

PLASTICS—AN INTRODUCTION

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Historical background

The wider acceptance of plastics as a basic packaging material took a positive step forward in the early 1950s, with the entry of polyethylene into full commercial use. Until that time the use of plastic in packaging had been mainly limited to certain thermosetting resins used for closures and a few containers (for menthol cones, shaving sticks, etc.). Reference to the history of plastics indicates that the knowledge of plastics was much further advanced in those early times than most packaging people would expect. Even today this state of affairs can still exist. Although specific substances, now recognised under the term plastics, can be identified as far back as the early nineteenth century, the name 'plastics' did not come into general use until the mid-1920s. These early plastic discoveries were generally scientific in nature without any insight into the possible applications. Phenol formaldehyde, for example, although a chemical entity in 1840, was not exploited until around 1916 when it became synonymous with the word 'Bakelite'. Nitrocellulose, which subsequently became known as 'celluloid', was also discovered in the nineteenth century and was exploited far more quickly. It became one of the first commercially accepted plastics when produced by the Hyatt Brothers in the USA around 1870. Celluloid subsequently found use for numerous household articles (brush backs, mirror holders, trays, etc.).

The objectives of this chapter are to provide a basic knowledge of plastic materials, their characteristics which are likely to appertain to pharmaceuticals and the processes by which they are converted into packaging materials.

What are plastics?

Plastics may be defined as any group of substances, of natural or synthetic origins, consisting chiefly of polymers of high molecular weight, that can be moulded into a shape or form by heat and pressure. They usually consist of large molecules of organic materials which are based on certain building block molecules referred to as monomers. When these monomers, which are relatively small molecules, undergo a process known as polymerisation, a plastic or long chain polymer is produced. This process of polymerisation may involve various chemicals which assist the process, such as accelerators, initiators, solvents and catalysts, and as a result are present to some small degree in the plastic produced. These, if found in the plastic after polymerisation, are generally known as process residues. Plastics may also incorporate processing aids (usually added to assist a process) and additives which modify the plastic chemically or physically in some way. Polymers can broadly be divided into two categories: thermosetting plastics and thermoplastics. Certain plastics may involve high pressure (LDPE) or low pressure (LLDPE, HDPE) processes.

Polymerisation

Plastics are basically produced by the process of polymerisation, which may be either addition or condensation polymerisation (see below)

Structure

Three structures are found—linear, linear branched, and cross-linked.

Linear

Linear polymer chains arise where the monomers join together in long chains with few or a limited number of side chains. These chains may, however, be in a twisted and tangled formation giving an amorphous type polymer or in a more orderly layout to give a crystalline structure. When the chains are made from a single (identical) repeating unit, a homopolymer is

produced. If there are two separate (different) repeating units (monomers), a copolymer is formed with either a random or a block structure.

Random: A+A+B+A+B+A+A+A etc

Block: A+A+A+B+A+A+A+B etc

Branched

These are again long chain type polymers with far more side chain branches. These usually occur randomly, producing a more open structure which will be reflected in certain physical and physical-chemical properties. Under selected conditions the repeating unit B may be 'grafted' onto the linear chain A. This formation is called a 'graft copolymer', i.e.

Cross-linked

Cross-linkage consists of joints between chains which occur in three dimensions. Cross-linkage usually again is reflected in physical properties, increasing, for example, polymer rigidity. In general, thermoplastic materials have linear and branched chains whereas thermosets are cross-linked.

Most polymers exhibit stereoisomerism, hence may appear in three forms:

- atactic, a random arrangement of the unsymmetrical groups
- isotactic, a structure where all groups are lined on the same side of the backbone chain
- syndiotactic, a structure where the placement of each group alternates on either side of the backbone chain.

Reference to the amorphous or crystalline nature of plastic has already been made. Crystallinity is supported by a regular chain structure whereas amorphous materials are irregular. Few polymers are, however, 100% crystalline or amorphous; frequently 'crystallite' or 'spherulite' areas of crystallinity are found in an amorphous background. Stretching a polymer by orientation increases the degree of molecular alignment, particularly with amorphous materials. Crystalline materials usually melt before a polymer degrades, hence have a melting point (T_m).

The presence of crystalline materials has a strong influence on their properties, e.g. polymer chains pack more tightly together, hence have a higher density, as shown by LDPE (60–65% crystalline), HDPE (90–95% crystalline), with densities of, say, 0.915 and 0.965 respectively.

General properties

Amorphous materials give good clarity, transparency, hardness with possible brittleness, are usually more permeable to gases and moisture and are less inert. Crystalline materials are opaque or translucent, more flexible, with low permeability to gases and moisture and are more inert.

Amorphous materials can be found as hard glassy plastics (polystyrene) or can be soft, flexible and rubbery (polyisoprene). This means that there is a temperature range where an amorphous material is in a glassy state and above which it is rubbery. This temperature is known as the glass-transition temperature T_g . However, a truly amorphous material cannot have a crystalline melting point (T_m). Crystalline materials (usually an amorphous—crystalline mixture) can have a T_g —in the case of polyethylene this is around -85°C .

For a specific grade of polyester, T_m is 267°C while T_g is 69°C .

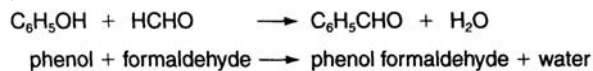
Thermoset polymers

These are polymers produced by a polymerisation process involving a curing or vulcanisation stage during which the material becomes 'set' to a permanent state by heat and pressure. Further heating leads to the decomposition of the plastic. Thermosets usually contain additional fillers and reinforcing agents to obtain the best properties. Examples of thermoset resins include phenolics, melamine, urea, alkyds, epoxies, certain polyesters and polyurethanes, and are predominantly cross-linked polymers. Typical packaging applications include closures, small cases (as one time used for menthol cones), protective lacquers and enamels (as applied internally and externally to metal containers) and a range of adhesive systems. Thermosetting contact materials, such as lacquers, will probably receive more attention in the future. This will involve more effective compatibility studies and the use of the newer surface analysis techniques.

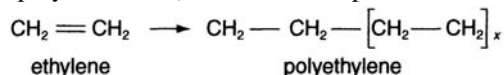
Thermoplastics

Thermoplastics are heat softening materials which can be repeatedly heated, made mobile and then reset to a solid state by cooling. Under conditions of fabrication these materials can be moulded (shaped in a mould) by temperature and pressure. Examples of thermoplastics are more numerous than thermosets, e.g. polyethylene, polyvinylchloride, polystyrene, polypropylene, nylon, polyester, polyvinylidene chloride, polycarbonate. Thermoplastics may be further divided into homopolymers which involve one type of monomer, e.g. ethylene polymerised to polyethylene, and copolymers, terpolymers, etc., which involve two or more monomers of different chemical substances. Polymerisation producing thermoplastics and thermoset materials usually follows two basic chemical mechanisms, i.e. condensation and addition polymerisation.

Condensation polymerisation (step reaction polymerisation), is where monomers combine with the loss of some smaller molecules in the process, e.g. water:



Addition polymerisation (chain reaction polymerisation) consists of simple addition



without the elimination of any smaller molecules, e.g.

where x is a large number, up to tens of thousands.

The polymer molecules may occur as long unbranched straight chains (linear polymers), branched chains, or a three-dimensional lattice work where the branches link the main chains together (i.e. cross-linked polymers). Properties of plastic vary according to their form of molecular structure. Materials may also be amorphous or crystalline, where the latter are generally less permeable. The degree of crystallinity is usually established by X-ray diffraction studies.

From here on this chapter expands the properties of various plastics, the means by which certain physical and chemical characteristics can be identified and quantified, together with the constituents which may be 'found' in a plastic. The converting processes may contribute other factors relevant to the selection and clearance of a plastic pack. The chapter concludes by reference to sterilisation methods and references. (The next chapter places particular emphasis on the 'clearance of a plastic pack', and should be read in conjunction with this section.)

It could or perhaps should be concluded from this background that the majority of pharmaceutical products could, with the rapidly expanding technology of today, be packed in one of the plastics available. In the ultimate choice the question may not be what is the ideal plastic to choose but what is the best combination of materials. This may include several layers of different plastics (e.g. coextrusions), laminations, coated plastics, or a low-cost material enclosed in one or more 'overwraps'.

Currently the greater part of usage lies with the economic five. These consist of the polyethylenes, polypropylenes, polyvinylchlorides and polystyrenes, all at similar prices per tonne, and polyester, which although nearly double the price of the other four offers special properties, usually in thinner sections etc.

The main thermosetting and thermoplastic materials are now briefly described.

Thermosets

Urea formaldehyde (UF)

UF is made by the condensation polymerisation of urea and formaldehyde. Although it has been widely used for closures (mainly in pastel shades), use is now in decline due to wadless thermoplastic systems. Density 1.47–1.52.

Phenol formaldehyde (originally Bakelite) (PF)

PF is made by the condensation polymerisation of phenol and formaldehyde. Due to the volatile and toxic/irritant nature of formaldehyde, this is usually 'fixed' with ammonia giving hexamine. Polymerisation of hexamine and phenol not only produces phenol formaldehyde but may release residues of phenol, formaldehyde or ammonia. In certain cases some residues may remain in the moulding and be released into the product. As with UF, PF is mainly used for closures but due to the fact that the material is naturally dark, it is used for dark or deep colours. PF is generally more resistant to heat and moisture than UF. Both UF and PF are used with a range of fillers, e.g. wood flour, synthetic fibre. Density 1.25–1.45. General pharmaceutical applications have now reduced.

Melamine formaldehyde (MF)

Although offering better resistance to water and heat, it is considerably more expensive than UF and PF and has found few packaging applications.

Epoxy resins (epoxides)

Epoxy resins are polymers offering higher performance than most other thermosets. Their main packaging applications are for protective lacquers.

Polyurethanes (PURs)

Thermosetting polyurethanes are used as adhesives and to a limited extent as coatings or lacquers. They can be found as esters and ethers.

Polyesters

Polyester thermosetting resins, which are made by the polymerisation of dibasic acids with poly-functional alcohols, find uses in chemical storage tanks and chemical piping rather than any direct pharmaceutical applications. Polyester thermosets offer high general strength, particularly when reinforced with glass fibre (GRP), excellent dimensional stability and good temperature resistance for temperatures up to 200°C. Recently metal tube enamels have used polyester-based resins.

Thermoset resins are normally moulded by compression, compression transfer or, more recently, injection moulding. Two-part resin systems are used for adhesives, coatings and lacquers. Pharmaceutical applications include closures (reducing), adhesives in laminations, protective lacquers, and enamels.

Thermoplastics

The five most economical plastics are the polyethylenes (ultra low, low, linear low, medium and high density), polypropylenes (homopolymer and copolymer), polyesters, polystyrenes and polyvinylchlorides (unplasticised and plasticised) and as a result these are the materials most widely used by the pharmaceutical industry. Polyethylene and polypropylene may also be grouped under 'olefins'. The list of plastics which follows is given alphabetically rather than in any order of use.

Acrylonitrile butadiene styrene (ABS)

ABS is composed of acrylonitrile, butadiene rubber and styrene and is therefore part of the styrene group. Styrene, basically a glossy, rigid, brittle material, becomes tougher and more flexible with the addition of the other constituents. ABS produces a high gloss finish which is particularly useful for injection moulded parts for devices and similar ancillary components. The acrylonitrile monomer was under a toxicity cloud following tests which established possible carcinogenic relationships. The primary danger is related to the polymerisation manufacturing plants, and steps have been taken to reduce significantly the free monomer level. Acrylonitrile levels of less than 0.1 ppm are now generally considered acceptable and safe.

Acetal polyoxymethylene (POM) (Delrin, Kemetal—trade names)

Acetals are obtained from the polymerisation of formaldehyde, and this is basically an engineering plastic with high stiffness, tensile strength and good fatigue endurance. Usage usually lies with devices, aerosol valves and similar engineering components. Being a polymerisation of formaldehyde, residues may have to be checked if grades and moulding conditions are not correctly selected. Copolymers are also available. The density of POM is approximately 1.41. POM is less hygroscopic than most nylons and provided it is correctly stored, it does not need pre-drying.

The acrylics

Polymethylmethacrylate (PMMA), found under the trade names of Perspex, Plexiglas, Lucite, etc., is one of the better known polymers in the acrylic group. PMMA is hard, rigid, with good clarity (92% light transmission equivalent to glass), good weather resistance and good dimensional stability. In common with polystyrene, PMMA will surface craze in contact with certain chemicals. PMMA has a density of 1.18. Acrylates are being increasingly used in adhesive systems and are found as a major constituent in heat sealants and in self-adhesive bases. PMMA has also found wide usage in hard contact lenses.

The cellulose

This group incorporates some of the earliest discovered plastics, which are detailed individually below.

Cellulose acetate (CA)

Cellulose acetate is a clear but highly permeable plastic made by a similar type of process as used for regenerated cellulose. Cotton fibres are acetylated using glacial acetic acid and acetic anhydride, with sulphuric acid as a catalyst, to give cellulose triacetate which is then hydrolysed. The precipitated acetate is dissolved in a solvent, plasticised and made into a film by either solvent casting or slot die extrusion. Dimethyl phthalate may be added as a typical plasticiser. Cellulose acetate has a relatively high permeability to gases and moisture. It is therefore used as a film which 'breathes', especially when highly plasticised. It also has high clarity, good resistance to oils and can be moulded by most conventional processes including thermoforming.

Cellulose propionate (CAP) and cellulose acetate butyrate (CAB)

Both CAP and CAB have superior properties to plain acetate, particularly with reference to toughness and impact strength. Their main uses are as engineering plastics and occasionally for pharmaceutical devices and administration aids. Hard, gas-permeable contact lenses may be made from CAB.

Regenerated cellulose group

Regenerated cellulose is included under plastics although it is a derivative of wood pulp, which is first reacted with sodium hydroxide and then dissolved in carbon disulphide. After maturing, it is converted into a film or sheet by slot extrusion into an acid bath, followed by washing to remove the acid, and then dried. Most cellulose films contain an humectant such as glycerol or ethylene glycol which reacts to humidity changes. Various coatings are applied to confer heat sealability and resistance to moisture permeation. The coatings include nitrocellulose, polyvinylidene chloride, polyethylene, etc. Uncoated regenerated cellulose film is very hygroscopic, highly permeable to water and has poor dimensional stability. It is otherwise a strong, flexible, transparent film with good grease resistance. Coated films are mainly used as transparent overwraps, strip packs and as an outer ply in laminations. Trade names such as Cellophane and Rayophane are widely used.

Cellulose nitrate or nitrocellulose (celluloid or xylonite)

This is made by the reaction of strong nitric acid with cellulose. Today it is mainly used as a coating to provide heatsealing with general barrier properties. It seals at a lower temperature than polyvinylidene chloride, but for the same coating weight offers a considerably inferior barrier. It is highly flammable.

Ethylene-based polymers

Ethylene-vinyl acetate (EVA)

EVA is a copolymer of ethylene and vinyl acetate which can have certain properties changed according to the proportion of each monomer. EVAs are soft, flexible compounds with high elongation and high impact strength even down to low temperatures. They are widely used in conjunction with LDPE and PP to increase flexibility and as an aid to heatsealing. EVA is also the basis for certain hot melts and is used as a compound lining in closures.

Ethylene vinyl alcohol copolymer (EVAL or EVOH)

EVOH is now widely offered as an extrusion ply for coextruded laminations, where it provides a good bond, acting as a good carrier for other plies and is increasingly popular as an excellent oxygen barrier. It has to be protected from moisture absorption since this significantly lowers its otherwise excellent barrier properties.

Ethylene acid copolymers

Ethylene acid polymer is obtained by the copolymerisation of ethylene with either acrylic or methacrylic acid. These copolymers are somewhat similar to LDPE and are found as ethylene acrylic acid (EAA) and ethylene methacrylic acid (EMA). Both are used in various packaging applications, i.e. flexible packaging, adhesive laminating, hot melts, and heat seal coatings.

Ethylene-ethyl acrylate (EEA)

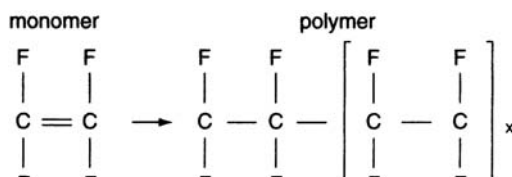
Ethylene-ethyl acrylate copolymers can produce very tough flexible materials and can vary from very rubbery low temperature melting products to polyethylene-like materials. EEA is used as a hot melt adhesive, for disposable gloves, tubing and sheeting.

The fluoroplastics

The fluoroplastics are a relatively pricey group which are generally more inert than most other plastics.

Polytetrafluoroethylene (PTFE)

PTFE (trade name Teflon, Fluon etc.) is probably the most well known of the fluoroplastics. It is, however, a relatively difficult material to process. The polymer is linear, with a very high molecular weight, a high density (2.2) and a high melting point (327 °C).



