5. Hysteresis of the immersional isotherm indicates that, once wetted, the solid holds water tighter at the same moisture content than when the water is adsorbed by dry solid.

6. Sorption hysteresis is of enthalpic and entropic origin.

The widespread use of microcrystalline cellulose powder in the pharmaceutical industry as a tablet excipient makes this specific information of particular relevance. However, the general experimental procedure represents a technique that has as its greatest potential application the determination of changes in surface characteristics as a result of formulation and/or processing.

REFERENCES

(1) G. E. Boyd and W. D. Harkins, *J. Am. Chem. Soc.*, **64**, 1190 (1942).

(2) W. D. Harkins and G. E. Boyd, *ibid.*, **64**, 1195 (1942).

(3) W. D. Harkins and G. Jura, *ibid.*, **66**, 919 (1944).

(4) M. Wahba, *J. Phys. Colloid Chem.*, **54**, 1148 (1950).

(5) G. J. Young, J. J. Chessick, F. H. Healey, and A. C. Zettlemoyer, *J. Phys. Chem.*, **58**, 313 (1954).

(6) G. J. Young and F. H. Healey, *ibid.*, **58**, 881 (1954).

(7) F. H. Healey and G. J. Young, *ibid.*, **58**, 885 (1954).

(8) A. C. Zettlemoyer, G. J. Young, and J. J. Chessick, *ibid.*, **59**, 962 (1955).

(9) H. B. Dunford and J. L. Morrison, *Can. J. Chem.*, **33**, 904 (1955).

(10) J. L. Morrison and J. F. Hanlan, *Nature*, **179**, 528 (1957).

(11) J. L. Morrison and M. A. Dzieciuch, *Can. J. Chem.*, **37**, 1379 (1959).

(12) Y. C. Wu and L. E. Copeland, *Adv. Chem. Ser.*, No. 33, 357 (1961).

(13) M. Dole and A. D. McLaren, *J. Am. Chem. Soc.*, **69**, 651 (1947).

(14) S. Brunauer, P. H. Emmett, and E. Teller, *J. Am. Chem. Soc.*, **60**, 309 (1938).

(15) S. Brunauer, L. S. Deming, W. E. Deming, and E. Teller, *ibid.*, **62**, 1723 (1940).

(16) W. D. Harkins and G. Jura, *ibid.*, **66**, 1362 (1944).

(17) R. H. Stokes and R. A. Robinson, *Ind. Eng. Chem.*, **41**, 2013 (1949).

(18) J. M. Sturtevant, in "Physical Methods of Organic Chemistry," vol. 1, A. Weissburger, Ed., Interscience, New York, N.Y., 1945, pp. 335–344.

(19) R. G. Hollenbeck, G. E. Peck, and D. O. Kildsig, *J. Pharm. Sci.*, **67**, 1592 (1978).

(20) G. H. Argue and O. Maass, *Can. J. Res.*, **12**, 564 (1935).

(21) J. D. Babbitt, *ibid.*, **20**, 143 (1942).

(22) S. J. Gregg, "The Surface Chemistry of Solids," Reinhold, New York, N.Y., 1951, pp. 24–26.

(23) Y. Nakai, E. Fukuska, S. Nakajima, and J. Hasegawa, *Chem. Pharm. Bull.*, **25**, 96 (1977).

(24) K. Marshall and D. Sixsmith, *Drug Dev. Commun.*, **1**, 51 (1974–75).

(25) F. W. Billmeyer, "Textbook of Polymer Science," 2nd ed., Wiley-Interscience, New York, N.Y., 1971.

ACKNOWLEDGMENTS

Supported in part by a Biomedical Research Grant, National Institutes of Health.

The authors acknowledge the technical assistance of Mr. T. McDaniels throughout the design, construction, and modification of the calorimeter.

R. G. Hollenbeck is an American Foundation for Pharmaceutical Education Fellow.

Glass Formation in Barbiturates and Solid Dispersion Systems of Barbiturates with Citric Acid

M. P. SUMMERS

Received September 19, 1977, from the *Department of Pharmaceutics, School of Pharmacy, University of London, London WC1N 1AX, England.* Accepted for publication March 13, 1978.

Abstract □ Glasses were prepared from a number of barbiturates. The viscosities and glass transition temperatures of the glasses were dependent on the structure of the groups present on the C-5 and N-1 atoms. Solid dispersions were prepared from three selected barbiturates formulated with citric acid. The glass transition temperatures of these systems indicated that a 1:1 molar ratio complex was formed between the two components and that intermolecular bonding was stronger in the complex than in the individual components.

