

Polymers and Additives Used in Fabrication of Disposable Bioprocess Equipment

by Michael A. Ruberto

The materials used to fabricate single-use processing equipment for biopharmaceutical manufacturing are usually polymers, such as plastic or elastomers (rubber), rather than the traditional metal or glass. Polymers offer more versatility because they are light-weight, flexible, and much more durable than their traditional counterparts. Plastic and rubber are also disposable, so issues associated with cleaning and its validation can be avoided. Additives can also be incorporated into polymers to give them clarity rivaling that of glass or to add color that can be used to label or code various types of processing components.

Given all the positive attributes that polymers possess, there are also some negatives to consider when working with them in pharmaceutical applications. In the presence of heat, light, oxygen, and various external influences (such as sterilization), polymers can degrade over time if not properly stabilized. Degradation can manifest itself as cracking, discoloration, or surface blooming/exudation — and this can severely affect the mechanical properties of the polymers. Stabilizing additives are incorporated into many polymers to prevent this degradation. However, the resulting formulation is more complex than that of metal and glass, and it makes materials such as plastic and rubber much more prone to leaching unwanted chemicals into drug product formulations when they are used in



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applications such as manufacturing or packaging.

That does not mean such materials should not be used in bioprocess applications. In fact, their benefits greatly outweigh their risks. However, the risk must be managed.

POLYMERS AND ADDITIVES

When a plastic resin is processed, it is often introduced into an extruder, where it is melted at high temperatures and mixed by a series of screws into a homogenous molten mixture. Additional heat and shear are encountered by the plastic when it is extruded and molded or shaped into a final product form, such as tubing or a bioprocessing bag. The degree of potential degradation depends on the nature of a polymer's chemical composition, the manner in which it is processed or molded, and the end use of the finished product.

For example, the inherent stability of a polymer substrate will be influenced by its molecular structure, polymerization process, presence of residual catalysts, and finishing steps

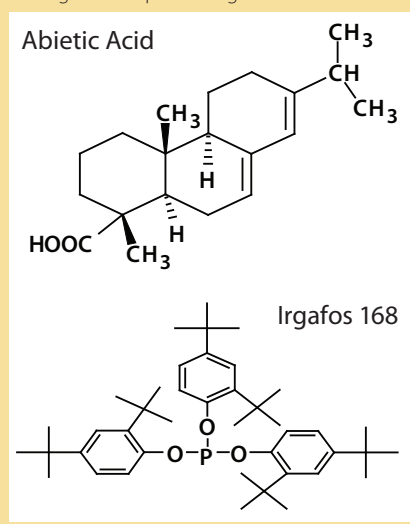
used in production. Processing conditions during extrusion (e.g., temperature, shear, and residence time in the extruder) can dramatically affect polymer degradation. End-use conditions that expose a polymer to excessive heat or light (such as outdoor applications or sterilization techniques used in medical practices) can foster premature failure of polymer products as well, leading to a loss of flexibility or strength. If left unchecked the results often can be total failure of the plastic component.

Polymer degradation can be controlled by the use of additives in the plastic or elastomer system. These are specialty chemicals that provide a desired effect to a polymer. The effect can be stabilization that allows a polymer to maintain its strength and flexibility or performance improvement that adds color or some special characteristic such as antistatic or antimicrobial properties. There are typically three classes of stabilizers:

- melt processing aids such as phosphites and hindered phenols, antioxidants that protect a polymer during extrusion and molding
- long-term thermal stabilizers that provide defense against heat encountered in end-use applications (e.g., hindered phenols and hindered amines)
- light stabilizers that provide ultraviolet (UV) protection through mechanisms such as radical trapping, UV absorption, or excited state quenching.

