(18) D. J. Shapiro and V. M. Rodwell, *J. Biol. Chem.*, **246**, 3210(1971).
(19) O. H. Lowry, N. J. Rosenbrough, A. L. Farr, and R. J. Randall, *ibid.*, **193**, 265(1951).
(20) S. G. Boots, M. R. Boots, and K. E. Guyer, *J. Pharm. Sci.*, **60**, 614(1971).
(21) L. A. Carpino, *Acc. Chem. Res.*, **6**, 191(1973).

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Physical Characterization and Activity *In Vivo* of Polymorphic Forms of 7-Chloro-5,11-dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxamide, a Potential Tricyclic Antidepressant

IRWIN S. GIBBS ˣ, ANTHONY HEALD, HAROLD JACOBSON, DEODATT WADKE, and IRVING WELIKY

Abstract □ The biological availability in dogs and humans of 7-chloro-5,11-dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxamide, a potential antidepressant drug, was increased when the compound was administered in capsule formulations as micronized drug coated with 1% sodium lauryl sulfate or as a lyophilate with poloxamer 407. This increase with these two formulations had been predicted by dissolution tests *in vitro*. The lyophilized combination with poloxamer 407 was more soluble in 0.1 *N* HCl than was the untreated compound. Characterization of the lyophilate by differential thermal analysis, X-ray diffraction, and IR spectroscopy indicated that the increase in solubility was attributable to the formation of a polymorphic form. A polymorph of the compound, designated Form B, was prepared. The solubility and dissolution characteristics of the two polymorphic forms, A and B, as well as of the lyophilized combination with poloxamer 407, were determined.

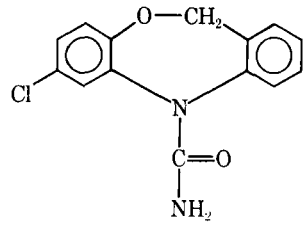
Keyphrases □ Dibenz[*b,e*][1,4]oxazepine, substituted—solubility, dissolution rate, and bioavailability, micronized and surfactant coated compared to lyophilate with copolymer formulation □ Bioavailability—substituted dibenz[*b,e*][1,4]oxazepine, micronized and surfactant coated compared to lyophilate with copolymer formulation □ Polymorphic forms—substituted dibenz[*b,e*][1,4]oxazepine, solid dispersion, solubility, dissolution rate, and bioavailability □ Antidepressants, tricyclic—substituted dibenz[*b,e*][1,4]oxazepine, solubility, dissolution rate, and bioavailability

In preclinical studies for the development of a new drug, its biological availability should be assessed (1). If a drug is incompletely absorbed, efforts are usually made to increase its biological availability.

The common causes of biological unavailability of a drug include poor solubility and slow dissolution in aqueous media, specifically GI fluids (1). When synthesis of a more soluble chemical derivative is not feasible, diminution of the particle size (2, 3) or utilization of another polymorphic form (4–7) or solid dispersions of the drug (8–12) may increase its biological availability.

In preformulation studies of a potential tricyclic antidepressant, 7-chloro-5,11-dihydrodibenz[*b,e*][1,4]-oxazepine-5-carboxamide[1] (I), synthesized by Yale (13), the drug was more readily and more completely absorbed when given to dogs orally as capsules containing a fine powder rather than a coarse powder[2].

The equilibrium solubility of I in aqueous solution at 37° is 0.04 mg/ml, irrespective of pH.



I

This report describes the methods evolved for increasing the bioavailability of this drug by increasing its dissolution rate and/or solubility. To accomplish these effects, the material was either micronized and combined with a wetting agent or prepared as a solid dispersion. During the preparation of the latter, the existence of a polymorphic form was discovered.

EXPERIMENTAL

Materials—The following was used: poloxamer 407[3], I polymorph Form A[4], sodium lauryl sulfate USP, magnesium stearate USP, an-

[1] SQ 10, 966.
[2] J. Dreyfuss, Department of Drug Metabolism, Squibb Institute for Medical Research, New Brunswick, N.J., unpublished data.
[3] Pluronic F-127, BASF Wyandotte Corp., Wyandotte, Mich.
[4] Squibb lot RR002RC (see Ref. 13).

hydrous lactose USP, starch USP, directly compressible starch[5], sodium glycine carbonate[6], and dioxane[7].

Dosage Forms—Bulk Formulation 1 was prepared by simple admixture of the ingredients. Microscopic examination showed a wide range of particle sizes for I, the largest being about 60 × 120 μm with variable thickness. Each unit dose, filled into a No. 3 gelatin capsule, consisted of: I, 100 mg; sodium lauryl sulfate, 1 mg; directly compressible starch, 20 mg; anhydrous lactose, 77 mg; and magnesium stearate, 2 mg.