Keyphrases □ Barbiturates, various—glass formation and solid dispersion systems evaluated □ Glass formation—various barbiturates evaluated □ Solid dispersion systems—various barbiturates evaluated □ Central depressants—various barbiturates, glass formation and solid dispersion systems evaluated

The use of citric acid as a glass-forming carrier in solid dispersions was studied previously (1–3). Although the dissolution rate of primidone formulated in such a system was faster than that of the pure drug, the glassy phase of this system was unstable and studies had to be performed on the devitrified solid (2).

To study the full potential of a glass system for improved drug dissolution, it is necessary to find a system with a glass transition temperature well above room temperatures so that a hard, usable glass can be formed. It would probably be advantageous if the drug could exist as a glass, which may stabilize the glass formed by the carrier.

The purpose of the present work was to study glass formation in a series of barbiturates and the formation of binary glass systems with citric acid to find a system that complied with the suggested criteria.

EXPERIMENTAL

Preparation of Barbiturate Glasses and Solid Dispersion Systems—Glass formation was studied in the following barbiturates: barbital[1], mephobarbital[2], phenylmethylbarbituric acid[3], pentobarbital[2], hexobarbital[4], phenobarbital[5], heptabarbital[6], butethal[3], amobarbital[3], ethylpropylbarbituric acid, cyclobarbital, and 5-ethyl-5-cycloheptenyl-1-methylbarbituric acid[6].

[1] BDH Chemicals Ltd., Poole, England.
[2] Siegfried, Zofingen, Switzerland.
[3] May and Baker Ltd., Dagenham, England.
[4] Sigma Chemical Co., St. Louis, Mo.
[5] Macarthys, Romford, England.
[6] Geigy Pharmaceuticals, Macclesfield, England.

0022-3549/78/1100-1606$01.00/0

Table I—Properties of the Barbiturate Series

Barbiturate	C-5 Groups	N-1 Group	Melting Point	Glass Transition Temperature (°C)	Glass Transition Temperature (°K) / Melting Point (°K)	Heat of Fusion, ΔH_f, cal/mole	Entropy of Fusion, ΔS_f, cal/mole/K	Solubility, g/liter	−Log Ideal Solubility
Cyclobarbital	Ethyl, cyclohexenyl	Hydrogen	163.0°	41.5	0.721	2025	4.64	430	0.4953
Phenobarbital	Ethyl, phenyl	Hydrogen	177.0°	40.5	0.697	6058	13.46	228.5	1.5762
Heptabarbital	Ethyl, cycloheptenyl	Hydrogen	176.5°	32.0	0.678	7288	16.23	50	1.8924
Phenylmethylbarbituric acid	Methyl, phenyl	Hydrogen	226.0°	—[a]	—	6594	13.21	48.0	—
Hexobarbital	Methyl, cyclohexenyl	Methyl	145.5°	9	0.674	5309	12.70	29.5	1.1874
5-Ethyl-5-cycloheptenyl-1-methylbarbituric acid	Ethyl, cycloheptenyl	Methyl	100.0°	7	0.751	5549	14.88	125	0.3655
Mephobarbital	Ethyl, phenyl	Methyl	181.3°	−3	0.594	9034	19.90	7.7	2.3921
Butethal	Ethyl, butyl	Hydrogen	126.0°	5	0.697	3630	9.1	612.5	0.7202
Pentobarbital	Ethyl, 1-methylbutyl	Hydrogen	132.0°	4	0.683	4919	12.15	300	1.1939
Amobarbital	Ethyl, isopentyl	Hydrogen	160.0°	−4	0.621	5297	12.23	275	1.2774
Ethylpropylbarbituric acid	Ethyl, propyl	Hydrogen	150.5°	—[a]	—	4340	10.25	300	—
Barbital	Diethyl	Hydrogen	188.5°	—[a]	—	5710[b]	12.37	180	—

[a] Crystallization of melt occurred. [b] Includes ΔH of polymorphic transition that occurred on heating.

Cyclobarbital was prepared from the calcium salt[3] by boiling with acidified water followed by extraction of the free barbiturate from the aqueous phase with ether[7]. After evaporation of the ether phase, the crystals were purified by recrystallization from 70% alcohol–water.

