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SOME RECENT ADVANCES IN THE PACKAGING OF PHARMACEUTICALS (I)

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I INTRODUCTION

Advances in packaging technology are closely tied to trends in materials and machinery, changes in legislation and the development of new types of products and the modes by which they are administered. If this background is considered together with a definition of packaging,

as being the economical means of providing protection, presentation, identification and convenience for a product until it is ultimately used then further areas of change can be identified. For example protection may be required against mechanical and climatic hazards, microbiological and human hazards (child resistance or pilferproofness) and it might be expected that packaging achieves this function better today than it did yesterday. However in some cases this is not true for a number of reasons, such as

i) The more rigorous and in depth testing employed today reveals limitations to both packs and products which were not identified under previous levels of testing. For instance a pack/product which showed no instability on a 1 year programme at 37°C might have been given a 5 year shelf life prediction based on very limited test procedures and data on both pack and product; under these circumstances there was no guarantee that a pack was 'suitable' for even a 2/3 year shelf life under normal conditions.

ii) The earlier belief that the ideal shelf life for a product was 5 years has now been largely dispelled. A minimum shelf life of two years, with an average of 3 years appears to be far more realistic as most product-pack systems show some natural deterioration over prolonged periods. Equally a product which is still in stock after 5 years must either suffer from poor sales or be a victim of unsatisfactory rotation of stock. Hence the likelihood of many products needing a five year shelf life becomes extremely rare.

Thus some recent advances in packaging technology must refer to more sophisticated test methods and greater in depth knowledge of well established materials, rather than new materials. However many advances are concerned

with in use convenience, security, hygiene, simpler formulations, new dosage forms, improved economy, etc or even a more modern image. It is therefore proposed to introduce this broad subject under the following headings

1) Product form and dosage
2) Packaging materials
3) Packaging Technology

but it must be recognised that each of these is interlinked.

II PRODUCT FORM AND DOSAGE PACKAGING RELATIONSHIPS

Irrespective of the final product form the need to comply with good manufacturing practice, to improve microbiological standards both in terms of residual contamination and the challenge of preservative systems, to reduce particulate contamination and toxicity risks, to check on bio-availability, dissolution, etc. have all had an influence on both packaging materials and components and how they are produced, cleaned, stored, assembled etc. Thus demands for higher product standards have been responsible for improved packaging standards.

Pharmaceuticals are still showing a steady growth rate due to increasing demands for medication on a world wide basis as the lesser priviledged countries become more prosperous and purchase the more sophisticated medicines. At the same time there is some evidence of a reduction in medical expansion due to both the cost of research and the lengthy and rigid procedures which now have to be satisfied in order to obtain registration of a new drug substance. Emphasis has been placed in finding the right product form, the right dosage, or range of dosages and the most suitable pack size for a treatment period. The solid dose form i.e. tablet, soft and dry capsule, first showed expansion due to obvious product convenience but this is now

related to dosage accuracy, bio-availability and attempts to minimise the number of excipients in any formulation. This is particularly relevant with a dry capsule,but even here other ingredients may have to be added to obtain good drug absorption. As a result oral liquid forms have been less popular except for paediatric usage. In turn the solid dose form can be more economically presented in a unit dose form than a liquid so any trend towards a unit dose has usually started in this area.

The unit dose form is also ideally suited for either sterile or 'clean' products such as eye, ear and nasal preparations, single dose injections and enemas, giving improved dose accuracy and simplifying formulation and assisting pack selection if a non preserved system can be employed. The advent of the single dose injection in a disposable syringe further shows how an apparently more expensive combination can actually save costs in that it eliminates the cleaning and resterilization of a reusable syringe which was very labour intensive. Thus the convenience factor of a product pack has proved an attractive objective over the past twenty years. The advantages of the unit dose system therefore combine product and pack features which can be further identified.

A The Unit Dose form for Ear, Eye and Nasal Preparations

A unit dose pack offers advantages over a preserved multidose preparation in that:-

i) No preservative is necessary, if the dose is to be restricted to one use or application and the product is presented in a sterile form (essential for eye preparations, optional for ear, nasal) or a 'clean' form (ear or nasal).

ii) Following from i) formulations are simpler thus needing less formulation work and minimum work related to microbial challenge. (Does not have to comply with USP XIX).

iii) Reduces the complexity of stability testing - particularly where the drug substance is simply a solution in water.

iv) It avoids risks associated with contamination in use and cross infection.

v) Provides an accurate dosage, which is personal to the individual.

vi) It is suitable for small dosages usually administered as drops or a powder.

vii) Containers are made from flexible plastics from which the contents can be readily expelled.

These advantages have to be equated with the higher cost of the unit dose form and the higher volume which is inevitably occupied.

A sterile or 'clean' unit dose form therefore offers a modern ethical image for eye, ear, and nasal preparations which are normally administered in relatively small doses. These unit doses may either be filled into small containers and then sealed (such as the Maxims*pack USA, Minims UK) or manufactured on a form fill seal basis. In the latter a container is normally moulded, filled and sealed on a single machine which is maintained under aseptic conditions so that a secondary terminal sterilization is usually

* Trade marks

rendered unnecessary. In either process the plastic material of choice can be varied but in general these are limited to low or high density polyethylene, polypropylene or copolymer combinations of these. The merits or demerits of each material depend on both the process and/or the design. For instance low density polyethylene when opened is likely to present a less hazardous surface but if it does not break cleanly this can alter the droplet size when the container is squeezed. Polypropylene being a more rigid material can be made in thinner wall section, and provide a cleaner tear but if this is not achieved, may present sharp and jagged edges. A general comparison table is given at the end of this section, but interpretation needs to be considered against a specific container design.