It is used as a coating for heat sealing jaws, as a low friction surface and as 'inert' coating for rubber stoppers.

Polymonochlorotrifluoroethylene (PCTFE) (trade name Aclar)

PCTFE is one of the most inert plastics, with the lowest permeability of all plastics to moisture. It has, however, higher permeabilities to O₂, N₂ and CO₂ than PVdC. The basic monomer, chlorofluoroethylene C₂ClF₃, has certain toxic properties. It is about the most expensive plastic (over £25,000 per tonne) and has so far only been used in packaging as a thin layer (laminated to PVC) for blister packing. Three types are in use: 22A, 33C and 88A. The first is usually used at 37 μm (on PVC) with a WVP figure of around 0.030g/100 in²/24 h at 38°C 90% RH. These all are copolymers. 33C is lower in cost because of higher yields but is far more difficult to form. 33C is used laminated to PVC at 18.75 μm and 50 μm; moisture permeation for 33C compared with earlier figure for 22A is 0.030g and 0.015g respectively for 38°C 90% RH, i.e. it has a similar permeability to 22A at approximately half the thickness. New homopolymers R_x 160, ultR_x 2000 and 3000, SupR_x 900 offer certain advantages over the copolymers, including lower costs.

Fluorinated ethylene propylene (FEP)

Has similar properties to PTFE but processes more easily. It has a crystalline melting point around 290°C.

Ethylene tetrafluoroethylene (ETFE)

This does not have the same wide temperature range as PTFE, but is easier to mould.

Ionomers (trade name Surlyn)

This group is relatively new to plastics, being available since around 1965. Ionomers are so named because of the presence of ionised carboxyl groups which provide a crosslinking effect on the molecular chain and are based on metallic salts of ethylene/methacrylic acid copolymers. The physical properties are somewhat similar to LDPE, with a lower melting point (around 70–80°C) and a relatively broad heat sealing range. Surlyn is therefore used as a heat sealing ply since it seals well in the presence of both powders and liquids (i.e. contaminated seals). It can therefore be sealed at higher speeds and with greater

security than most other heat sealants. It is more expensive than low density polyethylene, but as a heat seal ply it can be effectively used at approximately two-thirds the thickness of polyethylene (LDPE). Ionomers have excellent abrasion resistance and good resistance to puncture and impact. The side chain metals include Ca, Zn, Mg.

Liquid crystal polymers (LCPs)

LCPs are a group of aromatic copolyester polymers with high physical performance properties, high levels of inertness, low flammability with excellent high temperature resistance. Use for pharmaceuticals is predicted, possibly blended with PE or PET.

Methylpentene (TPX) polymers (ICI)—poly(4-methylpentene-1)

TPX is another relatively new plastic which was commercialised in 1968. It is an olefinbased resin with the lowest density of the plastics (0.83) but a high melting point of 240°C, which makes it a high-temperature-resistant plastic. Methylpentene can be a crystal clear or an opaque plastic. It is highly permeable to moisture and gases.

Nitrile or acrylonitrile polymers

Copolymers with a high acrylonitrile content (trade names Barex (Vistron) and Lopac (Monsanto)) have interesting properties. With a specific gravity of 1.15 these resins are glass clear, offer excellent impact resistance even at low temperatures, have good rigidity and offer high barrier to gases, especially oxygen and carbon dioxide. For instance, their oxygen transmission is approximately eight times better than PVC, 250 times better than HDPE and 300 times better than PP. Water transmission rates are higher than for PVC, e.g.

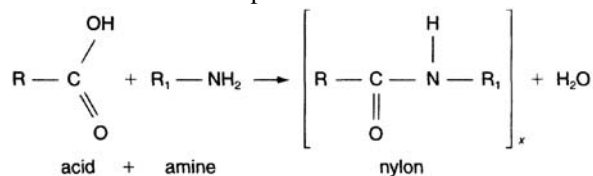
HDPE (1): PP (1.2): PVC (7.5): Barex (12.5): Styrene (40).

The material therefore readily absorbs moisture and must be effectively dried prior to moulding, otherwise a hazy or milky appearance may result. Polyacrylonitriles have a relatively low heat distortion temperature (around 75°C), hence they have limitations for products requiring a hot fill. The material is suitable for thermoforming operations but its relatively high moisture permeation is likely to restrict ultimate usage. The presence of acrylonitrile residues also placed the material under a cloud with the FDA, but use is now accepted provided acrylonitrile monomer does not exceed 0.1 ppm. Nitrile copolymers are usually copolymerised with methyl acrylate together with small quantities of butadiene/acrylonitrile rubbers.

The nylons (polyamides) (PA)

Nylon is the general name for the polyamide polymers. They cover a range of types, i.e. type 6, type 6:6, type 6:10, type 11 and type 12. The broad properties of the polyamides include low friction (good bearing properties), toughness, high fatigue resistance, high impact resistance, and good solvent resistance to aromatic hydrocarbons. Nylons 6 and 6:6, because of their lower price, tend to be the most used but have the highest absorption of moisture which tends to act as a plasticiser. The polymers are formed by a condensation reaction between amine groups and carboxylic acid groups to give an acid-basic type linkage known as amides. The nylons are classified by the number of carbon atoms in the diamine, followed by the number of carbon atoms in the diacid or by just the number of carbon atoms in the polymer chain (reference the monomer molecule).

The reaction acid+amine or diamine+diacid can be expressed as follows:



Diamine nylons

amine monomer + acid monomer
 Nylon 6 : 6 = hexamethylene diamine (6) + adipic acid (6)
 Nylon 6 : 10 = hexamethylene diamine (6) + sebacic acid (10)
 (number of carbon atoms in brackets)

The above are therefore copolymers. The homopolymer nylons are made from the following:

nylon 6 = amino caproic acid (6)

nylon 11 = amino undecanoic acid (11)

nylon 12 = amino dodecanoic acid (12)

Nylons have relatively high melting points and can be steam autoclaved. Nylons can be injection moulded, blow moulded or made into sheet or film, and have a density range of 1.14–1.16. Multi-ply materials are employed for their oxygen barrier properties.

Polyamide—imide (PAI)

Polyamide-imide represents another group of high-temperature engineering polymers, with good dimensional stability, impact and chemical resistance.

Polyaryletherketone

This is a relatively new crystalline plastic with a high melting point of 334°C. It has good abrasion resistance, with good chemical and solvent resistance.

Polybutylene (PB) and polyisobutylene (PIB)

Polybutylene is another new member of the polyolefin group, being similar to polyethylene but exhibiting better tensile strength. It is frequently used blended with polyethylene or polypropylene to modify the properties of films, i.e. to give a controllable peelable seal, and a good future as copolymers is predicted.

Polycarbonate (PC)

Polycarbonate is a copolymer of bisphenol A and phosgene or diphenyl carbonate. It is a transparent highly crystalline polymer with good mechanical properties, e.g. high impact strength plus high temperature resistance and fairly low moisture absorption. It is, however, attacked by alkalis and aromatic hydrocarbons. Certain reactions are similar to stress cracking. PC has a density of 1.2 with a moulding shrinkage of 0.5%. Permeation to moisture, however, is only fair. Growth in the medical area, particularly in coextrusion film applications, is predicted.

The polyolefins

The olefin group covers the following (density is shown on the right):

- | | |
|--|-------------|
| • ultra and very low density polyethylene | 0.89–0.915 |
| • low density polyethylene (LDPE) | 0.91–0.925 |
| • (and linear low density) (LLDPE) | 0.915–0.930 |
| • medium density polyethylene (MDPE) | 0.926–0.940 |
| • high density polyethylene (HDPE) | 0.940–0.965 |
| • polypropylene (homopolymer/copolymer) (PP) | 0.900–0.910 |

There are also ultra high molecular weight grades of HDPE.

Low density polyethylene (LDPE)

Low density polyethylene material has branched chains and limited crystallinity, which lead to an open structure and the low density. It is particularly soft and flexible, transparent to translucent, has good impact resistance and relatively low melting points, which give good heat sealability. Most LDPEs are made by a high pressure polymerisation process starting from ethylene gas. The proportion of crystallinity to amorphous is around 3:2 (i.e. 60–65% crystalline). Recently new linear polyethylene copolymers of 0.89–0.91 (ultra or very low densities) have been developed. Special antioxidant free grades are available for pharmaceutical applications.

Medium density polyethylene (MDPE)

As density increases, materials change in both physical and chemical properties, becoming more rigid, less impact-resistant, less translucent, stronger, less flexible with an increase in melt temperature. There is also a continuing improvement in moisture and gas permeability, chemical and oil resistance, absorbency to chemicals (e.g. preservatives), etc. There is a reduction in branching and an increase in crystallinity.

High density polyethylene (HDPE)

HDPE is the most crystalline material (around 95%) and virtually free of branching and as a result has the best chemical properties, i.e. best resistance and lowest permeabilities. It is also a relatively rigid, tough material with the lowest clarity. Extra high molecular weight (HMW and UHMW) grades find specialised uses, i.e. 25 l containers and larger, due to high shock resistance and good inertness.

HDPE exists as both a homopolymer and a copolymer with higher ethylene olefins. The latter offers properties which lie between low and high density, with typical densities of 0.945–0.950. Copolymers have found wide usage for extrusion blow, injection blow and injection moulding. They are, however, generally classified under HDPE. Virtually all high density polyethylenes contain an antioxidant.

Polyethylenes generally have a high coefficient of thermal expansion and suffer increasing vulnerability towards environmental stress cracking (ESC). LDPE when under stress in contact with certain chemicals, categorised as stress cracking agents, can lead to stress cracking. These agents include detergents, wetting agents, certain hydrocarbons, volatile oils, soaps, etc. Shrinkage is high with the polyethylenes, e.g. 1.5–2.0% (LDPE). The likely variables associated with the polyethylene are chain length, antioxidant, regrind, catalytic residues, filler, antistatics, lubricants, and slip additives. Tyvek (trade name) is a spun bonded fibrous sheet of HDPE with controlled porosity which has found many pharmaceutical/hospital applications for sterile components and instruments. The fluoride treatment of HDPE is widely used to further improve its resistance to organic chemicals (e.g. solvents).

Linear low density polyethylene (LLDPE)

LLDPE is a relatively new material in terms of commercial exploitation which is receiving enormous interest, particularly as a film material where it is replacing many conventional LDPE applications. Some of the more commercially viable applications lie outside the pharmaceutical industry. There is, however, every indication that LLDPE will also find pharmaceutical usages. More immediate applications are seen with extruded film, with long-term usage in other areas where grades are already available for injection moulding, rotational moulding and cast film. LLDPE is being used for plastic tubes and as a heat seal ply where it provides high seal strength. The main advantage of LLDPE is that it can be made at lower gauges while having similar physical strength to LDPE. It is made by a low-pressure Ziegler-Natta catalytic process.

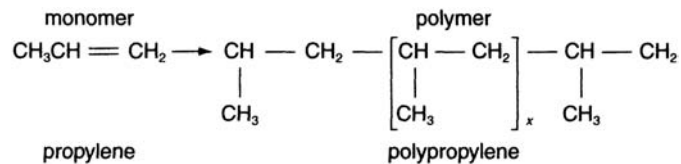
LLDPEs are usually referred to as comonomers and copolymers, where mixtures of higher olefins, butene, hexene, octene, etc. are used. Mixtures of LDPE, MDPE, HDPE, and ethylene vinyl acetate, etc. are fighting the introduction of LLDPE. LLDPE can be produced in grades which have good clarity.

Expanded low density polyethylene (EPE)

Expanded low density polyethylene is found as either a cross-linked foam or a noncross-linked foam, with significant developments being initiated in Japan. It has been offered as a replacement moulding material for closure wadding either with or without an additional facing. When used as a wadding material, densities can be varied to give different levels of compression.

Polypropylene (PP)

Polypropylene is somewhat similar to HDPE in general properties. It exists as a homopolymer and a copolymer with ethylene and other hydrocarbons. It can also be blended with polyisobutylene. PP is one of the lowest density plastics, translucent to natural milky white with a highly crystalline structure. PP homopolymer has poor low-temperature resistance but this has largely been overcome by copolymerisation with ethylene.



Copolymerisation with ethylene increases clarity and improves impact strength, particularly at low temperatures, while still providing good resistance to chemicals, abrasion and good barrier properties to water vapour transmission. PP made by certain polymerisation routes may contain trace mineral or solvent materials, i.e. up to 300 ppm, which can be detected by smelling supplies of material in a bulk state. Grades with low levels of odour are now available and hence preferable for pharmaceutical products. Most PPs contain an antioxidant at 0.005% to 0.01%. Although PP shows better mould shrinkage than PE, it is still fairly high at approximately 2%. High temperatures and contact with copper can lead to rapid degradation. PP has high flexural strength, as demonstrated by integral hinge mouldings. When orientated, clear grades of PP can be achieved.

Polystyrene (PS or GPPS, general purpose polystyrene)

The monomer has chemical similarity to propylene in that the methyl (CH₃) groups are replaced by benzene rings. It is a clear rigid hard material with good tensile strength but is one of the more brittle plastics when dropped or flexed. PS is reasonably resistant to mineral oils, water and alkalis but soluble in hydrocarbon solvents, hence it can be solvent welded (plastic model kits). Polystyrene is fairly permeable to moisture and is not generally a suitable packaging material for pharmaceutical products. To improve the brittle characteristic, materials are frequently impact modified with rubber polymers, polybutadiene and styrene butadiene (SBR) by either blending or graft polymerisation. As a result the material shows lower rigidity, hardness, clarity, chemical resistance and higher permeability. These materials are identified as HIPS (high impact PS) or TPS (toughened PS). Styrene can also be copolymerised with acrylonitrile (SAN) and acrylonitrile and butadiene (ABS). Polystyrene is widely used as foam or expanded material (open or closed cell), mainly in either a cushioning or a thermal insulation role.

Polystyrene can be polymerised by foam processes, mass polymerisation, solution polymerisation, suspension polymerisation and emulsion polymerisation. Each contributes to the final characteristics of the plastics and the likely residues. A limit for styrene monomer may be imposed. Styrene can be readily analysed down to a 0.01% level. Polystyrene exhibits low shrinkage, hence is an excellent moulding material.

Styrene acrylonitrile (SAN)

This copolymer offers better resistance, improved impact strength and heat distortion over GP polystyrene. It is basically an engineering rather than a pharmaceutical plastic (e.g. devices).

Styrene-maleic anhydride (SMA)

SMA exists as copolymers and terpolymers with ABS. It is mainly used as an engineering plastic.

The polysulphones

Polysulphone

Polysulphone is another high-performance engineering plastic which has excellent mechanical properties up to 165°C. It has very good resistance to acids, alkalis, oils, greases and detergents, but is attacked by solvents such as ketones, aromatic hydrocarbon solvents and halogenated solvents. Certain polysulphones need annealing, rather like glass.

Poly ethersulph one

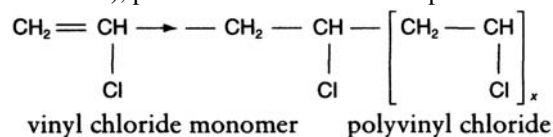
Basically similar to the above but with superior creep resistance at elevated temperatures, a higher heat distortion temperature and slightly better mechanical properties. Polyacrylsulphone is another engineering plastic.

The vinyl polymers

This group covers polyvinyl chloride (PVC), polyvinylidene chloride (PVdC), polyvinyl acetate and polyvinyl alcohol, each of which has packaging applications.

Polyvinylchloride (PVC)

PVC may be formed by the polymerisation of vinyl chloride emulsion under pressure, using a peroxide catalyst. Polyvinyl chloride is found as UPVC (unplasticised PVC), plasticised PVC or as an impact modified PVC.



Since PVCs show some deterioration or ageing under both normal or processing conditions, stabilisers are invariably added to improve stability. Rigid PVC used for blow moulding may have its impact resistance (resistance to drop tests) improved by incorporating an impact modifier such as methyl methacrylate butadiene styrene (MBS) at up to 15%. Thermoforming resins for films may also have impact modifiers (usually vinyl acetate) added as this increases the forming speed and lowers the forming temperature. However, modifiers may reduce chemical resistance and increase permeation.

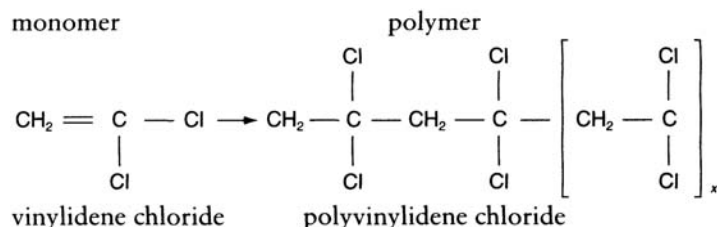
Plasticised PVC may sometimes seem a misnomer, as the plasticiser content can occasionally be greater than the PVC. Plasticisation also reduces chemical resistance and increases gas and moisture permeation. Typical plasticisers used include adipates, citrates, sebacates, phosphates and phthalates, e.g. di-iso-octyl adipate, acetyl-tri-n butylcitrate, di-octyl phthalate (DOP). Polymeric plasticisers and urethanes are also used. Plasticised PVCs are soft and very flexible (see IV bag usage).

