

**Table 7-6** Comparative Properties of Major Plastic Polymers

Property	PVC	LDPE	HDPE	PP	EVA
Compatibility with contained drug products	Poor	Good	Good	Good	Fair
Moisture permeation	Very poor	Good	Excellent	Good	Very poor
Heat sterilization	Fair	Poor	Good	Excellent	Very poor
Transparency characteristics	Good	Fair	Poor	Fair	Fair
Collapsibility characteristics	Excellent	Poor	Poor	Poor	Good
Disposability capability	Poor	Good	Good	Good	Fair

*Abbreviations:* PVC, polyvinyl chloride; LDPE, low-density polyethylene; HDPE, high-density polyethylene; PP, polypropylene; EVA, ethylene vinyl acetate.

molecules may penetrate to the inside of the container and cause oxidative or other degradation of susceptible constituents. *Leaching* may be a problem when certain constituents in the plastic formulation, such as plasticizers or antioxidants, migrate into the product. Thus, plastic polymer formulations should have as few additives as possible, an objective characteristically achievable for most plastics being used for parenteral packaging. *Sorption* is a problem on a selective basis, that is, sorption of a few drug molecules occurs on specific polymers. For example, sorption of insulin and other proteins, diazepam, methohexital sodium, procainamide, vitamin A acetate, warfarin sodium, and other drugs, has been shown to occur on PVC bags and tubing when these drugs were present as additives in IV admixtures (44).

### Flexible Container Film Types

PVC was the first polymer used in the manufacture of collapsible containers for IV administration. However, PVC performs poorly in tests of all properties, with the exception of collapsibility and transparency. In addition, the presence of plasticizers such as DEHP [di(2-ethylhexyl) phthalate] limits the type of fluids suitable for storage in PVC because of concerns that the plasticizers can leach into the contained product. Concerns over the long-term safety of exposure to DEHP have led several nations to ban the use of PVC materials (e.g., Germany, Sweden, France, Canada, Spain, South Korea, and the Czech Republic, among others). Lastly, environmentalists have condemned PVC because it produces dioxin when incinerated (45). To improve characteristics such as compatibility and moisture permeation, ethylene vinyl acetate (EVA) films were developed. While EVA does not contain plasticizers, it, like PVC, has poor resistance to moisture permeation and both types of single-layer bags required secondary overwraps. The problem of moisture permeation was solved with the development of multilayer films. In one case, ethylene (vinyl) alcohol (EVOH), which has a high gas barrier, is used as a core and is physically bonded between two layers of EVA film (46). Additional films are available that combine a polyethylene (PE) inner product contact film, with other barrier films such as EVOH. The PE product contact layer provides excellent chemical compatibility and is rated as having excellent resistance to acids, alcohols, aldehydes, alkalis, amines, esters, glycols, vegetable oils, and salts. Poor resistivity was observed for hydrocarbons, and resistance to essential oils and ketones was fair and good, respectively (47).

### Innovations in Flexible Containers

A number of suppliers now offer IV solutions, premixed medications, and custom manufacturing of IV solutions in flexible containers free of PVC and DEHP. These include Baxter's AVIVA and Galaxy lines, B. Braun's Excel and PAB containers, and Hospira's VisIV and CR3 container (48–50). While most large-volume flexible containers require terminal sterilization, Baxter's Galaxy lines offer proprietary aseptic filling processes for unstable and heat-sensitive drugs such as therapeutic proteins and monoclonal antibodies (51).

### Flexible Container Sterilization

The impact of sterilization methods on container properties must be carefully considered during package and process development. Many plastic materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic used and control of the