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RAPID ADSORPTIVE LOSS OF NITROGLYCERIN FROM AQUEOUS SOLUTION TO PLASTIC

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SUMMARY

In short time periods the loss of nitroglycerin from normal saline solutions to plastic polyvinylchloride tubing is treated as an adsorption process. The rate of adsorption is rapid and can be quantified as an apparent first-order process. The half-life of the loss at 21°C is 2.8 min. Temperature dependence of the rate constant gives a non-linear Arrhenius dependence between 6.5 and 21°C. Equilibrium amounts of nitroglycerin adsorbed at several constant bulk concentrations and 3 temperatures show a Type III adsorption behavior. At reduced concentrations of 0.1–0.8, the data conform to a Polanyi adsorption potential theory treatment. The amount of nitroglycerin adsorbed increases as temperature increases. This unusual behavior may be explained by analogy to systems where similar anomalies have been reported. The theoretical approaches presented here for a practical case provide a basis for studying systems involving general adsorptive phenomena.

INTRODUCTON

Over the past few years considerable interest has centered on the clinical use of intravenous nitroglycerin for the treatment of myocardial infarction and in open heart surgery (Ward et al., 1979; Fung, 1978). In its intravenous use, loss of the drug to polyvinylchloride bags has been identified as a problem and has been characterized as a diffusionally controlled absorption process having a half-life for fractional absorption of 3.2 h at 30°C (Yuen, et al. 1979). This time-course suggests a potentially significant loss of drug to container under clinical use but it was speculated that under other conditions adsorption onto the surface might become important and present the potential for an even greater clinical problem. One such potential problem situation resides with the administration set tubing that connects the solution to the patient because here there is a large ratio of surface area of the tube relative to a volume element of intravenous fluid that traverses its length. This suggests that, at least initially, there is a potential for drug loss via a rapid adsorption process in comparison with a generally much slower absorption path. Indeed, in recent qualitative studies administration set tubing has been implicated as the source for the observed loss of nitroglycerin from its solution (Crouthamel et al., 1978; Cossum et al., 1978; Baaske et al., 1980). No studies have been reported that quantitate or establish the mechanism of the loss. It was the purpose of this study to quantitate both the rate and mechanism of the short time loss of nitroglycerin to plastic intravenous set tubing.

MATERIALS AND METHODS

The polyvinylchloride plastic tubing used in intravenous administration sets [1] was cut length-wise, opened, and precisely cut into 1-cm segments. Such plastic segments had a calculated surface area of 2.38 cm^2. The actual area is unknown and probably differs from the calculated value because electron photomicrographs show the internal surface of the tube to be smooth but to have undulations longitudinally. The external surface appears quite smooth. An edge of the strip was pierced by a hypodermic needle and immersed in a normal saline solution containing nitroglycerin. The pH of the solution was 5.6 and did not change over the course of an experiment. The nitroglycerin solution used was prepared from a stock solution of neat nitroglycerin (Yuen et al., 1979) or an alcoholic extract of a 10% lactose adsorbate [2]. Both stock solutions were free of hydrolysis products as determined by HPLC and were standardized using a colorimetric assay previously reported (Dean and Baun, 1975). About 240 ml of nitroglycerin solution were used at concentrations ranging from about 20 to 1000 μg/ml. The volume and concentration were such that the amount of nitroglycerin removed by the plastic at equilibrium did not significantly change the bulk concentration of the solution. The nitroglycerin solutions were maintained at temperatures ranging from 6.5 to 21 ± 0.1°C using a jacketed beaker with a constant temperature circulating unit [3]. The solution was stirred rapidly using a magnetic stirring bar at a rate where uptake kinetics were independent of stirring. A plastic strip was immersed in the drug solution for a measured length of time, rapidly dipped into water to remove excess nitroglycerin solution clinging to the surface (a second short-term water wash contained no detectable nitroglycerin), and then quickly immersed for 2 sec in 250 μl of spectrograde ethyl acetate [4] to strip the surface of its nitroglycerin. It should be noted that nitroglycerin is very soluble in ethyl acetate and only slightly soluble in water. Separate experiments indicated that such short-term immersions in ethyl acetate removed all nitroglycerin from the plastic when the nitroglycerin concentration of the bulk solution was 500 μg/ml or less. At higher bulk concentrations an additional

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[1] Minidrip, 1.8 m long, Lot D27F4, Travenol Laboratories, Deerfield, Ill., 60015, U.S.A.

[2] Nitroglycerin 10% (w/w) in lactose, Lot K17-O-H, ICI America, Atlas Chemical Division, Wilmington, Dela. 19899, U.S.A.

[3] Haake, Constant Temperature Circulator, Model FK, Haake Instruments, 244 Saddle River Road, Rochelle Park, N.J. 07662 U.S.A.