Glass formation was investigated by gently melting barbiturate samples in small Pyrex tubes and pouring the melt into glass petri dishes. A barbiturate was considered to be a glass former if the melt did not crystallize at room temperature or when quenched in liquid nitrogen.

Solid dispersion systems of citric acid monohydrate[7] and the selected barbiturates were prepared as described previously (2) using concentrations of citric acid from 10 to 90% (w/w).

Melting Points, Glass Transition Temperatures, and Heats of Fusion—The melting points of the original samples were determined[8] as outlined previously (2), but the samples were not sieved before the determination. The glass transition temperatures of the barbiturate glasses and solid dispersion systems were determined[8] as described previously (3).

Heats of fusion were measured by determining[8] the area under the fusion peak of a known weight of each barbiturate and comparing it to the area under the fusion peak of a known weight of metal standard. Indium[9] (heat of fusion, ΔH_f, 781 cal/g mole) was used as the standard metal, and the same operating conditions of the differential scanning calorimeter were used for both barbiturate samples and reference metal. The areas under the peaks were determined by weighing the peaks after cutting them from chart paper equilibrated for 24 hr at room temperature. The heat of fusion of the barbiturate could then be found using the formula:

$$\Delta H_f(\text{barbiturate}) = \frac{\Delta H_f(\text{standard}) \times \text{weight of standard} \times \text{peak weight of barbiturate} \times \text{molecular weight of barbiturate}}{\text{weight of barbiturate} \times \text{peak weight of standard} \times \text{molecular weight of standard}} \text{ cal/mole} \quad \text{(Eq. 1)}$$

Three determinations were performed for each sample, and the mean value was calculated.

Solubility Determination—Solubilities were determined by equilibrating suspensions of the barbiturates in methanol[7] at 20° on a shaking water bath for 24 hr. Then 1-ml samples were withdrawn using a pipet fitted with a grade 3 sintered-glass filter stick, and the samples were diluted to suitable concentrations before assay. Replicate determinations were performed for each barbiturate.

The solutions were assayed using a UV spectrophotometer[10], and the concentrations of the solutions were calculated from a previously constructed calibration curve.

X-Ray Diffraction—X-ray diffraction[11] was used to assess the amorphous nature of those dispersions and barbiturate glasses that could be tested before they devitrified.

[7] Analar grade, BDH Chemicals Ltd., Poole, England.
[8] Using a differential scanning calorimeter 1B, Perkin-Elmer, Beaconsfield, Bucks, England.
[9] Koch Light Laboratories, Colnebrook, Bucks, England.
[10] SP 1800, Pye Unicam, Cambridge, England.
[11] Nonius Mk 2 self-focusing Guinier diffractometer.

RESULTS AND DISCUSSION

Table I shows the melting points (T_m) and glass transition temperatures (T_g) of the barbiturates studied.

Many barbiturates are capable of glass formation, and glass transition temperatures varied throughout the series. Low molecular weight compounds have the same viscosity at the glass transition temperature (4); above this temperature, their viscosity decreases as the temperature increases. Barbiturates with a glass transition temperature below ambient temperature are viscous liquids at this temperature, so only barbiturates having a glass transition temperature well above ambient temperature can be considered to be rigid glasses. Thus, phenobarbital, cyclobarbital, and heptabarbital are the only compounds in this category. However, the heptabarbital glass was relatively unstable when prepared in a large batch and showed evidence of devitrification (as shown by X-ray diffraction) after a few hours at room temperature. Phenobarbital and cyclobarbital glasses were more stable and remained amorphous for longer than 24 hr.

Although a full understanding of the reasons for glass formation has not been achieved (5), an attempt was made to elucidate the reasons for the difference in the glass transition temperature of the barbiturates. Two general types of glass-forming systems have been studied extensively: the inorganic glasses such as silicon dioxide glass and organic polymer glasses such as polystyrene. Different criteria for glass formation have been developed for both types; although some similarities exist, the two systems are generally different. The barbiturates probably more closely resemble the polymer glasses, although their low molecular weight may result in some differences.

