THE MELTING POINT OF ACETYLSALICYLIC ACID.*

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There has been some dissatisfaction expressed regarding the method of U. S. P. X for the determination of the melting point of acetylsalicylic acid. The method of the U. S. P. reads as follows:

"The melting point of Acetylsalicylic Acid, when finely powdered, and determined in a bath previously heated to 120° C., is not below 132° C."

According to D. A. B. VI, the determination is made as follows:

"For determination of the melting point the bath is brought to about 125° C. before introducing the melting point tube, and then heated with a greater flame, so that the temperature mounts at the rate of 1° every ten to fifteen seconds."

Both sets of directions evidently recognize the tendency of this acid to decompose while being heated, the products of decomposition forming an eutectic with the unchanged acid, thus depressing its melting point beyond the true value.

The U. S. P. X regards 132° C. as the melting point, the German Pharmacopœia 135° C., the British Pharmacopœia 133°–135° C. [135°–138° in the 1932 revision], the Japanese Pharmacopœia 135° C., and New and Non-Official Remedies 128°–133° C.

Attention has already been called to this by Carswell,[3] Dahm[4] and Putnam.[5] Carswell concludes that the melting point of the acid is dependent upon the size of the particles in the tube; that fine grinding is essential, 200 mesh being recommended; and that variations in melting point after crystallization from various solvents are caused by differences in the physical structure of the crystals, since fine grinding gives uniform values.

Dahm recommends a special form of apparatus, including a stirrer, and suggests an allowable range of 133°–135° C., which seems very wide.

Putnam recommends an initial bath temperature of 120° C., then heating the bath so that the temperature rise is 3° C. per minute, introducing the melting-point tube at 130° C. and continuing heating until the sample melts. The acid in melting passes through three stages; (*a*) moist stage, (*b*) formation of first globule, (*c*) complete liquefaction with definite meniscus. The second stage was taken as the true melting point. A value of 133.5 is therefore recommended as the true melting point.

In the authors' work sulphuric acid was used as the bath, in a round-bottomed Pyrex tube of 45 mm. internal diameter and 10 cm. long. A stirrer was made of a glass rod bent into a ring at a right angle to the stem, the handle then being bent back upon itself at two right angles. The thermometer had a range of 93°–165° C., was graduated in 0.2°, and had been calibrated at the U. S. Bureau of Standards. The bulb of the thermometer was placed at 2–3 cm. from the bottom of the bath,

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[3] JOUR. A. PH. A., 16 (1927), 306.

[4] *Ind. Eng. Chem.*, 11 (1919), 29. [5] *Ibid.*, 16 (1924), 778.

and submerged to the 136° mark, obviating an emergent stem correction. The capillary melting-point tubes varied in internal diameter from 0.8 to 1.0 mm., with walls not over 0.3 mm. in thickness.

The acetylsalicylic acid was powdered in a glass mortar and thoroughly dried in a desiccator over sulphuric acid. Separate portions were ground to 100, 150 and 200 mesh. The powder was charged into the tube to a height of 2.5 to 3 cm., and was lightly packed by drawing the corner of a file across the tube and then gently tapping the tube on a hard surface. The lower end of the tube was sealed in all instances, and some comparisons were made by sealing the top end as well.

The temperature at which the substance begins to collapse against the wall of the tube was recorded as the beginning of melting, while the temperature at which the mass became clear throughout was recorded as the actual melting point.

Four samples of acetylsalicylic acid, furnished by manufacturers, were used in these measurements. An initial bath temperature of 120° C. with increments of 3° and 5° per minute were used in the determinations recorded in Table I, and of 130° C. with the same increments in Table II.

TABLE I.—EFFECT OF FINENESS OF POWDER AND RATE OF HEATING. INITIAL TEMPERATURE OF BATH, 120° C.

Average of 8 Determinations.

Sample.	Fineness.	Heated 3° per Minute. Incipient Fusion.	M. P.	Heated 5° per Minute. Incipient Fusion.	M. P.
A	100	130.0	132.7	131.0	133.6
B	100	130.6	133.1	131.0	133.6
C	100	130.0	132.5	132.0	133.5
D	100	130.0	132.2	131.7	133.1
Average	100	130.15	132.6	131.4	133.45
A	150	130.0	132.5	130.0	133.5
B	150	130.2	132.5	131.0	133.6
C	150	130.6	132.5	131.3	133.65
D	150	129.0	132.3	130.0	133.5
Average	150	129.95	132.45	130.57	133.56
A	200	130.0	132.1	131.2	133.5
B	200	130.0	132.25	131.0	133.4
C	200	130.2	132.45	132.0	133.9
D	200	129.5	132.0	131.2	133.3
Average	200	129.9	132.2	131.35	133.5
		Tube sealed at both ends			
A	200	129.2	130.6		
B	200	129.4	130.9		
C	200	129.2	130.9		
D	200	129.0	130.7		
Average	200	129.2	130.73		

TABLE II.—EFFECT OF FINENESS OF POWDER AND RATE OF HEATING. INITIAL TEMPERATURE OF BATH, 130° C.