For bulk Formulation 2, I was micronized[8] to yield particles smaller than 25 μm as determined by an automated particle counter[9]. The micronized powder was granulated with an aqueous solution of sodium lauryl sulfate. The damp granulation was dried under vacuum at room temperature until the total volatiles content was 0%, as determined by thermogravimetric analysis. After the dried granulation was passed through a No. 100 mesh screen, the remaining excipients were introduced by simple admixture. The final dosage unit was quantitatively identical to that of Formulation 1.

For Formulation 3, a lyophilized combination of I and poloxamer 407 was first prepared as a 1:1 (w/w) combination. Equal amounts of I and poloxamer 407 were dissolved separately in dioxane to yield a 3.3% solution of each material. The solution was poured into shallow glass dishes, frozen solid at −20°, and then lyophilized in a laboratory model freeze dryer[10]. Residual dioxane was removed by fluid bed drying at room temperature for approximately 30 hr[11]. The final product contained less than 1% dioxane.

Lyophilized I Form B Alone—Compound I was dissolved in dioxane to yield a 3.3% solution. The solution was placed into a shallow glass dish, frozen solid at −20°, and lyophilized. Residual dioxane was removed by fluid bed drying for 5 hr at room temperature and 2 hr at 40°; the residual dioxane content was 0%.

Lyophilized Poloxamer 407 Alone—A 6.6% solution of poloxamer 407 in dioxane was frozen solid at −20° in a shallow glass dish and then lyophilized. Residual dioxane was reduced to 0% by fluid bed drying at room temperature for 5 hr.

Dissolution—The dissolution test was a modification of the NF XIII method (14), *i.e.*, 300 ml of 0.1 *N* HCl at 37° and 60 rpm. Ten-milliliter samples of solution were removed from each resin flask periodically during 1 hr. Sample solution was replaced with an equal volume of 0.1 *N* HCl after each sampling. Removed samples were filtered through a 0.45-μm filter, and absorbance values were measured[12] at 290 nm.

Differential Thermal Analysis—Thermograms were obtained on a thermal analyzer[13] fitted with 2-mm microsample tubes. The heating rate was 15°/min, and the differential sensitivity was 1°/2.54 cm. The thermograms were obtained in the presence of static air.

X-Ray Diffraction—Powder X-ray diffraction patterns were obtained[14] employing nickel-filtered copper K_α X-radiation collimated by a 1° divergence slit, a 0.3° receiving slit, and a 1° antiscatter slit. Detection was mediated by a transistorized scintillation detector, and the output was eventually monitored by a recorder. A scan speed of 1° (2θ) was utilized at 30 kv and 10 mamp.

Before measurement, each sample was ground for about 12 sec by means of a glass ball in a plastic vial mounted on a dental amalgam shaker[15].

IR Absorbance Spectroscopy—IR spectra were determined[16] with the drug as a mineral oil mull or dissolved in deuterated chloroform.

Comparative Bioavailability in Dogs—The three formulations were administered orally to 9-month-old male beagle dogs, 11–15 kg, as capsules containing 100 mg of drug in a 3 × 3 Latin-square study, with a 1-week rest between treatments. The dogs were deprived of food for 12 hr before and throughout the study, with water available *ad libitum*. Each dog was weighed before the administration of each dose.

After a control plasma sample was obtained, each dog was dosed orally with one capsule, washed down with water given by gavage, 20 ml/kg. Plasma samples were obtained at 0.5, 1, 1.5, 2, 3, and 4 hr after the dose. The second and third doses were given (crossover arrangement) at 8 and 15 days after the initial dose. Plasma samples were assayed for intact I by GC (15).

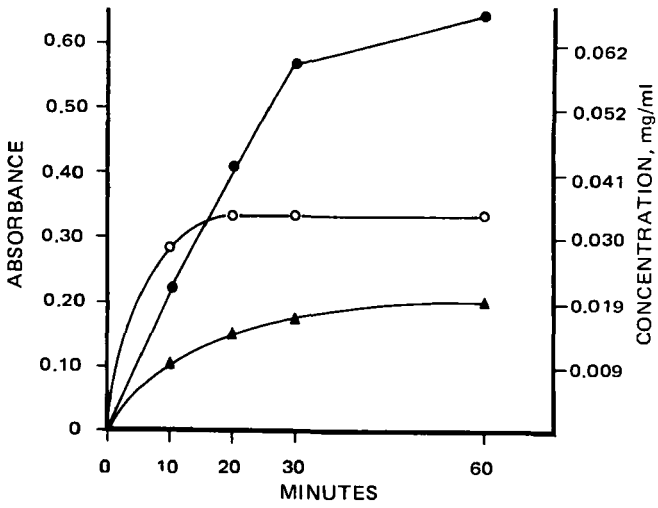


Figure 1—*Dissolution profiles (absorbance and concentration versus time) for three capsule formulations of I. Key: ▲, Formulation 1; ○, Formulation 2; and ●, Formulation 3.*

