groups, between the alkyl groups, or between the alkyl and phenyl groups of the interacting species. Also, in this context, the degree of effect of higher body temperature (fever) on the tertiary structure of vital biopolymers (enzymes), and consequently on their physiological activities, could be expected to depend on the nature of hydrophobic groups involved in hydrophobic bonding responsible for maintaining the tertiary structure of the biopolymers.

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# Preparation and *In Vitro* Evaluation of Cellulose Acetate Phthalate Coacervate Microcapsules

## H. P. MERKLE and P. SPEISER▲

**Abstract** ☐ Microcapsules of phenacetin were prepared by coacervation of aqueous cellulose acetate phthalate solutions. Appropriate solutions were made by dissolving cellulose acetate phthalate in an equivalent concentration of disodium hydrogen phosphate. A triangular phase diagram of the coacervation system was elaborated by using sodium sulfate as the coacervating agent, and the coacervation and encapsulation conditions were optimized. The amount of drug encapsulated has no significant effect on the particle-size distribution of the capsules; however, it influences the release rates of the drug, indicating that drug diffusion through the shells is the controlling step. When the shells are plasticized by imbibition with glycerol, the release rate is no longer controlled by drug diffusion through the shells but by the dissolution of phenacetin in the microcapsules.

**Keyphrases** ☐ Cellulose acetate phthalate coacervate microcapsules—formulation, *in vitro* drug (phenacetin) release rates, effect of glycerol plasticizer ☐ Encapsulation—formulation and *in vitro* testing of cellulose acetate phthalate coacervate microcapsules of phenacetin ☐ Coacervation of cellulose acetate phthalate—formulation of microcapsules, *in vitro* phenacetin release rates, plasticizer effect ☐ Microcapsules, phenacetin—formation from cellulose acetate phthalate coacervate system, release rates, plasticizer effect

The preparation of microcapsules by coacervation can be applied to various products (1). Different coating materials, suitable for coacervate encapsulation, were reported by Ranney (2). In pharmacy, however, the most common preparation technique is either simple coacervation of gelatin with ethanol or sodium sulfate as dehydrating agents (3–9) or complex coacervation of gelatin–acacia mixtures (10–12). Coacervation methods with pure gelatin and mixtures are rather complicated and difficult to keep under control, particularly with regard to the hardening of shells and the recovery technique of the microcapsules. The suit-

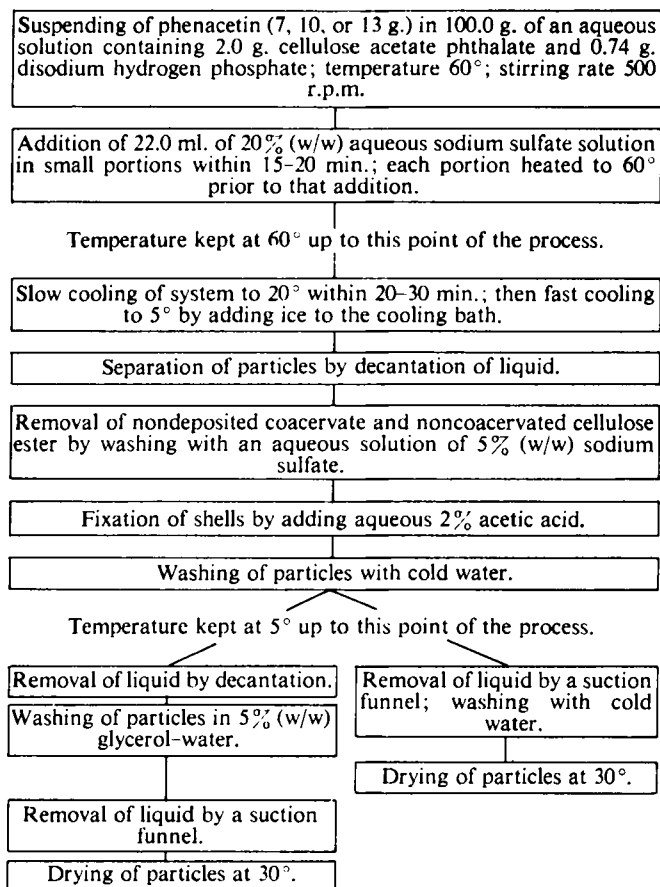ability of other coacervation systems for pharmaceutical purposes has not yet been studied.

