Tack experiments performed with petrolatum, a highly viscous semisolid did not show the region of "delayed elastic effects." This resulted in a rather short duration for filament elongation; hence the ft was relatively small.

The above observations suggest that the response of the concentrated polymer solutions (semisolids) to applied pull stress is a combination of viscous and elastic forces. The "delayed elastic effects" observed are the result of configurational elasticity, which is a process associated with orientation, alignment, and elongation by the uncurling of large chain molecules. Therefore, the ft required for the elongation of the filament will not only depend on the viscosity of the liquid, but also on the internal structure of the system.

Earlier investigators (10–12) suggested that tackiness is related to the geometry of the system and the rheological characteristics of the liquid. Therefore, according to this definition, lecithin, petrolatum, and even water added with high concentration of finely divided solids will be considered tacky, since these liquids or dispersions do offer resistance to flow. In actual practice, the above materials, unlike povidone solution, are not known to be tacky even though impulse for liquid film separation is required in both cases. Based on these observations, it can be concluded that a tacky material is one that displays "delayed elastic effects," and because of these effects it requires a long period of time for filament elongation. This provides a rather large impulse for a given force of separation.

Tack Effects in Tablet Coating—Coating solutions, when applied to the tablets during the coating process, are dilute solutions of polymers of low-viscosity grade. Separation of tablets stuck together by a freshly applied coating solution will occur by viscous flow. Therefore, the ft required will be equal for solutions of similar viscosity. As the solvent evaporates during the drying phase of the coating process, the solution will reach a semisolid state. At this point, resistance to filament elongation will depend on the molecular structure of the polymer.

Tablet coating solutions usually contain opacifier, plasticizers, and colorants to modify the physical characteristics and improve the film-forming properties of the polymers. The effect of these additives on the tack behavior of coating solutions is under investigation.

REFERENCES

(1) S. C. Porter, *Pharm. Tech.*, **4**(3), 67 (1980).

(2) H. A. Lieberman and L. Lachman, "Pharmaceutical Dosage Forms: Tablets," Vol. 3, Dekkar, New York, N.Y., 1982, pp. 73–117.

(3) J. Cooper and J. E. Rees, *J. Pharm. Sci.*, **61**, 1511 (1972).

(4) J. R. Cloche, *Labo-Pharma*, **157**, 41 (1967).

(5) "Cellulose Ethers in Aqueous System for Tablet Coating," Dow Chemical Co., Midland, Mich., 1977, p. 4.

(6) N. O. Lindberg and E. Jonsson, *Acta Pharm. Suecica*, **9**, 589 (1972).

(7) S. K. Chopra and R. Tawashi, *J. Pharm. Sci.*, **71**, 907 (1982).

(8) A. Voet and C. F. Geffken, *Ind. Eng. Chem.*, **43**, 1614 (1951).

(9) R. A. Erb and R. S. Hanson, *Trans. Soc. Rheal.*, **1**, 3 (1957).

(10) W. H. Bank and C. C. Mill, *J. Colloid Sci.*, **8**, 137 (1953).

(11) H. Strasburger, *J. Colloid Sci.*, **13**, 218 (1958).

(12) J. J. Bikerman, *J. Colloid Sci.*, **2**, 163 (1947).

(13) S. S. Voyutskii, "Autohesion and Adhesion of High Polymers," Interscience, New York, N.Y., 1963, pp. 235–248.

(14) A. D. Jenkins, "Polymer Science," American Elsevier, New York, N.Y., 1972, pp. 775–800.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Council of Canada.

Phase Diagram and Aqueous Solubility of the Lidocaine–Prilocaine Binary System

A. BRODIN *x, A. NYQVIST-MAYER *, T. WADSTEN ‡, B. FORSLUND ‡, and F. BROBERG *

Received December 28, 1982, from the **Astra Läkemedel AB, Research and Development Laboratories, Pharmaceutics, S-151 85 Södertalje* and the ‡*Arrhenius Laboratory, University of Stockholm, Fack, S-106 91 Stockholm, Sweden.* Accepted for publication February 17, 1983.