Comparative Bioavailability in Humans—The three capsule formulations were administered orally to two groups of six healthy male volunteers. The subjects ranged in age from 19 to 28 years (mean 23.2 years) and weighed between 68 and 96 kg (mean 79.6 kg). Each formulation was administered once to each subject before breakfast with 180 ml of water: Group I, single oral dose of 200 mg of I (two 100-mg capsules); and Group II, single oral dose of 400 mg of I (four 100-mg capsules).

Each group of six subjects was subdivided into groups of two, and each pair received a particular formulation on a given day. They were then crossed over at intervals of 7 days, so that each subject had received one dose of each formulation by the end of the study.

Individual 10-ml samples of venous blood were drawn from each subject and collected into nonheparinized tubes at 0 (pretreatment), 1, 2, 4, 6, 8, 12, 24, 48, and 72 hr after drug administration. Samples were permitted to clot and were then centrifuged. Serum samples were transferred to sterile tubes and frozen until assayed by a GC method specific for I (15).

RESULTS

Dissolution—The dissolution profiles of the three capsule formulations are shown in Fig. 1. Each point represents the average value obtained for three capsules of a formulation at a given sampling time. Formulation 1 yielded the slowest initial rate of solution for I. The concentration of drug in solution after 1 hr of study was approximately half of the equilibrium solubility of the drug (0.04 mg/ml).

Formulation 2, containing micronized I granulated with sodium lauryl sulfate, showed a faster initial rate of solution, and the concentration of I in solution after 1 hr of testing approached the equilibrium solubility of the drug. Formulation 3 showed an intermediate initial dissolution rate, similar to that of Formulation 2, but the solubility attained after 1 hr of study exceeded the equilibrium solubility of I by more than 60%.

Characterization of I Form in Lyophilate with Poloxamer 407—*Differential Thermograms*—Figure 2 shows the differential thermograms for I, lyophilized poloxamer 407, and the combination lyophilate of I and poloxamer 407. Compound I showed a melting endotherm at approximately 195°, followed by a decomposition exotherm at 250–300°. Lyophilized poloxamer 407 showed a melting endotherm at 48–50°, with no other thermal events of interest. The combination lyophilate product showed the characteristic melting endotherm for poloxamer 407, followed by a very small endotherm near 180°. The characteristic melting endotherm for I was not seen with the combination lyophilate, but the decomposition exotherm was apparent at 250–300°.

[5] StaRx 1500, A. E. Staley Manufacturing Co., Decatur, Ill.
[6] Edward Mendell Co., Carmel, N.Y.
[7] Spectroquality, Matheson, Coleman & Bell.
[8] Gem T research model pulverizer, Trost Equipment Corp.
[9] Coulter.
[10] No. 10-D1-SM, Virtis Co., Gardiner, N.Y.
[11] Model FBD/L72, Pfaltz and Bauer, Flushing, N.Y.
[12] Beckman model DU spectrophotometer.
[13] DuPont model 900.
[14] Philips X-ray diffractometer.
[15] Wig-L-Bug, Crescent Dental Manufacturing Co., Chicago, Ill.
[16] Perkin-Elmer 621 IR spectrophotometer.

