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Browning of Dextrates in Solid–Solid Mixtures Containing Dextroamphetamine Sulfate

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Abstract □ By using diffuse reflectance spectroscopy, the ethanol-mediated interaction between dextroamphetamine sulfate and dextrates in solid–solid mixtures was studied. Discoloration of the powder mixtures was accelerated by the presence of the amine and by storage at elevated temperatures. Heated samples showed two new absorption maxima at 330 and 300 nm in their reflectance spectra. The former was attributed to the chemisorption of the amine molecules on the surface of the dextrates, while the latter was attributed to the interaction between amine molecules and the dextrates. The rate of browning was determined by plotting remission function *versus* time at 300 nm for mixtures of dextroamphetamine sulfate and dextrates at three temperatures and two dextroamphetamine sulfate concentrations. Arrhenius-type plots were used to approximate the browning rate at 25°. The browning rate was considerably slower than that reported for solid–solid mixtures containing dextroamphetamine sulfate and spray-dried lactose USP.

Keyphrases □ Dextrates—browning in solid–solid mixtures containing dextroamphetamine sulfate, rate and variables □ Dextroamphetamine sulfate–dextrates—solid–solid mixtures, rate of browning, effects of temperature and concentration □ Discoloration—*dextrates–dextroamphetamine sulfate solid–solid mixtures*, rate of browning, effects of temperature and concentration □ Diffuse reflectance spectroscopy—monitoring rate of browning of dextrates–dextroamphetamine sulfate mixtures

Dextrates is dextrose prepared by the controlled hydrolysis of starch in combination with a special manufacturing process that yields spherical, porous beadlets[1]. It is composed of approximately 92% dextrose and 8% higher saccharides. The material is white, free flowing, and odorless and consists of aggregates of dextrose microcrystals intermixed and cohered with a small proportion of higher saccharides. The structure and dissolution characteristics of dextrates are unique when compared to those of dextrose USP and sucrose. Its absolute solubility is greater than that of dextrose USP but less than that of sucrose, yet its rate of solution is low when compared to dextrose USP and sucrose.

Henderson and Bruno (1) evaluated dextrates as an excipient in direct compression tablet production. It was concluded that dextrates and lactose[2] USP (beadlets) were superior to spray-dried lactose and lactose USP (anhydrous) for use as filler in direct compression. Both exhibited excellent flow characteristics, and dextrates showed improved compression and disintegration properties while lactose USP (beadlets) possessed greater physical stability.

A number of workers (2–4) reported that tablets prepared using lactose as a filler tend to discolor on storage. This phenomenon was accelerated by the presence of amines and/or certain lubricants and was dependent on the temperature, humidity, and light exposure at which the tablets were stored. With regard to color stability, tablets prepared with dextrates and stored at different temperatures and

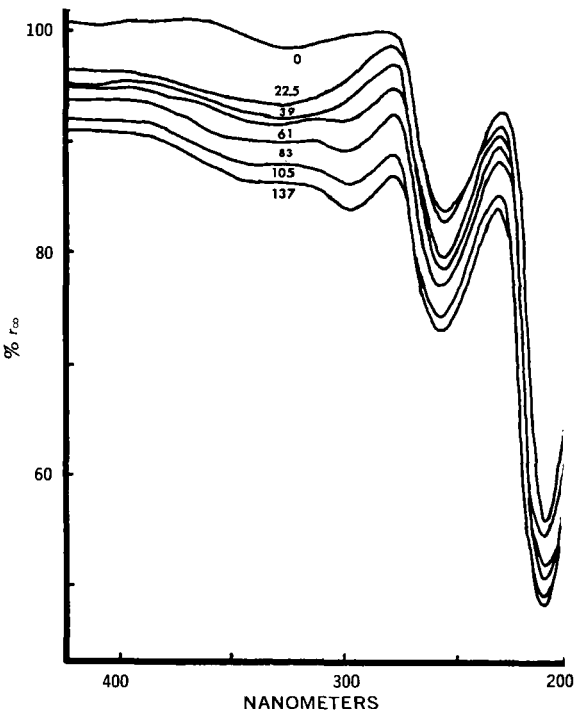

Figure 1—*Diffuse reflectance spectra of an equilibrated sample containing 10 mg of dextroamphetamine sulfate/g of dextrates after heating at 55° for various time periods (shown in hours).*

[1] Celutab, Penick and Ford Ltd., Cedar Rapids, Iowa.

[2] Foremost Dairies Inc., San Francisco, Calif.

