

## SUGGESTIONS RELATIVE TO U. S. P. X REVISION.\*

BY JULES BEBIE.

Revision of U. S. P. X is now under consideration and the Chairman of the Revision Committee has extended an invitation to submit suggestions for changes of the present official formulas, tests and assays.

In the course of our work in the manufacture and testing of pharmaceutical chemicals we have come across some U. S. P. tests and specifications which in our opinion are open for improvement and it is the purpose of this paper to bring these cases to your attention.

## I. ETHER SOLUBILITIES.

Literature references as well as our own observations differ more or less from the ether solubilities as given for several products in U. S. P. X. It is not stated there what kind of ether should be used for the determination. However, whenever reagents are required which are official in U. S. P., it is customary to use the U. S. P. quality as reagent. We have therefore been using U. S. P. X ether as well as U. S. P. procedure for determination of solubility in ether. Probably some of the published data on ether solubilities have been obtained by the use of absolute ether, free of moisture and alcohol, and this may account for some of the big differences.

These terms signify the numerical ranges given on page 458 of U. S. P. X.

TABLE I.—ETHER SOLUBILITIES OF U. S. P. X PRODUCTS.

Product.	U. S. P. X specification.	Solubility determinations by U. S. P. method.	Literature references.
Acetanilid	1 Gm. is soluble in 17 cc. ether at 25°	1 Gm. soluble in 18.3 cc. U. S. P. X ether. (Average of 3 determinations) 1 Gm. soluble in 53.1 cc. of absolute ether. (Average of 3 determinations)	Seidel 2nd Ed., Vol. I, p. 3, 2.8 Gm. per 100 Gm. saturated solution, or 1 Gm. in 49 cc. at 25° (Marden & Dover, <i>J. Am. Ch. Soc.</i> , 38 (1916), p. 1242) in ether distilled over sodium. Ph. Germ. VI. Soluble in 50 parts of ether (by weight), equiv. 1 Gm. in 70 cc.
Acetphenetidn	1 Gm. is soluble in about 130 cc. of ether at 25°	1 Gm. soluble in 148 cc. U. S. P. X ether, or in 306 cc. absolute ether	Seidel, 2nd Ed., Vol. I, p. 477, 1.56 Gm. per 100 Gm. saturated solution, or 1 Gm. in 89 cc. ether. Taylor and Bebie, <i>Am. J. Pharm.</i> , 1924, p. 597, 0.32 Gm. in 100 cc. absolute ether, or 1 Gm. in 310 cc. Taylor: 1 Gm. in 102 cc. U. S. P. ether. Bebie: 1 Gm. in 156 cc. U. S. P. ether. Average 1 Gm. in 129 cc. U. S. P. ether
Acetylsalicylic Acid	1 Gm. is soluble in 10-15 cc. of ether	1 Gm. soluble in 15 cc. of ether	Ph. Germ. VI, Soluble in 20 parts of ether (by weight), equiv. 1 Gm. in 28 cc.
Phenolphthalein	1 Gm. is soluble in about 70 cc. of ether	1 Gm. soluble in 105 cc. U. S. P. X ether. (Average of 4 determinations)	

\* Scientific Section, A. Ph. A., Rapid City meeting, 1929.

It should be specified in the Pharmacopœia what kind of ether is to be used for the solubility determinations.

The results are tabulated in Table I. It clearly shows the existing discrepancies and it is recommended that this should be investigated for the revision of U. S. P. X.

On account of slight variations in the composition of ether in regard to alcohol and water content, it is difficult to get checking results on some of the ether solubilities, when the determinations are made in different laboratories.

For this reason it would perhaps be advisable to eliminate exact ether solubility figures and to simply state that a substance is "freely," "sparingly," etc., soluble in ether.

#### OTHER SOLUBILITIES.

The solubility of Gluside (Saccharin) is given as 1 Gm. soluble in 290 cc. of water at 25° and in about 25 cc. of boiling water. It is proposed to change these figures to 1:325 at 25° and 1:30 for boiling water.

#### LITERATURE REFERENCES.

British Pharmacopœia: Soluble in 400 parts of water at 25°.

Japanese Pharmacopœia IV: Soluble in about 400 parts of water and in 30 parts of boiling water.

French Pharmacopœia 1927: Soluble in 400 parts of water at 15° and 30 parts of boiling water.

Nederlandsche Pharmacopœia: 1 Gm. in 360 parts of water at 15°.

Sodium Salicylate is stated to be soluble 1 Gm. in 9.2 cc. alcohol (94.9% by vol.) at 25°. We find it is soluble in 9.3 Gm. of alcohol or 10.2 cc.

#### LITERATURE REFERENCE.

Seidell, 2nd. Ed., p. 665, 12 Gm. per 100 Gm. saturated solution, using alcohol of 92.3% by weight = 94.9% by volume, equiv. to 1 Gm. in 10 cc. alcohol. See also Seidell, *J. Am. Chem. Soc.*, 31 (1909), 1164.

It is recommended to change the pharmacopœia requirements to: "One Gm. of sodium salicylate is soluble in 10.2 cc. alcohol at 25°."

TABLE II.

