13
BLISTER, STRIP AND SACHET PACKAGING

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Introduction

Although strip packs date from the late 1920s (starting with the single Aspro strip in waxed paper) and blister packs from the early 1960s, both are now well established forms of pharmaceutical 'unit dose' packaging. As unit dose packs offer individual protection until the dose therein is removed, personal dosage, tamper-evidence, child safety, no cross-contamination risks, no opening and reclosing problems, etc., their popularity has limited the growth of typical multipacks. Against these advantages, blisters and strips generally occupy larger volumes than their multipack equivalents. However, this increased pack external area, particularly when cartoned, may enhance the product display image and offer more label space.

Elderly patient compliance has been raised as a point for criticism. This has usually been a result of the question 'do you have difficulty in opening blister or strip type packs?' where 'have you tried opening them this way?' might have been more helpful.

Blister packs originally consisted of a thermoformed plastic tray with a lidding material made from plastic, paper, foil or a combination of these, with the product being removed either by pushing through the lid or via a peelable lidding. Today this definition has been extended by cold forming of plastic/foil combinations and the socalled tropical lidding over the blister.

Similarly, strip packs consists of one or two plies, made from regenerated cellulose, paper, plastics, foil or any combination of these, whereby an item is inserted into a pocket area against a recess in a heated platen or roller. However, some systems now involve the use of preformed pockets thereby making it increasingly difficult to differentiate between blister and strip packaging (Figures 13.1 and 13.2).

Blister packs

Blister machines utilise the fact that a plastic film can be softened by heat and then formed in a mould by:

1 mechanical forming between male and female moulds
2 vacuum or negative pressure—which draws the softened film over or into a mould
3 pressure—in which compressed air forces the film over or into a mould
4 combinations of the above.

The trays thereby formed are subsequently filled, lidded and cut out into specific tray sizes and configurations.

The distribution of the wall thickness achieved by the moulding operation depends on the process: whether the material is formed into or over a mould, film thickness, depth of draw, softening temperature, type of plastic, etc. For an identical blister shape, pressure plus plug assistance generally gives the most uniform blister. Pressure forming usually gives a thicker top section and vacuum is thicker near the base of the web, thinning towards the top. In-built strain within the blister can be observed by viewing under polarised light (provided it is a clear or natural material).

Basic equipment principles

Fully automatic machines are based on either continuous or intermittent movement of the web through the unit, or a combination of the two. Until recently this motion depended on whether certain processes were carried out on platens or cylinders. It is now possible to use platens which have a reciprocating action whereby continuous motion can be maintained. The basic machine operations performed on a machine are:

1 heating+thermoforming or cold forming
2 filling

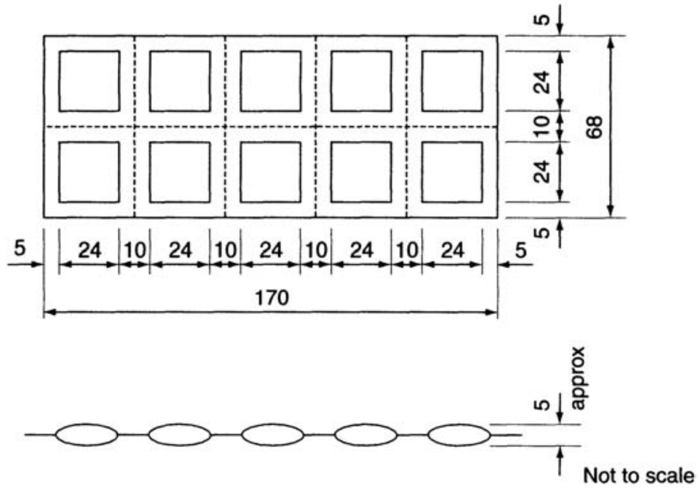

Figure 13.1 Strip pack (based on tablet 13×6 mm)

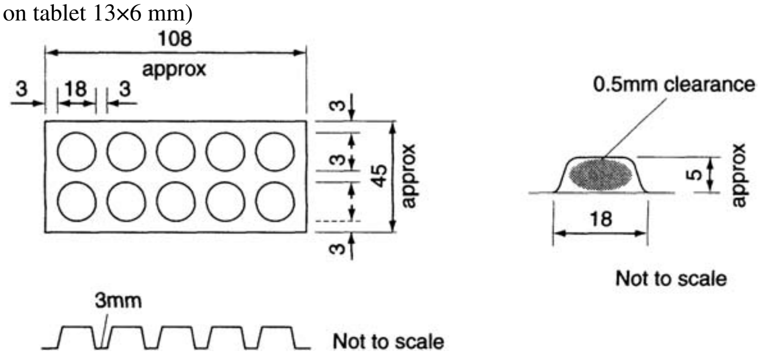

Figure 13.2 Blister pack (based on tablet 13×6 mm)

3 heat sealing of the lidding material
4 punching-out or guillotining the tray from the web.

Additional operations may be printing of the lidding web, registration reading units, batch marking, product check/rejection on not fully filled trays, perforating or scoring between blisters, code reading and disposal of trim (wind-up or shredding). Machines may also incorporate anticurl devices, stacking of the trays, cartoning, etc. (Figure 13.3).

Thermoforming

Heating of the reel-fed base (tray) web is usually achieved by either infrared heaters or contact heaters. Heat may be applied at the forming stage or at a preheat station with or without further heating. The preheat station may be either a cylinder or platens; in certain instances the platens may be differentially heated (top and bottom).

The moulds into which the plastic is formed can be cooled by air, water or chilled water.

The web may be held by grippers, rollers, etc. as it is passed through the machine. Platen machines usually impart less tension to the web but generally operate at lower speeds, i.e. 8–12 m/min whereas 12–16 m/min can be achieved by continuous motion or by reciprocating motion machine with platens.

In general only the simpler materials can be thermoformed on cylinders using vacuum (e.g. PVC, polystyrene, PVdC coated PVC). Platens using pressure forming, particularly with plug assistance, not only offer more uniform blisters but can utilise the more complex materials, e.g. Aclar/PVC, polypropylene, coextrusions (Figure 13.4).

Feeding and filling

The type of feeding mechanism largely depends on the product being fed, i.e. suppositories, ampoules, tablets, capsules, etc., size and the number of tracks across the web. Uncoated tablets and capsules are normally fed from a vibratory bowl via channels or tubes by gravity. Vacuum extraction is frequently applied to the bowl, tubes, etc. to minimise powder and tablet chips which may finish up in the seal or tray. Conventional flat-shaped uncoated tablets usually present no problems, but sugar-coated or bevelled tablets with little side edge thickness may cause difficulties due to dovetailing or shingling. In such cases a

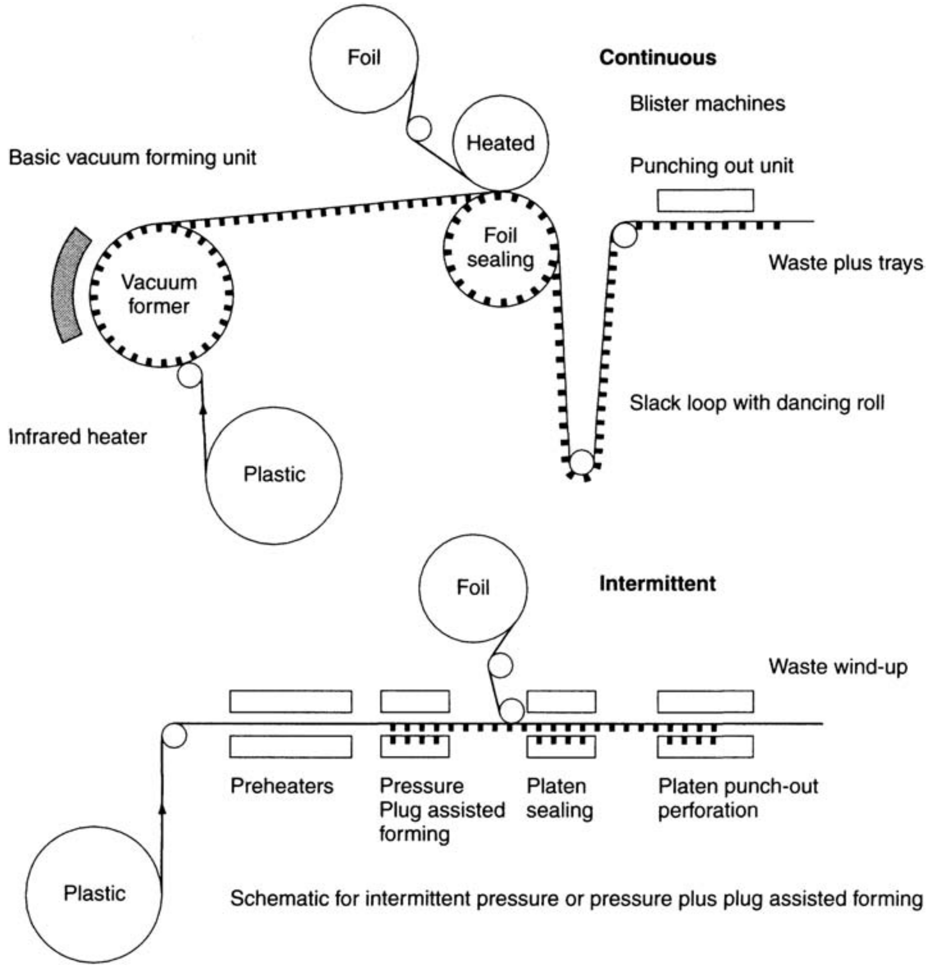

Figure 13.3 Blister machines

rotary table feed may be used. A flood and sweep fill may be employed for sugar-coated tablets when speeds in excess of 300 per track are possible.