It is the authors opinion that a unit dose pack should be restricted to one treatment, the eye(s), nostril(s), ear(s), etc and that any reclosure system should be avoided so as to discourage any risk of misuse. The presence of a reclosure immediately suggests that it should either be restricted to professional administration or raises the question as to whether a preservative should be incorporated thus removing one of the advantages identified in the introduction.

The use of a preformed container which is fabricated, transported then filled and sealed appears to have disadvantages over a form/fill/process. However the latter process is relatively expensive to install and requires rigid control in terms of aseptic techniques (the machine is normally steam sterilized on a daily basis). The production rate usually lies between 2500 and 5000 units per hour, but will invariably produce a unit at the lowest cost providing the process is operated on a multishift basis.

A preformed container is still a viable proposition as it offers greater flexibility at lower initial cost and can be filled and sealed at a higher speed 5000-7000 units per hour. These units can either be presterilized by ethylene oxide or gamma irradiation plus aseptic filling and sealing, or terminally autoclaved after filling and sealing under clean conditions. In the latter instance polypropylene can readily withstand normal autoclaving temperatures, whereas low density polyethylene usually requires lower temperatures and the use of a special equalizing pressure autoclave. With the latter it is important that units are separated from each other during the autoclaving process otherwise adhesion between packs may occur. A secondary overwrap such as a blister or sachet is applied prior to the sterilization of most eye preparations as this provides a pack which is sterile internally and externally, and also reduces moisture loss through the plastic. Whether such a double pack is essential for ear and nasal products is doubtful and even for eye drops there are differing opinions. The same types of pack are likely to find extension of usage with other products - for example sterile nebulization solutions of up to 5 ml in volume.

The comparative table which follows is generally based on preformed containers although certain aspects would also apply to a form-fill-seal process.

B Other Unit Dose Forms

Unit dose preparations have existed in such forms as the glass ampoule for injection and bottles for intravenous solutions for several decades. More recent investigations by hospitals in the USA have indicated that the

TABLE

Desirable properties required for a unit dose pack for ear, nose or eye preparations.	Comparative properties of Low Density Polyethylene (Softening point approx 85°C)	Comparative properties of Polypropylene. (Softening point approx 140°C)
1. The container shall hold one unit dose	Dependent on container design	Dependent on container design
2. It must be easy to open without spillage and preferably without the use of scissors or other similar implement	Dependent on container design	Dependent on container design
3. It should be easily emptied - and ideally not capable of multi use	Soft and flexible easily squeezed	More rigid, Less flexible more difficult to squeeze.
4. The dose must be accurate and uniform in delivery	Dependent on filling equipment, and design*. Design and ability to squeeze.	Dependent on filling equipment, and design*. Design and ability to squeeze.
5. There must be no reclosure device to encourage multi use	Dependent on design	Dependent on design
6. The tip exposed on opening should be free from sharp edges	May not tear cleanly - tends to stretch, but less sharp edges or point	Tears well although slightly tougher. Can leave rough edges or point which can be sharp but depends on design and method of break.
7. The pack should have sufficient area for name, concentration, volume and batch number	Dependent on design. Needs to have surface pretreated prior to printing. Readily heat embossed.	Dependent on design. Needs to have surface pretreated. Requires special inks. More difficult to heat emboss.
8. The material used should be compatible with the product. No substance absorbed from solution by pack or from pack by product.	Can be produced without additives. Poor barrier to oils, organic substances, e.g. preservatives	Can be produced without additives. Good barriers to oils, preservatives, organic substances.
9. The material must have good barrier properties against light, oxygen, moisture etc.	Can be rendered more light resistant by additives. Poor oxygen barrier fair moisture barrier.	Can be rendered more light resistant by additives. Fair oxygen barrier fairly good moisture barrier.

	Desirable properties required for a Unit Dose Pack for ear, nose, or eye preparation	Comparative properties of Low Density Polyethylene (Softening point approx 85°C)	Comparative properties of Polypropylene (Softening point approx 140°C)
10.	The cost must be acceptable	Basic material cost low, packs probably cheaper than p.p due to higher moulding speeds	Basic material cost low, usually slower moulding speeds than P.E.
11.	It must be capable of large scale (High Speed) production - preferably automation with the minimum of handling	Sealing fairly fast**	Sealing** much slower unless more complicated multi-head machines are used
12.	Terminal sterilization by autoclaving if preferred. Alternatively gamma irradation or gas sterilization plus aseptic techniques, or terminal gamma irradiation	Can be sterilized by autoclaving only under selected circumstances. Gamma irradiation has little effect. Ethylene oxide also O.K. Residual ethylene oxide levels must be controlled	Can readily be autoclaved*. Gamma irradiation can present difficulties (molecular changes) Ethylene oxide O.K.
13.	No hazards associated with disposal.	No serious disposal/pollution problems	No serious disposal/pollution problems.
14.	Provide reasonable child resistance.	Tends to relate to design	Tends to relate to design
	Consideration is also required on:		
15.	Pack transparency - particularly related to checking for particulate matter. This may directly oppose 9 where exclusion of light may be necessary	Clarity depends on wall thickness, but not 100% transparent. Thicker walled.	Clarity depends on wall thickness, but not 100% transparent. Thinner walls possible. Can be better than LDPE
16.	Capable of having delivery point maintained in a sterile state until pack is opened* (or used)	Dependent on design	Dependent on design
17.	Freedom from electrostatic effects: to minimise particulate contamination	Electrostatic, particularly under dry conditions	Electrostatic, particularly under dry conditions