Abstract □ The phase behavior of the lidocaine–prilocaine binary system has been studied by X-ray diffraction, differential thermal analysis, hot-stage microscopy, and IR spectrometry. No intermediate compounds or solid solubilities have been detected. The eutectic composition is close to 1:1, and the eutectic temperature is 18 ± 1°C. Aqueous solubility studies show that the lidocaine heat of solubility from the eutectic mixture is different from that of the pure drug, whereas it is the same for prilocaine. Investigations of various lidocaine–prilocaine ratios indicate that the two local anesthetics decrease the solubility of each other. The total solubility, however, is affected only to a minor extent.

Keyphrases □ Lidocaine—binary system with prilocaine, phase diagram and aqueous solubility □ Prilocaine—binary system with lidocaine, phase diagram and aqueous solubility □ Solubility—phase diagram of the lidocaine–prilocaine binary system in water □ Phase diagram—lidocaine–prilocaine binary system, aqueous solubility

Solid–solid interactions are of great interest in the development of pharmaceutical preparations. Dissolution rates, and thus bioavailability, of poorly soluble drugs can be enhanced by their fusion with water-soluble carriers such as urea or polyethylene glycol, which form solid solutions with drugs (1, 2). Eutectic mixtures may even be used to prevent freeze–thaw coagulation of suspensions (3). In powder technology, on the other hand, a eutectic interaction between substances may be considered as an incompatibility, making it necessary to use some auxiliary substance to inhibit adhesion of the powders (4). The physical state in which the drugs are present in such fused mixtures is debatable. The dispersion of phenylbutazone in urea represents a "plug compound" (5). Such solid dispersions are known to age (6, 7).

Studies on eutectic combinations of two drugs are rare (8). Recently, lidocaine and prilocaine have been reported to form a eutectic mixture (9). Since this mixture is liquid at room temperature, it has been possible to formulate an effective local anesthetic preparation for topical application. The purpose of this investigation is to characterize the lidocaine–prilocaine system from a physical point of view and to study its aqueous solubility.

EXPERIMENTAL

Materials—Lidocaine[1] and prilocaine[1] were used as obtained. To prepare the eutectic mixture (EMLA), 49.6% lidocaine and 50.4% prilocaine by weight were mixed and heated gently until liquefaction occurred.

X-Ray Diffraction—An X-ray powder diffraction camera[2] with a 50-mm diameter and strictly monochromatized Cu$K\alpha_1$ radiation was used. A small amount of the powder was spread out on the glue side of ordinary tape. The tape was attached to a thin metal plate, 30 mm in diameter, with an 8-mm

[1] Astra Pharmaceutical Production AB, Sweden.

[2] Guinier-Hägg.

0022-3549/84/0400-0481$01.00/0

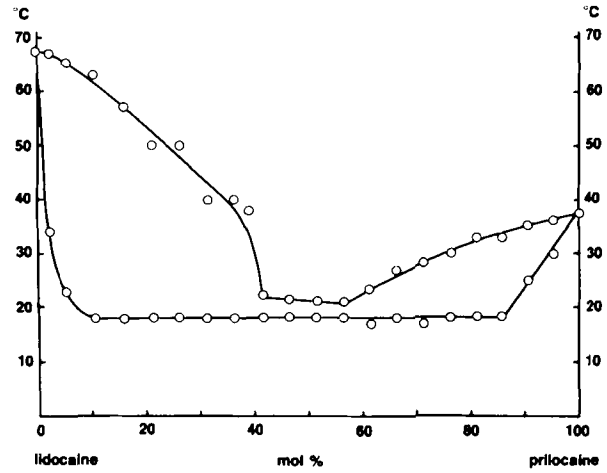

Figure 1—*Phase diagram of the nonequilibrated lidocaine-prilocaine system determined by hot-stage microscopy.*

central hole. This hole was covered with the tape and sample, and the X-ray was passed through; the exposure time was ~45 min. To obtain very accurate diffraction data, an internal standard of potassium chloride was added to the specimens.