The main factors affecting the glass transition temperature of the high molecular weight polymers are molecular chain stiffness, intermolecular forces, and molecular geometry (4). The glass transition temperature increases as the first two factors increase. Many attempts have been made to correlate the glass transition temperature with the melting point since the same factors affect both transitions. Lee and Knight (6), however, showed that no simple relationship exists between glass transition and melting point because of the fundamental differences between the crystal–liquid (T_m) and glass–liquid (T_g) transitions. Nevertheless, a plot of glass transition temperature against melting point has been useful to divide polymers into two groups, "sterically restricted" and "sterically nonrestricted" polymers (4), with the former having higher ratios of glass transition temperature to melting point.

The values of the ratio of glass transition temperature to melting point given in Table I appear to have little correlation, as does the relationship between glass transition temperature and melting point shown in Fig. 1. Amobarbital and mephobarbital were the only melts that required

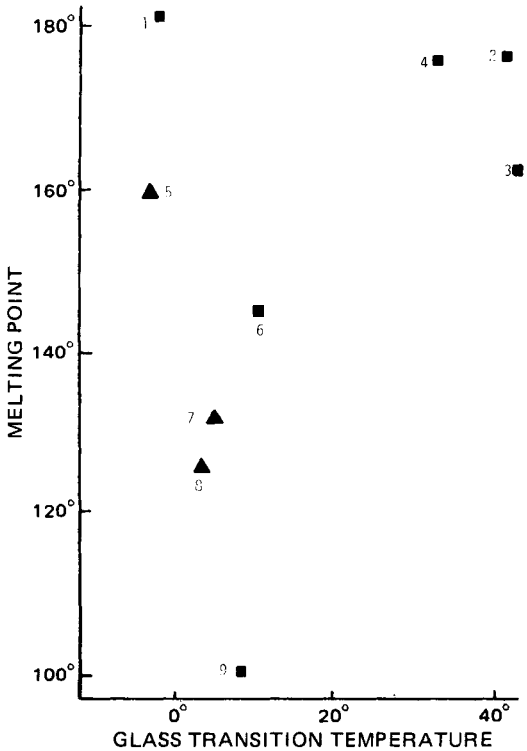

Figure 1—*Relationship between melting point and glass transition temperature. Key: 1, mephobarbital; 2, phenobarbital; 3, cyclobarbital; 4, heptabarbital; 5, amobarbital; 6, hexobarbital; 7, pentobarbital; 8, butethal; and 9, 5-ethyl-5-cycloheptenyl-1-methylbarbituric acid.*

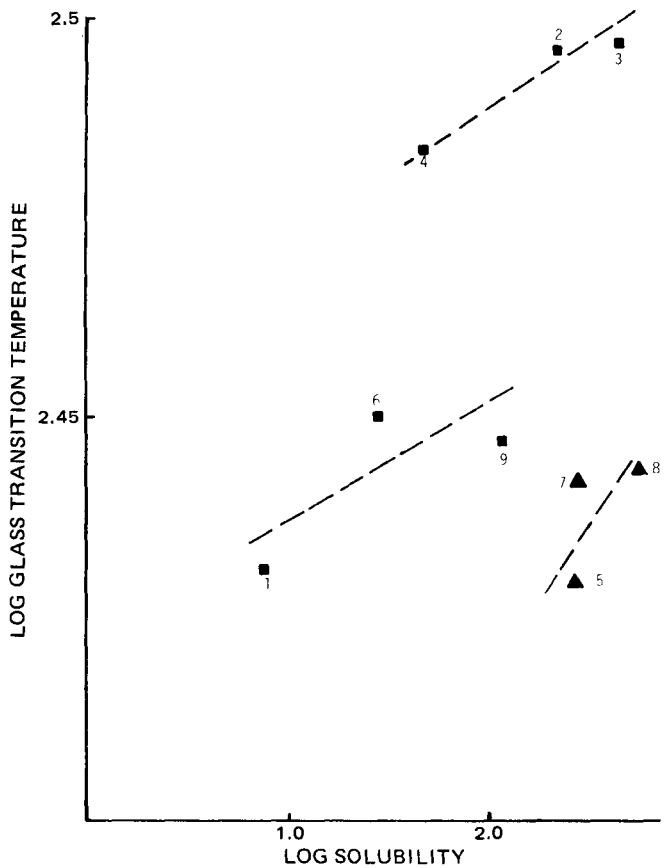

Figure 2—*Relationship between log solubility and log glass transition temperature. Key: same as Fig. 1.*

cooling in liquid nitrogen to form glasses, and they showed the lowest ratios of glass transition temperature to melting point. Therefore, Fig. 1 may separate the barbiturates into a main group of compounds that formed glasses with relative ease and the two that had to be quenched in liquid nitrogen. There do not appear to be any structural features, however, to separate these compounds from the others.