* Essential in hospital use; less essential for general consumer use.

* Drop size may depend on surface to which drop is attached i.e. shape, uniformity and smoothness.

** These features relate directly to the difference in softening point (See temperature at top of relevant column).

wider usage of the unit dose form can give a total cost saving even though the units are usually more expensive than an equivalent multidose presentation. Although other countries are now checking whether these same advantages apply to their hospital systems, any change is relatively slow when costs are nationally paid for, as any direct increase in the cost of packed drugs is difficult to support when this one aspect is considered in isolation. In any event, the unit packaging of solid dose items such as tablets, capsules and powders is usually considered first due to the availability of suitable blister, strip or sachet packaging machinery. With all of these packs the cost of the packaging materials tends to be related to the moisture protection afforded. For instance laminates using an adequate gauge of foil can give excellent protection in strip and sachet packaging; this protection can be superior to a multidose pack where the product is exposed to the atmosphere each time a pack is opened and reclosed (not actually guaranteed in use). However in the case of blister packs even the most expensive materials do not give total protection from moisture permeation, and in such instances it may be more economical to use a lower cost blister material and enclose each unit (or units) in a foil containing overwrap eg sachet or a lined carton system. In these instances it has to be established that the blister pack affords adequate short term protection once the overwrap is opened and the blisters are exposed to the atmosphere.

Strip packs can be fabricated from a range of materials i.e. regenerated cellulose, coated papers, to complex laminations incorporating various combinations of films, foils, paper, coatings and regenerated cellulose. In most instances the inner ply - which has to be heatsealable (cold seal plies are available but little used) - usually consists of a coating of PVdC, Surlyn, low density polyethylene, a vinyl polymer, or copolymer. The other plies are selected because of appearance, strength, cost, or protective properties. Foil of 1 mil thickness and above has

generally been recognised as commercially pinhole free, but lower gauges in the correct combination with other materials will afford excellent moisture protection. In laminates incorporating a foil ply the product shape and size and the pocket size may be critical as a too small pocket will put considerable strain on the foil and possibly lead to foil perforation with a resulting loss in protection. This situation can be improved by using a preformed pocket rather than a product extended pocket. The former method of forming a pocket (as exemplified by Wrapade equipment) can reduce the pocket size by 20-30% and eliminate any stress between the product and the pocket. Materials used for laminates to be subjected to a preform operation must be selected for their ability to withstand stretching without perforation and have limited elasticity.

Suppositories may be packaged into preformed strips or blister packs which are manufactured separate to the packaging operation or made on the machine into which a solid suppository is fed. Alternatively the strip or blister may be formed with an open end, into which the suppository mass is hot filled, sealed and cooled.

Blister packaging consists of a plastic tray with either a peelable or a push through type lidding. Europe more widely uses the blister pack than the USA with a preference for hard tempered foil lid which permits the product to be pushed or pressed through it. As a peelable type pack requires a perforated area surrounding each blister (to prevent the peeling exposing the product in the adjacent blister) the push through pack not only utilizes less material but it can be produced at higher speeds (machine output is based on web speed and number of units per unit area). However a few European machines are now converting to a peelable pack with hidden peel features in order to meet USA or impending European legislation on child resistant packaging. The push through pack is unlikely to offer

absolute child resistance. Although many papers have been written on blister packaging by European authors much of what has been said could be rendered out of date if substantial design changes are required to meet the child resistant function. The blister tray materials most widely used are unplasticized PVC, PVdC coated UPVC, UPVC/PVdC/UPVC sandwich combinations and PCTFE (ACLAR or polymonochlorotrifluoro-ethylene)/UPVC, being listed in ascending order of moisture protection. PVdC coatings of 24 g/m^2 to 60 g/m^2 are widely used in Europe with PCTFE (Aclar) PVC being used for the more moisture sensitive products. Even the latter provides insufficient protection for the most moisture sensitive products and in all instances the permeation largely depends on both the uniformity and thickness of the blister after forming. This in turn depends on a number of features, such as the blister design, web speed, temperature, type of heating of the web at the forming station and mode of forming. Pressure forming with plug assistance generally gives the most uniform wall thickness, particularly with the more complex laminates, but vacuum forming is quite satisfactory with a correctly designed blister with both straight UPVC and PVdC coated UPVC. A child resistant blister pack utilizing plastic for both the tray and the lid has been developed by Sauter-Sparks (USA).