Cellulose acetate phthalate was used by Jensen and Wagner (13) as a film-forming agent for encapsulation of a herbicide by simple coacervation. However, the encapsulation procedure presented in this patent is not practicable, owing to the insolubility of the cellulose ester in pure water and its total hydrolysis at pH 9.7, which is proposed as the encapsulation pH. Due to acidic groups, the cellulose ester is insoluble in strong acids but soluble in weak acids (>pH 5.5), neutral electrolytes, and bases. It is a suitable encapsulation material for timed-release dosage forms. Due to its very low acute and chronic toxicity, cellulose acetate phthalate was chosen as the encapsulating material in this study.

The present article reports a relatively uncomplicated process for the encapsulation of solid drugs by the simple coacervation of the cellulose ester, which is dissolved in appropriate disodium hydrogen phosphate solutions. The coacervation is induced by the dehydrating effect of the added sodium sulfate solution. Furthermore, the optimal coacervation and encapsulation conditions and the properties of the resulting microcapsules are examined with regard to drug content, size distribution, and release and release mechanisms of drugs.

## EXPERIMENTAL

**Materials and Methods**—The cellulose acetate phthalate used was of Ph. Helv. VI quality, containing 34.1% phthalic acid and 2.7% free acid, calculated as phthalic acid.

Phenacetin (*N*-acetyl-*p*-aminophenetidin), of Ph. Helv. VI quality (m.p. 134–135°), was chosen as the drug model for the encapsula-

Suspending of phenacetin (7, 10, or 13 g.) in 100.0 g. of an aqueous solution containing 2.0 g. cellulose acetate phthalate and 0.74 g. disodium hydrogen phosphate; temperature 60°; stirring rate 500 r.p.m.

Addition of 22.0 ml. of 20% (w/w) aqueous sodium sulfate solution in small portions within 15-20 min.; each portion heated to 60° prior to that addition.

Temperature kept at 60° up to this point of the process.

Slow cooling of system to 20° within 20-30 min.; then fast cooling to 5° by adding ice to the cooling bath.

Separation of particles by decantation of liquid.

Removal of nondeposited coacervate and noncoacervated cellulose ester by washing with an aqueous solution of 5% (w/w) sodium sulfate.

Fixation of shells by adding aqueous 2% acetic acid.

Washing of particles with cold water.

Temperature kept at 5° up to this point of the process.

Removal of liquid by decantation.

Washing of particles in 5% (w/w) glycerol-water.

Removal of liquid by a suction funnel.

Drying of particles at 30°.

Removal of liquid by a suction funnel; washing with cold water.

Drying of particles at 30°.

*Scheme I—Preparation of cellulose acetate phthalate microcapsules*

tion, primarily because of its sufficient stability and insolubility in aqueous cellulose ester solutions. These properties are the fundamental requirements for good core materials. Sieve fractions of 0.10–0.50-mm. diameter were used.

Sodium sulfate (reagent grade) in a 20% (w/w) aqueous solution was used as a coacervating agent. All other compounds used were reagent grade.

**Preparation of Cellulose Acetate Phthalate Solutions**—A certain amount of cellulose ester was agitated in an aqueous solution of stoichiometrically equivalent quantities of disodium hydrogen phosphate (Na$_2$HPO$_4$) (calculated on the basis of the acidity of cellulose ester amounts, including free and bound acid, with 1.0 g. of cellulose ester being equivalent to 0.37 g. Na$_2$HPO$_4$) by means of a high speed stirrer (Polytron type) at 60°. After 1 min., most of the cellulose ester suspended was dissolved. The remaining solid cellulose ester was dissolved by low speed stirring using a magnetic stirrer at 60°. The dissolution was completed in about 15-20 min. The resulting solutions were filtered and stored at room temperature. The solutions proved to be stable for at least 1 week and showed no variation in coacervation behavior during that time.