[4] Burdick and Jackson Labs, 1953 S. Harvey St., Muskegon, Mich. 49442 U.S.A.

11–15% more nitroglycerin was detected in a second long-term (2 min) ethyl acetate wash. Since data collected in the first 2-sec ethyl acetate wash at these higher concentrations yielded identifiable plateau regions in plots of amount sorbed as a function of time, it was assumed that the amounts of nitroglycerin detected in the second ethyl acetate wash represented amounts absorbed and not amounts adsorbed. Further support of the assumption that adsorbed (not absorbed) nitroglycerin was being extracted in the short-term ethyl acetate wash is that small amounts if any should be absorbed over the short time-course of the studies since in earlier absorption studies it was found that the diffusion coefficient of nitroglycerin in plastic had a high activation energy (20 kcal) and hence should decrease 2.2–13 times at the temperatures used (21°C–6.5°C respectively) compared to that of 30°C where the half-life for absorption was 3.2 h (Yuen et al. 1979). As seen later, the half-lives in the adsorption studies ranged from 0.31 h at 6.5°C to 0.047 h at 21°C.

Ten microliters of the ethyl acetate solutions containing extracted surface nitroglycerin obtained at lower concentrations of bulk solution were injected directly onto an HPLC. Some ethyl acetate extracts obtained at higher concentrations of bulk nitroglycerin were diluted with 60% methanol in water prior to injection. The concentrations of nitroglycerin in the ethyl acetate solutions were calculated from the peak height of the chromatogram relative to that determined using a standard curve run with each individual sorption study. The HPLC system is similar to one used previously (Yuen et al., 1979). A DuPont instrument, Model 830, was used with a Tracor model 970 variable wavelength detector using a wavelength of 205 nm. The column was a 4.6 × 250 mm Lichrosorb RP-18, 10 μm particle size column [5]. The eluting solvent was 60% methanol in water under a pressure of 2000 lbs/sq. in. The amount of nitroglycerin sorbed onto the plastic strip was calculated from the concentration and volume of the ethyl acetate wash solution, adjusted for dilutions where necessary.

RESULTS

Plots of the amount of nitroglycerin sorbed were constructed as a function of time at each temperature and bulk concentration used. Results obtained at 10.5°C using 4 different concentrations are presented in Fig. 1. A plateau region was easily identified in each study made. Semilogarithmic plots of the fraction of nitroglycerin remaining to be sorbed as a function of time were constructed from such data. The results obtained at five temperatures using, in some cases, data averaged for fractions measured at the same time at different bulk concentrations are presented in Fig. 2. Good linearity (correlation coefficients 0.97–1.0) was obtained and the rate constants generated by linear regression of such data at each temperature studied are given in Table 1.

The equilibrium amount of nitroglycerin sorbed at each individual temperature and bulk concentration was taken as the plateau value obtained in plots of amount sorbed vs time (Fig. 1 for example). The amount sorbed per sq. cm of plastic was plotted as a function of reduced concentration, C/C_0, where C is the bulk concentration and C_0 is the

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[5] Unimetrics Corporation, 1853 Raymond Ave., Anaheim, Calif. 92801 U.S.A.

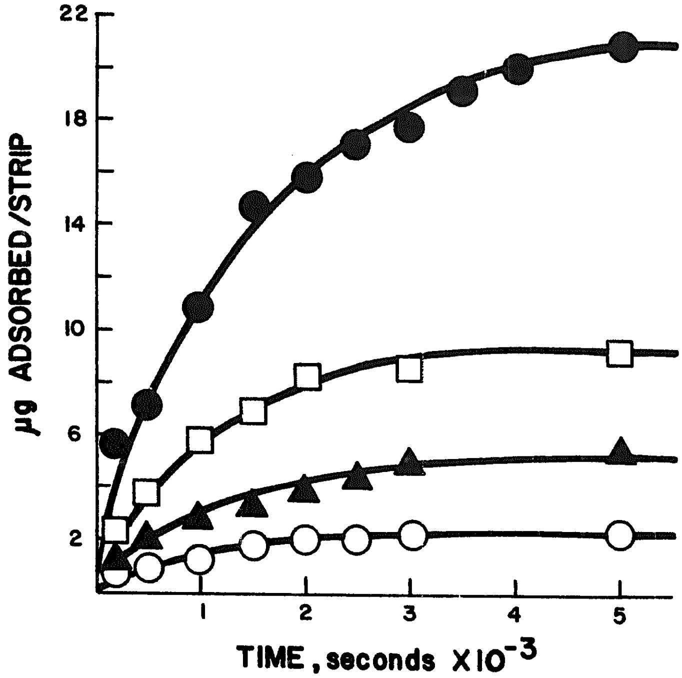

Fig. 1. Relationship between amount of nitroglycerin sorbed from solution onto plastic tubing (2.38 cm^2) at 10.5°C and 4 different constant bulk concentrations: ○, 20 µg/ml; ▲, 40 µg/ml; □, 80 µg/ml; ●, 160 µg/ml.