Other materials and combinations of material have been considered for blister packs but few have reached a stage of commercial success either because of the lack of barrier properties or because of poor performance on machinery. Polypropylene has frequently been tried but suffers from problems due to its high softening temperature, relatively narrow softening and forming range plus an inherent characteristic of giving an excessively thin blister thus giving little mechanical protection and negating any theoretical barrier properties. It has had limited success as a secondary

wrap for Minims*(a unit dose eye presentation) which with a paper/heatseal lid was suitable for terminal steam autoclaving. Copolymers of polypropylene and talc filled polypropylene will form far more satisfactorily but unfortunately these materials then possess moisture barrier properties which are similar to PVC. In further attempts to find a replacement for UPVC following the VCM saga, a range of modified styrenes and various thermoformable polyesters are being experimented with.

* Trade mark

C Packs for Intravenous Solutions

As indicated earlier IV solutions by their mode of usage can be considered as a unit dose form. Although glass has maintained a clean bill of health, it suffers from inherent weight and fragility factors which do not make it an ideal container in emergency situations where patient mobility is essential. In such situations plastics have advantages in lightness, non breakability plus an additional asset of collapsibility in certain designs which renders their use particularly suitable in conditions which are far less clean than hospitals. Plasticized PVC, which is discussed elsewhere, has so far been the main material of choice due to its inherent transparency. In Europe there is however a wide choice of containers in polyethylene, and polypropylene in both preformed containers and those produced by a form/fill/seal operation on Rommelag or similar type of equipment. Packs produced by this latter process invariably use a weld as the final seal but this does not exclude a use of rubber being used as a liner or stopper underneath a seal of plastic. Thus the giving set needle first pierces the plastic and then the rubber which provides a tight seal around the needle stem and eliminates a possibility that during piercing the inside and outside of the pack are exposed to the atmosphere by the needle taper.

The preformed polypropylene containers widely used in Sweden are of reasonable transparency and can be readily autoclaved without problems. Low density polyethylene containers in spite of their lower softening point can be satisfactorily autoclaved at a slightly lower than normal temperature provided an equalizing pressure autoclave is used and no contact is made between containers during the processing. This is sometimes achieved by individually enclosing each plastic unit in a metal container. Designs also vary in the number of ports available, i.e. an additive, filter and giving set port being a possibility. Single ports are used on the Braun polyfusor which now has a break off tip. The giving set then relies on a friction fit inside a tube. If in the use of such packs the rubber component can be dispensed with, this removes one other very obvious source of extractives and particulate contamination. PVC packs which are fabricated by high frequency welding from tubular or sheet material may have from one to three ports. Due to the static nature of the material, fabrication has to be carried out under ultra clean conditions with intermediate wrapping if component parts are made separately then brought together after a storage period, for welding. Under conditions of good manufacturing these units require no washing and can produce a product of extremely low particulate level provided the parts are sealed at the fabrication stage, only opened prior to filling and then immediately sealed. The flexible nature of PVC provides good collapsibility in use thereby reducing the risks of possible aerial contamination. Due to the relatively high moisture permeability of plasticised PVC an overwrap is essential to reduce moisture loss which consequently leads to concentrating of the solution. Some manufacturers actually add a drop of water to the overwrap which further reduces losses - this presence of water should not

* Trade mark

be confused with a dry overwrap where the presence of moisture then indicates a leaking container. In general plasticized PVC, as used for IV packs and blood bags contains no detectable level of VCM (vinyl chloride monomer).

D Administration of atomised products

Another product trend is to generate smaller particle sizes from liquids and powders as a means of either improving absorption or gaining access to certain organs of the body (i.e. lungs). Product dispersion or atomization has in many cases depended on both the formulation and how it is dispensed by a pack. Aerosols and squeezee spray bottles immediately come to mind. Metered dose aerosols can provide clouds of low particle size but are restricted to a low dose size with powders and are likely to contain propellants which are criticized due to alleged toxicity risks or affect on the earths ozone layer. The squeezee nasal spray bottle has served a useful purpose in spite of limitations related to spray break up and dose variability. However both these variables may make such a pack unsuitable for a more critical dosage product and therefore an improved pack is likely to be found in a metered dose pump coupled to a break up system. Such a pack or an aerosol system (based on a bag or piston) where the propellant is separated from the product or is an inert gas is likely to replace some of the more conventional aerosols if propellants continue to be subjected to criticism.

The quest for the finely divided particle form which leads to more rapid product absorption will stimulate further research into break up features based either on packs or as attachments or as separate devices.

III PACKAGING MATERIALS

A Plastics - Containers and Films

The percentage growth of plastics is higher than any other material even in the pharmaceutical industry where the stringency of the testing required to support the use of plastics is ever increasing. The uses of plastics for pharmaceuticals generally falls in three categories.

a) Primary packs where contact is made between product and pack.

b) Secondary packaging materials which may assist in presentation and protection.

c) Devices or administration aids which may be presented separately from the product or form an integral part of the primary pack.

Although packaging in plastic could be considered to give a modern image (use of flexible low density polyethylene bottles began in the early 50's) the majority of applications can be covered by four materials; all of which are well established i.e.

The polyethylenes, low, medium and high density.

Polypropylene and copolymers of Polypropylene.

Polystyrene with additional limited use of impact modified polystyrene.

Polyvinylchloride, unplasticized, modified and plasticized.

