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The influence of the moisture content of the fibrous support of a nasal inhaler upon the concentration of drug in the air stream

P. A. M. ARMSTRONG, J. E. CARLESS AND R. P. ENEVER
Department of Pharmacy, Chelsea College, University of London, London, S.W.3, U.K.

The moisture contents of cellulose acetate and paper fibrous support materials used in nasal inhalers have been determined by infrared drying and extraction techniques. The mutual solubilities of water and methylamphetamine have been investigated at various temperatures, and the results indicated that the system exhibited both upper and lower consolute temperatures. The effect of molar composition of water on the total and partial vapour pressures of methylamphetamine–water mixtures have also been investigated. Positive deviations from Raoult's Law were observed for both total and partial pressures. The present results have been related to data obtained previously with an inhaler system to show that the moisture contents of the fibrous supports are partially responsible for the discrepancy between the derived and absolute vapour pressure values for methylamphetamine.

Previously, Armstrong, Carless & Enever (1970, 1971) have discussed the factors affecting the dose of a drug delivered from a nasal inhaler. An attempt was made to relate the results obtained from the inhaler system with absolute vapour pressure measurements of the drug in simple liquid form under similar experimental conditions. It was concluded that an equilibrium is achieved between the liquid and vapour phases in the inhaler system and that this situation is analogous to that obtained with the simple liquid form of the drug. However, the numerical value of the vapour pressure exerted by a particular drug, as derived from the inhaler system results, was found to be smaller than that obtained by direct measurement of its vapour pressure. Some of the possible causes for the discrepancy are as follows:

(1) The air flowing through the nasal inhaler may not become completely saturated with the volatile drug vapour.

(2) The vapour pressure exerted by the drug in the finely porous support of the inhaler may be less than that achieved when the vapour is in equilibrium with a plane liquid surface.

(3) There may be physical interaction between the drug and the support material.

(4) The fibrous support material is hydrophilic, and therefore tends to take up water vapour from the atmosphere until equilibrium conditions are achieved. This water may well be miscible with the drug and cause a depression of its vapour pressure.

The work now presented considers this last aspect. The moisture contents of both cellulose acetate and paper fibrous support materials have been measured. An assessment has been made of the moisture that is available for solution in a volatile drug (methylamphetamine). Secondly, the solubility of water in this drug has been determined over a range of temperature. Finally, the total and partial vapour pressures of water–methylamphetamine solutions have been determined by absolute vapour pressure measurement.

MATERIALS AND METHODS

Materials

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

The purity of this material was checked by gas–liquid chromatography.

The experimental conditions have been described elsewhere (Armstrong & others, 1971).

Cellulose acetate and paper fibrous inhaler supports, both commercially available were used in the form of cylinders 22 mm long by 8 mm diameter; weighing 0·250 and 0·171 g respectively.

Methods

Determination of moisture contents of fibrous inhaler supports

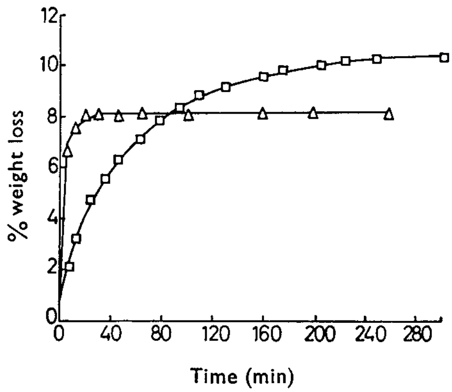
A Denwood 1F300 Infrared Drier was used to determine the rates of removal of water and the moisture contents of 2 g quantities of the cellulose acetate and paper support materials. The drying temperature was governed by the distance between the sample and the infrared lamp, and was adjusted to 70° to avoid charring of the sample. Readings of moisture content, in terms of percentage loss in weight on drying, were taken at frequent intervals until there was no further loss in weight of the sample. The fibrous supports were examined both in their original form and also when teased out to expose the maximum possible surface area for evaporation.

To correlate the moisture contents as measured by infrared drying with the water available from the fibrous supports for solution in impregnated volatile drugs, the water contents that could be extracted with n-propanol were determined. A batch of twelve supports of each type was extracted with 20 ml of n-propanol by shaking with the solvent for 1 h. The refractive index of the extracting solvent was measured ($\pm$0·0002) using an Abbé refractometer thermostatted at 20°. With the aid of a calibration curve previously prepared using water in n-propanol solutions of known concentrations, the amount of water extracted from each type of fibrous support was calculated. To ensure that the n-propanol did not extract material from the supports that interfered with this determination, both dried paper and cellulose acetate supports were extracted in the same manner. The refractive index of the extracting solvents was the same as that for pure n-propanol.