Product.	U. S. P. X specifications.	Melting points found in domestic and foreign samples.	Suggested change for U. S. P. XI.
Acetanilide	Melts between 113° and 115° C.	1. 114.4-114.8 2. 114.9-115.4 3. 114.6-115.0 Ph.F., 114, 1927	Melts between 114° and 115° C.
Gluside (Saccharin)	Melting point not below 220° C.	227.4-228.2; 227.1-227.9; 227.1-228.1; 224.7-225.6.	Melting point not below 225° C.
Vanillin	Melts between 80° and 82° C.	82.0-82.4; 81.7-82.2; 81.6-81.9; 81.8-82.1; 81.0-81.3; 81.7-82.1.	Melts between 81° and 83° C.
Salicylic Acid	Melts between 157° and 159° C.	158.8-159.1; 158.7-159.2; 158.5-159.1; 158.9-159.2.	Melts between 158° and 159° C.
Phenolphthalein	Melting point not below 256° C.	261.2-261.8; 262.3-262.8.	Melting point not below 258° C.
Phenol	Congealing point: not below 39° C.	40.1; 39.7. Ph.F., 42.5.	Congealing point: not below 40° C.

Phenyl salicylate (Salol) is stated to be soluble, 1 Gm. in 6670 cc. of water at 25°. According to our finding 1 Gm. is soluble only in 40,000 cc. of water. It is recommended to have this checked or to describe it as very sparingly soluble in cold water.

## 2. MELTING POINTS.

The melting point gives a good indication of the purity of organic substances and is therefore an important specification.

In some U. S. P. X products the melting point specifications are decidedly too low for present-day standards of purity, and it is proposed to give these higher standards official recognition by raising the melting point specifications as recommended in Table II.

### DETERMINATION OF MELTING POINT U. S. P. X PROCEDURE.

The rate of heating by U. S. P. X procedure is 3° per minute beginning 25° below the expected melting point, then when the substance begins to melt, carefully regulate to 0.5° per minute. We have found it practically impossible to change the rate of heating from 3° per minute to 0.5° per minute in the very short space of time this method will allow for most of our products.

We recommend that a uniform rate of heating be used so that no adjustment is necessary while the material is melting, thus simplifying the test materially. A rate that we find works very satisfactorily for routine work is to heat the bath rapidly until the temperature is about 10° below the expected melting point, then regulate the rise to 1° per minute maintaining this rate until the melting is complete.

## 3. DETERMINATION OF BOILING POINT.

According to U. S. P. X procedure (*Method I*) a 25-cc. sample is distilled in a 50-cc. flask at a rate of 1 cc. for each 15–20 seconds. The thermometer is read when five drops have distilled into the receiver, for the first point and when 95% (23.75 cc.) has distilled, for the end-point.

With high boiling liquids, such as methyl salicylate and guaiacol, we have not been able to distil 95% of the sample to obtain the second reading. There is always 2 cc. or more of the sample amounting to upwards of 8 per cent left in the flask as vapor and in the condenser as condensate at the point at which the last liquid evaporates from the bottom of the flask (the dry-point). To continue to heat the flask would overheat the vapor and give an erroneous figure for the end-point.

We recommend that this test be revised so that the last reading will be taken at a point readily obtainable and suggest either 92% (22 cc.) or dry-point as possible end-points.

We have had further difficulty with *Method I* in the rate of distilling notably methyl salicylate. The present method requires distilling at the rate of 1 cc. for each 15 to 20 seconds. It was practically impossible to obtain a rate of 15 seconds per cc. Distilling at 20 seconds per cc. the range of distillation was about 7° C. with a rapid rise toward the end whereas U. S. P. X specifies a range of 5° (219–224°). Incidentally only 94% of distillate was obtained after allowing the condenser to drain completely. Distilling at 30 seconds per cc., which is about one-half the speed required by the official method, the range was 4° C., but there was still a rapid rise at the end.

In the distillation of guaiacol (crystals) we did not experience any difficulty with rapidly rising temperatures when distilling at the rate of 20 seconds per cc. However, we again had to let the condenser drain completely to bring the final reading up to 94%.

For low boiling liquids, such as carbon tetrachloride for instance, the U. S. P. X procedure is quite satisfactory.

It is evident, however, that the official method, in regard to second reading and rate of distillation is not applicable to all products particularly the high boiling ones and should probably be investigated for each product separately in which the distilling range is specified.

It is of course desirable to have a method which will fit all products and only in case no agreement can be reached on such a method will it be necessary to make some specific specifications for products which do not lend themselves to the general procedure.

#### 4. ARSENIC TEST IN PHENOLPHTHALEIN.

According to U. S. P. X the sample is prepared for arsenic test by heating 0.2 Gm. in a crucible with a mixture of potassium nitrate and sodium carbonate. When using a porcelain crucible misleading results may be obtained due to presence of arsenic in the crucible.

We had 20 parts per thousand of arsenic reported in a sample in which practically no arsenic existed. When using a platinum crucible the mistake was corrected. This arsenic would have been of little consequence in a 1-Gm. sample but in a 0.2-Gm. sample as directed for U. S. P. test it appeared to amount to a serious contamination.

If this method is continued for arsenic test in phenolphthalein, it would appear advisable to use a 1-Gm. sample and to specify the use of a platinum crucible.

It is also recommended to investigate in a general way the method described on pages 171-173 of 2nd edition of "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists." In this method a 5-Gm. sample is used and the organic matter is destroyed by digestion in a mixture of sulphuric and nitric acid. This method was found satisfactory for preparing samples of phenolphthalein for arsenic test and it is possible it could be applied generally in U. S. P. products where organic matter is destroyed in preparing for arsenic test.

#### SUMMARY.

Ether, alcohol and water solubilities of several products could not be confirmed and rechecking and revision is recommended.

The melting point specifications of several synthetic drugs are too low for present-day standards of purity of these products. It is recommended to give these higher standards official recognition by raising the melting point specifications as proposed.

The directions for preparing samples for arsenic test in phenolphthalein are deficient and an improved procedure is suggested.

Changes in the methods of determination of melting and boiling points are recommended.