Acetylacroninium Salts as Soluble Prodrugs of the Antineoplastic Agent Acronine

D. W. A. BOURNE *§, T. HIGUCHI ‡, and A. J. REPTA ‡x

Abstract □ The low aqueous solubility of acronine (~2 mg/liter) has been overcome by identification of quaternary prodrug salts exhibiting apparent molar solubilities two to five orders of magnitude greater than acronine. The synthesis and kinetics of hydrolysis of the various prodrug acetylacroninium salts were studied, and the half-life for hydrolysis under conditions approximating the *in vivo* situation was estimated to be about 5 min. Such rapid reversion, together with the greatly increased solubility, appears to qualify the prodrug for intravenous use.

Keyphrases □ Acronine—quaternary salts of acetyl derivative synthesized as prodrugs for intravenous use, solubilities and kinetics of hydrolysis studied □ Acetylacroninium salts—synthesized as prodrugs for intravenous use, solubilities and kinetics of hydrolysis studied □ Prodrugs, potential—quaternary salts of acetyl derivative of acronine synthesized for intravenous use, solubilities and kinetics of hydrolysis studied □ Antineoplastic agents—acronine, quaternary salts of acetyl derivative synthesized as prodrugs for intravenous use, solubilities and kinetics of hydrolysis studied

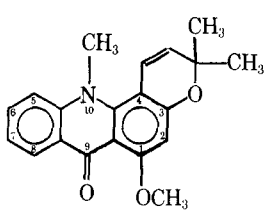
Acronine (I), a derivative of 1,3-dihydroxy-9-acridanone[1], was first isolated in 1948 (2, 3). Later, the compound was found to exhibit activity (4) against various rodent tumor system cultures when administered as an aqueous suspension by different routes. However, the extremely low solubility of acronine (2–3 mg/liter[2]) has presented problems in the clinical evaluation of the drug administered orally as a capsule[3].

A suitable intravenous formulation of acronine would obviate problems associated with the GI absorption of the nearly insoluble drug. However, the problem of low solubility, together with the estimated adult human dose of 100 mg[3], presented a significant barrier to intravenous use.

BACKGROUND

A coprecipitate of acronine with povidone (5) was about 15 times as water soluble as acronine alone, and the cytotoxic activity of acronine in the coprecipitate was about twice that of acronine itself. This study (5) demonstrated that increased solubility yielded improved drug activity, but the coprecipitate approach did not appear capable of producing the concentration increases necessary for a suitable intravenous dosage form.

The objective of the present study was to identify physical and/or chemical approaches for the solubilization of acronine in vehicle systems suitable for intravenous administration. Various approaches were considered including complexation, simple salt formation, and mixed solvent systems. Most approaches were ruled out due to the physicochemical properties of acronine (*e.g.*, its weakly basic nature) and/or the insufficient increase in solubility expected.



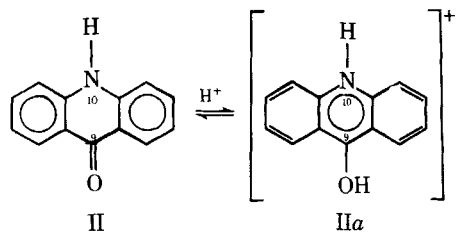
I

It was concluded that the required solubility increase would best be accomplished through the identification of a chemically derived prodrug of acronine. This report deals with the identification, synthesis, and properties of a derivative of acronine. It presumably satisfies the increased solubility requirement and yet lies within those constraints (6, 7) inherent in a satisfactory prodrug.

Acronine, mol. wt. 321.3, pKa (protonated form) 1.6, mp 176–178°, has solubilities at 25° of 3.2, 27.5, and 3×10^{-4} g/100 ml in acetone, chloroform, and water, respectively. The low aqueous solubility of acronine is probably due to its very hydrophobic nature rather than to strong interactions among molecules in the crystalline state. Therefore, a prodrug with greatly increased hydrophilic character (8, 9) might afford the greatest probability for attaining the desired solubility increase (~1 mg/ml).

Compound I contains no functional groups that could be derivatized to yield a soluble prodrug that would rapidly revert to I following intravenous administration. However, the apparent solubility of I in aqueous hydrochloric acid was >1 mg/ml at pH ~0. Although the pharmaceutical use of such a highly acidic solution is impractical, this observed solubility of acroninium chloride suggested that the presence of a formal charge on the acronine molecule might yield an increased solubility of the magnitude desired.