One exposure was performed at 4–5°C. The composition was 1:1, and the mixture was kept at 4–5°C for 10 d after having reacted at room temperature to form a viscous homogeneous mass. The material was spread out on extra-thin foil[3] covered with a thin layer of high-vacuum grease to avoid the influence of water. The sample holder was very rapidly transferred from the storing room to the camera. In this case, the internal standard was elemental silicon. No X-ray diffraction lines were registered from the grease-covered foil.

Differential Thermal Analysis (DTA)—A low-temperature instrument that covers the interval of 100–600 K (10) was used. Six different samples can be run simultaneously.

A rather unusual strategy was used to reach equilibrium, since a long time period was involved (several days). Different amounts of the components were weighed and mixed at room temperature in individual glass cups. After a few days, 20-mg portions were transferred to the DTA sample holders. These were

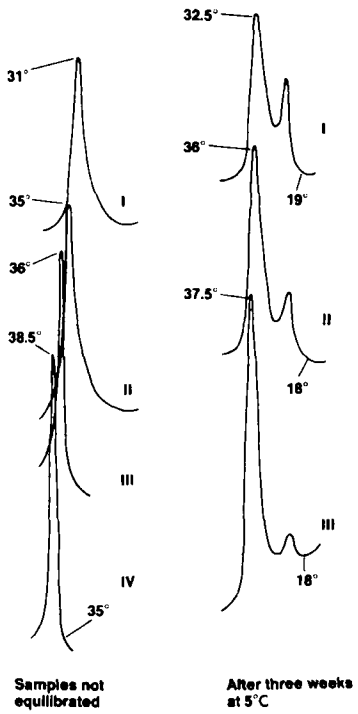

Figure 2—*Some typical examples of the DTA registrations of ~20 mg lidocaine plus prilocaine on heating showing the endothermic peaks. Prilocaine concentration (mol%): (I) 85; (II) 90; (III), 95; (IV) 100.*

[3] Mylar.

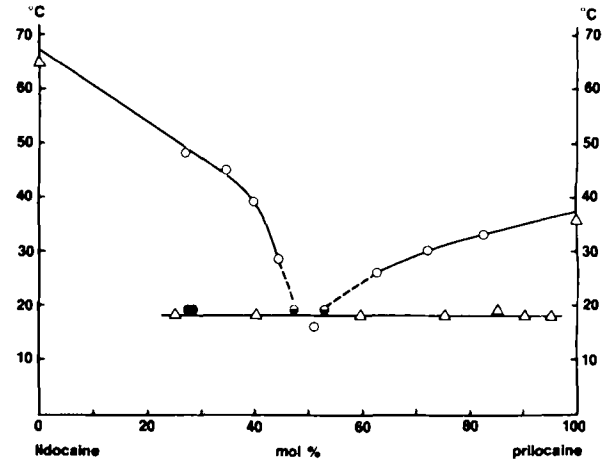

Figure 3—*Phase diagram of the equilibrated lidocaine-prilocaine system determined by hot-stage microscopy (○), long-time storage in a thermostat at 19°C. Key: (●) solid but no observed liquid phase; (◒) liquid phase clearly observed over solid; (△) DTA.*

stored at 4–5°C for different periods of time. The temperature was chosen to avoid ice formation. Just before a specific registration was to take place, the whole DTA measuring head was also cooled to 4–5°C. The filled sample holders were then rapidly moved from refrigeration to the instrument, which was evacuated and further cooled to ~−20°C before the heating program (3°C/min) was started in dry air at atmospheric pressure.

The accuracy of the temperature reading is estimated to be ±1°C according to the calibrating procedure performed with standard samples[4]. The time to obtain equilibrium was found to be longer in the lidocaine-rich part of the system than in the prilocaine-rich part.

