The analysis of a series of I standard solutions containing either II or III as an internal standard is presented in Table II. Where both internal standards were used, the results were the same, indicating that both standards were satisfactory. Furthermore, the results show that the overall procedure is very reproducible.

Table III presents the analytical results, corrected for the weight of stabilizer present, obtained when I ampul dosage forms were analyzed by the proposed NMR method. When the epoxidized oil was the stabilizer, II was used as the internal standard; when V was the stabilizer, III was the internal standard. The analytical values indicate good reproducibility for each of the two series of samples. Comparison of the NMR method with the titrimetric procedure (2), involving reaction of all nitrites with chlorate ion followed by the determination of the chloride formed, indicates that the classical titration method yields lower results. It is not possible to reproduce by calculation comparable results for the same lot from the data in Table III since each analytical result represents the analysis of a different ampul (with its own sample weight) from the indicated lot.

The problems involved in the analysis of I in ampuls have been evident from the standpoint of specificity. The NMR procedure described here uses a property that allows the absolute measurement of I in the presence of decomposition products. Furthermore, this specificity is achieved without any evidence of decomposition during the measurement. The analytical results indicate that this NMR method is precise.

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Utilization of an Enantiomer as a Solution to a Pharmaceutical Problem: Application to Solubilization of 1,2-Di(4-piperazine-2,6-dione)propane

A. J. REPTA [x], M. J. BALTEZOR, and P. C. BANSAL

Abstract □ An enantiomer of the cytotoxic agent (±)-1,2-di(4-piperazine-2,6-dione)propane [(±)-I] (ICRF 159) was utilized to overcome a solubility problem in the preparation of a solution suitable for intravenous use. The enantiomers were about five times more soluble and melted at about 40° lower than the racemic compound. This study appears to be the first reported instance in which the difference in the physical properties of a racemic compound and its enantiomers was utilized to improve a pharmaceutical formulation. The expected differences in the physical properties of racemic solids and their corresponding enantiomers are discussed briefly in relation to the three racemic modifications known to exist.

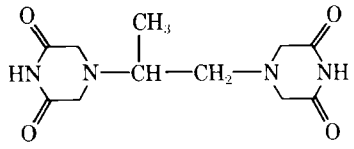
Keyphrases □ Enantiomers—physical properties compared to racemic substance, potential use in pharmaceutical formulations □ 1,2-Di(4-piperazine-2,6-dione)propane—solubilization of enantiomers compared to racemate, potential use in intravenous formulations □ Solubilization—enantiomers compared to racemates, pharmaceutical formulations

Some advantages of using various crystalline modifications such as polymorphs, hydrates, and other solvates in improving pharmaceutical formulations of drugs are well documented (1–5). An additional type of crystalline modification may be encountered when the drug molecules possess an asymmetric or optically active center. Although the employment of optically active compounds in pharmaceutical formulations is not new, their past and present usage has been due largely to one enantiomer exhibiting a quantitatively or qualitatively different biological activity than the corresponding racemic compound (6, 7). Examples of such drugs include epinephrine, ephedrine, hyoscyamine, and dextropropoxyphene (8).

The chemical and physical properties such as melting behavior, IR spectra, and solubility of crystalline racemic substances and their enantiomeric components have been well studied (9–15). The combination of these different physical properties with the stereochemical requirements of biological systems is an approach that has been largely overlooked as a means of formulation improvement.

BACKGROUND

In the case of solid crystalline compounds, the intercrystalline forces between molecules may be greatly affected by only a minor change in the crystal geometry (11, 13, 16). The intercrystalline forces between the two like (+ and + or − and −) enantiomer molecules are the same (16). Therefore, the physical properties of a pair of pure crystalline enantiomers are identical except for the direction in which they rotate plane polarized light. However, the intercrystalline forces between opposite (+ and −) enantiomer molecules are usually very different than those between like enantiomer molecules. Such differences may give rise to different solid-state physical properties, and the nature and magnitude of these differences between enantiomers and the corresponding racemic material are dependent upon the relative strength of the intermolecular forces in the crystal. Enantiomeric systems may fall into one of three possible types (11, 16), and the solubility behavior as a function of the composition for each of the three cases is shown in Fig. 1.



