Niche Containment

BFS Advancements for Aseptic Processing and Packaging

Blow/Fill/Seal technology, originally developed in Europe and introduced in the U.S. in the late 1960's, has emerged as a preferred method for aseptic packaging of pharmaceutical and healthcare products due to the flexibility in container design, overall product output and low operational costs.

Figure 1. A variety of polymers are used in the Blow/Fill/Seal process with low and high-density polyethylene and polypropylene being the most popular.

A variety of polymers may be used in the Blow/Fill/Seal (BFS) process; low and high-density polyethylene and polypropylene are the most popular. The innate ability to form the container and closure during the actual aseptic packaging process allows for the custom design of the container to meet the specific needs of the application. This flexibility not only improves container ease-of-use, but also provides a means of interfacing with many of today's emerging drug delivery technologies, most notably in the field of respiratory therapy.

Recent advancements in machine design allow for insertion of pre-molded, pre-sterilized components to be molded into the container, creating additional design options to create multi-use and injectable product containers. Furthermore, the BFS process flow is normally impacted by only two raw materials, product and polymer, that are each processed in-line, thereby making the process amenable to large uninterrupted batch sizes, some in excess of 500,000 units, and fill durations of up to 120 hours. The net effect routinely is an increase in production efficiency and a subsequent decrease in operational costs for the user.

According to Chuck Reed, of Weiler Engineering, Inc, (*www.weilerengineering.com*) "Blow/Fill/Seal systems represent a niche market within the larger form/fill/seal marketplace for pharmaceutical packaging equipment. The BFS process is a robust, advanced aseptic processing technology, recognized by worldwide regulatory authorities for its inherent operational advantages over conventional aseptic production. BFS systems offer a unique combination of flexibility in packaging design, low operating cost, and a high degree of sterility assurance. The machines require a minimum number of operating personnel and have a relatively small space requirement."

Weiler Engineering designs and builds its ASEP-TECH machine as part of a complete BFS process solution. The Weiler design incorporates the multi-step process of blow molding, aseptic filling and hermetic sealing of liquid products in one sequential operation on a compact, automated machine frame with fill volumes ranging from 0.1mL to 1000mL.

> Recent advancements in machine design allow for insertion of pre-molded, pre-sterilized components to be molded into the container.

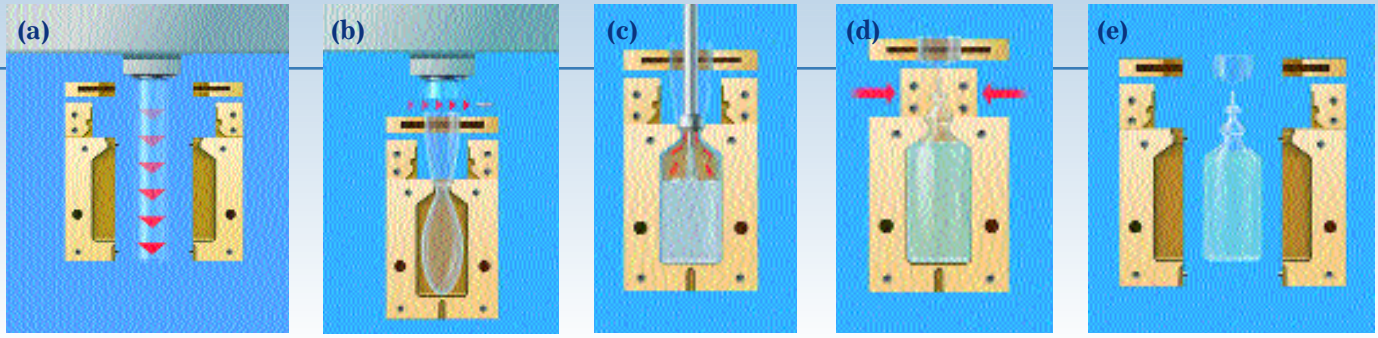
THE BFS PROCESS

Figure 2 on page 17 demonstrates the BFS process, which includes:

Container Molding – Thermoplastic is continuously extruded in a tubular shape (a). When the tube reaches the proper length, the mold closes and the parison is cut (b). The bottom of the parison is pinched closed and the top is held in place with a set of holding jaws. The mold is then transferred to a position under the filling station.