Table I—Relationship between Reflectance Values and Time for an Equilibrated Mixture of Dextroamphetamine Sulfate and Dextrates after Heating at 60°

Hours at 60°	Reflectance, %/100			
	10 mg Dextroamphetamine Sulfate/g Dextrates		15 mg Dextroamphetamine Sulfate/g Dextrates	
	$r_\infty 300$	$f(r_\infty)300$	$r_\infty 300$	$f(r_\infty)300$
0	0.995	0	0.995	0
21.3	0.895	0.0062	0.860	0.0114
37.5	0.882	0.0079	0.840	0.0152
59.0	0.873	0.0092	0.825	0.0186
80.5	0.857	0.0120	0.795	0.0264
106.5	0.830	0.0174	0.780	0.0310
144.0	0.800	0.0250	0.745	0.0436

humidities showed no substantial improvement over those prepared with spray-dried lactose (1).

Blaug and Huang (5) studied the interaction of dextroamphetamine sulfate and spray-dried lactose in solid–solid mixtures using diffuse reflectance spectroscopy. Discoloration of the powder mixtures was accelerated by the presence of the amine and by storage at elevated temperatures. The brown material from the discolored samples was identified as dextroamphetamine–hydroxymethylfurfural. Blaug and Huang (6) also studied the interaction of dextroamphetamine sulfate with dextrates in solution. By using TLC, IR spectroscopy, and elemental analysis, the brown material isolated from the discolored solutions was also identified as amphetamine–hydroxymethylfurfural.

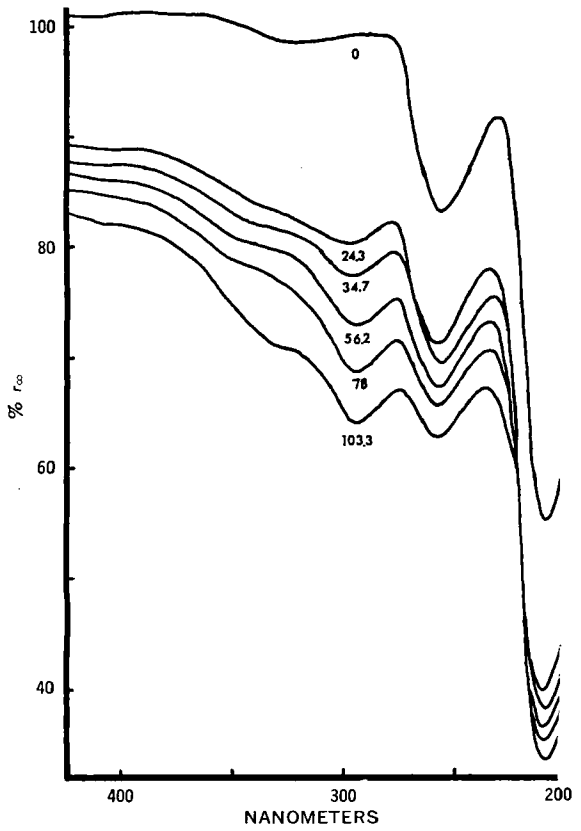

Figure 2—*Diffuse reflectance spectra of an equilibrated sample containing 10 mg of dextroamphetamine sulfate/g of dextrates after heating at 65° for various time periods (shown in hours).*

Table II—Relationship between Reflectance Values and Time for an Equilibrated Mixture of Dextroamphetamine Sulfate and Dextrates after Heating at 65°

Hours at 65°	Reflectance, %/100			
	10 mg Dextroamphetamine Sulfate/g Dextrates		15 mg Dextroamphetamine Sulfate/g Dextrates	
	$r_\infty 300$	$f(r_\infty)300$	$r_\infty 300$	$f(r_\infty)300$
0	0.0995	0	0.995	0
24.3	0.802	0.0244	0.700	0.0643
34.7	0.776	0.0323	0.695	0.0669
56.2	0.731	0.0495	0.670	0.0813
78.0	0.690	0.0696	0.646	0.0970
103.3	0.640	0.1013	0.613	0.1222

This study was undertaken to investigate and quantify the color reaction reported (1) to occur in tablets prepared using dextrates as a filler. A similar color reaction has been reported (4) in tablets prepared from dextrose. Since the discoloration is accelerated by the presence of amines, dextroamphetamine sulfate was used. Diffuse reflectance spectroscopy was used to study the interaction of dextrates with dextroamphetamine sulfate in the solid state.

EXPERIMENTAL[3]

Reagents—The following were used: dextroamphetamine sulfate[4] USP, mp >300°; and dextrates, mp 150–152°.