The substitution of different groups in the 5-position affects the polarity of the molecule. Since this factor may affect intermolecular bonding and, thus, affect the glass transition temperature, a correlation was attempted between glass transition temperature and solubility in an alcohol of short alkyl chain length.

The solubilities of barbiturates in methanol are given in Table I, and Fig. 2 shows log glass transition temperature plotted against log solubility. Plotted in this manner, the barbiturate series is divided into two or three groups. For reasons that will be evident later, it is convenient to divide the data into three groups: (*a*) barbiturates with a ring substituent on C-5, (*b*) barbiturates with a ring substituent on C-5 and a group other than hydrogen on N-1, and (*c*) barbiturates with alkyl substituents on C-5.

A similar relationship exists between log ideal solubility (as shown in Table I) and log glass transition temperature. The use of the ideal solubility removes any effect on the measured solubility of the crystal lattice energy that will oppose the solution process.

The ideal mole fraction solubility can be calculated from:

$$\log \text{ideal solubility} = \frac{-\Delta H_f}{2.303R}\left(\frac{T_m - T}{T_m T}\right) \qquad \text{(Eq. 2)}$$

where R is the gas constant and T (°K) is the temperature of solubility measurement.

Within each group, both sets of data are the converse of the partition coefficients (octanol–water) determined and calculated by Hansch and Anderson (7). Since these partition coefficients are considered to increase as the barbiturate polarity decreases, the methanol solubilities increase as the polarity increases.

The solubilities of barbiturates in Groups *a* and *c* are very similar, although the glass transition temperatures of compounds in Group *a* are much greater than those in Group *c*. This result is probably due to the ring substituent on C-5, which hinders molecular flow so that the glass–liquid transition occurs at a higher temperature. Differences within a group may be due to differences in intermolecular bonding, with those of higher glass transition temperature being more polar (having greater methanol solubility) and having greater molecular bonding. Molecular bond strength is important for the same reasons as the size of group substituents. If the size of the ring substituent is the only determining factor, one would expect that heptabarbital would have a greater glass transition temperature than cyclobarbital; therefore, both C-5 substituents and intermolecular bonding are important, the glass transition temperature being determined by a balance of these two effects.

The third group (*b*) contains the barbiturates with a C-5 ring and an N-1 methyl group. The N-1 substituent replaces a hydrogen and thus reduces hydrogen bonding, which, in turn, reduces intermolecular attraction and glass transition temperature. 5-Ethyl-5-cycloheptenyl-1-methylbarbituric acid deviates from the general trend in Fig. 2, having a relatively low glass transition temperature. The reason for this deviation is unknown. These results are consistent with the self-association constants of barbiturates calculated by Kyogoku *et al.* (8). Phenobarbital and pentobarbital had similar self-association constants (8.1 and 7.0 M^{-1}, respectively) but those for the N-1-substituted barbiturates were very much lower.

For three barbiturates in Table I, glass transition temperatures could not be obtained. Probably with barbital and ethylpropylbarbituric acid, the groups on the 5-position were not bulky enough to hinder free molecular movement when the melt was cooled, so crystallization took place. The intermolecular attraction of phenylmethylbarbituric acid molecules was probably insufficient to cause glass formation, despite the large group on the 5-position. High bonding in the melt prevents crystallization because these bonds have to be broken to reorganize the molecules into the lattice.

The thermodynamics of glass formation were discussed by Pye (5), and these aspects can be applied to the barbiturate systems. The heat of fusion (ΔH_f) and entropy of fusion (ΔS_f) are given in Table I; ΔS_f was calculated from:

$$\Delta S_f = \frac{\Delta H_f}{T_m \text{ (°K)}} \qquad \text{(Eq. 3)}$$

When the barbiturate series is divided into the three groups previously discussed, a general trend is evident; as the glass transition temperature

