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The effect of pore size of the inhaler support upon the concentration of volatile drug emerging in the air stream from a nasal inhaler*

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The effect that the pore size of the inhaler support has upon the concentration of methylamphetamine emerging in the airstream from a nasal inhaler has been investigated over a range of temperatures using a series of sintered glass plugs of differing porosity. The results showed that there was a reduction in the drug concentration with decrease in pore size of the plugs. An attempt was made to correlate these findings with the Kelvin equation. It was concluded that the degree of lowering of drug concentration was much greater than could be explained on the basis of this equation; and that this was due to the fact that the airstream was not saturated with the drug vapour. The degree of undersaturation appeared to be related to the porosity of the plugs.

Kelvin (1871) showed that the equilibrium vapour pressure above the meniscus of a liquid contained in a fine capillary is less than that over the plane surface of the liquid, provided the angle of contact between the liquid and capillary wall is less than 90°. Previous investigations of the physico-chemical factors governing the release of a volatile drug from a nasal inhaler indicated that the pore size of the fibrous support into which the drug is impregnated may influence the drug concentration in the emergent airstream (Armstrong, Carless & Enever, 1970). To study the effect of pore size further, and its relation to the lowering of vapour pressure predicted by the Kelvin equation, inert sintered glass plugs of various porosities have been substituted for the conventional fibrous inhaler support. Using a simulated inhaler system, the concentration of methylamphetamine emerging in the airstream from these glass plugs has been measured over a range of temperatures.

MATERIALS AND METHODS

Materials

(+)-Methylamphetamine (Aldrich Chemical Co. Inc. Milwaukee, Wisconsin).

NN-Dimethylaniline of Analar Grade (British Drug Houses, Poole, Dorset).

The purities of these materials were checked by gas-liquid chromatography using the experimental conditions previously described (Armstrong & others, 1970). Under these conditions, each compound produced a single peak.

Diethyl ether (May and Baker, Dagenham, Essex).

Glass plugs composed of sintered glass cores 5 mm diameter and 22 mm long enclosed in glass casings of 7 mm outside diameter. Grade 0, 1 and 2 sintered plugs were produced.

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Methods

Characterization of sintered glass plugs

Each plug was characterized with regard to its maximum and mean pore radius, pore size distribution and the total pore volume.

The maximum pore radius, r_{max}, was measured using the British Standard bubble pressure method (B.S. 1752:1963). Water (20°) was employed as the test liquid.

The mean pore radius, r_{mean}, was calculated from the results of air permeability studies. The surface area of each plug was found by passing air through at flow rates ranging from 500 to 2000 cm^3 min^{-1} and measuring the pressure differential across the plug using an inclined water manometer. The Kozeny-Carman equation was employed to calculate the specific surface at each flow rate from the data (Gregg, 1961). Extrapolation of the relation between air flow rate and specific surface gave the value for specific surface at zero flow rate, S. With a knowledge of the porosity of the plug, ϵ, the mean pore radius was calculated from the equation

$$r_{mean} = \frac{2\epsilon}{(1-\epsilon)S\rho} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where ρ is the density of the glass used to prepare the sintered plug. For the purposes of this calculation, the plug is regarded as an array of circular capillary tubes of varying cross-section arranged in parallel.

The pore size distribution of each plug was obtained by porosimetry. The volume of mercury penetrating the plug at different applied pressures was measured. The volume penetrating at a particular pressure, p, determines the contribution of pores greater than radius r to the total pore volume. The relation between p and r is given by

$$r = \frac{-2\gamma\cos\theta}{p} \text{ (Washburn, 1921)} \quad .. \quad .. \quad .. \quad (2)$$

where γ is the surface tension of mercury, and θ is the angle of contact between mercury and the pore surface (an average value of 140° has been found for a large variety of porous solids). In this work a low-pressure porosimeter based on the design of Cameron & Stacy (1960) was used and four determinations were carried out on each plug. The pore size distribution was obtained by differentiating the experimental applied pressure-volume uptake plot and calculating the pore size distribution function, D(r), at suitable pressure values (Ritter & Drake, 1945).

The total pore volume of each plug was obtained in the following manner. The mercury porosimeter was used to measure the volume of mercury displaced by the plug under vacuum. Under these conditions, the non-wetting liquid could not penetrate the pores. The volume of water (20°) displaced by the outgassed plug (complete penetration of the displacement medium into the pores) was then determined with a specific gravity bottle. The difference between the mercury and water displacement volumes gave the total pore volume. Four determinations were carried out on each plug and the mean value calculated.

