

The relation between the vapour pressure of a drug and its concentration emerging in the air stream from a nasal inhaler

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.

A method of determining the absolute vapour pressures of volatile drugs and drug-adjuvant mixtures is described. The absolute vapour pressures of methylamphetamine, propylhexedrine and eucalyptol have been determined over a range of temperatures. The concentrations of these drugs emerging from a nasal inhaler system have also been measured under similar experimental conditions. From the inhaler results, it has been possible to derive values for the vapour pressures of the drugs in the system and compare them with absolute vapour pressure values. The derived pressures were lower than the absolute pressures at any given temperature. Nevertheless, there seems to be reasonable agreement among the latent heats of vaporization of the three drugs using either parameter. The factors that may give rise to the low values of derived vapour pressure are discussed. Mixtures of eucalyptol and methylamphetamine examined using the same techniques, show that both with the inhaler system and with mixtures of the pure drugs a similar liquid-vapour equilibrium exists. The vapour pressure-composition diagram constructed from either set of results shows a positive deviation from Raoult's law.

Recently, Armstrong, Carless & Enever (1970) examined factors affecting the dose of a drug delivered from a conventional nasal inhaler. The drug concentration in the air stream emerging from the inhaler was measured for a variety of volatile drugs impregnated on fibrous support material. With a range of air flow rates and temperatures, it was found that, in all the systems studied, an equilibrium was established between the liquid and vapour phases. In addition, linear relations were obtained when the logarithm of the drug concentration was plotted against the reciprocal of absolute temperature. Since the drug concentration in the air stream is proportional to its vapour pressure, the relation is similar to that expressed by the Clausius-Clapeyron equation. It was therefore concluded that the partial vapour pressure exerted by the drug in the presence of other volatile constituents in an inhaler formulation is a major factor governing the dose delivered to the patient. An attempt has now been made to determine the absolute vapour pressures of small quantities of various volatile drugs and adjuvants so that these data may be correlated with the results obtained from our inhaler systems.

The techniques available for determining vapour pressure may be broadly classified into three categories. (1) Dynamic methods that involve the measurement of the boiling points of a substance at various pressures (Swietoslawski, 1953). Unfortunately, in many cases difficulty is encountered in accurately determining the point at

which the liquid boils because of superheating effects. In addition, relatively large quantities of liquid are necessary. (2) Gas saturation and effusion methods that necessitate measurement of the loss of material from the liquid to the vapour state (Halstead, 1970). Such methods are generally suitable for determination of vapour pressures of pure substances. Mixtures of volatile materials are not easily evaluated with these techniques. (3) Static methods that involve direct measurement of the pressure exerted by an outgassed sample of either a pure or multicomponent system. To this end, various pressure measuring devices have been used, including manometers, McLeod, Pirani and Bayard-Alpert gauges. For our purposes, the McLeod gauge is the most suitable since it is a primary standard of pressure measurement that can be used for a variety of substances provided condensation of the vapour does not occur in the gauge (Ede, 1947; Fleuss, 1924; Francis, 1936). The McLeod gauge which we have designed is capable of measuring pressures in the range 2×10^{-3} to 10 torr, and has been used to determine the vapour pressures of methylamphetamine, propylhexedrine, eucalyptol and methylamphetamine-eucalyptol mixtures.

Design of vapour pressure measuring system

The system (Fig. 1) consists of the McLeod gauge in a temperature controlled enclosure, a thermostatted sample tube, and an oil diffusion pump backed by a rotary vacuum pump. A cold trap surrounded by liquid nitrogen is interposed between the vacuum pumps and the remainder of the system to prevent contamination of the pump oil with organic vapours, and also to prevent the gauge and sample tube becoming contaminated with pump oil. Provision is also made for a second non-thermostatted McLeod gauge to be connected into the system for measurement of pressures in the range 5×10^{-2} to 1×10^{-4} torr.