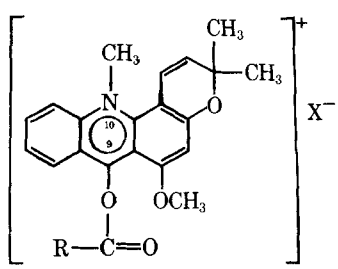
Evaluation of the reported acid–base behavior of 9-acridanone (II, Scheme I) indicates that protonation of that weak base occurs at the carbonyl oxygen (10), resulting in a fully aromatic 9-acridanonium ion (II*a*) where the positive charge resides on the nitrogen. Since acronine is structurally similar to 9-acridanone, an equilibrium similar to that shown in Scheme I may be found for acronine under strongly acid conditions. The existence of such an equilibrium suggests that the carbonyl oxygen of acronine might react under suitable conditions to form an ether or ester derivative at the 9-position.



II IIa

Scheme I

A derivative such as I*a* is a quaternary salt analogous to the protonated form of acronine and would be worthy of evaluation as a soluble prodrug of acronine, since its ester linkage might be more rapidly cleaved (6) to yield the parent drug than would the corresponding ethers. Various acetylacroninium salts (I*a*, R = methyl) were chosen as the desired candidates for initial evaluation. The anions expected to influence solubility were chosen from the more common strong inorganic acids.



I*a*

[1] All species discussed that contain the acridine skeleton are treated as derivatives of acridine. Therefore, the numbering system employed is that most widely used for acridine (1) and not acronine (3,12-dihydro-6-methoxy-3,3,12-trimethyl-7*H*-pyrano[2,3-c]acridin-7-one).

[2] See C. A. Hewitt, Stanford Research Institute Report (SRI 758 and 770) to the National Cancer Institute, Aug. 20, 1968.

[3] J. P. Davignon, National Cancer Institute, personal communication.

RESULTS AND DISCUSSION

Preparation and Characterization of Prodrug Salts—Acetylacroninium perchlorate was synthesized by heating a suspension of acroninium perchlorate in acetic anhydride[4] at ~100° for a short period and then cooling to room temperature. The acetylacroninium perchlorate formed was isolated as a burgundy-colored crystalline solid after the reaction filtrate was diluted with cold ether.

The solid material contained ~80% of acetylacroninium perchlorate; the remaining ~20% of the sample consisted of I and the perchlorate salt of I. Attempts to purify the samples (relative to acetylacroninium perchlorate content) were unsuccessful due to the instability of the compound. Since the impurities did not present a major problem in the evaluation of approximate solubilities and stability properties, extensive efforts to obtain high purity samples of acetylacroninium perchlorate did not appear justified.

The assignment of the structure of the acetylacroninium species was based on NMR and IR spectra and the fact that the compound hydrolyzed rapidly to yield acronine.

Solubility of Salts—Following the characterization of acetylacroninium perchlorate, the chloride, sulfate, phosphate, and bromide salts were prepared. These salts were appreciably less stable and less pure than the perchlorate salt. Because of the rather rapid hydrolysis of the acetylacroninium ion, it was not possible to obtain equilibrium data on the solubility of the various salts. However, approximate values were obtained by shaking excess quantities of the solid samples with 0.05 *M* phosphate buffer (pH 7.0) for several minutes, filtering, and allowing the filtrates to stand at 22° until hydrolysis of the acetylacroninium ion was complete. The acronine content of each filtrate was then determined spectrophotometrically. The salt solubilities, expressed as acronine content in grams per 100 ml, were: perchlorate, 0.025–0.030; sulfate, 0.15–0.2; bromide, 0.6–0.8; chloride, 1.2–1.5; and phosphate, 1.2–2.0. Since the aqueous equilibrium solubility of acronine was less than 1% of that observed for the various acetylacroninium salts, the acronine content of the filtrate was essentially completely attributable to the salt itself. Although considerable error was inherent in such determinations, the results appeared meaningful.

The solubility of the chloride salt was about the same as that of the phosphate salt, possibly because of the *in situ* formation of the phosphate salt under these conditions.

A comparison of the solubility values of the salts with those of acronine (about 2–3 mg/liter) demonstrated that even the perchlorate salt, which was the least soluble, exhibited about a 100-fold greater solubility than acronine; the more soluble chloride and phosphate salts were about 10,000 times more soluble than free acronine. Therefore, the use of any acetylacroninium salt would yield at least the minimum required increase in solubility necessary to formulate a parenteral solution of reasonable volume. However, it was yet to be determined whether these salts would be otherwise suitable for use in such solutions. Therefore, the hydrolysis of the acetylacroninium salts was studied.

