

Interaction of Dextroamphetamine Sulfate with Spray-Dried Lactose

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Abstract □ By using diffuse reflectance spectroscopy, the ethanol-mediated interaction between dextroamphetamine sulfate and spray-dried lactose 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. Two new absorption maxima were observed in the reflectance spectra of heated samples. One at 340 nm. was attributed to the chemisorption of the amine molecules on the surface of the sugar, while a second appeared at 295 nm. and was attributed to the interaction between amine molecules and the sugar. The brown material from the discolored samples was identified as dextroamphetamine-hydroxymethylfurfural, and the mechanism of the browning reaction was postulated. The rate of browning was determined by plotting remission function *versus* time at 295 nm. for mixtures of dextroamphetamine sulfate and spray-dried lactose at three temperatures. Arrhenius-type plots were also obtained and were used to approximate the browning rate at 25°.

Keyphrases □ Dextroamphetamine sulfate interaction with spray-dried lactose—ethanol mediated, mechanism and rate of discoloration □ Lactose, spray dried, interaction with dextroamphetamine sulfate—ethanol mediated, mechanism and rate of discoloration □ Discoloration of dextroamphetamine sulfate-spray-dried lactose mixtures—ethanol mediated, effect of storage and temperature □ Diffuse reflectance spectroscopy—monitoring, discoloration of dextroamphetamine sulfate-spray-dried lactose mixtures

The reactions of amphetamine with aldose, glycosylamines, and bisulfite were reported by Griffin and Banker (1). The complexation of amines with montmorillonite clays was studied by Slabaugh and Kennedy (2). Borodkin and Yunker (3) and Lach and Pauli (4) also studied the interaction of amines with polycarboxylic acid ion-exchange resin, β -cyclodextrin, sodium desoxycholate, and desoxycholic acid.

Spray-dried lactose is a free flowing, highly compressible powder which is widely used as a filler in tablet and capsule formulations. However, several investigators (5-8) found that tablets containing amine salts and lactose discolored slowly on storage. Gonsel and Lachman (5) evaluated the tableting properties of spray-dried lactose and noted that tablets containing spray-dried lactose darkened more rapidly than those containing conventionally processed lactose. Castello and Mattocks (6), studying the discoloration of tablets containing amines and lactose, indicated that the liberation of free amine by basic lubricants in the formulation was a prerequisite to the darkening of such tablets. Duvall *et al.* (7) studied the reactivity of amines with lactose and concluded that the lactose-amphetamine reaction was predominantly a primary amine-carbonyl type of reaction which did not depend on the liberation of free amine by basic lubricants to produce browning. Duvall *et al.* (8), in their study of the tableting characteristics of a commercial form of dextrose and spray-dried lactose in direct compression systems, found that dextrose produced less browning than spray-dried

lactose in formulations free of amines but it produced more browning when amines were present. However, the degree of browning was only estimated visually.

The purpose of this study was to investigate quantitatively the ethanol-mediated interaction between dextroamphetamine sulfate and spray-dried lactose using diffuse reflectance spectrometry. Theoretical considerations for the quantitative use of the diffuse reflectance equations were discussed and derived previously by several authors (9-14). The best known theory was developed by Kubelka and Munk (15, 16). The principles of chemical kinetics were used to study the rate of browning reaction.

EXPERIMENTAL¹

Reagents—The following were used: dextroamphetamine sulfate USP², m.p. >300°; spray-dried lactose USP³, m.p. 201-202°; and potassium bromide, IR quality⁴.

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 an adjuvant, spray-dried lactose, 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 the adjuvant 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 room temperature (25°). At the end of this time, the bottles were removed from the submersion 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 obtain a uniform sample. All samples were stored in a calcium sulfate-charged vacuum desiccator for diffuse reflectance study. After the initial spectra were taken, the samples and the reference were placed in the constant-temperature oven at 50, 60, and 65°. At appropriate intervals, samples were removed from the oven and allowed to cool to room temperature, and then additional spectra were recorded.

Preparation of Physical Mixture Samples—Sixty milligrams of dextroamphetamine sulfate was accurately weighed and transferred into a mortar. Four grams of spray-dried lactose was triturated with

¹ 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 special cell was constructed to hold the sample and reference powder. The cell consisted of a 4.8-cm. (1.88-in.) square aluminum block, 0.63 cm. (0.25 in.) thick, with a 3.5-cm. (1.38-in.) hole machined through the center. A piece of circular quartz (Suprasil), 3.2 cm. (1.25 in.) in diameter and 0.15 cm. (0.06 in.) in thickness, was fitted into the face of the block, covering the hole. An aluminum back cover was held in place by two metal bolts. Therefore, the powder compartment between the quartz face and the back cover was 0.51 cm. (0.2 in.) in depth. IR spectra were obtained using a Beckman IR-10 spectrophotometer. 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.