The various stabilising systems used for PVC include organotins, i.e. octyl thio—tin complexes, calcium-zinc salts, barium, cadmium zinc salts, epoxidised materials, and a newer group, the estertins.

PVCs frequently require other constituents as part of the formulation to aid processing or to modify the plastic. Typical requirements for processing include lubricants (examples include amide wax and calcium stearate). Other impact modifiers include ABS, MBS, and ethylene vinyl acetate.

The factors to consider when PVC is used for general pharmaceutical applications include plasticisers, stabilisers, modifiers, monomer residues, regrind, lubricants, catalytic residues and chain length.

Polyvinylidene chloride (PVdC) (trade name Saran)

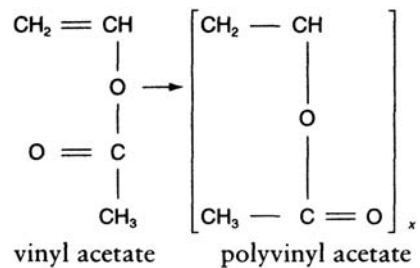


Straight polyvinylidene chloride is difficult to process, and Saran, the most widely used material (usually as a coating), consists of a copolymer of vinyl chloride or vinyl acetate and vinylidene chloride. These have excellent resistance to permeation by moisture and gases, very good chemical resistance plus toughness, flexibility and heat sealability. PVdC, although existing as a film, is more usually found as an aqueous dispersion or a solvent coating. Coating weights of 4 to 180 g/m² are found. It normally undergoes a maturing stage to achieve optimum barrier properties. Note that under certain long-term storage conditions PVdC may age and discolour.

Polyvinyl acetate (PVA)

Polyvinyl acetate polymer is generally a soft, flexible and low melting polymer. Copolymers with vinyl chloride combine the properties of the softness of PVA with the hardness of the former. PVA and copolymers find use as an adhesive (labelling paper to metal or plastic), and a heat sensitive base.

The chemical construction of PVA is as follows:



Polyvinyl alcohol

Polyvinyl alcohol, made by the polymerisation of vinyl alcohol, can produce a polymer which is fully water-soluble. Copolymers can also be produced with vinyl acetate. The material has excellent grease resistance and good gas barrier properties when dry. It has been used to produce water-soluble sachets.

Other vinyl plastics

Vinyl plastics also exist as plastisols, plastigels and organosols. These are usually based on PVC. A finely divided PVC powder dispersed in a plasticiser with a consistency of a cream to a thick paste is termed a plastisol. If this is thickened to a point where it will not run, then a plastigel is formed. An organosol is usually a suspension of PVC in a plasticiser with a volatile solvent which on evaporation gives a plastisol. This material is used as a dipping solution for closures and as a coating to glass (glass aerosols) and metals.

Polyesters (PET or PETP) (earlier use as Terylene (trade mark), polyethylene terephthalate)

Polyesters are formed by the interaction of acids and alcohols. The reaction is a condensation polymerisation process, producing an ester and releasing water. One of the most commonly used films (for tapes) is formed by the reaction of dimethylterephthalic acid and ethylene glycol to give polyethylene (glycol) terephthalate. PET films are particularly tough and very tear-resistant. Polyester has found wide application for 1–3 l stretch blown containers and pharmaceutical and cosmetic/toiletry usages as small mouldings.

Copolymers also exist such as PETG, offered by Eastman Plastics. The G indicates the use of a second glycol in the polymer, i.e. 1, 4-cyclohexane-dimethanol (CHDM). The resulting copolymer is an amorphous plastic which has a high degree of clarity, low haze, good resistance to acids, alkalis and many oils and excellent fragrance retention.

Polyethylene naphthalate (PEN)

PEN is a relatively recent resin based on the monomer dimethyl 2,6 naphthalate or naphthalene dicarboxylate (NDC). It is currently being commercialised as a copolymer or a blend with polyethylene terephthalate (PET), initially in order to raise the hot fill capabilities of the latter from around 75°C to 95°C or above. It is also alleged to provide improvements in moisture/gas barrier properties, give high levels of UV light exclusion and enable faster cycle times in the manufacture of bottles. PET/PEN combinations are believed to have good potential for the further replacement of glass by plastic, particularly as it is a very strong, clear material.

Rubber hydrochloride (Pliofilm—trade name)

Pliofilm was introduced by Goodyear in 1934 as the first non-cellulose transparent thermoplastic film. Until the arrival of polyethylene as a heat sealant, it was a popular heat sealing medium because of the relatively low temperature of sealing, the wide range of heat sealing temperature and the fact that a good seal could be obtained in the presence of contaminants, i.e. liquid- and powder-based products. Its use has rapidly declined, particularly in Europe, mainly because it ages fairly rapidly, becoming discoloured and increasingly brittle with time. LDPE, LLDPE and Surlyn are now utilised as heat sealing plies, particularly for pharmaceutical products.

The polyurethanes (PUR)

Polyurethanes are produced by the chemical action of di-isocyanate and polyol. The properties can be varied by the type of isocyanate used and the proportion of the two monomers. There are four main groups of classification for the thermoplastic groups of polyurethane, i.e. rigid foam, flexible foam, non-cellular and cellular polymers. Two main isocyanates used are toluene di-isocyanate (TDI) and diphenylmethane diisocyanate (MDI). Polyurethanes have limited application in the pharmaceutical or medical industries. Polyurethane is used as an adhesive for laminations (thermosetting material). Like thermosetting polyurethane, thermoplastic polyurethanes can be found as esters and ethers.

Polyetheretherketone (PEEK) and polyetherketone (PEK)

PEEK is a newer high-performance engineering plastic. It is strong, tough, rigid, with good chemical and water resistance, withstanding temperatures of 200°C. It has high crystallinity and excellent abrasion resistance. Possible use could be anticipated for sophisticated devices. (Trade name Victrex—ICI.)

Poly (para-xylene)—Parylene (trade name)

This polymer is of interest in that extremely thin films can be deposited when the vapour is condensed onto a cooled surface. Parylene film has been shown to offer a reasonable barrier to water vapour and a good barrier to essential oils. For example, LDPE coated with a thin film of parylene has substantially increased the retention of lemon oil which would otherwise have been lost rapidly. It also withstands high temperatures of around 220°C. It is, however, an expensive plastic and has been used as a coating onto rubber.

Polyimide

The polyimide molecule consists of heterocyclic rings bracketed by aromatic rings resulting in a stable, rigid construction which will withstand temperatures up to 600°C. As a result of this high temperature, films are made by a solvent process, which also involves the final stages of a reaction. It is an expensive material.

Synthetic rubbers (thermoplastic elastomers, TPE)

Since synthetic rubbers use materials common to polymers these are now listed:

- polyisoprenes (IR)
- polybutadiene (BR)
- polychloroprenes (CR) (Neoprene)—good oil resistance
- chlorinated polyethylene elastomers (CM)
- chlorosulphonated polyethylene elastomers (CSM)
- epichlorhydrin elastomers
- acrylonitrile butadiene
- styrene-butadiene rubber (SBR)
- polyacrylates (ACM)
- nitrile rubbers (NBR) Buna N
- ethylene/acrylic elastomers
- ethylene propylene diene terpolymers (EPDM)
- ethylene/propylene copolymers (EPM)
- butyl, chlorobutyl and bromobutyl rubber
- vinyl acetate/ethylene (VAE)
- polyurethane (TPU)
- silicone elastomers—inert, expensive but highly permeable, plus fairly high absorption levels (preservatives).

Newer materials are being developed which lie between plastics and elastomers. One of these is a polyether block amide copolymer developed by ATO Chemie, Europe, called Pebax. This is a tough, highly flexible material which by changing the ratio of ether and amide can have a wide balance between hardness and flexibility. Currently this material is relatively expensive (£3,000–£5,000 per tonne).

Natural rubber (NR) and synthetic rubber usually include a wider range of constituents than plastics. A broad list of these constituents is now given, since they bear similar names to those found in plastics: accelerators, activators, anti-staining agents, antioxidants, antiozonants, anti-blocking agents, emulsifiers, chemical and heat stabilisers, odorant inhibitors, extenders, fillers and reinforcing materials, peroxide decomposers, nickel quenching agents, plasticisers and softeners, radical terminators, UV screeners, tackifiers, lubricants (mould and internal), preservatives, dispersing agents and processing aids, retarders, vulcanising and curing agents.

Silicones

Silicones, particularly silicone rubber, have plastic-like properties and are based on inorganic alternating silicon—oxygen atoms with various organic side chains. These silicon elastomers, as they are known, although relatively inert, are readily permeable to moisture, gases, absorb preservatives, etc., but have high lubricity and slow ageing properties.

Alloys and resin blends

Alloys consist of a combination of two or more polymers where each is present above the 5% level. The alloy is usually made by mixing the resins in a molten state, resulting in a miscible or immiscible material which is devoid of a chemical-type reaction. These alloys have virtually an infinite number of resin combinations, for example, ABS may be alloyed with polycarbonate, polyvinylchloride, ethylene vinyl acetate, etc.

Data sheets: information and interpretation

In spite of the availability of many standard tests on plastics, it is sometimes difficult to compare materials in terms of their characteristics, performance, equivalency, etc., by simple reference to data sheets. It is therefore perhaps more important to understand the relevance of the tests compared with what is likely to be required in the practical performance of a plastic. For instance, a test for cure is an essential QC procedure for thermosetting plastics. This can be done by sectioning the item at its thickest point, boiling it in water for 10 min followed by a check on appearance and surface hardness (a soft surface indicates incorrect cure). General tests on plastics for pharmaceutical purposes include extractive and biological tests, chemical tests and selected physical tests. The biological tests and extractive procedures cover such aspects as acute toxicity, pyrogens, chemical extractives for non-volatile matter, heavy metals, ash, pH, reducible substances, ammonia, etc. Other tests cover stress cracking, impact, print adhesion, etc.

Chemical identity tests include IR and DSC. The list below provides a brief explanation of some of the standard test procedures applied to plastics. The main British Standard involving plastics is BS 2782, which is issued as a multiplicity of parts.

Density

Ref. ASTM D792. D1505–68 (kg/m^3). DIN 53479. Density is a relevant factor to container weight, hence cost and yield/cost in the case of film and sheet materials.

Melt flow index (MFI)

ASTM D1238; ISO R1133; DIN 53735. MFI is the amount of plastic as measured by flow through a given orifice size under standard conditions. It is a function of the molecular weight of the material and a particularly useful factor for the characterisation of polyolefins. High melt (flow) indicates lower molecular weights and low melt (flow), high molecular weights. Measured as dg/min or g per 10 min. Increase in melt flow index is related to:

- ease of moulding (increases)
- impact strength (decreases)
- stress cracking resistance (decreases)

but does not usually affect SG, tensile strength, softening point, rigidity, solvent absorption or electrical properties.

Standard International (SI) units

With standardisation on SI units in Europe and non-standardisation in other areas of the world, knowledge of conversion between units of measurements is essential, e.g.

Length

$$1 \text{ inch (in)} = 25.4 \text{ mm}$$

$$0.001 \text{ in} = 0.0254 \text{ mm}$$

Area

$$1 \text{ in}^2 = 6.45 \text{ cm}^2$$

$$1 \text{ cm}^2 = 0.155 \text{ in}^2$$

Mass

$$1 \text{ lb} = 0.445 \text{ kg}$$

$$1 \text{ kg} = 2.205 \text{ lb}$$

Density

$$1 \text{ g/cm}^3 = 1000 \text{ kg/m}^3$$

$$= 1 \text{ mg/mm}^3$$

Force and weight

All operate under the same units:

$$1 \text{ lb force (lbf)} = 4.448 \text{ newton (N)}$$

$$1 \text{ N} = 0.225 \text{ lbf}$$

$$1 \text{ kg force (kgf or kp)} = 9.81 \text{ N}$$

$$1 \text{ N} = 0.102 \text{ kgf}$$

$$1 \text{ tonne (t)} = 1000 \text{ kg} = \text{approx. } 1 \text{ ton (2,240 lb)}$$

Stress, strength, modulus and pressure

All operate under the same units:

$$1 \text{ lbf/in}^2 \text{ (or } 1 \text{ psi)} = 0.00689 \text{ MN/m}^2$$

$$1 \text{ MN/m}^2 = 145 \text{ psi}$$

$$1000 \text{ psi} = 7 \text{ MN/m}^2$$

$$1 \text{ kgf/cm}^2 = 0.0981 \text{ MN/m}^2 \text{ and } 1 \text{ MN/m}^2 = 10.2 \text{ kgf/cm}^2$$

$$1 \text{ N/mm}^2 = 1 \text{ MN/m}^2 = 1 \text{ MPa}$$

Pressure has a further unit, the bar

$$1 \text{ bar} = 10^5 \text{ N/m}^2 = 0.1 \text{ MPa}$$

Appearance—optical properties

Appearance of a plastic can be judged by a number of properties, i.e. gloss, or surface finish (a relationship of mould surface, moulding conditions, and material composition), haze, clarity, etc.

Gloss

ASTM 2457, ASTM D2456–65T and ASTM D523–62T measured at an angle of 45°C and expressed as a percentage (based on reflectance).

Haze and transmittance (Clarity)

D 1003–61, BS 2782 (515A). Again expressed as a percentage See-through D1746–62T (Transparency of plastic sheeting). Clarity BS 4618 Section 5.3.

Refractive index

ASTM D542.

Fastness to light

BS 1006, Fade-o-Meter ASTM G.23. The ability of a material to withstand light without discolouration (which may also indicate instability to light).

General physical properties

Prior to carrying out any comparative testing, preconditioning of the samples may be necessary. This is normally 20°C 65% RH for 15 days.

Tensile properties

Tensile testing is a widely used mechanical test from which not only tensile strength but elongation and modulus can be obtained. In the test a waisted or dumb-bell shaped sample is measured in the waisted region and then firmly gripped in machine jaws which draw away at a constant speed.

Resistance to stress and flexing

Various tests. See also folding endurance PIT 3402. The resistance to deformation is measured by a load cell connected to one of the jaws thereby producing a load-extension curve. The tensile stress applied extends the specimen so that a strain (E_1) can be equated against a change in length. The tensile strength at break is obtained by dividing the force at breaking point over the original cross-sectional area. Yield strength may be calculated from the load at which elongation continues without an additional load being applied. The ratio of stress/strain is called the elastic or Young's modulus. The value gives a clear indication of the stiffness for a set temperature. (Note that Young's modulus for polymeric materials is dependent on both temperature and speed of extension.)

Test ASTM D638; DIN 53455 (Films ASTM D-882), D1623 Tensile and elongation. Also BS 2782–326C.

- Stress at yield point— kg/mm^2 or lb/in^2 or MN/m^2 .
- Elongation at yield point %.
- Resistance to flow under tensile stress—a measure of creep resistance.

Flexural properties (flexural strength)

ASTM D790, DIN 53457. Flex durability (films) see ASTM F392.

- Maximum stress kg/mm^2 .
- Maximum deflection mm.
- Modulus of elasticity kg/mm^2 .

All are measured over a range of temperatures.

Compression

ASTM D695 also see ASTM D-642.

- Maximum stress kg/mm² or lb/in².
- Modulus kg/mm² or lb/in².

Torsion

ASTM D1043, DIN 53447.

- Modulus of rigidity kg/mm².

Shear (dynamic shear modulus G)

ASTM 732, DIN 53445.

Stress (kg/mm²)

The above may be measured against a number of factors: temperature, humidity, moisture content, etc.

Distortion and creep

Under conditions of stress most plastics will exhibit a degree of cold flow, distortion or creep depending on temperature, type and time of stress applied, and whether the moulding is restricted from movement by its surroundings. Once a moulding undergoes deformation the recovered deformation is known as elastic deformation and the permanent deformation as plastic deformation. The behaviour of a plastic material under constant tensile stress is usually estimated by creep tests. Such stress/strain behaviour as a function of time is given by isochronous stress/strain curves where tensile stress is plotted against elongation (DIN 53444). For longer periods tensile creep modulus is usually measured against loading time. Relaxation modulus as a function of loading time is described in DIN 53441.

Impact strength

Tests may be on the basic plastic or the material available as a film, sheet, component or container. One test is the Charpy notched impact strength, DIN 53453 standard. This involves either un-notched or notched samples tested against impact over a range of temperatures. The resilience is measured as kg/cm . The test is carried out on samples 15× 10×2 mm. ASTM D256 ft lb/in notch is found as the Izod notched impact test.

