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REVIEW: A FOCUS ON BLOW-FILL-SEAL TECHNOLOGY

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ABSTRACT:
For therapeutics administered by certain routes such as pulmonary delivery, plastic ampoules can offer many advantages over glass ampoules, vials, or syringes. Plastic ampoules are manufactured using blow–fill–seal (BFS) technology. The BFS process involves plastic extrusion, molding, aseptic filling, and hermetic sealing in one sequential operation. Unlike small molecules, biological drug products, such as proteins or monoclonal antibodies, are more prone to degradation during processing, which may result in loss of activity or safety concerns. The operating conditions for a BFS process and the nature of plastic ampoules pose many challenges to the stability and integrity of biological drug products. In this article, the authors discuss considerations in the development and manufacturing of biological products using the BFS process, including potential product exposure to elevated temperature, requirements for leak detection, and packaging operations. They also highlight challenges and strategies for BFS process characterization and validation in the context of biopharmaceutical manufacturing.

Keywords: BFS Process, Packaging, Applications, Future Trends

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INTRODUCTION

Blow-Fill-Seal Technology

Aseptic blow-fill-seal (BFS) technology is the process by which plastic containers are formed, filled with sterile filtered product and sealed in an uninterrupted sequence of operations within the controlled sterile environment of a single machine. The blow-fill-seal process is a robust, advanced aseptic processing technology, recognized 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. 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[1,2].

BFS MACHINE HISTORY

1960s

- Invention of the BFS process
- First bottelpack prototype 1963
- Low capacity with one mold
- Relay controlled
- No aseptic systems
- Bigger fill volume
- Customers in Germany and Europe

1970s

- Medium-high capacity machine with 2-10 molds
- Machine for small fill volumes (0.2 - 50 ml)
- Machine designs for aseptic filling (product filters, CIP, SIP)
- Piston dosing/tube dosing systems for big/small volumes relay-controlled machines

- Worldwide machine export; license production in USA

1980s

- High capacity machine for small fill volumes with 15 molds (type 4010M)
- Automatic machine program changes
- Time pressure dosing as standard system
- PLC controlled machines
- Alarm message on display
- Production documentation

1990s

- New bottelpack® machine generation (Types 321/321M - 360/360M)
- Clean/Dirty concept machine design
- Increased level of automation using PLCs
- Development of Co-extrusion and PET processing technique for BFS
- ISO 9001 Certificate

BFS MACHINE TYPES- TODAY

Single parison types for bottle manufacturing (50 - 2000ml).Machine Types:

- 3012 (one mold)
- 321 (one mold)
- 360 (two molds**)**

Capacity range: ~ 250 - 4,000 bottles/h

Multiple parison types for ampoule manufacturing (0,2 - 50 ml). Machine Types:

- 3012 M (one mold)
- 321 M (one mold)
- 360 M (two molds)
- 4010 M (fifteen molds)

Capacity range: ~ 2,500 - 30,000 ampoules/h

bottelpack® model 3012/321

Capacities up to 9,000 vials per hour

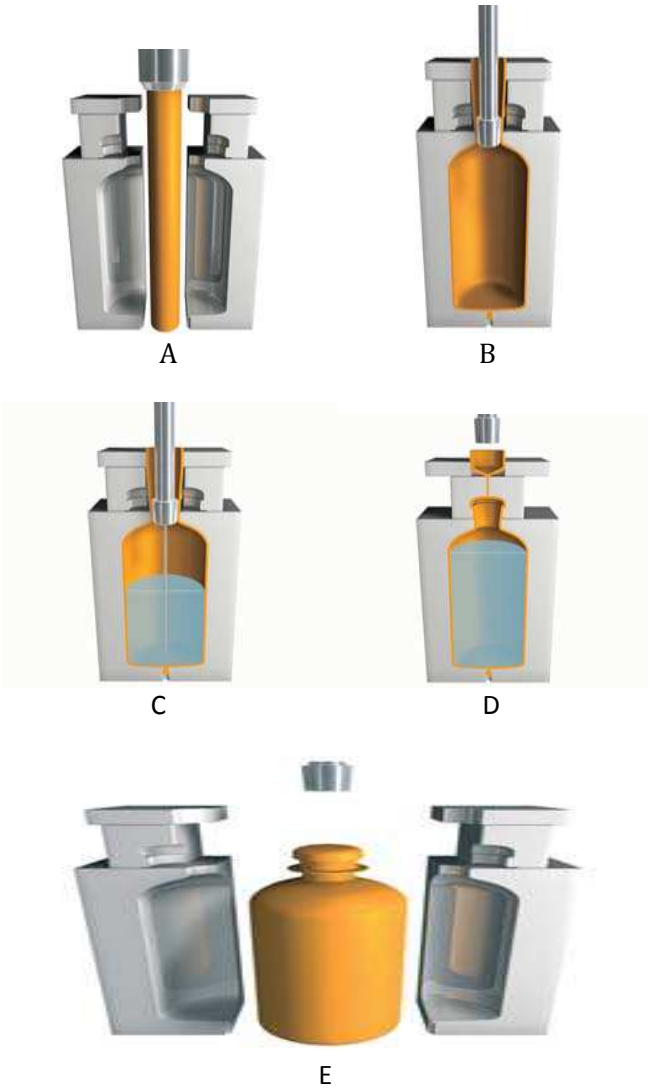
bottelpack® model 360

Higher capacities up to 18,000 vials per hour.