Container Filling – The nozzle assembly lowers into the parison until the nozzles form a seal with the neck of the mold (c). Container formation is completed by applying vacuum on the mold side of

Figure 2. The BFS process including container molding, filling and sealing.



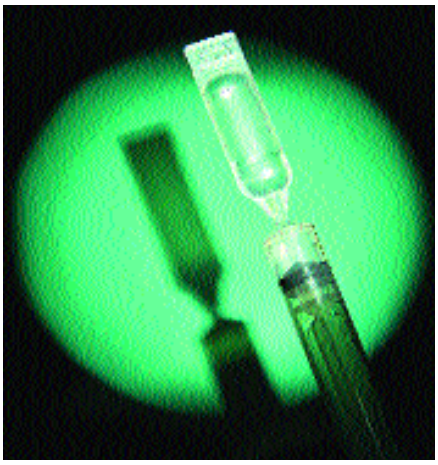


Figure 3. An example of a BFS produced single dose container.

the container and by blowing sterile filtered air into the interior of the container. The electronic fill system delivers a precise dosage of product into the container. The nozzles retract into their original position.

Container Sealing – Following completion of the filling process, the top of the container remains semi-molten. Separate seal molds close to form the top and hermetically seal the container (d). The molds open and the container is then conveyed out of the machine.

PROCESS PERFORMANCE

Increasing regulatory scrutiny in the area of product quality, most notably product sterility assurance, has challenged the pharmaceutical and healthcare industries to consider alternatives to traditional methods of aseptic packaging. Blow/Fill/Seal has been recognized by the U.S. Pharmacopeia (USP XXIV) and the PDA (Technical Report 26) as an Advanced Aseptic Process. This may be defined as a technology that can dramatically reduce the potential of contamination from human presence during aseptic processing operations due to its design and functionality.

The process reduces the amount of product contacting components, there is limited operator intervention and the critical fill zone is physically isolated under a continuous flow of filtered air. Since Blow/Fill/Seal is a completely automated technology that allows for remote operation it is an ideal system for examining the relationship between the level of airborne microorganisms in the environment and the product contamination rate. A series of published studies have been conducted to investigate and quantify this relationship and potentially provide a means for predicting sterility assurance levels[1,2,3].

This experimental work was performed by producing controlled challenges of microorganisms dispersed in air at concentrations extending over a 1000 fold range in a containment room housing a Blow/Fill/Seal machine producing containers filled with medium that supports the growth of the challenge organisms. Results of the studies demonstrated a direct relationship between the fraction of product contaminated and the level of airborne microorganisms.

The linearity of the curve provided a reasonable basis for extrapolation. The resulting predictions imply that a Sterility Assurance Level similar to that targeted for terminally sterilized product is achievable with a properly controlled Blow/Fill/Seal process. These challenge studies also provide a means to rationalize machine design and conditions of operation.

Figure 4. Examples of the various containers that can be manufactured using Blow/Fill/Seal technologies.

PACKAGING PARTNERS

To facilitate this design need, Weiler Engineering has established a development partnership with CHMS-ALP, a world leader in BFS contract packaging and Air Dispersions, Ltd, a top-ranked research firm.

This partnership approach has enabled Weiler Engineering to take advantage of a state-of-the-art Microbial Challenge Facility (MCF), designed and built at CHMS-ALP to allow detailed scientific assessment of the BFS process. The MCF is fully self-contained and includes

a machine containment room with a closed-loop HVAC system, a chlorine dioxide decontamination system, and a dedicated microbiology laboratory. Advanced controlled airborne microbial challenge studies are conducted under the research guidance of Air Dispersions, Ltd. (ADL) with staff from CHMS-ALP and Weiler[1,2,3].

"The main characteristic of the BFS process, key to its widespread acceptance, is the isolation of the critical filling zone within the machine," explains Weiler's Reed. "Sterile air management within this critical zone is typically verified through environmental monitoring for the presence of non-viable particulates."

It has been documented that non-viable particulates primarily originate from the electrically heated cut-off knife contacting the molten parison[3]. It has been postulated and

Figure 5. BFS technology includes integrating finishing lines, material handling systems coupled with leak detection, vision systems and labeling equipment.

generally accepted that better control of non-viable particulates will provide enhanced sterility assurance for the Blow/Fill/Seal process.

