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Use of Plastics for Parenteral Packaging

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I. INTRODUCTION

The field of parenteral packaging has changed in many ways since the advent of parenteral drug delivery technology. In the earlier days of practice, medications were almost exclusively packaged and dispensed in glass. This was the only material of choice because of its availability and physical properties. Glass has excellent clarity, thermal resistance, barrier properties, and is chemically inert. The use of other materials, such as rubber and aluminum, grew in popularity with the need for better packaging. Rubber was chosen to seal glass containers and aluminum to hold the rubber in place. There are several identified weaknesses for glass that have been considered acceptable due to its use over time as the material of choice. Glass breaks easily, is heavy, and requires a rubber closure as a seal.

Dramatic developments in polymer technology occurred during the 1950s that introduced the use of plastics to replace glass. Plastic resins overcome the weaknesses of glass but present a new set of possible problems that must be considered and understood. Plastics are relatively unbreakable and extremely light compared with glass. Their weight is approximately one tenth the weight of glass on a volume to volume basis. They are readily fabricated into a variety of complex shapes thereby providing ease of handling and packaging. Lastly, the cost for plastic products is generally less than glass.

The use of plastics for the medical industry has markedly expanded in recent years. Table 1 [1] summarizes the amount of plastics used in medical applications in the United States since 1984. The table is broken down by material, process types, and areas of use, and it shows that use of plastics for medical applications has grown since 1984 at an average rate of 5.7% per year, while the total plastics market has expanded at only 4.5% per year.

Table 1 U.S. Resin Sales by Process by Medical Market (millions of pounds)

Plastic material	Process and (market)	1984	1985	1986	1987	1988	1989	1990
Cellulosics	(Medical)	0	0	0	0	3	4	4
HDAP	Blow molding (pharmaceuticals/cosmetics)	155	165	182	194	202	198	202
Polypropylene	Blow molding (medical containers)	40	42	42	48	55	51	55
	Injection molding (medical)	115	115	120	148	160	154	168
Polystyrene	Injection molding (medical)	55	60	64	77	82	74	90
PVC	Calendering (hospital and health care)	22	23	26	33	35	40	44
	Extrusion (medical tubing)	43	50	54	70	71	73	76
	Dispersion coating (hospital & health care)	8	8	10	15	17	18	20
	Injection molding (hospital & health care)	20	25	28	41	42	42	40
Total pounds		511	542	584	696	740	727	777
Total U.S. market (lbs)		44500	46506	49495	54763	57952	58251	61480
Present usage for medical applications		1.14%	1.16%	1.28%	1.27%	1.28%	1.25%	1.26%

These figures illustrate the strong demand for plastics in medical applications. How much of these quantities are used for parenteral packaging is difficult to ascertain since there are a broad variety of products currently on the market that use plastics. Table 2 shows a list of typical parenteral products along with the plastic resins commonly used for each application.

The means for the selection of a plastic material that comes in contact with parenteral drugs are not simple. The properties of each resin must be thoroughly understood along with its manufacturing process. Plastics do not match the barrier properties of glass for oxygen and moisture transmission. With plastics, there must be special attention given to the additives present in the formulation due to the possibility of their migration from the resin. In most cases a compromise is required in the areas of clarity and temperature resistance when comparing plastics to glass. All of these properties will change to varying degrees depending on the type of plastic selected. The product design, fabrication process, environment for manufacture, and the method used for product sterilization will also require careful planning and are factors that will affect the properties of the final product. This chapter covers an overview of each of these areas, all realted to the development of plastic products for parenteral packaging.

II. FUNDAMENTALS

A. Definition of Plastics

Plastics are polymers, both synthetic and natural, which can be shaped when softened and then hardened to produce the desired structure. A polymer is

Table 2 Examples of Plastics Used for Parenteral Drug Containers

Sterile plastic device	Plastic material
Containers for blood products	Polyvinyl chloride
Disposable syringe	Polycarbonate Polyethylene Polypropylene
Irrigating solution container	Polyethylene Polyolefins Polypropylene
i.v. Infusion fluid container	Polyvinyl chloride Polyester Polyolefins
Administration set	Acrylonitrile butadiene styrene Nylon (spike) Polyvinyl chloride (tube) Polymethylmethacrylate (needle adapter) Polypropylene (clamp)
Catheter	Teflon Polypropylene

simply a large organic molecule built up from the repetitious joining of smaller molecules or monomers. Most polymers are linked together by carbon to carbon bonds with a variety of complex organic groups attached to the carbon molecular chain. The repeating monomers are joined together by a reaction process called polymerization that utilizes heat, pressure, and various reaction catalysts. The monomers commonly consist of atoms of carbon, hydrogen, oxygen, nitrogen, and halogens (fluorine, chlorine, and bromine) [2].

For example, if one takes ethylene gas and processes it by heat and pressure in a closed vessel utilizing a catalyst to bring about the reaction process, a repeating ethylene molecule is formed called polyethylene. After removal of the catalyst residue and drying, the polyethylene powder may be melted into a mold, or extruded into a tube or sheet to produce a useful shape or structure. Several processes may be employed to reshape the polyethylene, as discussed in later sections.

There are a variety of monomers that can be used to produce plastic polymers with different structures. For example, styrene monomer is used to produce polystyrene. The resulting polymer has a repeating aromatic ring attached to every other carbon in the structure backbone. This produces a plastic with markedly different physical characteristics from the previous example of polyethylene. The structural relationship between the monomer and repeating units of three common polymers is shown in Table 3.

B. General Classifications for Plastics

Thermoplastics Versus Thermoset Plastics

There are basically two main classes of plastics: thermoplastics and thermosets. At some stage of their conversion into finished products, both types are fluid enough to be formed or molded. Thermoplastics are polymers that soften upon heating to higher temperatures and solidify again upon cooling. Thermoplastics may be remelted repeatedly. They are reprocessible and therefore reusable. Thermosets in their fluid condition are still chemically reactive and harden by a further reaction, called crosslinking, between groups on nearby chains, forming a three dimensional network [3]. Subsequent heating that would somewhat soften the structure cannot restore the flowability that typifies the uncrosslinked, uncured resin. Therefore, thermoset plastics cannot be reprocessed once they are crosslinked. Typical thermosets are phenolics, formaldehyde resins, epoxies, and crosslinked polyesters. For

Table 3 Monomers and Repeat Units of Three Common Polymers[a]

Polymer	Monomer	Repeat unit
Polyethylene	$CH_2{=}CH_2$	$+(CH_2CH_2+$
Polyvinyl chloride	$CH_2{=}CHCl$	$+(CH_2CHCl+_n$
Polystyrene		

parenteral packaging, thermoplastic materials are preferred over the thermoset polymers due to their availability, reusability, and processability. Therefore, the remaining discussion will be confined to thermoplastics.

Classification of Thermoplastics

Engineering Versus Commodity Resins. Thermoplastics can be further classified into engineering thermoplastics and commodity thermoplastics. Engineering thermoplastics are normally plastics that are able to withstand a load or to be formed into some sort of structural product. These plastics are specifically formulated to achieve some desired set of properties, as for example, stiffness or impact resistance. These materials may be higher priced than commodity resins, but provide added value in being designable for various applications. One example of an engineering thermoplastic is an i.v. spike that is designed to penetrate a rubber i.v. stopper.

In this case, rigidity and resistance to breakage are engineering properties that are essential to the application. Commodity plastics are normally lower-cost resins that are designed for large volume production. The variety of formulations and performance features are limited since large volumes of a single plastic are important to maintaining low prices. However, many commodity thermoplastics have attributes desirable for parenteral packages and other applications. Polypropylene is an example of a commodity-type thermoplastic that has application in certain types of parenteral vials.

Rigid Versus Flexible Resins. Thermoplastics can be either rigid or flexible, depending on the complexity and degree of crystallinity of their polymer structure [4]. Polymers that are synthesized from simple monomer units such as polyethylene tend to be flexible. Bulky aromatic structures, as well as crystalline structures, tend to produce greater rigidity. Some thermoplastics such as polyvinyl chloride can be plasticized to achieve a high degree of flexibility utilizing additives such as dioctyl phthlate. Application examples are medical tubing, parenteral bags, and other flexible containers where lack of rigidity is desired [5].

On the other hand, many applications require rigidity and dimensional stability. Certain load-bearing applications such as rigid vials, clamps, etc., require substantial rigidity.

Transparent Versus Opaque Plastics. The degree of transparency, or opacity, exhibited by a plastic material is also related to its molecular structure. Perhaps the greatest influence on clarity is the degree of crystallinity. Highly crystalline materials, such as high-density polyethylene or nylon, tend to be opaque because crystallites refract light and, therefore, do not transmit light. Some amorphous plastics, such as general purpose polystyrene or polymethylmethacrylate, transmit light and exhibit a high degree of clarity.

Several plastics, including acrylics, polystyrene, polycarbonate, and polymethylpentene have light-transmitting properties close to, or better than, glass [6]. Other plastics, such as polypropylene, have good liquid contact clarity. This means that when liquid is in contact with the surface of the plastic, it appears clear. A list of common transparent polymers is shown in Table 4.

If plastics are to compete with glass in pharmaceutical packaging applications, clarity is one of the most important characteristics. Other necessary

Table 4 Transparent Polymers

Polymer	Symbol	Degree of transparency	Light transmission[a] (%)
Acrylonitrile methylmeth-acrylate styrene	Transparent ABS	Translucent	72-88
Acrylic	PMMA	Clear	88-92
Nylon (amorphous)		Clear	86-90
Polycarbonate	PC	Clear	87-91
Polyester	PET	Clear	90
Polymethylpentene	TPX	Clear	90
Polystyrene	PS	Clear	87-92
Polysulfone		Transparent (amber)	75
Rigid polyvinyl chloride	PVC	Transparent	74-76
Polypropylene[b]	PP	Translucent	<70

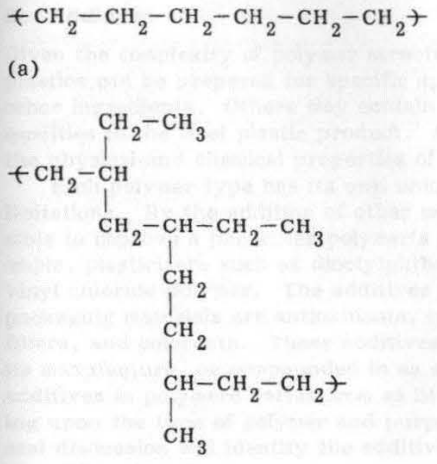
[a]Percentage of light passing through vs. light refracted as measured by refractometer.
[b]Polypropylene has good contact clarity.

properties to be discussed in later sections are heat resistance for sterilization, impact resistance (resistance to breakage and abuse), and barrier properties for adequate shelf life. Although there is a long list of plastics that can be made opaque, clarity is often more difficult to achieve. Applications where clarity is important are parenteral vials and bottles, syringes and i.v. bags. Opaque plastics are used in i.v. spikes, clamps, closures, etc., where properties other than clarity are needed.

C. Basic Polymer Structure

The chemical structure of a polymer molecule determines its physical, chemical, and mechanical properties, as well as its heat stability and resistance to aging.

Elements of structure such as molecular weight, molecular-weight distribution, degree of crystallinity, and additive content are primary determinants of these properties. Polymer properties can be varied during polymerization —the basic chemical process carried out to produce the polymer. As described in Section II.A, the polymer is formed under the influence of heat, pressure, catalysts, or a combination, within vessels called reactors. One special form of property variation involves the use of two or three different monomers as



(a)

(b)

Figure 1 The structures in parentheses represent arbitrary sections of polymer: (a) linear polyethylene and (b) branched polyethylene.

comonomers, i.e., copolymerizing them to produce copolymers (two comonomers) or terpolymers (three comonomers).

Polymers that are formed into long linear chains will have different performance characteristics than those that are branched or interconnected to form a three-dimensional structure. The arrangements of the repeating structural units in a linear and branched polymer are illustrated in Figure 1.

Multi- or copolymer systems are those that have more than one type of repeating unit, and this often results in more favorable properties, such as toughness or flexibility, than are present in the individual homopolymers. The resulting properties are also influenced by the "manner" in which the repeating units appear in the polymer chain. The specific properties will be discussed in a later section. By employing different synthesis techniques, copolymers can be made with alternating, random, block, or grafted repeating units within the polymer chain. Each type of copolymer structure is illustrated in Figure 2.

Unlike small organic molecules, polymers contain molecules with different chain lengths. The chain-length distribution of a polymer can be claculated statistically. This is generally referred to as the molecular-weight distribution (MWD) of the polymer. This information can be used to predict or evaluate polymer processing parameters and performance characteristics. When two polymers have identical chemical structures but have different MWD, the processing parameters and performance characteristics of the two polymers may be considerably different.

The degree of order in a polymer system is directly related to the degree of crystallinity. By definition, a crystalline polymer system is one in which a high degree of order prevails. Conversely, an amorphous (noncrystalline)

Alternating

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-A-B-A-B-A-B-A-B-A-B-A-B-A-B-
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Random

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-A-B-A-A-B-A-B-B-A-A-A-B-A-B-
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Block

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-A-A-A-A-B-B-B-B-B-A-A-A-A-A-
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Graft

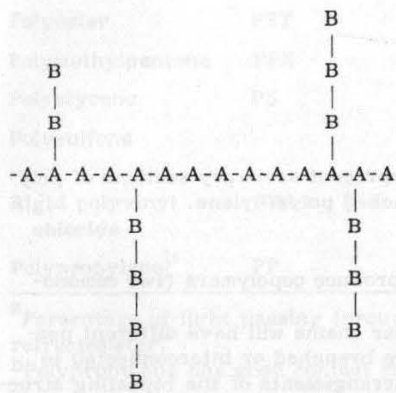


Figure 2 Four types of multicomponent polymer systems where A and B represent two different repeating units.

system is devoid of order. Generally speaking, most polymers have both amorphous and crystalline regions, the degree of each varying with the individual polymer system. Crystallinity is largely determined by the type and size of the repeating unit and how well the polymer chains are arranged in a lattice array.

Crystallinity is an important parameter in determining many of the plastic's physical and chemical properties. In general, the higher the degree of crystallinity a polymer has, the more brittle and rigid it will be. As stated earlier, such a polymer will also exhibit less permeability and transparency.

Since polymers are not generally as inert as glass, they may be subject to degradation and oxidation during the useful life of the product. Furthermore, degradation and processing difficulties may be encountered during the fabrication of the product. These problems can be reduced or eliminated by the use of additives to protect the basic polymer.

D. Additives

Given the complexity of polymer structures described in the previous section, plastics can be prepared for specific application without the addition of any other ingredients. Others may contain additives to impart specific desired qualities to the final plastic product. Additives are frequently used to modify the physical and chemical properties of the plastics.

Each polymer type has its own unique characteristics and often has use limitations. By the addition of other molecules as additives, it is often possible to improve a particular polymer's performance characteristics. For example, plasticizers such as dioctylphthalate give flexibility to a rigid polyvinyl chloride polymer. The additives most commonly found in thermoplastic packaging materials are antioxidants, heat stabilizers, lubricants, plasticizers, fillers, and colorants. These additives are combined with the polymer during its manufacture, or compounded in as a post operation. The concentration of additives in polymers varies from as little as 0.01% to as much as 60%, depending upon the type of polymer and purpose of the additive. The following general discussion will identify the additives sometimes used in parenteral plastic packages.

During storage of these parenterals, the additives could extract or leach into a drug solution in intimate contact with the plastic container. Therefore, it is important to evaluate the physical and chemical compatibility of a drug formulation in a packaging system under various storage and time conditions to insure safety and stability of the drug product. Whenever possible, evaluations should be conducted under conditions simulating those to which the product probably will be exposed. Evaluations should take into consideration not only the physical and chemical compatibility of the drug formulation with the primary packaging system, but also should include an investigation of the long-term effects (2 to 3 years) on mechanical properties of the primary packaging system.

Additives for specific types of plastic will be discussed in detail where appropriate in Section IV.

Antioxidants

Many plastic materials are susceptible to oxidative degradation and require antioxidants to slow down the process and to give them a longer shelf life.

Polymers are often exposed to heat, light, ozone, and mechanical stress in the presence of oxygen during the fabrication process and end use processes and storage. The resulting oxidative effects will cause the formation of free radicals, which contribute, in turn, to the degradation of the polymer with a gradual loss of important physical and mechanical properties of the plastic. The presence of effective antioxidants in the plastic formulation will significantly reduce the degree of degradation and, therefore, help to extend the lifetime of the plastic package.