Average of 8 Determinations.

Sample.	Fineness.	Heated at 3° per Minute. Incipient Fusion.	M. P.	Heated 5° per Minute. Incipient Fusion.	M. P.
A	100	133.0	135.4	133.0	135.6
B	100	133.0	135.6	133.0	135.6
C	100	133.0	135.4	133.6	135.8
D	100	132.4	135.4	133.1	135.7
Average	100	132.85	135.45	133.2	135.7

TABLE II.—EFFECT OF FINENESS OF POWDER AND RATE OF HEATING. (*Continued.*)

Sample.	Fineness	Heated at 3° per Minute. Incipient Fusion.	M. P.	Heated 5° per Minute. Incipient Fusion.	M. P.
A	150	131.7	135.1	132.4	135.3
B	150	132.2	135.3	133.0	135.3
C	150	133.0	135.1	133.0	135.4
D	150	132.0	134.8	132.5	135.3
Average	150	132.2	135.1	132.7	135.3
A	200	132.6	135.45	133.0	135.6
B	200	132.3	135.2	133.0	135.9
C	200	133.0	135.25	132.9	135.8
D	200	131.7	134.6	132.1	135.2
Average	200	132.4	135.1	132.75	135.6

A trial was made of Dahm's method. The same test-tube was used as a container for the bath, which in this case was of glycerine. A motor-driven glass stirrer was used. All other conditions were as previously described, the acid being ground to 200 mesh and dried over sulphuric acid over night.

TABLE III.—DAHM'S METHOD.

Sample.	Fineness.	Initial Temperature.	Rate of Heating ° per Minute.	M. P.	Sealed Tube, M. P.
A	200	130°	1	133.4	.....
A	200	130°	3	135.7	133.7
B	200	130°	1	133.2	.....
B	200	130°	3	135.7	134.8
C	200	130°	1	133.3	.....
C	200	130°	3	135.8	134.6
D	200	130°	1	133.0	.....
D	200	130°	3	135.2	134.5

Another series of determinations was carried out to determine the time required for complete fusion when the temperature of the bath was held at any given point. Glycerine was used for the bath. The samples were ground to 200 mesh and dried over night over sulphuric acid. All other details were the same except that the sample was introduced when the bath had reached the desired temperature and was then held at that point until melting had occurred.

TABLE IV.—NO. OF SECONDS REQUIRED FOR COMPLETE FUSION AT GIVEN TEMPERATURES.

Samples.	133.8°–134.4°.	134.8°–135.4°.	135.8°–136.4°.	136.8°–137.2°.
A	...	79 sec.	59 sec.	50 sec.
B	110 sec.	81 sec.	65 sec.	53 sec.
C	...	80 sec.	62 sec.	53 sec.
D	...	76 sec.	64 sec.	52 sec.
Samples.	137.8°–138.2°.	138.8°–139.4°.	145°–146°.	
A	39 sec.	25 sec.	10 sec.	
B	36 sec.	28 sec.	12 sec.	
C	39 sec.	31 sec.	11 sec.	
D	33 sec.	26 sec.	11 sec.	

The melting points of the four samples of acetylsalicylic acid were finally determined by means of the copper bar apparatus of Dennis and Shelton.[1] Melt-

[1] *J. Am. Chem. Soc.*, 52 (1930), 3128.

ing points were determined for both the crystalline samples and the samples when powdered to 200 mesh. All samples were dried in the desiccator according to our usual procedure. There was a slight reaction with the bar, evidenced by the appearance of a slight green color.

TABLE V.—MELTING POINT OF ACETYLSALICYLIC ACID BY DENNIS AND SHELTON COPPER BAR.