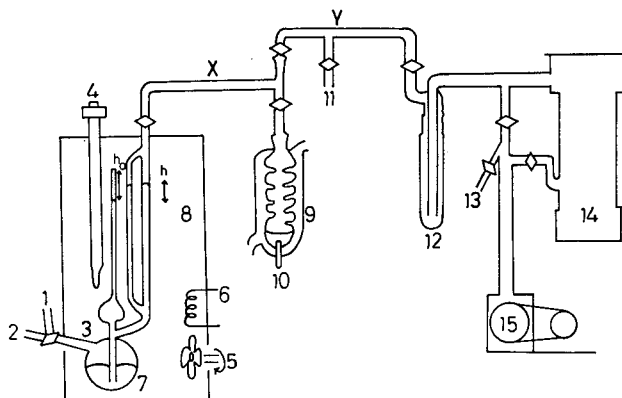


FIG. 1. Schematic diagram of apparatus used for determining vapour pressure of drugs at various temperatures. 1, 13, Airbleed; 2, water pump; 3, cut-off point; 4, mercury contact thermometer; 5, fan; 6, heater element; 7, McLeod gauge range 2×10^{-3} —10 torr; 8, temperature controlled enclosure; 9, sample tube; 10, tungsten wire; 11, additional McLeod gauge range 1×10^{-4} — 5×10^{-2} torr; 12, liquid nitrogen cold trap; 14, oil diffusion pump; 15, rotary vacuum pump.

The air thermostat is essential to maintain the gauge at a higher temperature (approximately 50°) than the sample tube and prevent condensation of the vapour in

the gauge. The air temperature around the gauge can be controlled to $\pm 1^\circ$, and it is accurately determined at the time of vapour pressure measurement by means of a calibrated bead thermistor system.

The sample tube is designed with many indentations on its inner surface so that a large temperature-controlled surface area is presented to both the liquid and the vapour phases. This ensures that temperature equilibrium is established. The temperature is controlled by circulating water through the sample jacket from a thermostatted water bath-pump system and monitoring the inlet and outlet temperatures by means of calibrated sensitive bead thermistors. The sample tube temperature is thus maintained within $\pm 0.1^\circ$ of the required value. A tungsten wire, fused into the base of the sample tube, serves as a nucleus for ebullition during outgassing.

Evacuation of the system is initially achieved by use of the rotary backing pump, and subsequently, when the pressure has dropped to 0.05 torr, the oil diffusion pump is switched into the system. The oil used in the diffusion pump (Silicon 704) is of high stability and has a low vapour pressure at the pump operation temperature. This arrangement enables a vacuum pressure of 1×10^{-5} torr to be drawn in the system.

The vapour pressure of a substance introduced into the sample tube connected to the evacuated system is determined by measuring the difference in the heights of mercury, h , in the open and closed capillaries of the McLeod gauge and the distance, h_0 , between the top of the closed capillary and the mercury meniscus in that capillary. A Vickers cathetometer (reading to 0.02 mm) is used for this purpose. From a knowledge of the cross-sectional area, A , of the closed capillary and the volume, V , of the bulb and closed capillary up to the cut-off point, the pressure, P , can be calculated using the relation:

$$P = \frac{h_0 Ah}{[V - h_0 A]} \quad \dots \quad \dots \quad \dots \quad (1)$$

With the present gauge designed for measuring pressures in the range 2×10^{-3} to 10 torr, the value of A and V are 8.720 mm^2 and 10318.6 mm^3 respectively.

The equation relating pressure to the heights of mercury in the gauge, assuming that Boyle's Law is obeyed and that the compressed gas does not condense in the bulb and capillary, has been verified for every volatile substance examined by measuring various values of h and h_0 for the same sample of trapped gas. From equation (1), assuming that $h_0 A$ is small in comparison with V , a graph of h against $1/h_0 A$ at constant pressure can be constructed. This will yield a straight line passing through the origin provided that condensation does not occur.

Since the gauge is maintained at a higher temperature than the sample tube to prevent condensation of the vapour, the pressure reading obtained from the gauge has to be corrected to determine the vapour pressure of the sample. In this system the mean free path of the molecules is large compared with the dimensions of the system, and heat transfer occurs through collisions with the walls rather than intermolecular collisions. Therefore a thermal transpiration correction (Bennett & Tompkins, 1957) has to be applied in the form

$$P_1 = \left(\frac{T_1}{T_2} \right)^{1/2} P_2 \quad \dots \quad \dots \quad \dots \quad (2)$$

where P_1 is the pressure at absolute temperature T_1
 P_2 is the pressure at absolute temperature T_2 .

MATERIALS AND METHODS

Materials

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

Propylhexedrine from Aldrich Chemical Co. Inc., Milwaukee, Wisconsin.

Eucalyptol B.P.C. from Bush Boake and Allen, London.

The purity of these materials was checked by gas-liquid chromatography using the column described below. Under these conditions each material produced a single peak.

The fibrous supports used for the inhaler studies were composed of cellulose acetate and were 22 mm long by 8 mm diameter.