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The first type, a racemic solid solution, occurs when there is little difference in the affinity between like and unlike enantiomeric molecules in the crystal. For compounds of this category, such as camphor oxime (9, 16), the physical properties (such as solubility) of the pure enantiomers, the racemic material, or any combination of the enantiomers vary only slightly and such variation is continuous (Fig. 1*a*).

The second situation, called a racemic mixture or conglomerate (16), occurs when there is a greater affinity between the molecules of like enantiomers than between opposite enantiomers. This type of system results in a gross mixture of the crystals of the two enantiomers, which in some cases may be physically separable (17). As is often the case in a normal binary mixture of solids, this type of system forms a eutectic with the eutectic composition identical to the racemic composition, which causes the minimum melting point and maximum solubility also to occur at the racemic composition. Figure 1*b* illustrates this type of system. Compounds showing this behavior include the dimethyl ester of *O,O*-diacetyltartaric acid (9, 10), β-benzoylhydratropic acid (14), and sodium ammonium tartrate (16).

The third and apparently most common situation (9, 10, 14, 16) occurs when opposite enantiomer molecules have a greater affinity for each other than do like enantiomer molecules. Such systems constitute true racemic compounds and normally exhibit solubility and melting-point behavior grossly different than those of the pure enantiomers. The racemic compound usually exhibits a higher melting point and lower solubility than either enantiomer. The solubility diagram of such systems exhibits a minimum at the racemic composition and two maxima symmetrically located at some composition between those of the pure enantiomers and the racemic compound (Fig. 1*c*). Tartaric acid (10), the dimethyl ester of tartaric acid (9, 10), and leucine (18) exhibit this behavior.

In some systems, the temperature at which the crystallization of a racemic substance occurs may determine the nature of the crystalline solid obtained. For instance, depending upon the conditions of crystallization, a compound might be obtained as either a racemic mixture or a racemic compound. Compounds exhibiting this behavior are sodium ammonium tartrate (16) and rubidium tartrate (16).

The fact that crystalline enantiomers often exhibit different physical properties than the corresponding racemic drug may be pharmaceutically useful in the formulation of some racemic drugs. The applicability of this approach depends upon the desired physical properties of the drug in the formulation[1] and the enantomeric system to which the drug belongs.

The remainder of this paper deals with the use of the observed differences in the physical–chemical properties of a racemic compound and its enantiomers in overcoming a problem encountered in the pharmaceutical formulation of a cytotoxic substance. The problem confronted stemmed from a request from the National Cancer Institute to develop an intravenous formulation of the racemic cytotoxic compound 1,2-di(4-piperazine-2,6-dione)propane[2] [(±)-I] (ICRF 159) suitable for clinical testing. A concentration of 25 mg of (±)-I/ml of solution was desired, and the adult dose was estimated to be about 1 g[3].

The solubility of (±)-I was only ~3 mg/ml in water at 25°. The use of cosolvents to overcome the low solubility problem was not a viable approach due to the low solubility of (±)-I in most solvents. Several alternative approaches were considered, including complexation, chemically derived prodrugs (19), and crystalline modifications of the drug. For reasons that will not be explored here, none of these approaches appeared very promising except the one involving physical crystalline modifications.

[1] In some cases, a decrease in solubility may be desired while in others an increase may be sought.

[2] This substance is also commonly referred to in the literature as NSC 129943.

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

Table I—Effect of pH on the Optical Rotation of (−)-(*R*)-I[a]

pH	$[\alpha]_D^{25}$
1	−63.47°
2	−58.92°
3	−44.32°
4	−40.92°
5	−40.80°

[a] The sample used in this study contained ~97.4% (−)-(*R*)-I.

Table II—Some Properties of (±)-I and the Enantiomer (−)-(*R*)-I

Property	(−)-(*R*)-I	(±)-I
Melting point	~192° dec.	~233° dec.
Solubility (water at 25°), mg/ml	~15	~3
Absolute rotation, $[\alpha]_D^{25}$ (c 0.5, water)	−43°	0

The low solubility of (±)-I in most solvents together with its high melting point (~233° dec.) indicated the existence of strong intercrystalline forces. Therefore, an approach aimed at decreasing the intercrystalline forces of (±)-I, thereby altering the physical properties of the solid so as to increase solubility, appeared to offer the greatest chance of success. A review of available data gave no evidence for the existence of polymorphs, hydrates, or other solvates of (±)-I that could be useful in overcoming the solubility problem. Consequently, an investigation of the properties of the crystalline enantiomers of (±)-I was undertaken.