**Preparation of Microcapsules**—As a preliminary proceeding, a triangular diagram was elaborated for the three phases participating in the cellulose ester coacervating system, i.e., water, the cellulose ester, and salt. The latter consisted of disodium hydrogen phosphate (solvating agent) and sodium sulfate (dehydrating and coacervating agent). Portions of 100.0 g. of the cellulose ester solution were placed in a flask, which was maintained at 60° in a thermostated water bath and equipped with a reflux condenser. The solutions were stirred by a two-blade propeller at 500 r.p.m. For the coacervation of the cellulose ester, a 20% (w/w) aqueous sodium sulfate solution was added in parts. The supply of the sodium sulfate solution was constantly maintained at 60° with the help of a thermostated heating mantle. The start of coacervation was optically observed under the microscope. Solutions with 0.5 and 1.0–10.0% (1.0% interval) of cellulose ester were tested.

For microencapsulation, the same procedure was repeated by adding 10.0 g. of phenacetin to each concentration of the cellulose

ester tested. The encapsulating and coacervating behavior of the slurries was observed microscopically. An optimum of coacervation and encapsulation was reached at a minimum agglomeration of the particles, a maximum deposition of coacervate on particles, and a minimum deformation of the liquid shells during encapsulation.

Following this procedure, all batches of microcapsules were produced within the field of optimum coacervation and encapsulation conditions. The method of preparation is shown in Scheme I. The encapsulations were made in a three-necked, 250-ml. beaker, equipped with a reflux condenser and a thermostated water bath for heating and cooling. The mixtures were agitated by a two-blade propeller-stirrer at a constant stirring rate of 500 r.p.m. The position of the stirrer was kept constant in all experiments. Special attention was given to the position of the stirrer, which must produce efficient mixing without nonconvected regions, an important requirement for preventing agglomeration of the particles. As may be seen from Scheme I, gelling of liquid shells was caused by cooling to 5°. The cellulose ester, which was not coacervated or deposited on the particles, was removed by washing and decanting with a 5% (w/w) aqueous sodium sulfate solution at 5°. Thereafter, the shells were fixed by addition of 2% acetic acid to the final pH 3.5. This process converted the solvatized cellulose ester gel to the non-dissociated insoluble cellulose ester acid. If desired, the shells of washed particles can be treated with water-soluble plasticizers by washing the particles, for example, with a 5% (w/w) aqueous glycerol solution for 15 min. at 5°. The plasticizer treatment of the microcapsules should prevent rupture of the shells during drying.

**Assay of Phenacetin Content**—Microcapsules, 100.0 mg., were thoroughly triturated in a mortar. The resulting powder was transferred to a 600-ml. beaker. After a thorough rinsing of mortar and pestle with water, the powder was suspended in approximately 250 ml. of water (including the water used for rinsing). For complete rupture of the shells, the suspension was treated with ultrasonics for 2 min.[1] The completeness of rupture by this treatment was observed previously. Heating to 40° and stirring with a magnetic stirrer for about 30 min. provide a complete dissolution of the phenacetin crystals. The resulting solution was filtered through a glass suction funnel (G3) to separate the shell fragments. After thorough rinsing of all equipment, the solution was transferred into a 500.0-ml. volumetric flask. More water was used for rinsing and to reach the total volume of 500.0 ml. Samples of this solution were diluted at a ratio of 1 to 20 with aqueous pH 1.2 buffer (0.1 M hydrochloric acid, 0.1 M sodium chloride) and assayed spectrophotometrically[2] at 245 nm.

**Particle-Size Analysis**—Before analyzing the particle-size distributions, the microencapsulated phenacetin was put through a 0.63-mm. analytical sieve to separate coarse, agglomerated particles exceeding this size. The following method for the determination of particle size and particle-size distribution was developed. Microphotos of pure and microencapsulated drug were enlarged on photographic paper. The reproduced particles were counted and measured with a semiautomatic particle-size analyzer[3]. For each analysis, a minimum of 500-600 particles was evaluated from several microphotos. The particle-size distributions were calculated by means of a computer program (ALGOL).

**Release**—The release of drug from microcapsules was followed by a flow cell column method, similar to that described by Langenbucher (14) and Tingstad and Riegelman (15). Column height was 3.0 cm. and cross-sectional area was 3.14 cm.[2] The solvent used was 0.1 M hydrochloric acid, which was brought to an ionic strength of 0.2 by addition of sodium chloride. Solvent was pumped with a two-roller silicone tube pump through the flow cell. The quantity of the solvent and the flow rate were kept constant for all experiments (500.0 ml. of solvent; flow rate of 50 ml./min.). Before passing through the flow cell, the solvent was thermostated at 37 ± 0.5° by a heat exchanger. An amount of microcapsules, equivalent to a mass load of 65.0 mg. of total drug, was taken for all experiments. To analyze the phenacetin content of the solution, samples of 2.0 ml. were taken out of the solution reservoir after appropriate intervals. After diluting with the same solvent, the samples were analyzed spectrophotometrically at 245 nm. The maximum drug concentration in the solution did not exceed 10% of the saturation