One application in which an additive can improve or alter the

Figure 1: Chemical structures of abietic acid and Irgafos 168 processing stabilizer

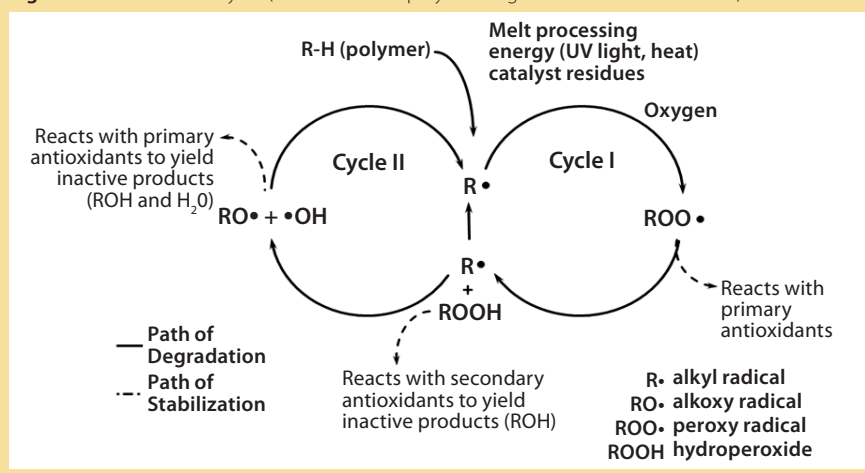


performance of a polymer is a filler or modifier that affects its mechanical properties. Additives known as plasticizers can affect the stress-strain relationship of a polymer (1). Polyvinylchloride (PVC) is used for home water pipes and is a very rigid material. With the addition of plasticizers, however, it becomes very flexible and can be used to make intravenous (IV) bags and inflatable devices. Lubricants and processing aids are also used to reduce polymer manufacturing cycle times (e.g., mold-release agents) or facilitate the movement of plastic and elastomeric components that contact each other (e.g., rubber stoppers used in syringes).

Techniques used to analyze polymer additives vary depending on their chemical structures. For example, abietic acid is routinely analyzed with gas chromatography (GC), whereas high-performance liquid chromatography (HPLC) is the method of choice for an organic phosphite stabilizer such as Ciba's Irgafos 168 product. Figure 1 depicts the molecular structure of both compounds.

Additives are not always single entities. Some are manufactured from naturally occurring raw materials such as tallow and vegetable oils that are themselves composed of many different components and can vary from batch to batch. Others are considered "products-by-process," in which the addition of A + B yields the additive C. Additive C is not necessarily a pure material, and the

Figure 2: Autoxidation cycle (mechanism for polymer degradation and stabilization)



concentration of its active components also varies with each synthesis — typically being reported in a compound's certificate of analysis (CoA) as a range. The issues an analytical chemist would face in chromatographic analysis of such compounds are twofold: very complex chromatograms and minor components in an additive formulation with greater migration rates than the main components have. In extractables and leachables testing, those lesser known minor chemical species may be the ones that leach into a drug product.

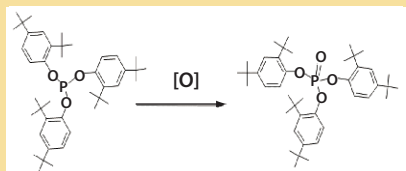
Stabilizers incorporated into plastic and rubber are constantly working to provide much-needed protection to the polymer substrate. This is a dynamic process that changes according to the external stress on the system. To help in understanding how stabilization occurs mechanistically, Figure 2 illustrates the chemistry that can occur in a typical polyolefin (e.g., polypropylene or polyethylene) in a schematic of the autoxidation cycle (2). As shown, the solid lines represent pathways of degradation, and the dashed lines are the paths to stabilization. The origins of polymer degradation are radical species such as alkyl, alkoxy, and peroxy radicals as well as hydroperoxide.

