Interaction of Sorbic Acid with an Insoluble Polyamide

By M. B. RODELL, W. L. GUESS, and J. AUTIAN

Specially treated nylon 66 strips were exposed to sorbic acid solutions at a number of different concentrations and at several temperatures and the quantity of drug sorbed determined by suitable means. Thermodynamic and kinetic treatment of the data permitted the evaluation of a number of constants such as (*a*) saturation value of drug in the plastic, (*b*) affinity of drug toward the plastic, (*c*) standard heat of sorption, (*d*) apparent diffusion coefficient, and (*e*) activation energy of diffusion. Changes in concentration of solution influenced both the apparent diffusion coefficient and the activation energy of diffusion. A nearly linear relationship was noted between the concentration of the solution and the diffusion coefficient, the diffusion coefficient decreasing with an increase in concentration of solution. The standard heat of sorption suggested that the interaction between the sorbic acid and the nylon might be due to a double hydrogen bond formation.

SORBIC ACID has been widely used in the food industry as an effective growth inhibitor for certain yeasts, molds, and bacteria. The pharmaceutical industry at times has also found important uses for sorbic acid as a preservative in certain dosage forms. The packaging of food and drug products in plastic containers has focused attention on the possible interaction between the plastic material and the preservative, reducing the concentration of the preservative to a level where the agent no longer exerts a significant effect. Marcus, *et al.* (1), noted the binding of sorbic acid by nylon. Autian and Shaikh (2) continued further work on the interaction of sorbic acid by nylon and found that solvent, temperature, and pH had an effect on the quantity of sorbic acid bound.

To gain more quantitative information on sorbic acid and nylon, which in turn could lead to more interesting results that were unobtainable in the previous studies, a series of sorption experiments was conducted with sorbic acid and one particular insoluble polyamide (nylon 66). This paper reports on the results of this particular study.

EXPERIMENTAL

Equipment and Supplies.—A Beckman DB spectrophotometer, (Beckman Instruments, Inc., Fullerton, Calif.), sorbic acid,[1] and nylon 66 (0.01 in. thick)[2] were employed.

Method of Analysis of Sorbic Acid.—In general, the analysis of sorbic acid in solution was conducted

by diluting a 1.0-ml. aliquot to a volume of 500 ml. with 0.1 *N* HCl[3] and measuring the optical density at a wavelength of 264 mμ in the spectrophotometer using matched 1-cm. silica cells. Appropriate blanks were utilized throughout the investigation. The difference between the concentration of sorbic acid in the original solution and that after exposure to the plastic was assumed to have been sorbed by the nylon. Control solutions of sorbic acid without nylon were run simultaneously with the samples to detect if degradation had occurred in the solution. For the temperatures and time periods used in this study, no significant degradation of sorbic acid was noted in the control solution.

Effect of Concentration on Sorption.—Solutions of sorbic acid at seven concentrations ranging from 0.15% down to 0.0125% were prepared using distilled water as the solvent, and exactly 100 ml. of each of these solutions was pipeted into specially constructed cylindrical glass tubes, measuring 12 in. in length and 1.5 in. in diameter. The tubes were fitted with a ground glass stopper attached to the tubes by metal springs, allowing for total immersion into the water bath at the desired temperature. After a period of time adequate for equilibrium temperature to be reached in the tubes, the tubes were lifted from the water bath, the stoppers removed, and a strip of nylon[4] (approximately 2.0 Gm.) placed into each tube. The tubes were once again stoppered and carefully placed back into the water bath. Sorbic acid determinations were made on each solution after sufficient time had elapsed to ensure that equilibrium had been reached. These experiments were run in duplicate and at three different temperatures (55 ± 0.02°, 61 ± 0.02°, and 67 ± 0.02°).

