addition of enzyme. Controls contained 5 μl of dimethyl sulfoxide. The reaction mixtures were incubated for 10 min at 37°. The acid-insoluble material from an aliquot (100 μl) of each incubation mixture was isolated by the procedure of Bollum (18), placed in 18 ml of scintillation fluid (6.0 g of 2,5-diphenyloxazole, 0.2 g of 1,4-bis[2-(5-phenyloxazolyl)]benzene, 1400 ml of toluene, and 600 ml of methanol), and counted in a liquid scintillation spectrometer[4]. In the absence of added drug, 1.05 nmoles of 8-^{14}C-ATP was incorporated into DNA during the 10-min incubation period.

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[4] Model LS230, Beckman Instruments.

ACKNOWLEDGMENTS

Supported by Contract N01-CM-43761 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

The authors thank Dr. R. L. Cysyk of the Laboratory of Chemical Pharmacology, National Cancer Institute, for performing the RNA polymerase studies.

New Method of Preparing Gelatin Microcapsules of Soluble Pharmaceuticals

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Abstract □ A new method of preparing gelatin microcapsules of soluble pharmaceuticals is described. Spherical droplets of a gelatin dispersion prepared in the drug solution were produced by the capillary method, and the droplets were congealed rapidly to yield discrete units in the form of a free-flowing powder. The microcapsules obtained were spherical in shape and showed no tendency to form agglomerates. Hardening of the microcapsules resulted in a significant reduction of the release rate without altering the reproducibility. The results indicated that the process of microencapsulation described is simple, reproducible, economical, and amenable to industrial application.

Keyphrases □ Gelatin microcapsules—method of preparation with soluble pharmaceuticals □ Microcapsules, gelatin—method of preparation with soluble pharmaceuticals □ Dosage forms—gelatin microcapsules, method of preparation with soluble pharmaceuticals

In recent years, microencapsulation has found increased use in pharmaceuticals from both clinical and therapeutic aspects.

Among the methods available for microencapsulation, the gelatin encapsulation process is the oldest and perhaps the most commonly used (1–4). Gelatin microcapsules have been prepared by complex coacervation (1, 2, 5), simple coacervation (3, 6), and emulsification (4). The emulsification process is the simplest technique, but apparently the microcapsules thus produced tend to adhere together and show poor flow properties (7). In addition, they are difficult to wet and display physical characteristics unsuitable for formulation purposes (7).

The process of encapsulation reported here makes use of the fact that aqueous dispersions of gelatin set to a gel when cooled (8).

EXPERIMENTAL

Materials—All materials were USP grade and were used as received without further purification or recrystallization. The gelatin[1] had the following specifications as provided by the manufacturer: type, B, edible; bloom, 303 g; viscosity, 58.4 mps; pH, 6.30; and moisture, 10.00%.

Microcapsule Preparation—A 30% dispersion of gelatin was prepared in a 5% aqueous solution of sodium salicylate by first soaking the gelatin in the sodium salicylate solution and then heating to about 50° to effect a homogeneous dispersion. The dispersion was maintained at 50° to prevent the gelation of gelatin, and small spherical droplets of the dispersion were prepared by a method similar to the capillary method reported previously (6).

The droplets leaving the capillary were gelled by collecting them in mineral oil USP, maintained at 5° in an ice bath. Visual observation

[1] P. Leiner and Sons, America Inc., St. Claire Shores, Mich.