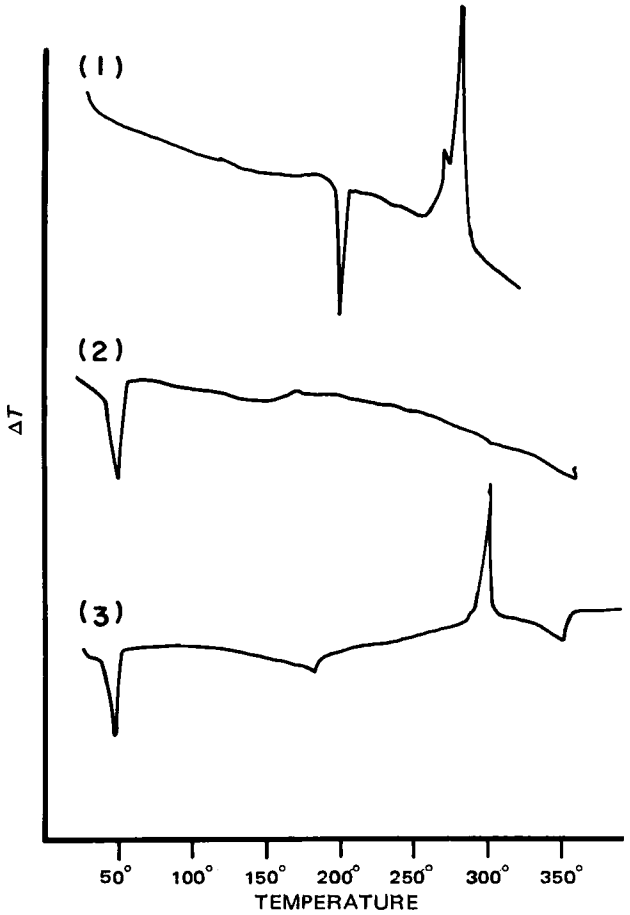


Figure 2—*Differential thermograms of I (1), lyophilized poloxamer 407 (2), and I–poloxamer 407 lyophilate (3).*

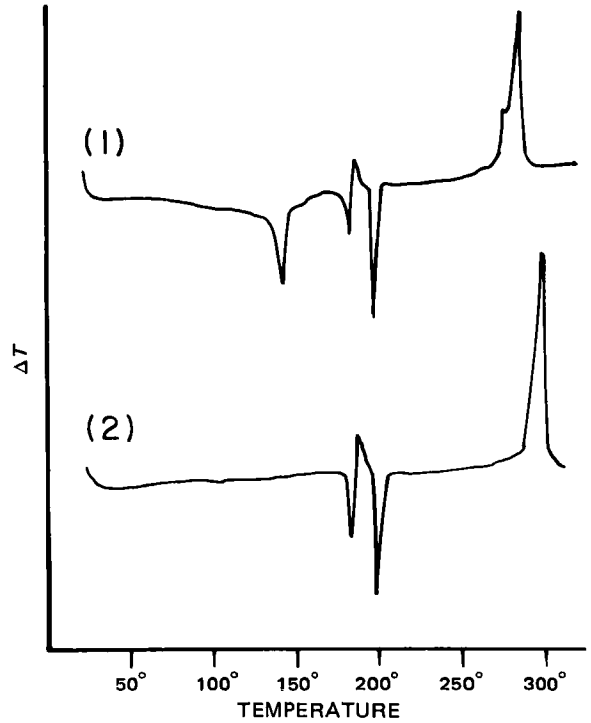


Figure 3—*Differential thermograms of undried (1) and dried (2) I lyophilized from dioxane.*

Figure 3 depicts the thermograms of I, lyophilized alone from dioxane before and after further drying as a fluid bed. The undried sample showed new endotherms at 140 and 180°, with a new exotherm at 183°. After fluid bed drying of the sample to 0% total volatiles, the endotherm at 140° disappeared; its presence can be attributed to solvate formation (dioxane), since the undried lyophilates characteristically contained more than 13% volatiles. The thermograms shown in Fig. 3 are strongly indicative of the possible existence of polymorphic forms of I.

X-Ray Diffraction—Powder X-ray diffraction patterns for lyophilized poloxamer 407, I, and the combined lyophilate product are shown in Fig. 4. Poloxamer 407 displayed two characteristic strong diffraction peaks of almost equal intensity at d values of 3.81 and 4.64 Å. Untreated I had a very rich diffraction pattern, as did the lyophilized combination product; however, there were marked differences between the patterns, *e.g.*, the triad of peaks near 5.90 Å in the case of the lyophilized combination product.

The X-ray diffraction pattern of a sample of I lyophilized alone from dioxane is shown in Fig. 5. Except for the peaks attributable to poloxamer 407, the X-ray diffraction patterns for the lyophilized combination I–poloxamer 407 and for lyophilized I alone were identical but different from that for untreated I.

IR Spectroscopy—IR spectra for untreated and lyophilized I, each prepared as mineral oil mulls and in deuterated chloroform solution, are shown in Fig. 6. The spectra for the two forms of I obtained as mulls differed, whereas the spectra for the two solutions were identical. This behavior is typical of polymorphic forms of a compound (6).

Comparative Bioavailability in Dogs—The mean plasma concentration–time curve for each of the three formulations is shown in Fig. 7; the mean area under the plasma concentration–time curve (*AUC*) for 0–4 hr is also included.

Comparative Bioavailability in Humans—Blood level–time profiles after single-dose administrations of 200 and 400 mg of I in each of the three formulations are shown in Figs. 8 and 9; the areas under the curves are also included.