The data were plotted by using a form of the Langmuir relationship

$$\frac{1}{q} = \frac{1}{KSC} + \frac{1}{S} \qquad \text{(Eq. 1)}$$

where *q* is the amount of solute sorbed by the nylon at equilibrium in moles/kilogram, *K* is a constant, *C* the equilibrium concentration of the solution in moles/liter, and *S* the saturation value in moles/

[3] Hydrochloric acid (0.1 *N*) was employed to suppress possible ionization of sorbic acid.
[4] In all instances the samples of nylon 66 used were washed as described in a previous paper (3).
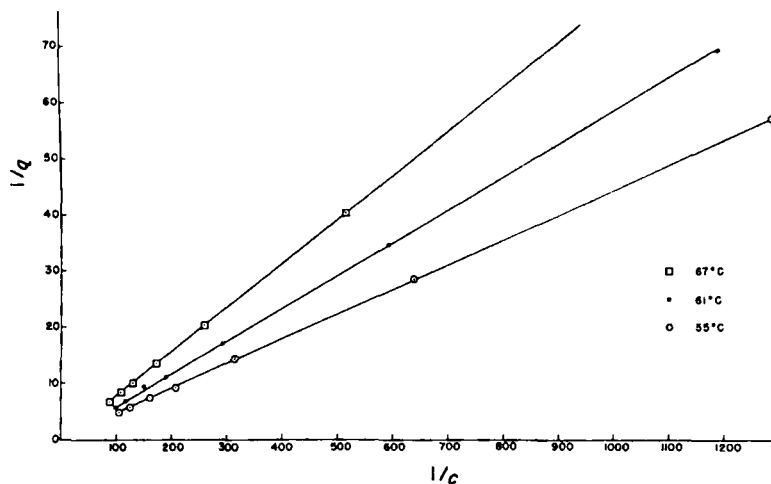
Fig. 1.—Sorption of sorbic acid by nylon 66 as a Langmuir plot at three different temperatures.

□   67°C
•   61°C
○   55°C

TABLE I.—EFFECT OF TEMPERATURE AND CONCENTRATION ON EQUILIBRIUM SORPTION OF SORBIC ACID BY NYLON 66

| —55° ± 0.02°C.— | | —61° ± 0.02°C.— | | —67° ± 0.02°C.— | |
$1/q^a$	$1/C^b$	$1/q$	$1/C$	$1/q$	$1/C$
4.850	104.8	5.770	97.64	6.863	87.32
5.770	124.9	6.916	116.2	8.628	108.5
7.496	161.3	9.025	151.3	10.26	129.9
9.285	207.3	11.34	190.3	13.74	173.4
14.53	314.4	17.09	293.5	20.33	259.2
28.65	641.3	34.84	594.2	40.65	518.4
57.14	1282.0	69.44	1189.0	75.18	1036.0
$S^c = 2.67$		$S = 5.69$		$S = 9.73$	

a q = Amount of solute sorbed by nylon at equilibrium in moles/kilogram. b C = Equilibrium concentration of solute in solution in moles/liter. c S = Saturation value of solute in nylon if all sites were taken in moles/kilogram.
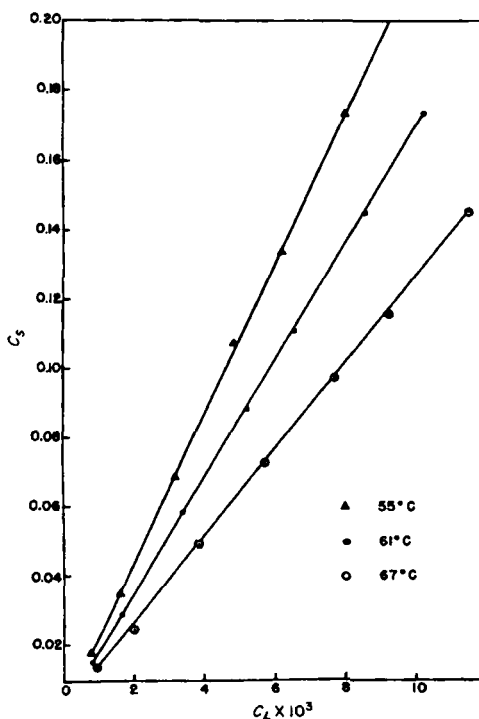

