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.

Table I—Effect of Sodium Bicarbonate on pH of Saliva and Urine in Adults

Hours	Saliva pH[a]		Urine pH[a]	
	Control	Sodium Bicarbonate	Control	Sodium Bicarbonate
1	7.25 ± 0.19	7.26 ± 0.15		
2			6.44 ± 0.44	7.30 ± 0.23[b]
3	7.24 ± 0.25	7.41 ± 0.26[b]		
4			6.30 ± 0.67	7.25 ± 0.32[b]
5	7.26 ± 0.11	7.38 ± 0.09		
6			6.09 ± 0.62	6.84 ± 0.63[b]
7	7.19 ± 0.16	7.34 ± 0.16		
8			5.99 ± 0.70	6.89 ± 0.28[b]

[a] Mean of five subjects ± 1 *SD*. [b] Statistically significantly different from control value ($p < 0.05$ by paired t test).

other factors, this ratio is a function of the degree of ionization of such drugs in saliva and plasma (9). The pronounced effect of pH on the renal excretion of many weak acids and bases is well known. This study was carried out to determine the magnitude of pH variation in the mixed saliva of healthy adults, the relationship between the pH of saliva and urine, and the effect of a systemic antacid on saliva and urine pH.

Five healthy male volunteers, 22–39 years old, who had not taken any drugs for at least 1 week before the study, ate their usual meals and followed their usual activities. Each volunteer voided his bladder at 8 or 9 am and collected urine and saliva at 2-hr intervals for 8 hr. About 5 ml of saliva was collected each time by salivation into a small glass vial; saliva flow was stimulated by chewing on a piece of Parafilm. The pH of the saliva and urine samples was determined[2] immediately after collection.

Two of the subjects received 5 g of sodium bicarbonate in five gelatin capsules, size 00, with 100 ml water at the beginning of the experiment; the other three subjects received water only. The experiment was repeated at least 1 week later, with the subjects who had previously taken water only now receiving sodium bicarbonate and vice versa.

The results of the study are shown in Table I and Fig. 1. The pH values summarized in Table I were averaged as such, *i.e.*, without prior conversion to molar concentrations of hydrogen ion and subsequent reconversion. Sodium bicarbonate increased urine pH by an average of 0.75–0.95 unit; this increase was statistically significant at all sampling times. On the other hand, the antacid increased the average pH of saliva by only 0.01–0.17 unit, and this change was statistically significant at only one sampling time (Table I). In a total of 40 urine and saliva samples, the pH ranged from 5.10 to 7.66 in urine but only from 6.89 to 7.68 in saliva. There was no significant correlation ($r = 0.19$) between the pH of saliva and the pH of urine (Fig. 1).

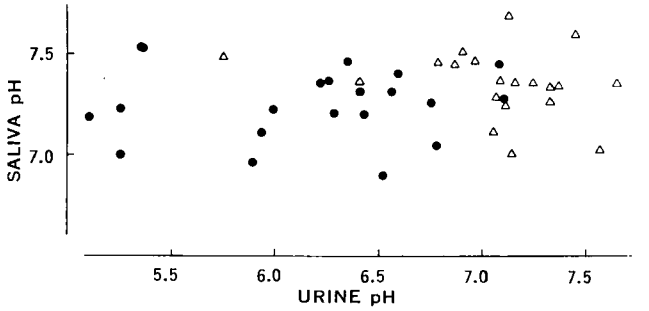

Figure 1—*Relationship between pH of saliva and pH of urine in five healthy adults. Each subject is represented by eight data points. Key: ●, control experiment; and △, after oral administration of 5 g of sodium bicarbonate.*

[2] Orion digital pH meter, model 601.

The results of this study show that:

1. Variations in the pH of saliva in normal subjects are much smaller than variations in the pH of urine.
2. It is apparently not possible to alter saliva pH significantly by acute administration of a systemic antacid.
3. There is no significant relationship between the pH of saliva and the pH of urine.

Since saliva pH varies less than urine pH, saliva concentrations may be more suitable than urinary excretion rates for an indirect estimation of the time course of plasma concentrations of certain weak acids and bases appearing in measurable concentrations in the saliva.

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