1. Liquid Oral Preparations

(A) INTENDED TO BE SWALLOWED

The main examples are draughts, elixirs, emulsions, a certain type of gargle, oral gels, linctuses, mixtures, paediatric drops, and syrups.

The container of choice for most of these products is the metric medicine bottle made to British Standard Specification 1679 : Part 6: 1967 (Fig. 3.1). This has the following features—

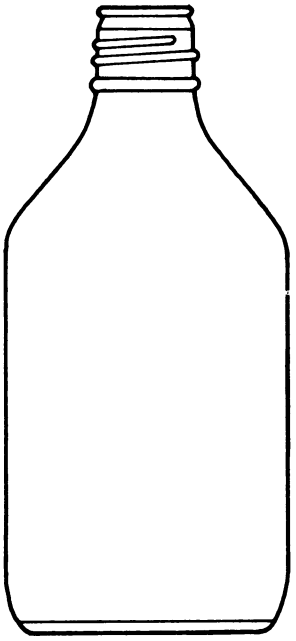

Fig. 3.1 GLASS MEDICINE BOTTLE
(BS 1679 : Part 6 : 1967)

(*a*) For cheapness, it is made from lime-soda glass (*see* p. 361).

(*b*) It is ovoid in section but the back is flatter than the front (Fig. 3.2); this allows the bottle to rest steadily on the bench while the label is fixed to the bowed front and the container is wrapped.

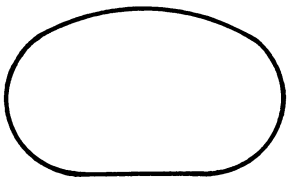

Fig. 3.2 SECTION OF MEDICINE BOTTLE

(*c*) It is free from the moulded graduations that used to be found on some Imperial bottles and which are not accurate enough for the measurement of dose volumes.

(*d*) It has a special lip that facilitates pouring.

(*e*) It can be fitted with either of two types of screw closure—

(i) White polypropylene, moulded to contain inside a crab's claw sealing ring that compensates for irregularities in the bottle lip and does not need a wad or liner (*see* Fig. 9.2 in *Tutorial Pharmacy*). Polypropylene is a useful closure material because of its low permeability to gases and vapours.

(ii) Black, thermosetting plastic. This requires an insert consisting of a resilient wad (usually of woodpulp) faced with an impervious liner (usually a plastics film or a resin-impregnated paper). The wad must be stout enough to resist distortion or fracture on repeated tightening of the cap.

Before use, bottles must be checked for chips or cracks on the neck that could prevent the closure from making an impervious seal.

(*f*) It is colourless. When protection from light is necessary light-resistant, emulsion-type or plastics bottles (*see* below) may be used or the patient can be instructed, by a label, to store away from light.

(*g*) It is available in six sizes (50, 100, 150, 200, 300 and 500 ml).

Containers of rigid polyvinyl chloride are obtainable. These are very light (about one-ninth of the weight of glass), virtually unbreakable and available either clear or amber; but they are less transparent than glass containers.

Additives such as plasticisers, stabilisers and antoxidants are included in plastic products to facilitate manufacture, confer special properties, and prevent deterioration during use. If these inclusions are yielded to the contents of a container, deleterious effects on medicaments or adjuncts, and harm to the patient, may result. Certain ingredients of medicines cause softening and distortion of plastics while others, including drugs, colourings, flavours and preservatives, may migrate into and, in some instances, permeate the container.

Some plastics are permeable to water, or other solvent, vapour (egress may lead to concentration of the contents) and/or oxygen (ingress may cause deterioration).

At the time of writing, the only polyvinyl chloride medicine bottle on the British market is the Certor type.

(*a*) The absence of identification in accidental poisoning can lead to delayed treatment, which can be fatal. For example, overdosage with iron preparations can do irreparable harm if not immediately treated.
(*b*) No other record of treatment may be available to a doctor called to another doctor's patient.
(*c*) For many medicaments, concealment is no longer possible. Some tablets are marked with their names, and it is almost impossible to remove the labels from the tubes of certain proprietary ointments.
(*d*) Marking of tablets with an identification, an idea favoured by some authorities, cannot be relied upon, because the container may have been emptied.
(*e*) Proper-name labelling prevents confusion when the patient is receiving several medicaments.
(*f*) The patient should be encouraged to understand his treatment.

Antagonists of the system argue that—

(*a*) The patient may recognise the drug as one given to an acquaintance with a dangerous disease, draw the wrong conclusion, and worry unnecessarily.
(*b*) It may lead to self-medication. Refusal by the pharmacist to supply could be embarrassing for him and the customer.
(*c*) Medical advice may be given by lay 'experts'.
(*d*) Patients are known to transfer drugs from one container to another.
(*e*) It might be used by doctors as a substitute for patients' records.
(*f*) The correct proper name is not always obvious and patients might be confused if different pharmacists used different names.