Good stabilizers are therefore efficient radical scavengers. For plastics, a two-tiered approach is often used to protect polymers from the heat and shear they encounter during processing. Primary antioxidants — e.g., hindered phenols such as butylated hydroxy toluene (BHT) and Ciba's Irganox 1010

and 1076 products — are added to polymers to provide protection during processing as well as long-term heat stability. Secondary antioxidants (e.g., Ciba's Irgafos 168 organic phosphite) are also added as process stabilizers. Such compounds are typically hydroperoxide decomposers that protect polymers during extrusion and molding while also acting as "sacrificial lambs" by defending the primary antioxidants against decomposition. The chemical species that result from reactions depicted by the dotted lines in Figure 2 are known in the polymer industry as *transformation products*. This is expected chemistry, and a good deal of information (e.g., toxicological data) is available for these compounds.

Figure 3 shows one predictable transformation reaction that occurs with organic phosphites. The phosphite entity transforms a phosphite. Both compounds are present in a plastic or rubber substrate and can leach into a drug product manufactured with polymer processing equipment containing it. Sometimes, unwanted chemistry can occur in a polymer substrate. The Irgafos 168 additive can react through an undesirable pathway that deactivates some or all stabilization sites on its molecule. Figure 4 depicts hydrolysis of the organic phosphate yielding mono- and disubstituted entities as well as 2,4-di-*t*-butylphenol. All those compounds become available to leach from polymers into a drug product. This example is relatively simple; often many different transformation and

Figure 3: Irgafos 168 transformation chemistry



degradation products can be produced from a single primary antioxidant such as a hindered phenol (Figure 5).

Elastomers sometimes have special stabilization needs. In the rubber industry, acid scavengers are used to neutralize traces of halogen anions formed during aging of halogen-containing rubbers (e.g., brominated or chlorinated isobutylene isoprene). If not neutralized, anions cause premature aging and a decrease in the performance of rubber articles over time. Metal oxides can be very efficient acid scavengers. Ions of copper (Cu), iron (Fe), cobalt (Co), nickel (Ni), and other transition metals that have different oxidation states with comparable stability are called “rubber poisons” because they are easily oxidized or reduced by one-electron transfer. They are very active catalysts for hydroperoxide decomposition (Figure 2) and contribute to the degradation of rubber vulcanizates. Even in trace amounts (<5 ppm), rubber poisons present in vulcanizates increase the decomposition rate of hydroperoxides and thus accelerate oxidation and aging of rubber goods. Rubber containing — or that may be in contact with — rubber poisons thus requires a specific stabilizer: a “metal deactivator.” Irganox MD 1024 metal deactivator — 2',3-bis[[3-[3,5-di-tert-butyl-4-hydroxyphenyl]propionyl]]propionohydrazide — binds ions into stable complexes and deactivates them.

EXTRACTABLES AND LEACHABLES

Leachables are chemicals that migrate from single-use processing equipment into various components of the drug product during manufacturing.

Extractables are chemical entities (organic and inorganic) that can be extracted from disposables using common laboratory solvents in controlled experiments. They represent the worst-case scenario and

are used as a tool to predict the types of leachables that may be encountered during pharmaceutical production. So extractables are the “potentials” and leachables are the “actuals.” More chemicals are available to leach from single-use processing equipment manufactured from polymers than from other materials such as glass and metal. Extractables can include

- monomer and oligomers from incomplete polymerization reactions
- additives and their transformation and degradation products
- lubricants and surface modifiers
- fillers
- rubber curing agents and vulcanizates
- impurities and undesirable reaction products such as polyaromatic hydrocarbons, nitrosamines, and mercaptobenzothiazoles (3).

Unexpected additives can also be present in a polymer system. During formulation, additives can be incorporated as either neat materials or in a masterbatch. A masterbatch, sometimes referred to as a *concentrate*, is a mixture of an additive at a relatively high concentration (5–30% or more) in a polymer matrix that acts as a carrier. The base polymer formulated with such an additive concentrate can be the same substrate (e.g., polypropylene) as the one used in the masterbatch. But polymers can be different grades or manufactured by different vendors and thus can contain different base-stabilizer systems. A masterbatch can also be earmarked for other nonmedical

applications and contain specialty additives that provide no value to typical single-use bioprocessing equipment. For example, it can be the source of unanticipated light stabilizers or more than one primary antioxidant.