Degradation of a plastic material is a sequential process involving initiation, propagation, and termination phases. Free radicals are formed on exposure to heat, radiation, or mechanical shear. Antioxidants intercept the radicals or prevent radical formation during processing or during the shelf life of the plastic.

There are two types of antioxidants. Primary antioxidants interrupt oxidative degradation of plastics by tying up the free radicals. Such primary antioxidants as the hindered phenolics and the aromatic amines both have a reactive NH or OH group and can donate hydrogen to the free radicals. Phenolics, such as butylated hydroxytoluene (BHT), are the most widely used in plastic parenteral packaging. BHT has a broad FDA approval and is used in polyolefins, polyvinyl chloride, and polystyrene, among others.

Secondary antioxidants decompose the unstable hydroperoxides formed in the plastic degradation process to inert products, thus preventing the proliferation of radicals. They are used in conjunction with primary antioxidants to provide added stability to the plastic materials. The most popular ones are thioesters and phosphites.

Antioxidants in parenteral packages can migrate to the surface and then leach out into the contents. Further, the combination of antioxidants with other additives may interact with the drug solution to alter its potency. Therefore, one must be aware of the antioxidant chemical species used when considering a parenteral package formulation.

Heat Stabilizers

During the manufacturing process of certain polymers, and/or the fabrication process for the final package component, heat, pressure, and shear energy can cause degradation of the polymer structure or cause discoloration of the polymer. Addition of a heat stabilizer will reduce these undesirable reactions. Heat stabilizers are generally required in the manufacture of polyvinyl chloride polymers (PVC). Metallic stearates and expoxidized plasticizers are the most commonly used heat stabilizers.

Stabilizers are also used to retard or to prevent the deterioration of plastic materials resulting from exposure to light, heat, and pressure and to improve their aging characteristics. The commonly used families of stabilizers include epoxy compounds (expoxidized soybean oil), organotins (octyltin), and mixed metals (barium and cadmium benzoate). Some of the stabilizers have some solubility in aqueous media and, consequently, could be extracted into a drug solution. Therefore, these stabilizers must be carefully chosen.

Lubricants

The term lubricant is used to describe a wide range of additive materials that ease the movement of a melted polymer against itself, or against other material surfaces, commonly metal. Lubricants can be classified into internal or external lubricants, depending upon their purpose in the polymer process. A principle difference between internal and external lubricants is their compatibility with plastic resins. Internal lubricants must be compatible with given polymers since their action is to reduce internal cohesive forces allowing the molecules greater mobility. The results are lower melt viscosity, increased flow, and reduced energy requirements for processing. Stated simply, internal lubricants enhance the ease with which polymer molecules slip past one another. Examples of internal lubricants are fatty-acid amides, fatty-acid esters, and polyethylene waxes.

External lubricants must be relatively incompatible with the polymer as they must migrate to the surface during hot processing to reduce friction

between the polymer and hot metal surfaces. The addition of a lubricant avoids resin sticking to the hot metal surfaces increasing material output and avoiding possible degradation. Examples of external lubricants are zinc stearates, silicones, and fluorocarbons.

The quantities of lubricants used vary significantly from one plastic to another. Typical concentrations of external lubricants such as metal stearates are 0.05 to 3.0%, while bisamide synthetic wax is used as an internal lubricant in concentrations from 0.5 to 3.0%.

Plasticizers

Plasticizers are a broad group of chemically and thermally stable materials, ranging from liquids to solids. They are used in plastic compounds to impart flexibility, resilience, reduced brittleness, and softness to various polymers. At the same time, they may facilitate processing.

Plasticizers may be liquid monomers, viscous polyesters and epoxides, or solid rubbery polymers. The most commonly used plasticizers in parenteral plastics are dioxtyl phthalate and low-molecular-weight polyesters.

More than 80% of all plasticizers are used with PVC; the rest go into such plastics as cellulosics, nylon, polyolefins, and styrenics. Phthalates are the most popular plasticizers. For example, 30 to 40% of phthalate ester is added to PVC material to produce a flexible intravenous fluid bag, such as the Viaflex (Baxter) and Lifecare (Abbott).

As is true of stabilizers, plasticizers can migrate to the surface of a plastic container and are, therefore, potentially extractable into a drug solution.

Fillers

Addition of fillers to base polymer may result in reduced flexibility and impact resistance, improved heat stability and/or reduced material cost. In the parenteral plastic containers made from such plastics as PVC, small amounts of submicron fillers are used as brighteners. The addition of these fillers may impair the transparency of the plastic container.

Colorants

Certain plastics have an inherent color that is not aesthetically desirable and, upon aging, the color becomes more intensified. To rectify this problem, parenteral manufacturers may add a colorant or tint to hide the undesirable color of the polymer. Both dyes and pigments are available for use in plastics. Experience has shown that dye molecules have a tendency to bleed out of the polymer matrix upon aging, but pigments have been shown to be nonbleeding. Ultramarine blue is one of the most commonly used colorants for parenteral plastics.

From the foregoing discussion, the reader is now aware of basic "plastics" vocabulary, making it possible to examine in some detail the important polymers for the parenteral industry. In Section IV, polymer types will be described in a systematic manner to facilitate comparison. They will be discussed with consideration for the physical, chemical, and mechanical properties of the plastic, the additives necessary for processing and stability, and the potential problems that they (polymer and additives) might present to the parenteral manufacturer.

III. FABRICATION PROCESSES

There are many processes used to convert plastic resins from pellets into desired shapes or configurations. As covered in the section on fundamentals, this means using heat to excite the molecules of a polymer in preparation for a forming process. All plastic processes are similar in the use of three basic elements to convert the resin from a pellet to its processed shape.

1. *Heat*: excites molecular structure to allow free movement of molecules
2. *Pressure*: to form the free flowing polymer into a desired shape
3. *Time*: required to allow for transfer of heat into the plastic followed by time for removal of heat (cooling)

These three basic elements will be discussed in detail for each of the processes covered in this section. When selecting a process there are several factors that must be considered. In most parenteral packaging applications, it is necessary to use several types of processes to complete a product for shipment to a customer. This is especially true when the product package is included in the overall project, as in fabrication of the outer package for protection during shipping. Use of flexible and rigid blister packaging is widely used as an outer protective pack. It can be clear, provide a large area for product labeling, and offers the potential to maintain product sterility.

Generally the product design or configuration will dictate what process must be used to manufacture the item. It is important in the design cycle to understand the strengths and weaknesses of the process alternatives. A product can be designed to utilize or, perhaps, eliminate a particular type of process. This is a critical step in the development stage, because the processes used will have a significant effect on the total manufacturing costs. There are times when making an intentional design modification will eliminate the need for a complete process step or change the efficiency or throughput of a manufacturing step.

With this in mind it is important, in the design cycle, to work closely with a group that has a high level of technical experience in the specific process areas that may apply to the product under development.

The following sections cover a review of each of the key plsatic processes used in parenteral packaging applications. Each process description will include a review of the basic steps involved along with the important factors affecting efficiency for each. Some examples will also be used to give a better understanding.

A. Extrusion of Plastics

The process of extrusion involves the melting of a plastic and forcing it through a die under pressure to form a desired shape. There are several different types of extrusion, depending on the die arrangement used to form the plastic. The three most widely used for parenteral packaging are flat-sheet extrusion, profile-tubing, and blown-film extrusion.

In each process, plastic resin is fed into a long barrel which converts the plastic into a homogeneous melt through the use of heat, pressure, and time. This equipment is known as the extruder, and is shown in Figure 3.

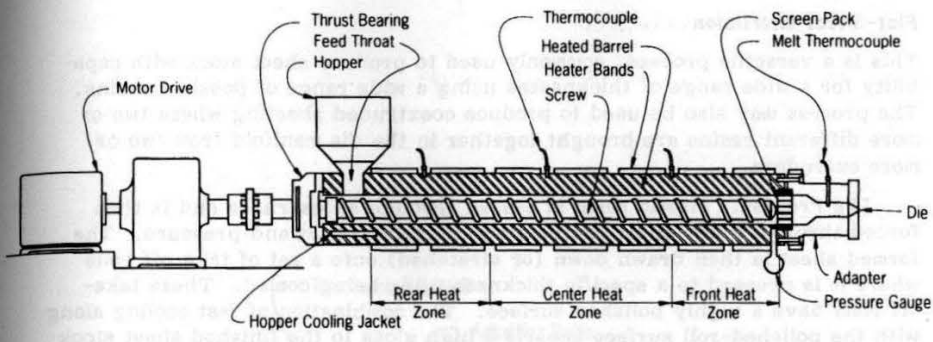


Figure 3 Various components of a single-screw extruder, showing three zones of the extruder barrel.

The extruder is powered by a drive motor used to turn a screw inside of a heated barrel. The screw is a large auger, made of a hard grade of steel and is closely toleranced to fit with a precise clearance through the length of the barrel. There are three zones; the *feed*, the *transition*, and the *metering* (Fig. 3) [7]. As the screw turns, material is fed by the hopper into the feed section of the screw. The material is melted as it feeds forward by heat applied on the barrel. As the material passes into the transition zone (center section), the pressure increases significantly due to a reduction in the screw flight width. This pressure increase is essential to create effective mixing of the resin and also creates a self generation of heat, called shear heating. After passing the transition zone the material goes through the metering zone (last section) where it is essentially conveyed forward with no change in pressure. The purpose for the metering zone is to allow time for a through mixing of the resin melt and to stabilize the pressure before entry into a forming die. A picture of a simple extrusion screw, illustrating the basic parts is shown in Figure 4.

The throughput or capacity necessary for a particular application will determine the required extruder size. Throughput is expressed in pounds of resin per hour which relates directly with the diameter of the screw.

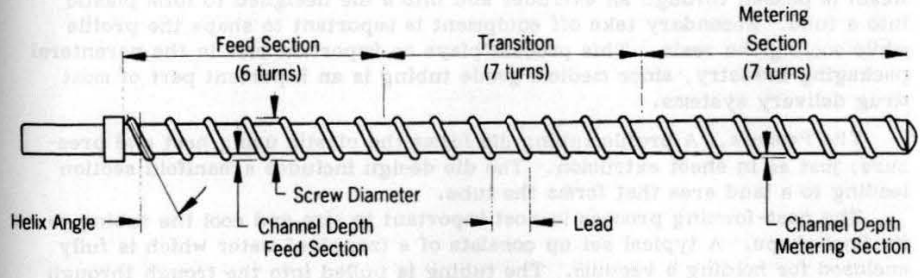


Figure 4 Illustration of a simple extruder screw, showing the basic parts.

Flat-Sheet Extrusion

This is a versatile process, commonly used to produce sheet stock with capability for a wide range of thicknesses using a wide range of possible resins. The process may also be used to produce coextruded sheeting where two or more different resins are brought together in the die manifold from two or more extruders.

The Process. Plastic resin is passed through an extruder and is then forced through a flat-sheet profile die at a specific heat and pressure. The formed sheet is then drawn down (or stretched) onto a set of take-off rolls where it is pressed to a specific thickness while being cooled. These take-off rolls have a highly polished surface. The combination of fast cooling along with the polished-roll surface imparts a high gloss to the finished sheet stock [7]. The sheet is then trimmed in a post-extrusion step to eliminate uneven edges and is cut into a fixed length or is taken up into roll stock.

The profile die consists of an internal manifold leading to a pair of die lips that are adjustable to a specific gauge thickness. The die is heated using flat plate heaters that are controlled by thermocouples. These dies may vary in size over a wide range of lengths and can be quite costly. An illustration of a simple sheet profile die is shown in Figure 5.

Applications. As stated above, the sheet extrusion process can be used for a wide range of applications because of its versatility for sheet thickness and resin seleciton. There is a significant volume of resin used in applications of blister packaging and "form, fill, and seal" packaging. The preference for clear grades of plastic that have a high degree of stiffness are common for these end uses. These resins will be discussed in more detail in the section on plastics for parenteral packaging. Another application for this process is large volume parenteral (LVP) containers. Extruded sheet can be made in multiple layers using a more sophisticated process with multiple extruders all feeding to one sheet die. The combination of several types of plastic can be used to increase performance of the final sheet with respect to impact strength, toughness and barrier properties. The use of multiple layers can open up new applications that were not possible with single-layer extrusion.

Profile Tubing

This process is similar to sheet extrusion in the basic process steps involved. Resin is passed through an extruder and into a die designed to form plastic into a tube. Secondary take off equipment is important to shape the profile while cooling the resin. This process plays an important role in the parenteral packaging industry, since medical grade tubing is an important part of most drug delivery systems.

The Process. A profile tubing die forms the plastic using heat and pressure, just as in sheet extrusion. The die design includes a manifold section leading to a land area that forms the tube.

The post-forming process is most important to size and cool the tubing to its final shape. A typical set up consists of a trough of water which is fully enclosed for holding a vacuum. The tubing is pulled into the trough through a series of external sizing dies. Vacuum is pulled in the chamber to create an

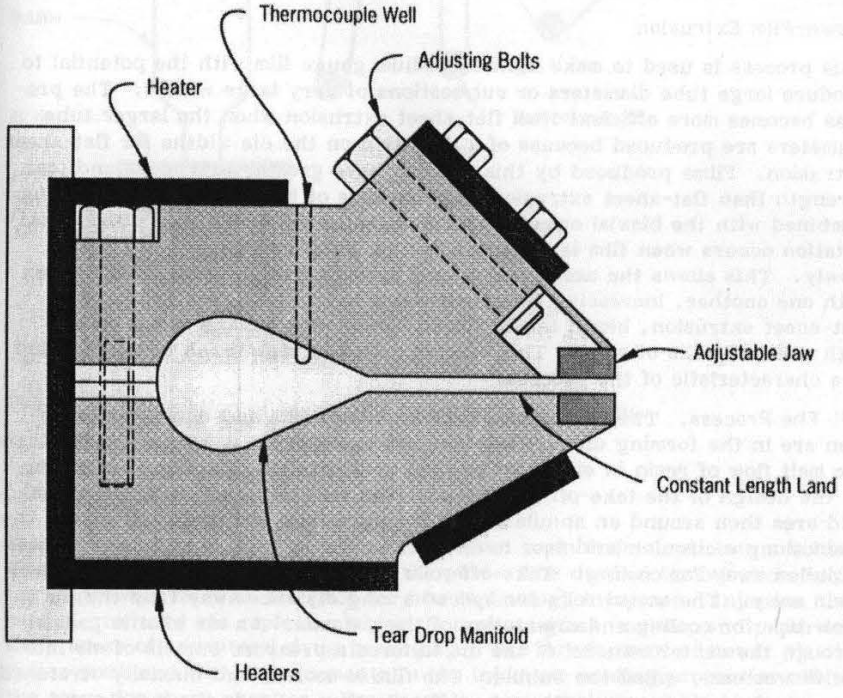


Figure 5 Illustration of a typical flat-sheet extrusion die.

internal pressure that forms the tubing along the sizing dies. A station then slices the product to its finished length. In cases where the tubing is flexible, it can be taken up onto rolls of finished stock.

Applications. Profile tubing is widely used as a part of LVP packaging to deliver i.v. solutions or drugs from the bulk container to the delivery site. Flexible polyvinyl chloride is the dominant resin used for this application, although use of this resin is being challenged because of concerns for migration of plasticizers and stabilizers into the i.v. solution. This will be covered in more detail in the section on plastics selection.

Blown-Film Extrusion

This process is used to make light to medium gauge film with the potential to produce large tube diameters or cut sections of very large widths. The process becomes more efficient than flat-sheet extrusion when the larger tube diameters are produced because of a limitation on the die widths for flat-sheet extrusion. Films produced by this process have greater toughness and tear strength than flat-sheet extrusion films because of the slower rate of cooling combined with the biaxial orientation that is imparted to the film. Biaxial orientation occurs when film is stretched in two directions while being cooled slowly. This allows the molecules of long polymer chains to align themselves with one another, increasing their resistance to breaking. In contrast to flat-sheet extrusion, blown film is cooled slowly with air and is not cooled with polished rolls of steel. This creates a dull or matt finish in the film and is a characteristic of the process.

The Process. The differences between blown-film and flat-sheet extrusion are in the forming die and the take-off equipment. A blown-film die turns the melt flow of resin in either an upward or downward direction, depending on the design of the take-off equipment. The melt is passed through a manifold area then around an annular die. Pressure from the extruder pushes the resin along a circular land area to an annular die lip area, where the material is pulled away for cooling. Take-off rolls are used to pull the formed ring of resin away. The actual rolls are spaced a long distance away from the die to allow time for cooling and orientation of the material. An air inlet is passed through the center mandrel of the die to force a pressure curtain of air into the film column, called the bubble. The film is cooled, and biaxially stretched through the bubble area. The take-off rolls then collapse the bubble and pull the sheet away where the film is trimmed and rolled up as finished product. An illustration of a simple blown-film line and die is shown in Figure 6.