[1] Elgasonic TS-100 ultrasonics generator, 25 kHz., Elgasonic SA, Biel, Switzerland.
[2] Zeiss PMQ II spectrophotometer.
[3] Zeiss TGZ 3 Analysator.
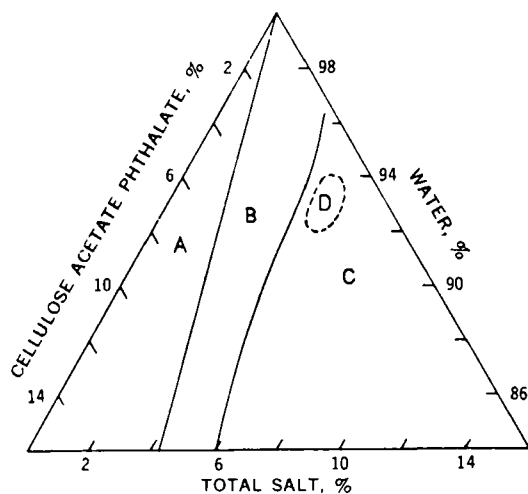
Figure 1—*Triangular phase diagram of the cellulose acetate phthalate coacervate system. Key: A, cellulose ester partially dissolved; B, clear solution of the cellulose ester; C, coacervate region (coacervate and equilibrium phase); and D, optimum encapsulation conditions. (Temperature 60°; pH 5.3-5.4; within field A, the salt consists of disodium hydrogen phosphate; within fields B, C, and D, the salt consists of mixtures of disodium hydrogen phosphate and sodium sulfate.)*

concentration of the drug, which guaranteed sufficiently good sink conditions.

## RESULTS AND DISCUSSION

**Triangular Phase Diagram of the Coacervate System**—The isothermal triangular diagram of phase boundaries of the coacervate system of cellulose acetate phthalate, water, and salt is shown in Fig. 1. The salt phase consists of two components: disodium hydrogen phosphate and sodium sulfate as solvating agent and coacervating agent, respectively. The values on the total salt axis in Fig. 1 are the additive percentages of the individual salt species in the system. A procedure to calculate these individual concentrations from this graph is given. The combination of both salt species to one phase was necessary to reduce the actual four-component system to a three-component system which can be visualized graphically by a usual triangular phase diagram.

The phase diagram presented is divided into three fields: A, B, and C. In field A, the cellulose ester is only partially dissolved. At the boundary between fields A and B, the ratio between the amounts of disodium hydrogen phosphate and the cellulose ester is constant. At this ratio, *i.e.*, 0.37, the cellulose ester is completely dissolved. Within field A, the salt phase consists only of disodium hydrogen phosphate. The salt species additionally added to the system in fields B and C is sodium sulfate. The coacervation starts at the boundary separating fields B and C. Field C indicates the

Table I—Effect of Drug Amount Encapsulated on Drug Content of Microcapsules[a]

| | Drug Content of Microcapsules, %[c] | |
| Amount of Drug, g.[b] | Without Plasticizer | With Plasticizer (Glycerol) |
|---|---|---|
| 7 I | 88.5 | 82.0 |
| 7 II | 88.5 | 81.5 |
| 10 I | 91.7 | 85.5 |
| 10 II | 92.5 | 84.7 |
| 13 I | 93.2 | 88.5 |
| 13 II | 93.2 | 88.5 |

[a] Encapsulation conditions: 60°, 100.0 g. 2% cellulose ester solution, 22.0 ml. 20% (w/w) sodium sulfate solution, and 500 r.p.m. [b] Each batch made twice (I and II). [c] Two determinations were run on I and II at each drug amount; the data presented are the means of the two determinations.