However, consensus of opinion has steadily moved to the view that medicines should be named on the label.

For some years, if the prescriber wanted proper-name labelling he had to use the method that still applies to private prescriptions (*see* p. 24). Later the medical profession recommended that the proper name should appear unless the prescriber indicated to the contrary. This was unacceptable to the Central N.H.S. (Chemist Contractors) Committee which represents pharmacists dispensing in the National Health Service; it insisted that the procedure should be seen to give pharmacists a clear instruction. The present method, outlined at the beginning of this section, was, after several setbacks, accepted in 1971. An introduction to the history of this decision can be obtained from articles in the *Pharmaceutical Journal* (Leader, 1963, 1966, 1968 and 1971) and the report of a symposium on the identification of drugs and poisons (Symposium, 1965).

From the rules outlined above it is clear that proper-name labelling is limited to—

Preparations included in an official book (B.N.F., B.P.C., B.P., etc.).
Preparations described by a proprietary name.
Preparations containing a single drug.

The strength need not be stated where it is obvious from the name of the preparation. For example, many official preparations are of one strength only and the name, followed by the appropriate letters, B.N.F., B.P.C., B.P. etc., defines the strength. Similarly, the strength is unnecessary for single-strength proprietary preparations. However, it must be given whenever it could be in doubt as, for example, with multi-strength products such as many tablets and capsules.

B. DIRECTIONS FOR USE

Generally, the prescriber writes these on the prescription; otherwise the directions in the B.N.F. under the heading 'Label' (below the formula for the preparation) or at the head of the section to which the product belongs (e.g. Mixtures), are used. For example, at the beginning of the section on Mixtures is the statement: 'In the absence of instructions by the prescriber, the dose given below the preparation should be stated; when no dose is given state *Two 5 ml spoonfuls to be taken three times a day in water*'. It is advisable to add the words *unless otherwise directed* since the prescriber may have given the patient verbal instructions even though he has not written these on the prescription.

Strictly, reference to the B.N.F. directions is not applicable to private prescriptions but there is no serious objection to the procedure where it is helpful and if it is used with circumspection.

Dosage instructions for mixtures, elixirs, linctuses and other oral preparations (except paediatric drops) must be stated in terms of the 5 ml spoon (*see* p. 33).

C. THE PATIENT'S NAME

Conventionally this is written at the right-hand side, just above the line separating the name and address of the pharmacy from the rest of the label.

D. THE PRESCRIPTION BOOK REFERENCE NUMBER AND/OR THE DATE

Private prescriptions are recorded in a prescription book that usually carries on the cover a capital letter for identification. The pages and the items on each page are numbered. Consequently, each prescription has a

this reason, among others that included cost, the spoon was chosen. Provision of both a 5 ml and a 10 ml spoon was also considered and rejected as too expensive.

It is advisable to emphasise to patients, especially old people, that they should not return to the use of tea- and table-spoons. This is particularly important in respect of the tablespoon; at the changeover to the metric system, adult mixtures were reformulated to contain in 10 ml the quantities of ingredients previously in a tablespoonful (14 ml) and, therefore, use of a tablespoon, especially a large one, could lead to overdosage.

Registered blind people can obtain free from the Royal National Institute for the Blind a special medicine measure. It is screwed on to the medicine bottle which is then shaken and inverted. A tap is rotated half a turn when the medicine fills a chamber holding 5 ml. Returning the tap to its original position simultaneously seals off the bottle and delivers the dose into a cup at the base of the chamber. The cup is removed by a downward pull and the contents can be taken from the cup or, if necessary, transferred to a tumbler for dilution.

This dispenser, known as the 'Rotadose', is of polypropylene and was developed by the English Glass Company of Leicester. It has an accuracy of ± 6 per cent, takes apart for cleaning, and will fit 200, 300 and 500 ml bottles (Rotadose, 1972).

REFERENCES

BRITISH STANDARD 1922 : 1969. *Dispensing measures for pharmaceutical purposes.* British Standards Institution, London.

BRITISH STANDARD 3221 Part 4: 1969. *Plastics medicine measuring spoons of 5 ml capacity (metric units).* British Standards Institution, London.

BRITISH STANDARDS INSTITUTION (1969) *The Use of S.I. units.* British Standards Institution, London.

CAPPER, K. R. and SMITH, G. (1960) Dose measurement of liquid medicines. *Pharm. J.*, **185**, 403–405.

CAPPER, K. R., SMITH, G. and BULLIVANT, J. M. (1962) Dose measurement of liquid medicines using a silicone-treated medicine glass. *Pharm. J.*, **189**, 527–529.

