(7) A. J. Repta, *ACS Symposium Series, 14*, **1975**, 197.
(8) I. Kovatch, I. H. Pitman, and T. Higuchi, *J. Pharm. Sci.*, **64**, 1070 (1975).
(9) V. Stella and T. Higuchi, *ibid.*, **62**, 962 (1973).
(10) A. Albert, "The Acridines," 2nd ed., St. Martins Press, New York, N.Y., 1966, pp. 371–373.
(11) C.-H. Huang, B. Kreilgård, and A. J. Repta, *Bull. Parenteral Drug Assoc.*, **30**, 1 (1976).
(12) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed., Wiley, New York, N.Y., 1967, pp. 87, 92.
(13) *Ibid.*, p. 137.

ACKNOWLEDGMENTS AND ADDRESSES

Received July 28, 1975, from the *Victorian College of Pharmacy, Melbourne, Australia 3052 and the ‡Department of Pharmaceutical Chemistry, School of Pharmacy, University of Kansas, Lawrence, KS 66045.

Accepted for publication June 21, 1976.

Presented in part at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Diego meeting, November 1973.

Abstracted in part from a dissertation submitted by D. W. A. Bourne to the University of Kansas and the Victorian College of Pharmacy in partial fulfillment of the Intersearch Doctor of Philosophy degree requirements.

Supported in part by Contract NO1-CM-23217 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare. Additional support was provided (to D. W. A. Bourne) by the Intersearch Fund.

The authors thank Wanda Waugh for technical assistance.

§ Present address: College of Pharmacy, University of Kentucky, Lexington, KY 40506.

ˣ To whom inquiries should be directed.

Microencapsulation of Phenobarbital by Spray Polycondensation

C. VOELLMY, P. SPEISER ˣ, and M. SOLIVA

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.

Table I—Effect of Ratio of Reactive Tenside to Monomer: Composition of Suspensions and Release Rate Constants K of the Respective Products

	Batch						
	800	801	802	805	806	807	808
Polyvinyl alcohol	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Water	46.0	46.0	46.0	46.0	46.0	46.0	46.0
Phenobarbital	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Reactive tenside IV	12.0	10.5	9.0	6.0	3.0	1.5	0
Monomer I	0	0.75	1.5	3.0	4.5	5.25	6.0
Approximate mole-percent of reactive tenside[a]	100.0	25.9	13.0	4.8	1.6	0.7	—
K[b]	35.9	41.3	42.1	41.3	32.6	25.4	25.5
$t_{75\%}$, min	4.4	3.3	3.2	3.3	5.3	8.7	8.6
K[c]	27.6	18.9	12.2	12.0	12.5	13.1	15.3
$t_{75\%}$, min	7.4	15.8	37.9	39.3	35.8	33.0	24.0

[a] Refers to total quantity of moles of reactive tenside and monomer. [b] No curing. [c] Curing for 1 hr at 100°.

(mol. wt. ~34,000) was used. As monomers, hexamethylolmelamine hexamethyl ether[3] (I), trimethylolmelamine trimethyl ether[3] (II), and dimethylolurea dimethyl ether[3] (III) were used as well as a cationic reactive tenside on a melamine–formaldehyde base[4] (IV). Hydrochloric acid (1 N) was added as a catalyst.

Microcapsule Preparation—After dissolving the polyvinyl alcohol, the monomers, and the precondensate in distilled water, the pH was adjusted[5] with hydrochloric acid. Unless specified otherwise, a pH of 2.5 was used. The phenobarbital was homogeneously dispersed with a high-speed stirrer[6] and immediately spray dried[7]. The following conditions were used: inlet temperature, 220°; outlet temperature, 90°; spray-disk speed, about 30,000 rpm; and feed rate, 1 liter/hr[8].

After spray drying, the product that adhered to the wall was brushed off and collected. The yield of microcapsules in the cyclone was low due to the small dimensions of the spray drier. Unless otherwise indicated, curing was performed in a drying oven under standard conditions (1 hr at 100°).