² Hexagon Laboratories, Inc., New York, N. Y.

³ Foremost Dairies, Inc., Wis.

⁴ Harshaw Chemical Co., Cleveland, Ohio.

Table I—Relationship between Concentration of Dextroamphetamine Sulfate and Reflectance at Different Wavelengths

Concentration		Reflectance, %/100					
mg. Dextroamphetamine Sulfate/g. Lactose	Mole Fraction	$r_{\infty 215}$	$f(r_{\infty 215})$	$r_{\infty 257}$	$f(r_{\infty 257})$	$r_{\infty 340}$	$f(r_{\infty 340})$
10	0.9289×10^{-2}	0.640	0.1013	0.890	0.0068	0.970	0.00046
15	1.3934×10^{-2}	0.675	0.0782	0.885	0.0075	0.980	0.00020
25	2.3223×10^{-2}	0.720	0.0544	0.850	0.0130	0.985	0.00011
50	4.6445×10^{-2}	0.780	0.0310	0.790	0.0290	0.990	0.00005

dextroamphetamine sulfate for 15 min. The mixture was transferred into a 120-ml. (4-oz.) amber glass bottle, sealed with a screw-cap lined with aluminum foil, and attached to the submersion rotator. The sample was tumbled for 24 hr. at room temperature to ensure the preparation of a homogeneous sample. At the end of this time, the sample was placed in a vacuum desiccator over calcium sulfate for the diffuse reflectance measurement. After the initial spectrum was obtained, the sample was stored in the constant-temperature oven at 50°. Each sample was run in triplicate. At periodic intervals, samples were removed from the oven and allowed to return to room temperature. Then additional spectra were recorded.

Reflectance Measurement—The prepared sample and reference adjuvant were packed into the sample and reference cells. Since it was reported (17) that the quantity of material in the cell and the pressure used during the packing can cause fluctuations in reflectance values, care was taken to maintain the same conditions for every sample packed. To minimize the regular reflectance (surface reflectance) so as to keep the scattering coefficient constant (18), the pure adjuvant was used as the reference.

RESULTS AND DISCUSSION

Diffuse reflectance spectra of various equilibrated samples containing 10, 15, 25, and 50 mg. of dextroamphetamine sulfate/g. of spray-dried lactose are shown in Fig. 1. Two absorption bands occurred in each spectrum, one at 257 nm. and the other at approximately 215 nm. One shoulder absorption peak was observed at about 340 nm. for the sample containing 10 mg. of dextroamphetamine sulfate. The two absorption maxima at 257 and 215 nm. were

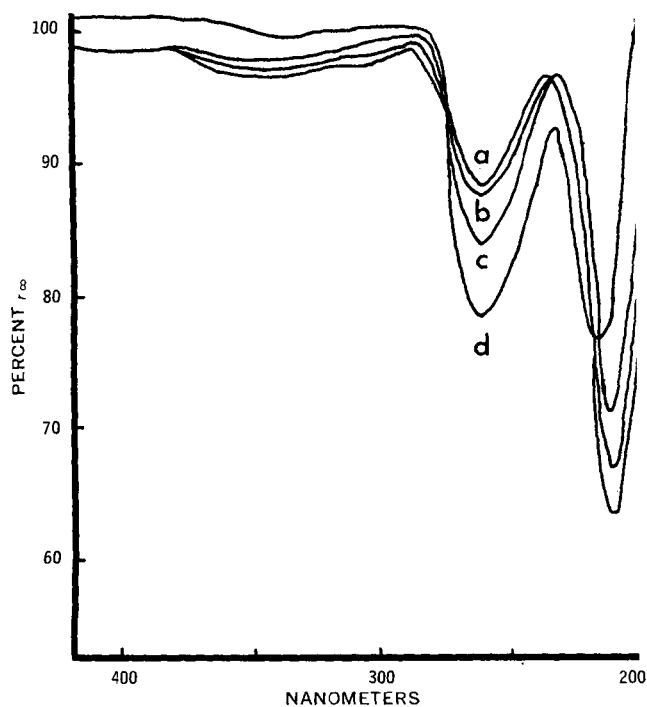


Figure 1—Diffuse reflectance spectra showing the effects of varying dextroamphetamine sulfate concentrations on equilibrated samples containing 1.0 g. of spray-dried lactose as the adsorbent at 25°. Key: a, 10 mg.; b, 15 mg.; c, 25 mg.; and d, 50 mg.

concentration dependent. As the concentration of drug was increased, the intensity of the band at 257 nm. increased while it decreased at 215 nm. It was also observed that the absorption maximum at 215 nm. tended to shift toward the shorter wavelengths as the dextroamphetamine sulfate concentration was decreased. However, the transmittance spectrum of dextroamphetamine sulfate in aqueous solution showed only one absorption maximum, at 257 nm., and end absorption at about 220 nm. It was reported previously (19) that the influence of solvent polarity on the position of this maximum was small. For example, the maximum absorption peak was at 259 nm. in chloroform and at 259.5 nm. in alcohol. The reflectance spectrum of dextroamphetamine sulfate indicated a reduction in end absorption at 200 nm. and the appearance of a new moderate intensity peak at 215 nm. This was probably due, in part, to the contribution of regular reflectance in the solid state (20). Furthermore, there was probably a coupling of the π -electron system of several molecules on the solid surface.

