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Physical and Chemical Changes of Medicinals in Mixtures with Adsorbents in the Solid State. III.[1] Determination of Vapor Pressure of Solid Drugs by Steam Distillation

Tsutomu KONNO

Exploratory Research Laboratories III, Research Institute, Daiichi Pharmaceutical Co., Ltd., 16-13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134, Japan.

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The vapor pressures of solid drugs were determined by the steam distillation method. Experiments using a series of benzoic acid derivatives indicated that this method offered consistent and satisfactory values for vapor pressure at about 100 °C. The vapor pressures of two nonsteroidal antiinflammatory drugs, flufenamic acid (FFA) and mefenamic acid (MFA), were found to be 3.8×10^{-3} and 1.8×10^{-4} mmHg, respectively. These values explain the difference in the rate of change to the amorphous state between mixtures of each with magnesium aluminum silicate (MAS) when they were stored under reduced pressure. It was concluded that the vapor pressures of solid drugs at about 100 °C, as determined by steam distillation, may be suitable indices for predicting whether or not these drugs have an inherent propensity to become amorphous readily in mixtures with an adsorbent.

Keywords vapor pressure; steam distillation; flufenamic acid; mefenamic acid; benzoic acid derivative; adsorbent; magnesium aluminum silicate; amorphous; reduced pressure; X-ray diffraction

In the previous papers,[1] we have reported that some organic crystalline compounds, when mixed with an adsorbent having a large specific surface area, became amorphous after storage under reduced pressure. This change could be applied to the improvement of dissolution of flufenamic acid (FFA), when magnesium aluminum silicate (MAS), which is used as an ingredient of pharmaceutical preparations, was chosen as the adsorbent. We recognized on examination that the vapor pressure of a compound is a very important factor in relation to such a change, since the rate of change of crystals to the amorphous state increases with their vapor pressure. It was considered that, if the vapor pressure of any drug were determined, the time required for that drug to change to the amorphous state could be estimated, so that the vapor pressure could be a suitable index of whether the drug readily becomes amorphous or not in mixtures with adsorbents.

In the last decade, various reports have described the growth behavior of needle-like crystals of some drugs on the surfaces of granules or tablets,[2] so-called whiskers, and intertablet migration of nitroglycerin[3] was demonstrated. Both behaviors were demonstrated to take place *via* the gaseous phase. It was also considered that knowledge of the vapor pressure of these drugs would be useful for the prediction of such pharmaceutical problems.

There are several reports[4] of determinations of the vapor pressures of certain solid organic compounds. Sidgwick[5] also demonstrated that the vapor pressure of organic substances at 100 °C could be determined accurately by steam distillation. In the present study, we set up a simple apparatus for steam distillation (a modification of Sidgwick's), and used it to determine the vapor pressure of two nonsteroidal antiinflammatory drugs, FFA and mefenamic acid (MFA). The relation between their vapor pressures and the rates of change of their crystals to the amorphous state in mixtures with MAS is discussed.

Experimental

Materials Since *o*-hydroxybenzoic acid of special reagent grade contained a small amount of impurity, it was recrystallized from water and used after checking its purity and its melting point. *m*-Hydroxybenzoic acid, *o*-, *m*- and *p*-chlorobenzoic acid of special reagent grade, and FFA and MFA purchased from Sigma Chemical Co., Ltd., and checked for purity by thin layer chromatography (TLC) and melting point determination, were used. MAS (Neusilin UFL$_2$, Fuji Chemical Industry Co., Ltd.) was passed through a No. 150 (mesh size: 105 μm) sieve, heated at 110 °C for 3 h *in vacuo*, and kept in a desiccator containing silica gel at room temperature. The specific surface area and pore size distribution have been described in a previous paper.[1b)]

Steam Distillation The apparatus is shown in Fig. 1. Steam from a boiler was passed through a trap to remove water droplets, and was then led through a short tube to the bottom of a gas-washing bottle (volume 250 ml, Ichinose style), in which a spiral glass strip had been attached to guide the bubbles of steam up a spiral pathway. The steam coming out of the bottle was passed through a condenser. A small sheet of aluminum foil was placed a little below the outlet of the gas-washing bottle so that splashes of liquid arising from the surface of the solution would not escape through the outlet. The trap and the gas-washing bottle were immersed in a steam bath and a stainless steel lid was fitted in order to maintain the temperature around the apparatus. The tube from the steam trap to the gas-washing bottle, and that from the bottle to the condenser were wrapped in glass wool.