Microcapsule Evaluation—*Phenobarbital Content*—A 60–100-mg sample was accurately weighed into a 100.0-ml volumetric flask. Then about 50 ml of 0.1 N NaOH solution was added, and the suspension was treated with ultrasound[9] for about 90 sec. The microcapsules were thereby ruptured, and the drug dissolved. Then 0.1 N NaOH solution was again added to give 100.0 ml, and a 1.0-ml sample was withdrawn through a G 3 sintered-glass plate. After appropriate dilution, phenobarbital was assayed spectrophotometrically[10] at 256 nm. All samples were analyzed in duplicate.

Release Studies—Phosphate buffer solution (200 ml, pH 7.2, μ = 0.2, 0.1% polysorbate 80) in a 400-ml beaker was maintained at 37° and stirred at a constant rate of 133 rpm[11]. The length of the stirring rod[12] was approximately 6 cm and its diameter was 1.1 cm. The sample containing 50.0 mg of phenobarbital was placed on a small sieve (mesh size approximately 0.75 mm) laid on the beaker. Scratching the sieve caused the powder to fall into the liquid without forming clumps (time t = 0). Filtered[13] 1-ml samples were removed after 1, 2, 4, 8, 16, *etc.*, min until about 90% of the core material was released. The samples were assayed as specified. The release rate studies were carried out in duplicate.

RESULTS AND DISCUSSION

Evaluation of Release Data—For the characterization and comparison of microcapsules prepared under different conditions, it is useful to express the release results by a representative constant.

In some cases, the release pattern follows a first-order mechanism (21). Other investigators suggested a linearization of release curves of different dosage forms by using the Weibull function (22). It was found that the calculation of the linear regression of:

$$y = K^* t^n \quad \text{(Eq. 1)}$$

where y is the percent drug released at time t and K^* is a constant, yielded an exponent, n, in the range of about 0.5. The release rate constant K was calculated by linear regression of:

$$y = Kt^{1/2} \quad \text{(Eq. 2)}$$

The fit of the experimental results with the calculated points was satisfactory, and the statistical linearity was significant for most cases.

Effect of Resin-Forming Agent on Microcapsules—No satisfactory microcapsules resulted with the exclusive use of either I or reactive tenside IV. In the former case, agglomerates of irregular shape and size, which can hardly be regarded as microcapsules, were produced (Fig. 1). In the latter case, the core material was completely coated by spherical microcapsules (Fig. 2) in which no defective coats could be discerned. However, these products were highly hydrophilic (but insoluble in water, acetone, alcohols, dimethylformamide, *etc.*) without any noteworthy sustained-release effect even after curing.

Spray polycondensation with mixtures of I and IV in different ratios was performed; the compositions and dissolution rate constants are given in Table I. The shape of the microcapsules of Batches 800–805 was spherical. Due to the low amount of reactive tenside, Batches 806 and

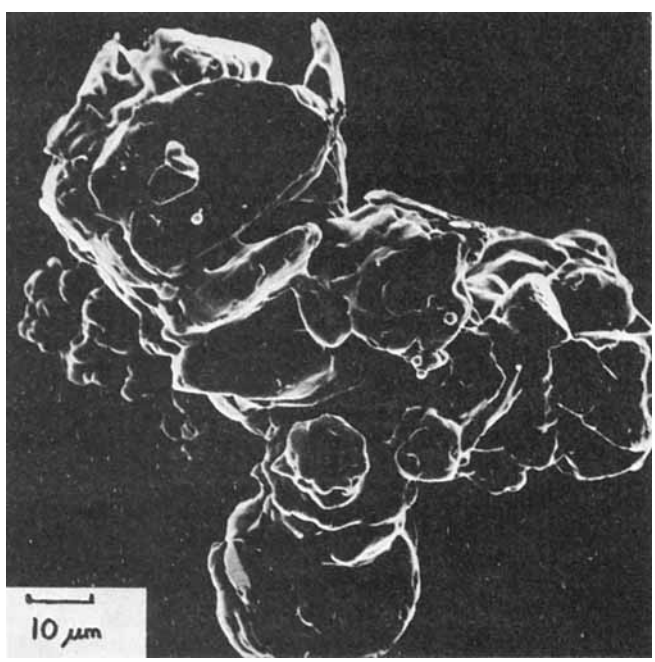

Figure 1—*Typical structure of product manufactured by spray polycondensation with monomer I (Batch 808). Coating is irregular and defective.*