Although the potential for success of such an approach was not quantitatively predictable, a number of features enhanced its probability and attractiveness. First of all, as previously mentioned, in a racemic modification the most common situation appears to be one where the enantiomers are more soluble than the racemic drug (9, 10, 14, 16) (Fig. 1*c*).

Second, one enantiomer may possess a greater biological activity than the other (8). If this were found to be the situation with either enantiomer, a lower dose would be required and the severity of the original problem would be decreased. It had already been shown that both enantiomers (20) of (±)-I exhibited the same qualitative biological activity (21), but no quantitative data for the relative activity of the enantiomers with respect to each other were available.

Third, since the use of an enantiomer would require no change in the molecular structure, there probably would be no change in the *in vitro* chemical stability such as might be encountered when using other solubilizing techniques such as preparing water-soluble prodrug derivatives (22).

EXPERIMENTAL

Chemicals—The (±)-I was used as obtained from the National Cancer Institute. Formamide was purified by vacuum distillation (75°/5 mm Hg) prior to use. All other chemicals used were of reagent grade. The water used was triple distilled, with the last distillation being from acid permanganate solution in an all-glass apparatus.

Synthesis and Characterization of (+)-(*S*)-I[4] and (−)-(*R*)-I—The synthesis of (+)-(*S*)-I was carried out asymmetrically as follows. (±)-1,2-Diaminopropane[5] (27 g) was resolved using (−)-*l*-tartaric acid[5] (80 g) according to the method of Dwyer *et al.* (24). The precipitate obtained was recrystallized five times from water to yield 27 g of (+)-(*S*)-1,2-diaminopropane bis(*l*-tartrate), mp 141.5° [lit (25) mp 142°].

The bitartrate salt (27 g) was suspended in methanol (135 ml). Hydrogen chloride was bubbled through the suspension for about 30 min, during which time the solid initially present completely dissolved (after about 5 min). After about 7 min, another white crystalline solid appeared. Excess hydrogen chloride was removed

[4] The assignment of (*R*)- and (*S*)-configurations is based on the configuration of the enantiomers of 1,2-diaminopropane (23).

[5] Aldrich Chemical Co.

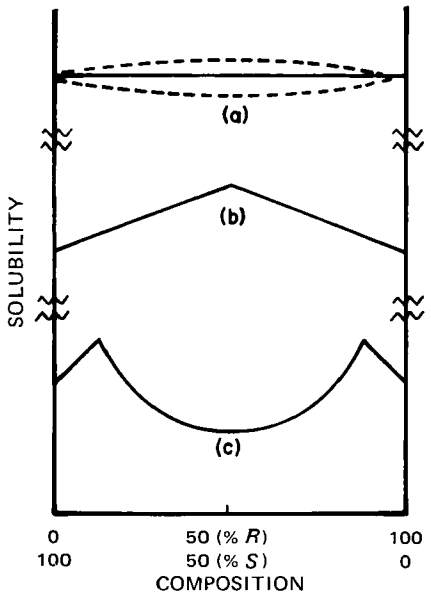

Figure 1—*Effect of enantiomer composition on solubility for the three racemic modifications:* (a) *solid solution,* (b) *racemic mixture, and* (c) *racemic compound.*

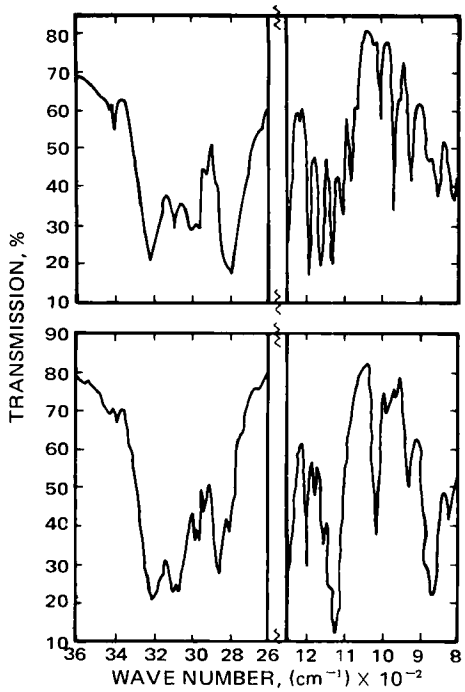

Figure 2—*Partial IR spectra of* (±)-*I (top) and* (−)-(R)-*I (bottom) as a 2% dispersion in a potassium bromide pellet.*