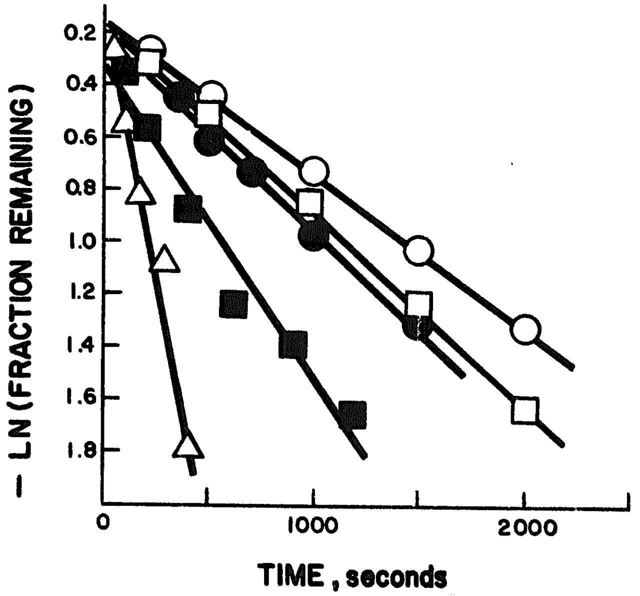

Fig. 2. Semilogarithmic relationship between fraction remaining to be sorbed and time at 5 different temperatures: 6.5°C (○), 8.5°C (●), 10.5°C (□), 15°C (■) and 21°C (△). Plots at 6.5, 10.5, and 21°C represent data averaged over several initial bulk concentrations (see Table 1).

TABLE 1

EFFECT OF TEMPERATURE ON THE RATE CONSTANT FOR SORPTION OF NITROGLYCERIN ONTO POLYVINYLCHLORIDE TUBING

Temperature (°C)	Rate constant ($sec^{-1} \times 10^3$) (S.D. $\times 10^5$)
6.5	0.605 [a] (0.842)
8.5	0.727 [b] (2.45)
10.5	0.754 [c] (1.54)
15.0	1.18 [b] (14.8)
21.0	4.08 [a] (34.5)

[a] Average of 3 different bulk concentration data.
[b] Single determination.
[c] Average of 6 different bulk concentration data.

saturation solubility of nitroglycerin at the temperature of the study. The solubilities of nitroglycerin used were obtained by interpolation at 6.5, 10.5, and 21°C from a plot of solubility vs temperature constructed from reported solubility values (Ledbury and Frost, 1927). The solubilities thus determined were 1360, 1230, and 1180 μg/ml at 21, 10.5, and 6.5°C respectively. Plots of the amount sorbed as a function of reduced concentration at the three temperatures studied are presented in Fig. 4.

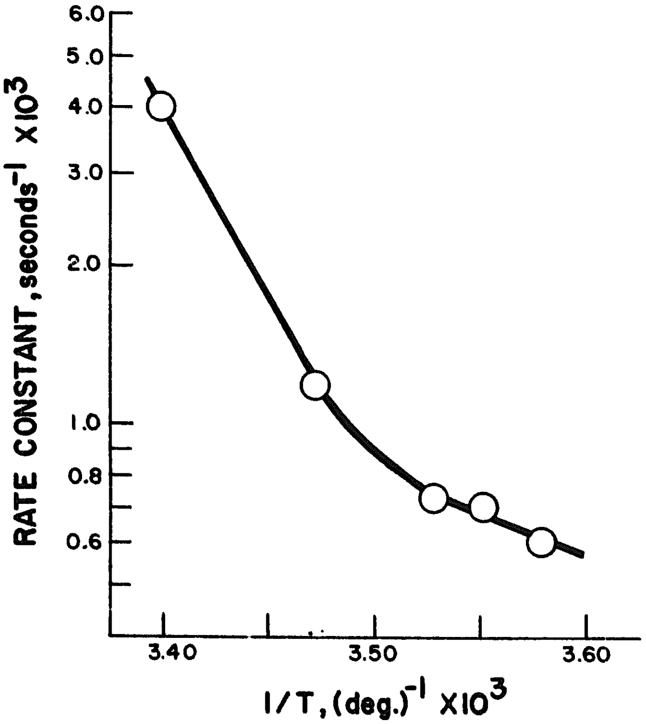

Fig. 3. The relationship between the logarithm of the rate constant for adsorption as a function of the reciprocal of the absolute temperature.