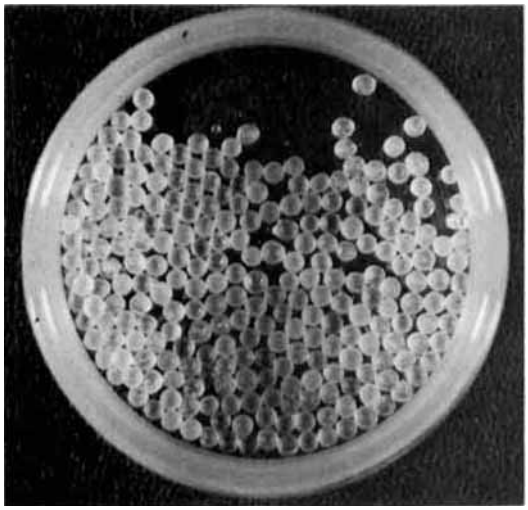

Figure 1—*Photomicrograph of microcapsules recovered as the final product.*

showed that the droplets collecting in the mineral oil exhibited no tendency to agglomerate. About 15 min was required to cause the gelling of the droplets; however, to ensure complete gelling, the droplets were allowed to remain in the mineral oil for 30 min.

After 30 min, the gelled droplets were removed and the excess mineral oil adhering to the droplets was removed by washing with acetone. A portion of the droplets was treated with formaldehyde solution USP to harden the capsules; the gelled, washed capsules were then air dried at room temperature. The final product obtained after washing and drying was in the form of discrete spherical units, recovered as a free-flowing powder. The microcapsules showed no tendency to agglomerate and displayed excellent flow properties.

Release from Microcapsules—Release of sodium salicylate from the microcapsules was determined by examining duplicate samples, containing approximately 25 mg of the drug, using the modified flask dissolution method. A 500-ml, three-necked, round-bottom flask had a 6-cm hole cut in the center to accommodate the entrance of the 40-mesh screen basket assembly used in the USP dissolution method. A 300-ml quantity of the dissolution medium (0.1 *N* HCl), preheated to 37°, was added to the flask immersed in a water bath maintained at 37 ± 0.5°. The basket containing the microcapsules was immersed in the dissolution medium, centered, and rotated at 100 rpm using a constant-speed motor.

Samples of the dissolution medium were withdrawn at predetermined intervals using a pipet fitted with a cotton plug. A constant volume of the dissolution medium was maintained by the addition of an equal volume of the dissolution medium after each sample was withdrawn. In each case, the cotton plug was added to the dissolution mixture. Concentrations were determined spectrophotometrically[2] at 304 nm after appropriate dilutions.

RESULTS AND DISCUSSION

Microcapsule Preparation—Sodium salicylate was used as the model drug because it lends itself conveniently to the spectrophotometric analysis.

This microencapsulation process makes use of the fact that aqueous dispersions of gelatin set to a gel when such dispersions are cooled (8). Various concentrations of gelatin dispersions were investigated; at concentrations below 30%, gelation was incomplete. The droplets tended to soften at room temperature and became sticky. Increasing the concentration above 30% did not decrease gelation, but the dispersion had to be maintained at higher temperatures to prevent gelation in the capillary which could result in gelatin degradation (8). At 30% and 50°, the gelatin dispersion did not gel in the capillary and the gelled droplets did not soften at room temperature.

Microscopic examination revealed that most of the microcapsules (>90%) were monodisperse, having a diameter of 185 μm (Fig. 1). The deviation of the microcapsules from monodispersity may be attributed to slight temperature fluctuations, which may have altered the viscosity of the gelatin dispersion, resulting in variations in the droplet size.

[2] Beckman model DB-GT.