Hydrolysis of Prodrug—When near-saturated aqueous solutions of the acetylacroninium salts were prepared and allowed to stand, a precipitate of acronine formed. Additionally, when aqueous solutions of the salts were prepared and examined by TLC [benzene–acetone (1:1) on silica gel] at various times, two spots were observed initially: a yellow spot (R_f 0.76) and a purple or wine-colored spot (R_f 0.17) corresponding to acronine and the prodrug, respectively. In several hours, the wine-colored spot disappeared completely and the acronine spot was enlarged, indicating a rapid and complete reversion of the acetylacroninium perchlorate (wine-colored spot) to acronine.

The rate at which the acetylacroninium perchlorate was hydrolyzed to yield acronine was studied quantitatively in pH 0–11 aqueous solutions. A plot (Fig. 1) of the logarithm of the observed half-life *versus* pH data indicated that the hydrolytic rate was pH independent at pH <8. The data for pH ≥2.6 were obtained in various buffers at 3×10^{-3} to 5×10^{-2} *M*. From these and other data[5], it appeared that the hydrolytic rate was relatively unaffected by various buffer components at low concentrations and that the spontaneous rate of hydrolysis under such conditions occurred with a half-life of about 20–25 min. At pH >8, however, there appeared to be hydroxide-ion catalysis, as evidenced by a negative slope of approximately unity at pH >9.

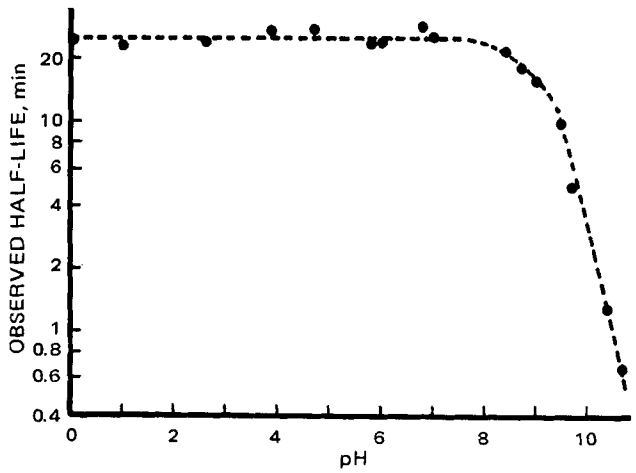


Figure 1—*Plot of observed half-life for the hydrolysis of acetylacroninium perchlorate at 25.4° in various buffers.*

The hydrolysis rate of the prodrug in pH 6.9 phosphate buffer (0.1 *M*) was also studied at 15, 25, and 30°; these data were used to construct an Eyring plot. From the slope and intercept of that plot were determined the enthalpy of activation (19.5 kcal/mole) and the entropy of activation (−16 cal/mole degree), respectively. On the basis of the temperature study data, it was estimated that the half-life for hydrolysis at body temperature of 37° would be about 5 min or even less if enzymatic enhancement (6) occurred *in vivo*.

Some studies of the influence of both the ionic strength of aqueous buffers and the dielectric constant of a mixed aqueous–organic solvent on the hydrolysis rate of acetylacroninium perchlorate were also carried out. When the ionic strength of an aqueous phosphate buffer (0.1 *M*, pH 7) was varied fivefold from 0.02 to 0.1 *M*, no significant difference was observed for the hydrolysis rate of the prodrug at 25°. However, when the hydrolytic rate of the acetylacroninium salt was followed in solutions prepared by mixing given volumes of acetone with a phosphate buffer (pH 7.0, 0.05 *M*, I = 0.1 *M*), the rate increased nearly linearly with the percent (v/v) acetone from 0 to 60%. The observed half-life of the reactions over that range of acetone concentration decreased from about 23 to 10 min.

These data suggested that the decrease in the dielectric constant when going from simply aqueous media to increasing concentrations of acetone enhanced the reaction rate. Since the reaction was hydrolytic, the rate was also a function of the water concentration. Therefore, the decrease in the water concentration at increased acetone concentrations perhaps accounted for the fact that little or no difference in the hydrolytic rate was observed in solutions containing 60 and 80% acetone in water.

When the hydrolytic rates of the other prepared salts were studied in phosphate buffer (pH 7, 0.05 *M*, I = 0.1), none differed significantly from that of the perchlorate. These latter results were not unexpected, since all prepared salts probably were completely dissociated in dilute aqueous solution and, therefore, the hydrolysis of the acetylacroninium ion should have been independent of the anion.