However, on most machines a fill speed of 250 items per minute per track is considered good. These speeds are related to the physical restrictions of feeding an item by gravity. Reciprocating tube fillers and chevron roller fillers are used on some machines where the close proximity of the tracks would cause restrictions to the filling speeds.

Lidding and heat sealing

As with the thermoforming process, heat sealing may be based on platens or cylinders or occasionally a combination of the two. Irrespective of the process the pocket must be sufficient to allow a clearance between the product and the lidding (normally around 0.5 mm), otherwise the product may adhere to the lid on heat sealing. The platen requires two uniformly flat surfaces with the base platen-shaped to accept the blisters. On certain machines one platen applies the heat via thermostatically or electronically controlled heaters and the other is cooled by air or water to facilitate rapid and effective sealing with minimum of web distortion. The platen process usually operates at a lower temperature and longer dwell time than cylinders, but can suffer from transferring more heat via the web to the product. On other platen machines the web passes through preheaters.

As stated earlier, uniformity of seal depends on the perfect matching of two platens which under well-controlled conditions undoubtedly gives a better seal. The pattern of seal may be line, pyramid or cross-hatch, but the last of these is invariably preferred. In the case of the cylinder type, the seal is achieved at the circumferential contact between two rollers, one of which is heated. As the process dwell time is very short, a higher temperature generally has to be employed.

It should be noted that the seal pattern is only on the heated platen or sealing roller, with the cooling platen or cylinder being smooth or flat (i.e. there is no impression or pattern on the plastic side of the web).

The effectiveness of either type of seal is checked by the uniformity of the seal impression, by vacuum tests or material deflection under vacuum/pressure.

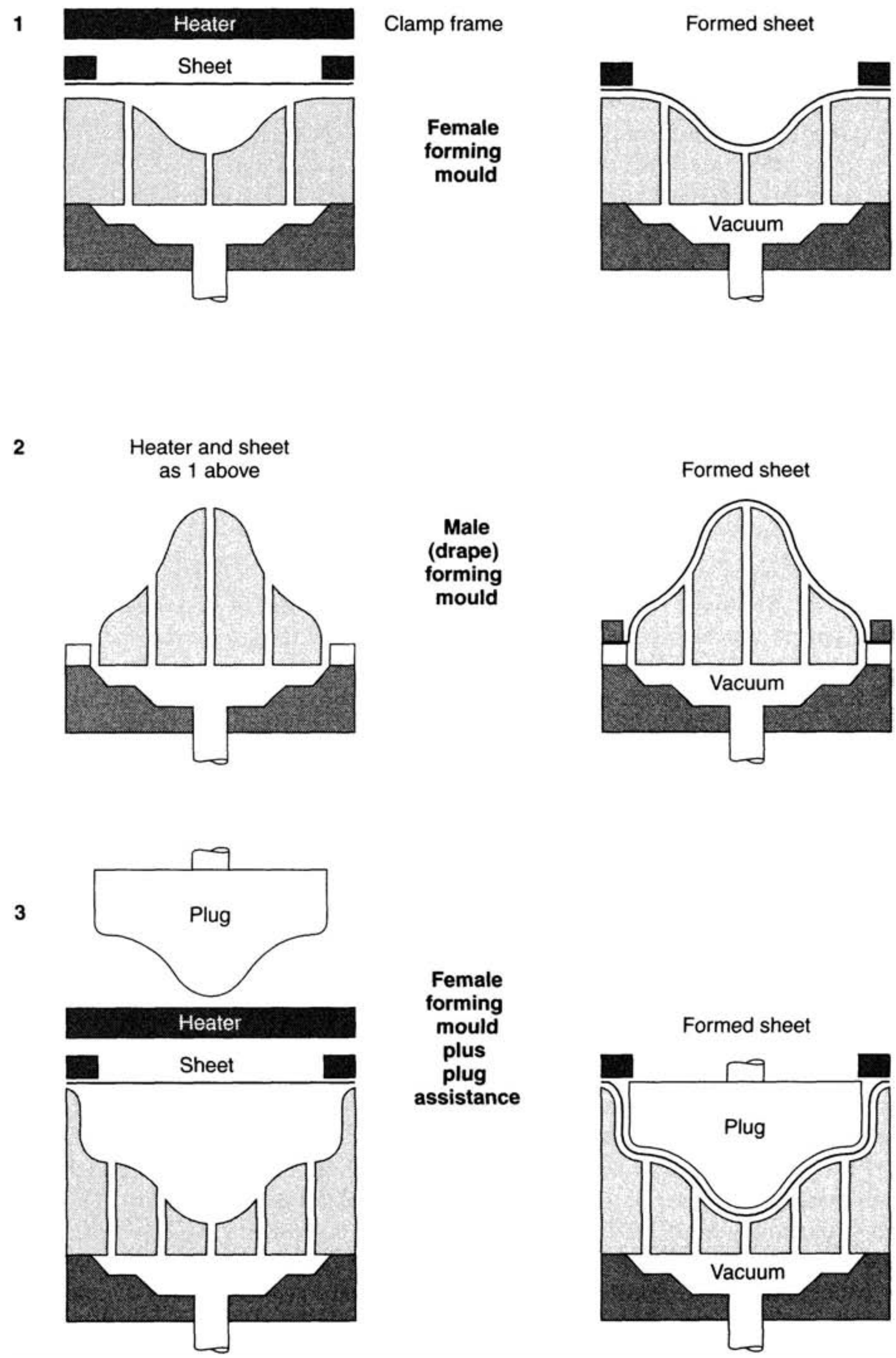

Figure 13.4 Thermoforming operations by vacuum

Curl of trays (particularly relevant with hard foil)

The heat sealing operation can impart a degree of 'curl' into the tray, thereby creating problems for automatic enveloping or cartoning. The amount of curl depends partially on the type of machine employed, the type of web and design of the tray and what happens to the web when it leaves the sealing station. Theory suggests that the different coefficients of expansion for foil and film are partly the cause, plus film shrinkage due to molecular reorientation. Curl can be reduced or overcome by incorporating thermoformed ribs in the tray, or by reversing the web curvature by passing over a tension roller or through radiused guides. In the last of these the radius of the bend back has to be ascertained by trial and error experiments. Curl is less of a problem with soft foil as it stretches more readily. Between-pocket perforations or cuts can also reduce curl.

Removal from web (after perforating, where carried out)

Removal of the sealed trays from the web by punching-out or die cutting enables shaped trays without sharp corners to be produced. Guillotining, if used, invariably produces sharp corners which if not carefully handled may penetrate pockets of trays. Punching-out (unless a reciprocating or rotary unit is employed) is usually carried out as an intermittent action with platens. In the case of continuous motion machines the web is usually converted to intermittent by a ‘slack loop’ prior to either punching-out or guillotining. However, continuous motion can be retained by rotary die cutting, which is inevitably more costly in terms of dies and equipment. Wastage can be minimised in platen punching by staggering the action, i.e. 2 then 1 in a 3 tray across the web configuration. Reciprocating cutting forms can also maintain a continuous motion, hence increase output speeds.

Product inspection and between-pocket perforation

Product inspection prior to lidding suffered problems when the web jerked or slowed down/accelerated whereby items could be thrown out of the previously filled pockets. Although this aspect has now been eliminated from most machines, the after-lidding option had further problems when clear materials were replaced with dark tinted or opaque or foil/foil blisters to improve either child-resistance or moisture, light, oxygen protection. Thus depending on the machine or/and web materials, the original before and after lidding options remain. Prior to lidding inspection now offers mechanical/electrical sensing or an imaging technique, while after lidding tends towards either infrared or X-ray methods.

Perforation or similar options offer a means by which pockets can be readily separated and/or the prevention of any opening method from exposing more than one product. In the US-type peelable packs, perforation or something similar is usually essential to control the peel. Perforation may be achieved by true perforation (a series of bridges and cut-through zones), a part cut through by sharp blades or knives, or the use of a form of laser technology. Such operations usually require a larger betweenpocket distance (3 to 4 mm increases to 5 to 7 mm), adding to the overall size of the blister. The operation is normally carried out either prior to the punching out or within the punching, guillotine stage. It must be performed on well-cooled trays, as warm or flexible materials are less easy to penetrate and can blunt the knives more easily.

Machine summary

Although individual machines may be built for specific functions, standard machines generally offer fixed platen or cylinder sizes. The factors which may have to be considered in the choice of a machine are:

1 area available per stroke on machine (width and length)
2 size and configuration of trays
3 area of wastage or minimum wastage
4 size of product and physical-chemical characteristics
5 type of material used for lid and tray
6 type of feed, number of feed tracks
7 output required or strokes per minute
8 critical nature of blister wall distribution and seal effectiveness
9 type of blister (push-through, peelable)
10 number and frequency of change-overs
11 type of forming available or necessary, e.g. vacuum, pressure, mechanical plug assistance, and combinations of these
12 type of heating available—radiant, conducted, preheat, etc.
13 type of web transfer, i.e. continuous, intermittent, or a combination of these
14 type of removal from web, punch or guillotine, etc.
15 need for perforations, scores or slits between pockets
16 whether machine is integral with a cartoning unit or can be coupled to one.