Kortum *et al.* (21) studied the absorption of anthraquinone at various dilutions on sodium chloride as well as the spectrum of anthraquinone in diluted alcoholic solution. Their observations were similar to those described for dextroamphetamine sulfate. They found that the reflectance spectrum, at mole fractions below 3×10^{-4} , became independent of the degree of dilution and mainly resembled the spectrum of the alcoholic solution. However, the reflectance spectrum of pure anthraquinone did not resemble the spectrum of anthraquinone in alcoholic solution, especially in the shortwave bands. In other words, the reflectance spectrum of a compound can depend on its degree of dilution.

The relationships between concentration and the intensity of absorption at the three absorption peaks, calculated from the data obtained in Fig. 1, are shown in Table I along with the calculated remission functions. A plot of the remission function, $f(r_{\infty})$, versus dextroamphetamine sulfate concentration, expressed in mole fraction, is shown in Fig. 2. It was observed that the band at 257 nm., the characteristic band of dextroamphetamine sulfate, obeyed the linear relationship between the remission function and the concentration as required by the Kubelka-Munk theory, whereas at 215 nm. the plot of the remission function versus concentration showed a deviation from linearity. It is well known that if molecular association occurs in a solution, it may cause deviation from the Lambert-Beer law. Molecular association can also occur on solid surfaces (22), as has been demonstrated with the pyrene-*s*-trinitrobenzene system, using dried silicon dioxide as the adsorbent. Deviation from linearity in the plot of the remission function versus concentration was attributed to the association reaction between molecules on the solid surface. Analogously, the deviation from linearity shown in Fig. 2 at 215 nm. may be attributed to molecular

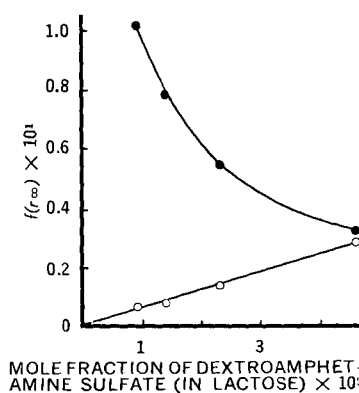


Figure 2—Relationship between reflectance and concentration of dextroamphetamine sulfate at 25°. Key: ○, at 257 nm.; and ●, at 215 nm.

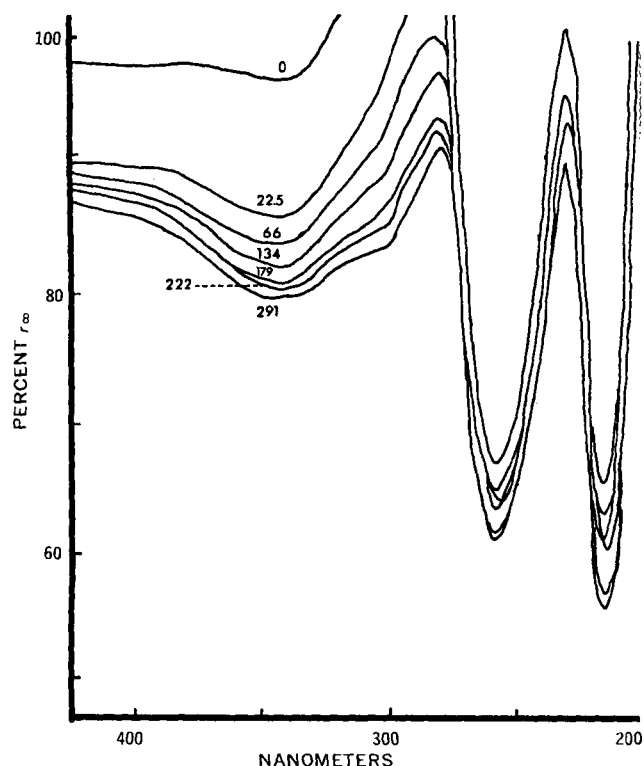


Figure 3—Diffuse reflectance spectra of a physical mixture sample containing 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose after heating at 50° for various periods (shown in hours).

association on the solid surface. This was consistent with the decrease in intensity observed at 215 nm. as the concentration of dextroamphetamine sulfate increased (Fig. 1).