Table II—Effect of Drug Amount Encapsulated[a] on Deposition of Shell Material

| | Shell Material Deposited, g.[c] | |
| Amount of Drug, g.[b] | Cellulose Ester | Cellulose Ester and Glycerol |
|---|---|---|
| 7 I | 0.91 | 1.55 |
| 7 II | 0.91 | 1.59 |
| 10 I | 0.90 | 1.77 |
| 10 II | 0.81 | 1.79 |
| 13 I | 0.94 | 1.69 |
| 13 II | 0.94 | 1.69 |
| Means of all formulations | 0.90 | 1.68 |
| Mean of glycerol deposited | 0.78 | |

[a] Encapsulation conditions: 60°, 100.0 g. 2% cellulose ester solution, 22.0 ml. 20% (w/w) sodium sulfate solution, and 500 r.p.m. [b] Each batch made twice (I and II). [c] Data calculated from corresponding data in Table I.

region of coacervate and equilibrium phases. The explanations demonstrate the recalculation procedure of the individual salt species in the system for any given point. Within field A, the salt consists of the phosphate only. Within fields B, C, and D, the point of intersection of the boundary A B and the line of a given constant concentration of the cellulose ester mark the phosphate concentration for that given cellulose ester concentration. For example, a coacervate mixture containing 6% cellulose ester and 86% water obviously contains 8% total salt. The line of 6% cellulose ester has an intersection point with the boundary A-B. This point indicates about 2% disodium hydrogen phosphate. Two percent phosphate subtracted from 8% total salt gives a 6% concentration of sodium sulfate for the mixture discussed.

**Microencapsulation**—After addition of the sodium sulfate solution, part of the total cellulose ester available is coacervated, separating in the form of viscous liquid drops. These drops tend to deposit on the surface of phenacetin particles suspended in the solution. The subsequent cooling of the system causes a continually passing coacervation of further cellulose ester. During the cooling
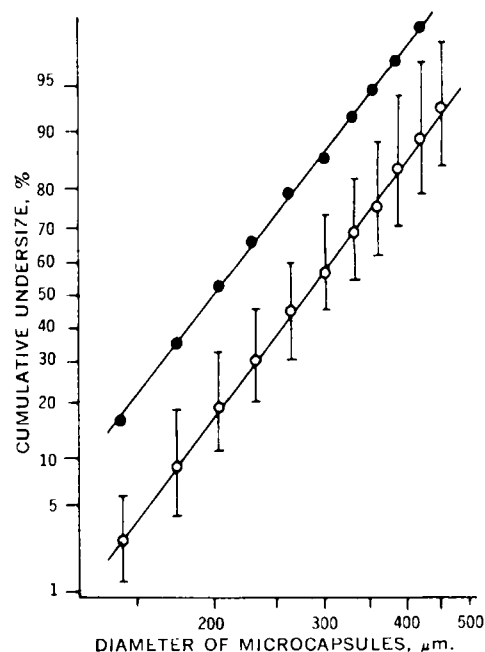


Figure 2—*Cumulative percent undersize plots of encapsulated and nonencapsulated phenacetin. Key: ●, nonencapsulated phenacetin; and ○, encapsulated phenacetin. [Encapsulation conditions were constant; amounts of drug to encapsulate varied (7, 10, and 13 g.); batches made with and without glycerol treatment; batches made twice; points are means of all formulations; bars indicate range of values.]*

**Table III**—Effect of Drug Amount and Plasticizer Treatment
on the Mean Cumulative Percentage Undersize
Diameter of Microcapsules[a]

| Amount of Drug, g.[b] | Mean Diameter of Microcapsules at 50% Cumulative Undersize, μm.[c] | |
|---|---|---|
| | With Plasticizer (Glycerol) | Without Plasticizer |
| 7 I | 300 | 320 |
| 7 II | 300 | 285 |
| 10 I | 280 | 245 |
| 10 II | 270 | 240 |
| 13 I | 265 | 280 |
| 13 II | 295 | 275 |

[a] Encapsulation conditions: 60°, 100.0 g. 2% cellulose ester solution, 22.0 ml. 20% (w/w) sodium sulfate solution, and 500 r.p.m. [b] Each batch made twice (I and II). [c] Data graphically determined from their individual logarithmic probability plots of the percent cumulative undersize distributions of all the different formulations.

process, the coacervate phase is gradually deposited on already formed walls of the cellulose ester coacervate.