On some machines printing of the lidding by gravure or flexography can be added. Batch marking can be achieved by printing, embossing or debossing. Various types of product detection systems are available.

Invariably any machine is a compromise between a number of the more important factors.

Tray and blister design

As indicated earlier, total efficiency will relate to the minimal wastage and the maximum throughput. Both imply that the layout of the trays allows the use of a full web and this therefore means that the theoretically ideal blister shape may rarely be possible. Blisters should avoid square or near right-angled corners or bases as this may make release from the mould difficult and lead to thinning in those areas. Similarly, undercuts should either be avoided or be well radiused. Generally blisters should have an adequate clearance with the product and have an adequate radius at both the top (dome) and where the blister emerges into the tray flange. As vacuum forming gives less uniform wall distribution, this can be partially compensated by changing the angle of the draw from say 6° to 12°–20°, but this may add to cost if the tray size is increased to a point where output/tray per area is reduced.

Similarly, the draw angle is less critical with pressure and pressure plus plug assisted forming, where a draw angle of 3°–6° is usual.

Satisfactory seals can be achieved with a separation of 2–3 mm between blisters but there may be some danger of exposing the adjacent pocket when a product is pushed out. Thus 3–4 mm is more general for both between blisters and margin seals. With inbetween pocket perforations or scores this distance becomes 5–7 mm. In the case of peelable blisters it is necessary to extend the peelable edge by at least 5 mm. Alternatively, a cut-away part of the blister tray either internal to the design or on an edge seal may be employed, to enable a good grip for the peel feature. Whether the edge seal remains uniform depends on such features as accuracy of registration, method by which web is held and drawn through the machine, method of tray removal from the web. If the tolerances of these is excessive then wider in-between blister and edges will be necessary. If a tray of the push-through type without perforations provides minimum wastage and maximum machine output, then any change to a larger tray (perforations, or perforations plus peel, etc.) will lead to fewer trays per stroke, more wastage and lower output. In the cost examples it has been assumed that the same output/wastage can be maintained with larger trays. This is based on the availability of machines with the best area per stroke. In practice this may not be possible.

Work in Germany by Professor Gadecke has shown that blister trays with properly designed perforations will meet the US protocol for child-resistant non-reclosable packs. In these tests children tended to be satisfied by tearing along the perforations rather than penetrating into the pack. Opaque or dark tinted plastics are essential to render the item contained therein less attractive. The advent of original pack dispensing (OPD) and the fact that the UK has not followed the European norm (European packs are based on 10s, 20s, 30s, etc., and UK on 7s, 14s, 28s, etc.) has led to various attempts to use common tooling for both. This has frequently meant that certain sizes have pockets blanked off, e.g. a 14 pack can be produced by incorporating a 'blank' in a 15 pack.

Protection and use

In order to obtain a full pack evaluation it is necessary to consider a number of requirements. For instance:

1 ingress from the atmosphere which may result in product deterioration, e.g. oxygen, moisture, carbon dioxide, microbiological hazards
2 migration of product ingredients from within the product to the outside atmosphere
3 migration from the pack into the product or reaction between the product and pack, e.g. discolouration, softening of the heatseal
4 mechanical damage to pack or product: note that on-edge stacking of blisters usually offers the best strength.
5 a convenient means for removing the product without exposing other units
6 the pack must satisfactorily retain the product for the declared 'shelf life'.

The above has to be established by laboratory testing prior to a formal stability programme. As with all pack selections, detailed knowledge of the product, the packaging materials and the process to be employed is an essential requirement. Blister packs are unlikely to give sufficient protection to products severely affected by moisture, oxygen, carbon dioxide, as all known plastic materials are to some degree permeable to these factors.

In such instances additional protection can be achieved by foil sachets, foil lined cartons or overwraps. If the last of these is used it is then necessary to establish that the 'shelf life' of a tray following its removal from its additional wrap is satisfactory for the 'in use' period.

Protection against moisture

The usual practice of making up a few blisters and placing them on test in a cabinet at 25°C 75% RH, 40°C 75% RH, etc., may produce very misleading results. In actual practice blisters may be enclosed in a carton (possibly overwrapped), placed *x* cartons per outer (overwrapped), *y* outers per pallet or with the pallet being shrink wrapped. All of these activities reduce the flow of moist air around the pack, and provide a possible series of moisture barriers. It therefore may not be surprising to find in 24–48 months' storage of a pallet that there is no actual moisture change in the product. Overwrapping of individual cartons or the outer can significantly increase the shelf life of the product. The predicted shelf life from a cabinet test may therefore carry an unnecessary safety factor or even indicate that a blister pack would not be suitable, when under actual conditions it could be acceptable.

Having established a pack/product by an adequate testing sequence, it is necessary to emerge with:

1 a fully and correctly specified product
2 fully and correctly specified packaging materials and finished pack
3 a recognised and defined means of bringing (1) and (2) together, i.e. SOPs.

The successful operation involves not only those who originated the pack and the product, but production and quality control. The latter will be involved in the inspection of incoming materials and the finished packed product.

Child-resistance, tamper-evidence/resistance and OPD (original pack dispensing, now called patient packs in the UK)

Blister and strips by their design are inherently both tamper-evident and tamper-resistant. In 1987 the PAGE, with the support of the ABPI, produced *Design Guidelines for Strip and Blister Packs,* which basically eliminates any 'flimsy' blister or strip packs that might be questionably child-resistant. The above design guidelines led to the issue of BS 7236 1989, *Non Reclosable Packaging for Solid Dose Units of Medicinal Products*. For further details see Chapter 11. An ISO standard based on ISO/EN 28317 has now been approved for reclosables but the standard for non-reclosables is still under debate. German standards for 'type approval' are based on DIN 55559 (more detail is given in Chapter 11).

OPD or patient packs

Although some people considered OPD as synonymous with blister and strip packs, any type of pack can be used. However, the advent of OPD will see a significant swing to blister and strip packs for a number of reasons, including the following.

1 Products are becoming more potent, hence tablets/capsules are smaller.
2 Sustained, delayed and controlled release products are reducing the 3 to 4 times a day dosage regime to 1 and 2, hence quantities and packs will become smaller.
3 Small packs are difficult to label and to accommodate the 70×40 mm or 70× 35 mm community pharmacist's label.
4 Cartoned blister and strip packs give adequate label space and provide a means of collating a patient leaflet (i.e. flat rectangular cartons).
5 Cartoned blister and strip packs also provide adequate space for a bar code and a removable bar code if required for pricing bureau costings.

It should be noted that the volume resulting from the use of blister and strips will be more significant in the warehousing activities of the pharmaceutical supplier and the wholesaler. It will probably be less critical than the community pharmacist envisages, since lower stock levels of OPDs are likely to be kept compared with a bulk pack of 500, 1,000, etc., and the dispensing containers which have to be kept for their use. An actual reduction in space could occur as cartons stack better than bottles, particularly if the bottles are not contained in cartons.

Blister materials—trays and lids

The majority of the packs used in Europe are of the push-through variety. In these instances hard foil of 0.015 mm and above is used. This is adequate as the permeability of the plastic tray tends to be far higher than the foil.

Opaque or tinted materials are necessary if the pack is to meet the UK child-resistant requirements. Opaque films (usually incorporating titanium dioxide) tend to be slightly more permeable than clear materials. Permeation increases with the filler or modifier content of the plastic.

Note that impact modified grades of PVC usually soften at a lower temperature hence may improve machine throughput. Vinyl acetate is widely used as an impact modifier. Impact modified grades generally show higher moisture vapour figures than UPVC.

Lidding materials can also use soft (annealed) foil (0.025 mm) or laminations of soft foil and other substances (tissue paper, glassine, etc.). Soft and embossed soft foil extends in the push-through stage, hence may give added child safety provided it does not damage the item concerned.

Environmental concern with reference to PVC and the fact that burning (possibly as a distinction from controlled incineration) may generate obnoxious acid fumes has created pressure on the pharmaceutical industry to move away from PVC. The alternative materials which have been considered include PET (polyester) and PP (polypropylene). Both require higher softening temperatures than PVC and good heat control, which can be more readily achieved with modern equipment with an effective preheat system. However, this only applies to certain selected and special material grades. Although these materials can be coated with PVdC to improve the moisture barrier, there are pressures to ban PVdC as it also contains a chloride component. Suffice it to say that the replacement of PVdC and its associated barrier/heat seal features may not be easy to achieve. Current opinion is that PVC will not be replaced.

Currently specific grades of PP are being preferred to PET and most machine manufacturers are offering modified machines which will handle these materials. For cold forming, multilayer materials are now being offered with two thinner layers of soft foil which are separated by a plastic ply.

Blister materials (tray—plastics)

In the following list, 1=moisture barrier provided by PVC; 2–10=times improvement in WVP.

1 PVC or UPVC (1). Homopolymer—may be opaque or tinted.
2 PVC (0.7). Impact modified (usually with vinyl acetate), up to 50% higher permeability. Can be opaque or tinted. Note that impact modified grades show white in fold area when bent over.
3 PVdC coated PVC (3–5). Usually 36–100 g/m^2 PVdC on various calipers of PVC.
4 PVdC coated PP (3–5).
5 Aclar*/PVC (10–15).

