Recent Technical Advancements in Blow-Fill-Seal Technology

a report by
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Blow-fill-seal technology, originally developed in Europe in the 1930s and introduced in the US in the 1960s, has emerged as a preferred method for aseptic packaging of pharmaceutical and healthcare products due to unrivalled flexibility in container design, overall product quality, product output and low operational costs. The Weiler design incorporates the multi-step process of blow moulding, aseptic filling and hermetic sealing of liquid products in one sequential operation on a compact, automated machine frame with fill volumes ranging from 0.1 millilitre (ml) to 1,000ml.

A variety of polymers may be used in the process, low and high-density polyethylene and polypropylene being the most popular. The innate ability to form the container/closure during the actual aseptic packaging process allows for custom design of the container to meet the specific needs of the application. This flexibility not only improves container ease of use, but 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-moulded, pre-sterilised components to be moulded into the container creating additional design options to create multi-use and injectable product containers. Furthermore, the blow-fill-seal process flow is normally impacted by only two raw materials, product and polymer, that are each processed inline, 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 is routinely an increase in production efficiency and a subsequent decrease in operational costs for the user.

Blow-fill-seal systems represent a niche market within the larger form-fill-seal marketplace for pharmaceutical packaging equipment. The blow-fill-seal process is a robust, advanced aseptic processing technology, recognised by worldwide regulatory authorities for its inherent operational advantages over conventional aseptic production. Blow-fill-seal 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.

Blow-Fill-Seal Process

Container Moulding

Thermoplastic is continuously extruded in a tubular shape (see *Figure 3a*). When the tube reaches the correct length, the mould closes and the parison is cut (see *Figure 3b*). The bottom of the parison is pinched closed and the top is held in place with a set of holding jaws. The mould 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 mould (see *Figure 3c*). Container formation is completed by applying a vacuum on the mould-side of the container and blowing sterile filtered air into the interior of the container. The patented electronic fill system delivers a precise dosage of product into the container. The nozzles then retract into their original position.

Container Sealing

Following completion of the filling process, the top of the container remains semi-molten. Separate seal moulds close to form the top and hermetically seal the container (see *Figure 3d*). The moulds 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 recognised by the US Pharmacopeia (USP XXIV) and the Parenteral Drug Association (PDA) (Technical Report 26) as an 'Advanced Aseptic Process', which may be defined as a technology that can dramatically

Figure 1: Blow-Fill-Seal Containers

Figure 2: Blow-Fill-Seal Machine

reduce the potential of contamination from human presence during aseptic processing operations due to its design and functionality.

The process reduces the amount of 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 micro-organisms 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.[1–3]

This experimental work was performed by producing controlled challenges of micro-organisms dispersed in air at concentrations extending over a 1,000-fold range in a containment room housing a blow-fill-seal machine producing containers filled with a 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 micro-organisms. 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 sterilised product is achievable with a properly controlled blow-fill-seal process. These challenge studies also provide a means to rationalise machine design and conditions of operation.

Advanced Technology

Good science drives good engineering and there is no room in today's regulatory environment for the "we have always done it that way" approach to the technology. The corporate focus of Weiler Engineering, Inc. is to provide the most advanced aseptic-liquid-processing technology available through the application of customised ASEP-TECH® blow-fill-seal machinery and integrated services. Weiler Engineering is committed to the advancement of blow-fill-seal technology and has established a development partnership with the world leader in blow-fill-seal contract packaging (Cardinal Health Manufacturing Services (CHMS-ALP)) and a top-ranked research firm (Air Dispersions, Ltd (ADL)).

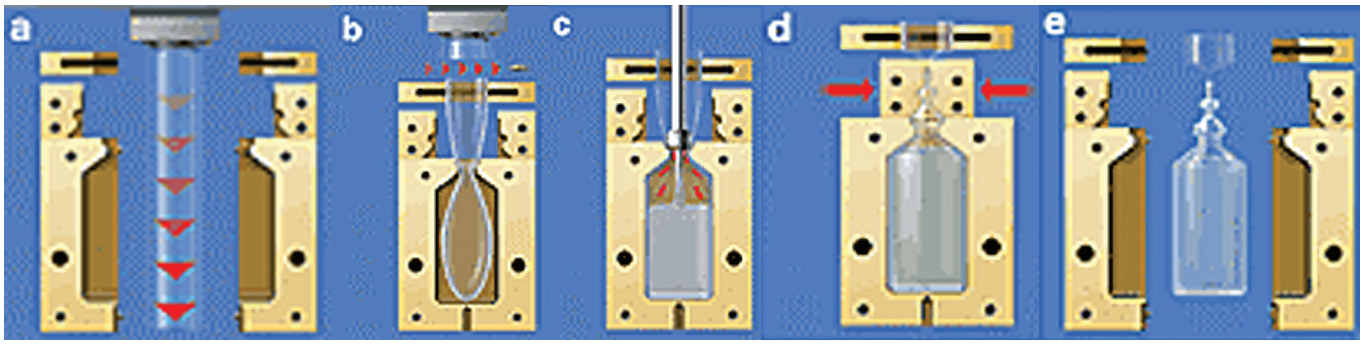
This partnership approach has enabled Weiler Engineering to take advantage of a state-of-the-art microbial challenge facility (MCF), designed and built at CHMS-ALP to allow detailed scientific assessment of the blow-fill-seal process. The MCF is fully self-contained and includes a machine containment room with a closed-loop heating, ventilation and air conditioning system, a chlorine-dioxide decontamination system and a dedicated microbiology laboratory. Advanced controlled