Other plastics are used in extremely limited quantities, for specialised purposes,as all are considerably more expensive than the main

four indicated above. For example the polyamides - a variety of nylons - are used for low friction bearings to limit wear in use of moving parts in devices. Nylon can withstand autoclaving and is useful for precision mouldings as is acetal (polyformaldehyde).

Polyester is used as a ply in laminates, particularly where child resistance is required because it is tough and difficult to tear. Polyester is now being tested as a container for carbonated drinks but has not been used, as yet, for packaging liquids in the pharmaceutical industry. Some thermoforming grades are being used for blister packs. As a thinner gauge can be used and the density is lower than PVC, polyester may become a competitive material.

Ionomer - Surlyn* (Dupont) - is used in laminates as a heat seal ply since it offers easier sealing than many alternatives particularly where the seal is contaminated with powder or liquid. It costs approximately twice the price of LD polyethylene but can be used at 2/3rds of coating weight. It can also be thermoformed as soft blisters.

Polyvinylidene Chloride (PVdC, Saran) is mainly used as a solvent or dispersion coating ranging from around 5 g/m^2 to 60 g/m^2. It is used as a heat sealing medium and a barrier coating. As the latter, it is low in odour, oxygen and moisture permeation. The properties of the film are poorer than the dispersion or solvent coating material. It has had limited use as an internal or external barrier coating for polyethylene bottles.

Aclar* - polymonochlorotrifluorethylene is currently the highest costing plastic in use but offers the best moisture protection.

* Trade mark

It is used laminated to UPVC for blister packaging, in two forms, Aclar 22A and Aclar 33C. The former is used in a lamination of 1½ ml and is suitable for all types of forming including continuous motion vacuum machines. The 33C material is used at half this thickness (i.e. ¾ ml) and requires pressure forming preferably with plug assistance. The latter is therefore more economical particularly as similar moisture protection is achieved from both materials when thermoformed.

Further plastics which have limited usage include polyurethane (lacquers, coatings and foams), polycarbonate, polysulphone, poly (4 methyl pentene -1) TPX, polytetrafluorethylene (PTFE), styrene - acrylonitrile, acrylonitrile butadiene styrene, ethylene vinyl acetate copolymers, and nitriles (Barex).

Polyurethane foams are prepared from the reaction of polyesters or polyethers with di or polyisocyanates in the presence of a foaming agent. Although both have been used to replace cotton wool filling in tablet containers in that they carry less absorbed moisture, the polyether versions are preferred as the polyesters are more likely to cause product discolouration due to surface alkali.

Co extrusion whereby two or more plies are extruded together may find pharmaceutical usage either as bottles or laminates in the future. The process enables a series of plies to be built up so that the proportion of each can be used to the maximum effect. The process does however have certain restrictions in that it is only suitable for long runs, the materials must not have greatly dissimilar softening points, and any wastage, being a composite material, cannot be directly reground and used.

Returning to the more widely used economical materials PVC tends to be subjected to the most criticism firstly because it invariably contains the most additives, and secondly because of the more recent scare on vinyl chloride monomer with its carcinogenic properties. Most rigid PVCs can now be produced with monomer levels of less than 5 ppm with some being less than 2ppm. In spite of this, its high clarity offers an advantage which none of the other lower cost plastics can match and this feature is frequently quoted to justify its use for IV products in Europe and the USA. The possible extraction of the plasticizer - which may be present in large amounts and also the stabiliser has been the subject of innumerable articles.

Criticism of PVC has therefore led to both more active investigations into alternative materials and more rigorous in depth investigations into both PVC and its additives. As a result of the latter, a situation could be reached, where certain PVC formulations with low extractives and high purity are verified as safer, in spite of containing higher levels of additives, than other materials which are considered safe today. These factors are therefore part of modern trends, although the basic plastic, as others, is well established. A plasticized PVC 'collapsible' tube has also been formulated which with the thicker wax/oil type of products actually does collapse in use and therefore does not suffer from the typical snap back feature of other plastics (PE, P.P), which permits entry of air and makes subsequent expulsion difficult. It is for this reason that plastics have not generally replaced metal collapsible tubes for ointments, creams etc. However the plasticized PVC tube has had a considerable success with eye preparations where it eliminates any risk of any shreds of metal being present.

Polypropylene, although a well established material is still a relatively newcomer to pharmaceutical packaging. Initially used in the film form as a replacement for regenerated cellulose due to its improved dimensional stability it is now finding growing usage as a laminate ply and as a strip packaging material. Heatsealable polypropylene is usually obtained by applying a PVDC coating (which in itself improves the barrier properties) or using an ethylene polypropylene copolymer or co extrusion. Plastic bottles are also being made from various grades of polypropylene, where a combination of rigidity and/or snap back can be achieved at a relatively low weight (density 0.91). Biaxial orientation improves both chemical properties and clarity. In the injection moulding field polypropylene offers containers with lids or closures with integrally moulded lids which exhibit high flexural strength.

Low, medium and high density polyethylene remain in use both as unsupported films e.g. low density for shrink wrapping and in laminates where low density is widely used as a heat sealing ply. They are also used extensively for containers and closures. Low density is the material of choice where flexibility is required (e.g. squeezee bottles) and high density where rigidity and barrier properties are preferred e.g. tablet containers.