Since multiple-layer adsorption may occur in physical adsorption, the increase in intensity observed at 257 nm., with increasing drug concentrations, may be ascribed to the physical adsorption of the dextroamphetamine sulfate molecules on the solid surface. This may be supported by the linear relationship between the remission function and concentration obtained at 257 nm. (Fig. 2). The shoulder band at approximately 340 nm. may be due to chemisorption. Chemisorption, which often occurs at a higher temperature and at a slower rate than physical adsorption, is associated with an activation energy (23). Therefore, it was reasonable to expect only a small shoulder peak in the initial state (Fig. 1). However, to complete the chemisorption of amphetamine molecules on the solid surface, an appreciable activation energy might be required, such as that supplied at higher temperatures, and this adsorption phenomenon will be discussed later.

Physical mixtures containing 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose were prepared according to the procedure previously described. The samples were heated in the oven at $50 \pm 0.5^\circ$, and their reflectance spectra were obtained at different intervals. The diffuse reflectance spectrum did change with temperature (Fig. 3). Browning of the samples also occurred, particularly in the samples heated for long periods. The rate of the

Table II—Relationship between Reflectance Values and Time for a Physical Mixture Containing 15 mg. of Dextroamphetamine Sulfate/g. of Spray-Dried Lactose after Heating at 50°

Time at 50°, hr.	Reflectance, %/100				
	$r_{\infty 295}$	$f(r_{\infty 295})$	$r_{\infty 340}$	$f(r_{\infty 340})$	$f(r_{\infty 295})/f(r_{\infty 340})$
0	—	—	0.974	0.0004	—
22.5	1.000	—	0.864	0.0107	0
66.0	0.953	0.0012	0.840	0.0152	0.076
134.0	0.920	0.0035	0.827	0.0181	0.192
179.0	0.887	0.0072	0.808	0.0228	0.316
222.0	0.876	0.0088	0.806	0.0234	0.376
291.0	0.859	0.0116	0.800	0.0250	0.463

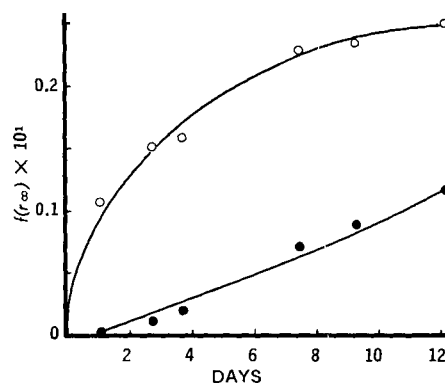


Figure 4—Relationship between reflectance and time for a physical mixture sample containing 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose after heating at 50°. Key: O, at 340 nm.; and ●, at 295 nm.

browning reaction will be discussed later. The shoulder peak at 340 nm. increased markedly after heating at 50°. These observations can be explained on the basis that physical adsorption occurred as a result of triturating the dextroamphetamine sulfate with lactose, with only a slight amount of chemisorption occurring at this early mixing stage. However, the extent of adsorption in the physical mixture sample was far from the equilibrium state, as can be seen from a comparison of the absorption maxima in Figs. 1 and 3. Reflectance values obtained at zero time from the physical mixture samples at 257 and 215 nm. were 31 and 36%, respectively; for the equilibrated samples, at the same drug concentration, the values were 11 and 36%. This difference may be due to the fact that trituration and tumbling during physical mixing were not sufficient to obtain an equilibrium state. Consequently, at this stage, most of the dextroamphetamine molecules were present in intact crystalline form, thoroughly distributed throughout the lactose mixture.