DISCUSSION

The increase in solubility of I in Formulation 3 (the combined lyophilate with poloxamer 407) compared with that of I alone can be attributed mainly to the existence of a polymorphic form of the compound, as shown by differential thermal analysis, X-ray diffraction, and IR spectroscopy. The thermogram of the combined lyophilate (Fig. 2) does not indicate conclusively the existence of a polymorphic form. Poloxamer 407 melts at 48–50°, and the molten polymer dissolves I as the temperature increases. This solution accounts for the disappearance of the strong melting endotherm of I near 196°. Only the thermogram of lyophilized I alone (Fig. 3) permits attribution of the small endotherm near 180° in the combination product to undissolved polymorph Form B.

The X-ray diffraction patterns (Figs. 4 and 5) and IR spectra (Fig. 6) prove conclusively that polymorphic Form B exists in the I–poloxamer 407 lyophilate. In addition, determinations of the equilibrium solubility of isolated Form B showed the material to be approximately 50% more soluble than untreated I (Form A), *i.e.*, 0.059 mg/ml. The dissolution rate of Form B, however, was less than that of the simple admixture formulation (Formulation 1), indicating the necessity for inclusion of poloxamer 407 as a wetting agent in the preparation of Form B for use in the capsule formulation.

Microscopic examination of the combined lyophilate after the addition of water showed the presence of small crystallites of drug, approximately 1 μm in diameter. Although attempts to isolate these crystallites for further study failed, it is reasonable to conjecture that I lyophilized in combination with poloxamer 407 exists, at least in part, as extremely small crystallites of the more soluble Form B intimately enmeshed with poloxamer 407. Although this mixture is not a solid solution, as shown by the X-ray diffraction pattern (Fig. 4), the contribution of these small crystallites, in intimate admixture with the wetting agent, to the increased solubility of I cannot be completely ignored. The X-ray diffraction pattern of the combination lyophilate product (Fig. 4) shows the existence of a crystalline, rather than of an amorphous, lyophilized material. In this laboratory, freeze drying of an aqueous solution resulted in the formation of amorphous materials almost exclusively.