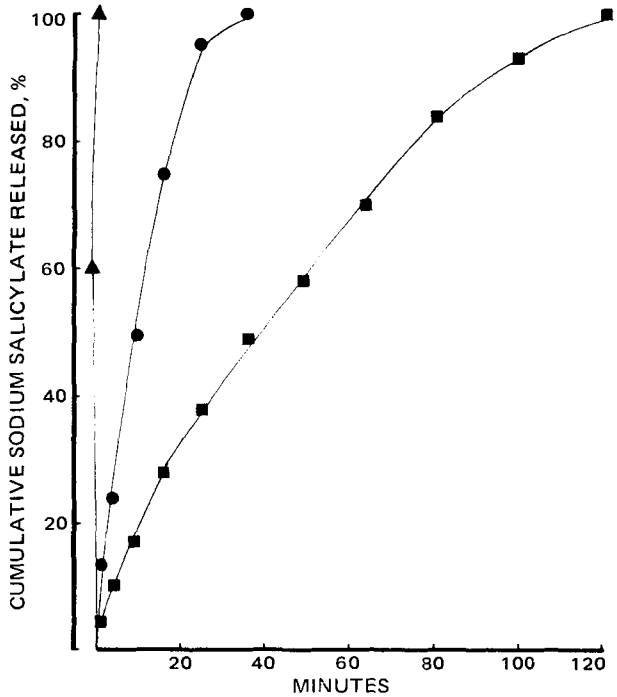

Figure 2—*Dissolution of sodium salicylate from unencapsulated drug (▲), unhardened microcapsules (●), and hardened microcapsules (■).*

The total recovery of the microcapsules from a given batch was almost 100%. Except for the last traces of the starting material, which tended to stick to the capillary apparatus, every single droplet collected in the mineral oil was recovered as a microcapsule. The drug content of the microcapsules, as determined by extracting the drug from the microcapsules (2), was 13.7% (w/w), in good agreement with the theoretically calculated value of 14.3% (w/w).

Release from Microcapsules—The release characteristics of the microcapsules are shown in Fig. 2. Included for comparison purposes is the dissolution pattern of the unencapsulated drug particles. Figure 2 shows that the encapsulation process produced microcapsules with controlled release of sodium salicylate. The unencapsulated drug particles dissolved completely in less than 2 min, but it took about 20 min for drug release from the unhardened microcapsules. Hardening the microcapsules

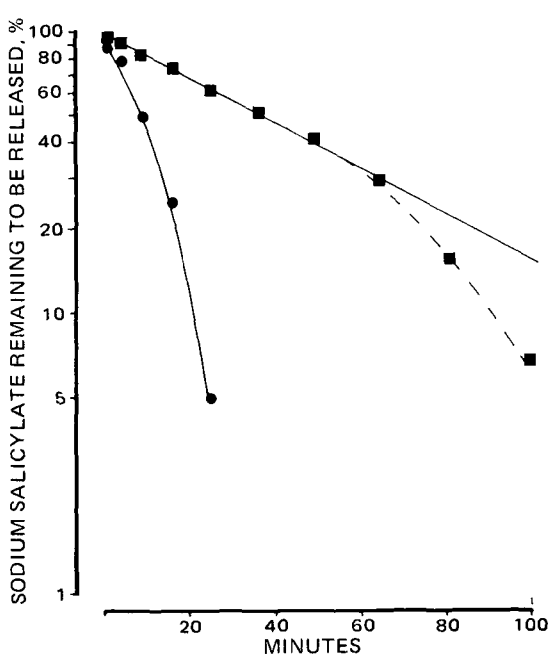

Figure 3—*Release of sodium salicylate from unhardened microcapsules (●) and hardened microcapsules (■).*

Table I—Salicylate Release from Microcapsules

Minutes	Salicylate Released[a], % Batch I[b]	Batch II[b]	Batch III[b]
1	4.5 (0.5)	4.0 (0.5)	3.9 (0.4)
5	10.0 (0.3)	10.1 (0.2)	10.2 (0.3)
10	18.1 (0.7)	17.0 (0.5)	17.5 (0.7)
15	27.5 (1.2)	28.3 (0.8)	28.0 (0.8)
25	38.0 (0.6)	37.7 (0.9)	38.1 (0.7)
35	47.5 (1.0)	48.0 (0.7)	48.2 (0.5)
50	58.3 (0.7)	58.9 (1.2)	58.5 (0.4)
65	70.0 (0.9)	71.0 (0.5)	71.0 (1.4)
80	83.5 (1.1)	84.1 (0.9)	83.7 (0.8)
100	93.1 (1.2)	92.5 (0.9)	93.5 (0.4)
120	100.0	100.0	100.0

[a] Each value is an average of at least two experiments. Values in parentheses indicate the ± range. [b] Each batch was prepared at a different time.

slowed the release significantly, increasing the time for complete drug release to about 2 hr.