- Copolymers (Aclar 22A/PVC, Aclar 33C/PVC, Aclar 88A/PVC)
- Homopolymers (Aclar R_x 160/PVC, Aclar R_x 160/PETG, Aclar UltR_x2000, 3000 SupR_x900).

6 Polystyrene PS (0.2). Rather more brittle than PVC—improved by the addition of modifiers (increases opacity).
7 Polypropylene—copolymer (3–5). Good resistance to WVP but poorer gas barrier. Not easy to control when thermoforming due to higher temperature involved, but improving with specialist grades.
8 Polypropylene—talc filled (1–1.5). Better thermoforming, but WVP only slightly better than PVC. Chalk filled PP is also available.
9 PVdC-PE-PVC, sometimes called triplex.
10 PVC PE PVdC PE PVC 100 30 180 30 100 μm
11 PET (polyester) selected grades (usually as a copolymer), e.g. PETG.

Blister lidding materials (push-through)

Foil hard 0.018–0.020 mm plus 6–8 g/m^2 wax, 4–12 g/m^2 vinyl type lacquer or PVdC coating of 10 g/m^2 and above. Lowest foil gauge in use is 15 μm. Note that special HS lacquers can be formulated to adhere to PVdC, Aclar, PP, etc.

Hard foil tends to be more expensive than soft foil if the former has to be subjected to the removal of lubricants by solvents before it can be washed, lacquered and/or printed. However, low-temperature heating (below the annealing temperature) has also been used to remove the oil-based lubricants.

Foil soft 0.025 mm and above plus wax, vinyl type, PVdC or HS coatings for heat seal—note that greater stretch risk with soft foil necessitates a thicker gauge. When soft foil is laminated with 35 g/m^2 glassine, improved child-resistance is achieved. Note that most foils have a primer coat applied on either side prior to coating, printing or laminating, etc.

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*Aclar is the trade name of polymonochlorotrifluoroethylene supplied by Allied Signal. (Generally, UltR_x3000 offers the best moisture barrier.)

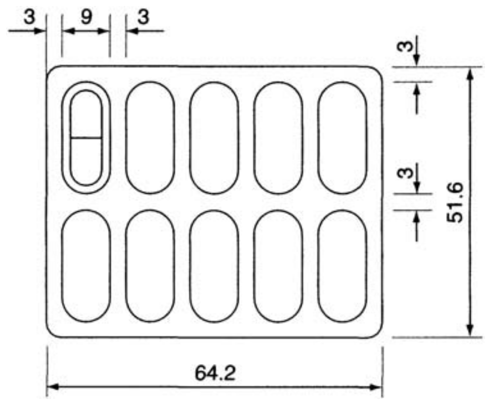

Figure 13.5 Conventional push-through pack

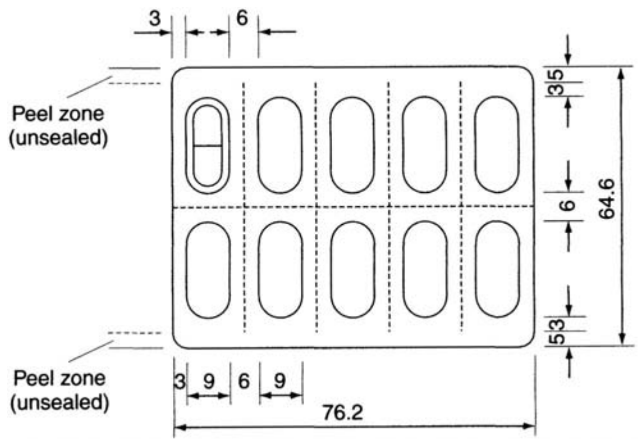

Figure 13.6 Same as Figure 13.5 but with peelable pocket perforations

Peelable

Paper-foil-heat seal lacquer of various combinations. Also cold seals.

Note that heat sealable lacquers have to be 'compatible' with the tray material. If PVC/PVdC is formed with the PVdC on the inside of the blister, a PVdC type compatible lacquer is necessary for the lidding material. All lacquers should be checked for peel strength both initially and at each shelf-life period (1, 3, 6 months, etc.) as ageing effects have been detected, e.g. push-through becoming peelable and peelable becoming permanent (Figures 13.5 and 13.6).

Cold forming (or mechanically formed blisters)

Laminations of plastic and foil, usually of 40 µm+foil, can be physically formed on modified blister packing equipment by a cold mechanical forming operation which is carried out between male and female dies. These laminations of plastic and foil enabled foil to flow without flex cracks during forming although limitations in draw angles and forming depth still remained. This limitation has been improved (but not totally overcome) by using a modified aluminium alloy, the selection of the lamination, the forming design and the best machine factors. The forming material currently consists of such combinations as a biaxially oriented plastic laminated to 40 to 60 µm, aluminium foil and an internal (third) layer of plastic (PE, PVC). Cold forming is also being achieved with multilayer materials containing two layers of soft foil separated by a polymer layer.

Cold forming processes have been developed using a number of basic ideas, as follows.

1. Clamping the material and carrying out a true punch action where the non-held area is extended (stretch forming).
2. Taking a foil which has been embossed or finely creased; can be extended by air or mechanical pressure without showing flex cracks.
3. Taking a reel of material with regular cross-direction slits (as used on Servac suppository machine). A male/female mechanical forming operation is carried out between each slit. This mechanical operation forms the foil and the slit area moves (opens), thereby preventing any high degree of stress (uses 12.5 µm OPP/40 µm foil/HSL).

4 Latest innovations include a double forming operation which reduces the tray size to 20% (Advanced Forming Technology (AFT) process). These tend to use Teflon stretching dies.

Stretch or cold forming

Although foil is an excellent barrier material, gauges of 40 μm and less were difficult to form without fracture. This was partly due to the fact that metallic materials have a crystalline structure and commercially pure grades of aluminium foil had a grain size of around 40 μm (foil of 40 μm was likely to be a mono-grain layer). By the production of special foils of smaller grain size, new 40 to 60 μm foils consisting of multiple layers can more readily stretch without any fracture risk. Laminating this foil to biaxially oriented polypropylenes, polyamides and polyester films further added to the stretch forming possibilities.

It was also shown that the better the laminating bond between the foil and the plastic, the better is the forming operation. To date a typical forming ratio is approximately 1:2.5 (i.e. a cavity diameter of 20 mm would have a depth of 8 mm), using polyamide/aluminium 40 μm/polyamide/PVC film.

In the development of the above technological progress, two selected techniques have been employed:

1 the MAD unit developed by Bosch (a machine to measure multiaxial elongation)
2 Hoogoven screen—a specially printed screen from which stresses and deformation during forming can be quantified (also useful for plastic films).

Summary

Cold or stretch forming is growing as a commercial operation. The factors which influence the stretch forming operation include:

1 the gauge and type of foil used
2 the fineness of the crystalline structure of the foil
3 the design of the formed area including angle of draw and the depth of draw (width to depth currently does not exceed a ratio of 2:5)
4 the structure of the supporting or carrier lamination including the uniformity of the oriented plastic
5 positive lamination between foil and outer ply
6 the forming speed and the friction properties of the laminate
7 the quality of the die, especially the surface finish.

However, further improvements should not be overlooked. New laminations and configurations have recently become available to improve further the child-resistance features of both blisters and strips. In the USA these are typically peelable configurations.

Tropicalised lidding

While cold forming remains relatively expensive, alternative ways of obtaining excellent moisture protection will be sought. Putting a foil lid over the tray section and sealing it to the blister margins, known as the ‘tropicalised’ blister, is now available from several suppliers. This type of lidding may be achieved by a preforming operation, thereby allowing a seal with relatively narrow margins or by direct lidding (no stretch) with a more gradual ‘draw’ and wider margins. Both methods increase the pack size and add to costs.

Costs

Costs are related to material prices, output speeds, wastage, machine depreciation, downtimes, etc. (see below). Depending on the choice of material, blister packs of the push-through variety can be as economical as glass bottles in quantities up to around ninety items per pack. At quantities below twenty-five items, there are positive cost advantages in most cases. Both these comments must be accepted as rather general statements—the actual break-even point has to be calculated for each set of circumstances. The above indications assume that both a glass bottle and the blisters have to be packed into cartons, with a CRC fitted to the bottle pack.

Greater emphasis has been put on blister packaging systems in recent European developments. Most machines can be coupled with a leaflet/cartoning system. In many instances the cartoning operation is an integral part of the blister machine.

Labour costs can change relatively rapidly, particularly at times of rapid technical development, allied to salary inflation, so it would be misleading to include details in this chapter. However, in general, labour costs on bottling/blister lines of a similar size will largely be comparable.

Continuing competition is expected between cold form and tropicalised blisters, which compared with straight PVC blisters, offer area ratios of 60×48 (PVC), 70×58 (tropicalised) to 112×66 (cold form) with cost ratios of approximately 100: 170:285.

Summary

Blister packaging equipment can extend from a fairly basic piece of machinery which covers a form fill seal, and removal from the web operation to a highly sophisticated unit covering a far more complex range of operations. Invariably complexity must be associated with higher prices, more highly trained operatives, less flexibility, etc. Plastic blister materials cannot offer full climatic protection, hence additional protection may have to be achieved by some form of overwrapping system.