Figures 7–9 reveal the increase in bioavailability of I that resulted

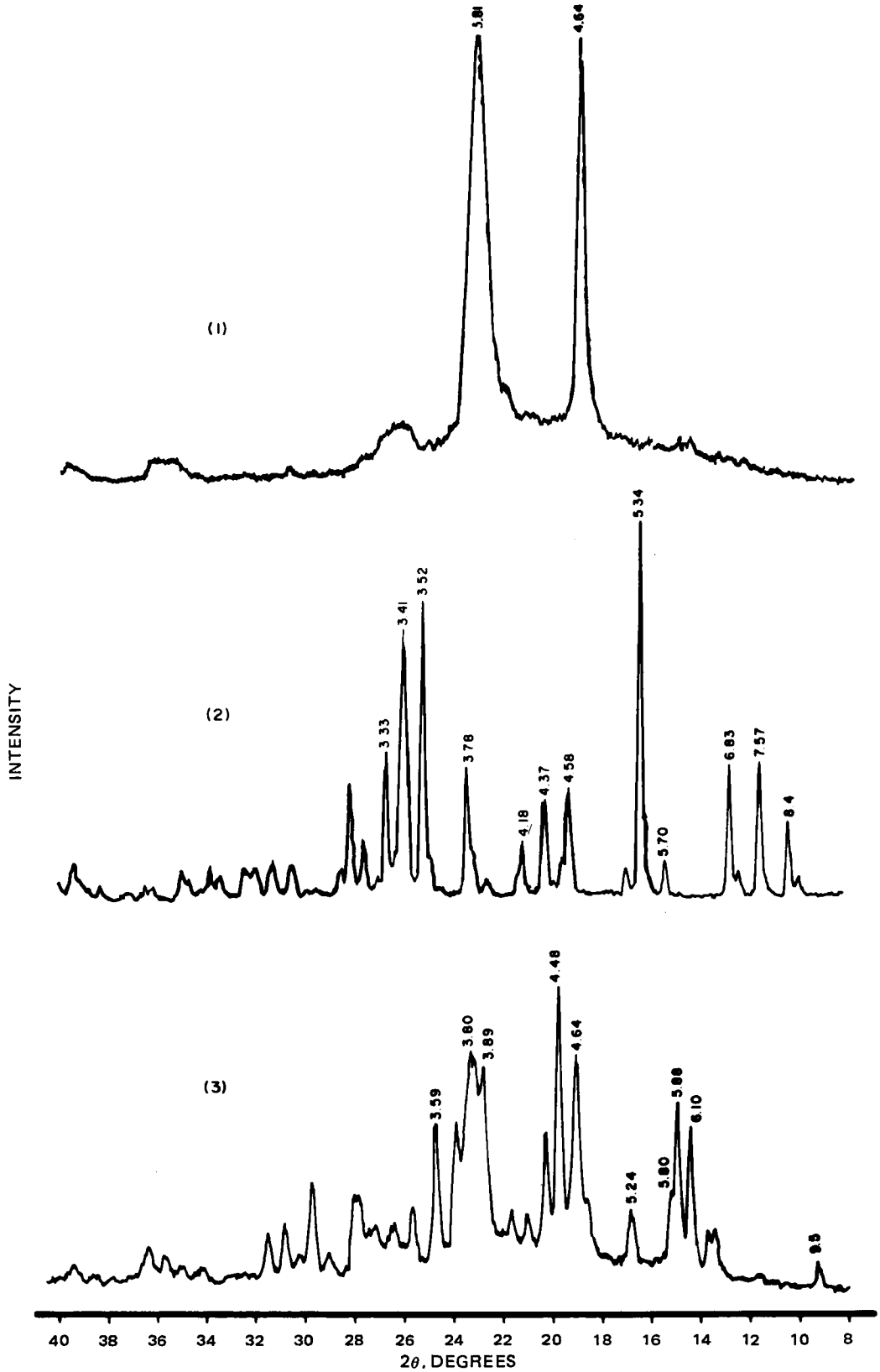


Figure 4—*Powder X-ray diffraction patterns for lyophilized poloxamer 407 (1), I (2), and I–poloxamer 407 lyophilate (3).*

from micronization of I followed by granulation with a wetting agent or from use of the combined lyophilate. In dogs given an oral dose of I, approximately 8.2 mg/kg, plasma levels were undetectable after the administration of Formulation 1, in which the untreated drug is in simple admixture with the excipients. Utilization of Formulation 2, in which micronized I exists as a granulation with sodium lauryl sulfate, led to blood levels detectable for 4 hr after dosing, with an area under the plasma level–time curve of 1.99 μg/ml × hr. Use of Formulation 3, containing the I–poloxamer 407 lyophilate in which the drug exists as polymorphic Form B, increased the bioavailability from that of Formulation 2 (peak height ratio of 1.2:0.7) and yielded an area under the plasma level–time curve of 2.78 μg/ml × hr.

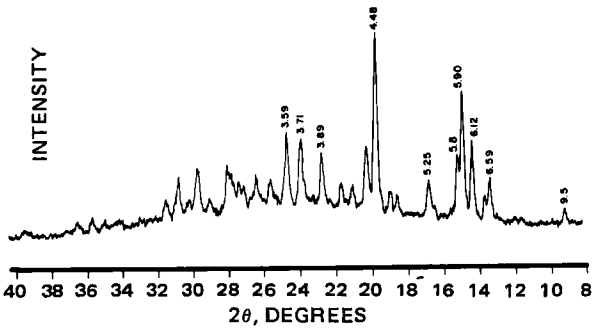


Figure 5—*Powder X-ray diffraction pattern of fluid bed dried I lyophilized from dioxane.*

In humans given oral doses of I of approximately 2.51 and 5.02 mg/kg, blood levels were detectable after the administration of each formulation. After administration of a 200-mg dose of I, the biological availability of the compound increased progressively for Formulations 1–3.

The ratio of peak heights after the administration to humans of a 200-mg dose of I as Formulations 3, 2, and 1 was 2.5:1.85:0.8; the respective areas under the serum level–time curves were 81.2, 68.2, and 43.6 μg/ml × hr. After the administration of a 400-mg dose of I, the formulations showed the same order of drug bioavailability, with peak height ratios of 3.90:2.92:1.23 and areas under the blood level–time curves of 132, 100, and 50.8 μg/ml × hr, respectively.

Within the limitations of the number of data points employed, a plot of the dissolution parameter, "amount of drug dissolved in 1 hr," *versus* blood level peak heights or areas under the plasma level–time curve yielded a linear relationship, with regression coefficients greater than 0.9 for both dose levels in the human.

In summary, the existence of a polymorphic form of I, a potential tricyclic antidepressant, has been proven. The utility of this polymorph in a solid dispersion with a polyoxypropylene–polyoxyethylene copolymer to enhance the biological availability of the drug has been demonstrated. An intermediate increase in biological availability was attained by the administration of a micronized form of the original polymorph granulated with aqueous sodium lauryl sulfate solution. Values obtained from dissolution profiles *in vitro* of the various for-

