BENTLEY AND DRIVER'S

TEXTBOOK OF PHARMACEUTICAL CHEMISTRY

DRIVER

SEVENTH EDITION

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J. E. DRIVER

PROFESSOR OF CHEMISTRY IN THE UNIVERSITY OF HONG KONG

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PREFACE TO THE SEVENTH EDITION

THIS book, which has for many years been widely used by those studying for examinations in pharmaceutical chemistry in Great Britain and other parts of the Commonwealth, was originally written by the late Mr. A. O. Bentley and myself when we were young colleagues on the staff of University College, Nottingham. After the publication of a second impression in 1929 I became solely responsible for it, although Mr. Bentley continued to give me the benefit of his advice on many pharmaceutical matters until his death in 1943. In successive editions it has been my endeavour to keep the book in line with current developments and advances in knowledge while preserving its original character as a students' textbook; it has, however, been found of use also to a wider circle of practising pharmacists and chemists.

The present edition has involved the heaviest revision of the book since its original publication. Most of the text has been completely rewritten, and although the previous form has been preserved as far as possible there are few passages of any length that have not been considerably changed.

I am very grateful to Dr. M. W. Partridge. He has rewritten the chapter on photometric methods, and many of the broad changes now introduced are the result of earlier suggestions by him. Mrs. D. A. Collins has kindly contributed the important chapters dealing with radioactivity, nuclear structure, periodicity, and valency. My wife has given me an immense amount of help and much valuable advice. Many other friends and users of the book have offered suggestions, or helped in other ways.

Manufacturing firms have willingly supplied information when it was needed, and the Radiochemical Centre, Amersham, has advised on various points.

The use of matter contained in the *British Pharmacopœia 1958* is by permission of the General Medical Council.

J. E. D.

University of Hong Kong
Hong Kong
November 1959

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INTRODUCTION

PHARMACEUTICAL chemistry is the chemistry of substances used in medicine. In this broad definition the terms 'substance' and 'medicine' are used in their wider senses, and it is injudicious to try to define the subject more narrowly: its scope expands with developments in medical and allied studies, and the emphasis shifts as knowledge advances and as fashions change.

The material in this textbook is arranged in an order designed for easy reference: it is not intended that the subjects should necessarily be studied in the order given. As far as possible the different sections have been made independent of one another, and cross-references are given where necessary.

Part I gives a general account of certain physical and chemical methods used in determining the purity of pharmaceutical substances. The detailed applications of these methods to particular substances are described where they naturally arise in Parts II and III.

Part II begins with some important general subjects but deals mainly with inorganic compounds in common use in pharmacy; the simpler organic salts of metals are also, for convenience, included here. A brief summary of the general chemistry of each element is followed by a description of those of its compounds that are defined in monographs of the Pharmacopœia.[1]

Under the descriptions of individual substances the impurities for which tests are prescribed in the Pharmacopœia are listed, together with any special notes about them. The tests themselves are described only where they have points of special interest, or where the chemical reactions which take place are not obvious from the Pharmacopœial description.

Part III comprises a description of organic compounds of pharmaceutical importance within a general framework of the subject. In this Part a description of the Pharmacopœial standards of official substances is placed at the end of the chapters in which they naturally fall.

The word '*official*' is used in this textbook to denote substances which are defined in the monographs of the Pharmacopœia. This meaning is a narrower one than that applied to the word in the Pharmacopœia itself (p. 1). It is important to appreciate the difference between a chemical individual and an official substance of the same name. The official substance is a commercial product which is required to comply with certain standards of purity, and may sometimes contain other substances, added for special reasons: thus chloroform of the Pharmacopœia contains 1 to 2 per cent. of added ethyl alcohol. Where it is considered essential to show that a substance referred to is of official standard, the official name with capital initial letters is used, for example Sodium Bromide, Dilute Ammonia Solution; capitals are, however, not used unnecessarily where the meaning is clear from the context.

PRACTICAL WORK

Inorganic preparations. Manufacturing processes which cannot be conveniently reproduced in the laboratory are described in brief and general

[1] When the Pharmacopœia is referred to (without any qualification) it is to be understood to mean the British Pharmacopœia 1958.

terms. For a few preparations of essentially pharmaceutical interest laboratory details are given, including quantities to be used.[1]

The methods of preparation of a substance often point to the source of likely impurities.

Tests for purity. A careful qualitative analysis will show whether a substance is in the main what it is represented to be, and may give a valuable indication of impurities present. It should be noted that an impurity is not tolerated in an official substance, even if it is not precluded by the prescribed tests, should rational considerations require it to be absent (B.P., p. 2).

General accounts of the official limit tests for chlorides, sulphates, and iron, and the quantitative tests for arsenic and lead, are given in Part I (Chapter 9). Other official tests for impurities are amplified in Parts II and III where the Pharmacopœial description is felt to be not detailed enough.

Reagents used in testing for impurities must be analytically pure. When any doubt exists, the reagents themselves should be tested. In descriptions in the text of analytical processes, the term 'water' means Purified Water.

