Packing errors

Products of similar appearance, such as tablets of the same size, colour and shape, packed in similar containers can constitute a potential source of danger through mislabelling of either or both. The handling of two such products in proximity should be avoided and control procedures should guard against the possibility of such mishaps.

Inadequate checks on the issue of labels, on the filling of labelling machines, on the setting of ampoule or other printing machines, and the destruction or return to stock of unused labels also constitutes a major packaging hazard. Such misadventures can only be avoided by care in manufacture, with particular attention to detail and cross-checks in the matter of stock records, process dockets and batch-marking of both raw materials and finished products.

Standardisation of pharmaceutical chemicals and formulated products

Two types of specification are used to control the quality of pharmaceutical products:

(a) manufacturing product licence standards
(b) pharmacopoeial standards.

Manufacturing standards are laid down by licensing authorities on the basis of information supplied by the manufacturer on the quality of trial (scale-up) and typical manufacturing test batches of the material. These are release specifications that provide for control of the product at the time of manufacture and usually represent the best minimum quality that can be consistently guaranteed. Such specifications are usually confidential between the manufacturer and the licensing authority, and, for this reason, are not generally available to independent analysts who may wish to check that the product is up to standard. In the United Kingdom, however, independent checks are applied to new and recently prepared products sampled by the Medicines Inspectorate against the manufacturer's licence specification (*release specification*). This work is conducted on a confidential basis by the Pharmaceutical Society's Medicines Testing Laboratory in Edinburgh on behalf of the Medicines Division of the Department of Health and Social Security.

In contrast, the published standards of the British Pharmacopoeia (BP), European Pharmacopoeia (Pharm Eur) and the United States Pharmacopoeia (USP) are available to all users of the material. They are designed primarily to set permissive limits of tolerance for the product at the time it reaches the patient. They do not necessarily equate with manufacturing specifications, since they must also take into account possible degradation of the product throughout its shelf-life up to the time it is prescribed and ultimately used. In this sense, pharmacopoeial standards are check specifications. Official standards must also encompass all known methods of manufacture and safeguard against varying standards of purity and

The optical rotation has a special significance in the control of *Camphor* where the use of either natural {$[\alpha]_D^{20}$ +40° to +43° (*c*, 10, 95% ethanol)} or synthetic camphor ($[\alpha]_D^{20}$ 0°), but not mixtures of the two, is permitted. This, although not specified explicitly, is definitely implied in the limits of specific rotation for synthetic camphor, which are −1.5° to +1.5°.

Rotation measurements are also used as an assay to control the content of Dextrose in *Dextrose Intravenous Infusion* (Dextrose Injection USP) and also of dextrans in *Dextran Intravenous Infusions*.

Viscosity; jelly strength; swelling power

Viscosity measurements are used as a means of distinguishing various grades of liquid paraffin. They are also used to control the molecular size of dextrans in *Dextran Intravenous Infusion*, the composition of *Iron-Sorbitol Injection*, the extent of nitration of *Pyroxylin* and in the standardisation of *Methylcellulose, Povidone* and similar additives.

The properties of materials, such as *Gelatin*, which are capable of forming visco-elastic gels, are controlled by the measurement of **jelly strength** (Gel strength USP) of gels prepared from them in a Bloom gelometer. The quality of *Bentonite*, a suspending agent which forms gels by the absorption of water, is controlled by its **swelling power**, a measure of its increase in volume in water.

Polymorphism and particle size

The physical state of most water-soluble compounds is of no therapeutic significance, though their solid state properties, like those of other less soluble substances, may affect mixing and handling characteristics in the preparation of solid dosage forms. On the other hand, solid state properties of insoluble drugs, which are necessarily administered in solid form, can markedly influence the rate of both solution and absorption of the drug. Crystal form and particle size in particular are the important factors controlling surface area, the property which determines the level of activity of such drugs as *Griseofulvin*, *Spironolactone* and *Digoxin*. Thus, the official monograph for *Griseofulvin* provides for standardisation of the powder such that the bulk of the material consists of particles not more than 5 μm in maximum dimension, with the occasional particle up to 30 μm.

Control of **sediment volume**, as measured by the depth of sediment after standing for a period of hours in a vessel of specified dimension, provides a simple alternative means of controlling particle size in *Tetracosactrin Zinc Injection*. The suspendability of *Barium Sulphate* is similarly controlled by a test for **sedimentation** (Bulkiness USP).

Certain products may always be produced in one particular pharmaceutically more desirable polymorphic form, which, although not specifically described in the monograph, is controlled by an identity test using the Infrared Reference Spectrum of that particular polymorph. Polymorphism, the ability to crystallise in alternative crystal forms, is a widespread phenomenon. Like particle size, it, too, can be significant in compounds of

Ash

A figure for the total ash content is valuable for drugs in which little calcium oxalate is present (*Ginger*). If much calcium oxalate is present then the value for the acid-insoluble ash is a better criterion of purity. Ash in *Sterilisable Maize Starch* (Absorbable Dusting Powder) limits the amount of magnesium oxide which it is permitted to contain.