Determination of drug concentration emerging in the airstream from a nasal inhaler

The sintered glass plugs were dried in an oven at 100° for 6 h and subsequently allowed to cool to room temperature in a vacuum dessicator. This treatment removed any moisture in the plugs which might have been soluble in the methylamphetamine and caused a depression in its vapour pressure (Armstrong, Carless & Enever, 1972). Each plug was then impregnated with 0·1 cm^3 of methylamphetamine and placed in the temperature-controlled simulated inhaler previously described (Armstrong & others, 1970). After allowing 45 min for temperature equilibration, air at a flow rate of 950 cm^3 min^{-1} was passed through the inhaler for 30 s periods with 2 min intervals between successive samples. Each sample of air was bubbled through diethyl ether at 0° containing the internal marker *NN*-dimethylaniline. The ether solutions were subsequently analysed for methylamphetamine using a Perkin-Elmer F11 gas chromatograph equipped with flame ionization detector. A column composed of 10% w/w carbowax 6000 and 5% w/w potassium hydroxide on Celite 545 was employed, and the experimental conditions were as previously described (Armstrong & others, 1970). For each sintered glass plug, the effect of temperature upon the airstream concentration of methylamphetamine was investigated over the range 10 to 40°.

RESULTS

Fig. 1 (a) and (b) are the pore size distributions of the five sintered glass plugs in the form of plots of the pore size distribution function against logarithm of pore radius. Table 1 shows the values for r_{max}, r_{mean}, the pore size range and the total pore volume

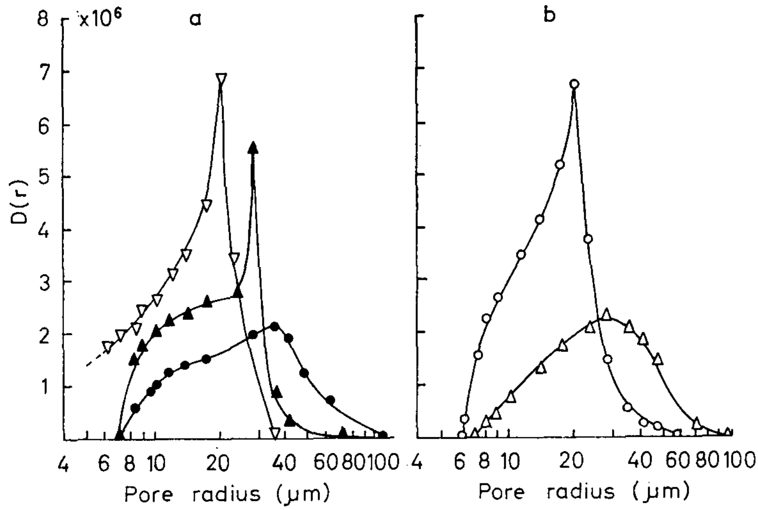

FIG. 1 (a) and (b). Pore size distributions of the five sintered glass plugs in the form of plots of the pore size distribution function, D (r), against logarithm of pore radius. Sintered glass plug code ●, A; △,B; ○,C; ▲,D; ▽,E.

Table 1. *Physical parameters of sintered glass plugs.*

Code letter of plug	Maximum pore radius (r_{max}) (μm)	Mean pore radius (r_{mean}) (μm)	Porosimeter pore size range (pore radius) (μm)	Total pore volume by displacement method (cm^3)
A	118	38	7–110	0·193
B	96	36	7·5–100	0·201
C	54·5	17·5	6·5–60	0·154
D	103	20	7–100	0·170
E	29·5	14	<6–35	0·216

for each plug. The data obtained from the three techniques of pore radius measurement were consistent in that r_{max} and r_{mean} were of the same order of magnitude and fell within the range of pore size for each plug. The total pore volumes of plugs A, B, C and D obtained by the displacement method agreed to within $\pm$ 3% of the corresponding volumes of mercury penetrating the plugs at the maximum pressure used (120kN m^{-2}), and it may be assumed that all pores were penetrated by mercury. With plug E, the total pore volume by displacement was 8% larger than the mercury penetration value, indicating that some pores less than 6μm in radius were present.