Preparations for multiple use which require a preservative system also present problems with many plastics due to sorption and if the preservative is volatile, loss from the outer surface of the plastic. One obvious way of overcoming this situation is to adopt an unpreserved unit dose form. However in many instances this is not practical or economical and hence alternatives have to be considered either in terms of preservatives or the plastic employed. Although it is difficult to generalise on preservatives

sorption tends to be greatest with low density polyethylene reducing with HD polyethylene, polypropylene and unplasticized PVC. Plasticized PVC again shows higher sorption. Although there are many papers listing preservatives which may or may not suffer from sorption there are many other factors which influence the situation e.g. differences between grades of plastic, surface smoothness and hence area available for sorption, volume and thickness of plastic, type of closure etc. The formulation of the product (particularly if surface active agents are included) also plays a part. Hence this information can only be used as a rough guide line. The final proof must rest with tests on the product in the container of choice. What probably is critical is the solubility level of the preservative in the plastic and the rate of loss from the external surface. If the former is low, which it is with a number of volatile preservatives, then preservative loss can be stopped or minimised by selecting a suitable overwrap system, such as a flow wrap, sachet, lined carton etc. Although both internal and external lacquer coating systems could also provide an effective means of retaining both preservatives and other migrating ingredients, fully commercial coatings have been difficult to achieve.

Irrespective of the type of plastic it is essential to identify all additives and/or residues which are or may be present. A plastic can include any of the following:- pigments and dyes, plasticizers, stabilizers, anti-oxidants, anti-static agents, U.V. absorbers, optical whiteners, anti-slip additives, slip additives, impact modifiers and lubricants plus naturally occurring residues which may consist of unconverted monomer, catalytic residues or traces of emulsifying agents. Although residues generally occur at the polymerisation stage some breakdown products can arise at the conversion stage. Additives can be incorporated during manufacture, the mixing prior to conversion or during the moulding cycle. In identifying

the total ingredients of a plastic material it is important to establish what is added or can arise from the three operations just mentioned. For instance a moulder may employ a heavy metal lubricant such as zinc or magnesium stearate which may create an incompatibility problem and unless asked whether lubricants are used this information may not be volunteered.

The properties of any plastic which govern its use for pharmaceutical purposes can be grouped under the following headings:- permeability, clarity, impact resistance, stress crack resistance, compatibility, sterilisability and cost.

Some reference to the sterilization of plastics has been made elsewhere in the text. Only a few can be sterilized by dry heat; these include TPX, PTFE and certain grades of Aclar and Nylon. Gamma irradiation, usually employing 2.5 mega rads, is now widely used for the pre-sterilization of containers used in aseptic packaging processes. As with ethylene oxide treatment it is normal to seal the containers in two separate polyethylene bags, the outer one being removed in the 'clean' area and the second in the sterile area. Gamma irradiation is unsuitable for a number of the halogenated polymers. Ethylene oxide treatment is only suitable for plastics which are permeable to the gas. After treatment the residual ethylene oxide levels have to be reduced due to the toxic and hazardous nature of the material. This can be achieved by forced aeration or allowing the containers (in double polyethylene bags) to remain in a clean area for 1-2 weeks for natural degassing. Although less than 200pm has been considered safe in the past,efforts are being made to reduce actual levels to less than 50 ppm. A move exists in France for a limit of 2ppm but at the moment this appears impractical.

The currently used manufacturing processes for plastic containers are injection moulding, extrusion blow moulding, and injection blow moulding. The latter process is now widely used for small pharmaceutical containers as it provides a better neck finish, less inbuilt strain and generally a higher quality product. For decoration purposes there is now a wide choice; in mould debossing and embossing, dry offset letterpress, hot die stamping, letraset, therimage, silkscreen and tampoprint. The latter produces half tone prints of up to four colours by an offset gravure process. It is now widely used in Europe and is particularly suitable for printing over radii and irregularly shaped items as the transfer medium is an inflated rubber bulb or balloon.

A particularly useful reference book is "Plastic Containers for Pharmaceuticals, Testing and Control" by Jack Cooper issued by the World Health Organisation, Geneva 1974. Chapters of the book include the following:

Plastics for Pharmaceutical Packaging (Current and Future) (IV)

Potential problems - plastic containers, including sorption, desorption, permeation, photodegradation, polymer modification (V).

Relationship of Plastic containers to Dosage Forms (VI)

Regulatory requirements (USP, NF, Swiss, French, Nordic, British, German and Japanese) (VII)

Standards Issued by Standards Institution. (VIII)

The respective chapter number is indicated in brackets.

B Glass

In considering recent advantages in pharmaceutical packaging it is easy to miss out glass simply because it is so well established. Glass

is not only one of the oldest packaging material but it has served the industry extremely well in a multitude of forms, colours and compositions. As a conventional container it has participated in recent trends leading to lighter or 'right' weight designs, which use less glass, have a more even wall thickness, are usually stronger and are produced at higher speeds. Surface treatment by which the lubricity is increased, have also reduced the likelihood of damage and subsequent breakage. The phrase 'glass is as strong as its skin' can readily be demonstrated if bottles are taken directly from the lehr end of a glass making machine (no previous glass to glass contact) and then put through a conveyor type packaging line which permits surface to surface buffeting. The burst strength of these bottles can be reduced by approximately 50% during such a test. The surface coatings used, include silicones, titanium dioxide, waxes, waxes in combination with polyethylene, stearates, or tin tetrachloride. With the latter, this is applied at the hot end of the lehr with a further treatment of polyethylene glycol or stearate at the cold end of the lehr. This is necessary for reducing impacts during the sorting operation as the slip properties of the tin treatment only becomes fully effective after a longer period of storage.