At the time this work was carried out, the relative humidity was 87% (20°).

Determination of the solubility–temperature relations of water in methylamphetamine

A range of methylamphetamine–water mixtures was prepared, and a 2 ml volume of each mixture was placed in a 5 ml glass ampoule held in a thermostatted water bath. A sensitive calibrated bead thermistor was immersed in the mixture to monitor its temperature. The temperature of the water bath was raised from 0 to 100° at a rate of 5° min^{-1}. Miscibility of the two liquids produced a clear solution, and the limit of mutual solubility was indicated by the onset of opalescence. The mixture was then cooled from 100° at the rate of 5° min^{-1} and again the points of immiscibility were recorded.



FIG, 1. Infrared drying curve for paper and cellulose acetate fibrous supports, at 70° △–Paper supports, □–Cellulose acetate.

Absolute determination of the total vapour pressure–temperature relation for methylamphetamine–water mixtures

The equipment and details of the experimental technique used for determining the absolute total vapour pressure of a mixture of volatile materials and the composition of the vapour phase have previously been described (Armstrong & others, 1971). Mixtures of methylamphetamine and water were prepared and their total vapour pressures were measured over a range of temperature. The composition of the vapour phase of each mixture was measured at 25·25° by collecting the vapour in a clean cold trap immersed in liquid nitrogen. The condensed liquid was then analysed for water content by determining its refractive index using the Abbé refractometer (20°) and referring to a calibration curve prepared using a range of methylamphetamine–water mixtures. Application of Dalton's Law of partial pressures then permitted the calculation of the partial pressures of the two components from the vapour phase composition.

RESULTS

Fig. 1 shows the infrared drying curves for the teased samples of the two inhaler support materials. The paper supports rapidly lost weight and constant weight was achieved within 30 min. Weight loss from the cellulose acetate supports was a much slower process, and the final percentage loss in weight was much higher than the paper supports. Similar curves were obtained with the supports in their original cylindrical form, although the rates of weight loss were slightly lower. When using either the teased or intact samples of the two support materials, the moisture content of the paper supports was found to be 8·1% w/w and that of the cellulose acetate supports to be 10·4% w/w expressed in terms of percentage loss in weight on drying. The water content extracted from paper supports with n-propanol was found to be 7·5% w/w and for cellulose acetate supports was 10·0% w/w. The precision of the infrared drying technique was ±0·1% w/w, and that of the solvent extraction method ±0·4% w/w.

Fig. 2 shows the solubility–temperature relation for mixtures of methylamphetamine and water. The shape of the region of immiscibility indicates that the system should possess both upper and lower consolute temperatures. Unfortunately these could not

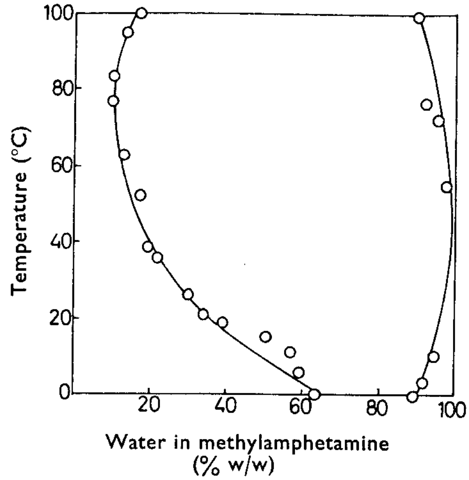


FIG. 2. The effect of temperature on the mutual miscibility of various concentrations of water in methylamphetamine. The area between the curves represents two liquid phases.

be precisely located, firstly, because it was not possible with the equipment available to cool the mixtures below 0°, and secondly, above 100° it was difficult to control the compositions of the mixtures because of evaporation of the liquids.