Hot-Stage Microscopy—*Nonequilibrium Conditions*—Weighed amounts of lidocaine and prilocaine in various ratios were mixed thoroughly and heated until melting occurred. The melts were cast on watch glasses and allowed to congeal at 5°C. The solidified mixtures were crushed and then homogenized with a mortar and pestle.

A binocular microscope with a hot stage and a control unit was used[5]. Phase transitions of the specimens were observed between crossed polars, both visually and by using a photoelectric sensor to record the changes in light transmission.

A proper amount of specimen was placed on a cooled slide. The specimen was observed from 5°C, with a heating rate of 1°C/min. The temperature at which the crystals just started to melt, or when using the photoelectric sensor the recorded curve started to change, was taken as the eutectic temperature. The temperature at which the whole field became dark was considered the melting point.

Equilibrium Conditions—To determine the liquidus curves of the lidocaine-prilocaine system and to supplement the results gained by the dynamic thermoanalytical methods, a number of equilibration experiments were undertaken. For these experiments, similar to those performed on ternary transition-metal oxide systems (11, 12), a simple microscope hot-stage device comprised of a copper reaction cell (Φ = 5 cm, height = 2 cm) and two 1-mm transparent quartz glass plates were used. The sample was held on the bottom plate, which was in direct contact with a copper block supporting the reaction cell, tempered by means of a circulating-water thermostat. Continuous observation of the sample with the help of a stereo microscope (40×) was made through the upper silica plate, and the temperature (5–75°C) of the sample was checked by a chromel-alumel thermocouple fixed in the copper block close to the sample. The melting temperatures of pure lidocaine, prilocaine, and ice (67°C, 37°C, and 0°C, respectively) served as calibration points in the temperature determinations. The gas-tight reaction cell was also provided with a gas inlet and outlet and a simple manipulator.

A typical run on this hot-stage was performed in the following way. A weighed mixture of lidocaine and prilocaine (in total ~5 mg) was kept at an appropriate temperature for enough time (~1 d) to get a homogeneous melt with a remaining solid phase centered in the droplet. The temperature during this primary stage must be low enough to preserve both kinds of crystals observed: thin platelets (lidocaine) and needles (prilocaine). When the coarse-grained original mixture finally was transformed into a more homogeneous crystalline mass of lidocaine or prilocaine, the temperature was raised in steps until very little solid phase was left in the melt droplet. During this second

[4] NBS-ICTA, Standard Reference Material 758.
[5] Mettler FP52 + FP5.

stage, lasting 1–2 d, checks for equilibrium attainment between solid and liquid were made by observing the growth-dissolution response of the crystals to small temperature changes. Finally, the highest temperature for a solid-liquid equilibrium, *i.e.*, the melting point, for the mixture was noted as that temperature at which the smallest solid residue to be observed in the microscope persisted and showed response to temperature changes.

For some mixtures the primary crystals were grown after the melting point determination by slow cooling and separated for subsequent X-ray analysis from the mother liquor by absorbing the liquor on a piece of porous filter paper. This was brought in contact with the melt by means of the manipulator. Albeit he equilibration experiments were performed in a dynamic atmosphere argon, ~10 mL/min) and lasted for long periods, no changes in size and color f the melt droplets were observed, thus indicating that evaporation losses were egligible.

IR Studies—The IR spectra of lidocaine, prilocaine, and EMLA were re-ɔrded using an IR spectrophotometer[6]. The EMLA samples were prepared : −6°C, and the resulting crystals were spread on potassium bromide disks. MLA was studied both in crystalline form at low temperatures and in liquid ɪrm at room temperature. The spectrum of each sample was recorded 3–4 mes in succession while its physical condition was observed.

Solubility Determination—The solubilities in 1 mM NaOH were deter-ıined for lidocaine, prilocaine, and EMLA at 25°C, 32°C, 37°C, and 45°C. ther combinations of lidocaine and prilocaine were studied in distilled water. quilibrated mixtures of the local anesthetics and water were filtered through ass wool and 0.1-μm polycarbonate filters[7]. The concentrations in the filtrate were determined by UV spectrophotometry[8] at 230 nm. The filtrate was analyzed at fixed time intervals until a constant concentration was obtained.