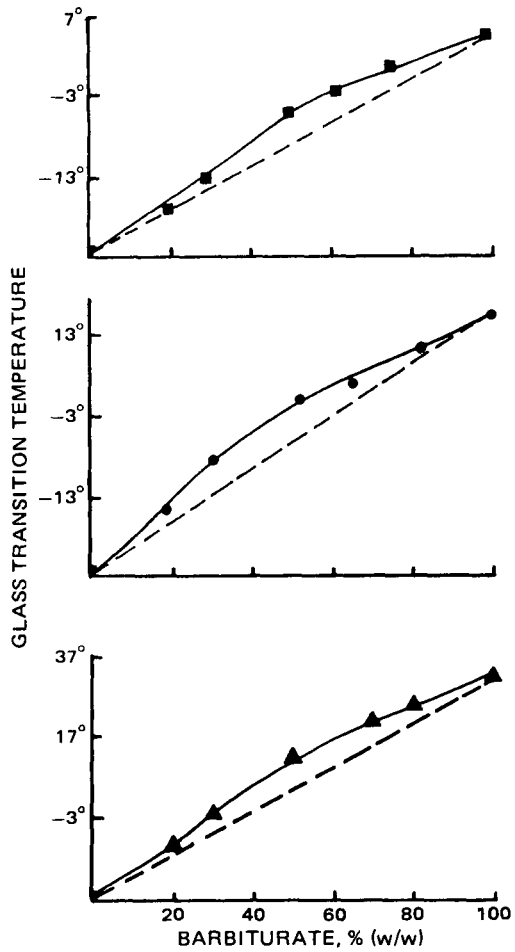

Figure 3—*Variation in glass transition temperature with barbiturate concentration. Key: ---, theoretical relationship; —, observed relationship; ■, pentobarbital; ●, hexobarbital; and ▲, heptabarbital.*

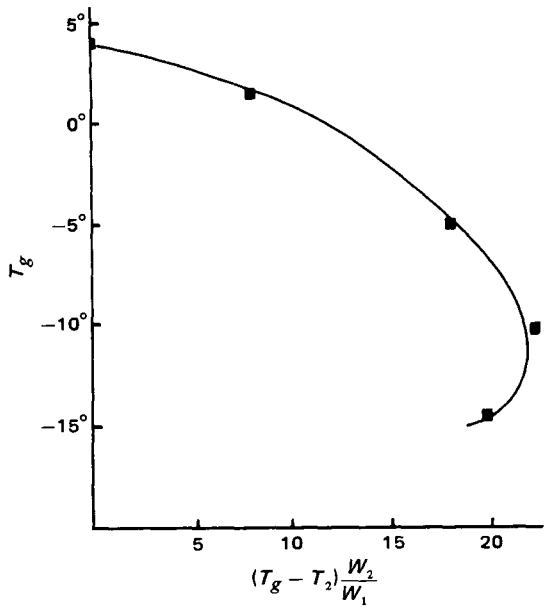

Figure 4—*Deviation of pentobarbital solid dispersion systems from the Gordon and Taylor equation.*

within the group decreases, ΔH_f, ΔS_f, and the melting point increase. It might be expected that ΔS_f would decrease as the glass-forming tendency decreases, since large structural differences between the melt and the crystal would be expected to hinder crystallization. This behavior apparently does not occur. In this respect, the system resembles silicon dioxide, which shows little structural difference between the melt and the crystal (ΔS_f 0.7 cal/K/mole).

The increase in ΔH_f as the glass-forming tendency decreases is consistent with the hypothesis that large energy differences between the crystal and the melt cause unstable supercooling. Thus, the crystalline phase is thermodynamically more favored as ΔH_f increases and the melt is more prone to crystallization. Amobarbital and mephobarbital required rapid quenching to prevent crystallization; within their respective groups, they had the largest ΔH_f values.

Within the barbiturate series as a whole, however, there was little correlation among ΔH_f, ΔS_f, and the glass transition temperature. This result is in general agreement with the observation of Pye (5), who suggested that there is no correlation between thermodynamic parameters and the glass-forming tendency when a large number of glass-forming materials is studied. Furthermore, the similarity of the thermodynamic parameters of materials with different glass transition temperatures and glass-forming tendencies suggests that the structural features previously outlined are more important in determining the ease of glass formation.

Attempts to investigate the structure of the glasses were unsuccessful because of their instability. Even the hard and relatively stable systems devitrified on grinding.