As indicated, improved techniques and designs have led to significant weight reductions and in some instances the container weight has been reduced over 50% over the past 10-15 years. Good designs now replace sharp corners by adequate radii, have a drawn in 'foot' at the base and an adequate insweep at the shoulder. In spite of all these improvements arguments still rage on the ideal shape, particularly for solid dose preparations. The round or cylindrical container with a full aperture neck is very strong, can be filled at high speeds but wastes space when stored. The square bottle with slightly radiused corners, can have a

reasonably wide neck, does not waste space, but is weaker and offers a much smaller labelling surface. One compromise has been the rectangular bottle which although having a smaller neck aperture (leading to an overhanging cap on many two piece child resistant closures) is quite satisfactory for most filling speeds up to 120 per minute.

Certain coloured glass, actinic green and amber have been used either for appearance or to reduce the passage of UV light. Other colours mainly used for their decorative appearance have until recently been only possible for large outputs as a glass furnace once installed runs from 3-5 years on one colour. A more recent system permits a colourizer to be added as a frit at the feeder conditioning stage prior to extrusion as gobs onto the blowing unit. Thus glass furnaces containing white flint glass can be quickly changed from one colour to another, allowing only a short run out time during changes. The process suffers from one disadvantage in that any unsatisfactory containers rejected at the sorting stage can be rarely reused as cullet. A minimum run involves about 20 tons of glass.

Containers such as ampoules, vials, cartridge tubes, and more recently the barrels of disposable syringes are made from tubular glass. Although ampoules have been widely used for over 50 years a number of points are worthy of note. A properly sealed ampoule not only provides an excellent closure but involves only one material - glass. The opening of a glass ampoule after scoring it by a suitable means has been improved by using a number of easy break features. However these have not overcome the fact that when broken, ampoules invariably shed fine particles of glass, which in the cases where coloured easy break bands are employed, are more readily visible to the user. A number of articles have been written on the hazards of injecting glass into the body but one must invariably reach the conclusion that the injection of any foreign body should be avoided. A further

development is the use of closed ampoules whereby ampoules are sealed by the manufacturer thus providing the pharmaceutical user with an ampoule that does not require washing prior to use. As the ampoules are sealed in a hot state, the atmosphere inside is under negative pressure and thus an inrush of air (and glass particles) occurs if the ampoule is not reheated prior to opening. Opening the sealed ampoule in the inverted position reduces the entry of any glass particles. As with blown glass containers the techniques of producing containers from tubular glass has also improved as seen by the types of disposable glass syringe now produced. These include dual compartment syringes with a by-pass zone which permits the mixing of two ingredients prior to use. This is useful for products which once mixed have relatively short shelf lives.

It has always been accepted that glass is relatively easy to clean. For instance, glassware for oral preparations are usually received in sealed outers and then subjected to air blowing plus vacuum, to remove any obvious contamination just prior to filling. In fact this has also been shown to give containers of lower microbial count than containers washed and allowed to stand prior to filling. Thus glass used for sterile products, using terminal sterilization, are invariably washed on the production line incorporating the filling process. There is evidence that if glass is permitted to become contaminated from general atmospheric and fibrous substances e.g. from fibreboard outers cleaning is not that easily achieved particularly if it is to meet the general rising standards for particulate matter as in IV solutions. In these instances the use of a rubber stopper adds another source of contamination and although there is strong evidence that this can be improved by using lacquered rubber stoppers some evidence indicates the contrary. One therefore might conclude that glass bottles should be washed and used as soon as possible after manufacture (a form/fill/seal operation would not be practical with blown

glass but might be possible with tubular glass) and that if rubber could be eliminated, particulate matter should no longer be a problem.

Glass can be sterilized by any process but dry heat is preferred if aseptic processing is to be used. Gamma irradiation causes discolouration to all glasses and although a sterile container results the unsightly appearance does not lead to ethical acceptance.

Any glass container is only as good as its closure. An effective seal is normally achieved by pressure between a hard material - the glass itself - and a resilient wadding into which the former embeds. The wad is faced with a material which is compatible with the product and has the appropriate barrier properties. Some one piece wadless closures moulded in thermoplastic materials have been shown to give adequate moisture protection at a lower cost than their wadded equivalents. Thermoplastic closures are also used on finishes other than screw necks eg. the push in or snap over types. Compartmental closuring systems are available so that a solvent or carrier and a drug substance can be separated in a container until the product is required for use. A diaphragm can then be broken and the granule or powder allowed to transfer to the solvent for dispersion or solution. This provides a convenience pack for items which have a limited shelf life once mixed with a solvent or carrier. Another more recent innovation is the use of a diaphragm seal based on polyester/ foil or other combinations. The diaphragm is integrally applied in a screw closure, following which the diaphragm is induction sealed through the cap. The principle can be used for plastic or glass but in the case of liquids the seal can be weakened or lost with time. On dry products it acts as both a moisture barrier and a tamperproof seal.