- 1 Impact breaking energy (tensile impact) ASTM D1822 ft lb/in².
- 2 Dart impact ASTM D1709A ASTM D3029 (Gardner).
- 3 High speed puncture test ASTM D3763.
- 4 Drop length to break D2436 65T.

Tear properties (tear propagation resistance)

ASTM D1922, usually known as the Elmendorf tear strength (related to test originally devised for paper and board), is carried out in the machine (MD) and cross (CD) direction of the material. Measured as kN/m. Test D689-44 also applies for films.

Torsion stiffness test

ASTM D1043.

Hardness

Hardness may be measured by several types of test:

- Rockwell hardness scale is widely used for plastics—test ASTM D785
- Shore hardness (Durometer) is another standard test—ASTM D1706
- ball indentation hardness is measured under DIN 53456.

Abrasion resistance (wear resistance)

Abrasion or resistance to abrasion is a function of the plastic, the ingredients in the plastic, the surface of the plastic, etc. Under test ASTM D1044 abrasion is related to loss in mg under standard conditions. Wear or abrasion has a relationship with the surface properties, i.e. coefficient of friction. DIN 53754E (Taber abrasion) is a similar test using a gritty material on an abrader wheel which measures wear against a number of wheel revolutions.

Coefficient of friction

D1894–63; DIN53375; BS 2782–311A, ASTM D1894–78. Here again a number of tests exist. A simple rule of thumb type procedure is an inclined plane test. This uses the plane for holding the material under test with an article or sledge (i.e. material) of a known weight. The plane is raised until the weight freely moves down the slope and the angle is measured. There are, however, a number of in-house and official variants for this type of test, i.e. dragging a sledge across a surface and measuring the resistance to movement.

Temperature and heat sensitive evaluations (thermal properties)

The procedure is to find whether a plastic converted material will distort or disfigure under a heat test, e.g. steam autoclaving, by carrying out tests on the material with and without the product present. The tests listed below, however, will give some degree of guidance.

Heat distortion temperature (or heat deflection temperature)

ASTM D648; ISO R75 measured as °C. A specimen bar is placed in a heated chamber, clamped in supports and loaded to 1856 KN/m² while temperature is raised 2°C every minute until the specimen bar has deflected by 0.25 cm. The apparatus used can be shared with the Vicat softening point.

Ball indentation

DIN 53456; ISO 2039 (as MPa). Measured as a constant indentation by a 5 mm steel ball under conditions of temperature, using a given (variable) load factor and a fixed time period. This is also a measure of hardness.

Melting point (T_m or crystalline melting point)

Many plastics may have an indistinct or wide melting range. ASTM D789.

Specific heat of latent fusion

ASTM C351–61. Measured as specific heat, kcal/kg/°C and latent heat of fusion, kcal/kg.

Vicat softening point

ASTM D1525, ISO 306, BS 2782 Pt 102D. A flat specimen (at least 20 mm wide×3 mm thick) is placed in a temperature-controlled oil bath, with a flat-ended needle resting on it. The bath is raised in temperature at 50 or 120°C per hour. When a gauge records 1 mm penetration, the temperature is recorded. The Vicat softening point should not be confused with a melting point, as it equates more closely with T_g (the glass transition temperature) with certain plastics.

Brittleness temperature

ASTM D746, i.e. how plastics stand up to low temperatures.

Thermal conductivity

DIN 52612, ASTM C177, BS 874. Measured as either, kcal/m/m²/h/°C or BTU/ft/ft²/h/°F Typical examples of other materials are:

- copper: 330 (kcal/m/m²/h/°C)
- glass: 0.6 (kcal/m/m²/h/°C).

Plastics usually have thermal conductivities (which may be changed by added ingredients) several times lower than glass and around 1000 times lower than copper. This indicates why plastics provide excellent insulation against heat.

Heat deflection temperature (see 'Heat distortion temperature' above)

DIN 53461, D648.

Coefficient of linear expansion

ASTM D696–44 and DIN 52328 measured over a range of temperatures but calculated as expansion per °C, i.e. °C⁻¹×10⁵.

The range for most plastics is 1–20, 10⁵ m/m/°C, which is higher than for most metals.

Shrinkage

Measured as a percentage, ASTM D1299. (Important for mould dimensions where allowance for shrinkage has to be made. This usually ranges from 0.5% to 5.0% depending on the plastic employed.)

Blocking (films and sheets)

ASTM D-1893.

Flammability

ASTM D635–72. Some plastics (without additives) may be self-extinguishing whereas others can be classified as non-flammable or flammable. Also classified are non-dripping and dripping. ASTM D2863, oxygen index, measured as a percentage.

Electrical properties

These do not normally have any pharmaceutical relevance unless the pharmaceuticals are part of electrical devices, hence are not discussed here.

Chemical-type evaluations*Gas permeation/gas transmission (cm³/m²/day—bar)*

DIN 53380, BS 2782–514A, ASTM D1463–63, ASTM D-1484 (films). Covers both oxygen and carbon dioxide.

Water vapour permeability/transmission (g/m²/day)

DIN 53122, ASTM E-96–63T, F.372, BS 3177.

Water absorption

ASTM D570–63 equilibrium measured at 23°C or 100°C in water as a percentage or mg weight gain. Also BS 2782–43OB; DIN 53495.

Total immersion test

Weight change in 7 days.

Resistance to weak acids/weak Alkalis

ASTM D543–56T

Resistance to strong acids/strong alkalis

ASTM D534–56T, PI-T1001.

Resistance to fats and oils

PI-T1003 (grease penetration ASTM F-119).

Environmental stress cracking (ESC)

Certain plastics suffer from a phenomenon known as environmental stress cracking, which occurs when a plastic under a physical stress is in contact with a chemical substance known as a stress cracking agent. The strain may be in-built from the moulding process or may arise from capping, plugging or top pressure (stacking pressure), etc. Stress cracking agents include most detergents, wetting agents and certain volatile oils. The preservative BKC is a mild stress cracking agent. Examples of tests to establish whether a plastic is stress crack prone include the following.

- 1 Bell telephone test: ASTM D1693–59T uses Igepal 630 at 50°C as a stress test. Results are given in hours to stress crack on a notched bent strip.
- 2 Pack test: known under different names including the Hedley test. Test details vary between companies and countries but generally the pack is filled, or part filled, with the product or selected commercial detergents (full concentration or a dilution) and then stored at 60–70°C for a period of 48 h to 1 week.

In the above tests plastics are likely to develop cracks if they have a tendency to suffer from ESC. Low-density polyethylenes of medium to high melt flow index are particularly prone to ESC. Moving to an LDPE of MFI less than 1.0 will normally overcome this problem.

Extractives

Simulants used for extraction procedures for foodstuffs include distilled water and aqueous solution of ethyl alcohol, or rectified olive oil. Under the EC global migration proposals, extraction is limited to either 60 ppm or 10 mg/dm², see EEC 90/128 plus amendments. Extraction resistance: see ASTM F-34 and USPXXIII.

Regulatory clearance

Clearance by official bodies such as the FDA, BGA (Germany), etc., on ingredients permitted to be used in plastics almost invariably relates to their use in contact with foodstuffs. Relatively few documents specifically cover pharmaceutical or medical clearance, e.g. use of PVC for blood bags, disposable syringes, etc. However, these specific clearances are slowly increasing in numbers (EP). When clearance is given for foodstuffs the recommendation states that such articles are suitable for their intended application and should not impart odour or taste to food, or yield any substance which is injurious to health. Permitted lists are currently being published for constituents which meet food grade approval.

Although clearance for use with food is a helpful check, prior to the use for a pharmaceutical purpose it remains the responsibility of the user (industry, hospital, etc.) to verify that the plastic and product are fully suitable (compatible) and safe. The EP now lists approved antioxidants for certain plastics. However, official approvals are related to human opinions which are based on the evidence available at the time when the approval was given. One should not blindly believe that such an opinion eliminates any risks and avoids the need for any additional tests.

The permeability of plastic to gases and organic substances

All plastics are to some degree permeable to atmospheric gases, i.e. nitrogen, oxygen and carbon dioxide. The first law that relates to the diffusion constant or diffusion coefficient is Fick's law, which states that the amount of gas passing perpendicularly through a unit surface against unit time is proportional to the concentration gradient, i.e.

$$q = \frac{-Ddc}{dx}$$

where D is the diffusion constant.

The negative sign shows that diffusion occurs in the direction of the lower concentration. The second law is Henry's law, which states that the amount of gas dissolved in a given mass (of plastic) is directly proportional to the partial pressure applied by the gas. It is expressed as:

$$C = Sp$$

where C is the concentration, p is the partial pressure and S is the solubility constant of the gas in the polymer. From these two laws it can be deduced that

$$P = DS$$

where P is the permeability coefficient (sometimes called the transmission factor, permeability factor, or permeability constant).

Permeability of gases and vapours through plastic involves absorption, followed by diffusion, followed by evaporation and desorption from the other face. Permeability is greatest with amorphous plastics where diffusion occurs via the spaces between the moving mass of molecular chains. Crystalline plastics or those with crystalline regions present a greater barrier to diffusion. With thinner materials where pinholes or micropores occur, diffusion may occur via these small holes. Various other factors influence permeation, including:

- 1 nature of the diffusing molecule
- 2 nature of the plastics
- 3 external conditions prevailing (especially temperature).

Nature of the diffusing molecule

An example of a factor influencing the diffusing molecule is whether the gases or vapour are difficult to condense or readily condensable. With gases such as oxygen, carbon dioxide and nitrogen, which are difficult to condense and where the intermolecular forces are weak, the solubility of a permanent gas in plastic is relatively low at normal temperature, i.e. usually less than 0.2%. Where condensable vapours are involved in which the intermolecular forces are stronger, then there are two possible modes of interaction.

- Where the cohesion forces of vapour are less important than the polymer-vapour interaction in which case organic substances dissolve in or plasticise the plastic.
- Where the cohesion forces of the vapour play a larger part, and the solubility of the vapour in the plastic is relatively low. This applies to hydrophobic polymers such as LDPE and PP, and organic vapour systems which are either non-solvent or slightly solvent.

The nature of plastic

Symmetry and cohesion energy

As a general rule the permeability coefficient is low when symmetry and cohesion energy are high. For example, although LDPE and PVdC have similar degrees of symmetry, PVdC has a very high energy of cohesion and therefore has a very low diffusion coefficient. LDPE and natural rubber have similar cohesion energies but due to the lack of symmetry and the looser structure of the latter, rubber is significantly more permeable.

Proportions of amorphous and crystalline regions

The proportion of crystallinity to amorphous regions has a marked influence on both diffusion and solubility of the diffusing molecules. The coefficient of diffusion decreases as the degree of crystallinity increases. For example, PVdC is very highly crystalline, and PS is very low. In terms of permeability to water, PVdC is very low, whereas PS is very high.

Structural similarity between polymer and diffusing molecule

Another general rule is that structurally similar materials will diffuse and permeate more readily. Similarity refers to both end groups and polar moments (measured as Debye units). For example, polyvinyl alcohol is highly permeable to water but has relatively low permeability to organic vapours. PVC is the opposite, i.e. has a greater affinity to organic vapours. Polythene shows higher permeability to benzene, carbon tetrachloride, cyclohexane and hexane, the Debye units for polythene and the organics all being nil. Substances with polar moments show lesser degrees of diffusion and permeation.

Other constituents in the plastic

Plasticisers generally increase diffusion and permeation (particularly when the levels are high) for a number of reasons:

- plasticisers open up the molecules of the plastic, thus increasing their mobility
- plasticisers possess their own diffusion coefficient
- plasticisers usually have a greater affinity for the diffusing molecules.

Fillers, pigments, opacifiers, etc. may increase or decrease diffusion and permeation. This is also true of solvent residues which may increase permeation to similar organictype solvents. Titanium dioxide usually reduces permeation; white talc and chalk as used in polypropylene will usually increase moisture permeation.

Effect of temperature

The permeability of a material generally increases with temperature, and a relationship can be derived in the form of an Arrhenius equation:

$$P = P_0 \times (-E_p/RT)$$

where T is degrees absolute, R is the constant of a perfect gas, P_0 is a constant (the vapour pressure for infinite time), E_p is the activation energy of permeation, and P is the permeability coefficient.

Gas permeation

The permeation for gases N_2 , O_2 , CO_2 is usually of the order of 1:4:20. Plastics with low permeabilities include polyvinylidene chloride, polyvinyl chloride, ethylene vinyl alcohol (if dry), nylon and PET.

Higher permeabilities are found with polyethylene, polypropylene and polystyrene. If, for example, an unbuffered product with a pH of around 7 is stored in LDPE the pH will ultimately shift to that of carbonic acid, i.e. pH 4.3–4.6, due to permeation of carbon dioxide.

Organic vapour permeation

Except in the case of dilute vapours, results are not always predictable. Two of the main parameters which control the rate of diffusion are the similarity of polar moments and the structural similarity of the polymer—diffusing molecule system. These may be placed in order of increasing polarity:

- 1 saturated aliphatic hydrocarbons
- 2 non-saturated aliphatic hydrocarbons
- 3 aromatic hydrocarbons
- 4 ketones
- 5 aldehydes
- 6 ethers
- 7 carbonic esters
- 8 alcohol

9 acids
10 water.

If the polarity and structural parameters are similar for two polymers then the diffusion will be related to the degree of crystallinity, i.e. HDPE, being more crystalline than LDPE, will be less permeable to organic vapours.

Constituents in plastics (residues, processing aids, additives and master batching)

Experience indicates that difficulties may occur in establishing the actual constituents in any plastic material. Certain manufacturers have at times either refused to identify constituents or only expressed a willingness to declare them to regulatory authorities. The latter compromise means that a pharmaceutical company may find itself in a difficult position, if as a result of the declaration one or more constituents are queried. Since the pharmaceutical company is legally liable for both product and pack it does seem relevant to have at least the opportunity of knowing what the plastic (or rubber, for that matter) contains. Constituents therefore may have to be quantified in terms of residues, processing aids, additives, etc. A question such as ‘what are the additives?’, if strictly interpreted, does not necessarily ask for the other two to be identified. Additives, which are basically constituents added to modify or change the characteristics of a polymer, can be itemised under a series of headings, for example:

- plasticisers/plasticiser extenders
- fillers, extenders, reinforcing agents
- lubricants
- stabilisers
- UV absorbers
- slip additives/anti-slip additives
- anti-blocking agents
- colourants—pigments and dyes
- antioxidants
- internal release agents
- inhibitors (mould and/or bacteria inhibitors or chemical inhibitors)
- nucleating or clarifying agents
- toughening agents—impact modifiers
- flame-retarding agents, e.g. opacifiers, whitening agents, antioxidants, biodegradable materials.

Although the number of additives used in any single plastic is likely to be low (most fall between zero and four), the list in total is fairly formidable. Several questions arise: are any of the constituents toxic or irritant, and are they extractable or simply removable from the surface of the plastic by abrasion? It should be noted that any additive which derives its effect from being present at the surface of the material may be physically removed by an abrasive action. Certain processing aids also operate at the material surface (lubricants, mould release agents, etc.). Interaction between product ingredients and plastic constituents, followed by extraction, is another, although remote, possibility. As additives are incorporated to obtain or enhance certain features considered desirable for the use of that plastic, they will be discussed in greater detail.

Plasticisers

Plasticisers improve the flow properties of a material, increase softness and flexibility, and are found mainly in polyvinyl chloride (plasticised PVC) and the cellulose. Occasionally the word may be misused (i.e. when the general word ‘additives’ should be used). There is therefore sometimes a belief that all plastics may contain migrating ingredients, hence the question most frequently asked is ‘what plasticisers do they contain?’. The most common PVC plasticisers are selected from phthalate esters, phosphate esters, sebacate and adipate esters, polymeric plasticisers and citrates. Dibutyl phthalate was once widely used, but due to its high volatility it was readily lost and is partly to blame for the belief that all plasticisers migrate. Materials of a low migratory level can now be selected from the relatively large list of plasticisers. Plasticiser extenders which are used in some non-critical applications consist of chlorinated paraffin waxes and oil refinery by-products. The plasticiser content can vary according to the properties required. As a generalisation, plasticised PVC usually contains at least 20% of plasticiser. With some plasticisers there is an upper content limit of compatibility or loading capacity. Plasticisers reduce hardness, increase elongation, tensile strength and modulus, improve low temperature resistance but usually reduce resistance to chemicals and increase permeation. For a highly plasticised PVC the moisture permeability can be four to ten times that of an unplasticised PVC. Plasticisers can also migrate via interface contact with other plastics, e.g. into unplasticised PVC, nitrocellulose, etc.

