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The sorption of benzocaine from aqueous solution by nylon 6 powder

N. E. RICHARDSON AND B. J. MEAKIN

Pharmaceutics Group, School of Pharmacy & Pharmacology, University of Bath, Bath, U.K.

The sorption of benzocaine by nylon 6 powder from aqueous solution has been examined under varying environmental conditions. The extent of sorption increases with increase in electrolyte concentration, and with pH up to about pH 4. Increasing temperature reduces the amount of drug sorbed. In all cases, the sorption isotherms were linear over the concentration ranges studied, and can be described by a simple distribution law which allows the effects of ionic strength and pH to be predicted. The interaction is believed to involve hydrogen bond formation between benzocaine and the amide groups of the nylon after penetration of the polymer matrix by the drug.

Plastics materials are widely used in pharmacy but their complex nature can lead to problems (Autian, 1964; Neuwald, 1965; Houta & Leupin, 1969; McCarthy, 1970; Patel & Nagabhushan, 1970). For example, various components of a plastics mix may be leached out into the product or drug and essential formulatory adjuvants may be lost by permeation and sorption processes.

As much of the published work on drug-plastics interactions relates to commercially available materials whose exact composition is largely unknown, we have investigated some fundamental physico-chemical factors involved in these interactions, using a polymer of known composition, in a model system.

Nylon 6 (polycaprolactam) was chosen as it is one of the class of structurally similar polymeric materials known as polyamides, of the basic structure—$(NH\text{-}[CH_2]_x^-NH\text{-}CO\text{-}[CH_2]_y^-CO)_z$, which can be obtained in almost pure form, and can be used without additives. There are few reports on the interaction of weakly basic organic molecules with plastics materials, and benzocaine was therefore selected as the model drug because it is a typical example of this type of compound used in pharmacy.

MATERIALS AND METHODS

Materials. Reagent grade benzocaine (BDH Ltd.) was twice recrystallized from 50% ethanol, m.p. 88·5° (lit. 88–89°, Merck Index, 1968). Buffer salts and potassium chloride of Analar quality were used throughout. Water was freshly distilled from an all-glass still.

Preparation and characterization of nylon 6 powder: Nylon 6 (BDH Ltd.), in the form of "chips", was dissolved in 98% formic acid and precipitated as a powder by the controlled addition of 50% methanol at 60° with vigorous stirring (Richardson, 1973). The dried powder had a melting point of 214–216° (lit. 215°, Brydson, 1970) and the density measured in water was 1·120 g cm^{-3} (Bauer & Lewin, 1963). The surface area was determined as 1·3 $m^2\ g^{-1}$ and 6·6 $m^2\ g^{-1}$ by the Fisher sub-sieve air permeability method and krypton adsorption at −192° respectively. The mean particle diameter from the air permeability method was 4·3 μm, and direct micro-

scopical measurement gave an average of 4·0 μm. Water and ethanol extractive were determined by shaking 2 g of powder with either 20 ml of water or ethanol at 50° for 24 h. The ultraviolet spectra of the filtered solutions showed a low constant absorption of 0·01 optical density units over the range 220–300 nm. This level of absorbance was insufficient to interfere with the assay procedures used. Infrared analysis of the original sample and the powder showed both consisted primarily of the α form of nylon 6, although the former contained a little of the δ form. The absence of a band at 870 cm^{-1} indicated that the amount of free monomer present was small (Haslam & Willis, 1965). Dilute solution viscometry in 85% formic acid gave a viscosity average molecular weight (M_V) of 28 900 which compares with an M_V value of 32 800 by gel permeation chromatography*. The latter technique also gave number and weight averages of 15 600 and 38 300 respectively, leading to a polydispersity ratio of 2·4, indicative of a narrow molecular weight distribution.

pH measurements. These were made at the temperature of the sorption experiments using a Radiometer type 27 pH meter fitted with a PHA925a type scale expander and a Pye-Ingold 405 combined glass-calomel electrode. Calibration was with two standard buffers, one above and one below the pH to be measured (Bates, 1954).