A broad summary can be made of machines, materials, outputs, costs, etc. in comparison with glass and plastic bottles, metal cans, and strip packs as shown by the general costings. As the requirement for a unit dose or multiple unit dose increases, both blister and strip packs are ensured of a significant increase. Blisters may gain in space and cost saving but lose out in climatic protection, unless cold formed foil, a foil tropicalised blister, or an overwrapping system is used.

New machines, cold forming, a plastic/foil blister/pocket, which use areas of materials between those of blisters and strips are also likely to increase. Whether these are actually strips or blisters will depend on the forming process used.

In summary, any individual type of dosage form offers obvious advantages in product hygiene, personalisation and protection if the correct materials are selected. It also enables the patient to carry a daily dose readily.

Finally, in small quantities of items (say fewer than seventy-five) blister packs are likely to be both economical and competitive with other packs, showing in addition a weight saving with a volume increase.

Normally the lidding is printed (for transparent trays both sides can be printed) but not the tray. On-line or in-house printing of lidding materials is increasing.

Note that semi-automatic blister packaging employing large preformed trays which are filled by hand then lidded from reel or sheet, followed by punching-out or guillotining, can offer speeds of around 1,200 items per minute with two or three operators. Under such conditions prices can be reasonably competitive with more sophisticated automatic equipment, particularly if runs are relatively short and a variety of tray and product sizes are involved. This can be particularly useful for clinical trial supplies.

Controlled or monitored dosage systems for the elderly

Various blister tray systems using large blisters which will take several products are now being offered for elderly, infirm, arthritic patients, etc. These trays normally hold twenty-eight to forty-two blisters, which are filled with the patient's medication and then lidded. The nature of the medication can be marked in various ways, i.e. water tablets, heart capsules, etc., with clear indication when each is to be taken, e.g. morning, mid-day, bedtime. In some systems these times are colour coded.

Examples of these include:

- Manrex Controlled Dosage Medication Systems
- Nomad by SurgiChem
- PCI (Pharmacy Consultants Incorporated)
- Webster Systems (now taken over by the Boots Company)

and may be found in the USA, Canada, the UK, Holland and Australia.

It is forecast that these systems will increase in popularity, particularly as the elderly population is showing a steady increase, often residing in special homes.

The pharmacist normally purchases the blisters in reels, and has a special sealing machine for the lidding operation. The pockets can usually be individually labelled (on the lidding) using a computer-based system involving self-adhesive labels.

Since the monitored dosage systems conflict somewhat with the OPD concept (a pharmacist does not like transferring products from blisters and strips) there may still be a need for a bulk pack, particularly if the use of these dosage systems continues to expand.

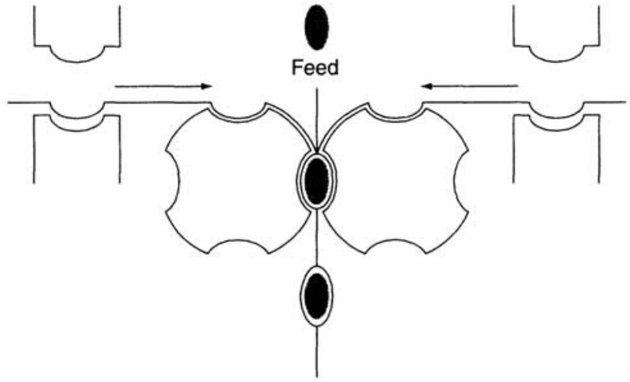

Figure 13.7 Strip pack preformed pocket

Blisters—liquids and semi-liquids

Although conventional horizontal formed blisters can be used with semi-viscous to viscous products (or even smaller quantities of liquid), it is necessary to turn them to a vertical position if a higher fill volume per pack is to be achieved. Filling single or double sided formed blisters in the vertical position can be carried out in cut individuals, cut sticks or an intermittently or continuously reel-fed system. Initial attempts to utilise a double sided formed blister led to low operational speeds. The introduction of laminate or coated webs whereby the sides of each web can be heat sealed led to significant increases in output. For example, the Lamps san Prospero, Unifill machines (Elopak) can produce packs with liquid volume fills between 1 and 90 ml with output speeds of up to 20,000 an hour, Dott. Bonopace also offers machines, a development of its suppository packs, where preformed blisters are delivered in reels. In theory machines of these types should be capable of aseptic production and hence in the long term could compete with other machines which operate on aseptic systems.

In the food industry such equipment would use either a presterilised web exposed by a removable peelable layer, or UV or hydrogen peroxide as an on-line surface sterilising agent. Currently none of these would be acceptable for a pharmaceutical operation, although use for sterile oral liquids might bear consideration.

Strip packs

Strip packs present an alternative form of pack for a unit dosage. Strips can be produced from single or multi-ply materials, provided the two inner plies can be sealed by heat or pressure (e.g. cold 'self-adhesive' seal). Materials can range from relatively permeable plies to those which incorporate a foil ply of sufficient thickness (and effectiveness of seal) that an individual hermetic seal is produced for each dosage. To date strip packs are usually produced at lower speeds and also occupy greater volume than blisters. The break-even cost with glass containers largely depends on the material used, output speed, and item size.

Strip packaging process

Basically a strip pack can be formed by introducing an item which extends a pocket area during insertion or by a preforming operation prior to filling (see Figures 13.7 and 13.8). As the latter method gives less strain (or more controlled forming) to the pocket area and reduces the material needed by 20–35%, it is suggested that this type of strip pack may increase. Either one or both sides of the plies may be mechanically formed, but this process can only be applied to materials which will 'stretch' without tearing.

Strip packaging machines are far simpler and smaller than blister packaging units, usually simply consisting of a feed system, product insertion plus heat sealing, and a guillotining operation to size.

Feed is usually via a vibratory bowl with feeding tracks (usually up to a maximum of sixteen). Alternatives are a rotating table plus drop or sweep. Most machines employ a

vertical feed (gravity drop) but occasionally the web is run horizontally with a platentype sweep. The pocket area is created by recesses either in a platen or more usually in a heat sealing cylinder, where a circumferential point seal is made between two intermeshing cylinders.

As with blister packs, the maximum speed depends on the size of the item and gravity. A maximum speed of 250–300 per track is likely with a 325 mg (five grain) type of aspirin product. Removal of powder, chips, etc. is achieved by vacuum extraction.

Cutting of the emerging web is invariably done by either a scissors or guillotine motion or rotary die cutting. Additional stages which can be incorporated into the machine include printing, perforating, batch coding, magic eye registration, etc. As

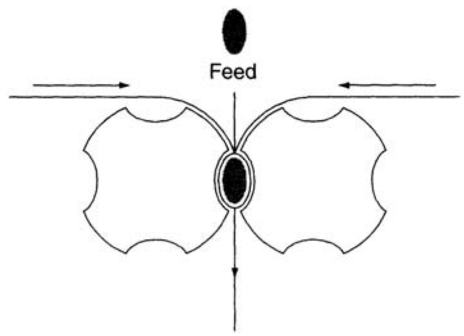

Figure 13.8 Strip packs in item formed pockets

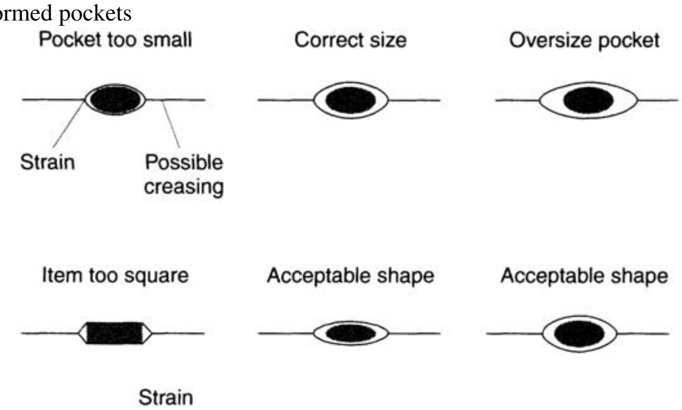

Figure 13.9 Strip packs in item formed pockets

distinct from blisters, perforation does not usually add to the seal width, as pocket seals are nominally 5 mm or more. Most machines use two separate webs but occasionally a single centrally folded web may be employed. Strip packaging is closely allied to sachet packing and in certain cases it is difficult to differentiate between the two. Two different plies can also be used (top and bottom) provided the sealants are compatible.

Machine speeds

A few eight-track machines exist (maximum output around 2,000 items per minute); four, two and single tracks are more usual with outputs of 1,000, 500 and 250 respectively. As a result of this speed limitation, few machines are coupled to a cartoning unit.

More recently sixteen- and thirty-two-track machines have achieved output of 4,000 and 8,000 items per minute. These are similarly priced to blister units and have an integral cartoning option.