Co-extrusion is also important with blown film as with extruded sheet. A combination of two or more resins can be used to obtain a unique set of properties for the resulting film. In applications where a film comes in direct contact with i.v. fluid, it is important to use cleaner resins such as polyethylene. Other materials may be used in the outer or center layers to improve other necessary properties, such as a barrier to oxygen or moisture.

Applications. Blown film is used to a great extent for LVP containers using PVC resin. As with flat-sheet extrusion, co-extruded films are entering this market due to the emphasis on cleaner materials with less extractables. Blown film is commonly used as flexible outer packaging for shipment of finished product and for bulk product shipped in corrugated containers.

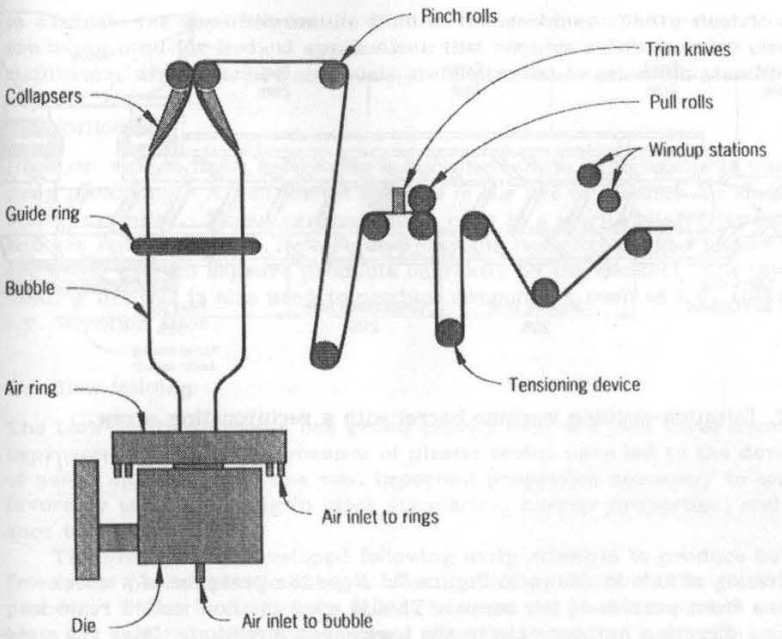


Figure 6 Illustration of blown-film extrusion line and die.

B. Injection Molding

Injection molding is a process used to convert resin from a melt into a molded shape using a mold pattern to form the part. The demand for injection molding is growing more as the pace for new technology increases. Injection molded products are replacing materials such as glass, metals, and paper in many areas of parenteral drug packaging. The development of newer plastic resins combined with improvements in the injection-molding process are setting the stage for these changes. For example, new copolymer resins have improved clarity along with higher heat deflection temperatures and improved barrier properties. Many of these newer resins are used for drug delivery systems that are replacing products traditionally made from glass.

The Process

In this process plastic resin is melted, using the extrusion process, and is injected into a mold where the resin is cooled enough to be removed in a solid state. Like the other plastic processes, heat, pressure, and time are used in each of the steps to produce a molded product.

There are two common methods to prepare material for injection into the mold. The first and most common is called a reciprocating-screw extruder, where material is accumulated in front of the rotating screw as the screw moves backward. It is this backwards motion that implies the name reciprocating.

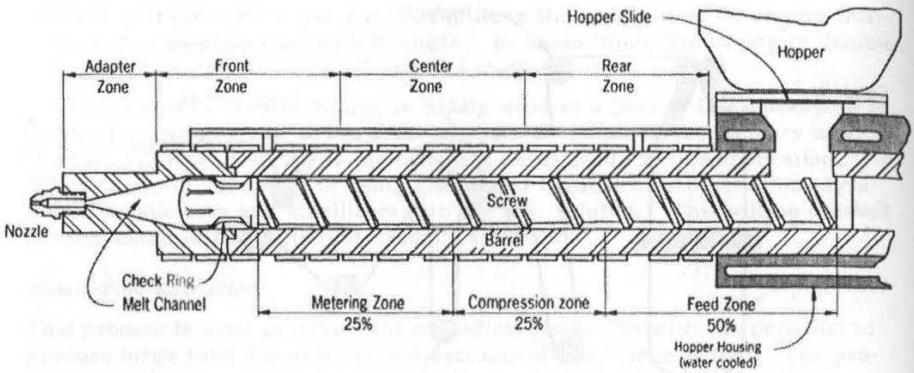


Figure 7 Injection-molding machine barrel with a reciprocating screw.

An illustration of this is shown in Figure 7. Note the presence of a check ring at the front portion of the screw. This is used to allow melted resin to pass in one direction but not pass in the backwards direction. Once the accumulation area is filled the screw is moved forward at a set speed and hydraulic pressure, applied to inject material into the mold area. The second type of injection unit is called the ram-assist plastication system. With this type a separate ram cylinder is filled as the extruder conveys material forward. Once filled, the ram piston is pushed forward at a set speed and pressure to inject material into the mold.

There have been many developments in injection-molding machines and in the molds that form the part. The use of computer-aided design (CAD) has helped make this possible. With injection molds, hot-runner systems are being more widely used to produce parts with high levels of quality. A hot-runner mold is one where the melted resin is conveyed directly to the part in a hot state with a hot-runner manifold and hot-runner nozzles. The term "runner" is used to define a channel of plastic used to convey material through the mold to the part. Hot-runner molds are used frequently for production of medical items, because they eliminate the use of regrind resin. In a cold-runner mold, the molded runner system is ground up and mixed back into the new material (called virgin resin). With medical items, especially those used in contact with drug for injection, it is important to use only virgin material. This eliminates the possibility for contamination from foreign particles and from resin that may be partially degraded by heat.

Injection molding machines are going through some dramatic changes. Process control and process/quality control tracking have improved part quality a great deal. Closed-loop process control is a development where inputs from the process are fed back into the controller. The controller then makes adjustments to the process to achieve tighter control of each process variable. The recent development of all electric molding machines has made it possible

to eliminate the use of hydraulic fluid in the machine. These electric machines are being used for medical applications that require molding under clean room conditions, where particulate levels are controlled to establish standards.

Applications

Injection-molded items are having many entries into applications in parenteral drug packaging. A well known example is the use of plastics for single use sterile syringes. These syringes often come in a sterile blister type package and are ready for use. Newer polypropylene resins that have higher clarity are being used to improve products currently on the market. The injection molding process is also used to produce components such as i.v. spikes and i.v. injection sites.

C. Blow Molding

The blow-molding process has grown rapidly over the past three decades. Improvements in the performance of plastic resins have led to the development of newer applications. The most important properties necessary to compete favorably with packaging in glass are clarity, barrier properties, and resistance to heat.

The process was developed following early attempts to produce bottles from a hot pool of plastic using a blowing needle, similar to the glass-blowing process. These first attempts failed, because the plastic materials would not blow out uniformly like molten glass. Shortly thereafter a solution was found wherein plastic resin was formed into a uniform tube with one end closed. This tube, called a parison, is blown outwards into a mold cavity using pressurized air.

The Process

There are two types of blow molding used in today's market. They are extrusion blow molding and injection blow molding. With extrusion blow molding a hot parison is formed and moved into a mold where the two ends are pinched off, and the material is blown outward into the shape of the mold. The injection blow molding process was later developed as a different means to handle containers of various shapes. In this process a pre-form is made using the principles of injection molding. The pre-form is molded using a first-stage mold and is transferred into a second mold. It is then blown outward using pressurized air to form the container. An illustration of the two types of processes are shown in Figure 8.

Containers produced for health care applications, such as tablet bottles, are made primarily using the injection blow mold process. With small containers this process is more cost effective than extrusion blow molding because of its capability for handling a large row of pre-forms at one time. It is not unusual to have a machine with an 8, 12, or even 20 cavity preform station. In addition, the threaded area of each container will have more detail and a higher quality appearance resulting from the preform step. Extrusion blow molding lends itself to larger containers where it becomes more economical and practical to eliminate the pre-form step. Specific decisions on what process should be selected will depend on requirements of the application combined with the size and geometry of the container.

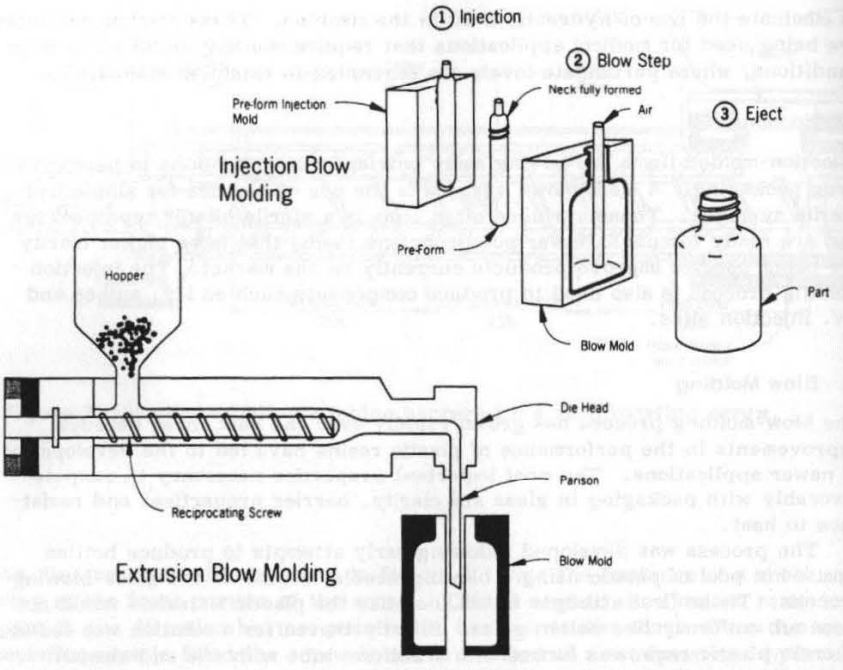


Figure 8 Shown at left is a parison being transferred directly into the blow mold (extrusion blow molding). At right, a pre-form is made using the injection-molding process. The pre-form is then transferred into a blow mold (injection blow molding).

Applications

The injection blow mold process has long been used for applications such as aspirin tablets, vitamin capsules, and other oral dosage forms. Until recently there has not been much use of plastic for containers in packaging parenteral solutions. Glass containers have dominated this market from the beginning.

The major reason for this has been a concern for contamination of the product from the plastic resins used. Also, there is a big concern for barrier properties and how this relates to shelf life of the packaged product. Improvements in the process and the plastic materials have addressed some of these concerns. The industry is becoming more aware of the advantages of plastic materials, and there is a better understanding of how certain plastic resins will perform with various drug solutions. Migration of extractables into solution has been found to be less of a problem than anticipated with the growing experience resulting from the use of plastic resins in other applications.

Polypropylene vials have recently been introduced on the market as a replacement for glass to package potassium chloride solutions for i.v. use. Polypropylene is a good candidate for this application because of its barrier properties for moisture vapor transmission.

PET (polyethylene terephthalate) is another resin being studied to replace glass in parenteral packaging. This resin has excellent clarity combined with good barrier properties. Large volumes of PET are currently used for soda beverage bottles because of these two properties combined with the advantage of a competitive resin price.

IV. IMPORTANT CRITERIA FOR SELECTION OF PLASTICS

A. Physical Properties

Two principal considerations in the selection and design of pharmaceutical packaging materials are mechanical properties and resistance to deformation during sterilization or other heat producing processes. A critical difference betwen plastics and glass is in the mechanisms by which they respond to dynamic stresses incurred during sterilization cycling, various manufacturing processes such as filling or lyophilization, transporting and shipping, and finally handling. Although plastics are to varying degrees affected by heat processes, they have the advantage over glass of flexibility and resistance to breakage during impact or dynamic vibration during transport.

In this section, physical properties related to the final package performance are discussed. Other physical attributes such as hardness, density, color, abrasion resistance, or coefficient of friction may be important dependant upon the specific packaging application being considered. This discussion is primarily limited to two dynamic properties, thermal and mechanical. These properties are greatly affected by the basic polymer structure described in Section II.C. Molecular weight and crystallinity are primary factors affecting the strength and stiffness of polymeric materials.

As molecular weight increases, molecules become highly entangled and the cohesive forces between them increase, affecting the mechanical strength. The thermal energy required to excite these molecules to the point of breaking down these cohesive intermolecular forces is determined by the molecular structure.

Mechanical Properties

When plastic materials are subjected to excessive mechanical stress, they will deform permanently or break catastrophically. Most plastics are viscoelastic in nature. This means that they exhibit both elastic qualities and viscous flow qualities. Representing the response (strain) of a given plastic to an applied force (stress), Figure 9 illustrates a linear elastic region, at the onset of the stress/strain curve, followed by a nonlinear region (both elastic and flow). The third region is basically horizontal (viscous flow). Brittle polymers break prematurely and, therefore, do not exhibit viscous flow. Also illustrated in Figure 9 is the effect of temperature on stress/strain behavior. At low extensions the plastic material can recover without any permanent deformation when the force is removed. At deformations beyond the elastic limit, molecules begin to slide past one another creating a permanent deformation.

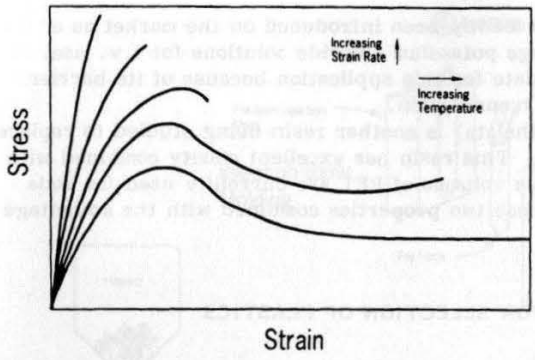


Figure 9 Stress/strain curves for plastics.

Catastrophic failure under gradually increasing mechanical stress is defined as the plastic's ultimate strength. The degree of deformation (strain) incurred as a result of this stress is termed the ultimate strain and is dependant upon rate of deformation. Many polymers exhibit a yield strain point prior to the onset of viscous flow. A yield stress can be measured at peak in the stress/strain curve. Whether the mechanical stress applied is tensile, flexure, compressive, torsional, or shear, the fundamental molecular mechanism is the same.

Impact Strength. Impact is one of the most important types of catastrophic mechanical stress failure. Impact strength represents the "toughness" or resistance of a material to sudden blows or application of a force. The force is normally applied at a very high strain rate.

Impact strength is normally expressed in terms of the energy required to break a material under a prescribed set of conditions. Unlike plastics, glass containers are particularly vulnerable to brittle failure upon impact due to vibration during transport or droppage. Most plastic packages resist brittle failure due to their ability to absorb energy upon impact. Viscoelastic polymers having relatively high fracture strains (elongation) can provide a cushioning effect and absorb substantial amounts of energy during initial deformation.

Generally, energy absorption through deflection is more readily achieved with relatively low modulus materials, but not exclusively. Package design can play a significant part in allowing the plastic to bend or deflect under stress. General purpose polystyrene, for example, is a rigid, brittle material, yet thin wall cups can withstand significant impact blows because their walls can bend. Other designs that can improve impact resistance are curved surfaces, bases, shoulders, etc., strategically located to blunt and distribute impact loads [8].

The most common testing methods used to evaluate impact strength of plastic packaging materials follow.

1. *Drop weight-ASTM D3029.* The drop-weight test is the best for material characterization, because it measures energy to initiate failure [9]. The

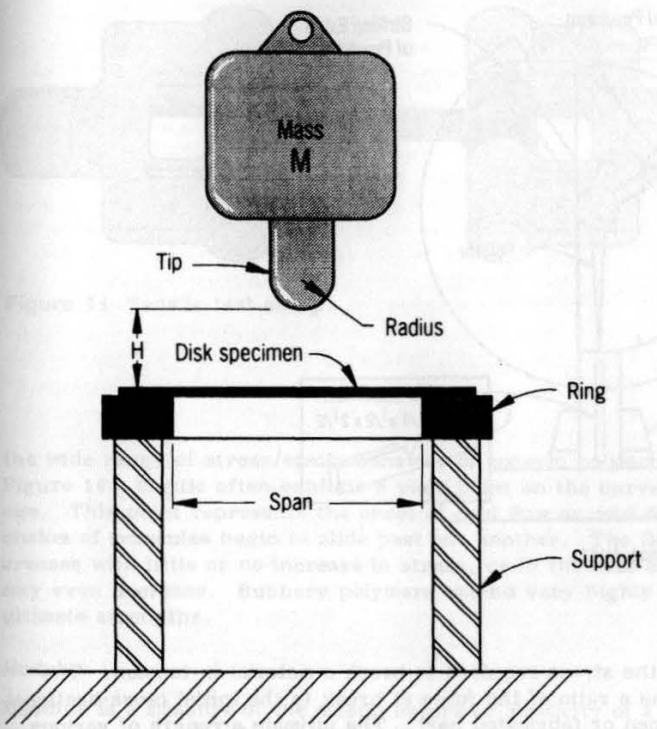


Figure 10 Schematic of drop-weight impact test.

test apparatus is simple in construction and easy to operate. Testing speed can be varied over a wide range, and low temperature testing can easily be performed. A schematic of the test apparatus is shown in Figure 10.

