Effect of Enantiomeric Purity on Solubility Determination of Dexclamol Hydrochloride

SUNG-TSUEN LIU and ARTHUR HURWITZ [x]

Abstract □ The solubility of (±)-(4a,13b-trans)-[3(OH),13b(H)-trans]-3-isopropyl - 2,3,4,4a,8,9,13b,14- - octahydro-1H - benzo-[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolin-3-ol hydrochloride [(±)-I] was 3.3 mg/ml in pure water. Its resolved enantiomers exhibited about a fivefold increase in solubility. Dexclamol hydrochloride, the (+)-I enantiomer, is bioactive as a neuroleptic and is soluble to the extent of 16.4 mg/ml. However, raw material purity in relation to the amounts of (±)-I racemate present significantly influences solubility and optimum conditions for dissolution. The effect of trace amounts of (−)-I or (±)-I forms on the solubility of (+)-I enantiomer raw materials was explained through phase solubility studies. Conditions required for preparation of clear solutions using raw materials of varying purity can be determined with derived expressions. The application and limitations of using an enantiomer as a tool to improve solubility are discussed.

Keyphrases □ Dexclamol hydrochloride—solubility, effect of enantiomeric purity □ Enantiomeric purity—dexclamol hydrochloride, effect on solubility □ Solubility—dexclamol hydrochloride, effect of enantiomeric purity □ Sedatives—dexclamol hydrochloride, solubility, effect of enantiomeric purity

Pharmaceutical formulations of a wide variety of optically active compounds have been prepared. Usually, enantiomers exhibit differences in biological activity, and one enantiomer has a distinctive activity or advantage compared to the racemate (1, 2). Furthermore, racemic substances and their enantiomers often exhibit differences in physical properties such as melting point or solubility (3, 4). Recently, the application of a tertiary amine enantiomer to improve a pharmaceutical formulation was reported (5).

Dexclamol hydrochloride, (+)-I, is a potential neuroleptic agent (6–9). Its solubility is 16.4 mg/ml in pure water; that of (±)-I, (±)-(4a,13b-trans)-[3(OH),13b(H)-trans]-3- isopropyl-2,3,4,4a,8,9,13b,14-octahydro- 1H- benzo-[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolin-3-ol hydrochloride, is only 3.3 mg/ml. Trace amounts of the bioinactive (−)-form or the (±)-form of I seriously interfere in the solubility determination of (+)-I.

The purpose of the present study was to investigate the interaction between (−)- and (+)-I. The effect of such interactions on solubility behavior was explained in terms of phase solubility. Effects of pH and common ion on the solubility of (+)-I also were investigated.

EXPERIMENTAL

Materials—Reagent grade chemicals and double-distilled water were

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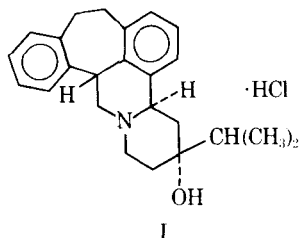
used. Compounds (+)-I, (−)-I, and (±)-I were used as obtained[1].

Solubility Determination—A jacketed 250-ml beaker was employed. Excess solid (+)-I, (−)-I, or (±)-I was introduced into 100 ml of water at 25 ± 1° in the beaker. The suspensions were stirred magnetically, and no significant differences in the solution concentration were observed after 4 hr of stirring. After equilibration, 10 ml of the suspension was sampled and filtered[2] for assay. A few experiments were carried out at 35°. The same experimental procedure was used to study the solubility of (+)-I and (±)-I in different concentrations of sodium chloride solutions.

Less than a 10% increase in solubility was observed for a 10° increase in temperature. Since solubility was relatively insensitive to small temperature changes, all phase solubility experiments were performed at room temperature (22 ± 2°). Physical mixtures containing 10% (−)-I–90% (+)-I, 30% (−)-I–70% (+)-I, and 50% (−)-I–50% (+)-I were used. Weighed amounts of these physical mixtures were introduced into 150-ml beakers containing a known volume of water. The suspended mixtures were stirred magnetically, and the solution concentrations were determined at intervals. To ensure equilibration, all reported phase solubility values were taken from samples after 24 hr of mixing. In most cases, equilibration was found in less than 10 hr.