In the case of EMLA and the other combinations of lidocaine and prilocaine, HPLC was used to analyze the two concentrations separately. For the HPLC method, a 20-μL loop injection valve and a column (200 mm × 3.0 i.d.) packed with Lichrosorb RP-8 (10-μm particles) were connected to an 8-μL flow cell in a spectrophotometer[9]. The column was eluted at ambient temperature with a methanol-phosphate buffer (70:30 v/v, pH 8.0, I = 0.05) at a rate of 1 mL/min. The eluant was monitored at 246 mm with a recorder setting of 0.05 AUFS. Before injection, the samples were diluted with eluant to a concentration of 120 to 140 μg/mL of lidocaine and prilocaine. The peak heights were compared with those of standards chromatographed under similar conditions. Doubling the excess of a mixture did not affect the individual solubilities.

RESULTS AND DISCUSSION

Phase Diagram—The phase diagram for the lidocaine–prilocaine system obtained by hot-stage microscopy is shown in Fig. 1. In the extreme regions, <25% on both sides, visual observations were necessary to estimate the initial melting temperature, while the photoelectric sensor could be used in between. The results obtained with the two methods were in agreement. In the regions of the higher concentrations of lidocaine and prilocaine, respectively, the diagram indicates the existence of solid solutions.

To investigate this further, ~0–15% on both sides were analyzed by X-ray diffraction. A solid solubility may be observed as a shift in the line positions according to changes of the unit cell dimensions if the second component is located in the interstitial spaces of the crystal lattice of the first component. Different amounts of the starting materials were observed, and no interstitial solid solubility between the components could be detected. This may not exclude the existence of noncrystalline solid solutions in which the one component replaces molecules from the crystal lattice of the other component. The formation of substitutional solid solutions is favored if the molecular sizes of the two substances are similar.

Another complication in the phase diagram is the shape of the melting point curve in the 40–60% prilocaine range. Instead of coming to a distinctive eutectic point, the curve only approaches, without touching, the line representing the eutectic temperature. This and the relatively poor reproducibility of the curve on the lidocaine side, may be due to interactions between lidocaine and prilocaine and/or to a very slow process to obtain equilibrium between the melted and solid phases. The latter may also explain the discrepancy between the phase diagram and the X-ray diffraction data about the existence of solid solutions.

Comparing the IR spectrum of crystalline EMLA with those of the single components, no significant difference was detected, which indicates that no chemical interaction takes place between lidocaine and prilocaine. When EMLA melts, the absorbance of some bands are changed in the manner expected in the solid to fluid transition. The characteristic X-ray diffraction lines

[6] Perkin-Elmer Model 298.
[7] Nuclepore Corp., Pleasanton, Calif.
[8] Zeiss DM4.
[9] Perkin-Elmer Model LC 75.

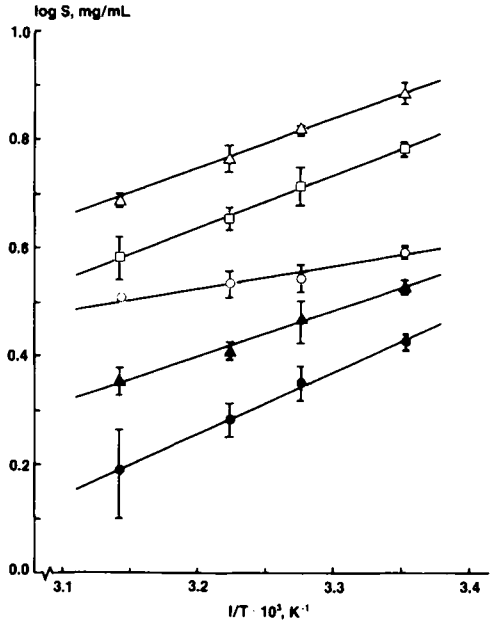

Figure 4—*Solubilities (S) in 1 mM NaOH plotted according to the van't Hoff equation (mean values and their 95% confidence intervals). Key: (△) pure prilocaine; (□) lidocaine plus prilocaine from EMLA; (○) pure lidocaine; (▲) prilocaine from EMLA; (●) lidocaine from EMLA.*

obtained at low temperature showed that EMLA contained nothing but the two single components. By slowly raising the temperature to room level, all lines completely disappeared and only an amorphous liquid remained.