2. *Izod-ASTM D256.* The energy required to break a rectangular-bar test specimen mounted as a cantilever and struck by a pendulum is measured (Fig. 11). A severe notch is built into the specimen in the plane of maximum stress to create a stress concentration point.

The Izod test, in addition to testing energy of impact, measures notch sensitivity of a plastic material. Materials that have very high Izod values such as high-impact ABS usually are relatively insensitive to stress concentration factors, and therefore, show good impact performance in parts. Low-density polyethylene and polycarbonate are other examples of plastics with good Izod impact values.

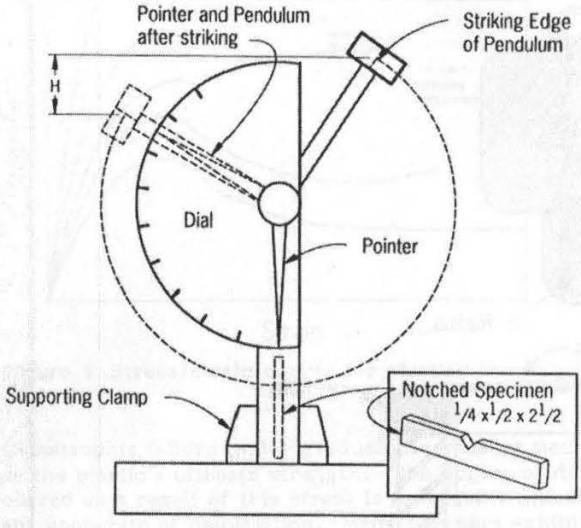


Figure 11 Izod impact test.

Tensile Strength

Tensile strength is the stress required to break a material in tension. The stress is measured as a ratio of the force at break to the initial cross-sectional area of a test specimen or fabricated part. The ultimate strength of various plastic materials to failure can be compared using tensile strength test as described in ASTM method D638.

Figure 12 and 13 show a typical test setup where a dog-bone shaped test specimen is pulled at one end while attached at the bottom. A load cell attached to the instrument measures the force required to extend the specimen to the point of yield and/or breakage. Force divided by cross-sectional area is reported.

Tensile strength and extension at break represent the maximum stress and maximum strain that a material can withstand. Typical curves illustrating

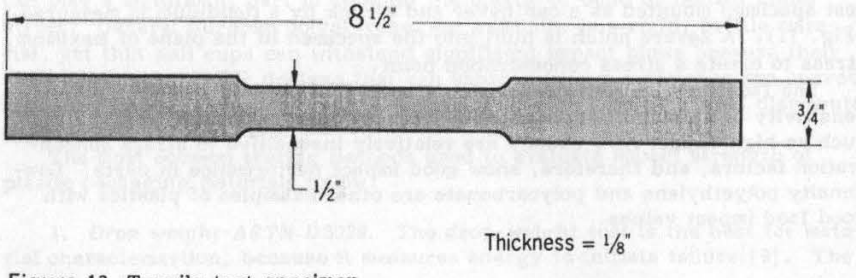


Figure 12 Tensile test specimen.

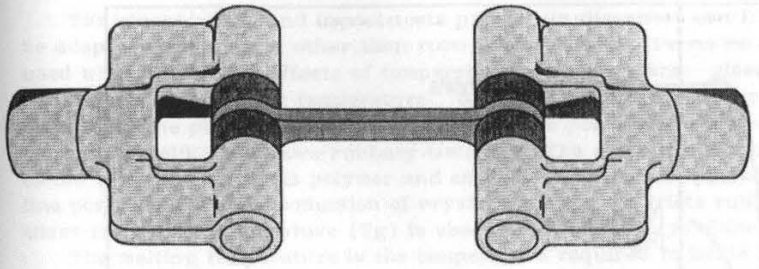


Figure 13 Tensile test setup.

the wide range of stress/strain behavior of common polymers are shown in Figure 14. Plastic often exhibits a yield point on the curve prior to breakage. This point represents the onset of cold flow or cold draw where the chains of molecules begin to slide past one another. The flow extension increases with little or no increase in stress, or in the case of polyethylene, may even decrease. Rubbery polymers extend very highly but have lower ultimate strengths.

Modulus

Modulus is a measure of the elastic nature or elasticity of a polymer. It is measured as a ratio of stress over strain, normally taken from the beginning elastic (straight line) region of the stress/strain curve described in Section IV above. Modulus is measured within the range where the deformation is reversible and proportional to the stress. The value of modulus indicates resistance of a material to reversible longitudinal deformation.

Modulus is very useful as a design parameter for pharmaceutical packaging. To prevent premature failure, materials should be slected to accomodate stresses well above the requirement of the package design. For some applications where almost rubbery elasticity is desirable, a material with high ultimate elongation and low modulus, may be an asset. For rigid parts, such as an intravenous spike, a higher modulus is desired. Table 5 lists comparative modulus values for some common plastics used in pharmaceutical packaging applications.

Thermal Properties

Physical properties of plastics are greatly dependant upon temperature. Plastics often stiffen and become brittle at low temperatures below what is often termed the brittleness temperature for that polymer. Conversely, they may begin to soften and become more rubbery and lose strength at higher temperatures. For these reasons, it is important to define the particular process and exposure temperatures of the pharmaceutical package. For example, if one is sterilizing by means of an autoclave, a minimum temperature resistance of 121°C may be required for the material.

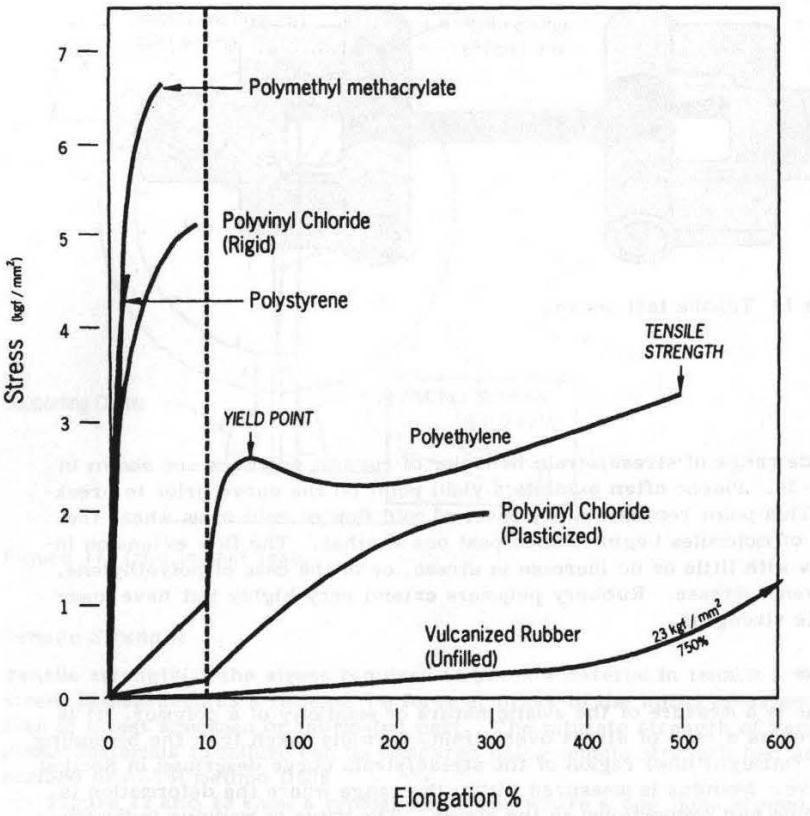


Figure 14 Stress/strain behavior of common polymers.

Table 5 Elastic Modulus of Common Plastics Used in Pharmaceutical Packaging

Resin	Tensile modulus PSI (ASTM D638)
Polyethylene	25,000-75,000
Polypropylene	100,000-225,000
PVC	50,000-80,000
Polycarbonate	345,000
Polyester (PET)	400,000-600,000
Polysulfone	350,000

The stress/strain and impact tests previously discussed can frequently be adapted to testing at other than room temperatures. Terms most commonly used when describing effects of temperature on plastics are: glass-transition temperature and melting temperature. Glass-transition temperature is a term describing the physical state of a polymer at the point where it changes from a rigid, glasslike to a more rubbery material. The glass transition is associated with an amorphous polymer and amorphous regions of partially crystalline polymers. The introduction of crystallinity also restricts rubberiness. Glass-transition temperature (Tg) is absent in a wholly crystalline polymer.

The melting temperature is the temperature required to begin melting the crystalline regions of a polymer, also known as the crystalline melting point. Crystallities cannot exist above a certain temperature, they melt. Amorphous polymers and/or amorphous regions of semicrystalline polymers soften and become rubbery or exhibit a highly viscous melt as temperature increases. Amorphous polymers, therefore, do not exhibit a crystalline melting point.

The test for semicrystalline polymers is accomplished using a fabricated, molded or extruded, specimen (ASTM D2111) [10]. Samples are heated by a hot stage/plate mounted under a microscope. The specimen is viewed through cross-polar prisms. The melting temperature is measured at the point where the crystals begin to disappear.

For primarily amorphous polymers not exhibiting a distinct melting temperature, a softening point can be measured using ASTM D1525. In this test a molded specimen of a specified height is used. An apparatus is used to slowly raise the temperature of the specimen with a flat ended needle sitting on it. The temperature at which the needle penetrates the specimen is the softening point of that polymer [11].

B. Optical Properties

The importance of optical properties, particularly clarity, in polymers for pharmaceutical packaging has been brought out in Section II.A, subsection on Fundamentals. Clarity in primary packaging of intravenous (i.v.) fluids is particularly important due to the need to see small micron-size particles called particulates which may be present [3]. Solid particles of any material, organic or inorganic, are viewed as contaminants in solution which, depending upon size, could lodge in the blood stream or body tissue and accumulate as foreign substances.

In addition to visualizing particulates, packaging clarity is important for dosage monitoring or measuring, and delivery of parenterals to the patient. Examples are syringes and i.v. tubing where delivery monitoring is important.

Transparent polymers are generally amorphous. Crystallinity tends to refract and scatter light that passes through the polymer. While it has been observed that molecular weight is not a determining factor for calrity or transparency, the nature of end groups, side groups, and molecular branching in the polymer structure will produce some changes in absorption and refraction of light. The use of additives, fillers, plasticizers, or reinforcing agents in the plastic can drastically affect optical properties, especially where the refractive indices of blended materials do not match. Lastly, optical properties of polymers can be significantly affected by polymer processing.

All processes produce varying degrees of molecular orientation which affects clarity/transparency. Also, cooling surfaces during polymer processing affect clarity and surface gloss of the finished product.

The optical properties of a plastic are normally expressed in terms of refractive index, light (or luminous) transmission, and haze. Refractive index is the ratio of the velocity of light in free space to the velocity of light in the medium. Light transmission is the ratio of the intensity of light exiting from an optical material to the intensity entering the material. Haze is "that percentage of transmitted light which is passing through the plastic specimen deviates from the incident beam by forward scattering" (ASTM D1003) [10]. Several plastics, including acrylics, polystyrene, polycarbonate, and polymethylpentene have light-transmitting properties close to, or better than, glass.

C. Chemical Properties

The primary pharmaceutical packaging material must be chemically compatible with and unaffected by the parenteral solution over the finished dosage form's intended shelf life. The plastic material or its additives should not extract or leach into the package contents. The plastic should not absorb any portion of its contents as occurs in the example of nitroglycerine solution in P.V.C. containers and tubing (PVC adsorbs a significant amount of nitroglycerine solution reducing the dosage received by the patient). To make an intelligent package material selection, a careful evaluation should be made of the composition of the packaging material in conjunction with the composition of the drug formulation. Drug compatibility will be discussed further in Section IV.F.

Polymer compositions with relatively saturated backbone structures are generally more inert and require fewer additives, such as antioxidants, which could migrate to the surface. Generally, structures with higher degrees of crystallinity and/or higher molecular weights are more inert to chemical attack and resist leaching of additive material(s). More complicated structures containing double bonds and aromatic rings tend to require more stabilization additives to protect them from degradation due to oxidation and heat during processing. Characterization of these additive compositions is necessary to evaluate their potential extractability and their effects on the package contents.

USP XXII [12] describes a battery of tests to be performed on aqueous extracts from plastics materials. These include tests for nonvolatile residues, heavy metals, buffering capacity, etc. The extract tests are designed to characterize leachable substances. The polymer material can be more completely characterized utilizing the following types of tests.

Infrared Spectroscopy

One of the most basic tests that can be performed on a plastic material or one of its components is an infrared (IR) spectrum. An IR spectrum provides a fingerprint or sharply defined identity of the material being tested. This fingerprint is a means to detect changes in the plastic's formulation or additives.

Ultraviolet Spectroscopy

Ultraviolet (UV) spectroscopy is a very useful tool in identifying and in some cases, quantifying extracted additives containing conjugated double bonds or

aromatic ring structures. Normally, plastics are extracted by autoclaving or, at the very least, boiling the sample in distilled water. Soxhlet extraction is used in cases where more extensive information concerning the additives in the package is needed. In this extraction method, a given quantity of polymer is palced in the extraction apparatus and then refluxed for up to 24 hr using a solvent such as methylene chloride, chloroform, or diethyl ether. The extract is then evaporated, quantified, and prepared for spectroscopic examination using UV and IR techniques.

Atomic Absorption Spectroscopy

This is a rapid technique [13] used to analyze for the presence of trace metal elements such as lead and calcium. Sample preparation is relatively simple, usually involving autoclaving a sample with a high surface-to-volume ratio of polymer to distilled water. Alternatively, total metals available in a polymer can be determined by ashing a test specimen and subsequently digesting the ash in a dilute hydrochloric acid solution before testing. Sensitivity in the parts-per-billion range can be routinely obtained.

Chromatography

Chromatography is a physical method of separation in which the components to be separated are distributed between two phases. One phase is a stationery bed of large surface area, and the other is a fluid or gas which perculates through or along the stationary bed. The technique is used to characterize the constituents of a mixture both qualitatively and quantitatively.

High Performance Liquid Chromatography (HPLC) has become an increasingly important tool in the last 10 years. The versatility of the technique lies in the wide range of organic samples that can be analyzed. This is made possible by the numerous types of solvents, columns, and detectors that can be utilized. For example, there are currently available fluorescence, UV, refractive index, IR, conductivity, and several other types of detectors. HPLC can be utilized in two ways. (1) Separation of additives individually from their base polymer can be accomplished and each component of the complex mixture extraction solution can be qualitatively and quantitatively analyzed. The separation is achieved by dissolving the polymer in an appropriate solvent and passing the liquid mixture through a separatory column. Each component elutes at a different time due to the column's ability to selectively retain and separate specific chemicals. Appropriate detectors, located at the end of the column, detect each component as it passes through the detector. (2) HPLC is also utilized to characterize the basic polymer in terms of its molecular weight distribution. In this technique, a size exclusion chromatography column is used to individually separate by chain-length molecular-fractions size. Through this procedure a molecular weight distribution curve is generated.

D. Barrier Properties

Protection of drug products for a commonly expected shelf life of up to 3 years is required to preserve the product safety and efficacy. Parenteral products may be affected by the permeation of oxygen or other gaseous substances,

such as water vapor, from the environment into the package, which may lead to oxidation or hydrolytic degradation of some susceptible constituents. Secondly, the concentration of the drug could be altered over time by the migration of water, in the case of aqueous drugs, from the dosage form through the package and into the environment. Therefore, a plastic packaging material with adequate barrier resistance over the intended storage life of the product must be chosen. Egress of volatile constituents, the protective gas in the headspace, or some selective drug species through the wall of the container to the exterior can result in loss of drug stability.

By definition, permeation is the process of crossing a barrier. The barrier is the plastic material used to fabricate the pharmaceutical package. Examples of permeation in sterile pharmaceutical products are: benzyl alcohol passing through intravenous palstic bags [3], chlorobutanol diffusing through polyethylene ophthalmic bottles, and oxygen passing through rubber closures. In each of these cases, permeation can be detrimental to the stability of the packaged pharmaceutical product.