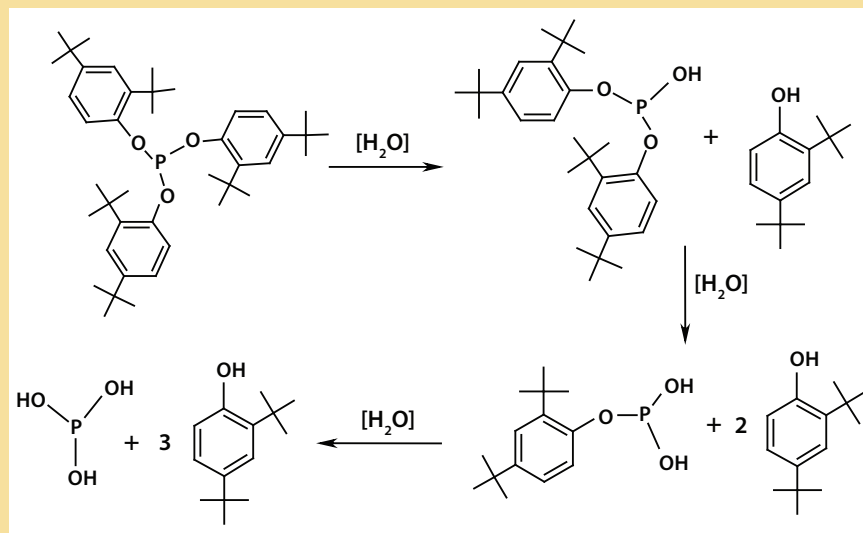
MANAGING THE RISK

The utility of polymers in disposable bioprocess equipment (and in all medical or pharmaceutical applications) far outweighs the risks associated with their use. The key is to manage those risks proactively. Three important steps can be followed: material selection, implementation of a proper testing program, and partnering with vendors.

Material Selection: It is important to ensure that the correct polymer is chosen for a given bioprocessing application. Many different types of plastic and elastomers are commercially available, each with different physical and chemical properties. Special consideration should be given to the compatibility of their additives. For example, many different phenolic antioxidants are on the market, each with the same active site (the hindered phenol moiety). The feature that sets them apart from one another is the remainder of each molecule, which is what makes them soluble or compatible with a given polymer substrate. An antioxidant that is compatible with nylon might not be the best choice for use in polyolefins.

Ensuring compatibility often lessens the amount of leaching that can occur.

Figure 4: Irgafos 168 degradation chemistry



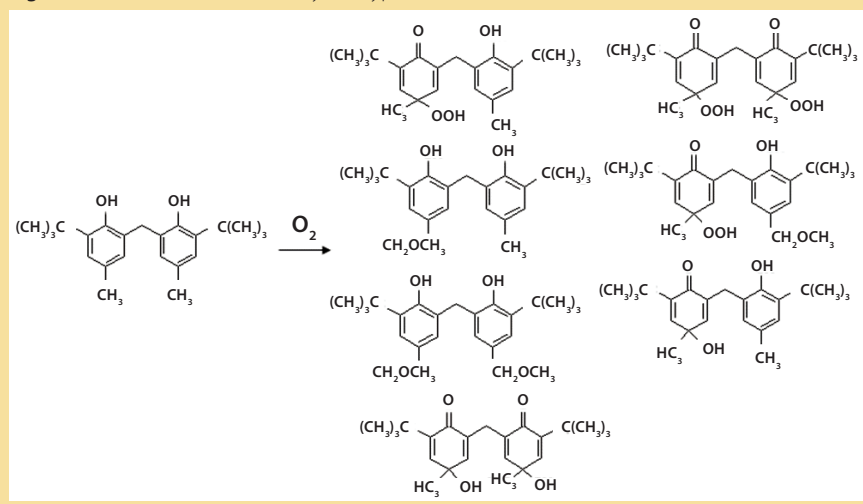
It is also very prudent to select polymers and additives that are approved for use in food-contact applications. Such compounds have already undergone a fair amount of analytical and toxicological testing, so a good amount of information is often available for them. These materials are often important products for resin and additive manufacturers, so there is less likelihood of product discontinuation. They are also regulated by the FDA, so significant changes in their composition or manufacturing processes have to be reported to the agency and customers that purchase the materials. Thus, a basic change control process is in place.