Applications—On the basis of these studies, it appears that the acylacroninium salts may be suitable for use as prodrugs of acronine. The major feature of the quaternary salts is the greatly enhanced solubility coupled with their rapid reversion to the parent alkaloid under conditions approximately like those encountered *in vivo*.

The information presented here together with data on the acetylacroninium perchlorate salt served as the basis for the formulation of an experimental intravenous prodrug formulation of acronine (11).

EXPERIMENTAL

Materials—Acronine[6] was used as obtained, mp 175–177° [lit. (3) mp 174–176°] and homogeneous by TLC [benzene–acetone (2:1) on silica gel[7]], R_f 0.45. All other chemicals were reagent grade. Water was distilled from acid permanganate solution in an all-glass still.

Procedures—*Acroninium Salts*—The simple acroninium salts were prepared by dissolving acronine (5 g) in acetone (175 ml) and adding 4

[4] When reactions were attempted using acetyl chloride as the acetylating agent under conditions similar to these described here, insignificant quantities of the prodrug salt were obtained.

[5] Changes in the acetate buffer concentration (pH 4.6) from 0.1 to 0.5 *M* decreased the half-life for hydrolysis by only approximately 5 min.

[6] Batch 1, Sample MH, CSIRO, obtained from the National Cancer Institute.

[7] Polygram Sil G/uv, Brinkmann Instruments.

ml of the appropriate aqueous acid. The acid solutions used were 37% (w/w) hydrochloric, 71% (w/w) perchloric, 53% (w/w) phosphoric, and 50% (w/w) hydrobromic acids. Upon mixing, the respective salts precipitated as bright red-orange solids. All but the phosphate were isolated at room temperature. The phosphate salt required cooling (~0°) to obtain good yields. The yield of all salts was 95% or better. All acroninium salts melted with decomposition as follows: perchlorate, 245–255°; chloride, 158–160°; bromide, 188–190°; sulfate, 158–160°; and phosphate, 182–184°.

Acetylacroninium Salts—Each acetylacroninium salt was prepared by heating the corresponding acroninium salt (~1 g) with acetic anhydride (~20 ml) at 100° for 10–15 min in a suitable flask fitted with a water-cooled condenser and calcium chloride-filled drying tube. The reaction mixture was then cooled to room temperature. Undissolved acroninium salt was removed by filtration, and the filtrate was quickly added to cold (~0°) ether (~200 ml). The acetylacroninium salt readily separated as a fluffy purple solid. This solid was immediately separated by filtration, rinsed with cold ether (50 ml), dried, and stored in a desiccator.

Solid acetylacroninium perchlorate was quite stable and could be stored at room temperature in a desiccator over calcium chloride for months with little or no change. However, the other salts were extremely hygroscopic and thus unstable due to hydrolysis. Therefore, these salts were stored in a desiccator cooled with solid carbon dioxide. The chloride salt was so hygroscopic that all handling procedures were carried out in a dry box under a nitrogen atmosphere.

Characterization of Acetylacroninium Salts—The characterization of acetylacroninium perchlorate was based primarily on spectral data and chemical behavior. The IR[8] spectra of acetylacroninium perchlorate and acroninium perchlorate (as potassium bromide pellets) were qualitatively quite similar, except for strong carbonyl absorption at 1790 cm^{-1} for the acetylacroninium salt. Absorption at that wave number was completely absent in the simple acroninium salt. The absorption at 1790 cm^{-1} was attributed to the carbonyl absorption (12) of the acetyl group.

The NMR[9] spectrum of the acetylacroninium perchlorate (in formamide and in dimethyl sulfoxide-d_6) exhibited a sharp singlet at δ 2.65, which integrated for about three protons and was consistent (13) with an acetate ester of the type Ia. Upon standing in such solutions, the absorption at δ 2.65 decreased and a new singlet appeared at δ 2.08. Since acetic acid also produced a sharp singlet at δ 2.08 when added to either of the solvents, it was concluded that acetic acid was being produced in the NMR tube as a result of the hydrolysis of the ester linkage. While ester hydrolysis was fairly rapid initially in the NMR studies, the rate decreased with time, apparently due to consumption of the limited amounts of water present in such solvents.

Another observation was that the *gem*-dimethyl protons of acetylacroninium perchlorate absorbed at δ 1.70 while those of acronine absorbed at δ 1.47. The hydrolysis of the ester (as already described) resulted in a decrease in the δ 1.70 peak and the corresponding appearance of a peak at δ 1.47.