Permeation of a vapor or a gas into a plastic package through the side wall also can cause physical or chemical change in a pharmaceutical product. Oxygen can degrade oxidizable substances in packaged products. Water vapor can hydrolyze moisture sensitive pharmaceuticals that had been packaged dry. Many dry pharmaceuticals have limited stability in solution, or even when a small amount of moisture is present. An example is cephalosporin antibiotics which are packaged dry because they have limited stability when exposed to moisture.

Many liquid pharmaceuticals require an overwrap to prevent loss of water due to permeation. Polyvinyl chloride bags, which are used for the storage of i.v. admixtures in hospital pharmacies, are often overwrapped with a high density polyethylene bag. Figures 15 and 16 show comparisons of oxygen and water vapor transmission values given respectively for some common polymers used in films so that the appropriate plastic package can be chosen where barrier properties are needed. Plastics commonly used in barrier film packaging are ethylene vinyl alcohol (EVOH), polyvinylidine chloride (PVdC), acrylonitrile (AN), polyethylene terephalate (PET), high density polyethylene (HDPE), polypropylene (PP), polycarbonate (PC) and amorphous nylon.

Permeation values are listed for generic polymers, although variations can occur with processing methods and material modifications.

Polycarbonate is given as a rather poor barrier material relative to materials like amorphous nylon which is excellent. Polycarbonate may be used in packaging construction for reasons other than barrier resistance (i.e., toughness and high heat).

E. Sterilization Requirements for Plastic Packages

There are two basic methods for obtaining a sterile packaged pharmaceutical product. Aseptic filling requires the use of sterilizing filtration of liquid pharmaceutical preparations in a sterile environment into a presterilized empty package. The second method, called terminal sterilization, requires sterilization of the drug product in its final package after it has been filled and sealed.

To effectively utilize plastics for pharmaceutical containers, they must be able to withstand some form of sterilization. Although autoclaving is the most

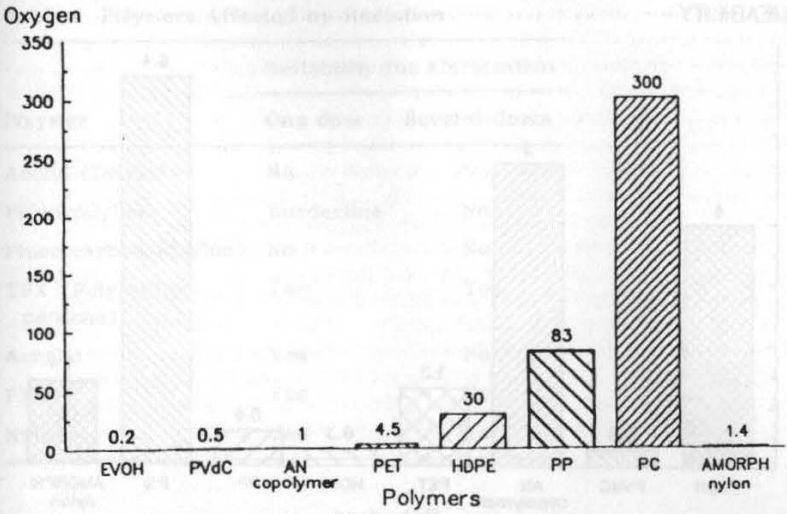


Figure 15 Barrier properties of common plastics to oxygen (cc/mil/100 sq. in./24 hr-atm at 23°C). ASTM method D1434 [10].

commonly used method, the practice of aseptic drug package filling provides an alternative process that does not require heating the final packaged products. Further, it may permit the use of some plastics which would not remain dimensionally stable under autoclave temperature cycles [14].

The most common methods of sterilization are:

1. Autoclave (steam under pressure)
2. Radiation (gamma or electron beam)
3. Gas (ethylene oxide)

Autoclave Sterilization

Although many drug products currently utilize aseptic filling techniques, the FDA now prefers that any new drug package be capable of terminal sterilization utilizing the autoclave. Radiation is not normally an option for terminal sterilization, since drug stability studies for radiation have demonstrated that many drugs are unstable during and after radiation exposure. Also, the gas ethylene oxide is not suitable for liquid pharmaceutical preparations. Therefore, autoclaving is necessary for new drug packages and others requiring terminal sterilization.

Typically, to sterilize, a pressurized steam autoclave operates at 121°C for at least 15 min. Some European countries are using lower temperatures and longer times to attain the same degree of microbial destruction. A reduced temperature may permit the use of plastics, such as polyethylene and polyvinyl chloride, which generally undergo distortion at 121°C.

Special autoclaves have been developed which apply overriding air or liquid pressure on the outside of the packaging equivalent to the internal

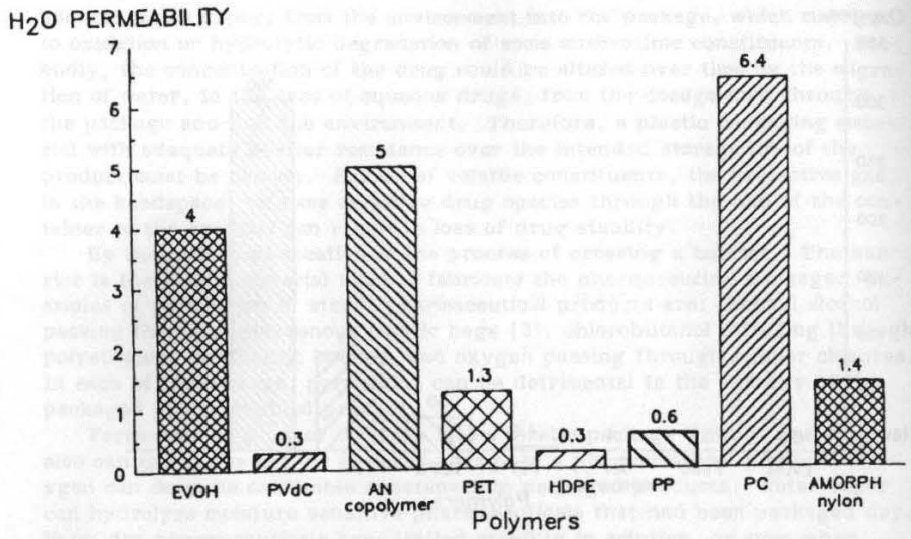


Figure 16 Barrier properties of common plastics-water vapor (g-mil/100 sq. in./24 hr at 23°C). ASTM method E96 [10].

pressure generated by the expanding liquid within the container. Pressure override prevents distortion of the plastic package under heat and allows plastics with lower heat resistance to be sterilized by autoclaving.

Radiation Sterilization

This method is effective for medical devices and pharmaceutical packaging components that can withstand the attack of gamma or electron bombardment [15,16]. It is especially useful for polymers that are sensitive to heat, moisture, or ethylene oxide. Radiation sterilization is accomplished in nuclear reactor facilities where gamma rays are emitted from radioactive materials such as Cobalt 60. Gamma rays penetrate both thick and thin objects, as well as densely packaged materials to be treated in bulk. The items to be sterilized are placed near the Cobalt 60 source until the required dose is absorbed.

In some plastics, radiation causes detrimental effects on the plastic's chemical structure, inducing the release of free radicals within the polymer. The activity of these free radicals can result in molecular scission or crosslinking of the polymer. In some cases this reaction can take place over many months rather than immediately. Therefore, when radiation sterilization is contemplated, one must choose a plastic which is stable under the radiation dosage level needed. This may require long term aging studies to evaluate the effects on plastics exposed to various radiation levels. Stabilized formulas are now available for some plastics, like polypropylene, which are suitable for radiation applications.

Polymers vary considerably in their ability to withstand radiation. Table 6 shows some common polymers which are susceptible to degradation by gamma irradiation. A single dose is assumed to be a maximum of 2.5 megarads.

Table 6 Polymers Affected by Radiation

Polymer	Suitability for sterilization	
	One dose	Several doses
Acetal (Delrin)	No	No
Polypropylene	Borderline	No
Fluorocarbon (Teflon)	No	No
TPX (Polymethyl-pentene)	Yes	Yes
Acrylic	Yes	No
PVC	Yes	No
Nylons	Yes	No

Gas Sterilization

Ethylene oxide (ETO) is a colorless gas that is widely used as a sterilant and is harmless to most plastics. ETO penetrates the microorganism and chemically reacts with its protein. Unfortunately, during this chemical process, which is catalyzed by moisture, toxic by-products are formed such as ethylene glycol and/or ethylenechlorohydrin. Additionally, residual ethylene oxide gas can be absorbed in the plastics. Pressure is being exerted on the industry to convert to radiation, autoclave sterilization, or some other alternative method. This is because of the potential toxic effects that this procedure has on the process operators and the adverse effects on the environment by the gas.

F. Drug Compatibility

Once the chemical and biological tests have been performed satisfactorily, the package is ready for drug compatibility testing in its final form. This involves filling the package with the actual parenteral product and putting the filled package through all intended processes, i.e., sterilizing, overwrapping, etc. This product is stored for a minimum of one year, and many extend the testing to three years. After storage, a test protocol is performed on the drug to detect any changes which might affect its performance of potency. Accelerated testing procedures, such as elevated temperatures (40, 60, or 70°C), are used to help predict a product's stability.

A full analysis of the drug contents should ascertain any alteration which may have occurred due to the plastic's inability to fully protect the contents. The data accumulated is then used to qualify or validate the package associated with the product and the processes to which it was exposed. Ultimately, the same data will be required by the Food and Drug Administration for the finished product approval. Included in the test protocol are tests such as:

1. The effect of the process and sterilization
2. Determination of specific product leachability
3. Physical and functional tests of the final packaged product
4. Long term stability testing of the final packaged product
5. Complete drug assay before and after aging.

G. Biological Toxicity

The basic tests are given in the USP XXII-NF XVI [12]. These tests include both biological and physicochemical tests. The biological tests are primarily toxicity screening tests, and all of the candidate raw polymer resins should be subjected to USP class VI biological testing (see Table 7).

Current official biological procedures are primarily designed to determine the suitability of plastic materials *intended for use in containers for parenteral preparations*. These tests are performed using injected extracts prepared in a manner similar to the condition under which it is meant to be used. If the plastic is to be exposed to any cleansing or sterilization process prior to its

Table 7 USP Class VI Biological Testing

Test material	Animal	Dose	Procedure
Extract of sample in sodium chloride injection	Mouse	50 ml/kg	Intravenous systematic injection
	Rabbit	0.2 ml/animal at each of 10 sites	Intracutaneous
Extract of sample in 1:20 solution of alcohol in sodium chloride injection	Mouse	50 ml/kg	Intravenous systematic injection
	Rabbit	0.2 ml/animal at each of 10 sites	Intracutaneous
Extract of sample in polyethylene glycol 400	Mouse	10 g/kg	Intraperitoneal systematic injection
	Rabbit	0.2 ml/animal at each of 10 sites	Intracutaneous
Extract of sample in vegetable oil	Mouse	50 ml/kg	Intraperitoneal systematic injection
	Rabbit	0.2 ml/animal at each of 10 sites	Intracutaneous
Implant strips of sample	Rabbit	4 strips/animal	Intramuscular implantation

end use, then the tests are to be conducted from a smaple preconditioned by the same processing.

To determine the reaciton of living tissue, the injectable preparations are made by extracting the sample in either sodium chloride for injection, a 1:20 solution of alcohol in sodium chloride, polyethylene glycol 400, or cottonseed oil at 50°C for 72 hr. After preparation of the extracts, specified doses are injected intravenously, subcutaneously, or intraperitoneally into mice or rabbits to observe for evidence of systemic toxicity or local tissue reaction. In these tests none of the animals injected with an extract of the sample should show a significantly greater reaction than that observed in animals injected with a blank.

Various biological testing of parenteral packaging materials using these extracts are outlined in Tables 7 and 8. Biotesting from a quality assurance viewpoint, once the plastic product is proven to be acceptable, is held to a minimum by most pharmaceutical manufacturers due to the expense and time tyically involved in performing these tests on a routine lot by lot basis. If there is no animal facility in-house, there are a number of reputable laboratories available to do such testing on a contract basis.

Table 8 Biological Testing of Polymers Used in Parenteral Packaging and Parameters Tested

Tests	Injection site	Tested parameters or result(s)
Subacute testing (<30 days)	Rabbit, ear/Mice, tail	Hematology, blood chemistry, growth, organ weight, lethality
Chronic testing (>45 days)	Mice, tail/Rabbit, ear	Hematology, blood chemistry, growth, organ weight, lethality
Acute toxicity	Rabbit, ear/Mice, tail	Behavior, and mortality and/or biopsy
Isolated muscle tests		Response versus a histamine standard (%)
Erythrocyte aggregation		Clumping of cells when neutralized indicates positive
Clotting time		Clotting time effects
Antigenicity		IP anaphylactic shock
Hemolysis		Comparison of positive and negative controls (15% used as a guideline for positive)
Dye extravasation	Subcutaneous infiltrating injection	Comparison of positive and negative controls

These tests merely represent examples of biotesting that may be employed. Many other tests also exist and their utilization varies from company to company. In addition, many USP tests may be used for product testing, depending on the plastic container and the enclosed solutions. Also, due to cost, contaminants, and certain scientific rationales, not all tests are performed at each time interval in stability programs of QC laboratories. Although all tests listed may be employed, usually acute toxicity and/or subacute testing are the ones most frequently employed.

Cytotoxicity or cell culture tests are recommended for screening purposes as an excellent predictor of potentially toxic extractable substances and of biocompatibility. These tests are sensitive, rapid and economical, making use of mammalian cells (often mouse or human) cultured with the specimen or its extract. The behavior of these cells exposed to candidate materials is used to judge the anticipated performance of these materials in subsequent preclinical animal tests (in vivo) as described above.

V. PLASTICS USED IN PARENTERAL PACKAGING

There are many types of plastics available on the market today that may be suitable for a particular medical application. It is important to understand the requirements of the intended application and to relate these with the appropriate plastic. To do this one must understand a number of general categories used to classify plastic resins, as described in Section II.B. In addition, there are a number of basic properties that are important to consider for parenteral packaging applications. A review of these two areas will follow before a description of specific resin types is given.

VI. RESIN CATEGORIES

Specific resins can be classified in general categories. Once these categories are understood it becomes less difficult to determine what group or family of material will best fit a product application.

The terms commodity resins and engineering resins are used frequently to classify two distinct groups of materials. Refer back to Section II.Ba for a complete explanation of these terms.

The term polyolefins is used to describe a group of the most widely used plastic materials in the industry. These are materials formed by polymerization of simple unsaturated monomers. The polymerized resin becomes a saturated polymer composed of only carbon and hydrogen atoms of a repeating order. Two of the most commonly used polyolefins are polyethylene and polypropylene.

A group called specialty resins refers to plastics designed to meet specific requirements for a target application or area of use. The base monomer has a characteristic that when polymerized, forms a resin with specific properties for the intended use.

A good understanding of the application is necessary to sort through strengths and weaknesses of different materials. The properties of different materials are best understood by thinking in terms of the resin groups de-

scribed above and relating these to a set of basic resin properties. A good example is with the polyolefins group. These materials characteristically have excellent chemical resistance. This is because of the molecular structure of saturated hydrocarbons. The polymer has a simple repeating monomer group which creates a high level of crystallinity, resulting in excellent chemical resistance.

Table 9 shows a summary of general resin properties that are important in many applications of parenteral packaging [17]. As shown in the table, there is a wide variation in properties between resins groups. When selecting a material there is a trade off in properties that must be considered. The polyolefins are strong in chemical resistance and barrier properties, while the engineering resins are known for their excellent resistance to heat and good thoughness. Specialty resins are developed to be strong in a specific set of properties.

A summary of the different resins follows with specific attention to the molecular structure of each and how this related to the physical properties. Typical applications are given to show what areas are most suitable for the different resin groups.

A. Commodity Resins

Polyethylene

Polyethylenes are one of the most commonly used plastics in the industry and are produced in volumes that exceed any of the other plastic resin groups. In fact, over the last year, approximately 20 billion pounds have been consumed in the United States market [1]. Polypropylenes and polyvinyl chloride are second and third in volume consumption, falling a good distance behind the polyethylene family. Polyethylene (PE) is a commodity resin that became popular in the 1950s with the development of a new catalyst system called the Zieglar catalyst [18]. This development made it possible to polymerize the ethylene monomer under lower pressures with greater control and speed. The Zieglar catalyst initiated the start of the technical boom age for plastics. PEs could now be produced in large volumes at competitive manufacturing costs.