Solid Dispersions of Citric Acid and Barbiturates—An initial study was conducted, using citric acid solid dispersions, to investigate the possibility of producing stable glassy dispersions containing barbiturates of a low glass transition temperature. Summers and Enever (3) showed that the glass transition temperature of solid dispersions may be greater than the expected glass transition temperature of the system based on the additivity principle inherent in the Gordon and Taylor (9) treatment of the glass transition temperature of copolymers. Illers (10) showed that the glass transition temperature of a copolymer system of vinylidene chloride and methyl acrylate can rise well above the glass transition temperature of either pure component. Therefore, it may be possible to produce solid dispersions having glass transition temperatures above ambient temperature but containing barbiturates of a low glass transition temperature.

Hexobarbital, heptabarbital, and pentobarbital were studied. Figure 3 shows the variation in the glass transition temperature with composition for these solid dispersion systems. All three compounds showed similar behavior when fused with citric acid, the glass transition temperature of the mixed glass rising and falling from the glass transition temperature of citric acid to that of the barbiturate. There was little effect at low concentrations of either component, and the effect was most marked at concentrations around 50% (w/w) of the barbiturate. None of these systems complied with the Gordon and Taylor (9) equation and thus resembled the citric acid–primidone system previously described (3). This equation:

$$T_g = -k(T_g - T_2)\frac{W_2}{W_1} + T_1 \qquad \text{(Eq. 4)}$$

predicts a linear relationship between the glass transition temperature of the mixture (T_g) and $(T_g - T_2)(W_2/W_1)$, where T_2 is the glass transition temperature of the second component, W_2 is its weight fraction in the mixture, and T_1 and W_1 are the glass transition temperature and weight fraction of the first component, respectively. Figure 4 shows the pentobarbital–citric acid system plotted in this manner to illustrate the deviation.

The increase in the glass transition temperature shown in Fig. 3 and the deviation from the Gordon and Taylor equation indicate that the strength of the interaction between the two components is stronger than the arithmetic mean of the bond strengths of the individual components (3). This situation could arise because of the formation of very strong bonds between the components, the formation of a greater number of bonds in the mixture than between the individual components, and some steric factors such as the restriction of movement of part of one molecule because of the presence of the second molecule.

Kyogoku *et al.* (8) showed that the interaction between barbiturates and 9-ethyladenine was stronger than that between the individual components, the association constants of the complexes being approximately 10 times greater than the self-association constants of the barbiturates. The different proton-donating properties of the individual components were responsible for the formation of stronger bonds, and a greater number of hydrogen bonds formed in the complex. The solid dispersion systems of this work show similar properties.

With 9-ethyladenine, the barbiturates formed dimers in solution (8).

A 1:1 mole ratio complex also was formed between 9-ethyladenine and barbital in the solid state (11), but a continuous chain of molecules was formed in this case. The formation of strongly bonded dimers or chains of molecules would increase the glass transition temperature of the barbiturate–citric acid glass, and evidence of a 1:1 molecular reaction is found in the presence of the glass transition temperature maximum, which occurs at approximately 50 mole % [51.8% (w/w) pentobarbital, 52.9% (w/w) hexobarbital, and 54.4% (w/w) heptabarbital, respectively]. At this concentration, each barbiturate molecule is complexed with one citric acid molecule. Therefore, the interaction and the deviation of the glass transition temperature are greater.

X-ray diffraction could not be used to investigate complex formation because the glass phase was amorphous. The devitrified glasses were simple eutectic mixtures, which suggested that crystallization involved the breakage of citric acid–barbiturate bonds to produce crystals of the pure components. Therefore, the X-ray diffraction patterns of the devitrified systems could not help to elucidate the structures of the complexes.

The increase in the glass transition temperature in these three dispersions was not great and did not exceed the glass transition temperature of the pure barbiturate. It may be possible to increase the glass transition temperature further by selecting other glass-forming compounds as carriers or formulating three-component glass systems. By selection of suitable barbiturates, glassy dispersions can be prepared for further studies to test the feasibility of the glass phase as a solid dispersion system. Work is continuing on this aspect.

Conclusions—Many barbiturates will form glasses when fused; the viscosity and glass transition temperature of the glass vary with the molecular configuration of the barbiturate molecule. The position of the glass transition temperature within the barbiturate series can be rationalized in terms of the intermolecular bonding in the glass and the restriction of molecular movement imposed by substituents in the C-5 position. Substituting a methyl group for hydrogen on the N-1 position reduces intermolecular hydrogen bonding and results in a relatively low glass transition temperature.

