SOME EXPERIENCES WITH CONTAINERS AND CLOSURES IN THE PHARMACEUTICAL INDUSTRY

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THERE are few standards available for containers as such. The British Pharmacopœia and the British Pharmaceutical Codex describe containers for injections; the United States Pharmacopeia XIV goes a little further and gives general definitions for containers and classifies them under the categories of well-closed, tight, hermetic and light-resistant containers. Standards for paper and board wrappers and containers and for films and foils are published by the British Standards Institution[1,2]. When the pharmacist has consulted all the available information he will still need to satisfy himself by suitable tests that the container and its closure are likely to maintain the product for a reasonable time without change.

The following notes are based upon some years of experience of the use of containers for pharmaceutical products by the author and his colleagues, past and present, and of tests carried out in the laboratory.

It is proposed to discuss the testing of pharmaceutical containers, relating some experiences with containers of materials other than glass and rubber, and then to discuss in more detail the subject of closures.

TESTS FOR EFFICACY OF CONTAINERS

1. *Test for Inertness to Product.* In the words of the U.S.P. XIV, "the container shall not interact physically or chemically with the drug which it holds so as to alter the strength, quality or purity of the drug beyond the official requirements."

Storage at normal, low, and elevated temperatures of container and product will be routine practice in pharmaceutical laboratories concerned with the development of medicinal products intended for widespread distribution in small containers. Periodic assays of the active ingredients will frequently be necessary. With dry solids an inspection of the drug and the inside of the container will generally be sufficient to indicate when interaction with the container is affecting the product. In the case of liquids a change in colour, clarity, or *p*H is frequently the first indication of reaction.

When liquids, jellies, creams, or ointments are enclosed in metallic containers evidence of corrosion of the metal lining should be sought—particularly at the liquid-air interface. The use of metallic collapsible tubes for liquids as well as ointments, creams, and jellies has been increasing; they are used for eye lotions, for unit dose containers for the convenient administration of veterinary intramammary injections[3] and for ampoule syringes for hypodermic and intramuscular injections.

An experience with ampoule syringes of tin illustrates very vividly how small and unsuspected changes can have far-reaching effects. For some years during the Second World War injection of morphine hydrochloride was successfully presented in such devices. The hydrochloride was chosen because less tin was dissolved (in laboratory tests) than when other salts such as tartrate were used, and because the hydrochloride solution was known to be more stable. The entire ampoule syringes were sterilised by dry heat at 140° C. for one hour, filled, and the tubes folded and electrically welded. Later attempts to repeat the process were not successful; local corrosion occurred, frequently resulting in perforation of the tubes in 2 or 3 months. No difference could be found in the composition of the tin of the tubes. Corrosion of tin is said to be accelerated by the presence of chlorides and by increasing acidity[4,5], but the fact remains that for several years injection of morphine hydrochloride, *p*H 3·7, was stored in tin tubes without corrosion taking place. No satisfactory explanation has been found for this immunity from corrosion.

Because of the relatively high cost of tin tubes, lead tubes, tin-coated lead tubes and aluminium tubes have been in wider use for pharmaceutical preparations. Whilst lead tubes might be satisfactory for use with certain products for external use, such as veterinary obstetric lubricants, tin-coated lead would be preferable for many medicinal products, but great care must be taken to ensure that contamination and discoloration of the contents of the tubes does not occur—it not infrequently happens that electrochemical reaction between the lead and tin in the presence of an electrolyte results in more contamination than would have arisen from an untinned lead tube.

The danger of concluding that a container of this type is suitable because of absence of evidence of deterioration in a few test specimens was well illustrated in 1943, when our laboratories were consulted about the condition of collapsible tubes of silver picrate tragacanth jelly of foreign origin imported and stored for 2 years in this country. In some of the tubes there was a darkening in the mass of the jelly and even complete coagulation had taken place so that nothing could be squeezed from the nozzle except a little watery fluid. Examination of the tubes revealed that they were of lead with a tin coating. Where the surface was cracked there was a dark stain indicating reaction with the product and possible deposition of metallic silver. Some of the silver picrate jelly from the tubes was examined and found to contain lead which had evidently displaced silver from solution. It was concluded that the product had been packed in an unsuitable container.

Aluminium tubes should not be used for aqueous base preparations or oil-in-water emulsions in which the continuous phase has a *p*H of less than 6·5 or more than 8·0. Aluminium tubes are now being sprayed internally with lacquers or microcrystalline waxes but the danger of cracks, scratches, or pin-holes occurring in the coating is still great.