Since sodium salicylate is readily water soluble, this amount of time corresponds to about a 103-fold increase in the time required for the complete dissolution of the drug particles.

The dissolution characteristics (Fig. 2) indicate that the release of sodium salicylate from the unhardened microcapsules approaches zero-order kinetics throughout much of the extraction process. For the hardened microcapsules, the dissolution shows essentially zero-order kinetics from about 30 to about 85% sodium salicylate release.

One aim with microencapsulation is to obtain zero-order drug release from the microcapsules (8). Unfortunately, experience shows that most microcapsule formulations release the drug at roughly a first-order rather than a zero-order rate (9). Figure 3 shows a first-order plot of sodium salicylate release from the microcapsules. While the unhardened microcapsules do not appear to follow first-order kinetics, the hardened microcapsules show a first-order release up to about 70% sodium salicylate released.

In most microencapsulation processes, microcapsule recovery involves a drying step that may influence the microcapsule integrity. For example, solvent evaporation during drying may cause shrinkage of the shell wall, thus creating coating defects, flaws, and/or deposition of a portion of the drug on the microcapsule surface due to the solvent migration effect. Because of these effects, either singly or in combination, the release patterns of the drug from the microcapsules may show an initial rapid drug release, which has been reported to range from about 10–20% (6) to as high as 50% (3). Since the microencapsulation process reported here uses gelation rather than drying, this effect was minimal in drug release from the microcapsules.

The microencapsulation process used in this investigation gave good reproducibility. Release rates obtained with the microcapsules from the same batch were within a narrow range, the maximum range observed being 3% (Table I). Duplicate batches of the microcapsules prepared at various times were identical to the original batch in terms of batch yield, microcapsule size and size distribution, and release rate profile. In addition, the process described is simple, economical, and amenable to industrial application.

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Synthesis of Methaqualone and Its Diphasic Titration in Pure and Tablet Forms

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Received April 4, 1977, from the *Departments of Pharmaceutical and Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, University of Alexandria, Alexandria, A.R. Egypt.* Accepted for publication June 13, 1977.

Abstract □ A one-step synthesis of methaqualone from *N*-acetylanthranilic acid and *o*-toluidine in the absence of a catalyst is described. A rapid diphasic titration procedure for its microestimation in pure and tablet forms, using dioctyl sodium sulfosuccinate and dimethyl yellow screened with oracet blue B, is proposed. The data were compared with those obtained from nonaqueous titration methods.

Keyphrases □ Methaqualone—one-step synthesis, diphasic titration analysis in bulk drug and tablets □ Titration, diphasic—analysis, methaqualone in bulk drug and tablets □ Hypnotic–sedatives—methaqualone, one-step synthesis, diphasic titration analysis in bulk drug and tablets

Methaqualone, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (I), is marketed both as a sedative–hypnotic and as an anticonvulsant (1). Several methods have been reported for its synthesis and evaluation as the base or hydrochloride in bulk drug and dosage forms.

Methaqualone has been synthesized by: (*a*) refluxing a solution of *N*-acetylanthranilic acid with *o*-toluidine in toluene in the presence of different catalysts (2–5); (*b*) by heating anthranilic acid, *o*-toluidine, acetic acid, and polyphosphoric acid (6); (*c*) by condensing 2-methyl-3,1,4-benzoxazone with *o*-toluidine (7, 8); or (*d*) by heating methyl anthranilate with *o*-toluidine *N*-(magnesium bromide) and acetylating the intermediate amide, which subsequently cyclizes (9). The hydrochloride of I was prepared by heating *N*-acetylanthranilic acid with *o*-toluidine hydrochloride (10).

For the estimation of I or its hydrochloride salt, diazometric (11), colorimetric (12), spectrophotometric (13, 14), complexometric (15), and nonaqueous titration (16–18) methods have been proposed.

In the present investigation, I was prepared by heating *N*-acetylanthranilic acid with *o*-toluidine in bromobenzene in the absence of a catalyst. This report also describes a