When an aqueous solution of acetylacroninium perchlorate was freshly prepared, it was deep burgundy in color. Upon standing, the color became yellow and a yellow precipitate formed. This precipitate was identified as acronine. The hydrolysis was also followed by TLC as described under *Results and Discussion*.

In view of the impurity of the samples obtained, elemental analysis data were not considered meaningful, although agreement with theory was good. On the basis of all of these data, the characterization of acetylacroninium perchlorate as having Structure Ia (R = methyl) seemed conclusive.

The other acetylacroninium salts were characterized mainly on the basis that color, spectral characteristics, and chemical behavior were essentially identical to those of the perchlorate salt.

Composition of Acetylacroninium Salt Samples—Acetylacroninium perchlorate samples were dissolved in acetone and subjected to TLC [benzene–acetone (2:1) on silica gel]. Three spots were observed directly: an orange spot at the origin corresponding to authentic acroninium perchlorate, a yellow spot at R_f 0.45 corresponding to authentic acronine, and a purple spot at R_f 0.05 due to the acetylacroninium salt. No other spots were observed using iodine or UV light.

When a TLC sample of acetic acid–acetone (1:5) on silica gel was used, only two spots were observed at R_f 0.77 and 0.25. The yellow spot at 0.77 arose when both acronine and acroninium perchlorate were used[10]. The spot at R_f 0.25 was purple, corresponding to the acetylacroninium salt. When the other acetylacroninium salts were studied using the acetic acid–acetone TLC system, they behaved almost identically. On the basis of these data, the sample appeared to consist of only the prodrug salts, the corresponding acroninium salt, and acronine.

An estimate of the acetylacroninium salt present in the prepared sample was made from the NMR spectra in formamide. The ratio of the peak height at δ 1.70 to that at δ 1.47, corresponding to the *gem*-dimethyl proton in the acetylacroninium salt and acronine, respectively, was used as a simple indication of the composition. Since decomposition occurred in these solutions, it was necessary to follow the ratio as a function of time and extrapolate back to the time at which the solution was prepared. The prodrug appeared to comprise about 80% of the acetylacroninium perchlorate-containing samples. The content of the acetylacroninium salt in the other samples, such as the chloride and phosphate, was only 50–60%.

Kinetic Measurements—The hydrolysis of the acetylacroninium salts was studied spectrophotometrically[11] (520 nm) by following the disappearance of the absorption peak due to the acetylacroninium ion. The reaction mixtures were prepared by shaking a sample of the salt ($\simeq$2 mg) for about 1 min with the buffer solution[12] (10 ml). This reaction mixture was then rapidly filtered through a sintered-glass funnel of a medium or coarse pore size and diluted to 40 ml with additional buffer solution.

A portion of this solution was transferred to a quartz spectrophotometer cell. The buffer solution was used as the reference solution. Cells with 10-cm pathlengths were selected so that dilute reaction mixtures could be used and, therefore, followed spectrophotometrically for longer times. The use of larger cells was necessary because, as the reaction proceeded, the reaction solutions became supersaturated with acronine and precipitation often occurred before an absorbance value could be obtained at the completion of the reaction.

Since acronine does not absorb energy at 520 nm, the spectrophotometer was balanced carefully against air prior to initiation of the reaction; a final absorbance value (at the end of the reaction) of zero was used in the calculation of the reaction rate constant. Some sufficiently dilute solutions that did not show precipitation were found to be first order in ester concentration over three to four half-lives.

Solubility Determination of Acronine and Acroninium Salts—Acronine solubility in various solvent systems was determined by shaking excess acronine with the solvent at room temperature ($\simeq$22°) until equilibration was reached ($\simeq$24 hr). The filtered solutions, after suitable dilution with water and adjustment to pH 7, were then assayed spectrophotometrically for acronine at 277 nm ($\log \epsilon = 4.60$).

Since the acroninium salts were hydrolyzed quickly in water, determination of equilibrium solubility values for these substances was not practical. The "estimated solubility" of the salts was taken as the amount of ester dissolved (expressed as acronine content) after 2 min of constant agitation of excess sample in buffer at 22°. The resulting solution was quickly filtered through a sintered-glass funnel or filter[13]. The filtrate was allowed to stand overnight to ensure the complete hydrolysis of the ester and then was diluted with methanol to dissolve the precipitated acronine. The resulting solution was assayed spectrophotometrically for acronine (277 nm, $\log \epsilon = 4.60$).