[3] Ciba-Geigy Ltd., Basel, Switzerland.
[4] Reactive tenside 709 LS 50% aqueous solution, Ciba-Geigy Ltd., Basel, Switzerland.
[5] pH Meter E 520, Metrohm, Herisau, Switzerland.
[6] Polytron PT 20 OD, Kinematica, Lucerne, Switzerland.
[7] Niro Minor, Niro A/S, Copenhagen, Denmark.
[8] Peristaltic pump LP-A Standard, W. Bachofen, Basel, Switzerland.
[9] Ultrasonic bath, Elgasonic TS-100 (50 kHz), Biel, Switzerland.
[10] Model 635, Varian, Basel, Switzerland.
[11] Magnetic stirrers were constructed using a Philips motor 9904 111 04131, transmission BA/UR, Philips, Zürich, Switzerland.
[12] Covered with Teflon (du Pont).
[13] Sartorius SM 113 03 1.2-µm membrane filters and Sartorius SM 165 14 filter-support, diameter 13 mm, Instrumentengesellschaft, Zürich, Switzerland.

Table II—Effect of Monomers: Composition of Suspensions and Release Rate Constants of the Respective Products[a]

	Batch		
	816	866	870
Polyvinyl alcohol	6.0	6.0	6.0
Water	44.0	44.0	44.0
Phenobarbital	10.0	10.0	10.0
Reactive tenside IV	6.0	6.0	6.0
Monomer			
Type	I	II	III
Amount	3.0	3.0	3.0
K	8.1	9.3	23.2
$t_{75\%}$, min	85.1	64.7	10.5

[a] Curing for 1 hr at 100°.

807 tended toward the structures shown in Fig. 1. In all cases, the release rate was high ($t_{75\%} < 10$ min) for the original products. This property differed distinctly after curing, depending on the ratio between I and IV. It was lowest when the fraction of IV was 0.25–0.75 based on the total amount of I and IV, as in Batches 802, 805, and 806.

To obtain products that best met the expectations (*i.e.*, spherical microcapsules with slow release effect and relatively low amount of reactive tenside used), a IV to I ratio of 1:1 was chosen for the subsequent experiments.

The excessive permeability of the original product could be explained by the relatively low molecular weight of the resin. The results demonstrate that curing distinctly reduced the permeability only of products containing I. The comparatively small molecular size of I probably formed a more intimate network than when using reactive tenside alone. A mechanism similar to steric hindrance can be assumed. Methanol evaporates when the ether groups of I are broken up; with reactive tenside, large and much less volatile molecules that could impede cross-linking are separated.

Effect of Curing Conditions on Release Properties—As already stated, curing is necessary to attain slow release microcapsules. It was found by microscopical examination that the morphology of the products was not affected by this process. The influence of the curing conditions on the release rate constant is shown in Fig. 3. The permeability of the products can only be reduced to a certain degree, characteristic for the respective formulation. The chemical reactions occurring during this process are, among others, the formation of methylene bridges by liberation of formaldehyde (organoleptic identification; see also Ref. 20) and the dehydration of resin and polyvinyl alcohol. The latter is characterized