Fig. 2.—Relationship of C_S (concentration of sorbic acid in solid) and C_L (concentration of sorbic acid in liquid) at equilibrium and at three temperatures.

kilogram, or the theoretical amount of solute which the nylon would sorb if all the sites were filled. Table I presents the data as $1/q$ and $1/C$ values, while Fig. 1 illustrates the sorption isotherms at three temperatures. Each line was then extrapolated to the $1/q$ axis by least squares to find $1/S$, from which S was calculated. These values are included in Table I.

Affinity and Heat of Sorption.—To learn more of the attraction forces between the sorbic acid molecules and the nylon, it was decided to determine the difference in standard chemical potential ($-\Delta\mu°$) between the solute in the liquid phase and the solute in the solid phase. This difference, or $-\Delta\mu°$, is often referred to as the standard affinity (4) and may be approximated by using

$$-\Delta\mu° = RT \ln C_s/C_L \qquad \text{(Eq. 2)}$$

where C_s and C_L are the concentrations in moles/kilogram of solute in the solid phase and the solute in the liquid phase, respectively. The ratio C_s/C_L was determined from the slopes of the line shown in Fig. 2 where C_s is plotted against C_L. The experimental data used for the evaluation of affinity were taken from the previous experiment (*Effect of Concentration on Sorption*). Standard affinities for the three temperatures are shown in Table II.

TABLE II.—STANDARD AFFINITIES FOR SORBIC ACID AT THREE TEMPERATURES (NYLON 66)

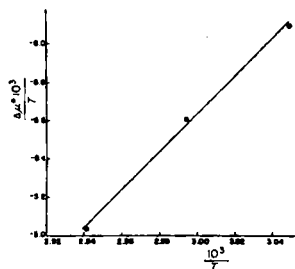| Temp., °C.	$-\Delta\mu°$ (Kcal./mole)
55.0	2.00
61.0	1.87
67.0	1.71

Fig. 3. — Relationship between affinity of sorbic acid (toward nylon 66) and temperature.

Standard heat of sorption ($\Delta H°$) for sorbic acid (in nylon 66) was calculated from the slope produced when $\Delta\mu°/T$ was plotted against $1/T$ as shown in Fig. 3.[5] This value ($\Delta H°$) was −9.77 Kcal./mole.

Diffusion and Activation Energy of Diffusion.— Since the sorption process of dyes and other agents in nylon is governed primarily by the diffusion step in the nylon, experiments were conducted to evaluate the apparent diffusion coefficient at three temperatures and at a number of original solution concentrations.

Exactly 300 ml. of sorbic acid solution at a definite concentration was placed in a 500-ml. three-necked, round-bottom flask. The solution was brought to the temperature of the water bath, at which time 6 Gm. of nylon (as strips) were introduced into the flask and the two outside necks sealed. A sealed stirring device was inserted in the middle neck of the flask and the glass rod adjusted so that the stirrer would fall just below the surface of the solution. The solution was stirred at a constant rate throughout all of the diffusion experiments. At various time intervals aliquots of solution were removed and sorbic acid content determined until equilibrium was reached. In each case the experiment was run in duplicate. Removal of aliquots from the solution did not materially alter the uptake of sorbic acid throughout the run.

The apparent diffusion coefficient was calculated for each original concentration at each temperature. An experimental plot of fractional uptake (M_t/M_∞) *versus* the square root of time is shown in Fig. 4 at one original concentration (0.075%). From the linear portions of these curves, D was calculated by using Berthier's method (5, 6) which has been explained in detail in a previous paper (7). These D values, as cm.²/second, are shown in Table III. Activation energy of diffusion (ΔE) was evaluated from the slope of the line when log D was plotted against $1/T$. Figure 5 shows these Arrhenius relationships, while Table III contains the actual ΔE values at the four original concentrations.