2. *Strength of Container.* The adequacy of the strength of the container can usually be judged by handling or a simple drop test. The degree of protection provided from shock by the immediate container will determine the extent of the protection required by the use of further packages such as carton, carton liner, outer, etc.

3. *Tests for Leakage.* These are preferably carried out at an elevated temperature rather higher than that which the container is likely to

experience; periodic temperature variations should be arranged. Containers should be inverted and laid sideways as well as upright, they should be weighed before and after the test period as well as examined for leakage. Vacuum tests should be used with discretion. They are most useful for eliminating unsatisfactory containers.

4. *Permeability Tests.* Containers should be sufficiently impervious to prevent loss of volatile constituents by evaporation or deterioration by absorption of moisture. If the product or one of its constituents is volatile, storage at an elevated temperature, with periodic temperature variations, of filled and partially filled containers previously weighed, with re-weighing at intervals, will be a useful guide to the suitability of the container.

When the product is to be protected from moisture the containers may be tested by storing filled and partially filled containers under conditions of elevated temperature and high humidity. The standard conditions which are generally used are: (1) 100° F., 90 per cent. relative humidity continuously. (2) 100° F. 90 per cent. relative humidity with a temperature fall to about 60° F. for approximately 8 hours out of the 24. A further test which may be found useful if the product is to be sent to the tropics is: (3) 100° F., 100 per cent. relative humidity with temperature changes as in (2). In this test, condensation occurs during the cooling period.

If the container in question is required for a number of different products, or if a quick answer is required to the question of its suitability, an accelerated test using a desiccant may be devised. (See closure test below.)

The value of such experiments can be greatly increased by the use of a tried and proved container as a control. If the container under test gives a performance equal to or better than that of the control, one is reasonably happy in its use. When the performance is less good than that of the control the difficult question to be decided is how significant the difference is. The most satisfactory assessment of a container or closure is to send experimental packages containing the product for storage in the countries where it will be used. After a suitable interval these are returned for examination.

Closures

During the Second World War tabletted products were marketed in two types of container. One type was the corked bottle and the other was a screw-capped bottle with aluminium screw-cap having a composition cork wad faced with "resistol" or "ceresine". Both types of container were widely considered to be satisfactory for all climates. In common with many other things at that time, these bottles were exposed at the docks to blast, fire, and the water of the fire-fighters. Many cases of goods were returned in which the two types of bottle containing products from the same batch had been packed side by side. In every instance the tablets in the corked bottles were in better condition than similar products in the screw-capped bottles. One variety of tablet contained sodium nitrite which is very slowly decomposed under normal conditions of storage.

The products from the corked bottles still assayed 100 per cent. of the labelled strength, whilst those in the screw-capped bottles had fallen to 55 per cent. of the labelled strength. This series of unpremeditated large-scale experiments impressed us to such an extent that we have since that time used the corked bottle as a control when carrying out closure tests on other types of bottles.

1. *Glass Bottles with Corks.* The taper of the cork and its resilience reduces the importance of variations in the internal diameter of the bottle neck. If the closure is being used for tablets or capsules which are wadded into the bottle with cotton or other wadding material the lower end of the cork usually pushes before it the strands of cotton and enables the upper conical surface to make close contact with the inner surface of the bottle neck. Dangers of an incomplete seal due to projecting wadding or crevices in the cork may be minimised by dipping the inserted cork and the bottle rim into a wax bath. Some of the new microcrystalline waxes are very resistant to the passage of moisture vapour, but have the disadvantage that being plastic they tend to collect dust particles, and become rather unsightly. Corks have for many years been protected from the attack of insects in tropical countries by dipping in sealing wax.

2. *Glass Bottles with Screw-caps and Lining Wads.* Here the closure is formed between the rim of the bottle and the face of the lining wad, which are pressed together by the tightening of the cap. It is most important when wadding material is used to ensure that wisps of the material are not left over-hanging the rim of the bottle, or a channel may be left through which moisture may be transmitted to the product.

Types of Bottle Rim. We have usually obtained the most effective closures using bottles in which the rims were flat and smooth. Other types are made, for example, corrugated, domed, and angular.

The presence of mould marks on the rim is to be avoided as these tend to tear the smooth surface of the wad as the caps are tightened and also prevent the face of the wad fitting closely to the entire circle of the rim.