Analytical Procedures—The (+)-I, (−)-I, and (±)-I all showed the same spectrum in the UV range. No significant differences in absorption intensity[3] were found at pH 2–9. Two absorption peaks were found at 263 and 270 nm. The molar absorptivity values, determined from Beer's law plots, were ϵ_{263} 610 M^{-1} cm^{-1} and ϵ_{270} 630 M^{-1} cm^{-1}.

In the solubility studies, the final saturated suspensions were filtered and the resulting precipitates were collected and then dissolved in the required amount of water. Both filtered saturated solutions and the solutions prepared by redissolving the precipitates were then checked by specific rotation measurement[4] at room temperature (22 ± 2°). The enantiomeric purity of these solutions was calculated from the measured specific rotation[4].

RESULTS AND DISCUSSION

Factors Influencing Solubility of Pure (+)-I, (−)-I, or (±)-I—At 25°, the aqueous solubilities of (+)-I and (±)-I were 16.4 and 3.3 mg/ml, respectively. The saturated solution pH values were 4.4 for (+)-I and 4.9 for (±)-I. The solubility of both materials decreased as the pH of the solution increased. For example, a nearly 100-fold reduction in solubility was found at pH 7 for (+)-I. The solubility–pH profile of (+)-I is shown in Fig. 1. Changes in solubility, S, with hydrogen-ion concentration can be expressed as:

$$S = [B] + [BH^+] = S_0 \left(1 + \frac{[H^+]}{K_a}\right) \qquad (Eq. 1)$$

where S_0 is the intrinsic solubility and has a value of 1.45×10^{-4} M; B and BH^+ are the neutral and protonated species of I, respectively; and K_a is the ionization constant. For this compound, the pKa value obtained by a solubility method was 7.3.

Solubility products of the hydrochloride salt, defined as K_{sp} (hydrochloride salt) = $[BH^+][Cl^-] \times f_1^2$, were 1.28×10^{-3} and 6.1×10^{-5} mole^2/liter^2 for (+)-I and (±)-I, respectively (where $[BH^+]$ is the protonated amine concentration, $[Cl^-]$ is chloride-ion concentration, and f_1 is the activity coefficient of univalent ions). The activity coefficient of univalent ions, f_1, was calculated from the extended Debye–Huckel equation derived by Davies (10):

$$-\log f_1 = 0.509 \left(\frac{\sqrt{U}}{1 + \sqrt{U}} - 0.3U\right) \qquad (Eq. 2)$$

[1] Ayerst Research Laboratories, Montreal, Quebec, Canada.
[2] With 0.22-μm Millipore filter membrane.
[3] Perkin-Elmer model 402.
[4] Perkin-Elmer polarimeter model 40.

Table I—Phase Solubility of (+)-I and (−)-I at Room Temperature

System Composition, mg/ml	Solution Concentration		$[\alpha]_D^{R.T.}$ Solution	Optical Purity of (+)-I in Solution, %	$K_{sp} \times 10^5$, moles^2/ liter^2
	mg/ml	$M \times 10^3$			
			30% (−)-I–70% (+)-I		
50.0	17.3	45.0	205°	92.3	—
33.3[a]	12.8	33.3	193°	87.0	—
25.0[a]	10.4	27.0	192°	86.5	—
16.6	7.31	19.2	188°	84.7	2.60
12.5	5.78	15.0	180°	81.1	1.93
8.33	4.63	12.0	150°	67.6	1.95
5.00	4.75	12.3	87°	39.2	3.20
3.33[b]	3.33	8.63	83°	37.4	—
2.86[b]	2.86	7.40	92°	41.0	—
			10% (−)-I–90% (+)-I		
30	16.7	43.3	209°	94.1	—
20	15.7	40.8	202°	91.0	—
15[a]	12.0	31.0	—	—	—
10	8.72	22.6	187°	84.2	3.71
5	5.01	13.0	174°	78.6	1.61
			50% (−)-I–50% (+)-I		
30	3.66	9.5	—	—	2.26
20	3.70	9.6	—	—	2.30
12.5	3.74	9.7	4°	~0	2.35
5	3.62	9.4	−2°	~0	2.21

[a] Precipitated solid was dissolved and analyzed for optical purity. [b] Clear solution with no solid excess.

where U is the ionic strength of the solution. In the sodium chloride-containing solution, solubilities of these hydrochloride salts decreased. For example, the solubility of (±)-I was 0.29 mg/ml in 0.14 M sodium chloride. For (+)-I, the solubility was decreased to 4.0 and 0.77 mg/ml in 0.2 and 1.0 M sodium chloride, respectively. The decrease in solubility of these hydrochloride salts in chloride-ion-containing solution was explained in terms of the common ion effect.