Methods

Determination of absolute vapour pressure of volatile materials. Since a static method of vapour pressure measurement was used, it was essential to outgas the equipment and sample to ensure that no air or water vapour contributed to the measured vapour pressure. Before it was filled with a volatile sample, the sample tube was cleaned with chromic acid, washed with distilled water, and dried by rinsing with absolute ethanol, acetone and then placed in an hot air oven at 90°. The tube was allowed to cool to room temperature while stoppered to prevent ingress of water. Using a cannula, 1 ml of the volatile material was introduced into the base of the tube, the tube was immediately immersed in liquid nitrogen and subsequently placed in position on the equipment. The McLeod gauge was isolated from the system, and the sample tube, still immersed in liquid nitrogen, was evacuated to approximately 1×10^{-5} torr. The sample tube was then isolated from the system and allowed to reach room temperature when the entrapped gases bubbled out of the liquid. This process was repeated 15 times to achieve complete removal of gaseous impurities. The water flow through the sample jacket was then established and sufficient time allowed for temperature equilibrium to be achieved. The sample tube and McLeod gauge were then connected together and successive pressure readings taken at 15 min intervals until a constant pressure was recorded. This pressure was taken to be the saturation vapour pressure of the volatile material after the thermal transpiration correction had been applied.

The McLeod gauge measures the total pressure in equilibrium with the sample, hence, if the sample consists of more than one volatile component, then the composition of the vapour phase must also be known in order to determine the partial pressure of each component. For example, to determine the partial pressures exerted by methylamphetamine and eucalyptol in mixtures of these materials at 25.25°, the following procedure was adopted. The mixture to be analysed was outgassed as described above, and then allowed to reach equilibrium at 25.25° with the gauge and vacuum pumps isolated. After equilibration for 1 h the sample tube was isolated from the system and the vapour present in the connecting tubes X and Y (Fig. 1) was sucked into a clean outgassed cold trap. The trap was removed, and to the condensed vapour was added diethyl ether containing a known amount of internal marker so that the solution could be analysed for methylamphetamine and eucalyptol content using gas-liquid chromatography.

Determination of drug concentration emerging in the airstream from a nasal inhaler. Commercially available cellulose acetate fibrous supports of the type used in nasal inhalers were used. The apparatus for this study has previously been described

(Armstrong & others, 1970). The fibrous supports were impregnated with 0.1 ml of the pure drug or mixture of drugs being examined, and air was allowed to flow through the inhaler system for 30 s at a rate of 0.95 litre min^{-1} . The drug content in the airstream was collected in diethyl ether and analysed using a Perkin Elmer F11 gas chromatograph equipped with a column composed of 10% w/w Carbowax 6000, and 5% w/w potassium hydroxide on Celite 545. The experimental conditions for analysis have been described by Armstrong & others (1970).

With this system, the relation between temperature and the concentration of eucalyptol, propylhexedrine, methylamphetamine and eucalyptol-methylamphetamine mixtures emerging from the inhaler was investigated.

RESULTS

Fig. 2 (a) and 2 (b) show the effect of temperature upon the concentration of drug emerging from the inhaler system using methylamphetamine, propylhexedrine and eucalyptol. For any temperature selected, the order of magnitude of drug concentration in the airstream is eucalyptol > propylhexedrine > methylamphetamine. With all three drugs there is an exponential relation between temperature and concentration.

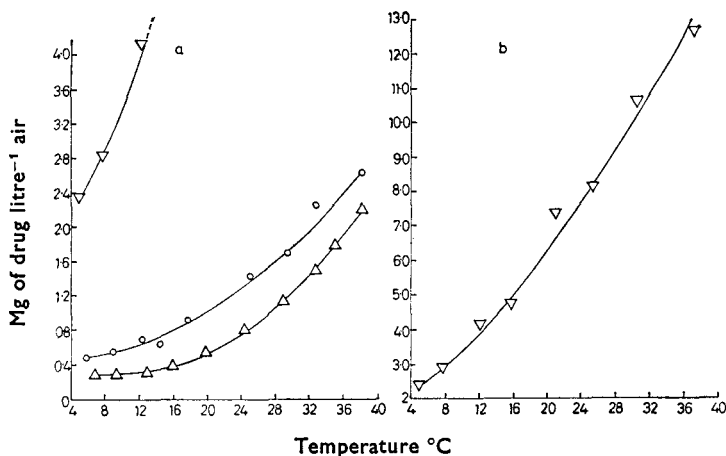


FIG. 2. Effect of temperature on amount of drug litre^{-1} air emerging from inhaler system: (a) methylamphetamine Δ ; propylhexedrine \circ ; eucalyptol ∇ . (b) Eucalyptol ∇ .