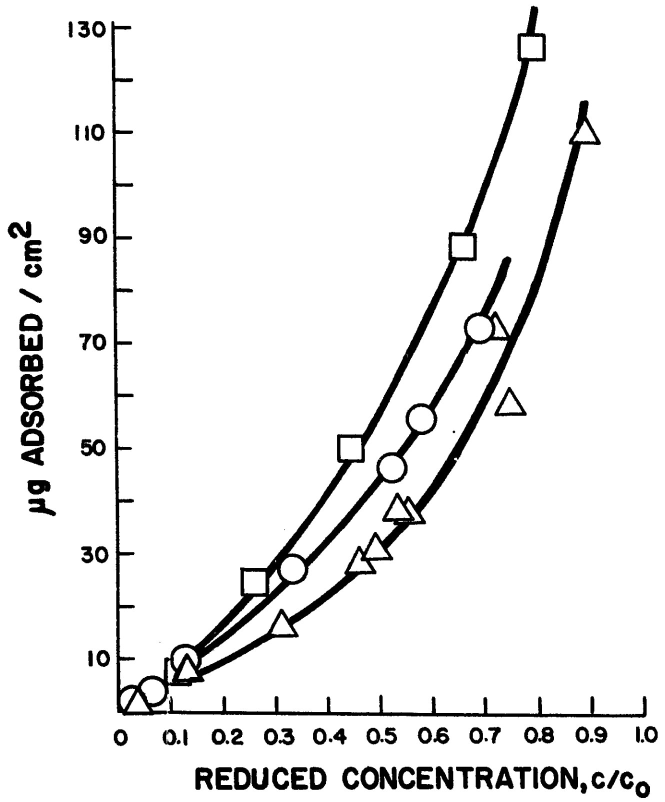

Fig. 4. Isotherms representing amounts of nitroglycerin adsorbed as a function of bulk concentration (C) divided by solubility (C_0) at 3 temperatures: △, 6.5°C; ○, 10.5°C; □, 21°C.

DISCUSSION

The rate at which adsorption occurs (Fig. 2) is, as expected, rapid. Temperatures below room temperature had to be used to be able to measure the rate process. At the highest temperature studied, 21°C, the observed half-life for attainment of equilibrium was 2.8 min. Such a short half-life certainly indicates that clinical practitioners should be alerted to the possible loss of nitroglycerin to polyvinylchloride administration set tubing at least in initial stages of drug delivery. Tasmanian workers avoided a potential problem with nitroglycerin by simply using a high density polyethylene tube (Cossum, 1978). The rates of adsorption can be characterized by assuming a first order dependence since semilogarithmic plots of fractional loss are linear over a large percentage of the interaction (Fig. 2). The adsorption of carbon tetrachloride on Teflon showed 3 first-order kinetic phases with half-lives of 29, 2.2, and 0.05 h at −14°C. Only the third, short half-life, was believed to be an adsorption process. No detailed mechanism was suggested (Wade, 1974). Among other studies that dealt with rates of adsorption, both a kinetic Langmuir approach (Peterson and Kwei, 1961) and a non-equilibrium thermodynamic approach (Fava and Eyring, 1956) indicate that a more complex dependence would be expected. The thermodynamic treatment results in a hyperbolic sine rate dependence and thus conceivably could approach a simple first-order dependence as found here. It may be that the controlling kinetics are indeed hyperbolic sine in nature but that the relative inaccuracy in the data cannot distinguish them from a simple first-order process.

If the rate constants are plotted in the Arrhenius fashion, the result found is given in Fig. 3. It appears that the relationship is not linear even over such a narrow temperature range. It is not possible to offer a quantitative explanation for this behavior at this time. However, one intersting observation may be made. If it is assumed that the curve in Fig. 3 is biphasic and straight lines are constructed in both the lower and higher temperature regions, the point of their intersection is around 13°C. The potential significance of this is in its closeness to the melting point, 12.86°C, of the more stable of the two possible forms for nitroglycerin (Davis, 1943). The other form has a melting point of 1.9–2.2°C. The possibility of a change in kinetic mechanism with temperature in a system such as nitroglycerin is an area that warrants further study for academic definition. In a study of the equilibrium adsorption of 4 solids in solution onto activated carbon at temperatures above and below solute melting points, it was found that adsorption was distinctly higher upon exceeding the melting point (Chiou and Manes, 1974). Enthalpy requirements were different in the two regions which may be extrapolated to suggest a change in kinetics. Chiou and Manes made no kinetic studies but at least the differences they observe above and below solute melting points offer a point of departure for further kinetic studies.

In a discussion of the results obtained under equilibrium conditions and the application of adsorption theories it should be noted that the polyvinylchloride plastic used is a homogeneous gel that is essentially a complex mixture of polyvinylchloride, plasticizers, fillers, and other ingredients. The surface involved is probably much more complex than the carbon, glass, polyethylenes, and other rather clean systems that were used in the development of theories.

