Entegris

Advantages of Single-layer Film vs. Multilayer Film for use in Bio-processing Bags

White paper

INTRODUCTION

Medical treatment, as we know it, is changing fast. Gone are the days where blockbuster drugs are developed and prescribed as one-size-fits-all solutions. Today, the trend is toward precision medicine with targeted therapies[1]. This single fact is significantly changing bioprocessing for pharmaceuticals.

Now more than ever, speed and flexibility are critical to succeed in the bioprocessing market. The first company to patent a process for a particular drug product reaps the most benefit. The use of polymeric bioprocessing components and systems provides the required speed to evaluate many more possibilities and get to the successful one quicker.

Plastics technology also enables small-batch, single-use packaging solutions for customized drugs to serve a smaller patient population. These solutions lower energy and water consumption while simultaneously improving facility utilization and creating a smaller carbon footprint, reducing the risk of contamination, as well as analytical and quality-control costs[2].

This paper takes a closer look at plastic storage bags for bioprocessing applications, the challenges associated with them, and technology developments to address these challenges. Specifically, it focuses on materials that enable a shift from multilayer to single-layer storage solutions.

Before we get into the details, let's explore the journey that got us to this point.

THE BACK STORY

Since the 1970s, plastic technology for the manufacturing of biopharmaceutical products according to the U.S. Food and Drug Administration's (FDA) *Current Good Manufacturing Practices* (CGMPs), has been steadily replacing traditional production facilities that relied on relatively inflexible, hard-piped equipment, including large stainless-steel bioreactors and tanks to hold product intermediates and buffers[2,3].

Contract manufacturing organizations (CMOs) with a relative lack of legacy production systems were early adopters of plastic technology, primarily as a capital expenditure (CAPEX) cost-saving measure. Historically, it cost $500M–$1B to build and outfit a new stainless-steel facility. Replacing traditional equipment with plastics technology allowed for quick change and easy setup. This improved productivity and reduced equipment expense.

First introduced in a clinical environment for media storage and transportation of blood and intravenous liquids such as saline solution, plastic technologies were adopted into the manufacturing environment in the late 1970s, about the time when multilayer food packaging films were being introduced to the market. This evolved over time to include three-dimensional process containers and filter assemblies.

In the late 1990s and early 2000s, a paradigm shift driven by several bioprocessing companies saw bioreactors moving away from glass and stainless steel, and converting to plastics as the fluid contact layer. This shift required some additional process adaptations.

For example, while steam-in-place (SIP) and clean-in-place (CIP) were sufficient sterilization methods for stainless steel, they were not suitable for plastics. Because of the high probability for cross contamination with plastics, a new approach to sterilization was needed.

The development of gamma-irradiation stable plastic technology is probably one of the most important evolutions seen in the industry, greatly advancing the application of single-use technology. Gamma irradiation, a common means of sterilization, kills bacteria at a molecular level by breaking down bacterial DNA and inhibiting bacterial cell division. This eliminates the need for subsequent sterilization of most single-use materials and products, making the disposable, plastic containers for drugs an even more attractive option[4].

With end-to-end plastic manufacturing in full swing, it was now possible to move from small-scale manufacturing of clinical-trial materials to full-scale CGMP commercial production.

Improving Biomanufacturing Performance Factors Creating "Significant" or "Some" Improvements

How much have each improved biomanufacturing performance over the past 12 months? (2010–2015)

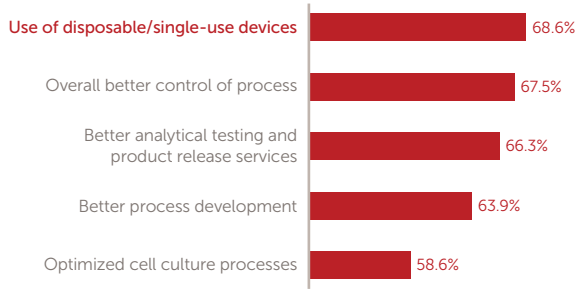


Figure 1. Source: "Twelfth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production," BioPlan Associates, Inc., Rockville, MD, April 2015, pp. 109

CHALLENGES

Plastic bags that store, transport, and protect valuable biopharmaceutical agents are designed with two distinct functions in mind: contact with biopharmaceutical fluids and functionality. As such, these bags need to meet a series of unique and different specifications.