PEs are in the polyolefins family. The polymer is based on a simple repeating carbon/hydrogen molecule which branches out during polymerization to form a polymer with a high degree of regularity. Figure 17 shows the chemical structure of polyethylene. The regularity creates the formation of crystal lattice structures. PEs are recognized for their high degree of crystallinity. During polymerization, the amount of branching that occurs during the process will determine the overall density and crystallinity of the resulting PE. This leads to the three common types of PE produced; low density PE (LDPE), medium density PE (MDPE), and high density PE (HDPE).

LDPE was the first commercial branched ethylene polymer. In many commercial applications LDPE is now being replaced by linear low density polyethylene of LLDPE. This newer resin is less expensive to produce and has more desirable physical properties than resin produced by the older catalyst system. LLDPEs are produced through a low pressure process with a specialized catalyst system, first developed by the Union Carbide Corporation. Because of their low softening points, LDPE and LLDPE have limited application for direct packaging of parenteral drugs. This is because a large percentage

Table 9 General Resin Properties

Material category	Material name	Heat resistance	Clarity	Moisture barrier properties	Oxygen barrier properties	Chemical resistance	Mechanical properties
Polyolefins	Polyethylene	Poor	Fair	Excellent	Fair	Excellent	Flexible material/excellent toughness
	Polypropylene	Good	Good	Good	Fair	Excellent	Semirigid/good toughness
	EP Copolymer	Good	Good	Good	Fair	Excellent	Semirigid/good toughness
Commodity resins	Polyvinyl chloride	Good	Good	Good	Good	Excellent	Flexible material/excellent toughness
	Polyester	Poor	Excellent	Good	Good	Good	Semirigid/good toughness
	Crystal polystyrene	Poor	Excellent	Poor	Poor	Poor	Stiff material/low-impact strength
Engineering resins	Poly-carbonate	Excellent	Excellent	Poor	Poor	Fair	Stiff material/low-impact strength
	Polysulfone	Excellent	Excellent	Fair	Poor	Fair	Stiff material/excellent toughness
Specialty resins	Amorphous nylon	Fair	Excellent	Good	Excellent	Fair	Stiff material/excellent toughness
	Poly methyl pentene	Good	Excellent	Good	Fair	Good	Semirigid/good toughness
	Modified acrylic	Good	Excellent	Good	Good	Fair	Stiff material/low-impact strength
	Ethylvinyl alcohol	Poor	Good	Fair	Excellent	Good	Flexible material/good toughness

$$-[-CH_2-CH_2-]-_n$$

Figure 17 Chemical structure for polyethylene. n signifies the finite number of repeating units that make up a single polymer chain.

of parenteral containers are subject to steam sterilization which utilize temperatures above the softening point of these resins.

HDPE has a higher degree of crystallinity and, as its name suggest, is higher in density. Typical density is in the range of 0.95 to 0.97 grams/cubic centimeter (gm/cc). This compares to LDPE with a density range of 0.91 to 0.94 gm/cc. Crystallinity is the main contributor to the overall difference in properties [19]. HDPEs have greater tensile strength, are stiffer, and have a higher melting point than the LDPE resins. Another important property is excellent chemical resistance, a characteristic of all polyethylene grades.

As previously mentioned, one of the weaknesses with PEs is their lower melting point. As the density of PE is reduced, the resistance to heat is also lowered. HDPEs are used for applications where resistance to higher temperatures is important. In Europe, heat sterilization cycles are being used for HDPE with lower temperatures and longer cycle times. This modified cycle makes it possible to use HDPE where modified sterilization cycles are acceptable. As of yet this technique is not widely used in the United States. PEs are an excellent resin where sterilization by gamma radiation is acceptable. The saturated and crystalline structure of PEs make it very stable to this type of sterilization.

Applications. PEs are being used in several areas of parenteral packaging where their chemical resistance and inert structure can be used to an advantage. They are being used in some of the newly developed large volume parenteral (LVP) bag applications as one of several film layers which make up the bag. PEs are a good material for use in direct contact with parenteral drugs because of their clean chemical composition. Other examples of use are in protective packaging of finished product. PE films play a big role in this area of use.

Specialized Polyethylenes. Ultralow density and very low density PE are synonymous terms referring to the category of linear PEs with densities below 0.915 gm/cc. Current technology provides a lower density limit between 0.880 and 0.890 gm/cc.

The importance of these polymers stems from their unique combination of strength, sealability, flexibility and optical properties. ULDPEs offer puncture, impact and tear properties that are superior to LLDPE with sealing and flexibility properties comparable to a flexible copolymer, such as ethyl vinyl acetate. The softening point of linear polyethylene decreases as density decreases, therefore, the sealing range of ULDPE is significantly improved over LLDPE. These properties make the resin an important material in many film packaging applications. The use of ULDPE for clear stretch packaging films is a good example.

Ultrahigh molecular weight polyethylene (UHMPE) is an important material that is commercially available. This polymer has a molecular weight that is typically in the range of 3 to 6 million. The high molecular weight makes

it a plastic that is extremely inert to chemical attack and superior in areas of abrasion resistance and impact strength. It cannot be processed through normal manufacturing techniques, because the liquid state will not flow. The use of powder processing is used for this reason. Because of its unique properties, it is used in specialized applications such as implanted medical devices.

Polypropylene

Polypropylene (PP) is the second most widely used polyolefin in the world. In the last year, approximately 8 billion pounds were consumed in the United States market [1]. The resin has a number of attractive properties for use in parenteral packaging. It has excellent availability and is among the least costly plastics on the market.

Polypropylene has a low specific gravity of approximately 0.90 gm/cc, making it the lightest density within the group of major use plastics. The low specific gravity combined with a simple monomer backbone are what support its low cost.

PP is a linear, high crystalline polymer. Its chemical structure is made up completely of carbon and hydrogen in a very orderly fashion as illustrated in Figure 18. The regularity of its structure imparts the high degree of crystallinity found in most commercially available PPs. Within the crystal array the added methyl groups impart stiffness to the polymer, making it different from its close relative, polyethylene. PP exhibits a high tensile strength, which is the ability to withstand forces tending to pull apart or distort the material. High tensile strength, in conjunction with a high melting point of 165°C, is particularly important for packaging of drugs. This material has the ability to withstand the high temperatures of steam sterilization.

Polypropylene is very resistant to chemical attack from organic solvents as well as strong acids and bases at room temperature. The polymer provides a good barrier to the transmission of water vapor because of its high crystallinity. It also has good abrasion resistance and is capable of retaining a high surface gloss. Many drug delivery products require a level of clarity that can be satisfied with PP. There are a number of factors affecting the clarity of the material, such as processing and thickness of the final part, resulting in products that will vary from translucent to semi-clear.

Because of the level of crystallinity present, it is not possible to achieve sharp clarity as with more amorphous resins. The crystal lattice sites tend to refract light which imparts haze.

The material can be autoclaved with steam but will not withstand these temperatures while under stress. An example of stress is in the use of PP for a closure sealed on a glass container. In this case the material may be under force from the contents of the container and will yield to stress from this when exposed to autoclave temperatures. PP may also be sterilized with

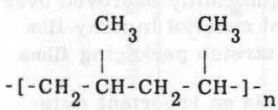


Figure 18 Chemical structure for polypropylene.

ethylene oxide with no effect to the material. Use of gamma radiation as a means for sterilization will cause a shearing of molecular segments within the polymer. This shearing of molecules may cause a shift in color toward yellow, an increase in brittleness and a loss in physical properties. There are grades specially stabilized for gamma radiation for use in parenteral packaging. These resins will withstand doses of gamma radiation at levels up to 5.0 megarads, and they are available from a number of suppliers at a premium in price.

Polypropylene Additives. Unstabilized PP degrades when subjected to heat, ultraviolet light, and oxygen. To prevent this, the resin must be stabilized through the use of antioxidants. If polypropylenes are not stabilized with antioxidants, degradation results in a material with low molecular weight and the generation of by products such as butyric acid. Degraded material will exhibit poor processing characteristics, combined with a loss of many of the plastic's useful properties.

There are a number of commercially available antioxidants that either alone or in synergistic system can stabilize PP against degradation. Hindered phenols, phosphites, and thioesters are the most common types of antioxidants used today. Table 10 illustrates some of the more common variations of three important classes of antioxidants used in PP and other polyolefins.

Choosing the proper additives and concentration levels in a polymer is extremely important. The volatility and mobility of additives must be examined in light of current literature as well as specific end use testing. Conversely, choosing an improper antioxidant or using an insufficient concentration can result in premature yellowing and a high degree of polymer breakdown. This may lead to the formation of undesirable by-products that can migrate into the packaged product. If an antioxidant is incompatible with the base resin or if too high a concentration is used, the manufacturer is faced with the

Table 10 Antioxidants for Polypropylenes and Other Polyolefin Materials

Chemical name	Type
Distearyl pentaerythritol disphosphite	Organo-phosphite
Tris nonylphenyl phosphite (TNPP)	Organo-phosphite
1,1,3-Tris-(2-methyl-4-hydroxy-5-t-butyl phenyl) butane	Hindered phenol
1,3,4-Trimethyl-2,4,6-tris [3,5-di-tert-butyl-4-hydroxybenzyl] benzene	Hindered phenol
2,6-di-t-butyl-p-cresol (butylated hydroxy toluene, BHT)	Hindered phenol
Octadecyl-3,5-di tert-butyl-4-hydroxy-hydrocinnamate	Hindered phenol
Tetrakis [methylene-(3,5-di-tert-butyl-4-hydroxyhydrocinnamate)] methane	Hindered phenol
Dilauryl-3,3'-thiodipropionate (DLTDP)	Thioester

problem of potential migration of the stabilizer leaching into the product or solution in contact with the polymer.

Besides antioxidants, lubricants are the only other additives used in any significant amounts with PP. Calcium stearate can be used to reduce frictional forces during processing of these resins. Such lubricants as calcium stearate are common in concentrations of 0.05 to 0.2 percent by weight. These lubricants may also be added at the processing location to aid in processing.

Applications. Polypropylenes are used in a wide range of drug packaging applications because of their unique balance of properties combined with their competitively low price. One application that well demonstrates the strengths of PP is disposable syringes. Sterile empty syringes are produced through the injection molding process and sealed in air-tight blister packs, all in a clean room environment. The packaged syringes are sterilized in bulk using gamma radiation and are ready for use. Newer grades of resin have been introduced that have better levels of clarity and are well stabilized for gamma radiation sterilization.

Polypropylene vials are being introduced in select areas for packaging of parenteral drug solutions. This new package offers several advantages over glass, which is the current material of choice in the market. A concern for the barrier properties of PP is one factor that has slowed the use of the material in this application.

The LVP container market is another area where PP has significant potential. Changes in the market are taking place away from the use of polyvinyl chloride. This is because of the serious concern for the migration of plasticizers and stabilizers from PVC into the parenteral solutions. PP is a more stable plastic and does not require use of plasticizers when used as a film laminate with other plastics.

Ethylene/Propylene Copolymers

Copolymers of ethylene and propylene are playing an important role in many areas of parenteral packaging. By combining a small fraction of ethylene as a block or random copolymer with propylene, a number of desirable properties can be attained. Figure 19 illustrates the chemical structure for this polymer. The addition of ethylene decreases the stiffness of polypropylene, improves processability, and only slightly decreases the melting point. Typical melt temperatures are between 145° and 150°C. This makes ethylene/propylene (EP) copolymers appropriate for use under some steam sterilization conditions. The clarity of most EP copolymers is better than straight homopolymer polypropylenes. This is because the presence of random ethylene groups tend to reduce the amount of crystallinity, which reduces the refraction of light.

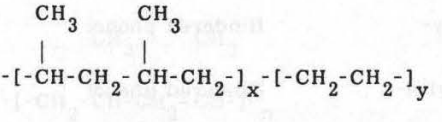


Figure 19 Chemical structure for ethylene/propylene copolymer, where x and y represent the size of the blocks of ethylene and propylene, respectively.

EP copolymers, as with other polyolefins, require minimal levels of additives for processing and long-term stability. Generally, less than 0.2% of a hindered phenol antioxidant (see Table 10) is sufficient to prevent degradation during processing. Antioxidants at such low levels do not usually present a migration problem where there is direct contact with a packaged drug. Generally, EP copolymer containers provide adequate moisture-vapor barrier properties to allow a shelf life for products of one year or more.

For sterilization purposes, this material will tolerate exposure to gamma radiation somewhat better than straight polypropylene, although there is still a need to purchase grades that are specifically stabilized for this purpose. The presence of ethylene groups provides a stabilizing factor that improves the resin's resistance to degradation.

Applications. This type of polymer will become more important as the technologies of polymerization and manufacture improve. Over the past ten years there has been significant development in the properties of EP copolymers. The amount of resin clarity and the resin's stability to processing have improved dramatically.

The areas of use for ethylene-propylene copolymers are quite similar to those for homopolymer polypropylenes. These random copolymers are more desirable where there is need for higher levels of clarity or greater amounts of flexibility. As described above, the presence of ethylene breaks up some of the regularity of propylene groups and reduces the percent crystallinity. In some applications this is a desirable quality.

Ethylene-propylene copolymers have been replacing straight PP in sterile empty syringes, a transition driven by the market's push for high clarity resins in syringe systems. It is important to visually see the drug contents in a syringe. This is especially important for aspiration purposes when administering the drug.

Another area of importance is the use of these resins in LVP containers. EP copolymers offer greater flexibility along with clarity, two important characteristics for this market. Outside of polyvinyl chloride, this is the most commonly used resin for LVP production. The shift away from use of PVC will be a driving force toward further use for EP copolymers.

Polyvinyl Chloride. Polyvinyl chloride (PVC) is the dominant polymer resin in the vinyl family. PVC is used in the United States alone at the rate of more than 7 billion lb/year [1]. Although PVC is the major polymer utilized in the medical industry, medical use of PVC represents only a very small fraction of the annual PVC production.

PVC is one of the oldest polymers. As World War II approached PVC became commercially significant, with the primary interest being to find synthetic replacements for rubber. Polyvinyl chloride, as the name implies, is based on the vinyl monomer of monochloroethene. PVC is produced by polymerizing vinyl chloride gas (CH_2=CHCl) in the presence of an initiator, such as an organic peroxide or an inorganic persulfate. The initiator acts to generate free radicals to propagate the polymerization reaction. This is illustrated as:

$$R_1OOR_2 \rightarrow R_1O\cdot + R_2O\cdot$$

where R_1OOR_2 represents an organic peroxide.

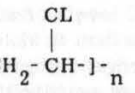


Figure 20 Chemical structure for polyvinyl chloride.

After the peroxide free radical (an unpaired electron) is formed, reaction with the vinyl monomer takes place and is propagated. The chemical structure for PVC is shown in Figure 20.

Of all products made from PVC, 45% are flexible. In the LVP industry, flexible PVC is used primarily for containers and rigid PVC as injection molded parts for i.v. administration sets.

In September 1975, the FDA proposed regulations to restrict the use of vinyl chloride (VC) in contact with food products. Since that time, great effort has been put forth by the manufacturers and users of PVC to reduce the residual levels of VC monomer to less than 1 ppm.

Properties. Plasticized PVCs have been used extensively in the LVP and medical industry because of their unique physical properties, versatile fabrication properties, and relatively low cost. In general, PVC is a tough and chemically resistant plastic. Polyvinyl chloride polymers are resistant to alcohols, aliphatic hydrocarbons, oils, weak acids and alkalies. Articles made from plasticized PVC are mark and dent resistant. The density of PVC (1.16-1.35 gm/cc) is significantly higher than that of other polymers, such as polyethylene (0.92-0.96 gm/cc) and polypropylene (0.90 gm/cc). The moisture vapor transmission rate (MVTR) for PVC is higher than that of polyolefins. Table 11 shows a comparison of MVTR values between the common commodity resins. Because of the high-moisture transmission rate of PVC polymers, most LVPs are packaged with an outer wrap to reduce water loss. Some of the important properties of PVC are summarized in Table 12.

Unstabilized PVC is very susceptible to degradation and discoloration by heat and ultraviolet light. Degradation proceeds as a chain reaction, initiated and propagated by a chlorine radical as illustrated in Figure 21.

Table 11 Comparative Barrier Properties of Plastics

Polymer	Mositure (water)[a]	Oxygen[a]
High density polyethylene	140	11
Polypropylene	672	23
Ethylene/propylene copolymer	609	20
Polyvinyl chloride	1550	1.2

[a]Permeation $\times 10^{10}$ (cc/cm^2 mm^{-1}/sec^{-1}/cm Hg^{-1}) at 90% RH and 25°C.