Nearly linear relationships were noted when the apparent diffusion coefficient at each temperature was plotted against the original concentration of sorbic acid in the solution. These relationships may be seen in Fig. 6.

DISCUSSION

Effect of Concentration on Sorption.—As the concentration of sorbic acid was increased, a related increase in the sorption of the solute by the nylon occurred. The Langmuir sorption isotherms for sorbic acid at three different temperatures followed the expected linear relationship for most of the points in the concentration range employed in the

experiment. It will be noted that the lines do not have the same slope but do converge to one point on the $1/q$ axis (or $1/S$ as intercept) in the figure. This is as to be expected, at least theoretically, since the saturation value (S) may be thought of as the total possible quantity of solute which can interact with all of the sites in the plastic. Actual calculations by least squares, however, indicated slight differences in the intercept, which in turn gave different S values as may be seen in Table I. The difference in S values for each temperature may appear to be large (*e.g.*, at 55° the S value is 2.67, while at 67° the S value is 9.73), but part of this difference may be attributed to experimental error since a very small change in intercept can produce a much larger change in S value. One may also speculate that a difference in S values may be due to slight alterations in the nylon as the temperature is increased, producing new sites for interaction. Complete reliance on saturation values (S) for nylon or for that matter any plastic material should be discouraged since slight changes in the "same" plastic sample or the study of equilibrium sorption in other concentration ranges will often produce different S values.

Affinity and Heat of Sorption.—Standard affinity ($-\Delta\mu°$) decreased as the temperature increased (Table II) and parallels what has been seen for dyes and weak organic acids. The affinity values found for sorbic acid in this study fell below 2.0 Kcal./mole which were lower than for a group of weak organic acids sorbed by nylon 610 by a factor of 0.5 to 1.5 Kcal./mole (3, 7). The affinity values reported here, however, for sorbic acid were approximately the same (at comparable temperatures) for salicylic acid sorbed by the same type of nylon (nylon 66). For example, at 60° the standard affinity for salicylic acid (7) was equal to 1.84 Kcal./mole, while sorbic acid came to (at 61°) 1.87 Kcal./mole.

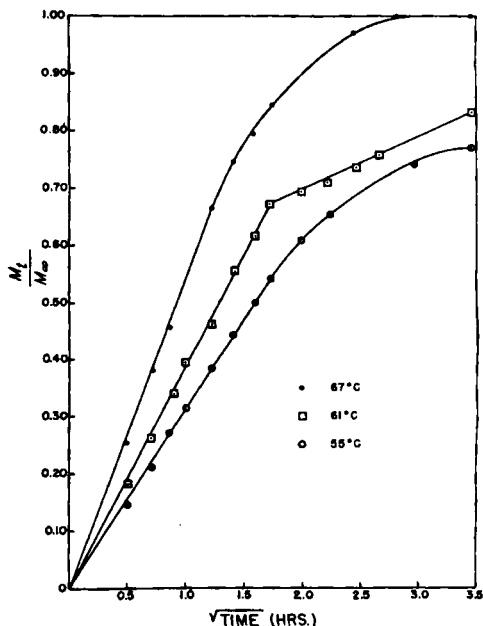The standard heat of sorption ($\Delta H°$) was equal to

Fig. 4.—Fractional uptake (M_t/M_∞) of sorbic acid by nylon 66 *vs.* square root of time at three temperatures.