Assay procedures. Unbuffered benzocaine solutions were diluted with water and assayed at 286 nm using a Unicam SP500 spectrophotometer. The molar extinction coefficient was found to be 16 953 from triplicate Beer-Lambert plots. Buffered solutions were diluted with McIlvaine citric acid-phosphate buffer at pH 7·0 to ensure the benzocaine was present in the unionized form, and the appropriate blank was placed in the reference cell.

pKa determination. The pKa of benzocaine was determined as 2·57 at 30° and ionic strength 0·5M by the spectroscopic method of Elving, Marowitz & Rosenthal (1956).

Solubility measurements. The solubility of benzocaine at 30° in aqueous potassium chloride solutions of varying ionic strength was determined as follows. About 30 ml of solvent was placed in a glass vessel (Richardson, 1973) together with excess solid benzocaine and heated to 90° until most had dissolved. The vessel was then transferred to a thermostatted jacket and the contents stirred rapidly whilst the temperature was allowed to cool to 30°. After a further 30 min at 30° the solution was sampled and assayed spectrophotometrically. No detectable hydrolysis occurred during this process. The solubilities are:

KCl (M) solubility at 30°	0	0·25	0·33	0·50	0·66	0·75	1·00
Benzocaine (M $\times 10^3$)	7·68	6·97	6·73	6·25	5·89	5·63	1·12

Equilibration time for sorption. Nylon 6 powder (0·2 g) was shaken between 10 min and 72 h at 30° with different concentrations of benzocaine solution (5 to 60 $\times$ 10^{-4}M, 10 ml quantities) in water. Equilibrium was always established within 30 min and a standard shaking time of 60 min was therefore adopted for the determination of the sorption isotherms. This equilibration time was always checked with the highest benzocaine concentration whenever the solvent composition was altered.

Determination of sorption isotherms. The method enabled both equilibration and sampling to be carried out under isothermal conditions. Samples of nylon 6 powder

* Polymer Supply and Characterisation Centre, Shawbury, Shrewsbury, U.K.

Table 1. *Data for the sorption and desorption of benzocaine from 0·5M aqueous potassium chloride at 30°.*

Sorption isotherm		Desorption isotherm	
Equilibrium concentration of benzocaine (M × 10^3)	Uptake of benzocaine (mol kg^{-1} × 10^2)	Equilibrium concentration of benzocaine (M × 10^3)	Uptake of benzocaine (mol kg^{-1} × 10^2)
0·37	1·17	0·25	0·84
0·79	2·05	0·52	1·39
0·80	2·11	0·54	1·50
1·19	3·07	0·80	2·08
1·61	3·97	1·32	3·38
1·99	4·97	1·57	4·26
2·33	6·17	1·88	4·58
2·79	6·92	2·11	5·42
3·20	7·97	2·67	6·47
K = 24·5 litre kg^{-1}		K = 24·0 litre kg^{-1}	
Standard error of K = 0·5		Standard error of K = 0·6	
Intercept = 1·7 × 10^{-3} mol kg^{-1}		Intercept = 2·2 × 10^{-3} mol kg^{-1}	

(0·2 g), accurately weighed, were placed in a series of dry test-tubes fitted with ground glass stoppers and 10 ml of the appropriate concentration of benzocaine solution added. The stoppered tubes were sealed with Apiezon T grease and clamped in a jig which allowed the tubes to be shaken horizontally while submerged in a thermostatted bath (±0·1°). No contamination of the solutions with grease was detectable by spectroscopy. After shaking at 70 cycles min^{-1} for 60 min the supernatant was sampled through a No. 3 sintered glass filter and assayed. At all stages before assay, including sampling, the liquid in the tube was below the water level of the bath.

The sorption-desorption isotherm at 30°. This was determined over the initial concentration range 2 to 60 × 10^{-4}M by the above procedure. Typical data from 0·5M aqueous potassium chloride are given in Table 1. Fig. 1 shows the isotherm is linear passing through the origin.