NATIONAL PHYSICAL LABORATORY (1969) *Changing to the metric system.* Her Majesty's Stationery Office, London.

ROTADOSE (1972) New medicine measure available for the blind. *Pharm. J.*, **209**, 283.

SPALTON, L. M. (1949) Teaspoons and tablespoons. *Pharm. J.*, **162**, 338.

SIZE REDUCTION OF SOLIDS

It is an advantage to use fine powders in pharmaceutical preparations because—

1. They mix more uniformly and suspend more easily.
2. If soluble, they dissolve more quickly.
3. They are absorbed more readily from the alimentary tract.
4. They yield preparations that are relatively free from grittiness; consequently, oral powders and suspensions are more pleasant to take and external preparations are less irritating.

In the dispensary, the two main methods of size reduction are—

Dry Grinding

The material is broken down in a mortar and pestle. The mechanisms are *compression,* between the flat head of the pestle and the bottom of the mortar, and *attrition,* by the shearing action of the pestle.

Levigation (Wet Grinding)

The material is made into a paste with the vehicle (e.g. water for an oral suspension and the molten base for a suppository, paste or ointment) and ground in a mortar (cold for oral suspensions, warm for pastes and ointments) or rubbed, with a large spatula, on a warm tile (for suppositories and ointments). Effort put in while the paste is thick, i.e. before further dilution with the vehicle, is most rewarding.

SIZE SEPARATION

In dispensing, the method used to separate particles of the required size from a powdered medicament is sifting. Generally, wire mesh sieves are used, the most suitable grades being No. 180 (for dusting powders and for those ingredients of semi-solid preparations for which a fine powder is specified in the formulae of the official books) and No. 250 (for external preparations when no particular grade of powder is directed and for oral powders).

When a powder is levigated at some stage during the making of a preparation, as is often the case with ointments, pastes, suppositories and oral suspensions, a No. 250 powder is usually fine enough because the levigation causes further size reduction.

Wire mesh sieves are made from a variety of materials, particularly brass and stainless steel. Stainless steel is best because it is attacked by very few of the powders commonly used in dispensing (p. 37). Care is needed with sieves of other materials; for example, severe corrosion is caused by salicylic acid, a common ingredient of creams, dusting powders, ointments and pastes.

Powders must not be forced through sieves as this distorts the apertures. Particles of correct size pass through easily if the sieve is tapped or is gently stroked with a bristle, but not a wire, brush.

Since some material is retained by the sieve, powders should always be sifted before weighing and a fresh sieve should be used for each ingredient.

Sifting tends to separate powders of different densities, and after mixtures such as dusting powders have been sifted they are remixed in a mortar or, if the quantity is small, with a large spatula on paper.

Sometimes, sifting aids mixing by splitting up aggregates of fine powder that have resisted breakdown in a mortar. White specks of light magnesium carbonate in Gregory's Powder (Compound Rhubarb Powder) can be dispersed in this way, and the distribution of colouring matter in powders is often better after sifting and remixing.

MICROBIAL CONTAMINATION OF NON-STERILE PHARMACEUTICAL PREPARATIONS

This subject is included in this chapter to draw attention to the importance of good hygiene when performing the fundamental operations of dispensing.

Sterility has been accepted as an essential requirement for parenteral products for many years and for eye preparations since 1963, but only recently has evidence suggested the need for control of the microbial quality of oral and topical preparations.

In Sweden, in 1964, eight cases of eye infection, involving partial or, in one instance, complete loss of sight, followed the use of an eye ointment containing hydrocortisone and two antibiotics. The cause was contamination of the ointment with *Pseudomonas aeruginosa,* an organism resistant to most antibiotics which tends to fill the biological vacuum created when more sensitive organisms are destroyed by these drugs. Investigation revealed more than 2000 pseudomonads per gram in most tubes of the ointment and demonstrated that these came from poor hygiene during manufacture. The ointment had been poured

marketing about 300 colours used in drugs and cosmetics under a total of approximately 1500 different names. For some colours as many as 30 synonyms were found (Calvery, 1942).

The Colour Index 1971, published jointly by the British Society of Dyers and Colourists and the American Association of Textile Chemists and Colorists is useful because it gives each dye a reference number (e.g. Amaranth, Colour Index 184) and tabulates its chemical composition, synonyms and properties. Confusion is avoided if the chosen name is followed by the Colour Index number.

Standards for Food Dyes

The British Standard Institution issues standards for the permitted food colours; dyes used in the Codex formulae must comply with the relevant specifications.