Kinds of Screw-caps. (i) There is one type of screw-cap which eliminates some of the dangers of the mould mark and the irregular rim. The screw-cap is supplied without screw-thread—the thread being formed by the special capping machine pressing the metal of the cap into the thread of the bottle whilst the former is pressed firmly against the bottle rim. Bottles must be specially made to take the "roll-on" caps; the screw-threads join the neck ring of the bottle to enable the formers of the machine to be spun off the cap and the cap to be unscrewed from the bottle. In closure tests using a desiccant this type of screw-cap with certain kinds of wad has given performances closely comparable with that of corked bottles waxed over.

(ii) Screw-caps which are screwed onto the bottle are usually used with bottles the screw-head of which is not connected with the neck-ring. It is extremely important that the caps should be tightened sufficiently to obtain the maximum efficiency of the closure, but not so tightly as to overcome the elasticity of the backing material of the wad or to deform the caps. One company manufacturing bottles and caps has introduced from America an instrument for measuring the torque applied to caps during tightening and the torque required to loosen the caps[6]. (The latter is about 50 per cent. of the former.) This apparatus promises to be useful in experimental work and in departments using large numbers of screw-capped bottles or pots.

The caps are usually of metal (aluminium or tinplate) or of plastic. Aluminium being softer and less resilient than tinplate it is more easily permanently deformed. Aluminium needs to be made from thicker sheet than tinplate and the presence of a strong beading is probably more important. Both kinds of sheet are frequently enamelled—the protection afforded is important in the case of tinplate to prevent the rusting which is frequently such a nuisance particularly in humid climates.

The plastics usually used in the manufacture of screw-caps are phenol formaldehyde resins or urea formaldehyde resins. Both are thermosetting resins. The former is brown and is usually made up only in brown or black moulding powders. Urea formaldehyde resin being pale can be used for the preparation of white or pale colours. Caps which can be autoclaved are made from phenol formaldehyde resin: the fillers and pigments used affect the properties of the caps but wood or paper fillers will both give satisfactory heat sterilisable caps.

Plastic screw-caps on glass bottles have a tendency to become loose on standing. This has been ascribed at different times to the swelling and contraction of the caps because of (i) temperature changes and, (ii) humidity changes. (The coefficient of thermal expansion of formaldehyde resins may be 6 times that of glass; that of aluminium twice and that for tinplate about $1\frac{1}{2}$ times.) Some recent experiments in our laboratory using wood-filled phenol formaldehyde resin caps and paper filled urea formaldehyde caps gave the following results. When caps which had been dried at 50° C. were put into air with a relative humidity of 90 per cent. they increased in weight by 3·5 to 4 per cent. and their dimensions increased by about 2 per cent. It seems from these results that humidity changes are the predominating factor.

It is usual to use with screw-caps a lining wad which makes the closure with the bottle rim when the cap is tightened. When metal screw-caps are made a recess is usually formed into which the wad can be pressed so that it is held and will not be separated from the cap by jostling in packaging machinery or fall out in use. The method of moulding plastic caps rules out the provision of a recess and wads are generally fixed into such caps with an adhesive.

The subject of screw-caps and liners was well discussed by Boardman at the Symposium on the Storage of Drugs and Medicines[7], but it should be reviewed in more detail here. Lining wads are usually stamped out of sheet material which is frequently in two layers, the backing layer or resilient layer and the facing layer, the latter usually provides the closure and must be resistant to attack by the product. The screw-caps should also be resistant to the product so that there is no danger of unsightly corrosion whilst the contents are being used or if leakage occurs during storage. The resilient layer is usually either pulpboard or cork—generally cork granules pressed together with an adhesive. Cork backing is considered to be liable to give rise to mould growth when used with aqueous preparations but is more resilient than pulpboard. The resistant surface may be of metal (tin or aluminium) or may be formed from suitable plastic materials spread on sulphite paper. The paper helps in smoothing out the irregular surface of pressed cork composition. Liner wads in general use are [8]:—

(i) *Tinfaced Pulpboard or Cork Composition.* Such wads are very useful in preventing loss of water or other volatile materials, and also frequently in preventing absorption of water vapour.

(ii) "*Blackol*" is a cashew nut oil polymerised resin pigmented with carbon black on a super calendered high varnishable kraft paper. The acid resistance of "blackol" is better than that of "ceresine" but this material is used generally for alkaline materials up to a *p*H of 9 or a little over.

(iii) "*Ceresine*" is an oil varnish base prepared with tung oil and linseed oil and coated onto paper. The acid resistance of "ceresine" is medium. These wads have occasionally developed a strong linseed oil odour. They can be satisfactorily sterilised by dry heat.