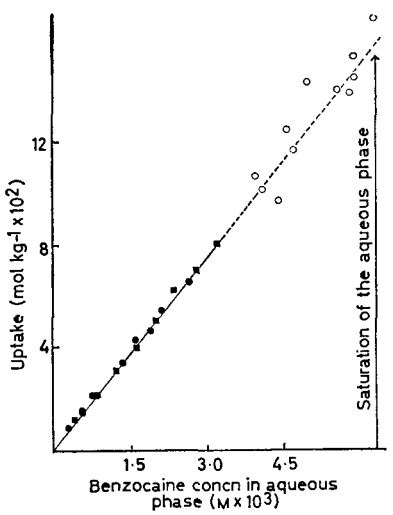

FIG. 1. Sorption-desorption isotherm of benzocaine by nylon 6 powder from 0·5 M potassium hloride solution at 30°. ■ Sorption. ● Desorption. ○ Sorption at high benzocaine concentrations.

Replicate determinations gave isotherms which were not significantly different ($t_{tab} = 2{\cdot}14$, $t_{calc} = 1{\cdot}14$, $P = 0{\cdot}95$). All isotherms obtained from aqueous solution were similarly found to be linear with correlation coefficients greater than 0·95 ($n_{min} = 9$) and the intercepts within $\pm$ two standard deviations spanned zero.

This pattern is characteristic of C type partition isotherms (Giles, McEwan & others, 1960). These linear isotherms are defined by their slopes (K values) which are the ratio of the uptake of the drug by the nylon to the equilibrium concentration of benzocaine remaining in solution.

The desorption isotherm was determined by removing 5 ml of the supernatant after equilibrium had been established, and adding 5 ml of 0·5M potassium chloride solution to the sinter sample tube which was then blown back into the sorption tube. After re-equilibration, a fresh sample of supernatant was drawn off and assayed. Loss of benzocaine during the process was negligible. The desorption isotherm shown in Fig. 1 was linear, and its K value did not differ significantly from that of the sorption isotherm ($t_{calc} = 0{\cdot}64$, $t_{tab} = 2{\cdot}14$, $P = 0{\cdot}95$).

Sorption at equilibrium concentrations of benzocaine approaching aqueous phase saturation was determined by adding measured concentrated solutions of benzocaine at 85° to the sorption tube and allowing the temperature to fall slowly to 30°, with shaking, over 2 h. The solutions were then shaken at 30° for 1 h, sampled and assayed. Sorption of the drug could thus be accomplished before crystallization occurred, and the resulting equilibrium concentration of the drug at 30° was below the solubility limit of $6{\cdot}25 \times 10^{-3}$M in 0·5M potassium chloride. The sorption isotherm in this high concentration region is also shown in Fig. 1, and even though the points are more scattered, it is evident that sorption continues to increase up to saturation of the aqueous phase.

The influence of ionic strength on sorption. The sorption isotherms of benzocaine by nylon 6 powder were determined from water and aqueous solutions of potassium chloride varying in ionic strength from 0·25 to 1·0M at 30°. The K values for these isotherms in Table 2 show that sorption increases with ionic strength.

The influence of temperature on sorption. Sorption isotherms were determined over the temperature range 30 to 56° from 0·5M potassium chloride solution. The K values in Table 2 show sorption decreases with increase in temperature.

The influence of pH on sorption. Sorption isotherms were determined from buffered benzocaine solutions over the pH range 0·2 to 8·9 at a constant ionic strength of 0·5M and at 30°. pH measurements before and after sorption showed a maximum drift of 0·05 pH units. K values in Table 2 show that sorption increases with pH up to a pH value of 4·1.

DISCUSSION

The nylon 6 powder used appeared to consist of a pure sample of nylon 6 polymer, having a surface area of about 6 $m^2 g^{-1}$ and a viscosity average molecular weight of about 30000. The difference in the values of surface area by the two methods used is probably a reflection of the porous nature and surface roughness of the powder. Scanning electron microscopy showed the surface to be very convoluted (Fig. 2), resembling the appearance of "brain coral". The porous nature of the powder is also reflected in the rate of sorption from water which is extremely rapid, 80% of the uptake occurring within 5 s and equilibrium being established within 2–3 min.