Strip designs

Strip designs are very basic, as the emerging units are invariably rectangular or square strips. The pocket portion can, however, be round, oval or square. The pocket area is critical to the diameter, shape and thickness of the product. If the pocket is too 'tight', tearing, perforation of the pocket periphery or wrinkling of the seal area may occur (Figure 13.9). The seal width may be as low as 4 mm, but usually 5 mm and above is employed. If the seal area is likely to wrinkle or crease then wider seals may be

necessary. It should also be recalled that the cylindrical-type sealing process does not usually have a distinct cooling cycle—hence any pull on the seal ply will tend to weaken the seal when the sealant is still pliable. This is particularly relevant with foil, where it may be necessary to have air cooling cylinders if a small seal margin is used. Warm materials are frequently more difficult to cut than cold materials. This may introduce a need for extra cooling or moving the cutting operation further away from the heat sealing area, as a 'soft seal' may string or prevent a clean cut. Use of cold seals (selfadhesive materials) is extending, particularly as such materials can be sealed at higher speeds than conventional heat seals.

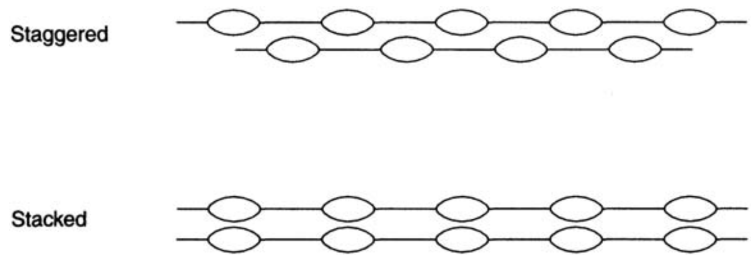

Figure 13.10 Staggered and stacked configurations

Machine sizes and heat control

Most strip machines consist of two cylinders driven from a large one-sided control box. This inevitably creates possible heat control difficulties, particularly as the cylinders get either wider or of greater diameter (i.e. the drives act as a heat sink, whereas the ends furthest away from the drives are exposed to air). Based on this, the greatest heat is likely to be retained somewhere between the two ends of the cylinder, possibly causing overheating, metal expansion, leading to pressure increases, etc.). Latest machines therefore incorporate two-ended supports (or drives), thus allowing wider diameter and longer cylinders to be used.

Materials

Full details and examples of typical materials are given in earlier chapters, so they are not covered here.

Materials employing foil inevitably provide the best, indeed excellent, protection provided an effective seal is achieved and the foil is not unduly stretched to form perforations during the handling.

Vacuumised metal coatings are gradually improving. Tests indicate that these substantially increase the protection offered by plastic materials but do not equate with a ply of foil. Two plastic plies, each with a vacuumised foil, when laminated in direct contact with one another, can give excellent barrier properties. The barrier properties achieved by metallisation may reduce somewhat once the material becomes creased. Protection from some of these creasing effects can be improved by the incorporation of a more flexible ply (e.g. LDPE), i.e. PET metallised/LDPE. PET is very resistant to tear, hence needs a tear initiation feature. It also confers child-resistance.

Costings

Good protection means the incorporation of a foil ply, but such packs are usually greater in cost than either a blister or blister with an overwrap. This is due to the cost of the material, the greater area involved and the likely lower production rate.

Cheaper plies such as regenerated cellulose film provide the lowest cost form of unit pack coupled with restricted protection, but this can be improved by an overwrap. PVdC coated PP is the preferred substitute material today.

Volumes

The volume occupied by strip packs is invariably high. Some reduction can be achieved by preforming the pockets. Cartoning with the more flimsy materials may create difficulties. For single strips, envelope or catch covers are a useful alternative to cartons. They also make cartoning a much easier operation. Particularly useful for clinical trial supplies (Figure 13.10).

Identification

Strip plies are usually printed by gravure or flexographic processes either on or off the strip pack machine. Registration is usually carried out on one ply. Repetitive printing is frequently employed, i.e. three repeats to two pocket areas, so that one full print will appear on each unit.

Conclusions

Strip packs incorporating a suitable foil ply offer excellent protection and are superior to all reclosable packs (there are no risks associated with opening and reclosure) and conventional blister packs. In general strips are produced at lower speeds than blisters, occupy a greater volume, and are more expensive. Cellulose or OPP films (single ply) are likely to break even with bottles of 100 items, and a foil ply with 20–25 items. However, certain sophisticated machines handling 1 inch effervescent tablets offer high speeds of over 7,000 items per minute, hence are faster than most blister machines.

Strip packaging machines are generally more flexible than blister packers; changeover times are shorter and much lower in cost (except for the very widest machines). They are, therefore, more ideal for short runs. The largest machines with integral cartoning are similar in price to the fastest and largest blister units.

Machines can readily be coupled with catch covers (Wrapade and Siebler machines) and due to their smaller size have versatility in movement between packaging lines.

One of the most widely used materials with excellent moisture protection is paper, 40–45 g, extrusion coated LDPE, 12 g/m^2, 7–9 m μsoft aluminium foil, 25 g/m^2 LDPE. The presence of two layers of plastic more than amply fills in any pinholes in the foil layer. The same laminate is also widely used for sachets and is technically preferred to a similar laminate with the foil on the outside.

Package integrity

The need to check pack integrity has increased in importance, both to guarantee product shelf life and to ensure that the product has not become ‘contaminated’ from some external source. Contamination may be related to organoleptic, physical, chemical or biological change, e.g. increase of bioburden, loss of sterility, which may be related to closure effectiveness.

Improving pack integrity can be related to on machine control (i.e. the quality assurance approach) or quality control (regular checks are made on the packs produced). Until recently the historical way of checking the integrity of blisters, strips, sachets, etc. involved the use of destructive-type testing, e.g. vacuum tests under water, burst tests. The more recent introduction of non-destructive tests should therefore not only improve output, but enable better on-line statistical evaluation to be carried out, thereby giving a better feedback on machine performance. This also means that where seal integrity is lost or is suspect more effective corrective actions can be undertaken, including improvements in on-line controls (i.e. more emphasis on quality assurance). Non-destructive testing equipment is usually based on a dry pressure vacuum procedure followed by detection of pack distortion (deflection) or non-distortion (nondeflection), i.e. packs with effective seals become concave then convex as positive pressure changes to negative pressure, while leaking packs either do not change or show less or limited distortion, depending on the scale of the leakage.

Vacuum tests

Vacuum tests under water vary from company to company. BS 7236 1989, NonReclosable Packaging for Solid Dose Units of Medicinal Products, gives the following seal integrity test.

> Immerse the test package in a container containing coloured water (15–25°C) and place the container in the vacuum chamber. Apply the appropriate vacuum of 33 kPa (250 mm of mercury) for strip packages or 24 kPa (180 mm of mercury) for blister packages, for 30 s. Restore atmospheric pressure and remove the container from the vacuum chamber. Remove the test package from the container and blot off the excess water. Examine the package for ingress of water into the pockets.

Pinholes and foil (aluminium)

Pinholes normally refer to the minute holes which may be present in the foil after conversion. Foil of 0.017 mm caliper and above is generally recognised as commercially pinhole-free. 0.025 mm foil can normally be ‘guaranteed’ pinhole-free. Foil below 0.017 mm gradually shows an increasing number of pinholes. However, the WVP of foil of 0.006 mm is lower than any nominal gauge of plastic when used in a heat sealing lamination. When foil is laminated or coated the initial pinholes tend to be ‘filled in’, thus reducing any permeation risk still further. Permeation is then related to the plastic which covers the pinholes.

In the case of blister packs permeability via the foil side is extremely low, hence permeability relates mainly to the plastic of the tray and the wall distribution. With strip packs permeation may occur through edge seals, or more likely capillaries created by creases in the edge seal, as well as actual foil perforations. In general pinholes and perforations cannot be detected by vacuum dye tests as the plastic plies normally remain intact. Capillary leakage can be detected by this method—it may be assisted by adding a wetting agent to the solution.

Although the effect of pinholes may be minimal, the shelf life of the product can be reduced where the pack is exposed to high humidities for prolonged periods. Pinholes are likely to be irrelevant for short shelf life or rapid turnover products, where a certain degree of risk can be taken. See Chapter 10 for more details.

Sachets

Sachets achieved success when the first effective heat sealants were marketed. Their use, initially as a replacement for powders in folded paper, was extended into granules, moisture sensitive solid products and liquids (particularly shampoos).

Sachets can be fabricated from a single web with a centre fold, using a three or four sided seal or two webs using a four sided seal. The reels may be fed horizontally or vertically and be sealed by a series of heated platens or rollers (cylinders) or a combination of the two. In certain ways they are an enlarged version of a strip pack. The sachet seal can also be made peelable by a non-seal part on the web which may involve a pattern lacquer rather than a full heat seal coating. Difficult to tear plies, like PET, can also be used provided a cut or V-notch is added to initiate the tear.

Small sachets usually start with narrow seal margins of around 5 mm, but become wider as the weight of the contents increases. Like strip packs, an over-tight fill should be avoided, as this can lead to perforation on the inner side of the heat seal and capillary channels, resulting from seal creases. Although seal patterns can follow strip packs, line seals, either all parallel or across at the top and down at the sides, tend to predominate. A cross seal at the top tends to give a more secure seal whereas parallel downward lines make for an easier tear open feature. Although sachets can be received preformed for filling, reel-fed processes based on a form fill seal principle are preferred. Speeds of between sixty and ninety sachets per track can usually be achieved.

Sachets also have the advantage that they can be used for liquid and semi-liquid packaging. Flow wraps are a further extension of a sachet-type pack. Both have been widely used as a protective overwrap to extend the shelf life of blisters.