About 150 ml of water and various amounts of compound were placed in the gas-washing bottle and heated until the solution reached the boiling point (its temperature was recorded), and then the steam was passed through the apparatus at a rate of 4 to 8 g per min. First, fractions of about 50 ml were removed because the value in them was sometimes low, and then 3 to 5 subsequent fractions (about 50 ml each) were collected and the concentration of the compound was determined. The compounds which remained in the condenser were removed by washing out with 0.1 N sodium hydroxide.

Calculation of Vapor Pressure Each fraction was diluted appropriately with 0.1 N sodium hydroxide, and the concentration of the compound was determined spectrometrically. The wavelengths used for measurement

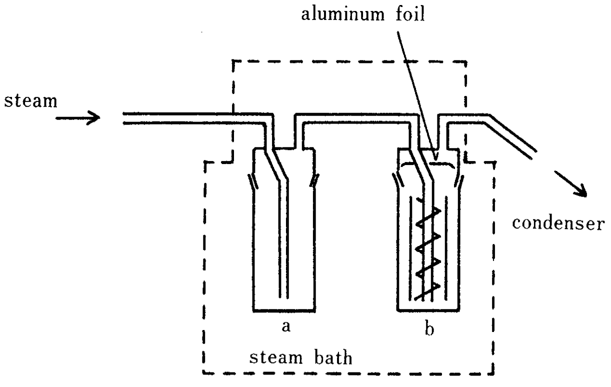

Fig. 1. Apparatus for Steam Distillation
a, trap; b, gas-washing bottle with spiral glass strip.

were 296 nm for *o*-hydroxy-, 311 nm for *m*-hydroxy-, 264 nm for *o*-chloro-, 277 nm for *m*-chloro- and 235 nm for *p*-chlorobenzoic acid, and 289 nm for FFA and 285 nm for MFA. The vapor pressure of each compound (P_c) was calculated from the formula

$$P_c(\text{mmHg}) = \frac{\text{wt. of compound}}{\text{wt. of water}} \times \frac{760 \times 18}{M}$$

where M is the molecular weight of the compound.

Preparation of Mixtures FFA and MFA, passed through a No. 150 sieve, were each mixed well with MAS in a porcelain mortar in the ratio of 2 : 8 by weight. Both mixtures were stored at 60 °C at a reduced pressure of about 2.5 mmHg achieved by using a vacuum pump.

Measurement of X-Ray Diffraction (Powder Method) A Geiger Flex 2012 diffractometer (Rigaku Denki Co., Ltd.) was used. The measurement conditions were the same as those reported in the previous paper,[1a)] but the voltage and current were 30 kV and 20 mA, respectively.

Results

Investigation of Effect of Experimental Conditions on Vapor Pressure by Steam Distillation It is a thermodynamic relationship that the vapor pressure of a gaseous solute, assuming that the vapor is a perfect gas, is proportional to its activity in the solution, and is equal to the vapor pressure of the solid material when this saturates the solution. It is therefore necessary to collect the vapor of a compound from its saturated aqueous solution in order to determine accurately the vapor pressure of the solid material. Figure 2 shows the relation between the amount of *o*-hydroxybenzoic acid that was placed in the gas-washing bottle and concentration in the distillate. The solubility of *o*-hydroxybenzoic acid in water at 100 °C is 6.45 g/100 g. The concentration increased with the amount of the compound until the solution was saturated, and then became constant when the amount in the bottle exceeded saturation. The amount of each compound placed in the gas-washing bottle was fixed from these results at 1.5 to 2 times the solubility at 100 °C.