In the area of injectable products which employ either a rubber stopper or disc the ideal rubber has yet to be found although there is a constant search for an alternative material which exhibits all the desired properties. Basically the problem can be identified between release of particles and foreign matter, compatibility in its widest sense, and physical characteristics. The latter include ease of piercing, resealability, coring and fragmentation whereby pieces of rubber are detached or cut out when the rubber is pierced by a needle.

Satisfactory performance with respect to these physical characteristics was more readily achievable when all rubbers were of natural origin. Synthetic rubbers are undoubtedly poorer in this respect but it must be emphasised that few countries have standard test procedures by which different rubber formulations can be compared or results equated with what is likely to occur in a practical situation. Over the years butyl and chlorinated rubber components have become widely used as these possess excellent ageing characteristics, low permeability to oxygen and moisture, low extractives and low absorption of preservatives (particularly phenol). Friction and leaching can also be reduced by using a facing of polytetrafluoroethylene but this adds considerably to the cost. Leaching is also greatly reduced by epoxy lacquer coatings. However as mentioned above the search is still proceeding for formulations which offer better physical characteristics. Newer rubber formulations include chlorinated butyl, polyisobutylene, ethylene-propylene-diene and specially cured grades free of sulphur or zinc oxide. In all instances the cleaning process is an essential part of preparation prior to use. This was given a thorough review by Hopkins in 1974. Most rubber components are lightly siliconised by the supplier unless ordered otherwise.

C Metal

Metals such as aluminium and tinplate find various uses in the packaging of pharmaceuticals both for containers and closures.

Perhaps the most widespread usage - in terms of packs if not tonnage is that of aluminium foil for blister, strip or sachet packaging. The main function of the foil - which is usually coated or laminated to other materials - is to provide a superior barrier against moisture vapour, gases etc which cannot be equalled by even the most impermeable plastics film. The use of aluminium foil for blister and strip packaging in particular will grow with any general trend towards unit packaging whether for child resistance, convenience, product security or other reasons. Gauges of foil are gradually being reduced but this trend has to be carefully balanced against the increased chances of pinholes in foil below 1 mil thickness and the subsequent reduction in barrier properties.

Extruded collapsible tubes fabricated from the softer metals (mainly aluminium) are still used for packaging many pharmaceutical ointments and creams. The impermeability of the basic material and the collapsibility of the tube ensures that the product is protected from atmospheric or bacterial contamination during storage and use. This is an advantage over most plastic tubes which are both permeable and tend to spring back during use i.e. they are not completely collapsible. However aluminium is a fairly reactive metal and developments have concentrated on improved internal coatings e.g. vinyls and epoxys which are applied by spraying and enable even aggressive preparations to be packed.

A recent development which combines the impermeability of aluminium foil, the compatibility of plastics films and the dispensing convenience of a collapsible tube is the "Glaminate" tube ex Continental Can. This consists of a cylinder of a complex foil based laminate which is heat sealed to itself to form a tube onto which is welded a plastics shoulder and nozzle. These tubes can be flattened in the same way as a conventional metal tube but cannot be rolled up as easily.

Rigid aluminium extruded containers are used for packing a range of dry products, tablets, capsules, powders etc as alternatives to glass or plastic bottles. Such containers are considered to have a more modern image than glass and rival their plastics counterparts in being compact light and robust. Although the basic material is as impermeable as glass screw closures tend to be less effective - especially in larger diameters - due to a lack of rigidity.

Similar aluminium extruded containers are used extensively for pharmaceutical aerosols e.g. inhalation devices, nose and throat sprays. These one piece (Monobloc) containers are elegant, clean, easily sterilized and can be fitted with a range of dispensing valves and applicators including dose metering devices.

In addition to Monobloc containers larger sizes of aerosols may be constructed from open ended aluminium extrusions with seamed on tinplate bases (for strength) or built up from tinplate sheet. The choice depends on many factors including appearance, product compatibility and cost. It is common to use internal coatings in order to achieve product compatibility and avoid the risk of corrosion where tinplate is involved.

Recent developments in can making such as the draw and wall ironing technique and the draw and re-draw technique tend to be adopted more slowly by the pharmaceutical industry due to the large capital investment required and the relatively small offtake for pharmaceutical packaging compared with foodstuffs and household consumer goods.

Sheet materials are also used for making shallow drawn containers for ointments, creams and solid dose forms. Although this type of container is losing ground to plastics for ointments and creams in particular on marketing considerations, certain pharmaceutical preparations are incompatible with the most commonly used plastics and will therefore remain in metal containers.

Metals are used as closures both of the pre-formed variety as alternatives to plastics e.g. tinplate screw caps and of the partly-formed type e.g. aluminium roll-on caps, roll-on-pilferproof caps and crimp on seals. These aluminium closures rely on the inherent malleability of the material for application. Metals are also used for components in aerosol valves metering pumps and as injection needles for administering fluids.

To summarize, although metal is still extensively used for pharmaceutical products the number of new applications is limited. Furthermore in areas where metals are well established there is a constant endeavour to replace them as the basic material cost and the cost of fabrication rises.

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