Quantitative determinations. The descriptions of assay processes are of a general nature. Details given sufficiently fully in the Pharmacopœia are not unnecessarily reproduced, but any points of special interest are commented on. The method of working each calculation is briefly shown; take, for example, the statement:

'1,000 ml. of N/10 alkali are equivalent to 1/20 H_2SO_4.'

This means that every 1,000 millilitres of decinormal alkali used in the assay are equivalent to one-twentieth of the gramme-molecular weight of sulphuric acid (i.e. 4·904 grammes).

Weights are expressed in grammes (abbreviation, 'g.'), a gramme being the one-thousandth part of the International Prototype Kilogram; volumes are expressed in terms of the millilitre (abbreviation, 'ml.'), which is the volume occupied by a gramme of water at the temperature of its maximum density. These units are used in the Pharmacopœia, and in scientific work generally.

The table on p. 705 summarizes the indicators used in various acid–base titrations, and the colour changes of the commoner indicators are shown in Fig. 18 (p. 39).

Although in the event of doubt or dispute the methods of analysis of the Pharmacopœia are alone authoritative, it is made clear (B.P., p. 4) that the analyst is not precluded from employing an alternative method where he is satisfied that it will give the same result as the official method.

To help in the selection of representative quantitative exercises from the many assays described in the Pharmacopœia, classified lists are given as an Appendix.

Organic preparations. Experimental details are given in Part III for the preparation of many typical organic compounds. The object should be to produce pure compounds in good yield. It is therefore advisable to test products for purity, and to record yields obtained. Without this control it is

[1] When 'parts' are given, solids are by weight in grammes, and liquids by volume in millilitres.

easy to fall into careless methods which result only in a waste of time and materials.

Alkaloidal assays. General descriptions of the alkaloidal assays of the Pharmacopœia are given in Chapter 68. These descriptions are purely explanatory: full details are given in the Pharmacopœia. Many alkaloidal assays are difficult, and it is generally advisable to gain experience in simple alkaloidal determinations, such as those of some of the official alkaloidal salts and their solutions, before attempting the more involved assays of drugs and their preparations.

PHARMACOPOEIAS

Pharmacopoeias[1] (i.e. collected lists of drugs and medicinal chemicals, with directions for making preparations from them) date from early times and have gradually, since the sixteenth century, come to have various degrees of authority in countries in which they are published.

The precursor to the British Pharmacopœia was the Pharmacopoeia Londinensis (1618) which appeared in various editions until 1851.

The original purpose of the British Pharmacopœia was the unification of the Pharmacopoeias of London, Edinburgh, and Dublin. For nearly 100 years the responsibility for its publication has rested on the General Medical Council, whose authority is derived in the first instance from the Medical Act, 1858.

The first British Pharmacopœia (of 1864) was quickly followed by a second in 1867. From that time intervals between editions have until recently been irregular but usually long, the successive years of publication being 1885, 1898, 1914, 1932, 1948, 1953, and 1958. In 1947 the General Medical Council resolved that the normal interval should be five years, and doubtless the practice, begun in 1874 and continued at various times since, of publishing Addenda for general or special purposes in the intervals between editions will be continued.

The Pharmacopeia of the United States of America first appeared in 1820, and is now published in quinquennial revisions which seem likely in the future, as they have done in recent years, to alternate in publication dates with new editions of the British Pharmacopœia. The current Fifteenth Revision was published in 1955, so that the Sixteenth Revision will appear in 1960. The U.S.P., to use the common abbreviation, is prepared by a committee which includes representatives from many medical and pharmaceutical organizations, and its standards receive official recognition in the United States.

In addition to national pharmacopoeias like these there is the Pharmacopoea Internationalis published by the World Health Organization (Vol. I 1951, Vol. II 1955). The object of this is to provide a unified list which will avoid the confusion caused by differing national standards, strengths, and names, especially to travellers who may need to have the same prescription dispensed in different countries. In accordance with this world-wide objective, the names of the drugs, chemicals, and preparations listed (but not the body of the text) are in Latin.

[1] There are various spellings of the word: Pharmacopoeia, Pharmacopœia, Pharmacopeia, and Pharmacopoea will all be noted in the paragraphs which follow.

The British Pharmacopœia 1958. This, the ninth British Pharmacopœia, has like its immediate predecessors been prepared by a Pharmacopœia Commission composed of persons with specialized knowledge in various medical and pharmaceutical fields. The function of the Pharmacopœia is stated in the Medical Act,1956, which consolidates former Medical Acts: 'The General Council [i.e. the General Medical Council] shall, at such intervals as they may determine, cause to be published under their direction new editions of the British Pharmacopœia, containing such descriptions of and standards for, and such notes and other matter relating to, medicines, preparations, materials and articles used in the practice of medicine, surgery, or midwifery as the Council may direct.' This significant change was first introduced with the 1953 Pharmacopœia as a result of the Medical Act, 1950; previously, the Pharmacopœia had been defined under the Medical Act, 1858, as 'a Book containing a list of medicines and compounds, and the manner of preparing them . . .'. As an immediate result of the wider scope, sterilized surgical catgut was included in the 1953 Pharmacopœia, and other materials used in surgery or midwifery have been added since.