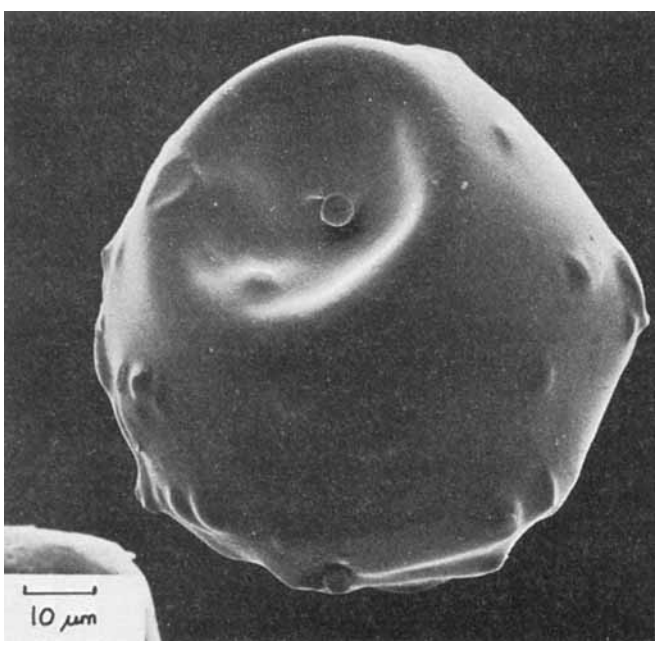

Figure 2—*Typical microcapsule manufactured using reactive tenside IV. Active substance is entirely coated.*

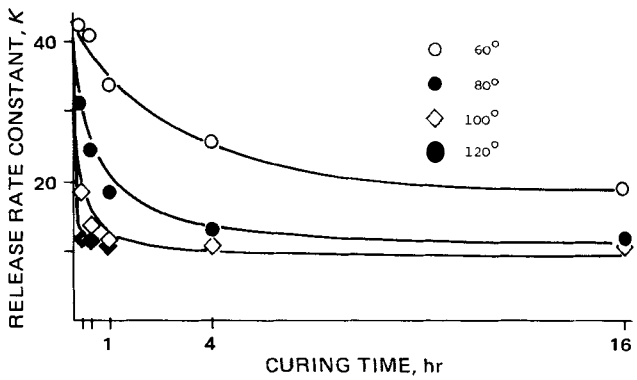

Figure 3—*Effect of curing conditions on release rate constant of Batch 805 (composition given in Table I).*

by a discoloration to yellow of the originally white product at 120° and after more than 4 hr at 100° (23).

Effect of Monomers of Low Tensioactivity on Release Properties—The composition and release rate constants are shown in Table II. The distinct differences in the release rate of the products depending on the chemical nature of the monomer used can be explained by the fact that I has more potential cross-linking sites than II and the latter has more than III. The consequence is a wall structure with a more or less intimate network which is primarily responsible for the different permeabilities. Microscopically (scanning electron microscope), no differences in the surface structure could be discerned.

Effect of pH on Release Properties—Polycondensation is catalyzed by acid pH. Consequently, pH influences the quality of the coat. The suspensions adjusted to different pH values were immediately spray dried and cured. The batches showed no morphological differences. The results of the release studies (Fig. 4) reflect the basic importance of this factor. The effect of pH on the release of phenobarbital was distinct and was not suppressed by the obligatory curing process.

A suspension with pH 1.5 could not be processed because it gelled in a few minutes; at higher pH values, gelling was observed only after several hours or days.

Effect of Viscosity on Microcapsules—Suspensions with identical compositions diluted with water to polyvinyl alcohol concentrations of 2, 4, 8, and 12% exhibited Newtonian flow[14]. The microcapsules resulting from the two high viscosity suspensions were spherical. The low viscosity suspensions, however, yielded products with irregular shapes similar to those shown in Fig. 1. The respective release patterns are shown in Fig. 5.

Viscosity is known to be an important factor in spray drying technology (24). Its influence on the formation and properties of the microcapsules is also demonstrated by the following experiment. A suspension with 16% polyvinyl alcohol does not yield discrete microcapsules but rather long and fine insoluble threads. It is obvious that in this case the water vaporizes before discrete droplets are formed by spraying; *i.e.*, the atomization of the dispersion is impeded by the high viscosity.