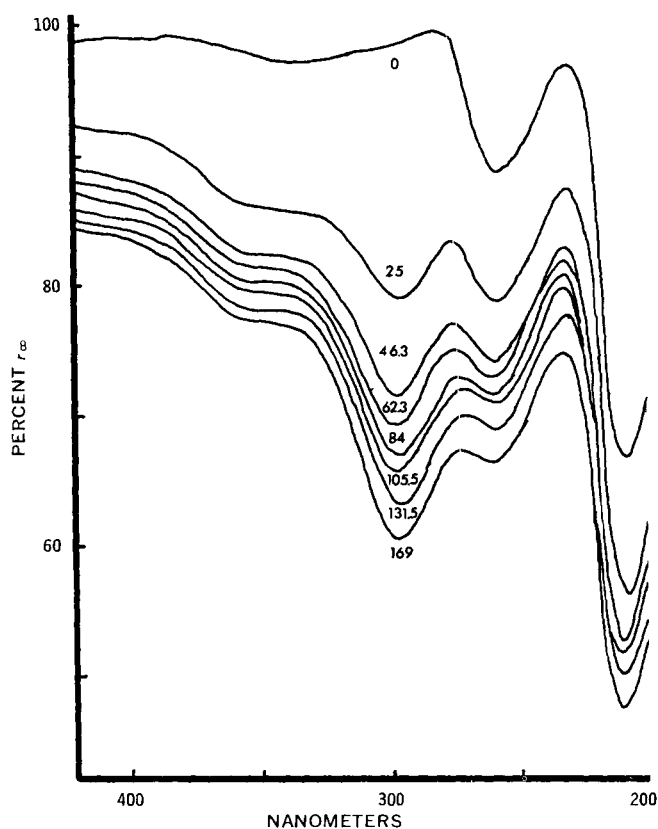


Figure 5—Diffuse reflectance spectra of an equilibrated sample containing 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose after heating at 60° for various periods (shown in hours).

Table III—Relationship between Reflectance Values and Time for an Equilibrated Mixture of Dextroamphetamine Sulfate and Spray-Dried Lactose after Heating at 60°

Time at 60°, hr.	Reflectance, %/100			
	10 mg. Dextroamphetamine Sulfate/g. Lactose		15 mg. Dextroamphetamine Sulfate/g. Lactose	
	$r_{\infty 295}$	$f(r_{\infty})_{295}$	$r_{\infty 295}$	$f(r_{\infty})_{295}$
0	0.983	0.0020	0.995	0
25.0	0.710	0.0592	0.770	0.0344
46.3	0.655	0.9008	0.698	0.0653
62.3	0.627	0.1109	0.677	0.0770
84.0	0.610	0.1247	0.652	0.0929
105.5	0.582	0.1501	0.640	0.1013
131.5	0.570	0.1622	0.617	0.1189
169.0	0.545	0.1899	0.690	0.1425

Therefore, the intensity of the absorption of these intact crystalline particles and the spectral contributions due to chemisorption were small. However, as the sample was heated in the oven, the intensity of the maximum at 340 nm. increased markedly. A careful examination of the spectrum also revealed the occurrence of a hump at about 300 nm. During the heating period the physically adsorbed drug molecules probably obtained sufficient energy to migrate to the unsaturated sites of the solid surface, where they underwent chemisorption. As the result of chemisorption, the intensity of the shoulder band at 340 nm. increased markedly. Langmuir (24) and Farnsworth and Madden (25) showed that, in a given adsorption system, a state of physical adsorption may precede chemisorption; hence, physically adsorbed molecules may, on obtaining sufficient energy, be transferred to a chemisorbed state.

The intensity relationships, calculated from the data obtained in Fig. 3, are shown in Table II, and a plot of the remission function versus time is presented in Fig. 4. It can be seen from Fig. 4 that the intensity of the maximum at 340 nm. increased as a function of time and gradually reached a plateau, whereas the absorption maximum at 295 nm. appeared after 2 days and its intensity increased almost linearly. Browning of the sample accompanied the appearance of the new absorption peak at 295 nm. Although the reflectance values obtained at 340 nm. were large, a comparison of the ratio, $f(r_{\infty})_{295}/f(r_{\infty})_{340}$, with time indicated that the rate of formation of the adsorption complex at 295 nm. was greater than that at 340 nm. If the sample is stored at 50° for sufficient time, the reflectance value at 295 nm. finally will be greater than that at 340 nm.

To study the browning reaction further, reflectance spectra were obtained for equilibrated samples containing 10 and 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose that had been stored at 50, 60, and 65 ± 0.5° for various periods. The spectra shown in Fig. 5 are of an equilibrated sample containing 15 mg. of dextroamphetamine sulfate after heating at 60° for various periods. The reflectance values and remission functions are shown in Table III. Similar results were obtained at 50 and 65°.

The literature on browning reactions has generally emphasized the complexity of the subject and the lack of specific knowledge of the chemical reactions involved. Koshy *et al.* (26) studied the browning of spray-dried lactose and conventionally processed lactose USP in aqueous solutions buffered to various pH's. They also reported the effect of heat, moisture, and tablet lubricants on browning. All of their studies were conducted in the absence of added amines. Spray-dried lactose was found to have a UV absorption maximum, whereas USP and analytical reagent grade lactose did not. A relationship between the intensity of this maximum and the 5-hydroxymethylfurfural content was shown. This absorbance was related to browning. Moisture, in addition to 5-hydroxymethylfurfural and/or related compounds, was shown to be a major contributory factor. Brownley and Lachman (27) investigated the relationship between the discoloration of spray-processed lactose and the presence of 5-hydroxymethylfurfural, using a spectrophotometer⁵ fitted with a reflectance attachment. Their results indicated that spray-processed lactose contains significant quantities of 5-hydroxymethylfurfural, while conventionally processed lactose contains essentially no 5-hydroxymethylfurfural. Their results also