The 1958 Pharmacopœia consists, like its forerunners, of the following:

(*a*) Introductory sections. Attention should be paid here particularly to the 'Introduction', which summarizes the changes in the current edition and provides a useful pointer to pharmaceutical progress, and the 'General Notices', which must be carefully studied at the outset if misunderstandings and misinterpretations of later parts of the text are to be avoided.

(*b*) Monographs of official drugs, preparations, and substances. The monographs are for convenience somewhat stereotyped in style, and those which may be regarded as falling within the field of pharmaceutical chemistry give some or all of the following information, in the order shown:

Main title.
Subsidiary titles.
Chemical formula, molecular weight, and (if necessary) systematic chemical name, general statement of some feasible method of preparation, and quantitative standards of purity or strength.
Description (a statement of those superficial qualities that can be determined without recourse to scientific examination).
Solubility (note the explanation (B.P., p. 3) of the difference between 'solubility' as information and as a standard; for an example, see Ichthammol).
Identification (various specific and non-specific tests).
Tests for purity, consisting of specified tests, some of a quantitative and some of a qualitative nature, including standards of melting-point, boiling-point, weight per ml., &c.
Method of assay.
Methods of storage and labelling.
Preparations.
Doses.

(*c*) Appendixes. These give details of general tests and methods of quantitative analysis, biological assays, and other processes to which reference is made in the monographs of the main text, as well as prescribing standards for materials and solutions employed in tests or quantitative determinations.

The early Pharmacopœias were written entirely in Latin. Latin persisted for official titles of the subjects of monographs until the 1953 edition, although it had been clear for many years that, with the introduction of synthetic medicinal compounds, it was becoming outmoded. In the 1953 Pharmacopœia the main titles were given for the first time in English; subsidiary Latin titles, where still now included, are relics from the older Pharmacopœias, and no new Latin names have been coined. The order of the monographs is essentially alphabetical, except that descriptive words like 'purified', 'dried', and 'fresh' are not taken into account, and that a preparation usually follows its most significant component (thus flexible collodion follows pyroxylin). Once the general idea has been grasped, any monograph can be quickly located by following the headlines on the right-hand pages. An imperfectly alphabetical order, however, always creates problems with no self-evident solution: for example, ammoniated mercury was grouped with mercury compounds in the 1953 Pharmacopœia, but is now to be found with ammonia and ammonium chloride.

It is expected that the reading of this textbook will be accompanied by a study of the corresponding parts of the Pharmacopœia. To illustrate the development of the subject, frequent reference is made to changes which have been introduced into the Pharmacopœia in the course of time.

PART I

ANALYTICAL METHODS

1

PHYSICAL TECHNIQUES

PHYSICAL constants are important criteria of the purity of many pharmaceutical substances: many materials of indefinite composition do not lend themselves to chemical methods of analysis, and, for these, examination by physical methods is of prime importance. A glance through the Pharmacopœia will reveal the importance attached to determinations of melting-point, boiling-point, weight per millilitre, viscosity, optical rotation, refractive index, and other physical measurements. An organic compound which appears on superficial examination to be reasonably pure may be found by its melting-point to deviate seriously from recognized standards; the boiling range of a liquid may be the only simple way of detecting the presence of a foreign substance present in appreciable proportions; and determinations of refractive index and optical rotation are routine matters in the examination of such materials as volatile oils, which are variable in composition and liable to adulteration. Critical solution temperature also is a physical constant, and it is a manifestation of this which is employed in the tests for solubility of volatile oils in aqueous alcohols.

The purpose of this chapter is to outline the principles involved in the measurement of some of the more important physical constants, and to describe the commoner forms of apparatus in use. Skill in these measurements, as in most experimental work, can only be acquired by practice.

Photometric measurements and measurements of radioactivity are dealt with in later chapters.

Melting-point. For the determination of melting- and boiling-points, accurate thermometers are a necessity. They should preferably be either of the short-stem type, graduated for total immersion of the mercury column, or of the 100-mm. immersion type. If an ordinary long-stem thermometer, graduated for total immersion, is used, and part of the mercury column is exposed, a correction has to be introduced which is only approximate and may lead to serious error if the exposed column covers a considerable range of temperature.

The observed melting-point of a powder may vary with such factors as its dryness and fineness, and the uniformity and rate of heating. The Pharmacopœia does not now specify the precise form of apparatus for the determination of the melting-point of readily powdered substances (i.e. the majority of those organic compounds which melt considerably above atmospheric temperature), but it does emphasize the need for rapid mixing of the heating liquid in order to avoid stratification. The official requirements are met by the apparatus which was specified in more detail in the 1932 Pharmacopœia. A glass heating tube of the ordinary boiling-tube type (Fig. 1) contains a suitable liquid, which should be clear and colourless, and have a boiling-point considerably higher than the melting-point of the substance to be examined. The heating tube is provided with a glass stirrer which can be moved from top