Interaction between (+)-I and (−)-I in Aqueous Solution—Typical results of the interaction between (+)-I and (−)-I are shown in Fig. 2. The physical mixture contained 30% (−)-I and 70% (+)-I. Curves A and B illustrate the change in solution concentration as a function of time upon introduction of 200 and 100 mg of a 30% (−)-I–70% (+)-I solid mixture into 10 ml of water. The added solid material readily dissolved initially. If no interaction occurs between (+)-I and (−)-I, dissolution should be complete and solution concentration should stay constant. However, the experimental results indicated that a strong interaction occurred between the dissolved (+)-I and (−)-I, which caused the precipitation of a new solid phase.

In 10 ml of water, the recrystallization process followed immediately after the dissolution when 200 mg of solid sample was used. In contrast,

precipitation occurred 50 min after the introduction of a 100-mg sample. The interaction forming the racemate was time dependent. Several factors such as the composition of the physical mixture, the system composition, temperature, and the degree of supersaturation after dissolution as well as the fluid dynamics of the solution affect the precipitation rate of the racemate.

In general, the higher the degree of supersaturation, the faster was the precipitation rate. All precipitation solids collected showed optical behavior similar to that of (±)-I. These data gave strong evidence that the interaction between (+)-I and (−)-I resulted only in the precipitation of (±)-I. The final equilibrium concentration after complete precipitation was taken as the solubility or solution concentration in the phase solubility study.

Phase Solubility—Experimental results of phase solubility measurements and specific rotation of the equilibrated solution are summarized in Table I, where the system composition represents the total amounts of solid mixture added per unit volume of water. Plots of solution concentration versus system composition are shown in Fig. 3. Since only
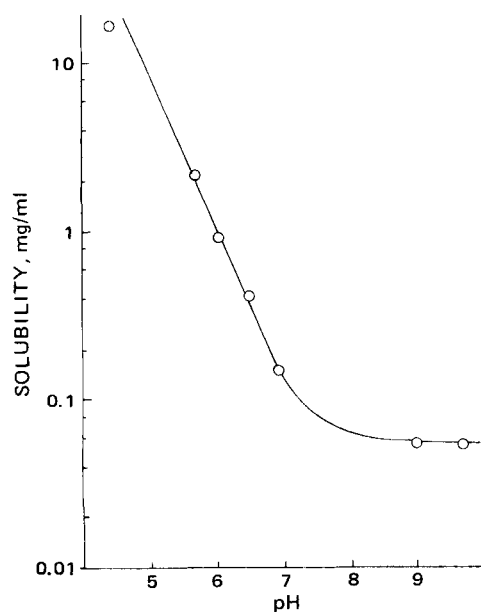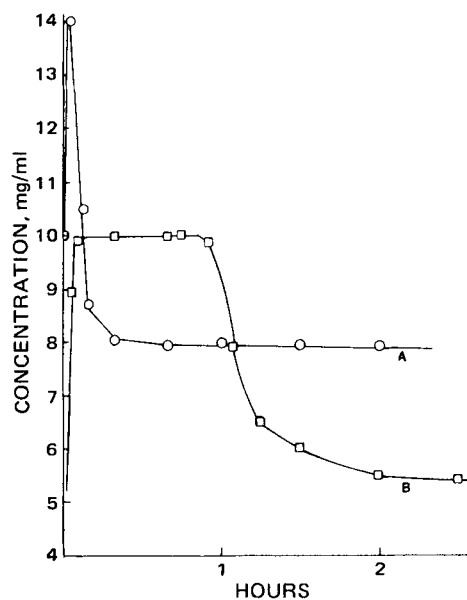

Figure 1—The pH–solubility profile of (+)-I at 25°.