Method for the determination of ash in ginger Ignite a silica dish to constant weight at a dull red heat in a muffle furnace. Spread 2 to 3 g of the powdered drug evenly over the bottom of the dish and weigh. Ignite at low temperature until vapours have almost ceased to be evolved and then increase the temperature slightly, not exceeding 450°, to burn off the carbon (Note 1). Cool in a desiccator and weigh. Repeat the heating and cooling until constant weight is attained.

If a carbon-free ash is not obtained in this way, extract the residue with hot water, filter through an ashless paper, incinerate the residue and filter paper in the silica dish until all carbon is removed, using a higher temperature than that used previously if necessary (Note 2). Add the filtrate to the dish, evaporate to dryness and ignite to constant weight using not more than a dull red heat.

Calculate the percentage of ash with reference to the air-dried drug.

Note 1 Too high a temperature would cause a loss of such substances as alkali chlorides which are volatile at high temperatures.

Note 2 Sometimes heating at a low temperature does not give a carbon-free ash because carbon particles are trapped in fused alkali carbonates or phosphates. Treatment of the ash with hot water dissolves the salts. The insoluble residue can then be ignited rapidly at a higher temperature to remove carbon without loss of inorganic material; the filtrate is added and subsequently evaporated to dryness when the whole residue can be ignited at the lower temperatures, at which alkali chlorides are not volatile.

Acid-insoluble ash

Crude drugs containing calcium oxalate can give variable results upon ashing depending upon the conditions of ignition. Treatment of the ash with hydrochloric acid leaves virtually only silica. Hence **acid-insoluble ash** forms a better test to detect and limit excess of soil in the drug than does the total ash.

Method for the determination of acid-insoluble ash in Rhubarb Wash the total ash (obtained as above) from the silica dish into a 100 ml beaker using 25 ml of dilute hydrochloric acid. Boil for 5 min. Transfer the insoluble residue to a previously prepared, ignited and weighed Gooch crucible, wash well with hot water, allow suction to remove most of the water and then ignite at a temperature not exceeding 450° inside an ordinary crucible used as a 'jacket crucible'. Cool in a desiccator and weigh. Calculate the percentage of acid-insoluble ash with reference to the air-dried drug.

Water-soluble ash and water-soluble extractive

These determinations are only specified in the case of one official drug, *Ginger*, where it is helpful in detecting samples which have been extracted with water.

Method for the determination of water-soluble ash in Ginger As for acid-insoluble ash, but use 25 ml of water in place of the 25 ml of acid; subtract the weight of the insoluble residue from the weight of the total ash; the difference in weight represents the water-soluble ash. Calculate the percentage of water-soluble ash with reference to the air-dried drug.

Method The amount of substance to be examined and any preliminary treatment required vary considerably and are specified in each individual monograph. The general method is to dissolve the substance in a mixture of *water* and stannated hydrochloric acid. For the examination of *Sodium Phosphate*, prepare test and standard solutions as follows:

	Test solution	Standard solution
(1)	Dissolve 0.2 g of sample in *water* (25 ml) in the flask.	Dilute 1 ml of Arsenic standard solution (1 ppm) with *water* (25 ml) in the flask.

(2) Add hydrochloric acid (15 ml) and tin(II) chloride AsT to each solution.
(3) Add potassium iodide solution (M; 5 ml) to each solution and allow to stand for 15 min. This liberates hydriodic acid which assists in the reduction of pentavalent arsenic to the trivalent state from which arsine is then formed in the subsequent reduction at Step 4.
(4) Add activated zinc (5 g) to each flask, and immediately insert the tube already assembled with the mercuric bromide paper in position as shown in Fig. 1.1.
(5) Immerse both flasks in a water bath at a sufficient temperature to allow a uniform evolution of gas for 2 h.
(6) Compare the test and standard stains produced on the respective mercuric bromide papers.

The substance is said to comply with the requirements of the test if the colour of the test stain is not darker than that of the standard stain.

Calculation. Sodium Phosphate is required to contain not more than 5 ppm of As.

If the stains obtained from 0.2 g of Sample and 1 ml of arsenic standard solution are equal:

$$0.22\text{ g of sample} \equiv 0.001\text{ mg As}$$
$$\therefore \quad 1\text{ g of sample} \equiv 0.00005\text{ g As}$$
$$\therefore \quad 1\,000\,000\text{ g of sample} \equiv 5\text{ g As (i.e. 5 ppm)}$$

Modification of the general method for arsenic

Insoluble substances. In general, no special treatment is required for insoluble substances (*Light Kaolin* and *Magnesium Trisilicate*). Their insolubility does not interfere with the solution and reduction of arsenic to arsine. They are, therefore, simply suspended in water and treated with stannated hydrochloric acid by the general method. In *Barium Sulphate*, however, where the risk of arsenic contamination from the sulphuric acid used in its manufacture is much higher, the material is submitted to a preliminary digestion process with nitric acid to ensure all the arsenic is in solution.

Substances which evolve carbon dioxide with hydrochloric acid, or which react vigorously with hydrochloric acid. At this stage, arsenic is usually converted to arsenic trichloride which is volatile and, therefore, may be carried off with large volumes of carbon dioxide if these are produced at the same time. The use of brominated hydrochloric acid avoids this difficulty, the bromine oxidizing arsenic to the pentavalent state, in which it is non-volatile. *Chalk* and *Calcium Hydroxide* are treated in this way.