Recent developments in blister and strip packaging

Although this question could be answered in terms of material, machinery and their performance, where each may be influenced by the properties of the product, costs, change-over time, output, etc., there are broader issues today, i.e. what standards should be used for child-resistance, how does one improve moisture protection, etc.

Although cold formed materials started with 40 μm foil and utilised a relatively shallow well-radiused draw, perforation problems with the foil have arisen. As a result, 45–50 μm foil has been substituted with gauges available up to 60 μm.

Most machines, which are now based on pressure forming with plug assistance, can be adapted to cold forming. There has been a tendency for a machine to occupy less length by operating over two levels or by doubling back on itself. Although maximum speeds of over 6,000 items per minute are still relatively rare for conventional blisters, higher speeds are predicted.

Aclar copolymer based materials using 22A, 33C, 88A have more recently been challenged by the homopolymer R_x series with lower costs coupled to good moisture barrier properties. However, there are many alternative overwrapping systems which may be used to improve moisture barrier. In this context the Japanese have recently introduced silicon oxide coated PET overwraps. Use for thermoforming, a multilayer material, a coated material, or the lowest cost material with some form of overwrap remains an emotive issue as to which is most environmentally friendly. Multilayer materials are likely to be the most difficult to recycle, but recovery of energy may be possible by effective incineration. One newer material for cold forming uses two thinner layers of soft foil separated by a polymer layer, while another has involved a double forming process (AFT).

Machinery and machine improvements

Machine improvements include use of larger reels (frequently now without joins), various forms of preheat with variable temperature ranges either side of web, preference for pressure forming with plug assistance, improved cooling of moulds, possible preheat for foil sealing section, automatic splice facility, Geneva driven notched drum for accurate forward progress and accurate registration, on-line printing, e.g. flexo, accurate perforation or cutting, minimising of curl, improved GMP, faster changeovers, integrated cartoning, microprocessor-computer controls and fault diagnosis, etc. Removal of the blisters from the web with the minimum of wastage is now the rule rather than the exception. Machines have also become more compact, with a trend towards more versatile units. Modular machines and Servo technology driven systems are also being offered.

Deblistering units (on and off the machine) are more readily available.

Tamper-evidence, tamper-resistance and child-resistance

Emphasis on the above continues to grow, with the result that some companies do not know the current state of the art. Companies therefore continue to present attractive looking products to children in clear materials and design blisters where the products interact when the blister is bent into an arc, with the risk of the items literally ‘popping out’. Fuller information on the subject can be found in Chapter 11. It is of interest to note that since the introduction of child-resistant packaging, commencing in the mid-1970s in the UK, there has been a significant reduction in the reported cases of child poisoning instances. This has involved those reclosable CRCs which have passed a test using children and non-reclosable packs which have not passed any test but have shown a significant growth in use over that same period. Although this implies that either many blisters, strips, sachets, etc. are inherently child-safe or children are less interested in a pack where the product is not visible or shows less rattle (compared with tablets in a container), there is still a need to improve the more ‘flimsy’ forms of pack. In addition, many child-resistant packs still present opening problems to the ever-increasing elderly population who rely on regular medication in order to survive. This can result in either inadequate replacement of the closure or the transfer to open containers, thereby exposing both the product and children at risk. The industry has still to address these concerns fully.

Costs

A summary of typical comparative costings based on glass, metal, strips and blisters is given in Table 13.1. Earlier published tables also gave comparisons in terms of volume and weight, related to both incoming materials and finished packs. It should be noted that costings can significantly vary according to individual circumstances.

It must be stressed that Table 13.1 gives examples based on specific circumstances where many of the factors can change between different companies, hence each organisation must do its own costing exercise for its own particular operation.

Table 13.1 Comparative costings (costs cover materials, labour, carton, outer pack, etc.)

Item	*Pack*	*Cost ratio*
Bottle glass	10s	1.15
Bottle glass	100s	1.9
Bottle plastic	10s	1.00*
Bottle plastic	100s	1.75
PVC push-through blister	10s	0.40
PVC push-through blister	100s	1.95
PVC blister, peelable, perforated	10s	0.55
PVC blister, peelable, perforated	100s	2.15
Can metal, aluminium	10s	1.70
Can metal, aluminium	100s	2.60
Strip (paper/foil/polyethylene)	10s	0.70
Strip (paper/foil/polyethylene)	100s	3.65

*Plastic pack taken as unity for ten items. Actual costs will vary according to the machine, output, labour, etc.

Semi-automatic blister packaging equipment

Other than being used to pack solid dose medication, blisters or bubble packs, as they are often known, may find further applications in pharmaceutical packaging. These may be as a protective overwrap against physical damage, to prevent ingress or egress, to aid display or to act as a tamper-evident/tamper-resistant feature (i.e. packs which are not involved with the solid dosage form).

Although the same principles apply to semi-automatic machines, sheets may be used instead of reels. The types of material and the process employed tend to be based on their economic and strength characteristics. Where a tray or container is not required for a direct form fill seal operation, the thermoformed item can be fabricated either in a female mould or over a male mould. The various combinations of vacuum, pressure and mechanical (plug assist) are indicated in drawings. With vacuum forming, and where a female die is used, the process is called straight vacuum forming. If a male die is used, the process is termed drape forming. In air pressure forming, greater pressures may be employed.

The majority of the individual type of blisters are made by vacuum forming either into or over (drape type) moulds, which are frequently made from metals such as aluminium. The choice between female and male moulds depends on a number of factors, as follows.

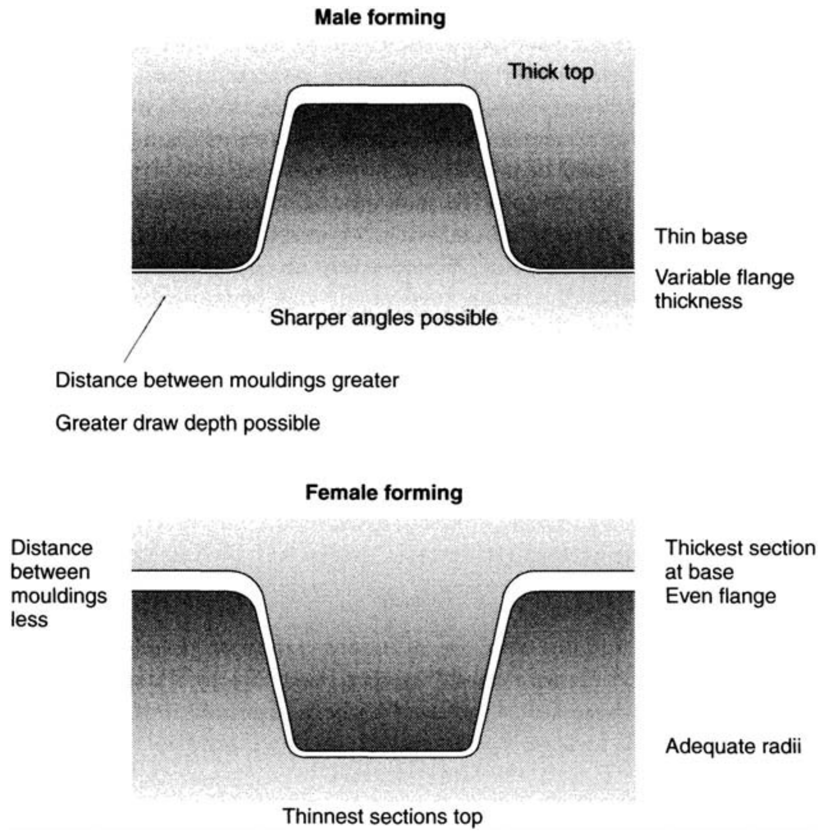

Figure 13.11 Male and female vacuum forming

Female

Base (flange) is thickest, and uniform; top of mould is thinner. Formings can usually be put closer together therefore more mouldings per sheet. No webbing between moulds. Limitations in depth of draw. Good radiused corners required—not suitable for sharp corners. See Figure 13.11.

Male

Base (flange) is thin and non-uniform; top of mould is thickest. Capable of greater depth of draw for a given caliper. May tend to web if layout is not properly designed. Needs greater space between mouldings (rule of thumb 1.5×draw height) therefore fewer mouldings per sheet. Capable of achieving relatively sharp corners. See Figure 13.11.

Plug assistance can be used, particularly where webbing is likely to occur, but this generally slows output. Air holes for venting vary between 0.50 mm and 1 mm for most small mouldings.

Mouldings can be ‘ribbed’ to improve strength or to enable a thinner material to be used, e.g. 300 μm reduced to 200 μm by ribbing. Improved wall distribution can also be achieved by extending the softened plastic sheet by vacuum or pressure prior to final forming (often known as balloon or bubble extension).

Materials

When clarity is required PVC, PS, PET, or cellulose acetate may be used. The last of these tends to cost more even though the moulding cycle is approximately 25% faster; this does not compensate for the higher material cost (+30%). Impact modified styrene or styrene is more widely used for coffret-type inserts which are invariably coloured or flock coated. Styrene offers a higher yield than PVC (note densities) and a faster forming time. PET is often the preferred material for surgical or medical device systems.

Some relatively simple blister packaging equipment is produced on a rotary table principle whereby a blister can be formed, hand filled, lidded and the completed blister pack removed after four 90° movements. Others work on a reciprocating bed principle of forming and lidding. These are often used for optic lenses and opthalmic-type solutions for lens cleaning.