Figure 2—Dissolution profile of 30% (−)-I–70% (+)-I physical mixture in water. Key: A, 200 mg of solid mixture in 10 ml of water; and B, 100 mg of solid mixture in 10 ml of water.
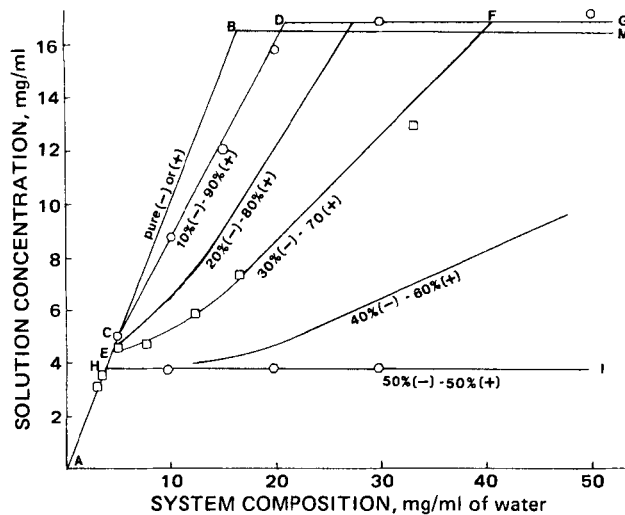
Figure 3—*Phase solubility of (+)-I and (−)-I mixture. Key:* ○, □, *and* ⊙, *experimental results; and* —, *calculated curves.*

(±)-I precipitated in all solution mixtures, these systems can be treated as simple systems containing (+)-I [or (−)-I] enantiomer, (±)-I racemate, and water (10).

In Fig. 3, line ABM is the solution–system composition curve of pure (+)-I or (−)-I enantiomer. Lines DG [10% (−)-I–90% (+)-I] and FG [30% (−)-I–70% (+)-I] represent systems saturated with both (+)-I and (±)-I forms. In this region, Eq. 3 and Schemes I and II should be satisfied and solution concentration should be constant:

$$K_{sp}[(\pm)\text{-I}] = [(+)\text{-}I_s] \times [(-)\text{-}I_s] \qquad \text{(Eq. 3)}$$

$$(\pm)\text{-(solid)} \rightleftharpoons (+)\text{-I (solution)} + (-)\text{-I (solution)}$$
Scheme I

$$(+)\text{-I (solid)} \rightleftharpoons (+)\text{-I (solution)}$$
Scheme II

In a system saturated with (+)-I enantiomer:

$$[(+)\text{-}I_s] = \text{constant} \qquad \text{(Eq. 4)}$$

and:

$$\text{solubility} = [(+)\text{-}I_s] + [(-)\text{-}I_s]$$

$$= [(+)\text{-}I_s] + \frac{K_{sp}[(\pm)\text{-I}]}{[(+)\text{-}I_s]} = \text{constant} \quad \text{(Eq. 5)}$$

where $[(+)\text{-}I_s]$ and $[(-)\text{-}I_s]$ are the solution concentrations of (+)-I and (−)-I, respectively, in a solution saturated with both (+)-I and (±)-I.

The regions where only (±)-I existed as the solid phase are shown by lines CD and EF in Fig. 3. From the phase rule (11), the solution concentration can be expected to change due to the existence of 1 degree of freedom. The solubility product for (±)-I, defined in Eq. 3, was calculated from the solubility data of a 50% (+)-I–50% (−)-I mixture. A value of 2.3 × 10⁻⁵ mole²/liter² was thus obtained. Solubility products obtained from different composition mixtures in solutions saturated with only (±)-I are also shown in Table I. The values are in good agreement with those obtained from pure (±)-I. This finding is additional support for the conclusion that only solid (±)-I precipitated.

Theoretical calculations of solution concentration in (+)-I and (±)-I mixtures saturated only with (±)-I were made using the following equation:

$$\text{solution concentration (mg/ml)} = \left[[(+)\text{-I}] + \frac{K_{sp}[(\pm)\text{-I}]}{[(+)\text{-I}]} \right] \times \text{mol. wt.}$$

$$\text{(Eq. 6)}$$

where $[(+)\text{-I}]$ is the concentration resulting from the amount of completely dissolved (+)-I together with the amount of dissolved (±)-I. Results of theoretical solubility curves are in excellent agreement with experimental data.