(iv) "*Resistol*" is a paper impregnated with melamine formaldehyde resin combined with an alkyd type resin. It is pale in colour and is widely used for pharmaceutical products.

"*Crystal Cap*" is a white form of "resistol".

(v) "*Vinylite*" is a paper coated with a copolymer of vinyl chloride and vinyl acetate. The material is soluble in ketones but is very acid and alkali resistant.

(vi) "*Permaceal*" is a rubber hydrochloride similar to "pliofilm" spread on paper. It is slightly more brittle than "vinylite" and is not now widely used.

(vii) "*Polythene.*" Polyethylene coated paper on cork composition is being widely used, giving excellent protection against moisture absorption. Polyethylene coated directly on to polyethylene bonded cork should be very moisture proof and resilient. Wads cut from polyethylene sheet have proved disappointing as liners.

(viii) *Rubber.* When rubber is used with a good rim, an excellent moisture-proof closure is obtained. Rubber washers are used in aluminium screw-capped tubes to protect photographic film in tropical climates. The disadvantages in our experience with rubber are: (*a*) The odour which seems to be inseparable from rubber. (*b*) There is a tendency for caps to spring back when being tightened on to rubber wads. (*c*) There is no means of sticking rubber wads into plastic caps.

Rubber, being a compounded natural product, is subject to change by the manufacturer. If changes in composition are made without reference to the user unexpected and even serious results can follow.

3. *Glass Tubes with Corks or Rubber Stoppers* are giving place to tubes of glass or plastic with polyethylene stoppers or with screw-caps.

Polyethylene stoppers of varied design have been used for some years in the U.S.A. and are becoming more readily available here. Moulded neck tubes and bottles are used with the stoppers, the wide variations in diameter of tubes made by cutting drawn glass tubing is too great to allow of a good closure. The stoppers are usually hollow; they have a short pronounced taper to permit of ready entry into the tube or bottle neck and then a slighter long taper to make the contact with the moulded neck which is the closure proper. In tests we have carried out polyethylene stoppered tubes have been shown to have a remarkably efficient closure (see Table I).

TABLE I

CLOSURE TEST ON GLASS TUBES WITH POLYETHYLENE STOPPERS

37° C.—SATURATED ATMOSPHERE

2 g. OF ANHYDRONE PER CONTAINER

No. of replicates	Type of closure		Months		
			2	4	12
20	Plastic stoppers	Mean increase in weight (mg.) ± standard deviation	27·1 ± 26·8	45·3 ± 36·0	136·4 ± 131·4
12	Waxed corks (controls)		49·1 ± 16·4	80·2 ± 27·3	255·8 ± 70·5
Probability of difference between means ("t" test)			0·008	0·007	0·004
"Efficiency" of polyethylene closure, per cent.			182	177	187

Screw-capped tubes may be internally or externally threaded but the efficiency of the seal decreases with the diameter of the tube. With internally threaded tubes the closure is obtained by a small washer which is fitted over the screw thread of the cap and rests against the projecting rim of the cap: in our experience this type of closure is not good.

4. *Plastic Tubes*. Tubes of cellulose acetate, polystyrene, polymethylmethacrylate, polyethylene, nylon, etc., are available with screw-caps or stoppers. They are most used for solid materials; their limitations are dependent upon their design and upon the properties of the plastics from which they have been formed.

5. *Aluminium Screw-capped Tubes* prepared by impact extrusion are used largely for tablets. The closure obtained is not so efficient as the corresponding closure of a screw-capped glass bottle. These containers provide the only example I can recall in which the results of closure tests with a desiccant did not predict the behaviour of the packing when used for a hygroscopic product.

6. In considering "*strip packs*," which are film or foil envelopes sealed at the edges, we may be concerned with consideration of the permeability of the material itself. Tables of relative permeability to water vapour of many of the films, laminates, and foils now available are given in British Standard Specification No. 1133[1], together with a standard method for the determination of permeability as g./sq. m./24 hours. In the Tables aluminium foil laminates are characterised as having "high resistance". We have found that aluminium foil made from 99·5 per cent. pure aluminium in 0·032 mm. fully annealed sheet coated with heat sealing lacquer gave for long periods—i.e., for more than 6 months—protection to hygroscopic material equivalent to that of a corked bottle.