Procedure—*Preparation of Equilibrated Samples*—Forty- and sixty-milligram samples of dextroamphetamine sulfate were accurately weighed and transferred to 90-ml (3-oz) amber glass bottles. Sufficient absolute alcohol was added to dissolve the drug. Then 4 g of dextrates was accurately weighed and added to each solution. The bottles were sealed with screw caps lined with aluminum foil and attached to the submersion rotator. For reference use, a similar bottle was prepared containing 6 g of dextrates and the same amount of absolute alcohol used to prepare the sample bottle. The reference bottle was sealed and attached to the submersion rotator. The sample and reference bottles were tumbled for 24 hr at 25°. At the end of this time, the bottles were removed from the rotator and placed in the vacuum oven where the solvent was removed at room temperature using a vacuum pump to provide the vacuum. After drying, the contents of each bottle were triturated in a glass mortar to provide a uniform sample. All samples were stored in a calcium sulfate-charged vacuum desiccator for diffuse reflectance study.

Reflectance Measurement—The prepared samples and reference adjuvant (dextrates) were packed into the sample and reference cells previously described (7–10). Since it has been reported (11) that the quantity of material in the cell and the pressure used during the process of packing can cause fluctuations in reflectance values, care was taken to maintain the same conditions for every sample packed. After the initial reflectance spectra were recorded, each sample and reference adjuvant were placed in a constant-temperature oven maintained at 55, 60, and 65 ± 0.5°. At periodic time intervals, a sample and reference adjuvant were removed from the oven and allowed to cool to room temperature in a vacuum oven containing calcium sulfate. After cooling to room temper-

[3] All diffuse reflectance spectra were measured using a Beckman model DB-G spectrophotometer with reflectance attachment. The spectra were automatically recorded on a Beckman model 1005 25.4-cm (10-in.) linear potentiometric recorder. A Sargent analytical oven, low gradient, and a Precision Scientific model 524 vacuum oven were used for storing and drying samples. Drug–adjuvant samples were equilibrated using a submersion rotator, model SR-250-V (Scientific Industries, Inc., Queen Village, N.Y.), to tumble the powders.

[4] Hexagon Laboratories, Inc., New York, N.Y.

Table III—Relationship between Reflectance Values and Time for an Equilibrated Mixture Containing 15 mg of Dextroamphetamine Sulfate/g of Dextrates after Heating at 60°

Hours at 60°	Reflectance, %/100				
	$r_\infty 300$	$f(r_\infty)300$	$r_\infty 330$	$f(r_\infty)330$	$f(r_\infty)300/f(r_\infty)330$
0	0.995	0.0000	0.986	0.0001	0.100
21.3	0.860	0.0114	0.842	0.0148	0.769
37.3	0.840	0.0152	0.838	0.0157	0.973
59.0	0.825	0.0186	0.825	0.0186	1.000
80.5	0.795	0.0264	0.801	0.0247	1.069
106.5	0.780	0.0310	0.790	0.0279	1.112
144.0	0.745	0.0436	0.762	0.0372	1.174

ature, additional reflectance spectra were recorded by scanning from 700 down to 200 nm.

RESULTS AND DISCUSSION

Figures 1 and 2 indicate absorption maxima at 215 and 257 nm, which correspond to the absorption maxima obtained in the dextroamphetamine sulfate–spray-dried lactose interaction previously reported (5). The band at 257 nm is the characteristic band of dextroamphetamine sulfate in solution as well as in the solid state. The two bands were attributed to the physical adsorption of the dextroamphetamine sulfate molecules by the lactose or dextrates.

However, the equilibrated samples of dextroamphetamine sulfate and dextrates that had been heated showed two new absorption maxima, one at 330 nm and one at 300 nm. Browning of the samples occurred, particularly in the samples heated for long periods. As shown in Tables I and II, the intensity of the absorption maximum increased markedly at 300 nm with time, temperature, and dextroamphetamine sulfate concentration. This finding was analogous to the results previously reported (5, 6). The solid–solid interaction between dextroamphetamine sulfate and spray-dried lactose resulted in the appearance of a new absorption maximum at 295 nm and discoloration. In dextroamphetamine sulfate–dextrates solutions that had been heated for varying periods, a new absorption maximum appeared at 298 nm. The solutions became discolored, particularly those heated for long periods at elevated temperatures. In both studies the browning reaction was the result of a Schiff base-type reaction involving the amine and the carbonyl group of the sugars. The brown material from the discolored samples was identified as dextroamphetamine sulfate–hydroxymethylfurfural (5, 6).