Some typical blister packs are shown in Figure 13.12. Various assembly and sealing methods can be used, e.g.:

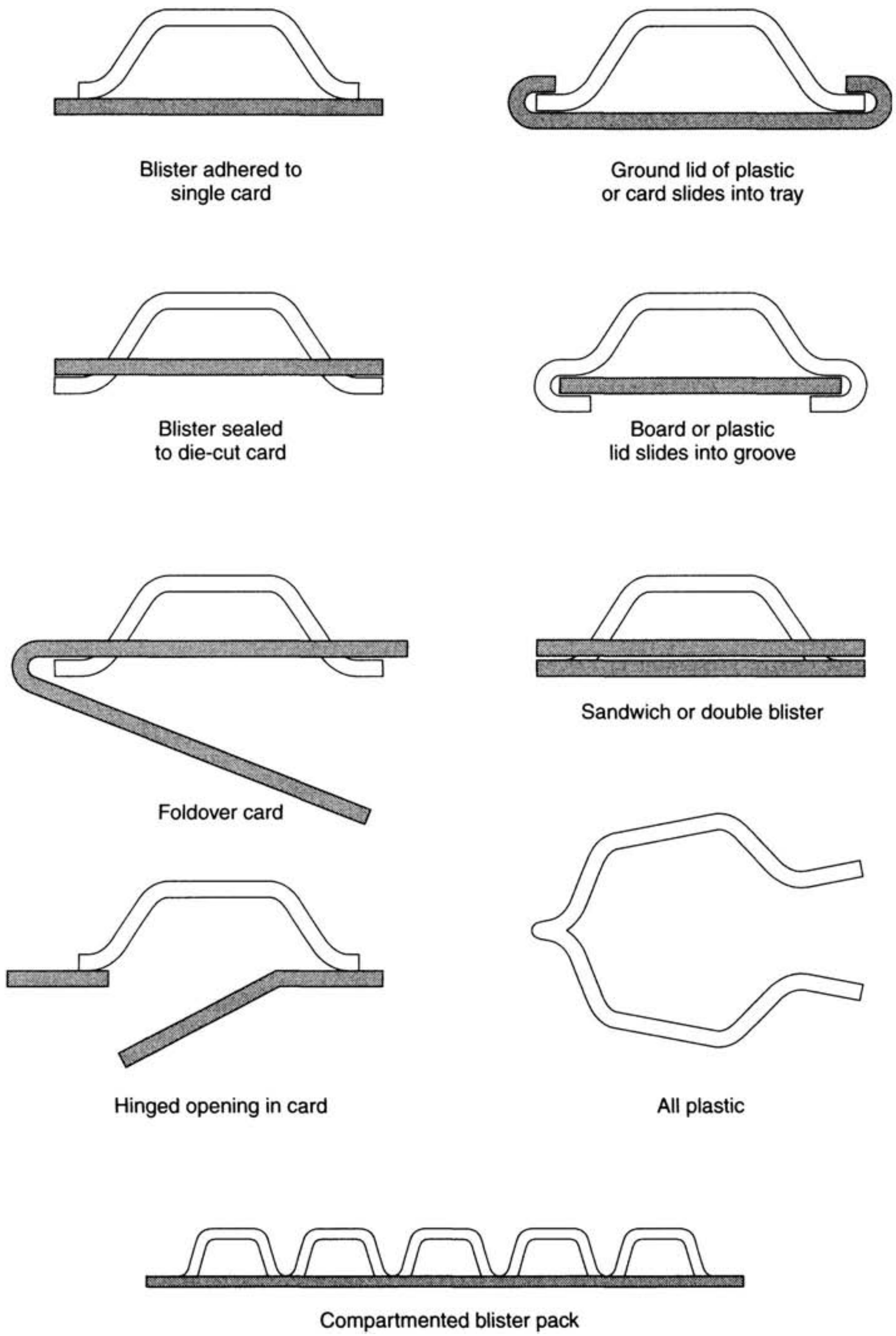

Figure 13.12 Thermoformed card pack constructions

- heat seal through lid (board, laminate or label)
- heat seal through plastic
- heat seal through plastic and lid
- blister locked between cards by adhesive or staples
- folded card—plus heat seal, adhesive or staples
- blister locked to card by label.

Blister packs offer good display advantage where clarity is essential. Punched hole systems provide for hanging cards.

Blister trays are particularly useful where several items are involved in the medication, i.e. lyophilised product plus water for injection.

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Awareness of the advances in technology are often correlated through national and international conferences and the subsequential technical papers. In 1998–9 a series of Blister-pack 2 day conferences were run in Cologne, Germany and Newark, USA to review and update blister packaging. Presentations were made by people well recognised within the industry and a list of papers, purchasable fron The Packaging Group Inc (US), 70 Valley Forge Drive, East Brunswick, New Jersey 08816, USA. is given below:-

September 23rd—24th 1998

1. A global view of Blister Packaging for Pharmaceuticals
   Stephanie Batz
   Kalle Pentaplast Gmbh, Germany
2. Why use Blisters?
   Dieter Janek ®
   Managing Director, Horn and Noack, Division of Romaco Gmbh, Germany
3. Alfoil Polymer High Barrier Films (PVDC)
   Monique Roulin, Manager Technical Sales
   Aerni Leuch AG(AEL) Switzerland
4. ACI-AR High Barrier Films
   Mike Phillips
   Allied Signal Speciality Films (UK)

5. Cold Formed Aluminium Foil and lidding concepts.
   DR Erwin Pasbrig ®
   Development Technical Application—Pharma
   Lawson Marden Singen Gmbh, Germany
6. Replacing PVC—the alternatives
   Dieter Laube
   PCI Allpack Gmbh Germany
7. Evaluation and Shelf life testing with reference to the ICH Guidelines
   Mervyn Frederick, Head of Packaging Development,
   NV Organon, Akso Nobel (Holland)
8. Heat Sealing—rotary v platen ®
   Dieter Janek, Magaging Director
   Horn and Noack, Division of Romaco
   Gmbh, Germany
9. Non destructive leak testing of blisters.
   Paul Sharpe Business Manager
   AI Qualitek (UK)
10. Preventing recalls—on line inspection and printing
    John Mackenzie, Sales Manager
    Romaco (UK) Ltd
11. Machinery—future trends in blister packaging
    Marielli Criscuolo, Marketing Research Manager
    IMA, Pharmaceurical Division. Italy
12. Machinery—flexibility of blister lines,
    Markus Mazger, Product Manager, Pharmaceuticals
    Robert Bosch, Gmbh Germany
13. Machinery—Thermoforming Machine and Lines-Latest
    Technology. Advanced Forming Technology (AFT)
    Dirk Briskorn, Managing Director
    Klockner Hansell, Gmbh, Germany
14. Machinery—lister packs for Clinical Trial supplies—
    Special equipment.
    Matthew Vogelsanger, Managing Director,
    Fleximation AG—Switzerland
15. Blister Packaging and Child Resistance—is there a future? Colin Scaife
    CE Packaging Partnership
16. Strip—a substitute for blisters.
    Paper by Siebler Verpackungstechnic
    Presented by Dixie Dean (Consultant)
17. The role of the Contract Packer
    Mr. G Russell, Sales & Marketing
    PCI (Unipack) UK
18. Mobile Blister Machines, and deblistering—The neglected aspects!
    A Ernest Parker, Managing Director
    Sepa Products (Ireland) Ltd
19. Liquids and semi liquids in blisters ®
    Werner Basler, Systems Manager
    Unifil (International) Ltd
    Krcuzlingen—Switzerland
20. The contract Packaging of Clinical Trial Supplies
    Mike O'Donnell
    Consultant acting on behalf of PCI—Unipack UK
21. Improving Barrier Properties by coating, coextrusion, lamination, metallisation and overwrapping
    Dixie Dean (Consultant)
22. Future trends in Pharmaceutical Blister Packaging—an industry's point of view Mervyn Frederick—
    Head of Pharmaceutical Development

NV. Organon, Akso Nobel (Holland)

A similar conference was run in the USA April 20th–21st 1999. The speakers from the above event ® also presented the same papers. Different papers were produced by the following:

1) Evaluation and shelf-life testing—the influence of the ICH Guidelines
   D A Dean (Consultant)
2) What's the Future for the Pharmaceutical
   Blister Packager?
   Dixie A Dean (Consultant)
3) Child Resitant Blister Packaging. US Regulations and Test Methods
   Dr Suzanne Barone
   Prof. Manager for Poison Prevention—US
   Consumer Products Safety Commision
4) Aclar High Barrier Laminations—update and New Structure
   Perry Fan General Manager
   Rigid Films, Tech-Plex-Inc
5) Archieving longer term stability with PVC/PVDC
   David Faghani, Marketing Sales Manager
   Perlen Converting AG, US Region
6) Blisters and Clinical Trials: Recent developments
   Mike O'Donnell—Consultant
7) Integrated Inspection on Packaging Lines
   Geert Coudizer
   CEO, Covan Vision Systems (Belgium)
8) Blisters and Contract Packaging—A Happy Marriage
   Renard P Jackson, Exc V P Sales and Marketing
   PCI USA
9) Blister Packaging—New Innovation in Child Resistance
   Thomas Toren
   Consulting Engineer, Australia