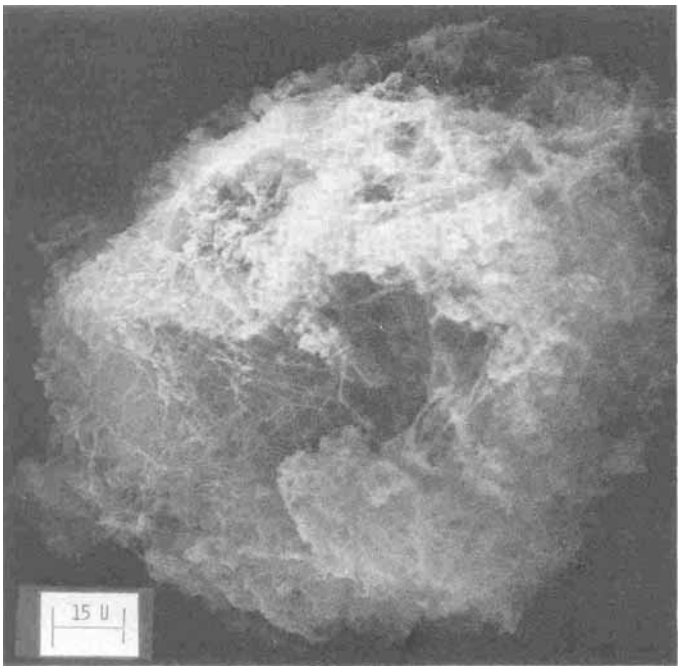

Figure 4—*Scanning electron micrograph of a nylon microcapsule containing morphine sulfate in a calcium alginate matrix (lyophilized for 5 days).*

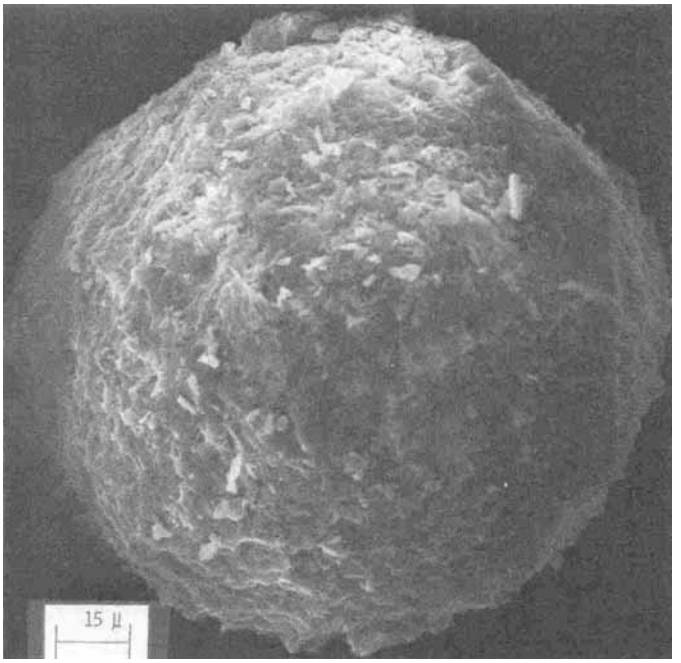

Figure 5—*Scanning electron micrograph of a nylon microcapsule containing morphine sulfate in a calcium sulfate matrix.*

Negligible quantities of drug were recovered in the organic phase, probably due to the very low solubility of phenytoin in both cyclohexane and chloroform. This was not the case with diazepam. Its yellow color was quite noticeable in the organic phase, and analysis confirmed the partitioning of the drug from the microcapsules.

Interesting results were seen with both the xanthine derivatives and the cationic drugs. The three xanthine derivatives included caffeine, theophylline, and theobromine. The caffeine and theobromine data can be explained on the basis of the relative drug solubilities in the organic phase. Caffeine has a solubility of 1 g in 5.5 ml of chloroform whereas theobromine is practically insoluble in both chloroform and cyclohexane. Theophylline microcapsules did not form when the matrix was calcium sulfate. The addition of theophylline to the calcium sulfate suspension and amine solution resulted in a very thick suspension, which was diluted with a small quantity of water. However, on addition to the organic phase, the aqueous suspension of calcium sulfate and theophylline did not emulsify in the organic phase and adhered strongly to the sides of the glass vessel and the stainless steel stirring apparatus, thus preventing the formation of microcapsules. The addition of formalin solution to the gelatin–theophylline microcapsules significantly decreased the amount of drug remaining in the capsules.

The two basic drugs studied were diphenhydramine hydrochloride and morphine sulfate. Small quantities of morphine were recovered in the organic phase. However, significant partitioning of the drug from the microcapsules was found only with the antihistamine due to its high solubility in chloroform.