The variation of the logarithm of total vapour pressure with reciprocal of absolute temperature of pure methylamphetamine and three methylamphetamine–water mixtures is shown in Fig. 3. For the methylamphetamine–water mixtures the range of temperature covered was −6° to 9·5°. The graph also includes data obtained from the literature (Osborne & Meyers, 1934) for pure water. Straight line relations were obtained for all five systems. To obtain values for the total vapour pressures of the methylamphetamine–water mixtures at 25·25° (335·1 × 10^{-5} °K^{-1} in Fig. 3) it was necessary to extrapolate these lines. The pressures exerted by the mixtures at this

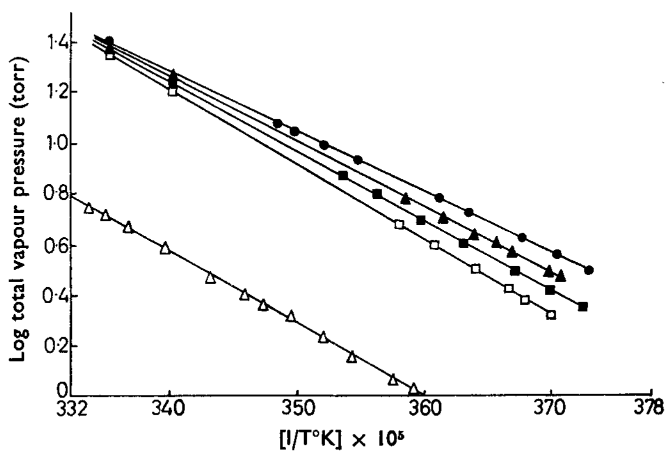


FIG. 3. Logarithm total vapour pressure against reciprocal absolute temperature for different mol fractions of water in methylamphetamine. △–pure methylamphetamine. □–0·412 Mol fraction water in methylamphetamine (7·81 % w/w). ■–0·483 Mol fraction water in methylamphetamine (10·13 % w/w). ▲–0·591 Mol fraction water in methylamphetamine (14·86 % w/w). ●–Pure water-literature values.

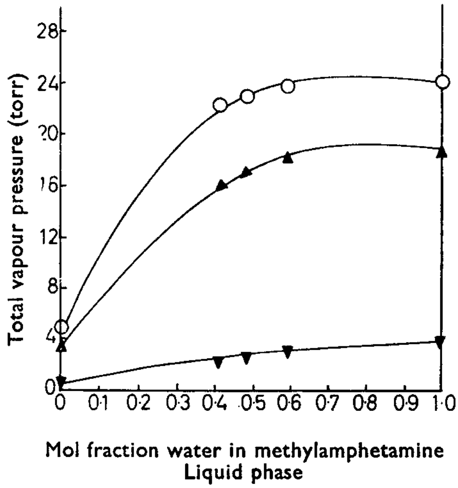


FIG. 4. Variation of total pressure with temperature for various methylamphetamine water mixtures. ○ 25·25°; ▲ 20·94°; ▼ −2·8°.

temperature were all in excess of that which could be measured accurately with the McLeod gauge (range 2×10^{-3} to 10 torr).

Fig. 4 illustrates the variation in the total pressure with mol fraction of water present in methylamphetamine at temperatures of −2·8° + 20·94° and +25·25°. As the temperature was increased there was increasing positive deviation of vapour pressure from the ideal situation predicted by Raoult's Law.

At 25·25° partial pressures were determined from a knowledge of the total vapour pressure and the composition of the vapour phase in equilibrium with each of the three methylamphetamine–water mixtures. The results are plotted in Fig. 5 together with the total pressure, and it confirms that partial pressures also exhibited positive deviations from Raoult's Law.

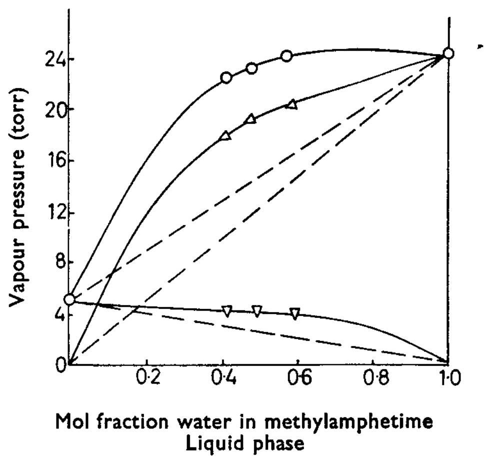


FIG. 5. Effect of mol fraction of water in methylamphetamine on total and partial vapour pressures of the mixtures at 25·25°. ○–Total pressure; △–Partial pressure water; ▽–Partial pressure methylamphetamine; ----Raoult's Law.