When fused with citric acid, heptabarbital, hexobarbital, and pentobarbital form binary glasses. The glass transition temperatures of these systems do not show a linear increase with composition but attain a maximum at approximately 50% (w/w) of the barbiturate. This deviation is consistent with the formation of a 1:1 mole ratio complex between the two components; it is postulated that there is a greater number of hydrogen bonds in the complex, probably of greater strength, than in glasses of the individual components.

REFERENCES

(1) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **58**, 1505 (1969).
(2) M. P. Summers and R. P. Enever, *ibid.*, **65**, 1613 (1976).
(3) *Ibid.*, **66**, 825 (1977).
(4) R. F. Boyer, *Rubber Chem. Technol.*, **36**, 1303 (1963).
(5) L. D. Pye, in "Introduction to Glass Science," L. D. Pye, H. J. Stevens, and W. C. La Course, Eds., Plenum, New York, N.Y., 1972.
(6) W. A. Lee and G. J. Knight, *Br. Polym. J.*, **2**, 73 (1970).
(7) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).
(8) Y. Kyogoku, R. C. Lord, and A. Rich, *Nature*, **218**, 69 (1968).
(9) M. Gordon and J. S. Taylor, *J. Appl. Chem.*, **2**, 493 (1952).
(10) K. H. Illers, *Kolloid-Z.*, **190**, 16 (1963).
(11) D. Voet, *J. Am. Chem. Soc.*, **94**, 8213 (1972).

ACKNOWLEDGMENTS

The author thanks Dr. R. J. Gilbert (School of Pharmacy) and the following companies for barbiturate samples: Siegfried (Switzerland), May and Baker Ltd. (England), and Geigy Pharmaceuticals (England). Thanks are also due to W. Dissanayake for technical assistance.

Improved Spectrophotometric Determination of Antazoline

NABIL M. OMAR

Received January 12, 1978, from the *Department of Pharmaceutical Chemistry, University of Assiut, Assiut, Egypt.* Accepted for publication March 21, 1978.

Abstract □ A simple, precise, and accurate spectrophotometric determination of antazoline salts was developed by improving the ceric sulfate procedure. Replacement of water with acetic acid for the preparation of all assay solutions permitted reproducible measurements of the chromogen that absorbed at 505 nm. An appreciable increase in color stability was attained by the controlled addition of perchloric acid to the ceric reagent prior to interaction with antazoline at room temperature. Evidence is provided to account for the oxidation of antazoline at the expense of a complex ceric species. Other 2-imidazolines or phenylephrine did not interfere with the investigated color reaction. In addition to the high value of the chromogen molar absorptivity, ideal adherence of color absorption to Beer's law permitted accurate and reproducible estimation of antazoline over the 1–10-μg range. The procedure was applied to the analysis of different antazoline dosage forms.

Keyphrases □ Antazoline—spectrophotometric analysis in prepared solutions and dosage forms □ Spectrophotometry—analysis, antazoline in prepared solutions and dosage forms □ Antihistaminics—antazoline, spectrophotometric analysis in prepared solutions and dosage forms

The frequent formulation of antazoline[1], 2-[(*N*-phenyl)benzylaminomethyl]-2-imidazoline, with other pharmaceutical amines and 2-imidazoline congeners motivated the development of a selective determination of this antihistamine.

BACKGROUND

Previous antazoline analyses primarily were based on spectrophotometry (1–8). Of the diverse chromogenic reagents adopted, only the sodium nitrite (5–7) and ceric sulfate procedures showed pronounced selectivity. The well-documented and popular ammonium reineckate (1, 2), sodium nitroprusside (3), and dipicrylamine (4) methods are not specific; other pharmaceutical amines and 2-imidazoline derivatives, likely to be present along with antazoline, interfere (9). Moreover, the nitroprusside method, while apparently specific for the intact imidazoline ring, is affected by the experimental buffer concentration and species, the age of reagents, and the intrinsic color of the sample (10).

The utility of the nitrite method is handicapped by interference of phenylephrine with color production (6), and the accuracy of the ceric sulfate procedure is questionable. Discrepancies in recovery studies attained by this latter method reveal considerable nonreproducibility, especially when compared to the nitrite procedure (11). In addition, no quantitative data could be supplied when the ceric reagent was not properly cooled prior to interaction with antazoline or when much water was present. These findings attest to the thermolabile nature of the antazoline–ceric chromogen as well as to its marked sensitivity to pH variations.

Such shortcomings in the available methods for the estimation of an-

[1] Antistine.

0022-3549/78/1100-1610$01.00/0