Table 2. K *values for the sorption of benzocaine from aqueous solution by nylon 6 powder under varying conditions.*

Effect of potassium chloride (30°)

Potassium chloride concentration (M)	K (litre kg^{-1})	Standard error of K
Nil	19·6	0·1
0·25	22·2	0·6
0·33	23·3	0·6
0·50	25·3	0·6
0·66	27·1	0·3
0·75	27·8	0·8
1·00	31·5	0·7

Effect of temperature (ionic strength 0·5 M)

Temperature (°C)	K (litre kg^{-1})	Standard error of K
30·0	25·3	0·6
39·0	22·3	0·5
43·8	20·6	0·4
49·4	19·4	0·4
56·0	17·0	0·4

Effect of pH (ionic strength 0·5M, 30°)

pH	K	Standard error of K
0·22	2·1	0·3
1·18	1·5	0·4
1·75	4·5	0·2
2·12	7·8	0·2
2·47	12·5	0·4
3·14	17·7	0·5
3·54	23·0	0·2
4·09	25·3	0·5
5·02	25·7	0·6
5·90	27·0	0·8
6·90	26·7	0·5
8·10	25·3	0·4
8·90	25·5	0·5

Both linear (C type) and Langmuir (L_2 type) isotherms (Giles & others, 1960) have been reported for the sorption of organic solutes by nylon polymers. Chipalkatti, Giles & Vallance (1954) found an L_2 isotherm for the sorption of phenol from water by nylon fibres, and Cole & Howard (1972) have also reported L_2 isotherms for proprionic and glutaric acids from both water and methanol. Autian and his colleagues (Kim & Autian, 1959; Guess, Worrell & Autian, 1962; Kapadia, Guess & Autian, 1964) have analysed data for the sorption of weak organic acids by nylon films using a linear form of the Langmuir isotherm.

In contrast, C type linear isotherms have been reported for phenol and benzoic acid on nylon powders (Browne & Steele, 1956) and s-triazines on nylon 6 powder (Ward & Holly, 1966).

We found the sorption isotherms for benzocaine onto nylon 6 powder from aqueous solution to be linear indicating that the drug penetrates the polymer matrix,

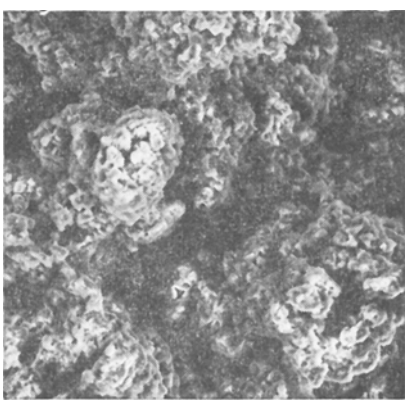

FIG. 2. Scanning electron micrograph of nylon 6 powder (magnification × 6300)

since the availability of the interaction sites appears to remain constant and independent of the amount previously sorbed. Calculations based on the figure of 6·1 $m^2 g^{-1}$ for the specific surface of the polymer and an area per molecule for benzocaine of 0·55 nm^2, calculated from Dreiden Stereomodels, confirm that the uptake is not just a surface interaction.

When a compound penetrates a polymeric material and exhibits ideal solution behaviour within the polymer, it will obey the generalized distribution law (equation 1)

$$K = \frac{C_p}{C_s} \qquad (1)$$

where K is the partition or solubility coefficient of the compound in the polymer, C_p is the concentration in the polymer and C_s is the concentration in the external environment. In the case of sorption from solution, C_p is thus directly proportional to the concentration of solute in solution at equilibrium, C_s, and the resulting sorption isotherm is linear, with a slope K. If the distribution law holds up to saturation, then equation 1 becomes equation 2, where S_p and S_s are the solubilities of the solute in the polymer and solution respectively:

$$K = \frac{S_p}{S_s} \qquad (2)$$

Fig. 1 shows that the linear relation does hold up to saturation of the aqueous phase. There is no indication of any plateau region which can be expected when a solute penetrates a polymeric substrate (Giles & others, 1960).