The relationship between the amount of nitroglycerin adsorbed at equilibrium and the reduced concentration is given in Fig. 4 at the 3 temperatures studies. The plots are typical Type III adsorption isotherms (Adamson, 1976). Type III isotherms represent multilayer formation of adsorbate and are rare. They result from systems having a heat of adsorption equal to or less than the heat of liquefaction accompanying multilayer formation. The heat of liquefaction of nitroglycerin is –25 kcal/mol (Kemp et al., 1957). Type III behavior is also found among liquid adsorbates showing mutual solubility with solvent. Water is soluble in nitroglycerin to a limited extent having just about twice the solubility of that found for nitroglycerin in water at a particular temperature (Gorbunov, 1963). An interesting feature of the isotherms is that at a particular bulk concentration the amount adsorbed increases with increasing temperature. At reduced concentrations of 0.4–0.7 the ratio of the amounts adsorbed at 21 and 10.5°C is about 1.25. Normally the amount adsorbed decreases as temperature increases.

The theory that is most often applied to the adsorption of liquid and solid solutes from their solutions on surfaces is the Polanyi Theory for which a concise summary and references are given in a recent publication (Schenz and Manes, 1975). The theory, first proposed for the adsorption of gases forming multilayers, considers a potential field at the surface of a solid into which molecules fall. The adsorbed layer is most dense at the surface of the solid and decreases in density outwards. Within the range of attractive forces of the solid surface, a heterogeneous 'adsorption space', the potential energy of the gas is reduced by an amount ϵ (the adsorption potential) that depends on the distance (x) to the surface. The liquid adsorbate condenses with thickness x and volume v to meet the condition that the adsorption potential be equal to the free energy of forming the adsorbed film from bulk liquid,

$$\epsilon(x) = RT \ln P_0/P \qquad (1)$$

where R is the gas constant, T is the absolute temperature, P_0 is the vapor pressure of pure liquid and P is the equilibrium pressure at the specified temperature. A plot of adsorbate volume vs equilibrium value of ϵ is called a 'characteristic curve'. Since the ratio of adsorption potentials of any two adsorbates in any equivalent location in the adsorption space should be constant over the entire adsorption space, the theory predicts that all 'characteristic curves' for a given adsorbent should be the same except for a scale factor for each adsorbate in the adsorption potential abscissa. The scale factor is proportional to the molar volume of the adsorbate so that a plot of adsorbate volume vs ϵ/v (called a 'correlation curve') should be the same for all adsorbates on a given adsorbent.

Several analytical functions of the adsorption potential are possible (Adamson, 1968 and 1976). At large x, $\epsilon(x)$ takes on a form that is expected from dispersion theory.

$$\epsilon(x) = \epsilon_0/(a + x)^3 \qquad (2)$$

where a is a distance of a molecular radius and where in first-order dispersion theory, ϵ_0 is precisely defined in terms of atoms per cubic centimeter of substrate, polarizability, and ionization frequency. For the first few molecular diameters of adsorbed film thickness, $\epsilon(x)$ may be more exponential than inverse cube,

$$\epsilon(x) = \epsilon_0 \, e^{-ax} \qquad (3)$$

Eqn. 3 can be used as an empirical representation of the fact that the summation of dispersion interactions departs increasingly from the cube law for small x. However, a can be theoretically defined for the situation of a propagated polarization of the adsorbate initiated by the electrostatic field (which can be large) at the surface of the absorbent.

In the adsorption from solution of a solid or a partially miscible liquid, similar to the gas-phase case, one gets condensation of the solid or liquid solute as a separate phase in the adsorption space. The driving force for adsorption, the adsorption potential ϵ_{SL}, is equal to the vapor phase adsorption potential of the solute, ϵ_S, reduced by that of an equal volume of displaced solvent. The Polanyi equations here are

$$\epsilon_{SL} = RT \ln C_0/C = \epsilon_S - \epsilon_1(V_S/V_1) \qquad (4)$$

or

$$\frac{\epsilon_{SL}}{V_S} = \frac{\epsilon_S}{V_S} - \frac{\epsilon_1}{V_1} \qquad (5)$$

where again C_0 and C are the saturation and equilibrium concentrations, ϵ_S and ϵ_1 are adsorption potentials of solute and solvent, and V_S and V_1 are corresponding molar volumes. Since ϵ/V is the abscissa of a correlation curve, Eqn. 5 implies that the abscissa in the correlation curve for the liquid solute may be estimated as the difference between the abscissae of the corresponding independently measured curves for solute and solvent. Since the latter are derivable from vapor-phase isotherms, Eqn. 5 links liquid to gas phase adsorption. Fitting of expected relations between gas- and liquid-phase adsorption is apparently better for partially miscible liquids than for solids; deviations occurred when the latter were studied under high loading conditions (Manes and Hofer, 1969; Wohleber and Manes, 1971). As expected from Eqn. 5 and as measured by Wohleber and Manes, the abnormally low ϵ_1/V_1 for water accounts for the strong adsorption of organic solutes from water.