by passing dry nitrogen gas through the suspension for about 20 min. The precipitate was separated by filtration to yield 9.3 g of (−)-(*S*)-1,2-diaminopropane dihydrochloride, mp 238.5°; $[\alpha]_D^{25}$ −4.12° (c 4.0, water) [lit. (26) mp 240°; lit. (25) $[\alpha]_D^{25}$ −4.08° (c 1.7 − 10.4, water)].

The optically active acid, (+)-(*S*)-1,2-propylene dinitrilotetraacetic acid, was synthesized using the (−)-(*S*)-1,2-diaminopropane dihydrochloride (9 g) according to the method of Wing and Callahan (27). After 7 days, the reaction solution was concentrated to about 50 ml and filtered. The isolation of the product from the filtrate was accomplished using a cation-exchange resin[6] (800-ml wet volume in a glass column, 5 cm i.d.). Elution of the column consisted of 2 liters of cold water (~50 ml/min) followed by 12 liters of hot (90°) water (~80 ml/min). The temperature of the column was maintained at 90° with a heating tape wrapped around the column.

The portion of the eluate containing the bulk of the optical activity (as determined by measuring the α_D of the eluate) was concentrated by heating. The crystalline material that formed on standing was separated by filtration, dried (120 hr at 110°/~10 mm Hg), and found to be (+)-(*S*)-1,2-propylene dinitrilotetraacetic acid (12.5 g), mp 199–200°; $[\alpha]_D^{25}$ +49.3° (water) [lit. (27) mp 198°; lit. (28) $[\alpha]_D^{25}$ +50° (water)].

The (+)-(*S*)-1,2-propylene dinitrilotetraacetic acid (12 g) was heated with formamide[7] (30 ml), according to the method of Creighton (20), to yield 4.9 g of a white crystalline powder, mp 193–194°; $[\alpha]_D^{25}$ +41.0° (c 0.5, water) [lit. (20) mp 193°]. This powder was shown to be (+)-(*S*)-1,2-di(4-piperazine-2,6-dione)propane [(+)-(*S*)-I] by NMR[8], elemental, IR[9], and polar rotation analyses; $[\alpha]_D^{25}$ +11.50° (5%, dimethylformamide) [lit. (20) $[\alpha]_D^{25}$ +11.35° (5%, dimethylformamide)].

The asymmetric synthesis of (−)-(*R*)-I [(−)-(*R*)-1,2-di(4-piperazine-2,6-dione)propane] was carried out by a procedure identical to that used for synthesizing (+)-(*S*)-I, with the exception that (+)-*d*-tartaric acid[10] was used to obtain the (−)-(*R*)-1,2-diaminopropane bis(*d*-tartrate) salt.

The characterization of (−)-(*R*)-I was based on the same types of physical and chemical information as were used for the characterization of (+)-(*S*)-I (as already described). NMR spectra (d_6-dimethyl sulfoxide), melting point, elemental analysis, and IR spectra (2% KBr pellet) for (−)-(*R*)-I were all essentially identical to those for (+)-(*S*)-I.

Solubility Determination—Due to the instability of (±)-I and both of its enantiomers in aqueous solution, equilibrium solubility values could not be determined. The approximate solubilities for each enantiomer and for (±)-I were obtained by the addition of increasing amounts of the solid into vials containing 5 ml of water. The closed vials were vigorously agitated at 25° for 1 hr.

With the enantiomers, the quantity of drug was increased by increments of 0.2 mg/ml in the range of 14–16 mg/ml of water. Similarly, the quantity of (±)-I was increased by 0.2-mg/ml increments from 2 to 4 mg/ml of water. Visual observation of these samples indicated a solubility of approximately 15 mg/ml for each enantiomer and of 3 mg/ml for (±)-I.