Today, these distinct criteria and characteristics are generally met through composite, multilayer, plastic, or polymer film constructs with a different and specific outer layer or shell to protect against environmental impacts and guarantee durability. Additionally, there is a contact layer on the inside of plastic vessels to keep the biopharmaceutical fluids safe. The various layers composing the multilayer construct are "tied together" with adhesives to unite incompatible materials harmoniously in single, homologous constructs[5].

Factors that May Restrict Use of Disposables in Biopharmaceutical Manufacturing

Percent Indicating "Strongly agree" or "Agree"

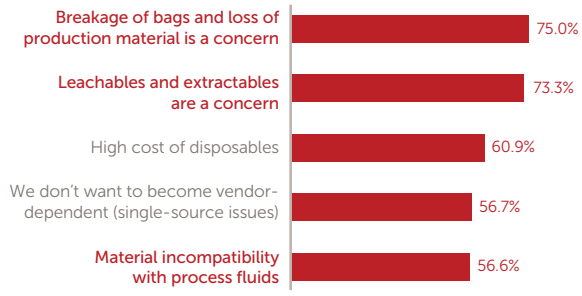


Figure 2. Source: "Twelfth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production," BioPlan Associates, Inc., Rockville, MD, April 2015, pp. 294

There has been an increased concern about process fluid contamination caused by extractables and leachables (E&L) coming from the film's multiple material layers used to manufacture single-use bags. Some E&Ls originate from the binding material used to adhere the layers, as well as other additives found in the multiple layers of polymeric film[6,7,8].

This contamination can impact cell growth and affect product yield, quality, or stability, leading to significant quality concerns. Recent studies show this may be due to an increase in the transition of products produced using plastic technology moving into later-stage clinical development[7].

THE WAY FORWARD: NEW AND IMPROVED MATERIALS

Historically, these complex, multilayer constructs were designed for storage and transportation of liquid materials and critical buffers and media. Now that materials are primarily transported in dry powder form, the concern has lessened, again allowing manufacturers to search for alternative materials for making plastic products. Therefore, homogenous, single-layer polymers without adhesives, and unitary molded, solid, and structurally self-supporting plastics are more suited to the needs of today's applications[7].

The chemical and physical properties of the polymeric materials used to manufacture bag layers are influenced by the molecular structure, polymerization process, stabilization, and processing additives, as well as manufacturing factors such as extrusion conditions. In addition, the physicochemical properties of these materials are affected by factors such as heat, light, oxygen, and sterilization (irradiation) conditions.

Single-use bags are generally made from multilayer films and may include variants of PE such as low-density polyethylene (LDPE), linear low-density polyethylene (LLDPE), ultralow-density polyethylene (ULDPE), ethylene vinyl acetate (EVA), ethylene vinyl alcohol (EVOH), polyamide (PA), or polyethylene terephthalate (PET)[5,7,8].

Each layer in these multilayer films contributes to the overall film properties, while resin selection is based on predetermined criteria, such as barrier properties or transparency requirements.

Because not all plastics are compatible with one another, the different polymer layers in a multilayer film structure may express limited interlayer adhesion. This is why the aforementioned "tie layer" is used to provide adhesion between adjacent film layers, helping these different polymer layers adhere (Figure 3)[9].

ALLEVIATING CONCERNS

To address ongoing contamination concerns, both manufacturers of plastic technologies and end-users in the biopharmaceutical industry are looking for new and improved plastics to use in their products. At the same time, purity-improvement measures for plastic technologies are being driven by the stringent technical and regulatory demands for high purity in biopharmaceuticals, the sensitivity of cell cultures to trace impurities, and the clinical impact of particulates on patient safety.

In similar fashion, both suppliers and end-users are striving to alleviate the cold temperature performance disadvantages of multilayer constructions. Because each layer has a unique coefficient of thermal expansion (CTE), delamination can occur when these bags are subjected to cryo conditions. Using homogeneous single-layer films is one way to eliminate delamination risks associated with intra-layer thermal stresses.

This is because in single-layer fluoropolymer plastics, CTE is uniform and will not cause microfractures across different layers that could potentially harm bag integrity, as often seen in multilayer plastic films. Overall, the increased strength and durability help to avoid costly bag assembly failure at downstream fill-finish operations[10].