Since both IR spectrometry and X-ray diffraction indicated that no chemical interaction existed between lidocaine and prilocaine, the effects of prolonged equilibration times were investigated. As can be seen from Fig. 2, in the region of high prilocaine content, DTA of nonequilibrated samples only showed a single peak. After equilibration of the samples for 3 weeks at 5°C, another peak corresponding to the eutectic melting point appeared. It was also observed that when crystals from a lidocaine–prilocaine mixture (55:45) stored for a long time at 5°C were analyzed after being washed with cold water and dried, only lidocaine was found. The analysis was made by IR spectrometry and by melting point determination. This, plus the results from the DTA and X-ray diffraction studies, strongly suggests that no solid solutions exist on either side of the phase diagram. These regions seem to be due to the formation of a metastable product during the fusion process. Thus, in an equilibrated system, the eutectic consists of a mixture of the pure components, not a mixture of two solid solutions.

To locate more accurately the eutectic point, a set of lidocaine–prilocaine samples (~5 g) were kept for several weeks at temperatures below the liquidus. Results of the 19°C runs are shown in Fig. 3.

Hot-stage microscopy was also performed under equilibrium conditions. From these results, giving the liquidus curves, and the DTA information, mainly giving the eutectic temperature, we arrived at a tentative temperature-composition diagram (Fig. 3) very similar to that constructed on the basis of the nonequilibrium experiments (Fig. 1). The main differences are in the extreme regions and next to the eutectic composition.

Solubilities—Both lidocaine and prilocaine decrease the surface tension of water very little and do not form micelles (13). However, to determine the extent of interaction between the two local anesthetics in aqueous solution, equilibrium solubility experiments were conducted. As can be seen from Fig. 4, the temperature dependence is smaller for pure lidocaine [$\Delta H = -7.6 \pm 0.69$ (12) kJ/mol, $\pm SE$ (df)] than for pure prilocaine [$\Delta H = -17.5 \pm 0.58$ (13) kJ/mol]. The lidocaine solubilities are in agreement with those reported previously (14), $\Delta H = -8.9$ kJ/mol. The total solubility of lidocaine and prilocaine when equilibrating water with EMLA has a ΔH value of -18.2 ± 0.80 (10) kJ/mol.

Analyzing the water for lidocaine and prilocaine separately showed that lidocaine, in this case, had a slightly higher heat of solubility than prilocaine, -21.5 ± 1.25 (10) and -15.8 ± 0.78 (10) kJ/mol, respectively. The different ΔH value of lidocaine in the presence of prilocaine and the lower individual solubilities of the combined substances demonstrate that solute–solute–solvent interactions take place in the aqueous solution. These interactions are also seen when the solubilities are determined from different mixtures of the two local anesthetics (Fig. 5). In one series of experiments, solidified melts of lidocaine and prilocaine were studied. Enough mixture to assure saturation