These results may be converted into values of vapour pressure for comparison with the absolute values by assuming that the inhaler system is analogous to that encountered when measuring the vapour pressure of a liquid by the gas saturation method. With this method, the flow of dry gas through the liquid is sufficiently slow to permit complete saturation of the airstream at the temperature of the determination. The loss in weight of the liquid after passage of a known volume of air is measured. The vapour pressure P is calculated from the equation:

$$P = \frac{G}{MV} RT \quad \dots \dots \dots (3)$$

where V is the volume of dry gas, in litres, containing G grams of material of molecular weight M . T is the absolute temperature and R the gas constant.

Equation (3) neglects the increase in volume of the gas caused by vaporization of the liquid. However, at low vapour pressures this is negligible, and the equation is sufficiently accurate for the present study where pressures of the order 2×10^{-3} to 10 torr are being considered.

Fig. 3 (a) and (b) shows the results of the absolute vapour pressure determinations of the drugs compared with the values derived from the inhaler systems. The two sets of $\log P$ vs $1/T$ data in each case for methylamphetamine, propylhexedrine and eucalyptol show that the derived values are always lower than the absolute vapour pressure values. At any given temperature the vapour pressure of the drugs is in the order eucalyptol > propylhexedrine > methylamphetamine.

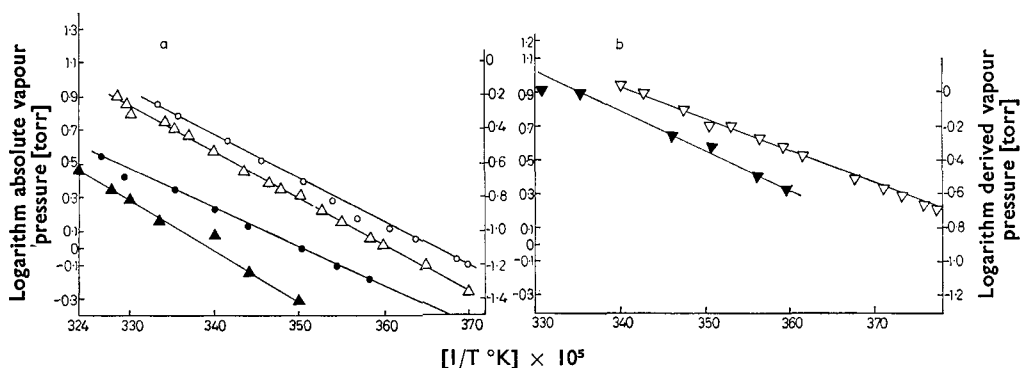


FIG. 3. Logarithm vapour pressure against reciprocal absolute temperature: (a) Methylamphetamine, Δ absolute values, \blacktriangle derived values. Propylhexedrine, \circ absolute values, \bullet derived values. (b) Eucalyptol, ∇ absolute values, \blacktriangledown derived values.

The log vapour pressure reciprocal of absolute temperature relation is commonly expressed by the Clausius-Clapeyron equation, where the change in pressure P with temperature T is given by:

$$\frac{dP}{dT} = \frac{P\Delta H_{\text{vap}}}{RT^2} \quad \dots \quad (4)$$

where ΔH_{vap} is the latent heat of vaporization of the material. Now ΔH_{vap} is constant over a small range of temperature, and hence eqn (4) may be integrated to yield

$$\text{Log } P = \frac{-\Delta H_{\text{vap}}}{2.303RT} + C \quad \dots \quad (5)$$

where C is the integration constant.

Therefore, the slopes of the lines in Fig. 3 (a) and (b) will give the latent heats of vaporization for the drugs. These values are: $[\text{kJ mol}^{-1} (\text{kcal mol}^{-1})]$ 53.1 (12.7), 48.2 (11.5), 36.4 (8.7) from absolute vapour pressure values and 52.7 (12.6),* 41.4 (9.9),* 40.6 (9.7)* from derived vapour pressure values for methylamphetamine, propylhexedrine and eucalyptol respectively.