The apparent solubility of I as a function of the enantiomer–racemate composition was determined using physical mixtures of two optically active samples. One sample exhibited a specific rotation of +39.4° (c 0.5, water), corresponding to a composition of 95.8% (+)-(*S*)-I and 4.2% (−)-(*R*)-I. The specific rotation of the other sample was −42.0° (c 0.5, water), corresponding to 98.85% (−)-(*R*)-I and 1.15% (+)-(*S*)-I. The composition of these samples was calculated on the basis of an absolute rotation of ±43° for a pure enantiomer sample as discussed later.

The mixtures of (+)-(*S*)-I and (−)-(*R*)-I were agitated with 5-ml portions of water at 25° for 2 hr and filtered. A weighed aliquot of the filtrate was placed in a small, tared evaporating dish, and the sample was slowly evaporated (35°/130 mm Hg) to apparent dryness. The samples were dried to a constant weight at 95° for 72 hr, and the weight of dissolved solid per milliliter of water was calculated.

Purity Analysis—Samples of (±)-I, (+)-(*S*)-I, and (−)-(*R*)-I appeared to be homogeneous when analyzed by TLC on silica gel plates[11], using chloroform–methanol–formic acid [(9:3:1) R_f 0.50, (7:2.5:2) R_f 0.37, and (6:3:3) R_f 0.45]. Spots were visualized using iodine vapor; no other spots were visible by UV or after development with ninhydrin. NMR spectra (10% in d_6-dimethyl sulfoxide) showed no extraneous peaks.

An estimation of the absolute rotation of the enantiomers was obtained by purification of an optically active sample with a high content of (−)-(*R*)-I, $[\alpha]_D^{25}$ −40.28° (c 0.5, water). A sample (one part) was partially dissolved (~90%) in methanol (300 parts) at

[6] Bio-Rad AG 50W-X8, 50–100 mesh, hydrogen form.
[7] Eastman Chemicals.
[8] Varian model T-60 NMR spectrophotometer (10% in d_6-dimethyl sulfoxide).
[9] Beckman model IR-33 IR spectrophotometer (2% KBr pellet).
[10] J. T. Baker.
[11] Macherey-Nagel Polygram Sil G/UV_{254}.

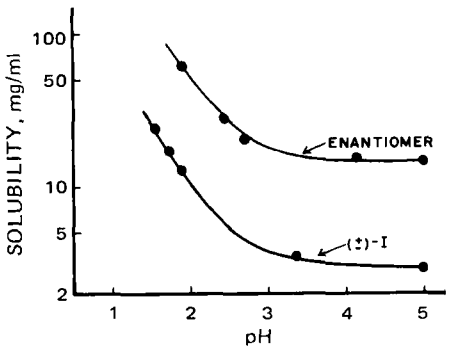

Figure 3—*Plot of solubility of (±)-I and an enantiomer as a function of pH. Solid lines were calculated on the basis of pKa 2.4, solubility of (±)-I = 3 mg/ml, and solubility of enantiomer = 15 mg/ml.*

25°, filtered, and then cooled (10°). The filtrate was slowly evaporated (150 mm Hg) to about 90% of its original volume, and the precipitate was removed by filtration and discarded.

The filtrate was then evaporated to dryness under reduced pressure (50 mm Hg) at room temperature, and the specific rotation of the solid obtained was determined[12] in water at a concentration of 0.5%. This procedure was repeated until the specific rotation obtained for three such successive treatments remained constant at a value of $[\alpha]_D^{25}$ −43.0° (c 0.5, water). This value was taken to be the value of the absolute rotation.

By comparison of specific rotations determined for other optically active samples of I with the value of the absolute rotation, the optical purity of less pure samples was calculated (16).

Lyophilization of Formulations—An initial solution containing 25 mg of (−)-(*R*)-I and 1.7 mg of hydrogen chloride/ml of solution was prepared [0.5 mEq of hydrogen chloride/mEq of (−)-(*R*)-I]. Optical rotation, pH, and TLC determinations were performed on this solution. Approximately 5 ml of this solution was placed into each of nine preweighed vials, and the total weight was determined. These vials were then placed into a dry ice–acetone bath and frozen. The samples were lyophilized[13] for 48 hr with an initial shelf temperature of −40°. The shelf temperature rose to about −20° during the first 24 hr, and then heat was applied to maintain a shelf temperature of 25° during the last 24 hr.