When unequal amounts of (+)-I and (−)-I are mixed, the solution

concentration would be expected to increase gradually as the solid material added or system composition increases. Finally, the solution should become saturated with both (+)-I [or (−)-I] and (±)-I, and the solution concentration should remain constant. Solutions can be prepared at concentrations as high as the solubility of pure (+)-I or (−)-I by increasing the system composition of any unequal (+)-I and (−)-I mixture. However, the common undissolved solids visual test of the approach and achievement of solution saturation cannot be used in this system. In enantiomer racemate mixtures, undissolved solids can be detected well below the saturation of the enantiomer form. Therefore, it can be seen from the phase solubility curves that clear solution preparation is impossible without filtration in the regions where system composition is greater than solution concentration. For example, the highest clear solution concentration that can be achieved by dissolving a 10% (−)-I–90% (+)-I solid mixture in water without filtration is about 5 mg/ml.

The slope of the phase solubility curve for pure enantiomer should be close to 1. The difference between a slope of 1 and the slope for a raw material is equal to the percentage of the racemate in the raw material. Since the raw material purity was about 98%, the slope was very close to 1. Therefore, it would be very difficult to determine the amount of impurity in this range by this method. However, a trace amount of enantiomer contained in a racemate raw material could be determined using phase solubility analysis. In this case, the solubility line would be slightly higher than line HI (Fig. 3) for the racemate and have a positive slope. The percentage of enantiomer impurity could be determined easily.

Application and Limitations of Using Enantiomer Resolution to Improve Solubility—Enantiomer solubilities are often higher than those of their racemates. The degree of increase in solubility may range from a few percent to about fivefold. Therefore, resolution of racemates as a tool to improve solubility is not as effective as some other methods such as preparation of different polymorphs, solvates, or salt forms (12). However, the resolution of racemates may be the best available method with certain compounds.

In those cases, caution should be taken to determine the presence of trace amounts of racemate in the enantiomer raw materials. The clarity of prepared solutions and the apparent solubility could be influenced significantly. For example, the aqueous solubility of (+)-I is 16.4 mg/ml. Clear solutions at concentrations as high as 16 mg/ml can be prepared by dissolving extremely optically pure material in water. However, raw material containing 1.5% (−)-I dissolved incompletely when 11 mg of solid material was introduced into 1 ml of water.

REFERENCES

(1) A. F. Casy, in "Medicinal Chemistry," 3rd ed., vol. 1, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, pp. 81–87.

(2) T. C. Daniels and E. C. Jorgensen, in "Textbook of Organic, Medicinal and Pharmaceutical Chemistry," 6th ed., C. O. Wilson, O. Gisvold, and R. D. Doerge, Eds., Lippincott, Philadelphia, Pa., 1971.

(3) K. Mislow, "Introduction to Stereochemistry," Benjamin, New York, N.Y., 1966.

(4) "Handbook of Chemistry and Physics," 52nd ed., Chemical Rubber Co., Cleveland, Ohio, 1971–1972, p. C-743.

(5) A. J. Repta, M. J. Baltezor, and P. C. Bansal, *J. Pharm. Sci.,* **65,** 238 (1976).

(6) F. Bruderlein, L. Humber, and K. Voith, *J. Med. Chem.,* **18,** 185 (1975).

(7) P. H. Bird, F. T. Bruderlein, and L. G. Humber, *Can. J. Chem.,* **54,** 2715 (1976).

(8) T. A. Pugsley and W. Lippmann, *Naunyn-Schmiedebergs Arch. Pharmacol.,* **295,** 117 (1976).

(9) J. Jaramillo, *Can. J. Physiol. Pharmacol.,* **54,** 140 (1976).

(10) C. W. Davies, "Ion Association," Butterworths, London, England, 1962.

(11) W. J. Mader, in "Organic Analysis," vol. II, J. Mitchell, Jr., I. M. Kolthoff, E. S. Proskauer, and A. Weissberger, Eds., Interscience, New York, N.Y., 1954, pp. 253–276.

(12) S. Agharkar, S. Lindenbaum, and T. Higuchi, *J. Pharm. Sci.,* **65,** 747 (1976).