Testing: Polymers used in medical and pharmaceutical applications should comply with the appropriate USP guidelines, and it is recommended that they meet USP Class VI testing as documented in chapter <88> of the *US Pharmacopeia*. Appropriate extractables and leachables testing programs should be implemented for all bioprocessing materials that come into direct contact with components of a drug formulation.

Two industry groups have published best-practice guidelines for conducting such testing. The first document was prepared by the Product Quality Research Institute (PQRI) for evaluation and safety assessment of extractables and leachables in orally inhaled and nasal drug products (4). Its recommendations apply to primary and secondary packaging associated with such pharmaceutical products. The Bio-Process Systems Alliance (BPSA) published a two-part technical guideline for evaluating the risk associated with extractables and leachables, specifically for single-use processing equipment (5).

Testing should not necessarily end once materials have been qualified. It is a good idea to put a thorough quality control program in place for testing new batches/lots of raw materials and/or final equipment components. The level and frequency of quality control testing is an individual decision made by each pharmaceutical company according to its own risk tolerance.

Figure 5: Transformation chemistry of a typical antioxidant



Partnering with Vendors: The burden of determining risks associated with materials for single-use bioprocessing can be lessened when a pharmaceutical company has a good working relationship with the equipment vendors. Communication is key to such a partnership. Vendors often have extractables data already on hand to share with their customers. In many cases, they will provide CoAs and even toxicological information associated with materials used to fabricate their products. Such data will help to facilitate materials evaluation and development of protocols and analytical methods for extractables and leachables testing.

Vendors also should have well-established change control processes for the products they sell. Communication of changes should be timely with sufficient notice for customers to deal with potential issues. In a successful partnership, the customer gets peace of mind that leads to better supply chain management and process control, and the vendor can distinguish itself by offering extra assurances and information, which should increase sales.

Polymers offer many advantages as the primary materials used in manufacturing disposable bioprocess equipment. Plastic and rubber substrates are susceptible to degradation during extrusion, molding, and certain end-use applications, so they must be stabilized with additives. Because of their complex formulations, these polymers are more prone to leachables than are some of the

traditional materials used in bioprocessing equipment, such as glass and metal. Managing risks associated with polymer use can be accomplished by proper material selection, implementation of the industry-recommended testing programs, and partnering with the vendors that manufacture and sell single-use bioprocessing equipment.

REFERENCES

- 1 Odian G. *Principles of Polymerization*, Second Edition. Wiley-Interscience Publication: New York, NY, 1981.
- 2 Zweifel H. *Plastic Additives Handbook*, Fifth Edition. Hanser Publishers: Munich, Germany, 2001.
- 3 Norwood DL, et al. Analysis of Polycyclic Aromatic Hydrocarbons in Metered Dose Inhaler Drug Formulations by Isotope Dilution Gas Chromatography/Mass Spectrometry. *J. Pharm. Biomed. Anal.* 13(293) 1995: 293–304.
- 4 PQRI Leachables and Extractables Working Group. *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products*. Product Quality Research Institute: Arlington, VA, 8 September 2006: www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.
- 5 Extractables and Leachables Subcommittee of the Bio-Process Systems Alliance. *Recommendations for Extractables and Leachables Testing*. *BioProcess Int.* 6(5) 2008: S28–S39.

Michael A. Ruberto, PhD, is president of *Material Needs Consulting, LLC*, 110 Chestnut Ridge Road, #311, Montvale, NJ 07645; 1-201-248-3782; www.materialneedsconsulting.com. *Irgafos* and *Irganox* are registered trademarks of *Ciba Corp.* (www.ciba.com).