Although the shoulder peak at 330 nm also increased in intensity with time and temperature, the rate of formation of the absorption maximum was faster at 300 than at 330 nm. Table III shows the reflectance values and remission functions at these two wavelengths for a mixture containing 15 mg of dextroamphetamine sulfate/g of dextrates that had been heated at 60° for varying periods. Table III also shows the ratio of remission function at 300 nm to remission function at 330 nm for each time period. A comparison of these values indicates that the rate of formation of the maximum at 300 nm was faster than it was at 330 nm. A plot of the remission function ratios *versus* time is shown in Fig. 3. From these data one can conclude that the rate of interaction between dextroamphetamine sulfate and dextrates was faster than the rate of chemisorption of dextroamphetamine sulfate. In other words, as soon as the drug was chemisorbed on the surface of the dextrates crystals, a Schiff base type of reaction occurred, leading to the formation of a new absorption maximum at 300 nm. Figure 3 shows that the curve gradually reached a plateau with time. Rideal and Trapnell (12) showed that there was no discontinuity between the end of chemisorption and the beginning of second layer formation. The end of first layer formation was continuous with the beginning of second layer formation. The formation of a second layer may be due either to a weak chemisorption or physical adsorption. The data in Table III and Fig. 3 indicate the formation of a weak second chemisorbed layer on the top of the first chemisorbed layer. This probably contributed to the increase in the intensity of the absorption at 330 nm with time, with a concomitant decrease in the rate of increase of the intensity of the band at 300 nm. Therefore, although the value of the ratio of $f(r_\infty)300/f(r_\infty)330$ increased with time, the increase became smaller, resulting in the plateau shown in Fig. 3. Browning did not occur until the appearance of the absorption band at 300 nm, and the intensity of the color increased with an increase in the intensity of absorption at 300 nm.

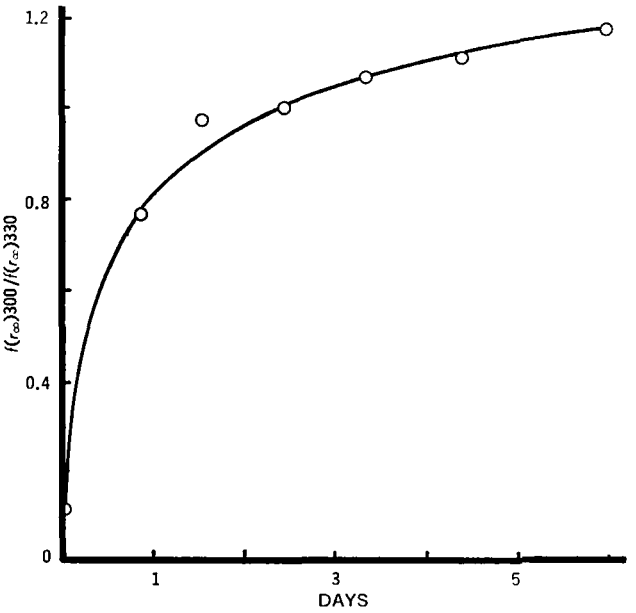

Figure 3—*Relationship between the remission function ratios at different wavelengths and time for an equilibrated sample containing 15 mg of dextroamphetamine sulfate/g of dextrates after heating at 60°.*

Since dextrates alone showed no browning, there was little doubt that the browning of the sample was due primarily to the interaction between the amine and the sugar on the chemisorbed surface, with the appearance of a new absorption peak at 300 nm. The latter wavelength corresponded to the new absorption peak at 298 nm in the heated solution containing dextroamphetamine sulfate and dextrates (6) and to the new peak at 295 nm in the equilibrated solid–solid mixtures of dextroamphetamine sulfate and spray-dried lactose (5).

The rate of the browning reaction was studied using the reflectance values obtained at 300 nm. The remission functions were calculated according to the Kubelka–Munk theory (13, 14). The results obtained at 60° are shown in Fig. 4. Critical examination of each curve showed that it consisted of two portions; in the first portion of the browning reaction, a hyperbolic curve was observed, whereas an almost linear relationship was obtained in the second