1 *C S Sinclair and A Tallentire, "Predictive Sterility Assurance for Aseptic Processing",* Sterilization of Medical Products, *(R F Morrissey, ed.), VI, 1993, Polyscience Publications, Montreal, pp. 97–114.*

2 *C S Sinclair and A Tallentire, "Performance of Blow-Fill-Seal Equipment under Controlled Airborne Microbial Challenges",* J. Paren. Sci. Technol.*, 49 (6) 1995, pp. 294–299.*

3 *A Bradley, S P Probert, C S Sinclair, and A Tallentire, "Airborne Microbial Challenges of Blow/Fill/Seal Equipment",* J. Paren. Sci. Technol.*, 45 (4) 1991, pp. 187–192.*

Figure 3: Container Moulding, Filling and Sealing



airborne microbial challenge studies are conducted under the research guidance of ADL with staff from CHMS-ALP and Weiler.[1–3]

The main characteristic of the blow-fill-seal process, key to its widespread acceptance, is the isolation of the critical filling zone within the machine. Sterile air management within this critical zone is typically verified through environmental monitoring for the presence of non-viable particulates. Control of non-viable particle generation within the manufacturing area has been investigated and detailed in several research papers dating back to the early 1990s.

It has been well documented that non-viable particles primarily originate from the electrically heated cut-off knife contacting the molten parison.[3] It has been predicated and 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 (pioneered by Weiler Engineering). Parison shrouding typically employs a controlled air environment blower system with differential pressure controls in conjunction with containment ductwork in the parison cut-off area to siphon away smoke created by the hot knife.

KleenKut™

The evolution of the technology has now reached a new level with Weiler's introduction of the patented KleenKut™ parison cut-off 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. A heated wire cut-off typically produces visible smoke, which must then 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 more than 99%.[4]

The KleenKut device has now been in place on multiple high-volume production blow-fill-seal machines for more than 18 months 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 0.3μm to 10μm in size are significantly reduced in quantity compared with the volume of particles produced during the use of a hot-knife cut-off mechanism.[5] Currently, KleenKut technology is available for both-low density and high-density polyethylene resin applications.

Product Applications

Blow-fill-seal 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 sterilisation, therefore, is not an acceptable method to produce a 'sterile' product. Bulk sterilisation, sterilisation by gamma irradiation or filter sterilisation followed by direct packaging utilising the blow-fill-seal process are often used successfully for these types of products. ASEP-TECH blow-fill-seal machines

4 *P Poisson, "Non-Viable Particle Management During B/F/S Manufacturing Operations",* BFS News, *Autumn Edition, 1999, pp. 12–16.*

5 *P Poisson, C Reed and C Sinclair, "Challenge Testing of the KleenKut Parison Cutoff Mechanism", Joint Presentation, BFS User's Group Annual General Meeting, Switzerland, 14 June 2001.*

from Weiler Engineering are operating in fully validated production applications demonstrating less than a 1°C 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 blow-fill-seal 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. Basically, if the solution will flow and if it can tolerate a minimum residence time, it can be packaged in an ASEP-TECH blow-fill-seal machine.

The product fill systems of the Weiler machines are also designed to minimise product hold-up volume. Combined with the precision fill accuracy achieved by Weiler's patented electronically controlled time-pressure fill system, significant savings can be realised for processing expensive complex solutions. Fill accuracies of better than ±5% have been demonstrated for container volumes as small as 0.5ml.

Ancillary Equipment

Advancement of blow-fill-seal technology includes the incorporation of the latest in industry trends. Weiler designs and builds highly integrated finishing lines to complement the ASEP-TECH machines. Sophisticated materials-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. Incorporation of 21CFR Part 11 compliant control systems is part of the evolution of the Data Acquisition packages now available on ASEP-TECH blow-fill-seal machines.

Future Efforts

Weiler Engineering, Inc. has held a leadership position for more than 30 years, serving the marketplace with the latest in advanced, sterile, aseptic liquid-packaging technology. Several key design/development initiatives are currently under way at Weiler, including a continuation of the joint studies in the MCF facility at CHMS-ALP.

Approximately 100 people are involved in the design and construction of the machines, providing 21st Century Solutions™ for parenterals, ophthalmics, respiratory drugs, biologicals, nutraceuticals and other complex solutions. Weiler's manufacturing facilities and corporate offices in Elgin, Illinois are conveniently located near Chicago's O'Hare International Airport. ASEP-TECH blow-fill-seal machines are designed and built in a new 120,000 square foot, state-of-art manufacturing plant. All equipment is manufactured in the US. ■