Various improvements in machine design have resulted over the years related to these environmental concerns. Past attempts to manage non-viable particulate generation were targeted to the removal of particles after they were produced. Included in these improvements was the development of parison shrouding. Parison shrouding typically employs a controlled air environment blower system with differential pressure controls in conjunction with containment ductwork in the parison cutoff area to siphon away smoke created by the hot knife.

The evolution of the technology has now reached a new level with Weiler's introduction of the KleenKut™ parison cutoff mechanism, which is designed to prevent the generation of particulates at the source. "The KleenKut is a 'cold knife' invention that accomplishes the cutting of the parison without the use of a heated high resistance wire," states Reed. "A heated wire cutoff typically produces visible smoke that then must be removed with a shroud/blower system. The KleenKut eliminates smoke generation through the patented application of ultrasonics, effectively reducing particulate generation at the source by over 99%[4]."

The KleenKut device has now been in place on multiple high volume production BFS machines for more than two years, operating in fully validated processes. Regulatory authorities today require sound scientific data to back up process improvement claims and additional follow-on studies have been conducted that provide supporting data for this new technology.

The data shows that direct contact between the KleenKut mechanism and the extruded parison does not cause microbial contamination of vials and confirms that non-viable particles 0.3 to 10µm in size are significantly reduced in quantity compared to the volume of particles produced during the use of a hot knife cutoff mechanism[5]. Currently, KleenKut technology is available for both low density and high-density polyethylene resin applications.

ANCILLARY EQUIPMENT

Advancement of BFS technology includes the incorporation of the latest in industry trends. Weiler designs and builds integrated finishing lines to complement its machines. Material handling systems can be coupled with leak detection, vision systems, overwrapping and labeling equipment to provide fully functional, integrated production lines requiring a minimum of operator intervention.

> The process reduces the amount of product contacting components, there is limited operator intervention and the critical fill zone is physically isolated.

BSF APPPLICATIONS

BFS technology has gained much market focus in recent years due to the increased focus on biologics, proteins and other complex solutions. These important products often cannot withstand exposure to high temperatures for extended periods of time without degradation of their active components.

Conventional terminal sterilization, therefore, is not an acceptable method to produce a "sterile" prod-

uct. Bulk sterilization, sterilization by gamma irradiation, or filter sterilization followed by direct packaging using the BFS process are often used successfully for these types of products. For example, BFS machines from Weiler Engineering are operating in fully validated production applications demonstrating less than a 1ºC temperature rise in a liquid pharmaceutical active packaged in a 5mL low density polyethylene vial.

Viscous products, with apparent viscosities of less than 15,000 centipoise, and suspension products can be handled by BFS machines with specially designed product fill systems. Weiler Engineering has pioneered the packaging of these types of products with the use of innovative liquid handling systems to maintain multiple component products in a homogeneous solution during the filling process.

REFERENCES:

1. Sinclair, C.S. and A. Tallentire, "Predictive Sterility Assurance for Aseptic Processing" in R.F. Morrissey, ed. *Sterilization of Medical Products*, **VI**, Polyscience Publication, Montreal, 1993, pp. 97-114.
2. Sinclair, C.S. and A. Tallentire, "Performance of Blow-Fill-Seal Equipment under Controlled Airborne Microbial Challenges," *J. Paren. Sci. Technol.* **49** (6) pp. 294-299 (1995).
3. Bradley, A., S. P. Probert, C. S. Sinclair, and A. Tallentire, "Airborne Microbial Challenges of Blow/Fill/Seal Equipment," *J. Paren. Sci. Technol.*, **45** (4) pp. 187-192 (1991).
4. P. Poisson, "Non-Viable Particle Management During B/F/S Manufacturing Operations," *BFS News*, Autumn Edition, pp. 12-16 (1999).
5. Poisson, P., C. Reed, C. Sinclair, "Challenge Testing of the KleenKut Parison Cutoff Mechanism," *Joint Presentation*, BFS User's Group AGM, Switzerland, June 14, 2001.

For more on BSF packaging visit www.weilerengineering.com.