Samples.	Fineness.	Actual Observations.	Average.
A	Crystals	142.3, 142, 141.9, 142, 141.6, 141.8	141.6
A	200	142, 141.8, 142.2, 142, 142	142.0
B	Crystals	142, 142.2, 141.5, 142.5, 142	142.0
B	200	142, 141.6, 141.9, 142.2, 141.8, 142	141.9
C	Crystals	141.8, 142, 142.2, 141.6, 142.4	141.96
C	200	142, 141.7, 142, 141.8, 141.5	141.8
D	Crystals	141.5, 141.8, 142, 141.4, 141.8, 141.6	141.7
D	200	141.5, 141.2, 141.8, 141.5, 142	141.6

It is very evident from these experiments that acetylsalicylic acid melts with decomposition, and that a part of this decomposition takes place before the acid has melted, resulting in a lowering of the melting point of the sample under observation. To test this further, melting-point tubes containing the various samples were allowed to solidify for 24 hours after the first melting, and were then subjected to a redetermination of the melting point, using exactly the same procedure as followed in the original determination.

TABLE VI.—DEPRESSION OF MELTING POINT OF ACETYLSALICYLIC ACID UPON REMELTING.

		Initial Bath Temp. 120° C. Heating Rate 3° per Min.		Initial Bath Temp. 130° C. Heating Rate 3° per Min.	
Sample.	Fineness.	1st M. P.	2nd M. P.	1st M. P.	2nd M. P.
A	200	132.1	129.7	135.4	133.5
B	200	132.2	130.0	135.2	134.1
C	200	132.4	130.4	135.2	134.1
D	200	132.0	129.1	134.6	133.2

To determine the effect of continued heat on the melting point of the acid, Samples B and C, prepared as usual, were placed in tubes in a bath heated to 125° C., and held at a temperature between 124° and 125° C. until the samples had melted. The experiment was also carried out at a temperature of 120° C. The tubes were then cooled over night and the melting point redetermined by the method we are recommending, *viz.*, an initial bath temperature of 130° C. and a heating increment of 3° per minute. The results were as follows:

TABLE VII.—TIME REQUIRED TO MELT ACETYLSALICYLIC ACID AT FIXED TEMPERATURES.

Sample.	Fineness.	Bath Temperature.	Minutes to Melt.	M. P. When Remelted by Standard Method.
B	200	124–5	21	134.0
B	200	119–20	63	134.2
C	200	124–5	23	130.6
C	200	119–20	69	131.0

It is believed that grinding the acid to a fineness of 200 mesh, and possibly even 150 mesh, causes some slight decomposition, as a slightly lower value is obtained in the routine procedure of Table II than when a 100-mesh powder is used.

Occasionally a slight odor of acetic acid is observed during this heavy grinding. For this reason it is thought that a 100-mesh powder represents the optimum of uniformity to be sought.

As a further test of the possibility of decomposition of acetylsalicylic acid during melting, an analysis, according to the saponification method of the U. S. P. X, was made of the four acids after melting. Melting-point tubes were weighed, charged with the acid, ground to 200 mesh and dried, and weighed again. The melting point was then determined, using an initial bath temperature of 130° C. and a rate of heating of three degrees per minute. After the samples had cooled and solidified, the tubes were freed from adherent bath liquid and weighed a third time. The combined tubes containing each sample were ground in a mortar and the acid dissolved in alcohol. Fifty cc. of half-normal sodium hydroxide were added to the solution and the assay completed according to the official method. The results follow:

TABLE VIII.

Sample.	Fineness.	Purity before Melting.	Purity after Melting.
A	200	99.05	98.40
B	200	99.20	98.27
C	200	99.78	98.40
D	200	99.75	98.80

Samples were also melted as recommended here, with a fine strip of blue litmus paper placed in the top of the tube. The paper became red as the sample melted, showing the evolution of acetic acid, also detectable by its odor.

CONCLUSION.

In the opinion of the authors, the melting point rubric of U. S. P. XI should read as follows:

Acetylsalicylic acid has a melting point not below 135° C. when determined by the following method. Crush the acid to a No. 100 powder and dry in a desiccator over sulphuric acid for twelve hours. Place a column of the powder 2.5 to 3.0 cm. in length in a capillary melting-point tube having an internal diameter of 0.8 to 1.0 mm., sealed at one end. Place the tube in a bath previously heated to 130° C. and continue the heating at the rate of 3° per minute until the acid melts.

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TINCTURE NUX VOMICA.*

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INVESTIGATION OF THE USE OF HYDROCHLORIC ACID AND ACETIC ACID FOR ACIDIFYING THE MENSTRUUM AND THE DETERMINATION OF THE EFFECT OF SLOW AND FAST PERCOLATION.

Experiments were carried out in an attempt to find a more satisfactory method of extracting Nux Vomica. The object was to determine the advantages and disadvantages of menstrua containing hydrochloric acid and acetic acid, respectively,

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