Fig. 2 shows the relation between the logarithm of methylamphetamine concentration emerging from the inhaler and the reciprocal of absolute temperature for

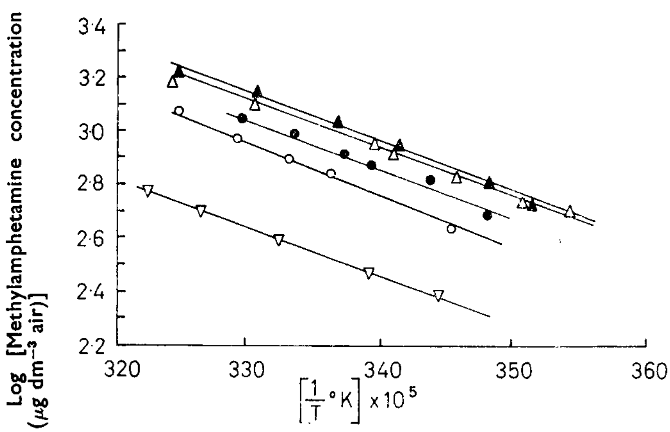

FIG. 2. Variation of logarithm of methylamphetamine concentration with reciprocal of absolute temperature for the glass plugs of differing pore size distribution. Air flow rate 950 cm^3 min^{-1}. 0·1 cm^3 of drug impregnated into the plugs. Code as Fig. 1.

each of the plugs. The data give a series of parallel linear relations showing an increase in concentration with rise in temperature. It is evident that, at any given temperature, the methylamphetamine concentration is dependent upon the pore size of the plug. The order of decreasing concentration is D $\approx$ B $>$ A $>$ C $>$ E and this roughly corresponds with the order of decreasing maximum pore radius.

If it is assumed that an equilibrium has been established between the liquid and vapour phases, it is possible to derive a vapour pressure value for the drug at a given temperature using the methylamphetamine concentration in the emergent airstream and the ideal gas equation (Armstrong, Carless & Enever, 1971). The linear relations between logarithm of methylamphetamine concentration and reciprocal of absolute temperature (Fig. 2) are then to be expected since they are analogous to the Clausius-Clapeyron equation which expresses the variation of vapour pressure with temperature. The slopes of the lines in Fig. 2 are a function of the latent heat of vaporization of methylamphetamine and it follows that a similar value should be obtained for all five sintered glass plugs.

DISCUSSION

The results show that the pore size of the inert glass support does influence the concentration of methylamphetamine emerging from the inhaler system. Thus, by analogy, this could also occur with the various commercial fibrous supports used in nasal inhalers.

In theory, the lowering of vapour pressure which occurs when a liquid is confined in a fine capillary is expressed by the Kelvin equation

$$\ln[P/Po] = \frac{-2M\gamma\cos\theta}{\rho.RTr} \quad \ldots \quad (3)$$

where Po is the vapour pressure of the liquid at a plane surface, P is the vapour pressure of the liquid in the capillary of radius r. ρ, γ and M are the density, surface tension and molecular weight of the liquid respectively. R represents the gas constant and T is the absolute temperature.

The angle of contact, θ, between the liquid and the capillary wall, assuming that complete wetting occurs, is taken to be zero. It follows that a plot of lnP versus 1/r should give a straight line of negative slope. In attempting to apply this equation to the present system there are complications in that there was a distribution of pore size within a plug, and the amount of methylamphetamine impregnated (0·1 cm^3) was not sufficient to fill all the pores. Nevertheless, with a knowledge of the total pore volume (Table 1) it is possible to calculate the proportion of pores that were filled (see Table 2). When the methylamphetamine was placed in contact with a sintered

Table 2. *Estimate of largest pore radii filled with methylamphetamine and comparison with theoretical values derived from Kelvin equation for sintered glass plugs.*