After lyophilization, the vials were weighed and found to contain about 2.4% more mass than expected if all water had been removed. This excess weight was attributed to residual water. Several vials were reconstituted to their original weights by the addition of water, and the optical rotation and pH of the solutions were measured. The solutions were also assayed by TLC as described previously.

Due to a slight increase in the pH of the reconstituted samples, the effect of pH on the optical rotation of aqueous solutions of the enantiomers at pH < 5 was determined in aqueous hydrochloric acid solutions. The results obtained for an optically active sample in the 1–5 pH range are shown in Table I.

RESULTS AND DISCUSSION

The enantiomers of (±)-I were prepared by asymmetric synthesis, and samples of (−)-(*R*)-I[14] and (+)-(*S*)-I[15] were sent to the National Cancer Institute for biological testing for relative activity. Data from these tests indicated that the antitumor activity for each enantiomer was equivalent to that of the (±)-I. Therefore, any pharmaceutical advantage to be realized from the use of an enantiomer could only arise from its significantly greater solubility relative to (±)-I.

The physical properties of (−)-(*R*)-I and (±)-I were studied[16] (Table II). The melting point and solubility data indicated that

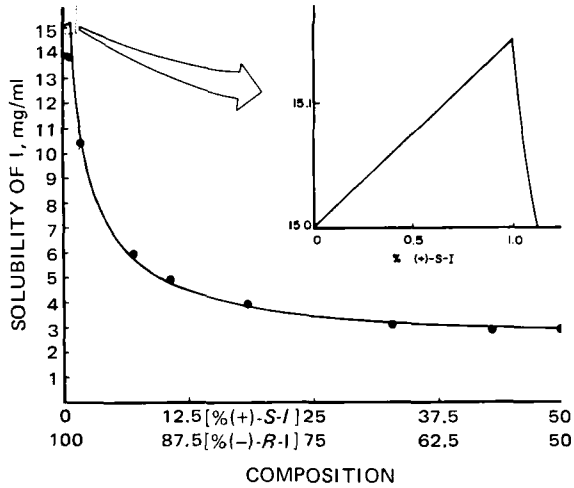

Figure 4—*Aqueous solubility of I at 25° as a function of the enantiomeric composition of the sample. The solid line was calculated (30) using solubility values of 15 mg/ml for (−)-(R)-I and 3 mg/ml for (±)-I.*

the naturally occurring racemic modification of (±)-I is that of a true racemic compound (Fig. 1c). This finding was demonstrated by the 40° decrease in the melting point and the fivefold increase in the solubility of (−)-(*R*)-I as compared with (±)-I.

Portions of the IR spectra of (−)-(*R*)-I and (±)-I (as 2% KBr pellets) are shown in Fig. 2. As expected (15), there were significant differences in the two spectra, and these differences were attributable to the differences in crystal structure (as evidenced by data in Table II). However, the IR spectra for (−)-(*R*)-I and (+)-(*S*)-I were identical. The NMR spectra (in d_6-dimethyl sulfoxide) and the values of pKa (~2.4) were identical for both enantiomers and (±)-I. Again these results were expected since the chemical properties in dilute solution would not be expected to be related to the enantiomeric composition of the sample.

A comparison of expected solubility as a function of pH based on solubility values of 3 and 15 mg/ml for (±)-I and (−)-(*R*)-I, respectively, is shown in Fig. 3. The experimental values obtained in a limited study are also shown and agree quite well with the calculated lines. From this figure, it is apparent that the desired concentration of 25 mg of I/ml of solution can be obtained using an enantiomer at pH ~2.5. To achieve a similar concentration using (±)-I, a pH of ~1.5 would be required.

The increased solubility of the individual enantiomers relative to the racemate also may be useful from the standpoint of formulating an oral dosage form, since the increased solubility should result in an increased absorption rate and, thus, improve bioavailability by that route.

An inherent drawback in the use of an enantiomer is the greater difficulty and expense of preparation relative to the racemic material. Generally, it is not particularly difficult to attain an optical purity greater than 90%. However, the preparation of essentially 100% optically pure material is extremely difficult and expensive. Therefore, it must be realized that it is not necessary to strive for 100% optically pure samples to obtain greatly increased solubility.