The addition of electrolyte, in the form of potassium chloride, results in an increase in the sorption of benzocaine from aqueous solution (Table 2). This is accompanied by a corresponding decrease in the solubility of benzocaine in the aqueous phase. An empirical expression (eqn 3) has been given by Setchénow for the effect of salt on the solubility of neutral molecules (Harned & Owen, 1958).

$$\log_{10} \frac{S_o}{S_s} = m.C \qquad (3)$$

S_o and S_s are the solubilities of the neutral molecule in the pure solvent and salt solution respectively, C is the molar concentration of electrolyte and m is an empirical constant. Combining equations 2 and 3 gives equation 4, which should predict the effect of electrolyte on the sorption isotherm.

$$\log_{10} K = \log_{10} \frac{S_p}{S_o} + m.C \qquad (4)$$

Fig. 3 shows that a plot of $\log_{10} K$ against C is linear, giving a value for S_p of 0·152 mol kg^{-1} which is close to the maximum uptake of 0·166 mol kg^{-1} obtained for the sorption of benzocaine from 0·5M potassium chloride (Fig. 1).

From equation 2 a plot of $\log_{10} K$ against $\log_{10} S_s$ should also be linear with a slope of −1. However, although the relation is linear ($r = 0{\cdot}998$, $P = 0{\cdot}95$, $n = 7$), the slope has a value of −1·14 and the intercept gives the value for S_p of 0·076 mol kg^{-1}. The deviation of the slope from unity, and the low S_p value, may be a reflection of the

effect of electrolyte on the activity of the solute in solution. If one assumes that the activity of the solute in the polymer is ideal, then equation 2 becomes

$$K = \frac{S_p}{\gamma S_s} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (5)$$

where γ is the activity coefficient of the solute in the liquid phase. An activity term correction should similarly be introduced into the Setchénow equation (equation 3). Combination of such a modified Setchénow expression and equation 5, however, results in the elimination of the activity coefficient, and leads directly to equation 4, which is therefore probably a better relation for assessing the value of S_p than the more simple equation 2.

With rise in temperature, adsorption processes usually decrease owing to a weakening of the attractive forces between the substrate and the adsorbent. For the solid-solute-solvent interaction, the effect is usually enhanced by the accompanying increase in the solubility of the solute in the solvent. The sorption of benzocaine from 0·5M

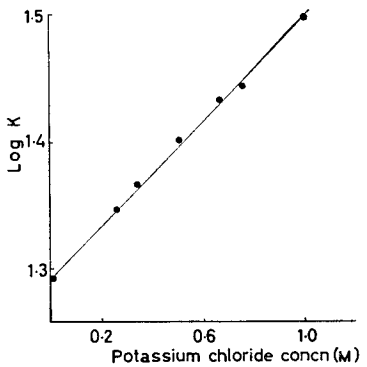

FIG. 3. Relation between K and potassium chloride concentration in the aqueous phase for the sorption of benzocaine by nylon 6 at 30°.

potassium chloride decreased with rise in temperature (Table 3). These data were fitted to the Van't Hoff relation, equation 6, and a linear relation was found between $\log_{10}K$ and the reciprocal absolute temperature (1/T), ($r = 0{\cdot}995$, $P = 0{\cdot}95$, $n = 5$)

$$\log_{10}K = \frac{-\Delta H^\circ}{2{\cdot}303} \cdot \frac{1}{RT} + \text{constant} \quad .. \quad .. \quad .. \quad (6)$$

A value of $-12{\cdot}4$ kJ mol^{-1} was obtained for the standard enthalpy of sorption (ΔH°).