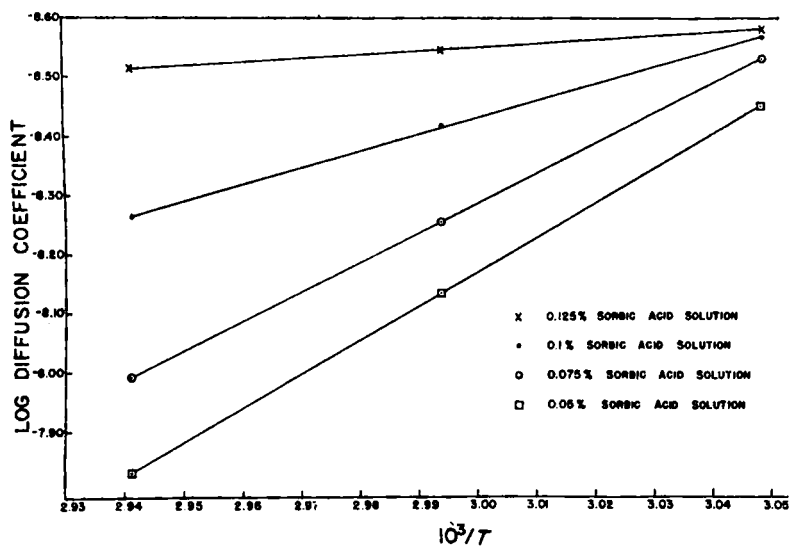[5] Figure 3 follows the relationship: $\Delta\mu°/T = \Delta H°/T + C.$

Fig. 5.—An Arrhenius plot of diffusion of sorbic acid in nylon 66 as log D vs. $1/T$.

TABLE III.—EFFECT OF TEMPERATURE AND CONCENTRATION ON DIFFUSION OF SORBIC ACID BY NYLON 66 AND ACTIVATION ENERGY OF DIFFUSION

—————55° ± 0.02°C.—————		—————61° ± 0.02°C.—————		—————67° ± 0.02°C.—————		
$C^a \times 10^3$	$D^b \times 10^8$	$C \times 10^3$	$D \times 10^6$	$C \times 10^3$	$D \times 10^6$	ΔE^c
11.53	0.262	10.67	0.285	10.98	0.309	3.07
9.276	0.270	8.681	0.383	8.907	0.542	12.8
6.978	0.295	7.019	0.555	6.731	1.01	22.7
4.453	0.353	4.515	0.729	4.535	1.46	26.2

^{a} C = Initial concentration of solute in solution in moles/kilogram. ^{b} D = Diffusion coefficient in cm.^{2}/second. ^{c} ΔE = Activation energy in Kcal./mole.
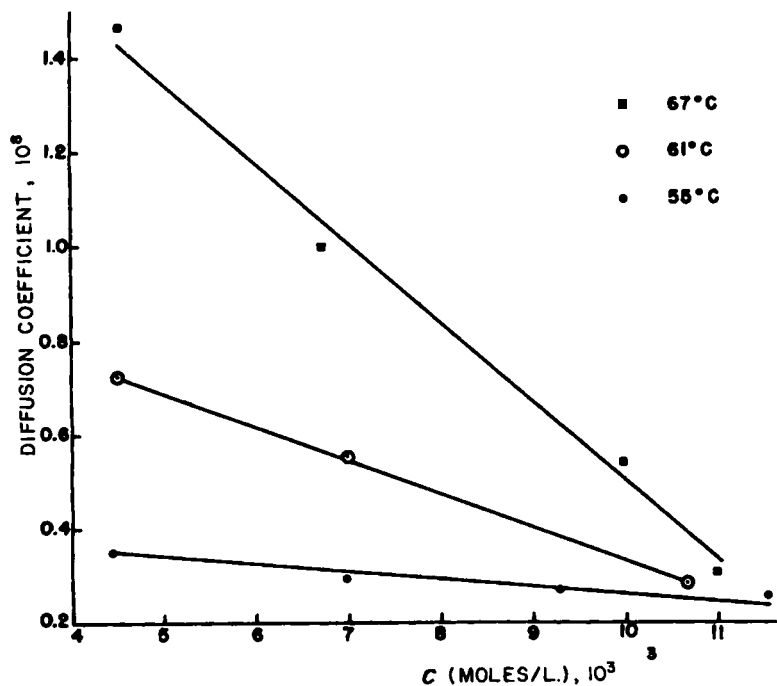

Fig. 6.—Relationship between apparent diffusion coefficient for sorbic acid in nylon 66 and original solution concentration at three temperatures.