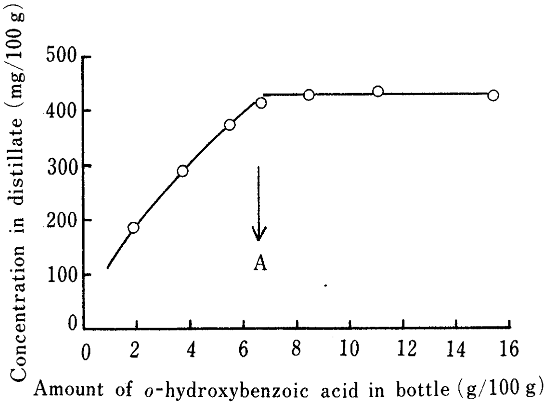

Fig. 2. Relation between Amount of *o*-Hydroxybenzoic Acid Placed in the Gas-Washing Bottle and Its Concentration in the Distillate

A, solubility of *o*-hydroxybenzoic acid at 100 °C.

It is suspected that the ratio of the vapor pressure of a material to that of water varies on different days owing to variations of barometric pressure. The experiment was repeated three times on different days. The day-to-day variation of concentration in the distillates was rather small (coefficient of variation: 1.4%), as shown in Table I. The mean value for concentration obtained on the three days was 421.1 mg/100 g, and the vapor pressure of *o*-hydroxybenzoic acid was calculated at 0.422 mmHg, which is close to the value of 0.397 mmHg obtained by Sidgwick.[5)]

Determination of Vapor Pressure of the Compounds With the other compounds examined, fewer measurements were made, only one day's data being used. Before the vapor pressures of FFA and MFA were determined, distillation experiments were carried out for four more benzoic acid derivatives, with the results shown in Table II. The coefficient of variation of the concentration of each compound was from 0.6 to 2.6%, and the mean values of our experimental data agreed quite well with those obtained by Sidgwick.[5)] It was considered that this simple apparatus for steam distillation could be very useful for determining the vapor pressure of solid materials at about 100 °C.

Distillations of FFA and MFA were then carried out, with the results shown in Table III. The vapor pressures of FFA and MFA at about 100 °C were 3.8×10^{-3} and 1.8×10^{-4} mmHg, respectively, showing an approximately 20-fold difference.

Changes in the X-Ray Diffraction Patterns of the Two Nonsteroidal Antiinflammatory Drugs with MAS on Reduced Pressure Treatment FFA and MFA were each mixed with MAS (20% drug) and stored at 60 °C under reduced pressure, and changes in the X-ray diffraction patterns were then compared. Figures 3 and 4 show the changes with time in the X-ray diffraction patterns of these mixtures. Curve 3A and curve 4A present the diffraction patterns of the freshly prepared mixtures, which exhibit peaks of diffraction by FFA or MFA crystals. For each mixture, the peak intensity due to the crystals decreased

Table I. Concentrations of *o*-Hydroxybenzoic Acid in Distillates Obtained on Different Days

Expt.	Barometric pressure[a)] (mbar)	Temp. (°C)	Concentration in distillate (mg/100 g)			
			1[b)]	2	3	Mean
A	1005.0	100.3	422.0	411.4	423.2	418.9
B	1006.6	100.8	427.6	431.3	432.7	430.5
C	1010.0	100.3	412.2	423.9	432.4	422.8

a) Values are quoted from atmospheric pressure data of the Meteorological Agency in Tokyo at each experimental time. *b*) Fraction number.