If one regards the foil as the container the closure might be considered to be the sealed join between the 2 layers. We have also found that a well-sealed British product would withstand being submerged in water—a vacuum being applied until about 500 mm. Hg. was reached, this being held for half an hour, the vacuum then broken and re-applied for a further half-hour. The tablets inside the foil were all quite dry and unaffected. Tablets in some foil packs of foreign origin—indistinguishable at sight from the British material were not protected, 9 out of 10 products being softened by water.

TABLE II

	Polyethylene	Polymethyl methacrylate	Polystyrene	Nylon
Transparency .. .	Translucent-transparent in thin film	Transparent-bright	Transparent	Translucent in thin film
Heat distortion temperature	80 to 100° C.	90° C.	Less than 100° C.	180 to 200° C. contracts
Water absorption	Nil	1·2 per cent.	Nil	7·6 per cent. at saturation
Permeability to: (1) oxygen (2) water vapour	Slightly permeable to both	Slightly permeable to both	Slightly permeable to both	Very permeable to both
Coefficient of thermal expansion	2×10^{-4} cm./cm./° C.	9×10^{-5}/ cm./cm./° C.	$8{\cdot}0 \times 10^{-5}$/ cm./cm./° C. (−10 to +45° C.)	10×10^{-5}/ cm./cm./° C.
Effect of dilute acids	Nil	Slightly affected	Nil	Nil
Effect of dilute alkalis	Nil	Nil	Nil	Nil
Effect of solutions of bactericides etc. In 0·5 per cent. phenol	No absorption in 3 months	No absorption in 3 months	—	Absorption of about 45 per cent. within 15 hours
Physical appearance of plastic sheet after 1½ months:—				
In 0·3 per cent. cresol	No change	Slight clouding of surface	No change	No change
In 0·1 per cent. chlorocresol	„	Surface appreciably clouded	„	„
In 0·5 per cent. chlorbutol	„	No change	„	„
In 0·001 per cent. phenylmercuric nitrate	„	„	„	„
In 0·001 per cent. phenylmercuric acetate	„	„	„	„
In ethyl oleate	Slightly permeated	„	Complete deterioration	„
In arachis oil	„	„	Slight distortion commencing	„
In liquid paraffin	„	„	„	„
In 1 per cent. aqueous methylene blue	No change	„	No change	Colouration throughout

Closure Test. It might here be of interest to describe in detail the method we have used. The desiccants preferred are freshly dehydrated magnesium perchlorate or anhydrous fused calcium chloride previously heated to 150° C. for 3 hours; usually the latter in granular form, 10 mesh B.S.S., with the fine powder removed through a 30 mesh B.S.S. sieve. A sufficient number of the bottles or tubes to be tested are half filled with the same weight of desiccant *via* a wide mouth funnel (to prevent a layer of dust from the calcium chloride being deposited on the neck of the bottle and forming a channel for transmission of moisture). A suitable number of controls is similarly prepared. The containers are then weighed and put into a closed atmosphere usually at 90 per cent. relative humidity at 38° C. and allowed to fall to 20° C. for about 8 hours out of the 24. The containers are re-weighed at intervals at first every week and then every month until sufficient data have been obtained: so that the behaviour of individual seals may be followed, the containers are all numbered. The result of a closure test recently carried out with polyethylene stoppers in moulded neck tubes using small corked bottles of similar capacity and neck dimensions as controls is given in Table I.

We have found it convenient to express the "efficiency" of the closure under test as a percentage calculated as follows:—

$$\frac{\text{Mean gain in weight of control}}{\text{Mean gain in weight of test}} \times 100.$$

All that has been previously said illustrates the fact that no one ideal material exists for the manufacture of pharmaceutical containers.

Glass has many desirable properties but is too easily broken and is not easily accurately moulded. Some of the newer plastics have many attractive properties, for example, polyethylene is very inert, is thermoplastic, almost transparent and of low density, but unfortunately most grades are deformed by boiling water and none can withstand autoclaving. In Table II a list of some of the properties[9] of four plastic materials which it is considered are of particular pharmaceutical interest is given. These have been chosen because they are obtainable unplasticised, the addition of a plasticiser introduces a factor which might be altered without the knowledge of the user. Nylon is the only one of these substances which can be sterilised by heat alone but the high moisture absorption of present forms makes it an unsatisfactory material for many pharmaceutical purposes. It seems highly probable that as more experience is gained in the field of plastics research and development materials will be obtained which are nearer to our ideal.

My thanks are due to Mr. P. A. Young for the statistical examination of the results which are embodied in Table I.

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