Effect of Resin to Polyvinyl Alcohol Ratio on Microcapsules—

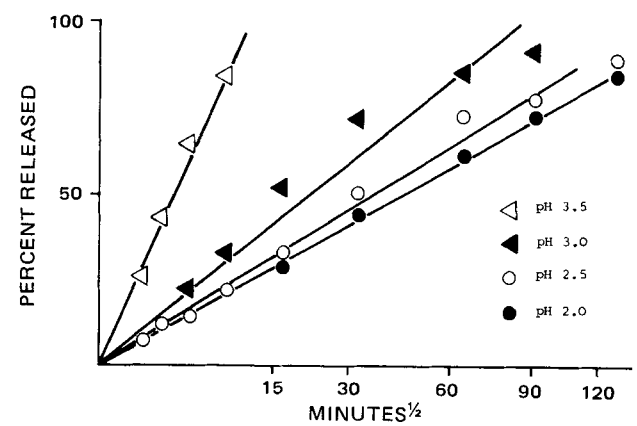

Figure 4—*Effect of pH on release rate.*

[14] Measured with a Epprecht Rheomat, Contraves, Zürich, Switzerland.

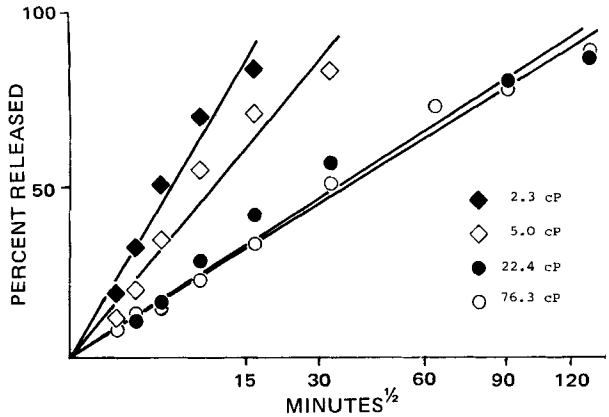

Figure 5—*Effect of viscosity on release rate.*

The composition of the batches, their respective release rate constants, and the evaluation of the results are shown in Fig. 6. In the evaluation of the results, the composition of the formulation with the maximum sustained release as well as its expected value for K was calculated. The following polynomial equation was computed after having found by analysis of variance that the regression of second order was adequate:

$$y = 33.084 - 6.133x_1 - 63.380x_2 + 25.251x_1^2 + 64.400x_2^2 - 43.796x_1x_2 \quad \text{(Eq. 3)}$$

where y is the dissolution rate constant, x_1 is the level of factor Compounds I and IV, and x_2 is the level of factor polyvinyl alcohol.

The coordinates x_{1s} and x_{2s} (Fig. 6) for the stationary point were computed by partial differentiation and setting the results equal to zero. By setting these values into the polynomial equation, the expected value for K, a true minimum, was calculated. The comparison of the computed and experimentally found values demonstrated a good fit when it was considered that the confidence limits were relatively large due to the not unimportant residual term in the analysis of variance.

The coordinates of the stationary point were within the experimental field. Thus, no significant improvement of the sustained-release effect could be expected by investigating further levels of these factors. The quality of the coat was largely determined by an interaction of the factors investigated. The slope of the ellipse in Fig. 6 and the results of the statistical analysis, however, indicated that the variable polyvinyl alcohol was somewhat more critical in its influence on the release rate constant.

