number of *Swertia* species (7), was reported to produce tuberculostatic activity, although the degree of its activity was not reported (8). The *Swertia* plant extracts are also reputed for their therapeutic uses in the treatment of tuberculosis.

The antitubercular activity of the total xanthones of *C. decussata* is particularly impressive because no adverse side effects were encountered. Also, no obvious toxicity was detected on prolonged administration of the total xanthones (50 mg/kg ip to albino rats) daily for 4 weeks.

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Improved Method for Microencapsulation of Soluble Pharmaceuticals

Keyphrases □ Nylon (formalin treated) gelatin microcapsules—preparation, physical properties □ Sulfathiazole sodium—microencapsulation, dissolution □ Microencapsulation—soluble pharmaceuticals

To the Editor:

Interest in microencapsulation technology and its application to varied problems is increasing. In addition to many nonpharmaceutical applications (1), microencapsulation has been utilized pharmaceutically to increase product stability, modify drug release, overcome drug incompatibility in formulations, and improve certain physical characteristics of formulations such as compressibility and flow (2). The technology and applications of microencapsulation have been discussed in several monographs and reviews (1–6). However, as Luzzi stated (5), much of this information is found in the patent literature and the control and testing data essential for reproducibility are frequently lacking.

Table I—Percent Sulfathiazole Sodium Released from Microcapsules[a] Prepared by the Formalin-Treated Nylon Gelatin Technique (Formula I)[b] and with Nylon Alone (Formula II)[c] in 0.1 *N* HCl and 0.1 *M* Acetate Buffer (pH 5.6)

	Recoveries[d], %			
	0.1 *N* HCl		0.1 *M* Acetate Buffer (pH 5.6)	
Minutes	Formula I	Formula II	Formula I	Formula II
2	24.5	35.7	4.3	3.8
4	36.5	56.1	11.6	6.5
8	51.5	76.1	22.3	12.5
12	62.5	87.5	29.1	17.5
16	73.0	93.3	34.1	23.4
20	80.5	96.7	37.5	26.7
30	92.0	99.0	45.1	37.4
40	95.5	100.6	51.3	46.9
50	97.5	—	57.0	54.3
60	99.0	—	60.7	59.9
120	—	—	77.3	81.5

[a] One hundred percent of unencapsulated sulfathiazole sodium passed into solution in less than 2 min in 0.1 *N* HCl and 0.1 *M* acetate buffer (pH 5.6). [b] Drug content, 21% (w/w). [c] Drug content, 49% (w/w). [d] Average of duplicate assays upon the same batches.

Of interest is the work of Chang *et al.* (7), in which enzymes in semipermeable microcapsules of nylon, collodion, and heparin-complexed collodion were prepared for potential use in enzyme replacement therapy. More recently, Luzzi *et al.* (8) used a modification of their technique (7) to encapsulate a water-soluble barbiturate in nylon. To prevent loss of the barbiturate from the nylon capsules, the microcapsules were washed in chloroform prior to drying.

The present communication outlines an improved method for microencapsulating soluble drugs. Nylon was used to coat a gelatin matrix containing the drug, and the resulting microcapsules were then hardened with formalin. Sulfathiazole sodium was used as the encapsulated drug. The concentration of reactants required to form nylon and the volume ratios of aqueous and organic solvents were the same as those reported by Chang *et al.* (7). Gelatin USP (5 g) and sulfathiazole sodium (3 g) were dissolved in 60 ml of aqueous phase prior to the encapsulation step. After the nylon-coated capsules containing gelatin and sulfathiazole sodium were formed, 20 ml of formalin (formaldehyde solution USP, 37%) was added to the total reaction volume (approximately 700 ml) and this mixture was gently stirred for an additional 10 min.

The capsules were allowed to stand at 5° for 24 hr to ensure that the hardening of the gelatin within the capsules was complete (9). The microcapsules were separated from the organic phase by vacuum filtration and were then air dried at room temperature to remove formalin vapors, organic solvents, and water. Microcapsules passing through a 100-mesh screen were assayed for sulfathiazole sodium content (21% by weight) and used for dissolution studies. As controls, nylon microcapsules containing sulfathiazole sodium without gelatin were prepared using the same procedure (assay 49% by weight).