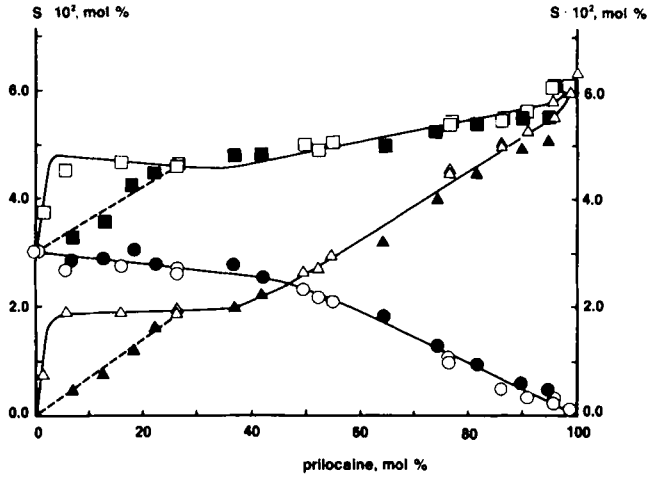

Figure 5—*Solubilities of lidocaine (○), prilocaine (△), and lidocaine plus prilocaine (□) from mixtures of the two local anesthetics at 25°C. Filled symbols represent experiments where the component with <50 mol% was initially dissolved in the water.*

with both components was used. After an initial increase due to a change in prilocaine solubility, the total solubility of the local anesthetics is affected very little compared with the solubilities of the individual substances when the molar ratio of the mixture is changed.

To obtain solutions saturated by only one of the substances, the substance with <50 mol% was dissolved in water before the other was added in excess. It was possible to make solutions where the prilocaine concentration did not reach its saturation level (Fig. 5). Due to the low saturation concentration and the relatively high molar ratio needed, this could not be achieved for lidocaine. In this case, the already dissolved lidocaine started to precipitate on the addition of prilocaine. The values for systems saturated with both substances simultaneously, *i.e.*, the first series of experiments, represent the highest obtainable solubilities. Concentrations lower than the solubility of prilocaine at <30 mol% in Fig. 5 do not influence the lidocaine solubility differently. Only the total amount of local anesthetics is changed. It can be noted that the total concentration of the local anesthetics only varies within 30% of the maximum concentration (that of pure prilocaine), in the range of 2–100 mol% prilocaine in the mixture.

Depending on the influence of additives, especially of salts, on the structure of water or their ability to compete with solvent water molecules, additives will affect the solubility of a solute. To quantify the effect of salts, the empirical Setschenov equation is convenient to use (15):

$$\ln (S_0/S) = k_s C$$

where S and S_0 are the solubilities with and without additive, respectively. The Setschenov coefficient, k_s, measures the sensitivity of the activity coefficient of the solute towards the additive. The concentration of additive, C, is expressed in moles per liter.

To illustrate the aqueous interactions between lidocaine and prilocaine further, the data were plotted according to the equation (Fig. 6). Data from both series of solubility experiments coincided. The Setschenov equation could be applied to prilocaine up to a lidocaine concentration of 0.013 M, with a k_s value of 0.68 obtained by linear regression through the origin. This corresponds to the linear part of Fig. 5 at >50 mol% prilocaine. As lidocaine approaches its highest value of saturation, ln (S_0/S) increases toward infinity. For lidocaine, k_s = 0.09; however, a second linear part with a slope of 1.88 seems to exist. The two linear parts correspond to those of lidocaine in Fig. 5. Since the intersection points in Fig. 5 at a prilocaine concentration of ~0.013 M do not coincide, an intermediate sensitivity of lidocaine to prilocaine might exist. This may also be the case for prilocaine. However, the experimental results do not permit any further evaluation of the intermediate regions using the simple Setschenov equation. As with prilocaine, ln (S_0/S) of lidocaine approaches infinity when the prilocaine concentration gets closer to the maximum saturation concentration. Other empirical expressions can be used to take this into account.

From a pharmaceutical point of view, the maximum aqueous total solubility of the local anesthetics is of interest. In nearly the entire range of lidocaine–prilocaine ratios studied, this solubility is ≥70% of that of pure prilocaine. Thus, the different pharmacological profiles of the two local anesthetics are more important than the aqueous solubility in selecting a suitable ratio for a pharmaceutical preparation. However, the eutectic mixture has the major advantage of being liquid at room temperature. For a preparation such as an oil-in-water cream for topical use, it is possible to emulsify the eutectic mixture directly without first dissolving the drugs in an inert oil.