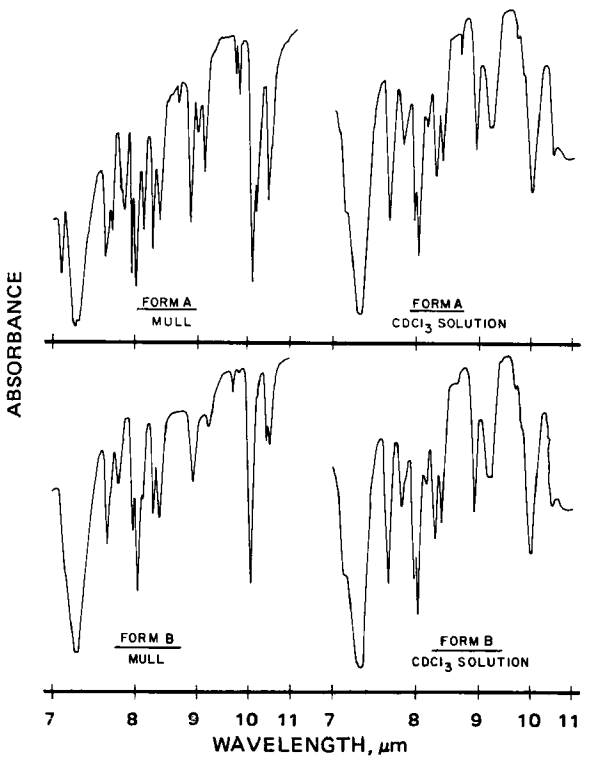


Figure 6—*IR spectra of I.*

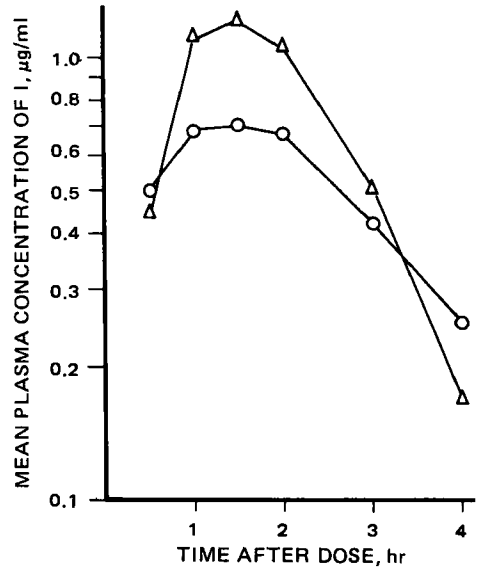


Figure 7—*Mean plasma concentrations of I after oral administration of 100-mg capsules to three male beagle dogs. Key:* ○, *Formulation 2* (AUC = *1.99 μg/ml × hr*); *and* △, *Formulation 3* (AUC = *2.78 μg/ml × hr*).

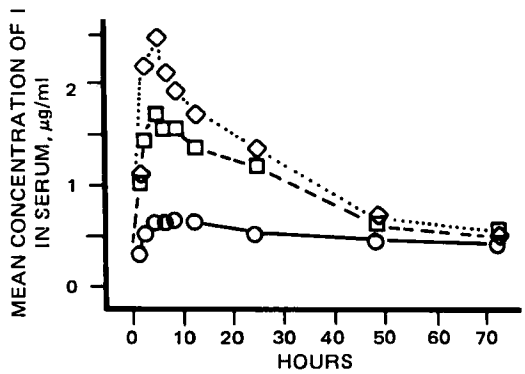


Figure 8—*Mean concentrations of unchanged drug in serum of six healthy male volunteers after oral administration of a 200-mg dose of each of three different formulations of I in a three-way crossover design study. Key:* ○, *Formulation 1* (AUC = *43.6 μg/ml × hr*); □, *Formulation 2* (AUC = *68.2 μg/ml × hr*); *and* ◇, *Formulation 3* (AUC = *81.2 μg/ml × hr*).

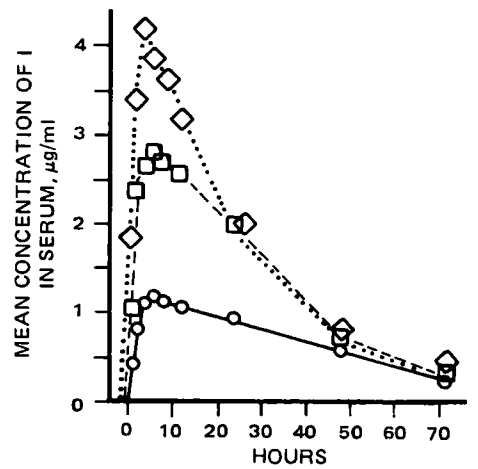


Figure 9—*Mean concentrations of unchanged drug in serum of six healthy male volunteers after oral administration of a 400-mg dose of each of three different formulations of I in a three-way crossover design study. Key:* ○, *Formulation 1* (AUC = *50.8 μg/ml × hr*); □, *Formulation 2* (AUC = *100 μg/ml × hr*); *and* ◇, *Formulation 3* (AUC = *132 μg/ml × hr*).

mulations could be correlated with the biological availability subsequently demonstrated in humans.