In defining an adsorption system two related parameters are often sought, the volume or amount of adsorbate forming a monolayer and the specific surface area for adsorption. Unfortunately, in systems showing Type III adsorption determining monolayer volume is a problem that is difficult to solve. It also has been shown that the Brunauer, Emmett, and Teller (BET) equation is not satisfactory for monolayer determination in Type III systems (Tornquist et al., 1978). Further, surface area determinations in adsorption from solution systems is dependent on knowing the size of the adsorbate molecule, solvation, its orientation, and being able to apply a definite adsorption model (Adamson, 1976). None of these parameters are known for the adsorption of nitroglycerin from its solution on polyvinylchloride plastic.

Defining the amount of nitroglycerin adsorbed (A) as the volume adsorbed (v) divided by density, ρ, and writing volume as the product of specific surface area, Σ, and distance x, the amount adsorbed then is

$$A = \frac{\Sigma x}{\rho} \tag{6}$$

Using eqn. 4 and the semi-empirical form for $\epsilon(x)$ as given in eqn. 3, the result

$$\ln \ln C_0/C = \ln \epsilon_0/RT - \frac{a\rho}{\Sigma} A \tag{7}$$

shows that a plot of $\ln\ln C_0/C$ vs A should be linear. Fig. 5 presents the adsorption data plotted in this fashion for reduced concentrations in the range 0.1–0.8 where in an anticipated analogy to gas adsorption, linearity should be found (Adamson, 1976). The fit of the data is good as seen from a linear regression analysis of the data. The slopes and intercepts obtained together with their standard deviations are given in Table 2.

It seems that a better fit can be obtained using the dispersion theory analytical form for the adsorption potential (Eqn. 2). Using Eqns. 2, 4 and 6, the following expression is obtained for the amount adsorbed.

$$A = -\frac{a\Sigma}{\rho} + \frac{\Sigma}{\rho}\left(\frac{\epsilon_0}{R}\right)^{1/3} (T \ln C_0/C)^{-1/3} \tag{8}$$

Hence, a plot of A vs $(T\ \ell n\ C_0/C)^{-1/3}$ should be linear. Such a plot for nitroglycerin

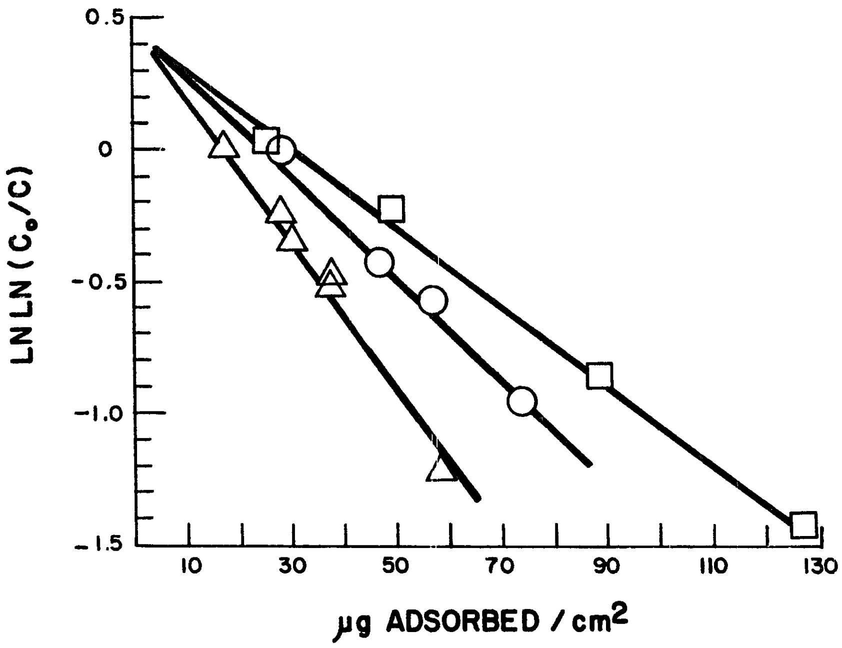

Fig. 5. The data for nitroglycerin adsorption plotted according to the exponential adsorption potential treatment (Eqn. 7) at 21°C (□), 10.5°C (○), and 6.5°C (△). The solubility of nitroglycerin is C_0 and the bulk concentration is C.

adsorption at the 3 temperatures studied is given in Fig. 6. The slopes and intercepts for these lines are listed in Table 2. Data in the 0.1–0.8 reduced concentration range were used since it is in this range that linearity is expected if results obtained in gas phase adsorption can be applied, and it appears that they can.