QUALITY OF PLASTIC

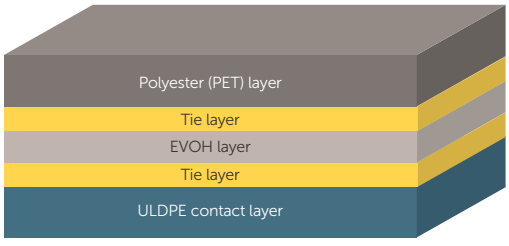
Currently, there are only a few resins that can be converted into a single-layer film that will meet the performance and purity requirements of today's bioprocessing applications.

Fluoropolymer plastics are a special class of fluorocarbon-based (PFC) polymers with multiple carbon-fluorine bonds characterized by a high resistance to solvents, strong acids, and bases. They are well suited to meet the requirements for challenging applications in which durability, inertness, purity, and cleanliness are important.

It's important to note that not all fluoropolymers on the market are the same. One of the most critical differences is that many (e.g., PTFE and FEP) are not gamma stable[8,9,12].

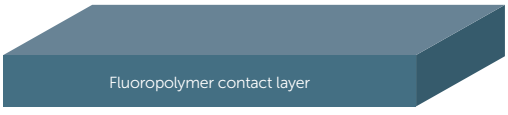
For example, polyvinylidene difluoride (PVDF) is a copolymer formulation often used to provide the bags with flexibility but using it can lead to additional E&L. Polytetrafluoroethylene (PTFE) and fluorinated ethylene propylene (FEP) are not gamma stable beyond 5 kGy, limiting use in bioprocessing as well.

Standard film material



Each layer in the multilayer films making up the standard film materials used in the manufacturing of plastic or disposable technologies attributes to the overall properties of the film. The implementation of an EVOH layer increases the risk of detrimental extractable compounds from the material and/or adhesives used to manufacture the multilayer bag.

Advanced film material



High-grade fluoropolymer, gamma-stable film in a single layer provides an increased level of security and protection from particles and eliminates many of the common extractables from traditional plastic or disposable bags that can leach into the process media.

Figure 3.

There is only one fluoropolymer film available on the market known to have the ultimate purity chemical resistance and be gamma stable (unlike PTFE and FEP) to address the market's concerns with E&L. It also serves a wide temperature range. This material promises to be a game changer for the industry, displacing the legacy products that are limiting consistency in bioprocessing production (Figure 3).

When used for manufacturing plastic products, such as vessels or bags, this novel fluoropolymer material, engineered and manufactured to be used in extreme environmental conditions, allows for increased efficacy in frozen applications, such as storage and shipment of stem-cell materials and critical buffers and media.

Using this novel fluoropolymer plastic reduces the risk of breakage while at the same time provides an increased level of security and flexibility. As the plastics don't contain curing agents, antioxidants, plasticizers, or adhesives, potential contaminants are reduced, improving overall universal material compatibility. When used in the development of plastic vessels or bags, these characteristics reduce the risk of material and assembly failures, limiting the potential impact on high-value biopharmaceutical compounds[13].

In addition, high-grade fluoropolymer resins are the only available plastics with a broad operating temperature range from 260°C (500°F) down to -240°C (-400°F). In fact, in comparative freeze-thaw cycles and frozen drop tests, one type of plastic 2D bag made from this high-grade, single-layered, fluoropolymer plastic and manufactured in an ISO Class 5 cleanroom, was proven most reliable under cryogenic temperature conditions, down to a temperature of -85°C (-121°F) or lower without negatively affecting the film.

Lastly, products made from single-layer fluoropolymer plastics offer universal material compatibility, a much-desired characteristic of these products.

CONCLUSION

As the market grows and the adoption of plastic technology expands, the materials used to design, develop, and manufacture these products are expected to greatly improve.

In particular, novel fluoropolymer plastics help to reduce costs, meet batch-size requirements, and protect and maintain the purity of bioprocess materials.

Additionally, integrity of the bag is improved to withstand a variety of temperatures, handling, and transportation. Bags made from single-layer fluoropolymer plastics equaled or surpassed the integrity of multilayer polyethylene bags. This helps meet the ever-changing and more stringent requirements of drug developers, biopharmaceutical manufacturers, and regulators.

ABOUT ENTEGRIS

Entegris is a leading specialty materials provider for the microelectronics industry and other high-tech industries. Entegris is ISO 9001 certified and has manufacturing, customer service and/or research facilities in the United States, China, France, Germany, Israel, Japan, Malaysia, Singapore, South Korea, and Taiwan. Additional information can be found at www.entegris.com

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