Fig. 4 (a) and (b) show the vapour pressure-mol fraction relation for mixtures of methylamphetamine and eucalyptol at 25.25° using absolute and derived vapour pressure values. In Fig. 4 (a), the partial vapour pressures of each component have

* Since calculation for the derived vapour pressures assumes that there is saturation of the air stream flowing through the inhaler, it is more appropriate to regard these figures as apparent ΔH_{vap} values.

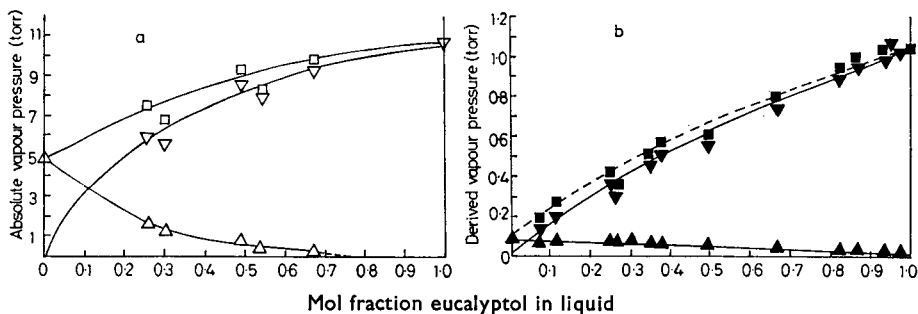


FIG. 4. Effect of mol fraction eucalyptol in methylamphetamine on total and partial vapour pressures of the mixtures at 25.25°C. (a) Absolute vapour pressure Δ partial pressure methylamphetamine, ∇ partial pressure eucalyptol, \square total pressure. (b) Derived vapour pressure values \blacktriangle partial pressure methylamphetamine, \blacktriangledown partial pressure eucalyptol, \blacksquare total pressure.

been calculated from a knowledge of the molar composition of the vapour phase and the total absolute pressure of the system. Fig. 4 (b) shows the partial pressures of each component as derived from the concentrations emerging from the inhaler system, together with the total pressure obtained by summation. This assumes that no other component is present that contributes to the total vapour pressure.

Fig. 4 (a) and (b) shows that the pressure exerted by either component is increasingly depressed by increasing mol fraction of the other component. In addition both graphs of total pressure show that there is a slight positive deviation from Raoult's Law.

DISCUSSION

It is evident from comparison of Fig. 3 (a) and (b) that the ratio derived vapour pressure : absolute vapour pressure at any temperature varies with the drug examined. The lowest ratio is obtained with methylamphetamine and the highest with eucalyptol. It follows therefore that, when comparing Fig. 4 (a) and 4 (b), the ratio derived total pressure : absolute total pressure will vary with the mol fraction of eucalyptol. Nevertheless, both diagrams show a similar pattern, since the binary mixtures of methylamphetamine and eucalyptol exhibit a slight positive deviation from Raoult's law. This is not an unexpected phenomenon and can be explained by hydrogen bonding between the amine groups of methylamphetamine molecules. Evidence for this has been obtained from infrared spectroscopic studies.

The partial vapour pressure-mol fraction relation for methylamphetamine as shown in Fig. 4 (a) and (b) are slightly anomalous. From the absolute values in Fig. 4 (a), methylamphetamine shows a negative deviation from Raoult's Law, whilst from the derived partial pressures in Fig. 4 (b) there appears to be no deviation from ideal behaviour. It can be shown theoretically that, when one component of a binary mixture exhibits positive deviation from ideality, the other component must do the same. The anomaly is probably the result of experimental difficulties encountered when analysing the condensed vapour phase containing a low mol fraction of methylamphetamine.

The experimental measurements of total vapour pressure of methylamphetamine-eucalyptol mixtures have been made in the region of 0.25 to 0.65 mol fraction of eucalyptol for two reasons. Firstly, it is difficult to control the composition of mixtures containing a low mol fraction of either component due to the loss of the

more volatile component during outgassing. In all instances, analysis of the bulk liquid phase was made before and after a vapour pressure determination to check that no change in liquid composition had occurred. Secondly, deviation from Raoult's law will be more easily detected in this region. As the mixture approaches either pure eucalyptol or pure methylamphetamine, the partial pressures exerted by the components approximate to the ideal values predicted by Raoult's law.

The difference in absolute and derived vapour pressures of the drugs and also the binary mixture may be due to a number of factors. A combination of some, or all, of these may explain the discrepancy.