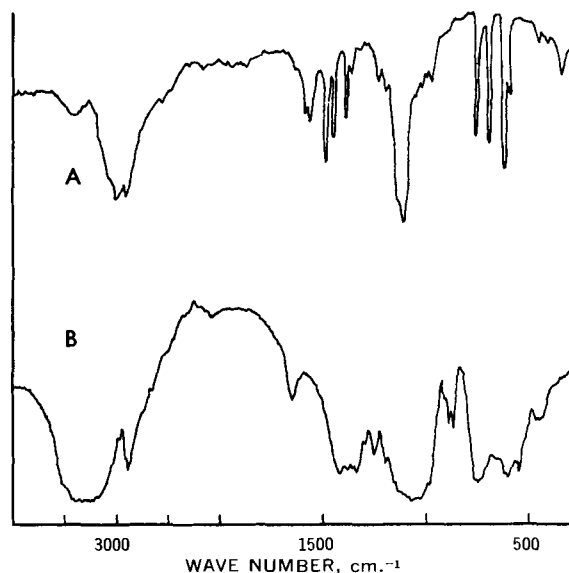


Figure 6—IR spectra of dextroamphetamine sulfate (A) and a mixture (B) containing 10 mg. of dextroamphetamine sulfate/g. of spray-dried lactose after 5 days at 60°.

implicated the presence of free 5-hydroxymethylfurfural in lactose with resultant browning. Samples of conventionally processed lactose free of 5-hydroxymethylfurfural, heated for 24 hr. at 80° and stored at ambient conditions for 36 months, showed no darkening. Similarly treated samples of spray-processed lactose containing free 5-hydroxymethylfurfural darkened significantly.

The most common type of browning, especially in dairy products, involves carbonyl-amine reactions, including the reactions of aldehydes, ketones, and reducing sugars with amines, amino acids, peptides, and proteins. This type of browning has been referred to as Maillard-type browning (28) and is well known to dairy chemists and food technologists. This type of browning requires a relatively low order of energy for its initiation and exhibits autocatalytic qualities once it begins.

The reactions of carbohydrates with amines are well known and were reviewed by Pigman (29). Reactions occur with aldehyde groups of open-chain forms of the carbohydrates to form Schiff bases, as well as with the aldehyde group of ring forms to produce glycosylamines. Duvall *et al.* (7) investigated the browning reaction of dextroamphetamine sulfate solutions (pH 8) containing lactose. A marked change in the absorbance curve was noted after 1 week of storage at 50°. A new peak appeared in the region of 320 nm., and the solution became progressively darker with the appearance of a brownish-black precipitate. IR spectra and TLC data were also obtained to support the conclusion that the reaction associated with this maximum at 320 nm. was of a Schiff base type involving the primary amine and the carbonyl group of the sugar.

In this study, the thermal effect did produce marked changes in the reflectance spectra in the solid state. A new peak appeared at about 295 nm., and its intensity increased considerably when the sample

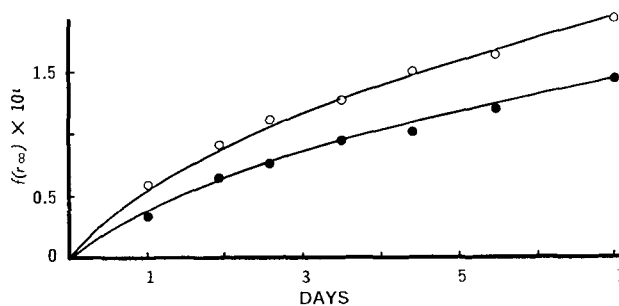


Figure 7—Rate of browning of dextroamphetamine sulfate-spray-dried lactose equilibrated mixtures at 60°. Key: ○, 10 mg. of dextroamphetamine sulfate/g. of spray-dried lactose; and ●, 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose.

⁵ Beckman model DU.

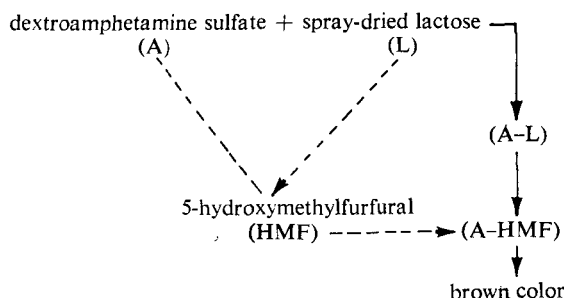
Table IV—Apparent Zero-Order Rate Constants for the Browning of Dextroamphetamine Sulfate–Spray-Dried Lactose Mixtures