An approximation of the particle-size distributions for the two batches of microcapsules was determined using a light microscope and the calibrated counting field of a hemocytometer. The formalin-treated nylon gelatin microcapsules had an average diameter of 135 μm with a range of 70–197 μm. The particles encapsulated with nylon alone had an average diameter of 98 μm with a range of 40–170 μm.

Drug release characteristics of microcapsules containing 20 mg of drug were studied in 1500 ml of 0.1 *N* HCl and 0.1 *M* acetate buffer (pH 5.6). The dissolution apparatus consisted of a 2000-ml, three-necked, round-bottom flask maintained at 37°. A polyethylene stirring blade (7.6-cm diameter) was vertically centered and lowered to a depth of 2 cm above the bottom of the flask. The stirrer was attached to a synchronous motor and rotated at 100 rpm. The release of drug was followed spectrophotometrically at 280 nm for hydrochloric acid and at 283 nm for the acetate buffer. The reported data are the averages of duplicate runs on the same batch of material.

As can be seen from Table I, the release of sulfonamide in dilute acid from the nylon-coated and the formalin-treated nylon gelatin capsules was delayed only slightly. A greater retardant effect could be expected at the lower agitation rates used by Luzzi *et al.* (8), but it was felt that the stirring rate of 100 rpm provides results that are more realistic in terms of their release patterns. The release of drug from both nylon and formalin-treated nylon gelatin in acetate buffer at pH 5.6 is considerably slower than in dilute hydrochloric acid. A similar pattern of curves was also obtained in pH 7.6 phosphate buffer. As with dilute acid, the release rates into 0.1 *N* NaOH from both types of microcapsules were rapid and complete. Since unencapsulated sulfathiazole sodium readily passed into solution in all media tested, the reason for the slower release rate at pH 5.6 and 7.6 is unclear. Because several factors may be involved, further studies to determine the mechanisms are being conducted.

The microcapsules of formalin-treated nylon gelatin displayed ideal physical characteristics for formulation purposes. They were gritty and dense and, because of the nylon coating, they did not adhere together. The capsules had excellent flow properties and could be made of very small diameter by controlling the stirring speed during nylon formation.

Nylon microcapsules of sulfathiazole sodium containing unhardened gelatin, various cellulose gums, proteins, alginates, and other carrier materials were generally difficult to separate. In addition, they did not possess the superior physical characteristics of the formalin-treated nylon gelatin capsules.

Formalin-treated gelatin micropellets were prepared by Tanaka *et al.* (10). Such pellets have been reported to have timed-release properties in humans (11). Gelatin micropellets containing sulfathiazole sodium were prepared but showed poor flow properties even after several rinses in benzene. They tended to adhere together and were difficult to wet.

By combining the techniques of Tanaka *et al.* (10) and Chang *et al.* (7), we have successfully encapsulated a water-soluble drug in formalin-treated nylon gelatin microcapsules. Various drug–gelatin ratios are currently being studied to optimize drug release and, alternatively, to sustain the release of soluble drugs. The effects of different conditions using formalin are also being investigated.

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Relationship between pH of Saliva and pH of Urine

Keyphrases □ pH—saliva and urine, relationship □ Salivary pH—relationship to urinary pH □ Urinary pH—relationship to salivary pH

To the Editor:

A number of drugs appear in significant concentration in the saliva, and the ratio of their concentrations in saliva and plasma is relatively constant (1–7). It is feasible, therefore, to monitor the concentrations of these drugs in plasma indirectly by determining their concentrations in saliva (8). This noninvasive, convenient, painless, and safe method of indirect plasma concentration monitoring is particularly useful for children and for out-patients regardless of age.

Preliminary observations in this laboratory and by others[1] indicate that the saliva–plasma concentration ratio of certain weak acids and bases may be affected by the pH of the saliva, apparently because, among

[1] J. R. Koup and W. J. Jusko, personal communication.