The amount of drug remaining after the preparation of microcapsules containing the calcium alginate matrix was dependent on the volume of saturated calcium chloride used to form the calcium alginate. Calcium chloride solution was added to the reaction vessel following the formation of the nylon membrane. The electrolyte diffused into and reacted with the sodium alginate matrix. Since excess electrolyte stays in the aqueous phase, the percentage composition of drug in the microcapsules increases as the volume of calcium chloride solution decreases. When 10, 5, and 1 ml of saturated calcium chloride were added to alginate microcapsules containing sulfathiazole sodium, 7.35, 12.57, and 17.98% of drug were in the microcapsules, respectively.

Scanning electron micrographs of nylon microcapsules containing morphine sulfate and the three different matrixes are shown in Figs. 1–6. A microcapsule containing the formalized gelatin matrix is shown in Figs. 1 and 2. The surface appears to be rough and porous with a plate-like structure. However, these surface photographs do not indicate the inner structural features of the membrane, which may exhibit different morphology at the matrix interface. No drug particles were seen on the surface of the microcapsules. Nylon microcapsules containing calcium alginate were very similar to the formalized gelatin capsules (Fig. 3). As previously

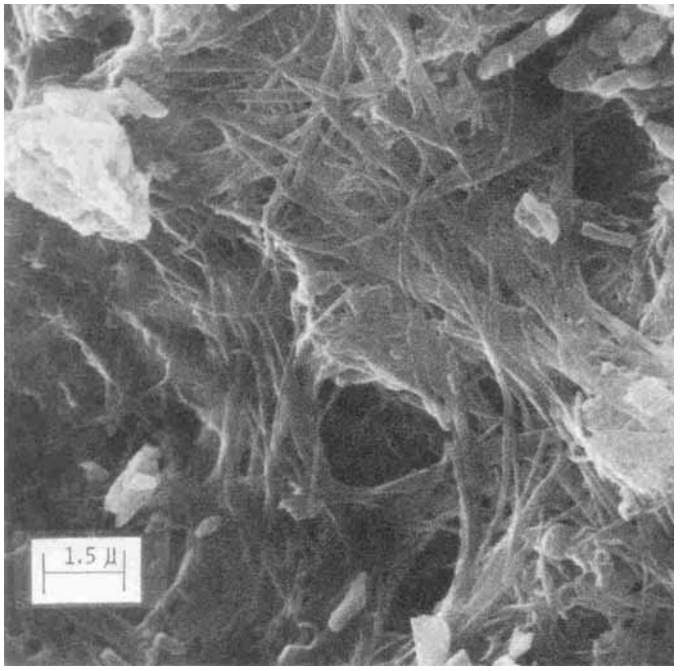

Figure 6—*Scanning electron micrograph of the microcapsule surface in Fig. 5.*

mentioned, the calcium alginate microcapsules were lyophilized for 2 days. Lyophilization for longer than 4 days resulted in disruption of the nylon membrane and loss of the matrix (Fig. 4). Figures 5 and 6 show morphine-containing microcapsules with a calcium sulfate matrix. The presence of calcium sulfate crystals on the surface is quite evident in Fig. 6. The surface appears to be very porous and fibrous in comparison to the other capsules.

Calcium sulfate hemihydrate (known as plaster of Paris) is formed by heating the dihydrate material (gypsum) (Scheme I).

$$2(CaSO_4 \cdot 2H_2O) \rightleftharpoons (CaSO_4)_2 \cdot H_2O + 3H_2O$$

Scheme I

When mixed with water, the equilibrium is reversed and the plaster sets to form a mass of gypsum crystals. The setting results in an increase in volume, which causes the nylon membrane to stretch. This expansion of the matrix helps explain the fibrous appearance of the nylon membrane in Fig. 6. The plate-like surface features seen with the formalized gelatin and calcium alginate matrixes and the fibrous structure seen with the calcium sulfate matrix differ markedly from the pitted surface of the nylon microcapsules containing polyoxyethylene glycol 400 shown by Jenkins and Florence (25).

In summary, the nylon encapsulation technique is applicable to a wide range of pharmaceuticals. Two major problems include drug partitioning into the organic phase and the possibility of decreased drug stability as a result of the alkaline pH inside the capsules. Preliminary results suggested that both problems may be overcome by altering the composition of the organic solvents and by adding small quantities of dilute acid to the reaction vessel following the formation of the nylon membrane. Future efforts will be directed toward optimizing the formulation to improve the retention of drugs that partition into the organic phase. The microcapsules also will be examined for their dissolution behavior, sustained release, and drug stabilizing properties and for the separation of incompatible ingredients.

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