Temperature	10 mg. Dextroamphetamine Sulfate/g. Lactose		15 mg. Dextroamphetamine Sulfate/g. Lactose	
	$k(\text{day}^{-1})$	$\log k$	$k(\text{day}^{-1})$	$\log k$
50°	1.284×10^{-2}	-1.8928	0.827×10^{-2}	-2.0830
60°	2.063×10^{-2}	-1.6861	1.550×10^{-2}	-1.8097
65°	2.850×10^{-2}	-1.5452	2.400×10^{-2}	-1.6198

was continuously heated. Extensive browning also occurred on heating. The reaction associated with the appearance of the peak at 295 nm. was probably analogous to the reaction that caused the appearance of a new peak at 320 nm. in the dextroamphetamine sulfate–lactose solution, *i.e.*, a Schiff base-type reaction involving the primary amine and the carbonyl group of the sugar. The shift in the λ_{max} from 295 nm. in the solid–solid mixture to 320 nm. in the solution was probably due to a pH effect, since the solution was buffered to pH 8 and the solid system was probably close to neutrality.

IR spectra were obtained to support the above observation and are shown in Fig. 6. Spectrum B was obtained after the equilibrated sample containing 10 mg. of dextroamphetamine sulfate with 1 g. of spray-dried lactose was heated at $60 \pm 0.5^\circ$ for 5 days. Spectrum B exhibited a C=N stretching band (VC=N) at 1650 cm.^{-1} , which lends additional support to the conclusion that the reaction associated with the appearance of the peak at 295 nm. was of a Schiff base type.

From these results the browning reaction can be attributed to one or more of the following (Scheme I):



Scheme I—Postulated interaction of dextroamphetamine sulfate with spray-dried lactose in the solid state

1. Initially, the dextroamphetamine sulfate molecules were chemisorbed on the surface of lactose crystals in the equilibrated dextroamphetamine sulfate–lactose sample (abbreviated A-L).

2. On prolonged heating, the chemisorbed molecules underwent a Schiff base-type interaction on the adsorption surface to form dextroamphetamine–5-hydroxymethylfurfural (abbreviated A-HMF) and extensive browning occurred.

3. The degradation of lactose produced 5-hydroxymethylfurfural which reacted with dextroamphetamine molecules to form A-HMF.

Since this study was conducted at the relatively low temperatures of 50–65°, the quantity of 5-hydroxymethylfurfural formed due to the degradation of lactose was probably very small. This was substantiated by a study of Koshy *et al.* (26) on the browning of buffered aqueous solutions containing spray-dried lactose and conventionally processed lactose. Visual observations of the solutions revealed that, after 1 week at 50°, they underwent faint changes in color ranging from yellow at pH 1, to colorless at pH 2–6, to faint yellow at pH 7, and to deep yellow at pH 8. Although solutions at pH 2–6 were colorless, they exhibited an absorption peak at 275–285 nm., indicating the presence of 5-hydroxymethylfurfural. Therefore, the probability of the formation of dextroamphetamine–5-hydroxymethylfurfural from Step 3 was very low at these temperatures, and Step 3 was not necessary in the browning reaction. In other words, the discoloration of the sample was primarily due to Steps 1 and 2.

The browning reaction was studied in a more quantitative manner by plotting the remission functions, $f(r_\infty)$, obtained from the reflectance values at 295 nm. against time. The results obtained at 60° are shown in Fig. 7. Careful examination of each curve showed that

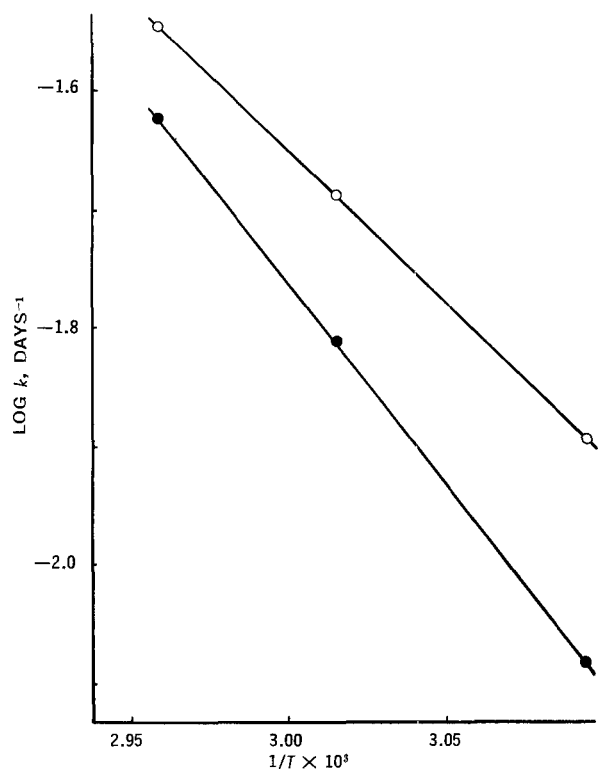


Figure 8—Arrhenius-type plots showing the temperature dependence for the browning of dextroamphetamine sulfate–spray-dried lactose equilibrated mixtures. Key: ○, 10 mg. of dextroamphetamine sulfate/g. of spray-dried lactose; and ●, 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose.