Exchange between product and pack can occur in both directions, e.g. certain labelling materials such as heat sensitive and self-adhesive labels when in contact with plastic materials. Both the plastic and the adhesives may contain plasticisers or migratory constituents. Most cellulose use phthalate, sebacate, phosphate-type plasticisers (e.g. methyl phthalate (DMP) may be used in cellulose acetate). Plasticisers may also be found in poly vinyl chloride/acetate copolymers, polyvinyl acetate and polyvinyl alcohol formulations, polymethyl methacrylate, nylon and certain thermosetting resins.

Typical plasticisers include dimethyl phthalate (DMP), diethyl phthalate (DEP), dibutylphthalate (DBP), di 2 ethylhexyl phthalate (often known as DOP). Other plasticisers include epoxy-based materials, e.g. octyl epoxy stearate, and, more recently, polyurethane-based materials.

Fillers

A filler by definition is an inert solid substance. Examples include carbon black (up to 5%), chalk or calcium carbonate, talc, china clays, silica and magnesium carbonate. Fillers may reduce degradation of the plastic (carbon black may significantly reduce sensitivity to light) or be used simply to reduce cost. The maximum limit of fillers is around a 1:1 ratio, after which binding power with the plastic is lost. The more fibrous fillers such as fabric, carbon fibre, and glass fibres are usually found under the title of reinforcing fillers. Carbon black also provides some reinforcement properties. Fillers for thermosetting materials include wood flour, paper, glass fibre and natural fibres, i.e. cotton, fabric, etc. Moisture absorption, shrinkage and contraction vary considerably according to the fillers used. This is an important feature with closures, particularly if subjected to steam autoclaving, e.g. phenol formaldehyde caps are more stable than urea formaldehyde caps. The addition of fillers (excluding reinforcement fillers) to thermosetting plastics generally reduces physical properties and, depending on the actual filler(s) used, is likely to reduce chemical resistance and increase permeability. Occasionally coloured fillers may be used to achieve a dual role. Titanium dioxide is frequently used up to a 3% level but is frequently classified as an opacifier rather than a filler.

Filler reinforcements

Filler reinforcements are generally applied to products other than pharmaceuticals and are not covered in this chapter.

Toughening agents/impact modifiers

A few plastics which tend to be naturally brittle require an improvement in both their drop (impact) strength and their top loading (compression) strength. In the case of polystyrene, rubber is widely used as an impact modifier. Rigid PVC, particularly when used as a container, may suffer weakness when subjected to, say, a 3–4 foot drop test. Up to 15% of methyl methacrylate butadiene styrene (MBS) copolymer is usually added to improve impact strength. Chlorinated polyethylene has more recently been introduced as a PVC impact modifier. Vinyl acetate is frequently used as a modifier for PVC film. Polythene, LDPE-HOPE can have resistance to stress (environmental stress cracking), improved by the use either of rubber or polyisobutylene. These modifications have not as yet had any pharmaceutical applications.

Lubricants (may also be used as internal release agents)

Lubricants may be added either as an additive or at the fabrication stage as a processing aid. In general lubricants prevent adhesion with metal parts. Lubricants may be solids, such as waxes, stearates, i.e. fatty acid esters, fatty acid amides, or liquids such as liquid paraffins. Lubricants may also improve the flow and thereby lower the temperature of the moulding operation. For example, a silicone additive polydimethyl siloxane may be used in LDPE and HOPE films to improve flow. Stearamides are also used.

Lubricants may therefore act as either as an external or an internal agent. Depending on their chemical nature, a few may have secondary actions such as dispersing agents, plasticisation, or slip agents. These are usually included up to a 1% level.

Stabilisers

Stabilisers increase the stability of plastic either during processing or during the moulded life of the material. Heat stabilisers are essential to PVC, taking up any released hydrochloric acid from product decomposition. The broad categories of stabiliser used are found under 'Polyvinyl chloride' above. Stabilisers are frequently used to combat the combined effects of heat and light.

Ultraviolet absorbers

UV absorbers may be used for two reasons: to protect the plastic from UV degradation, and to prevent product degradation due to UV rays passing through the plastic. Chemically UV absorbers may be based on substituted phenols or benzophenones. Examples include 2-hydroxy-4-n-octoxybenzophenone, other hydroxy-benzophenones and compounds of oxalic anilide. These are usually added at a 0.1–0.2% level. Prevention of light penetration and protection of the plastic from light degradation can also be achieved by the addition of iron oxides and carbon.

Flame-retarding agents

To date flame-retarding agents have not consciously been used for pharmaceutical products, and are not covered here, except to note that electrical or electronic equipment involved in drug administration normally has to use flame-resistant materials for safety purposes.

Slip additives

Slip additives are widely used for films either made or used on relatively high-speed equipment where any non-slip or drag properties might be detrimental to output. The most-used slip additives are oleamide and stearamide; since these operate at the film surface they can be physically removed by abrasion. Although oleamide and stearamide are currently rated non-toxic, any solution contaminated by them may show a slight haze or milkiness. Thus a product with a clarity of solution test may have this feature jeopardised by storage in contact with a material containing these slip additives (e.g. LDPE liners or bags).

Anti-slip additives

These were primarily developed to provide good bonding for palletised loads of plastic sacks and bags. Without the additives plastic sacks would tend to destack and slide off when the pallet is moved or jerked. However, palletised loads can be stabilised by alternative methods, e.g. shrink and stretch wrapping.

Anti-blocking agents

Both reel-wound and sheet stacked materials may be difficult to separate due to blocking. This may be caused by the smoothness of two surfaces giving rise to surface adhesion. It can be prevented by the incorporation of finely divided silica or diatomaceous earths at a level of up to 0.2%, e.g. mica.

Antioxidants

Antioxidants are fairly widely used at a 0.01–0.4% level to prevent or retard oxidative degradation of certain plastics. Polymers may be subject to various forms of oxidative attack during all stages of their life cycle, i.e. from polymerisation through processing to final end usage. The more used antioxidants include:

- hindered phenols and cresols (known as primary antioxidants and radical scavengers)
- secondary amines (known as primary antioxidants and radical scavengers)
- phosphites and thioesters (secondary antioxidants which operate as peroxide decomposers)
- butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) (typical primary antioxidants).

Variants of the above are found under many trade names.

Colourants

Colourants can be listed either under pigments, which are insoluble dispersible powders, or dyes which are liquid- or solid-based soluble materials. As well as simple colouring, new appearances are being achieved: pearlescent, tortoiseshell, marbled, metallised effects, etc. Colouring a plastic may be achieved in several ways, i.e. masterbatch (solid or liquid masterbatching), dry colouring and precompounding, etc. Details of these are given below.

Masterbatching

SOLID MASTERBATCHING

Solid masterbatching consists of a high concentration of pigment in a carrier. The carrier can be the plastic with which it is to be compounded, a similar plastic or low molecular weight carriers. The ideal is a masterbatch which is miscible and dispersible with all types of plastic. The pigment level has conventionally been 10–20%. Recently more concentrated masterbatches with 40–60% pigment, usually in a carrier, have been made for use at an approximately 1% addition level.

LIQUID OR WET MASTERBATCHING

These are usually used as part of an automatic system whereby a supply of a liquid colourant is metered into the plastic. As a let down material, substances such as liquid paraffin may be employed. It is essential to ask what the diluent is.

DRY COLOURING

This term applies to two processes:

- 1 automatically adding a dry colourant by a metering system
- 2 the use of prematched blends with other ingredients so that a small quantity can be added with thorough premixing prior to moulding.

PRECOMPOUNDING

This involves the preblending and extrusion of pigments, fillers, additives with the moulding polymer. It is then a ready to use, prematched material. Pigments can include metallic materials (aluminium powder) and materials which provide opalescence.

While masterbatching systems have received little attention to date, there is now awareness of the importance of various constituents such as carriers of a similar plastic but of a different MFI, different types of plastic, paraffins, oils, etc., and certain added lubricants, etc. Even though they are present at low levels after dilution, knowledge is becoming more relevant. As an important step in knowing the constituents of a plastic, details on the master batch should therefore be included. Using a reputable masterbatcher (i.e. one aware of pharmaceutical concerns) overcomes the above risks.

Antistatic agents

Antistatic additives or agents operate by being present at the surface of the plastic where they attract a layer of moisture which acts as a conductor for electrostatic charges. They are normally incorporated at a level of 0.01–0.2% and are usually surfactants, i.e. cationic, anionic and non-ionic compounds.

Opacifiers

The most widely used opacifier is titanium dioxide at a level of 1–3%. Two types occur, Anastase and Rutile, with the latter being more widely used.

Whiteners—optical brighteners

Whiteners involve similar ingredients to those so well accepted in washing powders to give a ‘whiter than white’ appearance. Since this may relate to a degree of colourising, i.e. a very pale blue or violet, its presence can frequently be seen by viewing the inside of an apparently white opaque container. ‘Whiteness’ may be achieved by the addition of a material such as ultramarine.

Extenders

These are somewhat similar to fillers. They are used as a lower cost substitute for the plastic.

Internal release agents

These agents are somewhat similar to lubricants in that they provide release, particularly from metals, i.e. moulds. The substances include metal stearates, i.e. zinc, calcium, magnesium stearates, stearic acid and silicone fluids (0.25–1%), e.g. poly (dimethyl) siloxane.

Inhibitors

Not a widely used additive but may be used for specific purposes, e.g. as a copper deactivator or as a microbiological inhibitor.

Blowing agents

Cellular products may be formed by incorporating blowing agents. These are usually hydrazine derivatives which evolve nitrogen. A typical material example is expanded polyethylene which has been used as a closure wadding material. However, such materials may contain ammonia residues and lead to changes in product pH, hence alternative agents are used for expanded PE wadding.

Regrind

Regrind consists of reworked material, i.e. either natural plastic or plastic plus other constituents as per material being moulded. Regrind is usually used to specific levels, e.g. 10%, 15%, 20%, 25% maximum. However, continuous use of regrind may lead to some degradation of either the basic polymer or the other constituents. If regrind is not permitted a specific instruction has to be included in the specification. Some countries do not permit the use of regrind for certain types of product (e.g. for IV, injectibles.)

Degradable (biodegradable) additives

Some 20 to 25 years ago there was a popular belief that plastics should be made degradable and a series of additives were developed to achieve this end. These substances included photodegradable chemicals, chemicals slowly attacked by light and heat, starches which are subjected to microbial attack, e.g. edible substances, and water hydrolysable substances. More recently it has become preferable to reuse, recycle or incinerate plastic so that energy can be either conserved or recovered.

Residues in plastics

Residues in plastics, other than monomers, are not easy to define since each is dependent on the process of polymerisation. However, a list of residue headings can be identified as follows:

- catalysts, initiators or hardeners
- solvents
- suspending agents
- emulsifiers
- accelerators
- monomers
- dispersing agents, etc.

Catalysts vary according to the process of polymerisation, e.g. in the polymerisation of PE by the Ziegler process, triethyl aluminium and titanium tetrachloride are used. Certain polymers may contain peroxide residues from the use of benzoyl peroxide.

As an example of monomer residues and the possibility of toxicity risks, the case history of the vinyl chloride monomer (VCM) in polyvinylchloride (PVC) bears some study. Up to late 1973 PVC had been in use for over 40 years before the possibility of VCM being a carcinogen was established. Trials which followed earlier findings in 1971 showed the presence of both tumours and angiosarcoma of the liver, which is a relatively rare liver cancer. Further investigation established that deaths of workers or exworkers employed on PVC polymerisation plants could be associated with long-term exposure to VCM. In the period 1976–1980 work to reduce VCM residues established the likely loss of VCM from a rigid pack (approximately 30% is lost to the atmosphere after 1 year) and the VCM equilibrium between pack and contents, and

calculated the likely partitioning between product and pack. Latter extensive studies on food have shown VCM levels of the order of 0.005 ppm and less. It therefore now seems reasonable to meet the EU limit of 1 ppm (1 mg/kg) or less in rigid PVCs and a limit of 50 ppb (0.050 mg/kg) in food-based products. It can therefore be concluded that virtually all PVCs, whether plasticised or unplasticised, are now 'safe' (author's opinion) provided these limits are achieved. For those involved in the 'VCM' era there has always been difficulty in dealing with the emotive issue. That people have died on PVC polymerisation plants due to VCM monomers is not in doubt, whether the lower limits now imposed are necessary will probably never be established, but undoubtedly all have benefited from the early discoveries with animals when VCM was established as a carcinogenic substance.

Processing aids

Processing aids cover chemicals used for specific purposes to assist processing. Some are identical to those included under additives, e.g. lubricants, antioxidants, mould release agents. The last of these may be regularly sprayed onto moulds and may occasionally lead to poor label adhesion or oil-like contaminants.

Moisture content

It should be noted that certain plastics absorb moisture more readily than others. This moisture absorption may be related to the plastic itself or the constituents. Plastics with higher levels of moisture absorption invariably require 'predrying' as excessive moisture can boil off during moulding and give rise to imperfections. Moisture content may also influence permeability, particularly to moisture but also to oxygen and carbon dioxide (EVOH is a good example).

General properties

Any plastic constituent in addition to the function it serves must have heat stability, UV light stability, weather resistance, low solubility in terms of extraction, compatibility with other constituents and good dispensability. Where plastics have to be sterilised by irradiation, certain constituents may be degraded, or even continue to degrade after irradiation. Certain antioxidants are degraded by gamma irradiation.

Detection of constituents in plastics

Identification of constituents in plastics depends on a number of factors, i.e. the solubility or insolubility of the constituent in the plastic matrix, the fact that many are incorporated at relatively low concentrations, their reactivity and stability. The chemical identity and analysis for constituents may use both chemical and physico-chemical analytical procedures. These range from estimations on density, melt flow index (MFI), ash, melting point, observation of burning, visual characterisation to more sophisticated analytical techniques such as:

- infrared (IR)
- thin layer chromatography (TLC)
- high-performance liquid chromatography (HPLC)
- ultraviolet absorption (UV)
- mass spectrometry (MS)
- nuclear magnetic resonance (NMR)
- atomic absorption (AA)
- gas chromatography (GC)
- differential scanning calorimetry (DSC) and other thermal analysis techniques (TGA, DMA, DTA, TMA, etc.)
- multiple internal reflectance (MIR)
- attenuated total reflectance (ATR)
- Fourier transform infrared spectrometry
- gel permeation chromatography
- X-ray diffraction studies
- time of flight secondary ion mass spectrometry (ToF SIMS)
- X-ray photospectroscopy (XPS).

Chemical or physical tests can be broadly divided into those applied directly to the plastic and those involving some form of extractive procedure. When some constituents are segregated by the latter process they may be relatively unstable and rapidly

degrade. To minimise such degradation it may be necessary to store extractives in the dark, in neutral glass, in light-resistant containers and/or under nitrogen. The possible degradation of constituents while they are still in the plastic cannot be ignored, i.e. when the plastic is gamma irradiated. It is therefore important to identify whether degradation has occurred either in the plastic or following an extractives procedure. Newer techniques include various methods of surface analysis, e.g. XPS, SIMS, AES, ESCA.

Fabrication processes for plastic films and containers

According to the end use of the plastic, different fabrication or conversion processes may be employed. Each may influence the type and the grade of plastic selected, the constituents therein and the processing aids to be used. It is essential for the packaging technologist to have knowledge of all conversion processes as this is critical to the design and constituents. The next chapter emphasises this latter point in that the final properties of a plastic may be influenced by the residues, additives and processing aids. The fabrication of plastic invariably involves a moulding or shaping process and although this was originally considered to involve heat and probably pressure, cold moulding or shaping processes are now finding commercial applications. With isolated plastics and processes, complex mouldings may need 'jigging' or annealing. (Jigging is where dimensional changes are restricted during cooling by placing in a 'jig'.)

Orientation

When materials are stretched just below or above their softening point the molecular structure undergoes orientation. If the stretch is the same in the machine and the cross direction then a biaxially oriented plastic is obtained. Depending on the degree of orientation, significant changes can occur in both the physical and chemical properties. For example, stretched or oriented films will return to their unstretched state when heated to a temperature at or above that used for the original orientation process. If such films are to be heat sealed then either a special heat sealing process has to be used (e.g. hot wire sealing in shrink wrapping which localises the heat applied) or a heat seal coating has to be applied to the material which will seal at a temperature below the shrink or deorientation temperature. If the oriented film is held under restraint while given an additional heat treatment then a heat set oriented film can be produced. The general properties which arise from orientation include improved clarity, reduced haze, greater rigidity and impact strength, better barrier properties and chemical resistance.

Orientation can be applied to films, sheets and containers. Recent examples in containers have used polyester, polyvinyl chloride and polypropylene. In these orientation processes, called stretch and blow in the case of containers, polyester and polyvinyl chloride achieve excellent clarity, and polypropylene considerably improved clarity. It should be noted that orientation of plastics with relatively low to medium melting points frequently will not allow autoclaving by steam or hot filling, since distortion or deorientation will occur.

