PHARMACOPŒIAS AND FORMULARIES

PHARMACOPŒA INTERNATIONALIS

SOME CRITICISMS OF THE PROCEDURES AND MONOGRAPHS

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The chemical procedures and requirements of the International Pharmacopœia agree closely with those of the British Pharmacopœia but, as is to be expected in an International publication, the influence of the United States Pharmacopeia and of certain Continental Pharmacopœias can be traced. To have obtained agreed methods and standards from a Technical Commission of Experts accustomed to such diverse methods as exist in the present National Pharmacopœias is a remarkable achievement.

The criticisms in this review are in the main on minor points of detail but it is considered that these should be noted with the hope that they may lead to improvement in a subsequent edition.

Criticisms of Procedures

Appendix 5.—*Determination of density.* From the point of view of the British user it is to be regretted that "density" is used and not "weight per millilitre in air" as in the B.P., a conversion figure having to be applied in each case in order to compare the limits specified in the two pharmacopœias.

Appendix 6.—*Determination of melting range.* The use of soft glass capillary tubes is specified, although the use of soft glass has been shown to be unsatisfactory for certain substances owing to the high alkali content.[1] The method described is very time-consuming since one is directed to heat up from room temperature at the rate of 3° C. per minute to a temperature 15° C. below the expected melting point, thus for substances such as caffeine and sulphamerazine, melting above 200°, the total time required exceeds 1 hour. The use of a melting range and the definition thereof as "the range between the corrected temperature at which the substance begins to form droplets and the corrected temperature at which it completely melts as shown by the formation of a meniscus," is an improvement over the British Pharmacopœia definition of the melting point. It is possible to pass materials as complying with the B.P. in that a meniscus is *not* formed until the required temperature is reached, although the presence of an impurity may have been indicated in that the first sign of change such as the formation of droplets, takes place several degrees below the official definition of the melting point, namely, the formation of a meniscus. In practice it has been found that for substances which melt without decomposition (phenacetin, sulphanilamide, caffeine, etc.) the melting point determined by the B.P. procedure was either at the mid-point or towards the higher limit of the International Pharmacopœia range. In the case of substances such as ascorbic acid or succinylsulphathiazole which undergo some decomposition at the melting point, the

longer period of heating required by the International Pharmacopœia results in decomposition commencing at a lower temperature and proceeding to a greater extent than in the B.P. method, causing the final melting point to be some degrees lower (Table I). In such cases the results cannot be regarded as reliable and it is therefore suggested that the International method should be revised or at least the required range of melting points of materials of this class investigated.

TABLE I

Substance	B.P.		Ph.I.	
	Requirement	Found	Requirement	Found
Ascorbic acid.	190° to 192° C. with decomposition.	Begins to char 190·4° C. Meniscus formed at 191·4° C. followed by decomposition.	191° to 194° C. with decomposition.	Begins to char 182° C. forms droplets and fuses on outside 185° C. Starts to form meniscus then shrinks and rises in tube 186·8° C.
Succinylsulphathiazole.	188° to 195° C. with decomposition.	Forms meniscus 189·5° C. Decomposes 190° C.	188° to 193° C. with decomposition.	Fuses on outside 183° C. Starts melting 184° C. bubbles form in semi-molten mass and material rises in the tube 185·5° C.

The apparatus for determination of boiling range is of a type which is unfamiliar to British or American analysts and does not include a draught screen, and in this respect is less satisfactory. The apparatus is not suitable for use for liquids which boil at approximately room temperature or below (æthylis chloridum).

Appendix 14—*Determination of nitrogen.* It is rather surprising that the use of selenium should have been permitted in view of the adverse criticisms of this catalyst[2,3,4] while further criticisms have appeared since the pharmacopœia has been in the press.[5]

Appendix 20—*Determination of residue on ignition.* It would be preferable to specify "sulphated ash" rather than direct ignition since, unless the temperature for ashing is prescribed, there is the danger of low results due to loss of volatile chlorides.

Loss on drying. For materials containing water of crystallisation the International Pharmacopœia frequently gives both upper and lower limits for moisture (quinini hydrochloridum, sulphaguanidinum, etc.) thus establishing a more rigid control of the strength than the British Pharmacopœia which in many instances gives no indication of the lower limit of moisture permitted.