The solubility of a sample is dependent upon its composition with respect to each enantiomer. Since the solubility in such systems is governed by a solubility product relationship, it is possible to predict solubility as a function of the enantiomeric composition of the solute sample[17]. Figure 4 shows a theoretical plot of the total solubility of I (sum of both enantiomers) as a function of solute composition. The data points shown demonstrate the excellent agreement of the predicted values and the solubility actually obtained with the samples of various compositions.

The theoretical plot (30) is based on a solubility of 3 mg/ml for (±)-I and of 15 mg/ml for the pure enantiomer at 25° in water. From the calculated curve in Fig. 4, it is clear that the maximum solubility corresponds to a composition containing about 2% race-

[12] Perkin-Elmer model 141 polarimeter with 1-dm cell (3.5-ml volume).
[13] Virtis model 10-800 freeze dryer.
[14] NSC 169779; also ICRF 186.
[15] NSC 169780; also ICRF 187.
[16] Subsequent to completion of this study, it was discovered that A. M. Creighton had also noted enhanced solubility for the enantiomers relative to the racemic material (29).

[17] A rather complete and concise discussion of the effects of enantiomeric composition on solubility was provided by Mader (30).

Table III—Comparison of Some Properties of the Formulated Solution of (−)-(*R*)-I prior to Lyophilization and following Reconstitution at Different Times following Lyophilization[a]

Sample History	Properties of Solutions		
	$[\alpha]_D^{25}$	pH	TLC[b] (R_f Values)
Freshly prepared solution prior to lyophilization	−51.8°	2.37	0.50
Solution reconstituted immediately after completion of lyophilization	−51.0°	2.41	0.51
Solution reconstituted 5 days after lyophilization	−51.0°	2.42	0.50
Solution reconstituted 35 days after lyophilization	−48.3°[c]	2.58[c]	0.51

[a] Samples were stored in closed vials at room temperature. [b] All exhibited only one spot. [c] The higher pH value of this solution apparently caused the lower specific rotation. When using the data in Table I, at pH 2.4 the corrected value is $[\alpha]_D^{25}$ −51.0°.

mic material. Furthermore, the solubility is relatively independent of composition at higher optical purity. Thus, it would be unnecessary to strive for a completely optically pure product when a sample containing 2% or less racemic material would be essentially equally soluble and more readily attainable than a more optically pure sample.

The equations used in calculating the theoretical curve in Fig. 4 were discussed by Mader (30). It may be shown that the closer the values of the solubilities are for the racemic compound and the enantiomers, the less optically pure the solute need be to achieve maximum solubility. However, if the solubilities of the enantiomers and the racemate are similar, little advantage would be realized by their use in the formulation.

As a test of the usefulness of an enantiomer in solving the problem of formulating I, a prospective formulation was developed and evaluated. Due to the instability of I in aqueous solutions[18], a lyophilized formulation to be reconstituted just prior to use appeared to be most suitable. An aqueous solution of (−)-(*R*)-I at a concentration of 25 mg/ml at pH 2.5 was prepared, and aliquots were freeze dried in serum bottles. The resulting lyophilized samples were stored in a desiccator at 25° and reconstituted at various time intervals. Reconstitution to a concentration of 25 mg of (−)-(*R*)-I/ml was rapid (less than 2 min) and complete.

Some properties of the solutions prior to lyophilization and after reconstitution at various times were measured (Table III). These data indicate that no significant degradation of (−)-(*R*)-I occurred during lyophilization or after storage for more than 1 month. The slight decreases in the absolute rotation may be attributed to the fact that some hydrochloric acid was probably lost during the lyophilization process and the observed rotation decreased with increasing pH (Table I).

CONCLUSION

On the basis of this study, it is apparent that the utilization of an enantiomer of I resulted in improved solubility properties which, in turn, permitted the development of a formulation suitable for parenteral use without requiring modification of the basic molecular structure of the drug and without other pharmaceutical additives. This study appears to be the first reported instance in which the differences in the physical properties of a racemic compound and an enantiomeric component were used explicitly to overcome a problem in pharmaceutical formulation.

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