Several surprising results were found that may have a single cause although the cause

TABLE 2

SLOPES AND INTERCEPTS OF ADSORPTION DATA PLOTTED ACCORDING TO INVERSE CUBE LAW AND EXPONENTIAL TREATMENTS FOR ADSORPTION POTENTIAL AT 3 TEMPERATURES

		Slope [a] (S.D.)	Intercept [a] (S.D.)
6.5°C	Cube law [b]	486 (29.2)	−52.3 (5.29)
	Exponential [c]	−0.0330 (0.00141)	0.703 (0.0520)
10.5°C	Cube law	719 (12.8)	−78.2 (2.19)
	Exponential	−0.0226 (0.00144)	0.686 (0.0773)
21°C	Cube law	953 (13.5)	−104 (2.40)
	Exponential	−0.0169 (0.0087)	0.660 (0.0709)

[a] Obtained by linear regression.

[b] Using Eqn. 8.

[c] Using Eqn. 7.

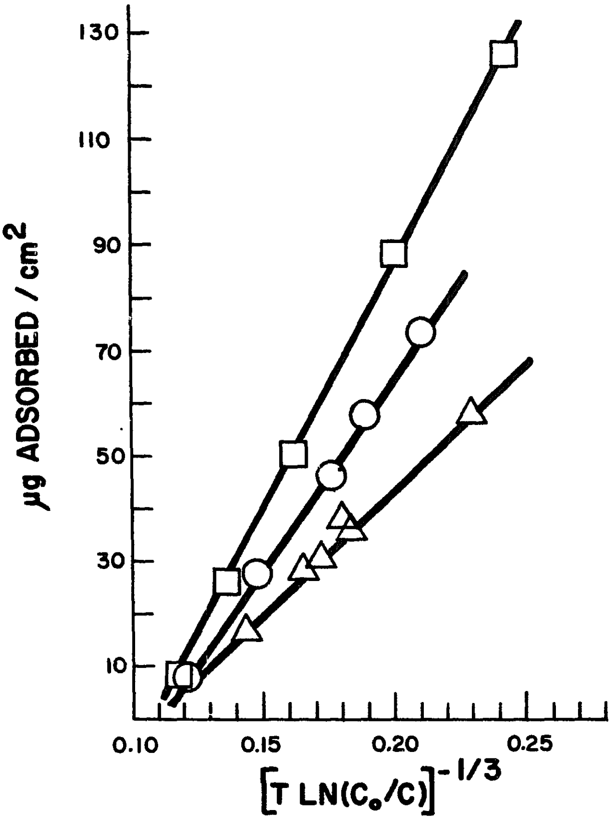

Fig. 6. The data for nitroglycerin adsorption plotted according to the inverse cube adsorption potential treatment (Eqn. 8) at 3 temperatures: (□), 21°C; (○), 10.5°C; (△), 6.5°C. T is absolute temperature and C_0/C is the inverse of the reduced concentration; C_0 = solubility, C = bulk concentration in µg/ml.

may be elusive. Fig. 4 shows that the amount adsorbed, at a particular reduced concentration at the 3 temperatures used, increases as temperature increases. Normally the amount adsorbed decreases as temperature increases at a constant equilibrium concentration. Fig. 5 shows that the slopes of the lines ($= -a\rho/\Sigma$) plotted according to Eqn. 7 become more negative as temperature decreases and the intercepts change only slightly (Table 2). The slopes should not change with temperature and the intercepts should indeed change only slightly. Fig. 6 and Table 2 show increasing slopes (although corrected for temperature) and intercepts as temperature increases but Eqn. 8 does not predict such changes; slope = $(\Sigma/\rho)\,(\epsilon_0/R)^{-1/3}$ and intercept = $-a\Sigma/\rho$. One factor common to the slope of Eqn. 7 and the slope and intercept of Eqn. 8 is Σ, the specific area. If the inverse ratio of slopes at any two temperatures plotted according to Eqn. 7 is compared with the ratio of slopes or intercepts plotted according to Eqn. 8, it is found that all ratios are the same. This leads to the speculation that area is changing. It must be kept in mind that in the adsorption of molecules from solution in the model used here, the surface area is primarily a function of adsorbate and not adsorbent (Adamson, 1976). Thus, if there is some change in the form of the adsorbate that precipitates on the surface, it is possible that surface area, as reflected by adsorbate, may change.