Table II. Vapor Pressures of Benzoic Acid Derivatives Obtained by Steam Distillation

Compound	Temp. (°C)	Concentration in distillate (mg/100 g)						Vapor pressure (mmHg)	Value from Sidgwick[5)] (mmHg)
		1[a)]	2	3	4	5	Mean		
m-Hydroxy	101.3	1.77	1.87	1.83	1.89	1.87	1.85	0.0018	0.00149
o-Chloro	100.6	216.7	218.0	217.7	207.5	220.8	216.1	0.189	0.1803
m-Chloro	101.0	253.8	255.1	257.0	249.2	258.1	254.6	0.223	0.1970
p-Chloro	101.5	51.9	51.8	52.1	52.1	51.4	51.8	0.0453	0.0450

a) Fraction number.

Table III. Vapor Pressures of FFA and MFA Obtained by Steam Distillation

Compound	Temp. (°C)	Concentration in distillate (mg/100 g)						Vapor pressure (mmHg)
		1[a]	2	3	4	5	Mean	
FFA	100.5	8.14	7.73	7.85	7.86	7.93	7.90	0.0038
MFA	101.0	0.309	0.324	0.316	0.323	0.304	0.315	0.00018

a) Fraction number.

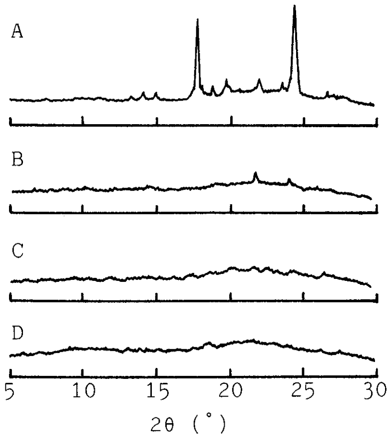

Fig. 3. Changes in X-Ray Diffraction Patterns of Mixtures of FFA with MAS Stored under Reduced Pressure at 60 °C

A, fresh; B, stored for 1 h; C, stored for 2 h; D, stored for 5 h.

with time, and halo patterns were observed. However, the times required for the mixtures to become amorphous were quite different. It was observed that FFA required 1—2 h, whereas MFA, whose vapor pressure is one-twentieth of that of FFA, required about 40 h.

Discussion

The steam evaporation technique is a convenient and accurate method for measuring the vapor pressure of solid compounds, although it can evaluate the vapor pressure only at the distillation temperature. Sidgwick[5] has demonstrated the general relation between temperature and vapor pressure to hold for many organic materials. He suggested that the vapor pressure at about 100 °C may be considered a suitable index of volatility at other temperatures when the order of the volatilities of compounds is estimated.

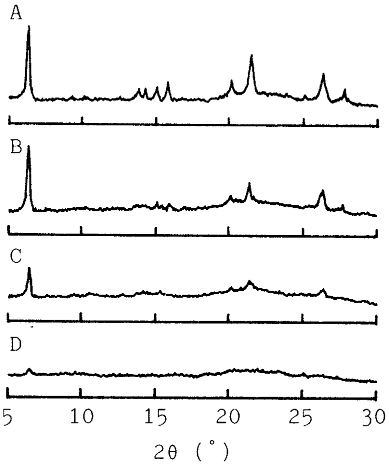

Fig. 4. Changes in X-Ray Diffraction Patterns of Mixtures of MFA with MAS Stored under Reduced Pressure at 60 °C

A, fresh; B, stored for 5 h; C, stored for 20 h; D, stored for 40 h.

In a previous report[1a)] we demonstrated that, when benzoic acid and a series of its derivatives were mixed with activated carbon, the rates at which the crystals changed to the amorphous state increased with their vapor pressures at 100 °C. In the present study, it was also recognized that the difference in the times required by the two nonsteroidal antiinflammatory drugs to become amorphous, can be explained well in terms of their vapor pressures.

The above facts lead to the conclusion that the vapor pressures of solid drugs at about 100 °C, as determined by steam distillation, may be suitable indices for predicting whether or not these drugs have an inherent propensity to become amorphous readily in mixtures with an adsorbent.

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