The standard conditions for drying would seem to be 100° to constant weight, but instructions are given, in some cases, for drying at this temperature for specified periods which vary from 1 to 6 hours. A variety of other temperatures are used for one or more chemicals, thus, 70°, 80°, 105°, 103 to 105°, 110°, 120°, 130° and 150°, and either drying to constant weight, or for prescribed periods which vary from only 30 minutes for

caffeine to twenty-four hours for thiopental sodium. A few substances which decompose on heating are directed to be dried over sulphuric acid for a specified time or to constant weight; vacuum drying at room temperature is directed sometimes with sulphuric acid, sometimes with phosphorus pentoxide as dessicant, with times ranging from 4 to 48 hours, or to constant weight. Finally two substances are directed to be dried *in vacuo* at 100° C. and one substance (stibophenum) at 140° to 150° C. While a number of different drying conditions are obviously required, it would seem that the variety is greater than necessary and it would be a great convenience to the analyst if drying conditions, particularly as regards temperature, were made more uniform whenever possible.

Determination of non-volatile residue. There is a lack of uniformity, and in some instances ambiguity, in the directions given in the various monographs regarding the methods and particularly the temperature for drying the residue obtained on volatilisation of a sample. For example, under chloroformum the directions read "When evaporated . . ." no temperature or method being stated, whereas the directions under carbonei tetrachloridum read "Leaves, on evaporation in a water-bath. . . ." Under tetrachloroæthylenum, fuller directions are given, "Leaves on evaporation and drying at 105°. . . ." The residue from æther vinylicus is directed to be dried at 50° for two hours, but the residue from æther anæstheticus is dried at 100°, time not specified. Under bromoformum the unusual requirement is stated that "on evaporation of 3 ml. *no* residue remains." In almost all cases the directions could be unified to read "On evaporation on a water-bath and drying at 105° leaves not more than . . . ."

Criticisms of Individual Monographs

Æther anæstheticus. Density. A range of 0·002 is permitted, this is in marked contrast to the present requirement of the British Pharmacopœia; a range of 0·714 to 0·715 should suffice.

Æthylis chloridum. Boiling range. This is stated as 11·8 to 13° C. It would seem hardly necessary to specify so exact a temperature as 11·8° C. for the lower point of the range, especially as the apparatus and procedure for determination of boiling range described in Appendix 6 is not specially adapted for liquids which boil below room temperature.

Barbitalum. Neutral and basic substances. Directions should be given as to the amount of ether to be used for extraction; also the separated ether should be washed with water before evaporating, to remove traces of alkali or sodium barbitone.

Barbitalum natricum. Although a maximum of 1 per cent. of moisture is permitted, the assay, unlike that of phenobarbitalum natricum, is not calculated with reference to the dried material.

Benzylis benzoas. Assay. No blank is specified, instructions should be included to carry this out.

Cocainum. Specific rotation. The rotation is required to be determined in a 3·0 per cent. w/v solution in water containing 15 ml. of 0·1N hydrochloric acid in 20 ml. of the solution. Therefore, for 0·6 g. of

alkaloid the use of only 15 ml. of 0·1N hydrochloric acid is directed, but theoretically 19·78 ml. of 0·1N hydrochloric acid is required to form the hydrochloride and the alkaloid is not soluble under the conditions specified in the Pharmacopœia. The figures for the rotation are not in agreement with the requirements for the hydrochloride and to be comparable should be $-63{\cdot}4°$ to $-65{\cdot}2°$.

Cocaini hydrochloridum. Ash. The limit of 0·25 per cent. is unnecessarily high, 0·1 per cent. is easily achieved. *Temperature of drying.* Whereas in all other cases one specific temperature is prescribed, in this case the unusual conditions of 103° to 105° C. are directed, actually a temperature of 100° or 105° C. is satisfactory. *Specific rotation.* In view of the permissible limit of 1 per cent. of moisture it would be preferable to specify the limits for specific rotation calculated with reference to the dried material.

Morphini hydrochloridum. Specific rotation. Despite the fact that a variation in morphine content is permitted, there is no tolerance for the specific rotation, as only one figure is quoted. A range should be allowed as in the case of all other monographs.

Morphini sulphas. No specific rotation is included although this is given for morphini hydrochloridum (see above).

Phenobarbitalum natricum. Assay. The residue of phenobarbitone can be equally well dried at 100° C. as at the specified temperature of 90° C. It is desirable so far as possible to unify the temperature of drying as a matter of practical convenience.

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