Table 12 Properties of Polyvinyl Chloride

Property	Plasticized/calendared PVC
Density (gm/cc)	1.16-1.35
Tensile strength (psi)	1400-9000
Elongation (%)	100-500
Water absorption, 24 hr (%)	Negligible
Resistance to:	
Strong bases	Good
Strong acids	Good
Alcohol	Good
Aliphatic hydrocarbons	Good
Sunlight	Fair
Heat sealing range (°C)	175-232

The chlorine radical extracts a hydrogen from the polymer chain which then activates the polymer chain by forming a new chain radical and hydrogen chloride. The polymer chain then deactivates to form a double bond and another chlorine radical. This process of polymer breakdown proceeds until total decomposition has occurred. Color change, due to decomposition, usually begins to develop when five to seven conjugated double bonds have been formed.

The degradation of PVC can generally be reduced sufficiently by the addition of stabilizers. It is important that sufficient levels of stabilizer be added to protect against degradation during the manufacturing process and stabilize the container for the life of the intended product. The HCl generated during decomposition can adversely lower the pH of many LVP solutions, due to their

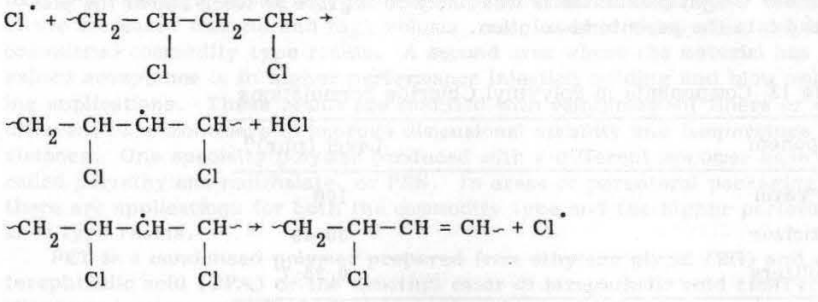


Figure 21 Degradation reaction of PVC.

relatively low buffering capacity. A certain amount of decomposition occurs during processing of PVC film, therefore, it is essential to set stringent specifications for processing.

Additives. Flexible PVC is compounded by combining polyvinyl chloride (homopolymer or copolymer), stabilizers, lubricants, and other additives necessary for a given final product. There is no single "standard" composition. Each flexible PVC formulation is designed for a specific product and most are proprietary. However, some general well-known guidelines can be discussed. A summary of additives and the levels present in typical flexible PVC formulations is shown in Table 13.

The principal properties of an ideal PVC stabilizer could be summarized as an ability to absorb HCl, displace chlorine radicals, disrupt double bonds, provide antioxidant protection, and provide UV screening [20]. As with any additive, it should be nonmigratory, nontoxic, and odorless. In addition, it should not affect the physical properties of the compound, such as clarity or color. Special attention is required to select a stabilizer system that will perform best for the process being used and at the same time, be FDA approved for the intended application.

Lubricants are an important part of any PVC formulation. They facilitate the melt flow of the plastic during processing and prevent adhesion to metal surfaces. Addition of the proper lubricant can also result in much better appearance of the final product. The most common lubricants are fatty acid esters, fatty acids and alcohols, fatty acid amides and metallic soaps.

Plasticizers are used to modify a normally rigid PVC into a flexible plastic. As the amount of plasticizer in the formulation increases, the degree of "limpness" and "softness" of the material also increases, which dramatically improves low temperature properties of the material. Plasticizer and stabilizer migration is of primary concern when PVC is used for LVP containers. There is an ongoing controversy surrounding the use of certain plasticizers. The issue has centered around use of di-2-ethylhexylphthalate, commonly referred to as DEHP [21]. Because of its wide use, economic considerations, and long history, this plasticizer will continue to be used unless there is conclusive evidence of toxicity in the medical industry. The hint of potential human mutagenicity has caused some PVC, medical device, and parenteral manufacturers to investigate alternatives to DEHP. Some of the alternatives are listed in Table 14. Two of the key factors considered in designing alternative plasticizers are molecular weight and polymer miscibility. In general a higher molecular weight plasticizer is less likely to migrate or leach out of the plastic and into the parenteral solution.

Table 13 Components in Polyvinyl Chloride Formulations

Component	Level (phr)[a]
PVC resin	100
Plasticizer	30-40
Stabilizers	0.25-7

[a]phr = parts per hundred parts of resin by weight

Table 14 Common High-Molecular-Weight Plasticizers

Plasticizer	Type	Molecular weight
Trioctyltrimellitate (TOTM)	Nonpolymeric	567
Polyester adipate	Polymeric	2000-3500
Polyester glutarate	Polymeric	2500

Trioctyltrimellitate (TOTM) is an example of a higher molecular weight plasticizer that is gaining acceptance. It has been demonstrated that TOTM exhibits less migration from PVC than DEHP [22]. There are some disadvantages in the use of TOTM. It is more expensive, and PVC compounds formulated with TOTM are slightly more difficult to process.

The migration of plasticizers is virtually impossible to predict based on chemistry and processing alone. The safest approach is to evaluate the plasticizer under consideration in use with an appropriate PVC formulation. The formulation should be put on test with the solution to be packaged to measure actual migration of plasticizers. This approach, known as long term stability testing, is the best method of evaluation.

Applications. The medical use of flexible polyvinyl chloride resins encompasses i.v. tubing and drip chambers, catheters, blood bags, mixing bags, and LVP containers. PVC was the first polymeric material to replace glass for blood storage and LVP applications.

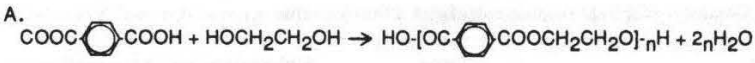
As referenced above, a great deal of testing is being done to evaluate better formulations with emphasis on the migration of extractables. More recently, there has been strong emphasis placed on finding alternate materials that contain little or no plasticizers and do not present problems with extractable constituents. This is especially true in the European market, where the use of polyethylenes and ethylene-propylene copolymers have replaced PVC across a wide front of applications.

Polyesters (PET, PEN)

Polyester resins can be categorized in a number of ways, depending on the end use application. Use of this material has grown rapidly in the areas of food and beverage packaging, especially for carbonated beverages. Because of the increased demand and high volume, resin used in these areas can be considered commodity type resins. A second area where the material has gained acceptance is in higher performance injection molding and blow molding applications. These resins are modified with reinforcement fillers or with different base monomers to improve dimensional stability and temperature resistance. One specialty polymer produced with a different monomer base is called polyethylene napthalate, or PEN. In areas of parenteral packaging, there are applications for both the commodity type and the higher performance type resins.

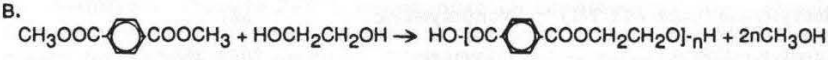
PET is a condensed polymer prepared from ethylene glycol (EG) and either terephthalic acid (TPA) or the dimethyl ester of terephthalic acid (DMT). The two reactions are shown in Figure 22. The EG monomer is prepared using

A.



TPA EG PET

B.



DMT EG PET

Figure 22 Chemical reactions used for polymerization of PET.

ethane as feedstock and the TPA is manufactured using paraxylene as feedstock. TPA can then be purified by reaction with methanol to form dimethyl ester of terephthalic acid, or DMT.

PET can exist in an amorphous state (non-crystalline), an oriented and partially crystalline state, and a highly crystalline state. The amorphous polymer exhibits a glass transition temperature of about 74°C, and the crystalline melting point ranges from about 255° to over 270°C. Glass transition is the temperature where the polymer structure changes from a glassy (or rigid) state to a rubbery (or flexible) state. The crystalline melting point is where crystal regions of the polymer structure begin to melt or soften. Most applications require orientation and/or crystallization in order to take advantage of the dramatically increased strength and improved serviceability at high temperatures. This is where the selection of the resin manufacturing process can have a significant effect on the properties of the finished product. With blow molding, there is a high level of orientation imparted into the material during the blow step.

A process for producing containers, called stretch blow molding, creates a high level of bi-axial orientation, which greatly enhances the physical, chemical, and barrier properties of PET. Also, bi-axial orientation extends the range of temperature resistance for PET.

As referenced above, a new high barrier polyester material has been developed and is available in limited quantities. The commercial name of this material is polyethylene napthalate (PEN). This material has five times the oxygen barrier properties of PET, as well as higher heat resistance. Its glass transition temperature is around 248°F, compared with 158°F for PET. When water is boiled in two identical containers of PET and PEN, the PET container collapses, while the PEN container does not. PEN's high barrier properties can be a significant advantage, resulting in increased shelf life of packaged pharmaceuticals.

Polyester resin has good oxygen and moisture vapor transmission barrier properties. It is noted for its high clarity when the material is in a high amorphous state (low crystallinity).

The amount of crystallinity can be controlled in the cooling phase of the particular process used. A fast rate of cooling will minimize the amount of crystal growth, assuring a higher degree of clarity. Slow cooling will cause the growth of the crystal lattice sites, which impart haze.

Because of its low glass-transition temperature, PET will not tolerate autoclave sterilization. The material does hold up well to gamma radiation, making it the preferred method for sterilization. Ethylene oxide is the other method for sterilization and is acceptable with PET resins.

Applications. As mentioned above, the predominant application for PET is the carbonated soft drink container. The material properties required for this application are also important for use of PET in parenteral applications. The combination of barrier properties and high clarity make this material an excellent candidate for packaging of drug solutions. PET film may potentially be used as a co-extruded layer of LVP bags (replacing use of PVC resins).

There is significant potential for PET resin in plastic vials that would replace the use of glass. In this case, one limitation is in barrier properties. Even though PETs are strong compared with other plastics, they cannot compete with the barrier properties obtained with glass. Shorter shelf life expiration periods are used in the case of carbonated soft drink containers to address this issue.

PET is gaining acceptance in blister packages and packaging films. These are recent developments made possible through newer grades of PET, which are modified for the extrusion process.

B. Engineering Resins

Polycarbonate (PC)

Polycarbonate is one of the more widely used engineering resins. It is especially known for its toughness and high clarity properties. These two properties make it very useful in specialized areas of parenteral packaging. Because of its higher cost, compared with commodity resins, it is used only in applications where the high performance of engineering resins are a necessity.

PC resin contains repeating aromatic rings in its main chain structure. The material is a polyester of carbonic acid and is generally produced using an interfacial reaction between dihydric or polyhydric phenols and a suitable carbonate precursor such as dichlorocarbonate [17]. At present most PCs are produced with a reaction between bisphenol A and carbonyl chloride in an interfacial process. Other polyhydric phenols are sometimes used to form copolymers for special end uses. Figure 23 shows the chemical structure for PC resins.

As with other polymers, specific property enhancements of PC are accomplished by additives and modifiers like thermal stabilizers, ultraviolet stabilizers, release agents, colorants, and flame retardants.

Although the material is noted mostly for its high-impact resistance, the real strength of PC lies in its overall combination of properties. PC stands out as a superior impact-resistant material among other engineering thermoplastics. Its functional performance extends to a wide temperature range. It shows good property retention at -60°F, with minimal loss in impact strength. The upper limit heat deflection temperature* at 264 (psi) is a respectable 270°F.

Natural PC resin is water-clear and transparent, having roughly 89% transmittance and less than 1% haze. The material is well suited for the injection molding process. A low, uniform mold shrinkage of 0.5 to 0.7% makes it suitable for molding precision parts. It is not uncommon to hold a dimensional tolerance of 0.002 in./in. and sometimes as tight as 0.001 in./in. with high-

*Heat deflection temperature is a common term used to define the temperature that a material will yield at when under a specified amount of stress.

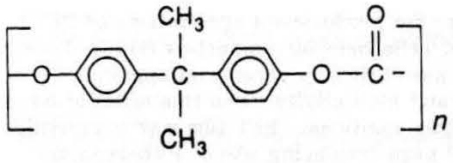


Figure 23 Chemical structure for polycarbonate.

quality molds. PC also exhibits good electrical properties. Its dielectric constant (measure of its electrical insulating properties) is independent of temperature.

One of the most important considerations for using engineering resins is their resistance to creep. PC shows excellent creep resistance over a broad temperature range, enabling its use in applications previously open only to thermoset materials.

Some of the other properties responsible for PCs use are its colorability, stain resistance, biocompatibility, and the ability to be sterilized. However, there are some areas where PC resins are weak. PC materials have limited chemical and scratch resistance. The resin has tendency to yellow with long term ultraviolet light exposure. These characteristics can be related back to chemical structure. The molecular structure is unsaturated, making the material more susceptible to reaction or molecular breakdown. In addition, the structure is amorphous (or nonorderly). These characteristics together make the resin less tolerant to solvent attack.

Polycarbonate can be sterilized by the most frequently used sterilization techniques. The material may be autoclaved. It has a heat distortion temperature of 133°C, while typical autoclaving temperatures run at 121°C. The number of autoclaving cycles polycarbonate can withstand depends on part design and processing parameters. In general, polycarbonate is not recommended for applications which require more than a few steam sterilization cycles.

Containers made of polycarbonate can also be gas sterilized using normal sterilization cycles. The common mixtures of ETO in Freon or of ETO in CO_2 can be used for repeated sterilizations. Studies of ETO residuals on polycarbonate have shown levels well below the present proposed limits established by the FDA.

The use of gamma radiation sterilization has gained popularity since its commercial introduction. Polycarbonate will turn yellow following exposure to this process. For this reason, specific transparent colors have been developed for polycarbonate which will permit its exposure to gamma radiation. The resin itself will maintain good mechanical properties under exposure to typical dosage levels for sterilization purposes.

Applications. Because of polycarbonate's high-impact strength, finished parts can be made both lightweight and shatter resistant, a combination that permits it to be used in a variety of pharmaceutical applications. Some typical examples are in i.v. connectors and luer lock components for i.v. sets. Polycarbonate is a good housing material for many devices that are used in combi-

nation with or as part of i.v. sets. Use of polycarbonate as a reusable holder for prefilled syringe cartridges is another example.

In each of these examples, there is need for a light-weight material that has good toughness, is crystal clear and can be sterilized easily. These are the major strengths for use of polycarbonate as an engineering resin.

Polysulfone

Polysulfone, also called PSO, is a high performance engineering resin that is transparent and has excellent resistance to heat. It is a widely used material for medical products because of its excellent toughness and resistance to heat at autoclave temperatures.

The material is amorphous in nature and has a chemical structure as illustrated in Figure 24. The unique properties of this material can be attributed to the sulfone group, located in the para position (between 2 phenyl rings). This group tends to attract electrons from the phenyl groups, while oxygen atoms, in a second para position, tend to enhance resonance, thereby producing oxidation resistance. This state of high resonance strengthens the bonds in all areas which helps fix the planar configuration of the molecules. The end result is a polymer with excellent heat stability and rigidity at high temperatures. The characteristic of toughness is made possible through the presence of the ether links, between phenyl rings that permit rotation of the adjacent chain sections.

Polysulfone has high resistance to acids, alkalies, and salt solutions, and good resistance to detergents, oils, and alcohols, even at elevated temperatures under moderate stress. It is attacked by polar organic solvents such as ketones, chlorinated hydrocarbons, and aromatic hydrocarbons. In addition to the properties described above, commercial polysulfones are similar in that each is transparent with a varying degree of amber color.

Due to the material's molecular configuration, PSO can withstand exposure to repeated autoclave cycles at temperatures up to 320°F. The actual glass transition temperature is 374°F. Studies have been performed showing parts made for hospital use can withstand hundreds of autoclave cycles, permitting longer life cycles. The material will also withstand exposure under gamma sterilization techniques, although some color shift is expected to occur. The material can be tinted using color concentrate to hide the color shift effect.

Applications. PSO is widely used in the medical industry for applications that vary from syringe holders, to instrumentation, to trays that hold instruments during sterilization. A special medical grade is available that meets U.S.P. XXII [12] Class VI requirements.

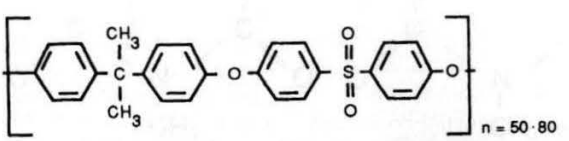


Figure 24 Chemical structure for polysulfone.

The material is more expensive per pound than polycarbonate materials, and the resin prices will vary, depending on the particular grade selected.

C. Specialty Resins

Polymethylpentene

Polymethylpentene (PMP) is a highly transparent olefinic plastic [23]. This material finds applications in packaging, films, vials, and microwave containers. If generally has excellent chemical and extraction resistance, as well as nontoxic characteristics.

The material was developed as a high-performance plastic for use where clarity and temperature resistance are necessary. The density of polymethylpentene is 0.835 gm/cc, the lowest of any available thermoplastic material. This low density approaches the theoretical lower limit of polymer density.