The increase in amount adsorbed with increasing temperature for nitroglycerin may be similar to some other systems that have been reported. Chiou and Manes (1974) studied the adsorption of solutes from solution at temperatures above and below the solute melting point. The isotherms showed lower amounts adsorbed at temperatures below the solute melting point which was ascribed to a relatively inefficient packing of the solid compared to the liquid. With nitroglycerin, one equilibrium study was made above the 13°C melting point of nitroglycerin and two studies below. All 3 systems showed an increase in amount adsorbed with increased temperature. Hence Chiou and Manes' observation would not explain the increased adsorption observed between 6.5°C and 10.5°C. However, other systems have been reported indicating that there may be packing inefficiencies of not only solids but of liquids as well at low relative equilibrium activities of adsorbate. Tornquist, et al. (1978) in studying the adsorption of water on quartz found increased adsorption with increased temperature. All their isotherms were Type III in nature and in agreement with low S-values (actually less than one) for the Frenkel-Halsey-Hill equation (FHH). By way of introduction, the FHH equation is fundamentally the same as, and precedes Eqn. 2 with a = 0, where the cube exponent is generalized to be an empirical S-value, and where for gaseous adsorption it has the form (Zettlemoyer, 1968).

$$\left(\frac{v}{v_m}\right)^S = \frac{h}{\log P_0/P} \tag{9}$$

Here v is volume adsorbed, v_m is the volume for a monolayer, h is related to adsorption energy, P_0 and P are pure liquid and equilibrium pressures, and S is the empirical number related to the diminution of forces emanating from the surface with successive layers in the adsorption space. It it assumed that the lower the value for S, the less polar the surface. For dispersion forces S is 3 (inverse cube law) and S-values between 2 and 3 are normally found in gas adsorption. Zettlemoyer (1968) used the FHH plots to identify and characterize surfaces in terms of being able to predict surface heterogeneity and thus effective 'cloud seeders'. Making the usual analogy to adsorption from solution, if the log of the amount adsorbed is plotted as a function of log $[(\log C_0/C)^{-1}]$ the slope of the resulting line is $(S)^{-1}$. This plot was made using the nitroglycerin data and is presented in Fig. 7 for studies at 10.5°C and 6.5°C. The data at 21°C follow the same trend but there were not enough data points at low C/C_0 to give a reliable analysis and hence were not included. It is clear that two branches are found at each temperature: a slope of around 3 at low reduced concentrations and another of about 1 at higher reduced concentrations. Such branching has precedent in the literature (Zettlemoyer, 1968) where the branch of higher slope is attributed to a looser packing of molecules in the first adsorbed layer in comparison with a more normal packing in the multilayer region (higher C/C_0). It thus seems that differences in packing efficiencies could exist for nitroglycerin even at a single temperature. Zettlemoyer has further shown that increased adsorption with increased temperature requires a heat of adsorption less than the heat of liquefaction (Type III isotherm) and a high entropy of adsorption: both of which indicate a mobile adsorbed phase. Since nitroglycerin adsorption is Type III, which shows branched FHH plot and a tendency toward low S-values, it parallels those systems where adsorption increases with temperature.

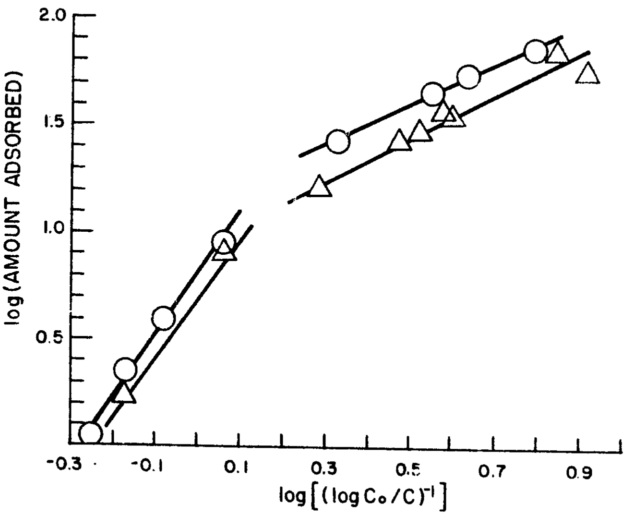

Fig. 7. The Frenkel-Halsey-Hill plot (Eqn. 9) for nitroglycerin adsorption at 10.5° (○) and 6.5°C (△). At 10.5°C the slope of the steep curve (low C/C_0) is 2.96 ($r = 0.995$) and that of the lower slope (high C/C_0) is 0.94 ($r = 0.999$). At 6.5°C the steeper slope is 3.1 and the smaller one is 0.97 ($r = 0.964$).

The application of exact equilibrium adsorption theories to a system that is complex must be semiquantitative at the best. That adsorption of nitroglycerin from solution is complex is evident. Nitroglycerin can exist in two solid forms and gives mutually soluble systems with water.. The forms of nitroglycerin thus condensed or precipitated on a solid surface can be varied and dependent on temperature. The plastic material used in these studies is likewise a complex system. Nevertheless, it is possible to at least semiquantitatively characterize kinetic and equilibrium aspects of the interaction. Both kinetic and equilibrium behavior of the adsorption of drugs from their solutions can be significant to pharmaceutical and biological systems. The approaches presented here for a somewhat practical and complex system will be explored further for their general applicability in predicting adsorptive behavior.

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