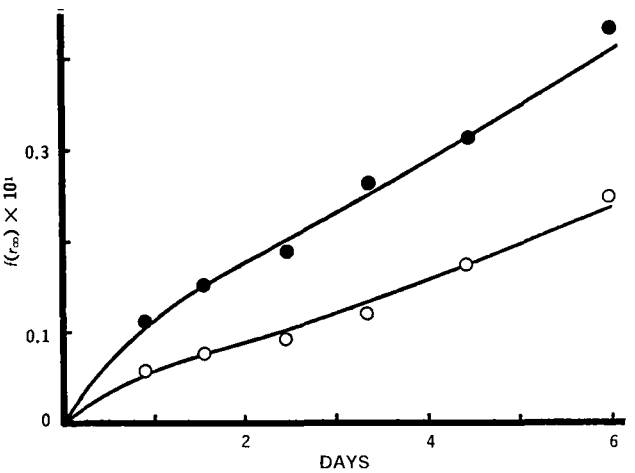

Figure 4—*Rate of browning of dextroamphetamine sulfate–dextrates equilibrated mixtures at 60°. Key: ●, 10 mg of dextroamphetamine sulfate/g of dextrates: and ○, 15 mg of dextroamphetamine sulfate/g of dextrates.*

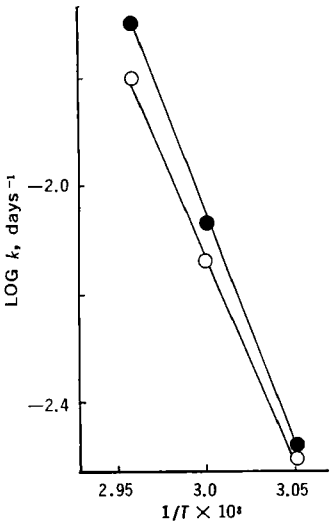

Figure 5—*Arrhenius-type plots showing the temperature dependence for the browning of dextroamphetamine sulfate–dextrates equilibrated mixtures. Key:* ●, *10 mg of dextroamphetamine sulfate/g of dextrates; and* ○, *15 mg of dextroamphetamine sulfate/g of dextrates.*

portion. The higher rate of browning in the initial stages may have been due to the liberation of small quantities of bound water from the dextrates, with the participation of the liberated water in the initial stages of the reaction due to the formation of a solution phase containing dextroamphetamine sulfate and dextrates molecules. Duvall *et al.* (3) reported that the rate of browning between dextroamphetamine sulfate and lactose was faster in solution than in the solid state, and Blaug and Huang (6) reported a high rate of browning in solutions containing dextrates and dextroamphetamine sulfate.

Figure 4 indicates that the rate of browning was faster in the samples that contained 15 mg of drug compared to the samples that contained 10 mg of drug. Similar results were obtained at 55 and 65°. Apparently, in the drug–dextrates mixtures the adjuvant surface was not saturated with dextroamphetamine sulfate molecules, so the surface coverage increased with increasing drug concentrations, resulting in a higher browning rate in the equilibrated mixtures containing 15 mg of drug as compared to those containing 10 mg.

Following the initial browning reaction (Fig. 4), a linear or almost linear relationship was obtained between remission function and time. Similar plots were obtained at 55 and 65°. From this relationship, the browning reaction may be assumed to follow an apparent zero-order reaction. Thus, the browning rate constants shown in Table IV were obtained from the slopes of the straight-line portions of the plots. Since the mechanism involved in the actual browning reaction was very complex, the apparent zero-order rate constants obtained do not have the usual kinetic significance. However, the rate constants do represent a total overall reaction rate that enables one to estimate the rate of browning at other temperatures.

Arrhenius-type plots of log k *versus* $1/T$ are shown in Fig. 5. The browning rate constants were determined at 25° by extrapolation, and the times required for browning to occur at 25° were calculated as approximately 845 and 793 days for the samples containing 10 and 15 mg of dextroamphetamine sulfate. These rates were considerably slower than the browning rate reported (5) for mixtures containing spray-dried lactose and dextroamphetamine sulfate. The differences observed in the browning rates could have been due to the unusual physical characteristics ascribed to the dextrates (1) due to their special manufacturing process that yields spherical, opaque, and highly aggregated crystals with a closed pore network structure of microcrystals. The microcrystals are reported[5] to be less than 5 μm in diameter. Each particle of dextrates has open connective pores between the microcrystals which are accessible to the incorporated drug.

Table IV—Apparent Zero-Order Rate Constants for Browning of Dextroamphetamine Sulfate–Dextrates Mixtures

Temperature	10 mg Dextroamphetamine Sulfate/g Dextrates		15 mg Dextroamphetamine Sulfate/g Dextrates	
	k, day^{-1}	Log k	k, day^{-1}	Log k
55°	0.310×10^{-2}	−2.5086	0.333×10^{-2}	−2.4776
60°	0.725×10^{-2}	−2.1397	0.859×10^{-2}	−2.0660
65°	1.550×10^{-2}	−1.8097	2.000×10^{-2}	−1.6990

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