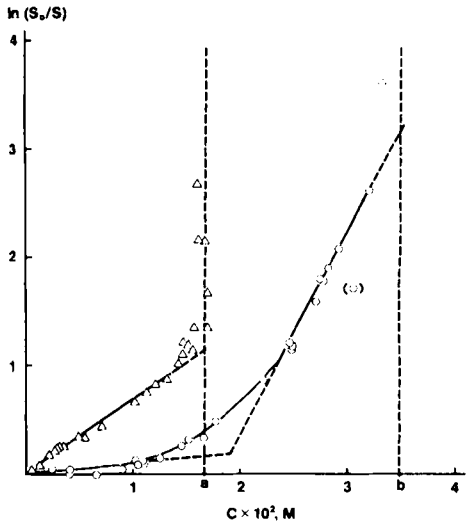

Figure 6—*Setschenov plots for lidocaine (○) and prilocaine (△) in solutic of the other component. Key: (a) solubility of lidocaine, 1.66 × 10⁻² M; solubility of prilocaine, 3.47 × 10⁻² M.*

CONCLUSION

The lidocaine–prilocaine binary system is a simple eutectic containing no intermediate compounds. The eutectic composition is close to 1:1, and the eutectic temperature is 18 ± 1°C. No solid solubility could be detected.

The temperature dependence of the individual solubilities of lidocaine and prilocaine from the eutectic mixture compared with that of the pure substances was higher for lidocaine and the same for prilocaine. For both substances, the individual solubilities from the mixture are lower than those obtained using the single components in the temperature range studied. This was also found for mixtures other than the eutectic. Complex aqueous interactions take place between lidocaine and prilocaine. These interactions depend on the initial ratio of the two drugs.

REFERENCES

(1) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60,** 1281 (1971).

(2) J. L. Ford and M. H. Rubinstein, *Pharm. Acta Helv.*, **53,** 93 (1978).

(3) A. Nakamura and R. Okada, *Coll. Polymer Sci.*, **255,** 362 (1977).

(4) M. Kata and M. Wayer, *Pharmazie*, **30,** 382 (1975).

(5) K. Kreuschner, K-H. Frömming, and R. Hosemann, *Acta Pharm. Tech.*, **26,** 159 (1980).

(6) S. S. El-Gamal, V. F. B. Naggar, and A. M. Motawi, *Sci. Pharm.*, **49,** 20 (1981).

(7) J. L. Ford and M. H. Rubinstein, *Int. J. Pharm.*, **8,** 311 (1981).

(8) H. M. El-Banna, S. A. Khalil, and M. W. Gouda, *J. Pharm. Sci.*, **67,** 1112 (1978).

(9) B. F. J. Broberg and H. C. A. Evers, *European Pat.* no. 0,002,425, (1981).

(10) T. Hörlin, T. Niklewski, and M. Nygren, *Chem. Commun. Univ. Stockholm*, **No 9,** 1975.

(11) B. Forslund, *Chemica Scripta*, **11,** 93 (1977).

(12) B. Forslund and B. Jelinski, *Chemica Scripta*, **15,** 13 (1980).

(13) K. Thoma and C. D. Herzfeldt, in "Proceeding, 1st International Conference on Pharmaceutical Technology," Paris, May 31–June 2, 1977, pp. 157–166.

(14) N. I. Nakano, *J. Pharm. Sci.*, **68,** 667 (1979).

(15) B. E. Conway, "Ionic Hydration in Chemistry and Biophysics," Elsevier, Amsterdam-Oxford-New York, 1981, p. 444.

ACKNOWLEDGMENTS

We are grateful to Bohdan Jelinski at the Arrhenius Laboratory and to Wiia Steenhoff, Kjell Mattsson, and Ann-Charlotte Dahlquist at Astra Läkemedel AB for their skillful technical assistance. Bo Runesson, at the same company, is acknowledged for the IR investigations.