(1) The calculation of vapour pressures from the results obtained with the inhaler system assumes that the system is analogous to a dynamic method of vapour pressure measurement. In the calculation, we assume that the air stream is saturated with vapour. At the air flow rates used in this work, saturation of the air may not have been achieved. Under these circumstances one might expect the derived vapour pressure values to vary with the flow rate of air. However, we have previously shown (Armstrong & others, 1970), that the drug concentration in the air stream, and therefore the derived vapour pressure, is constant within the range 0.3 to 2.0 litre min^{-1} at any given temperature. Hence there is no clear evidence as to the degree to which possible undersaturation of the air stream may influence the derived vapour pressure values. In any event, it is clear that there is an equilibrium between liquid and vapour phase.

(2) With the static vapour pressure measurements that have been made, the vapour is in equilibrium with a plane liquid surface. However, in the inhaler system, the drugs impregnated on a fibrous support are present in capillaries throughout the material. From the Kelvin equation (Gregg, 1961) it can be shown that the vapour pressure exerted by a liquid when confined in a finely porous medium is less than that exerted by a liquid at a plane surface.

(3) There may be some physical interaction between the impregnated drug and the cellulose acetate support material, e.g. hydrogen bonding, or solubility of support material in the drug. This could cause a depression of the vapour pressure exerted by the drug, and account for the difference in the ratio derived vapour pressure-absolute vapour pressure with the three drugs examined.

(4) Since the cellulose acetate support material used in the inhaler systems has an affinity for water, it is probable that it will contain traces of moisture. If the water is soluble in the impregnated drug, then a binary water-drug system will be produced with the pure drug, and a ternary system will result with the methylamphetamine-eucalyptol mixtures. It is then necessary to include this partial water vapour pressure in any calculation of the total pressure of such systems.

Factors (3) or (4), or both, might be expected to affect the values of the apparent latent heats of vaporization (ΔH_{vap}) of methylamphetamine, propylhexedrine and eucalyptol obtained from the inhaler experiments. In fact, the results show that there are differences between the ΔH_{vap} and the apparent ΔH_{vap} values for each drug that could be accounted for in this way. It is important to note that the ΔH_{vap} values obtained from the inhaler experiments are independent of the flow rate of air through the inhaler within the range 0.3 to 2.0 litre min^{-1} .

Despite the numerical difference between the absolute and derived vapour pressure values of the eucalyptol-methylamphetamine mixtures, the similarity of the two vapour

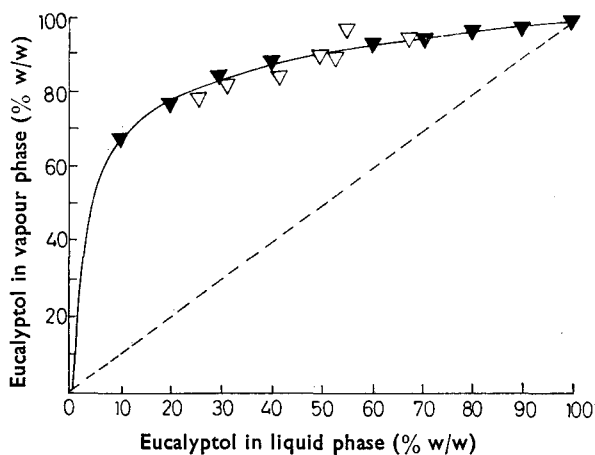


FIG. 5. Effect of composition of liquid phase on vapour phase composition using methylamphetamine, eucalyptol mixtures. ▼ from derived vapour pressure results; ▽ from absolute vapour pressure results.

pressure-composition relations is evident from Fig. 5. The relation between percentage concentration of the eucalyptol component in the vapour phase and its percentage concentration in the liquid phase is identical for the two sets of data. This therefore confirms that the same equilibrium situation occurs for the inhaler system and for the solution of the pure drugs. Fig. 5 further shows that an azeotropic mixture is not formed. If present, the composition of the azeotrope would be given by the point of intersection of the experimental curve and a straight line of slope equal to unity drawn through the origin.

As might be expected, the study of the eucalyptol-methylamphetamine mixtures shows that the concentration of methylamphetamine emerging from the inhaler is markedly reduced by the presence of the aromatic adjuvant. In order to mask the smell of the amine, it is necessary to use a mixture containing at least 0.3 mol fraction of eucalyptol, and this results in a reduction of approximately 30% in methylamphetamine concentration. Since the results presented also show that the same equilibrium situation occurs in both the inhaler system and the solutions of the pure drugs, absolute vapour pressure measurements of other volatile drug-adjuvant formulations will be of value in predicting their performance.

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