—9.77 Kcal./mole, a value much higher than for other weak organic acids previously studied which had $\Delta H°$ values in the range of —2.0 to —3.63 Kcal./mole (3, 7). The higher $\Delta H°$ value for sorbic acid would seem to suggest that the molecule (sorbic acid) is interacting with the polyamide through two hydrogen bonds with secondary valence

forces stabilizing the interaction. There may be one other possibility for the high $\Delta H°$ value for sorbic acid. A slight chemical reaction might be taking place. This possibility is now being investigated.

Diffusion and Activation Energy of Diffusion.— Table III illustrates the effect of temperature on

the apparent diffusion coefficients, an increase in temperature causing an increase in the rate of diffusion. The diffusion coefficients have an order to around 10^{-9} cm.^{2}/second. These values were slightly less than, but not too far from, the values observed with a group of weak organic acids reported previously (3). Table III and Fig. 6 reveal that the original concentration of solution will have a direct effect on the apparent diffusion coefficient at any particular temperature or, in this case, as the original concentration in the solution is increased, the apparent diffusion coefficient decreases. These results suggest that the larger number of sorbic acid molecules (at the higher concentration) will have a tendency to reduce the mobility of the molecules as they attempt to traverse the matrix of the plastic. Conversely, in a more dilute solution of sorbic acid, less of the sorbic acid molecules will enter the plastic and less hinderance to passage or diffusion will occur.

The activation energy (ΔE) further confirms the effect concentration of the solution has on diffusion—from a low value of 3.07 Kcal./mole for the highest concentration of sorbic acid studied to a value of 26.2 Kcal./mole for the lowest concentration employed.

SUMMARY

Sorption studies were conducted on sorbic acid at a number of concentrations and at several tem-
peratures, nylon 66 being used as the substrate. From these experiments it was possible to evaluate a number of constants such as (a) saturation value of solute in plastic, (b) standard affinity of solute for nylon 66, (c) standard heat of sorption, (d) apparent diffusion coefficient of sorbic acid in nylon 66, and (e) activation energy of diffusion in the plastic. The value of approximately -10.0 Kcal./mole for $\Delta H°$ suggested that there was a possibility of a double hydrogen bond formation between the sorbic acid and a reactive site in the plastic. Some evidence during the experiments also suggested that a slight chemical reaction might be taking place between the sorbic acid and the nylon 66. This point must, however, be further investigated. Results of the diffusion experiments revealed that concentrations of the original solutions influenced the rate of diffusion: the higher the concentration the slower the rate.

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Wurster Coated Aspirin II

An *In Vitro* and *In Vivo* Correlation of Rate from Sustained-Release Preparations

By JOHN H. WOOD and JOHN SYARTO

In vitro and *in vivo* evaluations have been made of the salicylate release characteristics of aspirin coated by the Wurster process. The films used were of methyl and ethyl cellulose plasticized by glycerol. The *in vitro* release rates of such coatings were shown to be first order. The *in vivo* release may be best represented as first order. A mathematical correlation between *in vivo* and *in vitro* rates is possible, but this correlation is directly dependent on film composition. It is shown that the slower the release pattern, the less complete is the apparent plasma availability, due to incomplete physical release and insufficient time for complete biologic absorption.

THE LAST DECADE has seen an exponential increase in number and diversity of publications, both original and review, dealing with some aspect of the controlled rate of release of medicament following oral administration. These have covered both *in vivo* and *in vitro* evaluation and their possible correlations.

As part of our program of the study of dosage forms suitable for proprietary use, we were inter-ested in release performance of crystalline drugs coated in the Wurster apparatus (1) to yield delayed release characteristics. The first paper of this series (2) describes the preparation of granules and their incorporation into a rapidly disintegrating tablet. The coatings were made of various ratios and amounts of ethyl and methyl-cellulose plasticized with glycerol.

Since it has been shown that stomach pH's may be quite variable (3) and since the normal stomach residence time and average emptying time may range up to several hours (4, 5), it is desirable for more uniform release between individuals