PMP is a plastic that excels in its resistance to heat and chemicals and also in transparency. Its chemical structure is illustrated in Figure 25. Since PMP can withstand autoclave sterilization, it has found use in biochemical lab containers, labware, and medical instruments, which are subjected to steam sterilization. When PMP is exposed to electron and gamma radiation, its properties measured immediately after exposure remain almost the same as those of unexposed PMP. However, in the course of exposure to radiations, the stabilizers contained in PMP are altered, resulting in a shortened storage life. Radiation resistant PMP grades are currently under development.

Applications. PMP resins are used in medical applications for items such as centrifuge tubes, syringes, filter housings, graduated cylinders and i.v. connectors. The material costs more per pound than the commodity materials, but this is offset by the extremely low resin density. This can be considered another strong advantage for certain medical applications. In summary, polymethylpentene is a specialty resin with special properties that are suitable for medical use.

Modified Acrylics

A new modified acrylic copolymer has been developed, which has higher heat resistance and is capable of being autoclave sterilized without softening. This specialty resin is called an acrylic-imide copolymer [17]. The copolymer resin has significantly improved resistance to oxygen, moisture, and gas permeation, which is essential for shelf life when packaging liquid drug products.

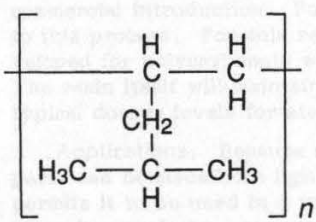


Figure 25 Chemical structure for polymethylpentene.

Since this material has high clarity, it may be considered in glass replacement applications. The material is somewhat brittle, but impact grades are available with some sacrifice in heat resistance.

Acrylic plastics comprise a general family of polymers where the base monomers belong to two families of esters namely, acrylates and methacrylates. These two monomers are used by themselves or with other monomers to produce a wide range of plastics with a wide range of characteristics. The acrylic-imide copolymer is part of the family of resins called acrylics. The chemical structure is illustrated in Figure 26.

The polymer has a unique combination of barrier properties, high flexural modulus (stiffness), good temperature resistance and clarity. These properties can be related directly to the chemical structure, consisting of an imide ring which includes the presence of a nitrogen atom. The nitrogen atom imparts a high degree of polarity, which can promote strong molecular ties or bonding.

The acrylic-imide copolymers are a family of resins that provide heat resistance that range from 250 to 300°F under a load of 264 lbs/in.^{2}. They have an extremely high degree of stiffness, referred to as flexural modulus. This property results in the brittle nature of the material, which can be considered a weakness in some applications.

Applications. Acrylic-imide copolymers are relatively new on the market. This material, based on its unique properties, is an excellent candidate for medical applications where heat resistance and clarity are required. Its good barrier properties make it a candidate resin to replace the use of glass in some drug packaging areas.

VII. QUALITY ASSURANCE OF PARENTERAL CONTAINERS

A. Qualification of Packaging Materials

Raw material qualification of parenteral packaging components is the first important step in designing a final product package. Maintenance of the packaged product's integrity is ultimately dependent upon the quality of the primary package. Qualification of the package material and the final package consists of verifying, through documented testing, that the package will per-

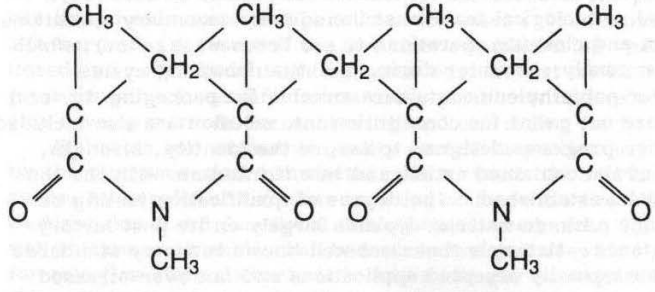


Figure 26 Chemical structure for acrylic imide copolymer.

form its intended function reliably under the most adverse conditions in which it will be used. Early and detailed qualification testing is essential in understanding the chemical and physical stability of the parenteral package.

Materials and components used in packaging must be carefully selected using the requirements of the packaged product as a guide. Such materials should be chosen and shown not to be adversely affected by the manufacutring process of the final container (i.e., molding process). Specific information msut be introduced such as how will the container be processed in the packaging operation and what additional stresses will be imposed on the container and its contents. Such stresses as heat and pressure exerted on the container during the rigors of sterilization should be thoroughly investigated during the qualification phase. These stresses may result in deformation of the final container as well as degradation of the polymeric structure.

Radiation sterilization processes have been shown to affect the polymeric structure of some materials, thereby resulting in further degradation of the package over time. Consequently, where degradation of a material is suspected as a result of a secondary manufacturing operation (i.e., therminal sterilization), such material and process interactions should be extensively investigated over a time equivalent to the product's shelf life. Accelerated aging studies can be performed by exposing the actual sterilized containers to various elevated temperatures and relative humidities for periods of time up to several months.

Once the materials have been exposed to the accelerated conditions, testing for impact resistance, color change, brittleness and stress cracking can be compared with non-irradiated or nonterminally sterilized controls. Other properties that may affect the suitability of a particular container and that may be influenced by secondary operations include oxygen and moisture permeability, melt index and modules of elasticity.

Many plastic containers used for pharmacopeial articles require furhter testing to assure the safety of the packaged product. Standards have been developed and are further described in the U.S. Pharmacopeia National Formulary for applicable plastic pharmaceutical containers. Physicochemical tests should be performed on plastic materials used on compendial article packages during the qualification phase of the material. Additionally, biological reactivity tests, both in vitro and in vivo, are described and prescribed in the USP. These tests are designed to determine the biological response in mammalian cell cultures and animals following contact with elastomeric plastics and other polymeric materials with direct or indirect patient contact [12]. Any physicochemical or biological tests must include any secondary operations such as sterilization and cleaning operations (i.e., Freon wash, etc.), which the material would normally encounter during the manufacturing cycle.

Specific tests for polyethylene containers suitable for packaging dry oral dosage forms that are not meant for constitution into solution are also included in the USP. Stability programs designed to assure the identity, strength, quality and purity of the contained article and how it interacts with the container material must be established. The degree of qualification testing required on a particular package material depends largely on its past history and industry acceptance. Materials that meet well known industry standards and are used in their normally accepted applications and not over-stressed should only need minor testing. Regardless of the degree of testing, a well

documented record of all qualification testing must be maintained. This record should include protocols used for testing as well as the actual test data, results and conclusions.

B. Final Product Testing

The Current Good Manufacturing Practice regulations require that all packaging components receive at least a visual inspection for contamination and damage. A pharmaceutical manufacturer purchasing packaging components from a supplier must be prepared to demonstrate the statistical rationale for any sampling plan used [24]. Such sample plans may be established by statisticians or quality engineers or may be taken from established standards such as MIL-STD-105 [25] or MIL-STD-414 [26]. These standard sampling plans have a built in risk of accepting a bad lot, which varies in accordance with the severity of the defect, but can be used for dimensional and attribute inspection.

Dimensional inspection requirements for the container lot should be held to minimal defects and include those dimensions that are critical to the packaged product and processibility of the container. Container height, wall thickness, inside/outside diameters and container-closure interface are examples of dimensional parameters that may be critical to both product and processibiulity factors.

Functional testing should include those characteristics that may affect the end use of the package. Container-closure interface and torque testing should be checked. Where tamper evident or sterility barriers are a factor, sealability of the protective barrier should be tested. Difficulty with adhering label material to containers has been associated with elevated levels of the slip agents that are used in the container manufacturing process and should, therefore, be demonstrated to be under control.

Attribute testing is another important area for final product testing. Color variation within a given lot will present concerns to marketing and sales. Limit samples demonstrating acceptable and undesirable color variations should be readily available to inspection personnel and should be agreed to with the component supplier. Likewise, transparency and light transmission properties may be critical to the stability of the packaged article and should be evaluated accordingly.

Sensitivity to cleanliness, as it relates to particulate contamination both on the visible and subvisible level, has increased to the point where the USP has issued standards that products must meet [12]. Consequently, particulate burden as a result of the container manufacturing operation must be monitored and controlled. Although most current test methods are applicable to glass containers, manufacturers using plastic containers or components should also develop methods for monitoring and controlling particulates [27].

Elaborate and extensive quality control inspection may often be limited by the pharmaceutical manufacturer as a result of historical data. For example, by careful and routine trending of inspection results, attributes, such as dimensional and functional testing may be reduced. If, for instance, the wall thickness dimension has been demonstrated over time not to be a reason for rejection, this characteristic may no longer be required for routine inspection. This does not imply the dimension should be taken from the specifica-

tions. Instead, this characteristic can be measured periodically or as required by the manufacturing process. Another factor for establishing inspection criteria is the review of complaint records. Such reviews may identify problems in the field associated with the manufacturing of the container. These problems should be addressed internally through an adequate specification and inspection plan. Paramount in resolving such problems is immediate feedback to the supplier with well documented proper investigation and corrective action.

There is another alternative to reducing the dependency on inspection. Recognizing that the vendor is in the business of making parenteral containers and utilizing his expertise in this area, a vendor certification program can be established. The current GMP regulations in 21 CFR 211.84(d) (paragraph 3) allows for acceptance of container lots by vendor certification provided: (1) a visual identification is conducted on such containers by the pharmaceutical manufacturer, and (2) the reliability of the vendor's test results is established. This latter requirement necessitates regular audits of the vendor's manufacturing operation.

Although suppliers of pharmaceutical packaging are not required to comply with pharmaceutical GMPs, most are familiar with them. It is therefore not unreasonable to require the supplier to develop controls and systems that will insure the delivery of the highest possible quality of containers and components. Continuous feedback to the vendor on nonconforming material, continual improvements and positive reassurance is a powerful tool for affecting change.

C. Packaging Procedures and Specifications

Although 21 CFR 211.122 requires written procedures for the examination of packaging materials, it does not specify what criteria must be included. Paragraph (c) of this section requires that written records be maintained for each shipment received. Lot traceability, both for internal and vendor processes, must be maintained for all shipments. Component specifications must be well designed and acceptable internally and to vendors. These specifications should describe quality characteristics, dimensions, raw material requirements, performance characteristics and sampling plan criteria. Adequate documented and change control procedures must be maintained and followed with adequate notification time and agreement by the vendor. All inspection documents and test data must be reviewed and approved by a qualified individual before release of components for product manufacturing. Periodic and documented audits of the inspection department should be performed by an independent party to insure compliance to procedures and specifications.

D. Microbiological Testing

The current GMP regulations require microbiological testing of drug product containers where microbiological contamination may cause an adverse affect on the final product [24]. Microbiological contamination on the container or component is commonly referred to as bioburden. A bioburden monitoring program is of the utmost importance when utilizing bioburden based sterilization or decontamination cycles (e.g., radiation processes). It is critical to under-

stand and evlauate not only the average bioburden but also the variability in the types of organisms found.

Variations in bioburden, as determined by routine monitoring, normally will result in adjusting process parameters to obtain the same degree of sterility assurance as previously validated [28].

In the typical plastic molding operation the temperatures achieved during the molding process are sufficient to produce a microbiologically clean component. However, from the moment the component is ejected from the mold the ambient conditions will begin to "contaminate" the surface of the item. Whether the component is cooled in the mold (e.g., injection molding) or as it exits the die (e.g., extrusion molding) the quality of the air is critical in maintaining the microbiolgoical cleanliness of the component.

The possibility of pyrogenic material left behind by the manufacturing process is of concern and should be evaluated and controllefd accordingly. Testing of containers and components using the Limulus Amebocyte Lysate (LAL) test has become an acceptable industry method to replace the USP rabbit pyrogen test [29]. Adequate validation of this test is important when using it as a screening method for raw materials.

Maintaining a clean production environment and eliminating or restricting the handling of the molded items should result in a microbiolgoically clean component. Suppliers of pharmaceutical packaging have experienced an increase in the demand for "white room" and even "clean room" molding oeprations in order to produce a "clinically clean" product.

Cleaning procedures to remove particulate matter, manufacturing materials (i.e., mold release agents), pyrogenic matter and microbiological contamination must be established and validated, when applicable. Mild solvents such as Freon and alcohol have been used to remove particulate matter and modl release agents. Pyrogenic matter and microbiological contamination may require heat treatment and decontamination processes prior to using the containers in the parenteral manufacturing environment. Such cleaning operations must be properly validated and demonstrated to not have adverse effects on the end product.

REFERENCES

1. McGraw Hill Publication, "Modern Plastics Magazine," January issues 1985-1991.
2. Driver, W. E., *Plastics Chemistry and Technology*, Van Hostrand Reinhold, New York, 1979, pp. 1-35, 191-231.
3. Wang, J. and Chien, Y. W., Technical Report No. 5, Sterile Pharmaceutical Packaging; Compatibility and Stability, Parenteral Drug Assoc., Inc., 1984.
4. Francis, D. and Williams, R., *Engineering thermoplastics in reusable medical application, Materials Engineering*, February, 1988.
5. Czerniawski, B., Flexible packaging of disposable medical devices-a review, *Packaging Technol. and Sci.*, 3:203-217 (1990).
6. Bucher, J., Transparent plastics for high performance applications, *Plastics Design Forum*, January/February, pp. 33-38 (1989).
7. *Guide to Methods, Machinery and Auxiliary Equipment*, McGraw Hill, New York, 1969, p. 21.

8. Scott, J. and Roff, W., *Handbook of Common Polymers*, Butterworth & Co., Ltd., 1971.
9. Thuen, J., Managing Editor, *International Plastics Selector, Plastics Edition 9*, San Diego, California, 1990.
10. Annual Book of ASTM Standards, Plastics (1) (11), Volume 08.01 (.02), C-177-D3099. ASTM, Philadelphia, Pennsylvania, 1990.
11. *Modern Plastics Encyclopedia*, McGraw Hill, New York, 1988, pp. 11-104.
12. The United States Pharmacopeia, 22nd Revision National Formulary, 17th Revision, Mack Publishing Co., Easton, Pennsylvania, 1990, pp. 1235-1238, 1495-1500, 1596-1599.
13. Craver, C. D., Polymer characterization, spectroscopic, chromatographic, and physical instrument methods, *Advances in Chemistry Series 203*, ACS, Washington, D.C., 1983.
14. Klein, A. J., Plastics that withstand sterilization, *Plastics Design Forum*, November/December, pp. 45-54 (1987).
15. Landfield, H., Radiation effects on device and packaging materials, *Medical Device and Diagnostic Industry*, Vol. 2, No. 5, May 1980, pp. 47-48.
16. Hensley, D. S., The effects of electron beam and gamma radiation sterilization on nine general purpose thermoplastic resins, *Proceedings, Second Annual Medical Plastics Conference*, The Society of Plastics Industry, Inc., September, 1984, pp. 27-45.
17. *Modern Plastics Encyclopedia*, McGraw Hill, New York, 1991.
18. Craver, J. K. and Tess, R. W., *Applied Polymer Science*, 1975, pp. 328-348.
19. Deanin, R. D., *Polymer Structure Properties and Applications*, Cahners Books, Division of Cahners Publishing Co., Inc., Boston, 1972.
20. Nass, L. I., *Encylcopedia of PVD*, Volumes 1-3, Marcel Dekker, New York, 1976, 1977.
21. *Food Chemical News*, June 15, 1981, pp. 55-56.
22. Kurachi, C. E., Wong, K. L., Sacena, S., and Solomon, D. D., *The 1982 Pacific Conference of Chemistry and Spectroscopy*, San Francisco, October 27-29, 1982.
23. TPX, Methylpentene Polymers, Mitsui Petrochemical Industries, Ltd., Tokyo, Japan, 1975.
24. Code of Federal Regulations 21, Ch. 1, Subpart G, Section 211.84 (b), U.S. Government Printing Office, Washington, D.C., 1990, p. 82.
25. Military Standard 105E, Sampling Procedures and Tables for Inspection by Attributes, Department of Defense, May 10, 1989.
26. Military Standard 414, Sampling Procedures and Tables for Inspection by Variables for Percent Defective, Department of Defense, June 11, 1957.
27. Fritz, B. L., Lockhard, H. E., and Giacin, J. R., Chemical stability of selected pharmaceuticals repackaged in glass and plastic, *Pharm. Technol.*, *12*(11):44-52 (Nov. 1988).
28. AAMI Guideline, *Process Control Guidelines for Gamma Radiation Sterilization of Medical Devices*, Association for the Advancement of Medical Instrumentation, Arlington, Virginia, 1984.
29. *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices*, U.S. Dept. of Health and Human Services, Public Health Service, Food and Drug Administration, Rockville, Maryland, December 1987.