The fabrication or conversion processes for plastics vary according to what is being produced, i.e. films, sheets, laminates, components or containers. Films or sheets are produced by similar processes. Laminates may be produced by adhering films to other materials or by coextrusion. The use of the latter, a process more ideal when high quantities are required of certain constructions, is increasing. Coextrusion can therefore combine the properties of several materials in thinner gauges, and frequently more economically than other alternative processes. However, normal lamination techniques have to be used if plies of paper or foil are involved (see [Chapter 9](#)).

Film and sheet forms

Films have a wide variety of uses, as bags, sachets, plies in laminates, etc., and can be produced by a number of processes, as follows.

- 1 Extrusion: either via a longitudinal slit (slot die) to give a flat film or via a circular die as a tube (lay flat tubing).
- 2 Solvent casting: for example, cellulose acetate dissolved in acetone. The liquid is metered onto a continuously moving belt which then passes through a drying tunnel where the solvent is driven off.
- 3 Calendering process: a process whereby molten plastic is passed through a series of highly polished (heated) rollers followed by a cooling roller nip.
- 4 Coextrusion: an extension of the extrusion process where two or more plies can be extruded in combination, i.e. as a multi-ply layer.

Although films and continuous sheet materials can be produced by the same processes, films normally have a gauge of below 0.010 inch or 0.25 mm.

Moulding processes

Moulding processes for solid, hollow components and containers include the following conventional processes:

- injection moulding (and coinjection moulding)/injection blow moulding
- extrusion moulding (tubing)/extrusion blow moulding
- compression moulding/compression transfer moulding
- thermoforming by pressure, vacuum, mechanical forming or combinations
- scrapless forming process (SFP)
- solid phase pressure forming (SPPF)
- dip moulding
- rotational moulding
- injection stretch blow moulding/extrusion stretch blow moulding
- reaction injection moulding (RIM)
- soft moulding

and variants of these.

Moulds and some moulding factors

Each of the above processes requires a form of mould or moulds, i.e. single cavity or multicavity, which involves capital expenditure. Depending on the design, the initiation costs will vary considerably. As the mould number increases, capital investment and machine complexity become more critical to a point where unit costs may pass beyond the minimum costs due to downtime, mould refurbishing, setting-up time, maintenance, production duration, etc. So although a two impression mould will give a lower priced article than a single impression, four than two, etc., the final choice has to be balanced against factors less obvious than simply output against downtime, labour, depreciation, etc.

For a more complex moulding (e.g. by injection moulding), 3–6 months might be necessary to produce satisfactory components from initial drawings, involving a detailed drawing, mould drawings, mould production, setting-up and approving the new moulds, evaluating out-turns to final approval for production purposes. In addition, extra time must usually be allowed for adjustment to moulds and retesting. Even when one mould from a single cavity tool has been approved it is equally important to check mouldings from all cavities from a multi-impression tool since heating and cooling cycles may have to be significantly changed from the former.

This not only may give rise to subtle changes, but mouldings may also change slightly (sometimes critically) when a new item is run over an extended production period. It should therefore be noted that the first-off item for a short run may not represent that achieved from normal running during continuous production. Technical discussions between the supplier/moulder and the user are therefore advised from initial choice of supplier through to satisfactory production. The options of adjusting items to drawings or alternatively drawings to match samples needs careful evaluation.

Where new company mouldings are involved, it may be advisable to proceed via a soft (or hard) prototype, single impression tooling stage, before being involved with the higher cost of 'hard' multicavity production tools. These prototype mouldings will usually take a similar time scale to produce, i.e. 3–5 months from a concept sketch stage. Soft tooling is only suitable for a limited number of items but is particularly useful for the testing of new device type concepts.

Although most moulding processes involve heating and cooling phases with or without the use of pressure, some newer processes have eliminated or reduced the application of heat (i.e. those involving mechanical forming under pressure or compression). The 'cycle-time' involving the heating and the subsequent cooling stages is usually critical to the cost in that it may influence not only output speed but quality and finish, etc. Some of the more important moulding methods are given below.

Injection moulding

Injection moulding is based on a reciprocating piston or screw process whereby a shot of molten plastic is delivered under pressure into a cooled mould, then held until hardened sufficiently to be ejected from the mould. The time taken by the total process to deliver a moulded article is known as the cycle time and the amount of plastic used per cycle as the 'shot', which must not exceed the weight capacity of the machine. In conventional machines the shot includes the articles moulded and supporting sprue and runners. In moulding smaller items, the sprue and runners may actually weigh more than the moulded articles, so it is therefore not possible to cost the material used without reference to the cost of this wastage which in certain processes may be used as 'regrind'. If this is not permitted, the scrap may be sold off at a substantially lower price. Newer hot

runner techniques offer a means of reducing scrap which may then be limited to fairly short sprues. However, hot runners are more expensive to install and are not always economical or successful. The ultimate success of any injection moulding depends on:

- 1 the use of the correct grade of material
- 2 a well designed item
- 3 a satisfactory mould design
- 4 correct moulding conditions, temperature, (heating), cooling and cycle time.

If these are not correct, problems may arise from distortion (e.g. differential shrinkage between the flow and transverse direction), sink marks and voids (i.e. different rates of cooling between thicker and thinner sections), moulded-in strains (detectable in clear or semi-transparent mouldings by polarised light; cf. strains in glass), holding dimensional tolerances, gate brittleness, etc. Factors to consider in mould design include the following.

- 1 Adequate taper (where relevant) to allow extraction from the mould.
- 2 Minimum of changes in section thickness.
- 3 Avoidance of substantial undercuts.
- 4 Use of adequate radii to aid flow into and around corners etc.
- 5 Proper temperature control channels to maintain correct balance between heated plastic and cooling via metal mould.
- 6 Effective cavity layout, including sprues, runners, gate sizes and location of injection points, etc.
- 7 Proper venting of mould to allow escape of any possibly entrapped air.
- 8 Correct location of ejector points.
- 9 Control of shrinkage. Shrinkage is normally calculated as thou per inch. HOPE, for example, has a high shrinkage of 2.5 to 5.0%.
- 10 Mould finish. For a high-gloss finish a highly polished steel mould or a chromium plated mould is required and the mould temperature and material temperature are critical. Finishes or textured surfaces offering stippled, matt, satin, etc. are also widely available.
- 11 Mould layout becomes more critical in the case of multicavity mouldings where it is essential that each mould operates under similar conditions. Although it may occasionally be necessary to 'blank off' a mould or moulds (e.g. damaged mould inserts), there is always a possibility that this may upset the delicate balance between mouldings.

Poor design and/or poor mould design may lead to other problems such as flashing, i.e. feather-like protrusions at mould joints, or between moving parts of mould, inserts, butting surfaces, etc., which in turn will lead to excessive manual trimming operations, or rejects. However, it must be stressed that good mould design practices will not overcome a poor component design. In understanding the manufacture and design of moulds it is essential to appreciate whether a mould can be adjusted to make a dimension smaller or larger. While it is not technically impossible to add metal to a mould, it is relatively simple, particularly prior to having a mould hardened or polished, to take metal off by grinding, spark erosion, etc. However, it must be noted that any moulding with a sunken or hollow area will require a similar protrusion (frequently called an insert) in the mould. Thus if the insert has metal taken off the internal size will reduce and if metal is taken off the main (body) of the moulding the size will increase.

As the more critical dimensions of a moulding may require proving by several adjustments to a mould, moulds will therefore be made to a maximum or minimum size at these critical areas and then be adjusted by taking metal off. Tolerances therefore cover such aspects as variable shrinkage, initial dimensional accuracy against a drawing and wear on the moulds during use. In the last case, wear will normally cause a metal-off situation whereby components will either slightly increase in size (body moulds) or reduce in size (inserts).

The option to use a hard metal for prototype tooling (i.e. in place of 'soft') may be worth considering, particularly as the quantity obtainable from a softer type metal may be relatively small and quantities cannot be guaranteed when the tool is refurbished or in some instances until a further new tool is made. With a hard mould, adjustments may be less easy or occasionally impossible but greater quantities for testing purposes (possibly for small tests markets or clinical evaluation trials) can be achieved. When new designs are involved it should be recognised that first drawings may be a best intention rather than a definitive recommendation. When first mouldings are received the option of adjusting the drawing (which is not then a specification) or the moulding must receive careful evaluation. Let it be stressed that the chances of either producing exactly correct drawings or mouldings at any initial stage (prototype or production tooling) are fairly rare, hence it is virtually essential to allow an adjustment phase in the programme. Computer technology can improve these initial design stages (CAD/CAM). The points considered above may also apply to other moulding processes.

Injection moulding is ideally suited to most types of component, e.g. various closure systems (screw, press-in, push-over), valves, metered dose pumps, plugs, and full aperture (wide mouthed) containers such as vials, tubes, tubs, jars. More complex mouldings can be used for more intricate designs which may employ split moulds, retracting core pins, travelling inserts, etc., all of which add to the initial mould costs. A simple single impression mould could cost £950 or \$1,600, four impressions £3,250 or \$5,300, and sixteen impressions £10,000 or \$16,800, but an extremely intricate moulding could cost £29,500 or \$49,000 for a four impression tool. Cost therefore reflects the complexities of the design and the moulding operation.

Coinjection moulding involves two or more materials into one mould.

Injection blow moulding

In this process a container is moulded in two stages. The first stage involves a hollow injection moulded parison during which the neck is formed, with an initial body shape around a pin or spigot. This is then transferred to a cooled finishing mould where the original parison shape is blown to the final shape. As with blow moulding of glass, the parison design is critical to quality and final container wall distribution. Since the neck section is injection moulded at the parison stage, better control can be achieved on this part of the moulding than with extrusion blow moulding. It is also possible to produce undercuts within the neck bore (for plug retention), and provide better control (e.g. eliminate sinkage) of the neck bore wall. The process is generally more expensive (e.g. mould costs) than extrusion blow moulding, hence it tends to be restricted to smaller sizes of containers. Many dropper and spray bottles (usually 40 ml and less) are produced by this process using multicavity tooling, i.e. six to twelve cavities.

Reaction injection moulding (RIM.)

RIM is a relatively new process where the plastic is obtained by a reaction prior to the final injection process. A typical reaction is that which occurs between polyol and isocyanate.

Thermoset injection moulding (TIM)

TIM is another special process, which can enable thermosets to be produced more economically.

Extrusion blow moulding

Extrusion blow moulding is an extension of the extrusion process whereby an extruded tube is clamped in a cooled mould and then blown into a container. The tubular section may be of uniform wall section or variable wall thickness (usually achieved by cam parison controls). The latter permits the thicker sections to be positioned in the zones where the tube is to be blown out to the greatest diameter. In this way an irregularly shaped container can be blown with a more even wall section. The conventional extrusion blow moulding operations involve a nip or pinch off at both the base and the neck of the container. Since both of these involve a weld between opposing parts of the tube, the ultimate strength of any container depends on both these weld areas and the blowing operation. A container may be formed either neck-up or neck-down. Processing factors which may affect the final container are as follows:

- 1 process by which parison is cut off, i.e. knife, hot wire
- 2 the die design for tube
- 3 the blow-up ratio (the ratio of the parison tube diameter to the maximum diameter of the formed container)
- 4 material distribution—related to weight extruded, the temperature of the extrudate and the rate of extrusion
- 5 pinch off design—for both base and neck areas
- 6 surface finish, temperature (cooling) and venting of mould
- 7 blowing operation including blowing pressure and rate of blow
- 8 the design of the mould, particularly the avoidance of sharp corners with attention to adequate radii
- 9 finishing operations—any subsequent trimming or stripping operations, e.g. topping and tailing, may be done automatically or manually.

Among the latest techniques is the Japanese Culus blow moulding process which produces a preclosed tube from an extrusion process. It is argued that the absence of a base pinch off eliminates the weakest part of a conventionally moulded bottle. The process is suitable for single layer and multi-layer bottles with a wide variety of shapes.

Extrusion stretch blow moulding

Stretch, or more correctly bi-orientation, of a plastic offers considerable advantages in terms of reduced weight, better rigidity, clarity and barrier properties. Stretch moulded containers can be achieved by both extrusion and injection moulding techniques. Extrusion stretch blow moulding normally takes place in three stages. A mould based on a preform shape closes around the parison (tube) taking it to a second point where following the insertion of a blowing pin the parison is lightly blown into the preform shape. At this stage the neck is formed and any pinch off removed. The preformed mould is held at a constant temperature (to suit the material) and then transferred into the stretch blow station. Here a stretch blow pin passes into the neck, stretching the container down to a predetermined point giving longitudinal orientation. Final blowing then occurs from the top of the blow pin, to give 'hoop' stretch followed by a cooling period. Materials such as PVC, PET and PP can be used in stretch blow moulding. Sizes, although the process was originally associated with containers of over 1 l with either a separate base or a petaloid base, are now getting smaller, with more conventional shapes, and the process is finding use in the pharmaceutical and cosmetic industries. In the case of PVC, bi-orientation provides sufficient resistance to impact as to eliminate the need for an impact modifier (thereby reducing cost).

Injection stretch moulding

Whereas extrusion stretch moulding was originally suited to PVC, injection stretch moulding became more widely used for polyester (PET). The process is somewhat similar to that described for extrusion stretch moulding except that the initial stage is an injection moulded parison. This parison is then passed through a tempering phase where it is cooled to the optimum stretching temperature. The preform is then mechanically stretched, followed by a stage where it is blown to the final shape. The stretch blow moulding process just described is known as the 'single stage' process in that a series of operations is carried out on a continuous basis. There is also a two stage/step process which involves preform which is then cooled, stored and can be transported to another operational area (e.g. in plant operation as part of filling line). The preform is subsequently reheated, stretched and then blown into the final shape. Smaller injection stretch blow containers are now used for a range of liquid products with PETP being the currently preferred material. Greater use of injection stretch moulded polypropylene is also predicted.

Compression moulding

One of the earlier means of moulding, it is used for thermoset resins and certain rubber formulations, both of which undergo a 'curing' operation during the process. The powdered resin or rubber mix is placed into the lower half of a metal mould and the top half (female/male moulding) is brought together. The mould is heated and the molten materials are held under pressure (compression) until the hardening (chemical interaction) is completed. A catalyst is frequently used to accelerate the pressure, temperature, time cycle. During this cycle, gases and moisture vapour are released hence the mould has to be vented. Excess powder is usually added to ensure that the mould is completely filled, causing (with venting) flash at the mould joints, which is usually removed by tumbling or freeze tumbling. Since this gives rise to dust, mouldings frequently require an additional cleaning/washing process.

Compression transfer moulding (Thermoset)

This process is frequently used for more intricate mouldings. The thermoset powder is placed in a heated chamber, where it is liquefied and then transferred by a piston through a channel into a second mould, where the material is kept heated under pressure while the curing cycle is completed.

Although the above are the major moulding processes for thermosets, injection moulding can now be used for the selected thermoset moulding operations. The major use of thermosets still remains with screw closures. These are made on either a multicavity platen tool (up to 96 cavities) or a rotary type press which resembles a rotary tableting machine.

Thermoforming and blister (bubble) packs

Rigid blister packs may serve as a primary pack for a range of oral solid products (tablets, capsules, etc.), as a secondary display pack, to provide additional protection (physical and climatic) to a primary pack or as a security tamper-evident system for a product or pack. Soft blisters made from a flexible base can also be produced to contain liquids or semiliquids which can be dispensed by exposing a dispensing orifice.

Blisters can therefore extend beyond the simple solid dose form which is discussed in depth in [Chapter 13](#).

Rotational moulding

Although rotational moulding is used for both plastics and rubber, pharmaceutical applications, other than for rubber mouldings, are unlikely.

Dip moulding

This moulding process is normally applied to a rubber latex or plasticised PVC (plastisol) whereby a solid shape is dipped into a mobile liquid. When the material has set the formed shape is stripped from the mould.

Ancillary processes involved in plastic conversion

These ancillary processes include deflashing, removal of prominent injection points, welding, heat sealing, general sealing, and the addition of coatings and/or the incorporation of special barrier additives. Decoration and printing are covered separately and may be part of a coating stage.

Welding methods

Welding methods are listed in [Table 7.1](#). Ultrasonic welding is one of the most efficient methods of joining plastic parts, and different materials can be welded so long as they have a common monomer. While particularly useful for hard rigid materials, it may generate particles.

High frequency (HF) or radio frequency can be used on some flexible materials, e.g. PVC, PVdC, EVA and certain newer types of nylons and polyurethane coated materials. PVC blood bags and IV packs are made by HF welding methods in clean rooms.

Spin/friction welding primarily finds usage with engineering plastics such as acetal. It is occasionally used with plastic components found in packaging.

Adhesive and solvent bonding

Newer adhesives based on modified cyanoacrylates or chlorinated polymers, e.g. super glues, have increased the capabilities of adhesive bondings. These may occasionally be used on devices.