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 portion. Each lactose molecule contained one molecule of water of hydration, and the liberated water probably participated in the initial stage of the browning reaction due to the formation of a solution phase containing dextroamphetamine sulfate and lactose molecules. Duvall *et al.* (7) visually observed the browning reaction between dextroamphetamine sulfate and lactose. They reported that the rate of browning was faster in solution than in the solid state; hence, it is reasonable to expect that the liberation of bound water from lactose molecules increased the rate of browning in the initial stages.

During the second stage of the browning reaction, a nearly linear relationship was obtained between the remission function and time. From this relationship, the browning reaction may be assumed to follow an apparent zero-order reaction. Then it was possible to obtain rate constants from the slopes of the straight-line portions of the plots. However, since the mechanism involved in the actual reaction in the solid state was very complicated, the apparent zero-order rate constants in this case only represent a total overall reaction rate that enables one to estimate the rate of browning at other temperatures.

Apparent zero-order rate constants were calculated from the slopes of the straight-line portions of the curves obtained by plotting the remission functions, $f(r_\infty)$, obtained from the reflectance values at 295 nm. against time at 50, 60, and 65°. Figure 7 shows a typical plot obtained at 60°; the plots obtained at 50 and 65° were similar. The calculated rate constants are shown in Table IV, and an Arrhenius-type plot of $\log k$ versus $1/T$ is shown in Fig. 8. The browning rate constants were determined at 25° by extrapolation, and the times required for browning to occur at 25° were calculated as approximately 50.7 and 79.3 days for the samples containing 10 and 15 mg. of dextroamphetamine sulfate/g. of spray-dried lactose, respectively.

A comparison of the browning rate constants in Table IV reveals that the rate of browning was higher in the sample containing 10 mg. of dextroamphetamine sulfate than it was in the sample containing 15 mg. of dextroamphetamine sulfate at temperatures below

65°. However, at higher temperatures the samples containing 15 mg. dextroamphetamine sulfate should show a faster rate of browning (Fig. 8). At higher temperatures, sufficient energy was obtained to enable additional intact drug molecules to interact with the lactose. Therefore, the rate of the browning reaction in solid-solid mixtures of dextroamphetamine sulfate and spray-dried lactose is dependent on the concentration of drug in the mixture and the temperature at which the mixture is stored.

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Permeation of Aromatic Organic Compounds from Aqueous Solutions through Polyethylene

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Abstract □ The permeation, through polyethylene, of various aromatic acids, alcohols, amines, esters, aldehydes, and ketones in aqueous solution was investigated at 50°. The studies were conducted in a glass cell with two chambers separated by a thin film of polyethylene. Studies at several temperatures indicated activation energies ranging from 12.9 to 21.4 kcal./mole. The applicability of Fick's first law was established with solutions of varying initial concentrations. An inverse relationship was observed between the permeability constant of several compounds and the proportion of ethanol present in the solvent. Studies at various pH's demonstrated transport of only the unionized species. Films exposed to permeant solutions, prior to the permeation experiments, exhibited reduced permeation rates. Experimental permeability constants (P) and hexane-water partition coefficients (PC) were subjected to

regression analysis. A good correlation was obtained with the empirical equation: $\log(P) = 1.06 \cdot \log(PC) - 7.76$.

Keyphrases □ Permeation—aromatic organic compounds from aqueous solutions through polyethylene films □ Partition coefficients, hexane-water—used to study permeation of aromatic acids, alcohols, amines, esters, aldehydes, and ketones in aqueous solutions through polyethylene films □ Polyethylene films—permeation of aromatic organic compounds from aqueous solutions, hexane-water partition coefficients, permeability constants □ Organic aromatic compounds—permeation from aqueous solutions through polyethylene films □ Films, polyethylene—permeation of aromatic organic compounds from aqueous solutions, hexane-water partition coefficients, permeability constants

A previous report in this series (1), involving polyethylene films, demonstrated a relationship between hexane-water partition coefficients and permeability constants obtained for aqueous solutions of aniline and various substituted anilines. As an extension of this work, the permeation of 19 aromatic compounds,

representing various chemical classes, was studied in a similar system. The objective of these investigations was the development of correlations, between the physicochemical properties of the compounds and their permeation from aqueous solution through polyethylene, that might serve for the convenient prediction of