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[8] Beckman model IR-33.

[9] Varian model T60.

[10] Apparently, the acroninium perchlorate salt underwent hydrolysis in the presence of the developing solvent.

[11] Cary model 14, 15, or 16 spectrophotometer.

[12] Buffer systems used in the various pH ranges were: pH $\leq$ 1, hydrochloric acid; pH 2.6, chloroacetate; pH 3.5–5.80, acetate; pH 6–7, phosphate; pH 7–10, borate; and pH > 10.7, sodium hydroxide.

[13] Millipore.

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Microencapsulation of Phenobarbital by Spray Polycondensation

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Abstract □ A new method for the microencapsulation of solids is described. It is based on the polycondensation of amphiphilic and, thus, tensioactive precondensates on a melamine–formaldehyde base on the surface of suspended particles during spray drying. A film-forming agent, preferably one that reacts chemically with the resin, is indispensable for spray drying and also for the formation of an efficient membrane around the drug particles. The resulting microcapsules are essentially spherical and have, after appropriate curing, a sustained-release effect *in vitro*. The factors that most influence the formation and properties of the microcapsules are the composition (qualitative and quantitative), pH, and viscosity of the suspension.

Keyphrases □ Phenobarbital—microencapsulation by spray polycondensation, effect of composition, pH, and viscosity □ Microencapsulation—of solids by spray polycondensation, effect of composition, pH, and viscosity □ Spray polycondensation—microencapsulation of solids, effect of composition, pH, and viscosity □ Technology, pharmaceutical—microencapsulation of solids by spray polycondensation, effect of composition, pH, and viscosity

Microencapsulation can be defined as a method to provide solid particles or liquid droplets with an individual coat, thereby modifying their physical, chemical, and physiological characteristics. This effect is useful for separating reactive or incompatible components, covering disagreeable odors and tastes of substances, and converting liquids into solids.

In pharmacy, microencapsulation is used to improve the stability and handling properties of drugs and to prepare controlled-release products. Release may be accomplished by rupture (mechanical or after swelling) or diffusion through the intact or swollen wall. The size of microcapsules generally ranges from several microns to about 200 μm (1).

Various specific technological aspects and limitations of microencapsulation have been studied (2, 3), as have the different variables that influence microcapsule formation. In most cases, the microcapsules were prepared by simple coacervation (4–9). The aim of this work was to gain insight into the possibilities and limitations of a new microencapsulation method; the influence of some important technological variables on the properties of the microcapsules was studied.

THEORETICAL

Spray drying is used to separate the microcapsules from the vehicle (8, 10) or to prepare microcapsules in a single operation (11, 12). The procedure is, in principle, as follows. After dissolving the coating material in a preferably aqueous medium and dispersing the core material in it, the dispersion is spray dried. The core material is thereby microencapsulated in its original state.

Clearly, different products are obtained when a true solution of coating material and drug is spray dried. The active substance is in an X-ray amorphous state and shows crystallinity only when the drug–polymer ratio is increased (13, 14).

The fundamentals of spray polycondensation were presented previously (15, 16). One processes a dispersion of core material that contains in the continuous phase aminoplast monomers or aminoplast precondensates of relatively low molecular weight in addition to other coating material (film-forming agents) and the catalyst. The resin-forming monomers and precondensates play an essential role. In contrast to the monomers, the reactive tensides (17–19) exhibit pronounced tensioactive properties. They are derived from hexamethylolmelamine whose hydroxymethyl groups are substituted partly with hydrophilic polyglycol ethers and partly with lipophilic alcohols (usually C_4–C_{18}), forming low molecular weight precondensates. Due to their physicochemical properties, they are adsorbed selectively at the surface of the inner phase of the dispersion.

The insoluble polymer microcapsule is formed upon spray drying at 150–200° by vaporization of water and simultaneous polycondensation of the monomers and the precondensates by acid catalysis. Details of the basic chemical reactions can be found in textbooks (20). The quality of the shell can be improved by the use of a film-forming agent that reacts chemically with the monomers and also by curing.

EXPERIMENTAL

Materials—Phenobarbital[1], with a mean particle size of 30–35 μm, was chosen as the model drug. As a film-forming agent, polyvinyl alcohol[2]

[1] Phenobarbital Ph. Helv. VI pulvis alcoholisatus, Siegfried Ltd., Zofingen, Switzerland.
[2] Mowiol 4-88, Hoechst, Plüss-Stauffer, Oftringen, Switzerland.