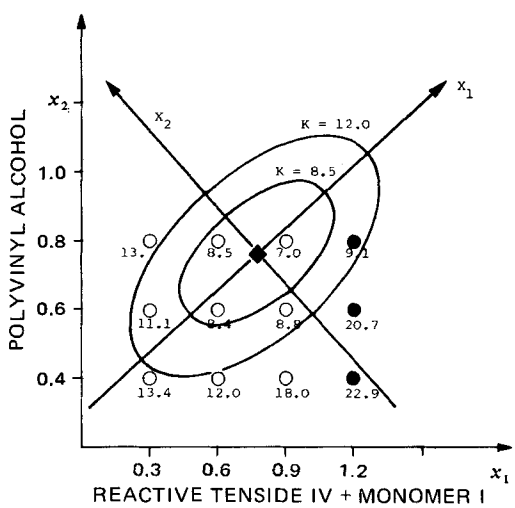

Figure 6—*Contour plot for release rate constants* K = *12.0 and 8.5. The numbers inserted give the experimental* K; x_1 *and* x_2 *are relative amounts of reactive tenside IV + monomer I and polyvinylalcohol, respectively. The relative amount of phenobarbital is unity. The polyvinyl alcohol concentration is 8%. Key:* ○, *experimental range evaluated;* ●, *residual experimental range; and* ♦, *stationary point,* K = *6.39.*

REFERENCES

(1) L. A. Luzzi, *J. Pharm. Sci.*, **59**, 1367 (1970).

(2) J. A. Herbig, in "Encyclopedia of Chemical Technology," vol. 13, Wiley, New York, N.Y., 1967, p. 436.

(3) C. E. Anderson, "Microencapsulation," Management Reports, Boston, Mass., 1963.

(4) L. A. Luzzi and R. J. Gerraughty, *J. Pharm. Sci.*, **56**, 634 (1967).

(5) *Ibid.*, **56**, 1174 (1967).

(6) *Ibid.*, **53**, 429 (1964).

(7) H. P. Merkle, Ph.D. thesis, Swiss Federal Institute of Technology, Zürich, Switzerland, 1972.

(8) J. R. Nixon, S. A. H. Khalil, and J. E. Carless, *J. Pharm. Pharmacol.*, **20**, 528 (1968).

(9) N. N. Salib, *Pharm. Ind.*, **34**, 671 (1972).

(10) L. A. Luzzi, M. A. Zoglio, and H. V. Maulding, *J. Pharm. Sci.*, **59**, 338 (1970).

(11) H. J. Robinson and E. V. Svedres, U.S. pat. 2,805,977 (1957).

(12) N. Macaulay, U.S. pat. 3,016,308 (1962).

(13) H. Junginger, *Pharm. Ind.*, **36**, 100 (1974).

(14) *Ibid.*, **36**, 333 (1974).

(15) DT (OS) 2,233,428 (1973, unexamined).

(16) H. P. Merkle and P. Speiser, *Pharm. Ind.*, **37**, 555 (1975).

(17) C. Voellmy, Ph.D. thesis, Swiss Federal Institute of Technology, Zürich, Switzerland, 1975.

(18) L. Schibler, French pat. 1,381,811 (1964).

(19) L. Schibler, French pat. 1,470,103 (1967).

(20) R. Wegler, in "Methoden der Organischen Chemie" (Houben-Weyl), vol XIV/2, E. Müller, Ed., Thieme Verlag, Stuttgart, Germany, 1963, pp. 319, 357, 361.

(21) "Theory and Practice of Industrial Pharmacy," L. Lachman, H. Lieberman, and J. Kanig, Eds., Lea & Febiger, Philadelphia, Pa., 1970, p. 384.

(22) F. Langenbucher, *J. Pharm. Pharmacol.*, **24**, 979 (1972).

(23) J. G. Pritchard, "PVA, Basic Properties and Uses," Gordon & Breach Science Publishers, London, England, 1970.

(24) W. Beuttner, Ph.D. thesis, Swiss Federal Institute of Technology, Zürich, Switzerland, 1959.

ACKNOWLEDGMENTS AND ADDRESSES

Received April 15, 1976, from the *Department of Pharmacy, Swiss Federal Institute of Technology, CH 8006 Zürich, Switzerland.*

Accepted for publication June 23, 1976.

Abstracted in part from a thesis submitted by C. Voellmy to the Swiss Federal Institute of Technology in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors thank Dr. H. P. Merkle, University of Heidelberg, Germany, for valuable suggestions and Dr. L. Schibler, Ciba-Geigy Ltd., Basel, Switzerland, for the synthesis of the monomers and the reactive tensides.

[x] To whom inquiries should be directed.