DISCUSSION

The two, distinct drying curves shown in Fig. 1 for cellulose acetate and paper inhaler support materials indicate that there is a difference in the internal structures of the supports and the manner in which moisture is held on their surfaces. It is evident that the difference is not solely due to the differing surface areas of the materials exposed during the drying process since only minor changes in the shapes of the curves are observed when the results obtained from teased and intact supports are compared. Most of the water present on both the cellulose acetate and paper supports is accessible to an organic liquid such as n-propanol since the moisture contents obtained by the extraction technique are only marginally lower than those determined with the infrared dryer.

The data plotted in Fig. 2 confirm that water in the quantities present in both types of inhaler support would be soluble in methylamphetamine at the temperatures used in previous experiments with the inhaler system (Armstrong and others, 1970, 1971). Solutions of pairs of liquids such as methylamphetamine and water, which have limited mutual solubility, exhibit positive deviations from ideal behaviour because the forces of attraction between like molecules are greater than those between the different species of molecules. These positive deviations will be at maximum in the temperature region where the liquid pair show least miscibility—for methylamphetamine and water this is between 70 and 80°. When such systems have both an upper and a lower consolute temperature, increase or decrease in temperature from this region will result in a reduction in the positive deviations from ideal behaviour. Fig. 4 confirms this for the methylamphetamine–water system, for it is evident that a decrease in temperature from 25·25° to −2·8° produces a marked reduction in the positive deviation from Raoult's Law.

It is evident that, when either type of fibrous inhaler support is impregnated with methylamphetamine, the presence of water, which is soluble in the drug, will depress the partial vapour pressure of the drug and consequently reduce its concentration emerging in the airstream from a nasal inhaler. If we can assume that the physical properties of the water–methylamphetamine mixtures are not affected by the presence of the support materials, then the degree to which the vapour pressure will be depressed can be calculated. This involves a knowledge of the moisture contents of the fibrous supports, the quantity of methylamphetamine impregnated, and the vapour pressure-composition diagram in Fig. 5. For example, for the initial studies made with the inhaler system (Armstrong & others, 1970, 1971), 0·1 ml (92·1 mg) of methylamphetamine was impregnated on cellulose acetate and paper supports weighing 0·250 and 0·171 g respectively. If it is assumed that the water content extractable with n-propanol is also available and soluble in the drug, calculation shows that on cellulose acetate supports there is a solution of 21·2% w/w (0·69 mol fraction) of water in methylamphetamine, and on paper supports the concentration of water is 12·2% w/w (0·54 mol fraction). From Fig. 2 it can be seen that 22% w/w water (0·70 mol fraction) is soluble in methylamphetamine even up to 40°. Fig. 5 shows that at 25·25° pure methylamphetamine exerts a vapour pressure of 5·0 torr. A methylamphetamine–water mixture containing 0·69 mol fraction of water would exert a methylamphetamine partial pressure of 3·2 torr, whereas a concentration of 0·54 mol fraction of water would result in a partial pressure of 3·9 torr. On the basis of this calculation, one would expect the drug concentration emerging from an inhaler containing a paper support to be higher than that emerging from an inhaler containing a cellulose acetate support.

This expectation relates well with our previous findings (Armstrong & others, 1970). At 25·25° the derived vapour pressures of methylamphetamine, calculated from the results of the previous inhaler studies, are 0·110 and 0·089 torr for paper and cellulose acetate supports respectively. The calculation assumes that the inhaler system is analogous to that used for measuring the vapour pressure of a liquid by the gas saturation method. The ratio of the absolute partial pressures of methylamphetamine for the paper and cellulose acetate supports is 1·22 and the ratio of the derived vapour pressures is 1·24. This indicates that the concentration of water present in the supports is a significant factor governing the dose of a drug delivered from a nasal inhaler.

Even when the effect of moisture is accounted for, there is still a considerable discrepancy between the derived and absolute vapour pressure values. It will be necessary to examine the system further to determine the effect that the porous nature of the support material, the degree of undersaturation of the airstream, and the physical interaction between the support material and the drug have upon the dose of drug delivered from the inhaler.

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REFERENCES

Armstrong, P. A. M., Carless, J. E. & Enever, R. P. (1970). *J. mond. Pharm.*, **13**, 5–13.

Armstrong, P. A. M., Carless, J. E. & Enever, R. P. (1971). *J. Pharm. Pharmac.*, **23**, 473–481.

Osborne, N. S. & Meyers, C. H. (1934). *J. Res. natn. Bur. Stand.*, **13**, 1–20.