Advantages and Disadvantages of Coal Tar Dyes

The advantages of coal tar dyes include precise chemical nature, dependable method of assay, ready solubility in water, high and reliable tinctorial power and relatively high stability to pH, light and other storage factors. Nevertheless, problems occur as the following examples illustrate—

Gershenfeld (1945) reported loss of antibacterial activity in two solutions when coal tar dyes were used as colouring agents.

Fading is occasionally caused by sunlight (e.g. in amaranth solutions that are dilute and acid) and often by the reducing agents, sulphur dioxide and sulphites.

Many dyes behave as feeble indicators and alterations in pH may be accompanied by changes in colour and tinctorial power, e.g. green S is greenish blue in acid, and blue in alkaline solutions.

Information on the effects of pH and sodium metabisulphite on many colours is given in reports from the Pharmaceutical Society's Science Laboratory (1956a, b) and the *National Formulary* of the United States includes data on the fastness of colours to light and chemicals.

Lakes

The colouring of liquid oral preparations in which fractionated coconut oil is used as a non-aqueous vehicle (p. 117) is difficult. Only two of the food dyes permitted in the U.K. are soluble in oil and both are yellow (Oil Yellows CG and XP). One possibility is to disperse the lake (i.e. the insoluble aluminium or calcium salt) of a suitable water-soluble food dye in the oil.

Lakes of water-soluble food dyes, often extended on aluminium hydroxide, are also used to colour capsule shells and tablets.

Amount of Dye Required

The concentration needed to colour aqueous solutions is approximately 0·001 per cent but one-tenth of this is enough in some instances. It is affected by the depth of colour required, the thickness of the solution to be viewed, the presence of suspended powders and, in emulsions, the fineness of the dispersed globules.

The use of stock solutions greatly simplifies dispensing and the Codex includes concentrated preparations of amaranth, tartrazine with orange G and green S with tartrazine.

High concentrations are necessary to colour powders; approximately 0·1 per cent produces a pastel shade. The dye may be incorporated dry or dissolved in a volatile solvent in which the powder is virtually insoluble.

Blending

The permitted colours do not always give satisfactory shades when used alone but most popular tints and shades can be obtained by blending.

Green S gives a greenish blue solution in distilled water and a more satisfactory green is produced by mixing it with tartrazine as in Green S and Tartrazine Solution B.P.C.

Tartrazine is yellow green in solution and to obtain a saffron yellow colour it is mixed with orange G as in Compound Tartrazine Solution B.P.C.

The *National Formulary* of the United States gives information on the proportion of various water-soluble and oil-soluble dyes necessary to give particular hues to liquid preparations and drug powders.

For further information on colouring see Swartz and Cooper (1962).

FLAVOUR

Adults used to expect medicines to have an unpleasant taste and a strong odour but nowadays they hope for palatability and it is an aim of formulation to satisfy this wish. An objectionable taste may lead to nausea, retching and vomiting, and refusal to take the preparation regularly or at all. On the other hand, an attractive flavour will encourage continuation of the treatment.

Identification of Flavours

Complex mechanisms are involved in the appreciation

Contents

PREFACE page vii

Part One
General Dispensing

1 Introduction 3
2 Types of Dispensed Preparation 8
3 Containers and Closures 13
4 Labelling 24
5 Weights and Measures 31
6 Fundamental Operations 35
7 Colour and Flavour 47
8 Calculations 54
9 Solutions 67
10 Suspensions 100
11 Emulsions and Creams 120
12 Powders and Oral Unit-dosage Forms 168
13 Ointments, Pastes and Jellies 192
14 Suppositories and Pessaries 232
15 Incompatibility 253
16 Dispensing of Proprietaries and Manufacture of Nostrums 265
17 Surgical Dressings 270
18 Medical Gases 288

Part Two
Sterilisation Practice

19 Microbiological Aspects of Sterilisation Processes 299
20 The Formulation of Injections 314
21 Containers and Closures 357
22 Sterilisation by Heat 395
23 The Preparation of Heat-sterilised Injections 442
24 Aseptic Technique 494
25 Sterility Testing 541
26 Aseptic Processing 579
27 Gaseous Sterilisation 614
28 Sterilisation by Radiations 623
29 Ophthalmic Products 634
30 Sterilisation of Equipment and other Articles 663

Appendixes

1 Reducing Agents and Antoxidants 677
2 Pyrogen Tests 682
3 Incompatibilities of Bactericides for Parenteral Use 686
4 Classification of Injections under Methods of Sterilisation 687
5 Classification of Injections under Methods of Stabilisation 689
6 Sterilisation Methods, Preservatives and Stabilisation Methods for Eye-drops 693
7 Packaging and Labelling of Non-sterile Dispensed Preparations 696
8 The Imperial System 699
9 Latin Terms and Abbreviations 720
10 Posology 724

INDEX page 745