Improving the barrier properties of plastic

In the case of plastics, weaknesses in barrier properties can be substantially reduced by the use of glass-like or metal coatings based on silicon oxide, metal and metal oxides. These coatings use a range of techniques, e.g. dip coating, solvent, aqueous and aqueous dispersion coating, plasma enhancement, vacuum deposition. Carbon (diamondlike) coatings have recently become available (internal coating).

In addition to internal or external coatings, barrier enhancers can be incorporated into the plastic as additives. These can include various metal oxides, glass fibre, mica, etc. Incorporating a foil ply between layers of plastic is a further way of obtaining excellent barrier properties, e.g. multilayer laminated tubes, cold formed blisters, and additional overwraps should not be ignored.

Sterilisation of plastics

One of the early restrictions with plastic and pharmaceutical usage was associated with difficulties related to suitable sterilisation processes. The processes which can now be used include all conventionally available, i.e.

- autoclaving by steam sterilisation (moist heat)
- dry heat
- gamma irradiation

Table 7.1 Welding methods

<i>Material</i>	<i>Ultrasonics</i>	<i>High frequency</i>	<i>Spin/friction</i>	<i>Hot plate</i>	<i>Hot gas</i>	<i>Adhesive/solvents</i>
Acrylic/acrylic	E	F	E	E	E	F
Acrylic/styrene	F	NA	F	F	F	F

<i>Material</i>	<i>Ultrasonics</i>	<i>High frequency</i>	<i>Spin/friction</i>	<i>Hot plate</i>	<i>Hot gas</i>	<i>Adhesive/solvents</i>
Acrylic/polyolefins	P	NA	P	P	P	P
Acrylic/PVC	P	NA	F	F	F	F
Styrene plastics/ styrene plastics	E	E	E	E	E	E
Styrene plastics/ polyolefins	P	NA	F	F	F	F
Styrene plastics/ PVC	P	NA	P	P	P	F
Polyolefins/ polyolefins	F	F	E	E	E	F
Polyolefins/PVC	P	NA	P	P	P	F
PVC/PVC	F	E	E	E	E	E

Approximate comparative welding times: ultrasonics 100; spin 150; friction 200; hot plate 600. Key to compatibility: E=excellent, F=fair, P=poor or unsuited, NA=not applicable.

Taken from *British Plastics and Rubber*.

- accelerated electrons or beta irradiation
- gaseous treatment, i.e. ethylene oxide
- UV treatment
- heating with a bactericide (BP 1980)
- chemical treatment
- high-pressure sterilisation, i.e. 10 bar and more.

Steam autoclaving—moist heat sterilisation

Autoclaving with steam involves time/temperature relationships, i.e. 134°C for 3 min or 121°C for 15 min or 115°C for 30 min or such combinations of temperature and time which ensure sterilisation. It is advisable to carry out autoclave tests on any plastic as part of the development programme. Now that autoclaves have balanced or overpressure facilities, experiments have to be carried out in order that the correct conditions can be selected. It should be noted that distortion or extension (initially due to internal pressure in the pack) is likely to occur during the cooling cycle and it is during this period that additional pressure is required to overcome the internal pressure.

Steam autoclaving may be used for both filled (water-based) and empty packs and components which are subsequently assembled by aseptic processing. The plastics which can be steam sterilised include HDPE, PP, PC, PA and, under selected conditions, plasticised PVC.

Dry heat sterilisation

Dry heat sterilisation is rarely used for plastics, mainly because materials that can be subjected to temperatures of 160–180°C for 1–3 h are few and relatively expensive.

Gaseous sterilisation—ethylene oxide

Basically two processes are used: 100% ethylene oxide under negative pressure to ensure that any leakage is inwards, thereby reducing the risks of explosion; the alternative process uses ethylene oxide at a concentration of 10–15% with an inert gas diluent. Suitable diluents include nitrogen and carbon dioxide. Both methods need degassing processes to remove excess residual ethylene oxide levels which are absorbed by the materials. This may be done by a series of vacuum cycles, possibly with a raised temperature or natural degassing for, say, 7–14 days in a well-vented area either at ambient or a raised temperature. Testing for ethylene oxide retention is therefore advised for each different grade of plastic with extended periods of extraction until total extraction of ethylene oxide is proven. Extraction from LD polythene and plasticised PVC is relatively fast; it is relatively slow from polystyrene. Although ethylene oxide has low chemical activity and interaction with plastic or the ingredients of plastic are relatively rare, interactions with formulated products are occasionally found.

FDA recommendations have advised limits for ophthalmic and sterile injectable products. These limits include ethylene glycol from the hydrolysis of ethylene oxide and epichlorhydrin which results from the interaction of chloride ions with ethylene oxide. However, significantly lower levels are currently being advised, i.e. down to 2 ppm in Europe.

Gamma irradiation

25 kGy (2.5 Mrad) is the standard condition for the sterilisation of filled and packed products, packaging materials and components, and medical accessories. It is again advised that each material (type and grade) be thoroughly checked, by both an extractives procedure and chemical analysis of the plastic, before and after irradiation. Physical assessment is also advised, as most plastics when irradiated show an increase in the cross-linkage of the molecules which in the more flexible materials can be detected as a reduction in flexibility coupled with a reduction in impact strength and elongation. However, it should be remembered that irradiation may affect both the basic plastic polymer and any constituents included in the material. The fact that changes may not be apparent from visual examination does not preclude some form of chemical degradation. Smelling of components before and after treatment may occasionally indicate that a change has happened. Certain grades of LDPE have produced small quantities of formic acid/formaldehyde. Gamma irradiation has been used as a terminal sterilisation process where both product and pack are not affected.

Accelerated electrons (beta irradiation)

The accelerated electrons method is similar to gamma irradiation but milder in its effects on plastics. For this reason its usage is slowly increasing, with a number of plants now in use. Accelerated electrons or beta rays have lower penetration powers (compared with gamma irradiation) and sterilisation is normally achieved in seconds rather than hours. Effective checks are essential to establish whether any physical or chemical changes have any significance.

UV light radiation

This is not recognised by the BP or USP as a formal sterilization process. UV light is basically a surface sterilising process and is used in some sterile (class 1) areas to reduce any airborne contamination.

Hydrogen peroxide

Although not normally used for pharmaceuticals, hydrogen peroxide has been recognised by the FDA for the sterilisation of plastics (usually films) for the packaging of foods. A solution of 30–35% by volume hydrogen peroxide is normally used, with a residual limit of 0.1%. Filtered hot air is frequently used to remove and degrade hydrogen peroxide residues, sometimes in conjunction with exposure to UV light.

Heating with a bactericide (tyndallisation)

The British Pharmacopoeia 1980 included this as a sterilising process for aqueous products where the drug entity exhibits thermal instability but will withstand up to 100 °C for 30 min. The process was subsequently excluded from the BP 1988.

Problems associated with preservative 'loss' with plastic materials are expounded under aseptic processes and preservative systems.

Aseptic processing and preservation

Sterile pharmaceutical products may be achieved by either a terminal sterilising process or an aseptic process. The former, although normally involving steam, may occasionally be done by gamma irradiation. This latter process needs more rigorous monitoring, since changes may occur not only to the pack but also to ingredients in the formulation. In aseptic packaging, sterilisation of the packaging components may be achieved by any of the processes previously described. Since the product formulation may vary according to whether the pack is unit dose or multidose and the latter has to contain a preservative system, loss of preservative into (absorption), or onto (adsorption) the plastic is a factor to consider. In order to ascertain whether such a loss may be critical, it is necessary to identify the general properties which may be required from a preservative system, i.e.:

- 1 to offer a high level of antimicrobial activity against all micro-organisms
- 2 to be effective over a wide range of pH and temperature and remain stable

- 3 to be free from toxic, irritant and sensitising effects
- 4 to be compatible with the product constituents and acceptable in odour, taste and appearance
- 5 to be readily soluble at the concentrations used.

Examples of widely used pharmaceutical preservatives include benzoic acid, benzyl alcohol, para hydroxybenzoates, 2 phenylethanol, phenyl mercuric nitrate. Whereas some have been known to suffer from absorption in certain plastics, others have been known to suffer from variable adsorption, which is far less predictable than absorption since it depends on the surface area involved.

It can therefore be concluded that all plastics are capable of sterilisation but need the selection of the most suitable process. Plastics will not support the growth of microbial contaminants unless the surface is wet or a high storage RH is involved. The bioburden may be increased by certain particulates, particularly if these consist of materials which will support growth. Material cleanliness and low particulate levels are therefore a prerequisite for a fully effective sterilisation process.

Clean manufacturing facilities plus adequate GMP back-up are now essential for producing many plastic containers and components for pharmaceutical applications.

Conclusions

Plastics undoubtedly have an increasingly useful role to play in both the packaging and administration of pharmaceutical products. To summarise, emphasis is placed on their advantages and disadvantages together with advice on the information required to prove their general suitability.

Possible advantages

- 1 Light weight.
- 2 Reduced volume, (these two result in significant savings in warehousing and distribution costs plus advantages to the consumer).
- 3 No corrosion problems.
- 4 Good resistance to mould and bacteria.
- 5 Generally inert chemically, but be wary of 'solvents'.
- 6 Usually have good impact strength; difficult to break, if breakage occurs fragments tend to be less hazardous than glass.
- 7 Wide design and decorative possibilities.
- 8 Offer a wide range of moulding processes, enabling designs to be produced with fewer assembly operations, resulting in less labour-intensive activities; can be produced by form, fill, seal processes thereby giving low particulate levels with low microbial levels, e.g. blow, fill seal.

Possible disadvantages

- 1 No plastic is totally impermeable to moisture, gases, etc.
- 2 Most plastics permit some passage of light. Even highly pigmented plastics and those with UV absorbers are likely to let certain wavelengths through.
- 3 Many are difficult to clean or are liable to attract dirt and dust under unfavourable conditions (electrostatic). This can be reduced by minimal or controlled handling.
- 4 May be permeable to, or subject to attack by, organic substances, particularly solvents.
- 5 Subject to adsorption and absorption according to formulation ingredients (see section on preservatives).
- 6 Light weight and thin wall sections may require specific production line handling.
- 7 Fully effective closing systems are sometimes difficult to achieve.
- 8 Certain designs may show panning or cavitation.

No plastic will have all these advantages or disadvantages. A compromise between these factors will usually achieve an acceptable pack (for example shelf life could be reduced from 3 years to 2 years where a product shows some susceptibility to moisture). If in this example plastic offers certain plus factors, e.g. easier to handle and dispense, less risk in terms of safety, then the shorter shelf life compromise may well be worth while.

Setting the specification

To make certain that the plastic pack chosen has a high chance of success, it is perhaps worth concluding this chapter on plastics by repeating the list of points which need considering, i.e. a check list from which tests relevant to a particular pack should be selected.

- 1 Knowledge of formulation.
- 2 Information on plastic: type, grade, residues, additives, processing aids, details of masterbatching, if used; DMFs.
- 3 Toxicity/irritancy and the clearance of plastic and its constituents (reference to permitted lists including food grade approval).
- 4 Design and moulding process(es).
- 5 Physical and chemical analysis of plastic components against specification.
- 6 Handling onto, along and from production line.
- 7 Decoration, printing and identification.
- 8 Stress challenges—drop, impact, sterilisation, etc.
- 9 Cleanliness—microbiological and particulate.
- 10 Investigation tests with product accelerated tests.
- 11 Formal stability testing with product.
- 12 In-use tests, etc. (i.e. checking possible misuse, abuse by patient or user).
- 13 Storage, distribution and display (testing procedures).
- 14 Monitoring of complaints and customer reaction, interactions, comments.

As with all packaging materials, the ultimate specification is critical. Material purchase under warranty, provided the converting company operates a functional QC system and maintains good manufacturing practices, usually gives a good assurance that the material specified is supplied. In the long term this means that only specialist moulders with, for example, 'clean' production facilities will have the capability of reaching the standards required by the pharmaceutical, cosmetic and possibly the food industries. This may be coupled with minimum handling and possibly not supplying 'open' containers.

With the fast developments in the plastic industry, some of the lesser known plastics will either find future usage or already be used for devices, general medical instruments and apparatus or as implant aids. Certain plastics now involve alloys, i.e. mixtures of thermoplastics, and thermoplastic and thermoset resins. Improvements in what were the economic five plastics, i.e. polyethylenes, polypropylenes, polyvinylchlorides, polystyrenes and polyesters, are constantly occurring. Use of metallocene catalysts is likely to produce plastics of a controlled chain length.

Whether a moulding uses a virgin polymer or allows the use of regrind (plastic scrap from the moulding process) is a matter of an ongoing debate. However, as the continued use of regrind (i.e. regrind as regrind) can lead to some degradation, its use may have to be carefully controlled or a clause such as 'use of regrind not permitted' included as part of the specification.

Computer-aided design and computer-aided manufacture (CAD/CAM) may enable the lead times quoted earlier to be reduced.

Plastic technology is now reaching a stage where over 99% of pharmaceutical products could be packed in plastics within the next 5–10 years. How far this happens largely depends on the environmental debate. Thus when new products appear or old products are to be repacked, plastics rather than glass have now become the material of choice.

However, this choice initially starts with polyethylenes, the polypropylenes, the polystyrenes, the polyvinyls and more recently the polyesters. These relatively economical materials undergo continuing development and modification. For example, whereas LDPE was a hazy milky material where visual inspection might be considered suspect, higher clarity materials are becoming increasingly available. Antioxidant free grades of LDPE are also now offered (an EP requirement). The author therefore argues that most pharmaceutical products can be packed in these economical grades without resorting to the more expensive alternatives. If these economic grades lack certain barrier properties these can usually be overcome today by either suitable coating or overwrapping options.

Any new super-plastic, unless it matches the economics of the above, will take at least 10–20 years before it becomes a commercially successful material with wide pharmaceutical applications.

The emotive issues related to plastic and the environment have yet to be logically and scientifically resolved. However, predictable future trends which will increase the use of plastics in pharmaceutical applications are likely to include:

- 1 use of coextrusions for reel-fed blister packs
- 2 use of coextrusions for containers
- 3 increased use of unit dose packaging

- 4 extension of original pack (OP) dispensing which will increase the usage of smaller packs
- 5 greater use of combined packs and devices
- 6 increased usage of separate devices which will in the main be made from plastic.

Finally, recent guides offered by the FDA have identified the need for the following information when a plastic is used for parenterals (now similarly covered by EN 9090/III).

- 1 Name of manufacturer.
- 2 Type of plastic.
- 3 Composition, method of manufacture of the resin and the finished container, plus a full description of the analytical controls.
- 4 Physical characteristics (size, dimensions, whether flame treated, etc.).
- 5 Defect classifications (weight, seams, seals, wall thickness, pin holes, etc.).
- 6 Light transmission test, USP (particularly if product is photosensitive).
- 7 Tests (USP):
 - biological
 - physico-chemical
 - permeation.
- 8 Vapour transmission test (if appropriate).
- 9 Toxicity studies not included in USP:
 - sub-acute on extracts
 - cell culture.
- 10 Tests for leaching and migration.
- 11 Compatibility.
- 12 Sampling plan.
- 13 Acceptance specifications.

Although the list is substantial and useful, it ultimately should be possible to reduce it by increased knowledge and attention to QA and QC procedures.

It can therefore be concluded that a steady increase in the use of plastic for packaging materials, components and devices can be envisaged. Any trend to identify plastics suitable for pharmaceuticals (as already exists for foods) could possibly assist the industry, at least in the initial selection of materials. The fact that the quantities used by the pharmaceutical industry will never be large compared with, say, the food industry should make the industry aware that any increase in more stringent standards can only be achieved by an on-cost. Sharing standards with the food industry, whether it is related to materials or converted items, may produce an acceptable compromise.

However, it is inevitable that no textbook on plastics will ever be up to date, as technology and enterprise are constantly advancing. If this chapter creates an 'awareness' of the subject, the reader should be in a better position to keep abreast with new developments. There are, however, plastics which have not been mentioned together with variants of the moulding processes. Each plastic family also exists in many grades which, although initially quantified by melt flow index and density, may be far more complex as both homopolymers and copolymers may exist. Knowing the basics on polymers is essential to all activities involving polymers from creating designs, testing and approving them, right through to a successful product launch.

Although data sheets from polymer suppliers are a starting point for information on the properties of polymers, there is always a chance that materials may modify at least slightly during any conversion or treatment process. Such potential changes have to be checked by more and more sophisticated analytical methodology. This has to be supported by more in-depth knowledge of the polymers themselves.