Optimum encapsulation conditions were found at about 1–3% cellulose ester and 5% total salt concentration (D in Fig. 1). Higher concentrations of the cellulose ester (5–6%) produced filiform bulks of coacervate surrounding the core particles. A higher total salt concentration than 6% caused agglomeration of particles and deformation of the coacervate films still in the liquid state. The deposition of coacervate onto the particles (examined microscopically) was nearly complete at the optimum encapsulation conditions. The encapsulation technique was simple in the region of optimum coacervation and encapsulation. The agglomeration of particles and the deformation of the liquid coacervate films by the shearing forces of the stirring occurred only to a small extent.

For better utilization of the cellulose ester available in solution, it is desirable to work at higher sodium sulfate concentrations, which produce higher portions of coacervate. But this is not possible by simply increasing the sodium sulfate concentration owing to the increased agglomeration and deformation tendency at high salt concentrations. Therefore, a technique was developed for the continuous addition of sodium sulfate during the cooling of the system. Suitable cooling with addition of sodium sulfate produced thicker coacervate films than the coventional method. These films were found to be laminated, and the inner layers were heavily vacuolized. However, after washing and drying, no significant increase of the cellulose ester content of the microcapsules would be noticed.

**Drug Content of Microcapsules**—Table I shows the drug content of several formulations of microcapsules. The amounts of the cellulose ester available in solution and the coacervation conditions were kept constant, whereas the amount of drug to encapsulate and the use of glycerol as shell plasticizer were varied. The data show good reproducibility of the encapsulation process with regard to the drug content. When glycerol was used to plasticize the shells, it was incorporated in the shell structure and so decreased the drug percentage of the microcapsules as compared with the corresponding nonplasticized formulations. Table II shows the amounts of shell material deposited on the drug particles in the encapsulation process. The figures in this table were deduced from Table I using the following formula:

$$\text{shell material deposited} = \frac{\text{amount of drug encapsulated} \left(100\% - \dfrac{\text{percent drug content}}{}\right)}{\text{percent drug content}}$$ (Eq. 1)

The mean amount of glycerol deposited was calculated from the difference of the arithmetic means of the shell material deposited in both procedures. Table II indicates that the amounts of the cellulose ester deposited on the phenacetin crystals and the glycerol uptake by the cellulose ester shells are almost constant. The data clearly show that the described encapsulation process is able to produce microcapsules of varying drug-to-shell ratios in a reproducible way. This is a fundamental requirement for controlling release rates by shell thickness. Other information about the encapsulation process is provided by the calculation of the utilization
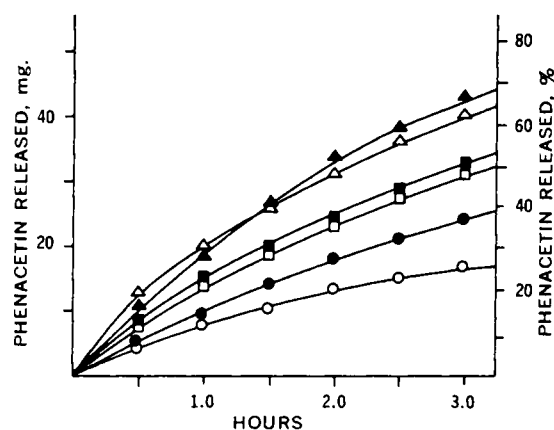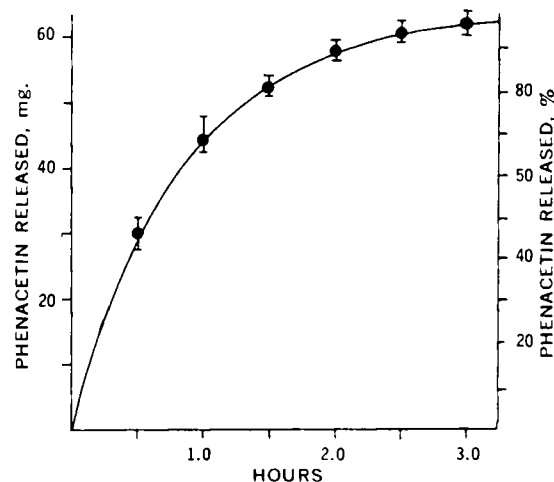


**Figure 3**—*Release plots of microencapsulated phenacetin, non-plasticized formulations. Key:* ●, *7 g. I;* ○, *7 g. II;* ⊏, *10 g. I;* ■, *10 g. II;* ▲, *13 g. I; and* △, *13 g. II. [Temperature 60°; 100.0 g. 2% cellulose ester solution; 22.0 ml. 20% (w/w) sodium sulfate solution; 500 r.p.m.; each batch made twice (I and II); points on plot indicate mean of two determinations; amounts of drug varied.]*

factor of the cellulose acetate phthalate in the system used to prepare the microcapsules. Out of the 2.0 g. cellulose ester available in the system, about 0.9 g. was deposited on the drug crystals; therefore, the utilization factor of the ester was about 0.45.