The standard free energy of sorption, ΔG°, and the standard entropy of sorption, ΔS°, were calculated as $-8{\cdot}1$ kJ mol^{-1} and $-14{\cdot}2$ J mol^{-1}K^{-1} respectively, using equations 7 and 8.

$$\Delta G^\circ = -RT \log_e K \quad .. \quad .. \quad .. \quad (7)$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad .. \quad .. \quad .. \quad (8)$$

The value of ΔH° is of the order normally associated with Van der Waals forces or weak hydrogen bond formation. The latter mechanism has been postulated by other workers for the interaction of polyamides and organic acids (Chipalkatti & others, 1954; Kapadia & others, 1964; Rodell, Guess & Autian, 1964), and could operate in

this case between the amino-group of the drug and the carbonyl oxygen of the polyamide. The low standard enthalpy indicates that chemisorption is not involved in the sorption process which is substantiated by the superimposability of the sorption and desorption isotherms (Fig. 1), which shows that sorption is fully reversible.

Dearden & Tomlinson (1970) have postulated that the positive entropy change found for the interaction between p-substituted acetanilides and bovine serum albumin was indicative of a hydrophobic bonding mechanism between the solute and the protein. However, although nylons have a structural similarity to proteins, the negative entropy change found for the sorption of benzocaine would suggest that such a mechanism is not playing a large part in the drug-nylon interaction, although some contribution from this mechanism cannot be ruled out.

The influence of pH at ionic strength 0·5M and 30° on the sorption of benzocaine by nylon 6 powder is shown in Fig. 4. Below pH 2·0 sorption is low, but rises to a maximum at about pH 4·0 and thereafter becomes constant. The extent of sorption at pKa 2·57 (determined under analgous conditions) was about half that of the maximum uptake. The mole per cent free base, determined from the Henderson-Hasselbach equation, is also plotted against pH in Fig. 4, which shows that the drug dissociation curve is almost superimposable on the pH sorption profile, clearly indicating that it is the unionized form of the drug which is sorbed.

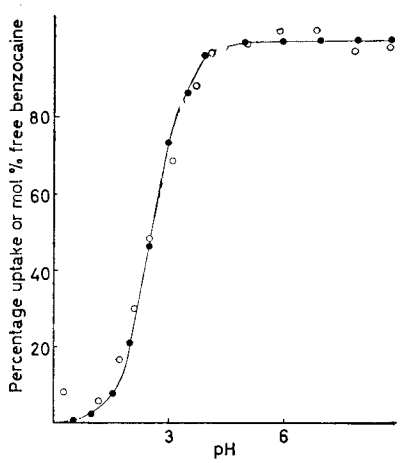

FIG. 4. pH profile for the sorption of benzocaine by nylon 6 powder from buffered solutions at 30° and ionic strength 0·5 M (○) and the corresponding drug dissociation curve (●).

This is believed to be direct evidence of hydrogen bond formation between the drug and the amide group in the nylon (Kapadia & others, 1964; Rodell & others, 1964). However, the sorption of alkyl *p*-hydroxy benzoates by polyethylene has also been shown to be greatest when the compounds are in the unionized form (Kakemi, Sezaki & others, 1971). As polyethylene has virtually no polar sites, this would indicate that the drug had to be in the unionized form so that Van der Waals forces could operate between drug and polymer. Kapadia & others (1964) believe that weak hydrogen bonds are formed between drug and nylon, which are then stabilized by Van der Waals forces. It is probable that when water is present as solvent, hydrogen bond formation between drug and polymer is not alone sufficient to bind the drug molecules to the polymer, due to the massive number of water molecules which would compete for the sorption sites.

The interaction of benzocaine with nylon 6 powder appears, therefore, to involve penetration of the drug into the polymer matrix, the drug probably being bound by weak hydrogen bond formation with the amide groups of the polymer, which is stabilized by Van der Waals interactions between the aromatic ring and the methylene groups of the chain. The extent of the sorption is influenced by a number of factors, including temperature, electrolyte concentration and pH, which can be predicted by simple distribution and dissociation theory.

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