Code letter of plug	Percentage of pore volume filled with methylamphet-amine	Radius of largest pore filled with methylamphet-amine (μm)	Kelvin pore radius (nm)	Ratio of pore radius (Largest/Kelvin)
A	52%	38	1·29	$2·9 \times 10^4$
B	50%	36	1·38	$2·6 \times 10^4$
C	65%	22	1·17	$1·8 \times 10^4$
D	59%	29	1·39	$2·1 \times 10^4$
E	46%	18	1·01	$1·7 \times 10^4$

glass plug, the drug would have penetrated most rapidly into the largest pores since, from the Rideal-Washburn equation (Davies & Rideal, 1963), the rate of advance of a liquid into an air-filled pore is directly proportional to its radius:

$$\frac{dl}{dt} = \frac{r\gamma\cos\theta}{4\eta l} \quad \ldots \quad (4)$$

where l is the distance the liquid of viscosity, η, has travelled along the pore in time t. Subsequently however, the plug was allowed to equilibrate for 45 min before use. Within the enclosed environment of the plug there would have been sufficient methylamphetamine to produce a saturated vapour phase, and it is reasonable to assume, from the Kelvin equation, that redistribution of the drug would have occurred from the large to the small pores.

At equilibrium the drug should have been exclusively in the fine region of the pore size distribution and the vapour pressure exerted within the sintered plug should be equal to that exerted by the liquid held in the largest pore containing methylamphetamine. This pore size can be calculated since the proportion of pores filled with methylamphetamine and the pore size distribution are known for each plug. The results of the calculation are shown in Table 2, and Fig. 3 shows the plot of natural

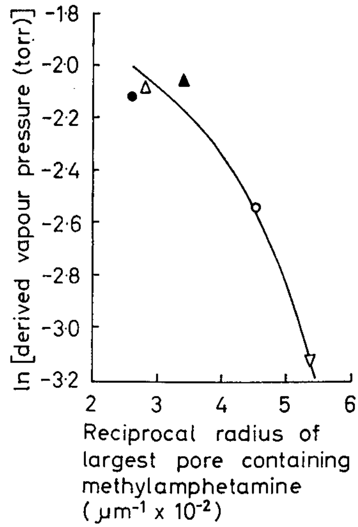

FIG. 3. Relation between natural logarithm of derived vapour pressure and reciprocal of largest pore radius containing methylamphetamine for the glass plugs of differing pore size distribution. Code as Fig. 1.

logarithm of vapour pressure as derived from the inhaler system data at 25° plotted against the reciprocal of the radius of the largest pore containing methylamphetamine. It can be seen that the plot is a curve rather than the straight line predicted from equation (3).

Furthermore, for each derived vapour pressure, using the absolute vapour pressure of methylamphetamine at a plane surface, Po, (Armstrong & others, 1971) and its surface tension (determined with a Du Nouy Tensiometer to be $32{\cdot}4 \times 10^{-3}$ N m^{-1} at 25°), it is possible to use equation (3) to calculate the theoretical radius of the pore (Kelvin radius) which would produce such a lowering of vapour pressure. Table 2 shows these Kelvin radii, and it is evident that they are smaller by a factor of approximately 10^4 than the largest pore containing methylamphetamine. Even if the assumptions concerning redistribution of methylamphetamine during equilibration are incorrect, mercury porosimetry showed that for plugs A, B, C and D the smallest pore radii present were in the region of 6 to 8 μm which is still 10^3 larger than the Kelvin radii. Despite the fact that the minimum pore radius of plug E could not be determined with the low-pressure porosimeter, it is unlikely that there were a significant number of pores with radii in the nanometre region since the r_{mean} value obtained from air permeability experiments was of the same order of magnitude as the r_{max} value (Table 1). Hence, the depression of vapour pressure produced by the various sintered glass plugs is much greater than would be predicted from the Kelvin equation. Other workers have shown that the lowering of vapour pressure of a liquid in fine capillaries is greater than would be expected from the Kelvin equation. Shereshefsky (1928) carried out very careful experiments with toluene using fine quartz capillaries (5–6 μm radii) and found that the lowering of vapour pressure was eight times as great as predicted by the Kelvin equation. Harbard & King (1940) also noted a similar discrepancy when examining the adsorption properties of chromic oxide. The assumptions implicit in the Kelvin equation that the surface tension of the liquid in a fine capillary is the same as that of a bulk liquid and that the meniscus in the capillary is hemispherical were questioned by these workers. However, Guggenheim (1940) has shown theoretically that the surface tension should be independent of capillary radius when this exceeds 0·1 μm. Notwithstanding these facts, the present discrepancy between the theoretical and experimental data appears to be too great to be accounted for in this way. It seems certain therefore that there must be undersaturation of the airstream with methylamphetamine at the air flow rates used and that the degree of undersaturation is in some manner governed by the lowering of vapour pressure produced in the sintered glass plugs of varying porosities.

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