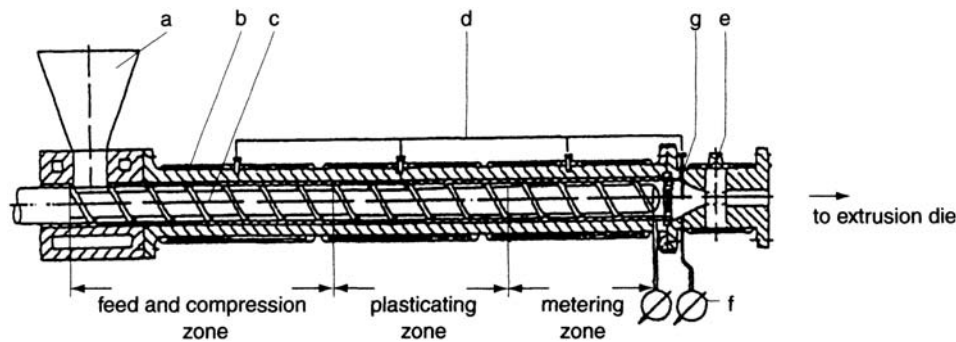


Figure 7.1 Design of an extruder plasticating barrel: (a) feed hopper; (b) heaters; (c) screw; (d) thermocouples; (e) back pressure regulating valve; (f) pressure gauges; (g) breaker plate and screen pack

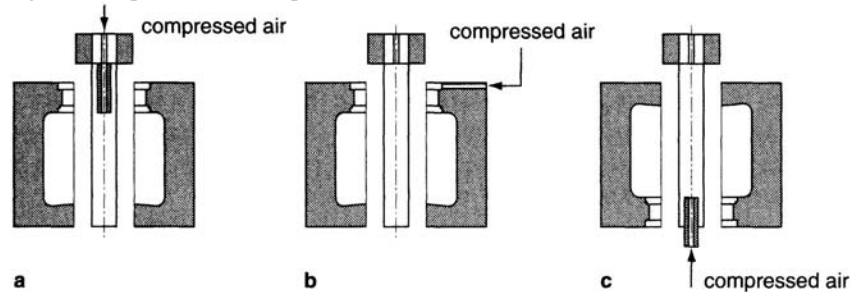


Figure 7.2 Blow moulding methods: (a) Plax method; (b) Mills/Pirelli method; (c) Kautex method

Appendix 7.1:

Processes used in the conversion of plastics

Extrusion and the extruder

Plastic granules fed via a hopper ((a) in Figure 7.1) are moved forward by a rotating screw (c) in a cylinder which has heating bands (b). The rotating screw compacts the material which undergoes plastication due to the heat and pressure. Although the process is usually continuous it can be made intermittent. In the continuous process the softened mass can be ‘extruded’ via a solid or hollow die to give a solid moulding, a sheet, a tube, etc., which is then cooled in water or air. The extruder is the work-horse of the plastic converting industry.

Extrusion blow moulding

This is based on the unit in Figure 7.1. An extruded tube flowing downwards is enclosed by a cooled finishing mould with a nip-off/weld at the top and bottom of the bottle (trim/waste) where it is then compressed air blown and cooled to the final shape. The mould(s) may be neck up or down in a straight line or as rotating carousel (see Figure 7.2).

Extrusion blow moulding

See Figures 7.2 and 7.3.

Lay flat tubing or tubular film

This is a further extension of the extrusion process. A tubular film emerging from a circular die is internally pressurized with air. This extends the film which, together with the temperature and draw off rate, decides the material gauge and degree of orientation. The film may be blown upwards, downwards, or horizontally (Fig. 7.4).

Injection moulding

The basis of an injection moulding is a modified extruder where there is an additional reciprocating action which enables a ‘shot’ to be forced into single or multicavity moulds. The design of the extruding screw is critical to the operation (Figures 7.5 and 7.6).

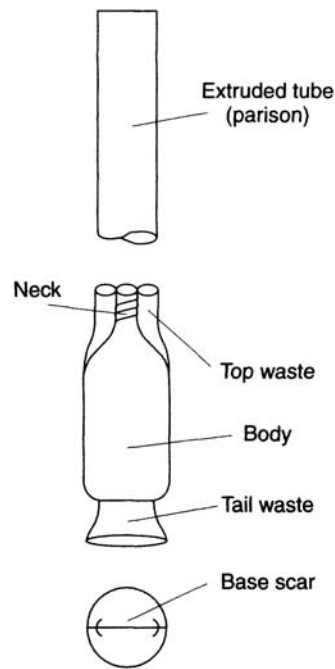


Figure 7.3 Extrusion blow moulding

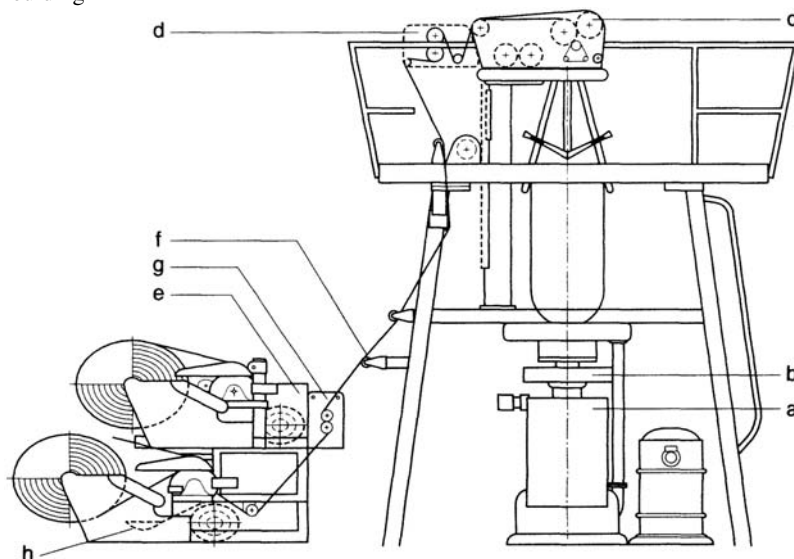


Figure 7.4 Tubular film apparatus: (a) extruder; (b) rotating blown film die; (c) haul-off unit; (d) pretreatment unit; (e) wind-up unit; (f) edge trimmer; (g) longitudinal cutter; (h) transverse cutter

Injection blow moulding

In this process a tubular-like shape is injected around a spigot or core pin (Figure 7.7). When released from the mould it is transferred to a second finishing mould where it is then further blown by compressed air to its final shape and cooled prior to removal from the mould. The operation is usually carried out on the rotating table principle. As in the process the neck of the container is moulded in the first stage, a higher quality is achieved compared with extrusion blow moulding. However, moulds are considerably higher in cost. As a result it tends to be restricted to smaller sizes, with particular application to pharmaceutical containers.

Extrusion and injection stretch blow moulding

Although both processes can produce reasonably good quality large containers, injection stretch blow moulding is more widely used for pharmaceutical containers. The first stage of moulding is basically as injection blow moulding. In the second

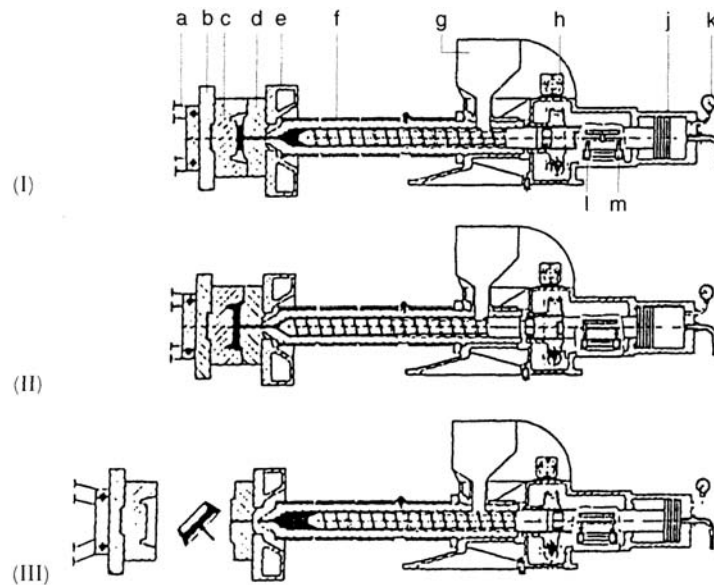


Figure 7.5 Injection moulding: design and operating sequence of a screw plunger injection moulding unit. (I) injection; (II) cooling (curing in the case of thermosets) under follow-up pressure; (III) ejection of the injection moulded part. (a) Clamping mechanism; (b) mould clamping; (c, d) injection mould; (e) mould clamping plate; (f) plasticating cylinder with screw plunger; (g) feed hopper; (h) screw drive; (j) hydraulic cylinder; (k) pressure gauge; (l) follow-up pressure limit switch; (m) screw stroke adjustment

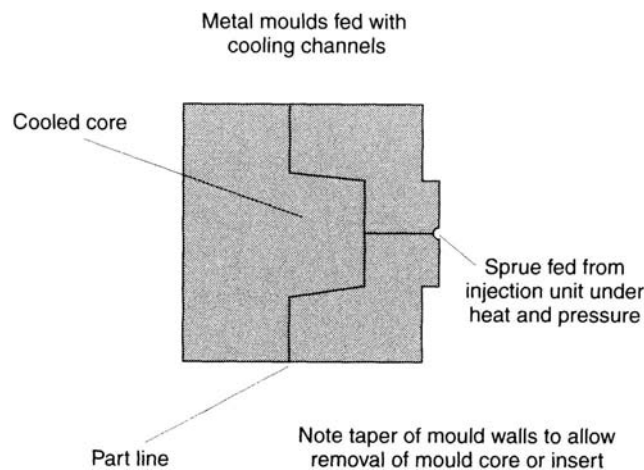


Figure 7.6 Typical two-piece mould for injection moulding

stage the preform is conditioned to the specifically required temperature and then stretched in the finishing mould longitudinally and axially in that order. The first stretching operation is carried out by a descending rod and the second by compressed air (Figure 7.8).

In extrusion stretch blow moulding the first stage is similar to the first stage of extrusion blown, but the parison formed is conditioned to a specific temperature prior to stretching initially by a descending rod and then by compressed air (Figure 7.9).

Thermoforming

Thermoforming consists of softening a material and then shaping it in a mould by vacuum, positive air pressure, or mechanically or a combination of these. Forming can be into or over (drape) a mould. The material following softening by heat can be directly moulded or extended by vacuum or pressure prior to being finally formed (Figure 7.10).

References

Metallocene—catalysed Cyclo Olefin Copolymers Vincent Sullivan—Medical Device Technology Oct 1998
 Developments in Technology of Polymer Mike Gaffrey, Development Engineer Hoechst UK Ltd

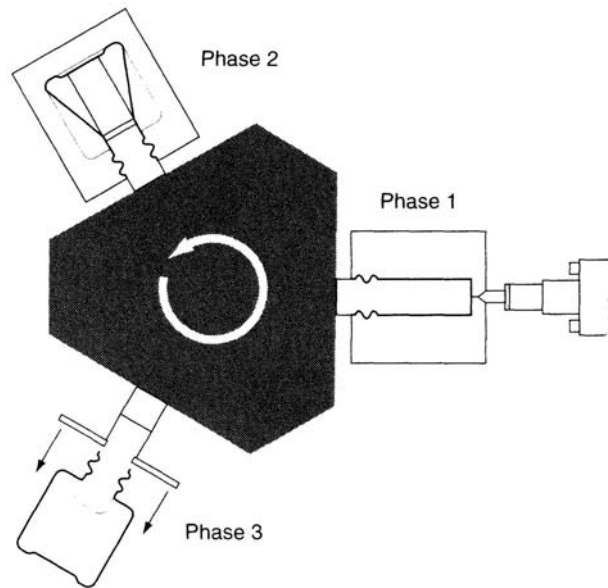


Figure 7.7 Injection blow moulding

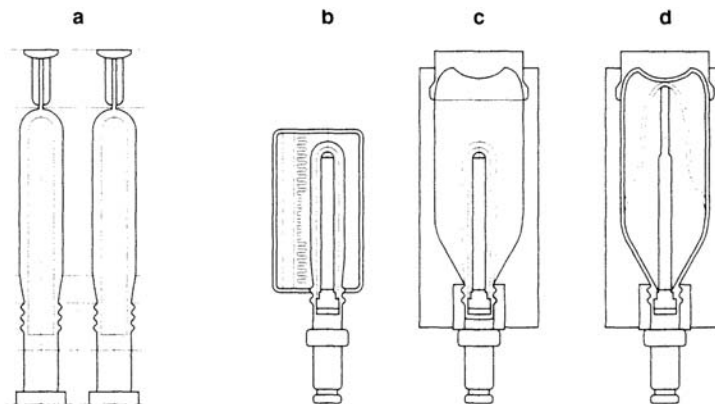


Figure 7.8 Injection stretch blow moulding

Polymer Thin film Biosensors and their possible application in Medical Packaging Technology, Lars Lindvold, Riso National Laboratory, Roskilde, Denmark Pharmaceutical and Medical Packaging Technology 1998 Vol 8, 21-1-21-2 ISBN 87-89753-24-0

Security Applications by Injection Moulding of Micro Structures and Medical (Devices) Packaging Henrich Gunstrip, Krukson Plast A/S Fredinchsvaerk, Denmark Pharmaceutical and Medical Packaging 1998 Vol 8, 21-1-21-2 ISBN 87-98753-24-0

The use of Holograms in Pharmaceutical and Medical Packaging Jan Stensborg, Centre of Advanced Technology, Roskilde, Denmark Pharmaceutical and Medical Packaging 1998 Vol 8, 20-1-20-4 ISBN 87-89753-24-0

Static Electricity Fire Hazard, Restricted or Cleanroom Areas. Martin Hughes. Stat attack, Buckinghamshire, UK Pharmaceutical and Medical Packaging 1998 Vol 8, 19-1-19-2 ISBN 87-89753-24-0

Vitamin E, as an antioxidant choice for Polyethylene Medical Packaging, Anthony O'Driskoll, Ciba speciality Chemical Inc. Basel, Switzerland.

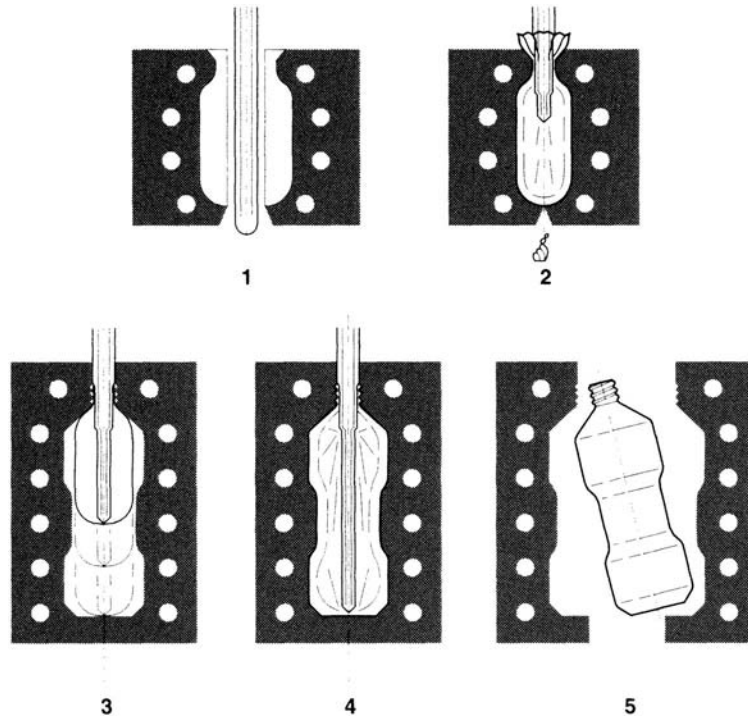


Figure 7.9 Extrusion stretch blow moulding: (1) extrusion; (2) blowing and conditioning; (3) stretching; (4) blowing; (5) ejection

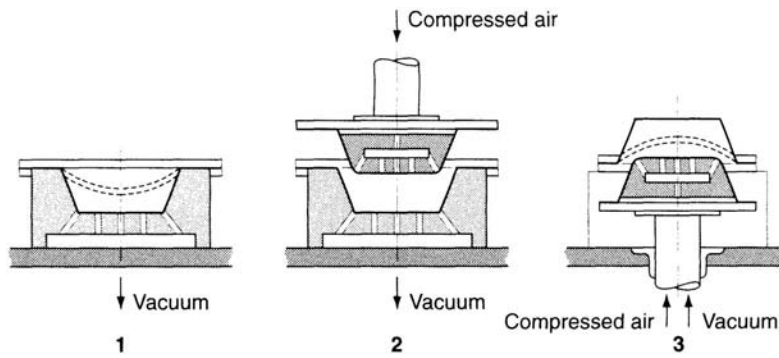


Figure 7.10 Thermoforming: (1) female mould, vacuum, no prestretching; (2) female mould, pressure forming with male or plug, prestretching; (3) male mould, vacuum, with pressurised air prestretch