**Particle Size of Microcapsules**—The amounts of coarse and agglomerated particles larger than 0.63 mm. in diameter, as determined by sieve analysis, never exceeded 3% of the total mass of the final encapsulated product. The mean geometric diameters of different formulations, which were graphically determined from the individually obtained logarithmic probability plots of the percent cumulative undersize curves, are shown in Table III. The data show small variations between the different formulations, which are, however, within the confidence limit of the determination method. It is, therefore, assumed that the amount of drug to encapsulate, as well as the treatment with glycerol as plasticizer, has no significant influence on the particle size. The mean logarithmic probability plot of percent cumulative undersize is shown in Fig. 2. The mean plot of all encapsulated formulations is transformed to a greater diameter than compared with the nonencapsulated phenacetin.

**Drug Release**—The formulations of microcapsules previously assayed for drug content were examined for drug release. The re-



**Figure 4**—*Release plots of microencapsulated phenacetin, plasticized formulations. [Temperature 60°; 100.0 g. 2% cellulose ester solution; 22.0 ml. 20% (w/w) sodium sulfate solution; 500 r.p.m.; each batch made twice (I and II); amounts of drug varied (7, 10, and 13 g.); two determinations were run on I and II at each drug amount; points on plot are means of all determinations, batches, and drug amounts; bars indicate range of values obtained.]*

lease plots for nonplasticized formulations shown in Fig. 3 demonstrate a good correlation between the drug content of microcapsules and the release rate, i.e., between the shell thickness and the release rate. The release of parallel batches with the same drug content can be considered as reproducible, because the noticeable differences between two parallel batches are inevitable due to individual technological variations. In contrast, all batches of plasticized capsules showed identical release curves in spite of different drug contents (Fig. 4).

To explain this obvious difference in the release mechanisms of plasticized and nonplasticized formulations, the individual steps of drug release from microcapsules are illustrated. In the first step, the film of cellulose ester takes up solvent by imbibition. In the second step, the solvent diffuses into the free space within the capsules. In the third step, the dissolution of drug takes place; and in the fourth, the dissolved drug is released by diffusion through the coacervate film, whereas further drug is continually dissolved. In the case of plasticized films, the porosity of these films is supposed to be so high that the dissolved drug can easily diffuse through the pores, which are formed by washing out glycerol, without any hindrance. Under this assumption, drug release depends only on the dissolution rate of the encapsulated phenacetin. In the case of pure, nonplasticized films of cellulose ester, the data show that the film thickness influences the release rates of a drug, indicating that diffusion of a drug through the shells is the controlling factor of release. Along with analogous results for ethylcellulose-coated microcapsules (16), it is indeed reasonable to assume that this is the only way release might occur for the capsules tested; leaching of the drug out of the microcapsules is, therefore, regarded to be negligible.

In contrast to the typical release curves of Nixon et al. (5) and Nixon and Walker (9), which show an extremely rapid initial release from gelatin coacervate microcapsules, the release of drug in the present studies was more regular and the release curves are smoother. This may be due to the more complete encapsulation of the core material. Furthermore, in contrast to the findings of these authors, the release of drug from microcapsules can be controlled significantly by the ratio of the amounts of drug to shell substance, i.e., the technological formulation.

## CONCLUSIONS

The results of this investigation show that cellulose acetate phthalate coacervate encapsulation is a more suitable encapsulation technique, less complicated and less difficult to control than other methods of coacervate encapsulation. The data demonstrate clearly that simple variations of the encapsulation process can significantly affect drug release rates. The importance of these accurately defined release rates on the therapeutic application of drugs is well known

and has often been described. Owing to the broad variety of film-forming materials, which are not yet tested for this purpose, more research is needed in the field of preparation and evaluation of coacervate microcapsules.

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