REFERENCES

(1) D. J. Jollow and B. B. Brodie, *Pharmacology*, **8**, 21(1972).
(2) R. M. Atkinson, C. Bedford, K. J. Child, and E. G. Tomich, *Antibiot. Chemother.*, **12**, 232(1962).
(3) J. H. Fincher, *J. Pharm. Sci.*, **57**, 1825(1968).
(4) J. D. Mullins and T. J. Macek, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 245(1960).
(5) G. S. Mewada, D. R. Parikh, and S. Somasekhara, *Sci. Cult.*, **39**, 378(1973).
(6) J. Haleblian and W. McCrone, *J. Pharm. Sci.*, **58**, 911(1969).
(7) K. Münzel, *Pharm. Acta Helv.*, **46**, 513(1971).
(8) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **54**, 1145(1965).
(9) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and M. Mayersohn, *ibid.*, **55**, 581(1966).
(10) W. L. Chiou and S. Riegelman, *ibid.*, **58**, 1505(1969).
(11) *Ibid.*, **60**, 1281(1971).
(12) E. I. Stupak and T. R. Bates, *J. Pharm. Sci.*, **62**, 1806(1973).
(13) H. Yale, *J. Med. Chem.*, **11**, 396(1968).
(14) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 802.
(15) A. O. Niedermayer and R. G. Koski, *J. Pharm. Sci.*, **64**, 1531(1975).

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Real Flow Measurements on Time-Dependent Thixotropic Fluids

ROGER L. SCHNAARE [x], RAFIQ M. SHEIKH [*], PAUL J. NIEBERGALL, and EDWIN T. SUGITA

Abstract □ An experimental procedure was developed in which shear stress *versus* time data at a constant shear rate are extrapolated to structural equilibrium conditions utilizing both the upcurve and the downcurve. This procedure allows the construction of a flow curve by plotting the equilibrium shear stress, F_e, *versus* the shear rate. Such an equilibrium flow curve is independent of all experimental conditions and of shear history and does not exhibit a hysteresis loop. The method also yields apparent rate constants for characterizing thixotropic behavior on an unequivocal basis. The extrapolation procedure was developed using a cup and bob viscometer but is generally applicable to any continuous shear viscometer.

Keyphrases □ Thixotropic systems—equilibrium flow curve constructed from shear stress and shear rate data, apparent rate constants calculated □ Viscosity—thixotropic systems, equilibrium flow curve constructed, apparent rate constants calculated □ Shear stress and rate—thixotropic systems, data used in construction of equilibrium flow curve

A thixotropic material, as defined by Bauer and Collins (1), exhibits a "time-dependent, reversible and isothermal decrease of viscosity with shear in flow." This behavior is universally accepted as being indicative of an equilibrium process between the breakdown and buildup of structure as the material is subjected to shear (2–6). It follows that quantitative measurements of the viscosity or flow of such a system must be dependent on how close the system is to equilibrium. To be completely rigorous, a flow curve should be three dimensional, including time as the third variable (4) in addition to shear stress and shear rate.

BACKGROUND

This time dependency is experimentally evident from the common observation that flow curves are highly dependent on experimental conditions, *i.e.*, the rate at which the shear rate is increased or decreased, the length of time a sample is subjected to any one rate of shear, how many times the flow curve is repeated, and the degree of agitation of the sample prior to measurement (7–9).

It is common practice to report flow data indicating as explicitly as possible the exact experimental conditions. This practice is based on the assumption that variability can be eliminated by duplicating experimental conditions, allowing results to be compared on a relative, albeit arbitrary, basis. This assumption has not been found to be true in actual experience, and experimental data will be presented to illustrate this point.

The difficulty arises from the inability to duplicate the "shear history" of the sample and the uncertainty in the degree of structural equilibrium at a given shear rate. Other investigators simply admit that certain flow curves are not reproducible (2).

It is generally agreed (10, 11) that the structural state of such a material under shear can be represented by a first-order equilibrium process (Scheme I):

$$\text{(structure)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{(nonstructure)}$$

Scheme I

and that the shear stress is a function of structure such that, at equilibrium for a given shear rate:

$$\left[\frac{d(\text{structure})}{dt}\right]_S \equiv \left[\frac{dF}{dt}\right]_S = 0 \qquad \text{(Eq. 1)}$$

The correct procedure then for determining a time-dependent flow curve would be to indicate the point in time relative to the degree of structure at which shear stress measurements are made (4). The two simplest references points are at time $t = 0$, corresponding to the