WHY MANUFACTURERS OF I.V SOLUTIONS CHOOSE BLOW–FILL SEAL CONTAINERS.

- Transparent
- Fully collapsible
- Closed System
- Unvented use
- Light weight
- Unbreakable
- Good grip
- Self standing
- Drug compatibility
- Inert raw material
- No contact between cap and solution
- Resealing ports
- Good admixture volume
- Permanent in container Batch and Expiry information
- Low production cost[4,5,6,7].

BLOW FILL SEAL PROCESS



Extruding

The plastic parison, extruded from polymer, is accepted by the opened blow mould and cut below the die of the parison head.

Moulding

The main mould closes and simultaneously seals the bottom. The special mandrel unit settles onto the neck area and forms the parison into a container, using compressed air. Small containers are formed by vacuum.

Filling

By way of the special mandrel unit, the product, precisely measured by the dosing unit, is filled into the container.

Sealing
After the special mandrel unit retracts, the head mould closes and forms the required seal by vacuum.

Mould opening
With the opening of the blow mould, the container exits from the machine and the cycle repeats itself. Transfer for further processing is achieved by means of conveying. The cycle is then repeated to produce another filled container. The filled containers are tested and checked to ensure that they meet the very strict specifications laid down for such products. The duration of the complete cycle is between 10-18 seconds, depending on the container design and the amount of liquid to be filled[4,5,6,7].

PROCESS PERFORMANCES

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 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.

RECENT TECHNICAL ADVANCEMENT IN BLOW FILL SEAL TECHNOLOGY

Advanced controlled 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. 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 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[8,9].

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 customized ASEPTECH 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 (CHMSALP)) 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. 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 nonviable 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. 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 devices 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 cutoff mechanism.5 Currently, KleenKut technology is available for both-low density and high-density polyethylene resin applications[10,11,12].

ADVANTAGES OF BFS TECHNOLOGY

BFS technology offers considerable advantages over conventional aseptic filling of preformed (plastic or other) containers, which are described as follows:

1. BFS technology reduces personnel intervention making it a more robust method for the aseptic preparation of sterile pharmaceuticals.
2. There is no need to purchase and stock a range of prefabricated containers and their closures. Bulk containers of plastic are required.
3. Cleaning and sterilization of prefabricated containers and closures is not required. A clean, sterile container is made within the BFS machine as it is required for filling.
4. The cost of material transport, storage and inventory control is reduced.
5. Validation requirements are reduced.
6. The technology allows the design of high-quality, custom-designed containers with tamper-evident closures in a variety of shapes and sizes.
7. There is a large choice of neck and opening device shapes.
8. A single compact BFS machine takes the place of several conventional machines, saving floor space. In addition, zones for transport to successive filling and closing procedures are not required because these operations all take place in the BFS machine itself.
9. The operation of BFS machines is less labor intensive than conventional aseptic filling.
10. The code numbers and variable data such as batch number and expiry date can be molded into the container itself rather than being added at a subsequent stage.
11. The process lends itself to the production of single dose containers and therefore preservatives are not necessary as they are with multi-dose containers.

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

CONCERNS WITH BFS TECHNOLOGY

Despite these sound advantages, wider use of B/F/S has been limited by concerns such as nonviable particulate levels in the environment surrounding the B/F/S machine exposure of product to the elevated temperature of the formed container gas and moisture barrier properties of container plastics.

1. Particulate control:

Relatively high levels of nonviable particulates are generated by the plastic extrusion and cutting process. B/F/S machine manufacturers have taken steps to address the plastic particulate issues by designing better machine enclosures to isolate and protect the product contact surfaces from environmental conditions. Some B/F/S line designs place particle-generating equipment away from the filling zones and isolate with walls and barriers. For some products, closed-parison systems, in which the inside of the parison is continually bathed with sterile air and is not cut, can be used to further protect product contact surfaces.

2. Temperature effects:

B/F/S containers remain at an elevated temperature of up to 60ºC for several seconds after filling. It is speculated that other types of plastic with a lower

processing temperature can be used to reduce this temperature. To reduce the effect of exposure to elevated temperature container surfaces, filled product can be cooled soon after filling and sealing.

3. Oxygen and moisture effects:

Plastics typically used for B/F/S containers provide a relatively low barrier to oxygen or moisture, especially as compared to traditional glass containers (i.e., vials and syringes). For oxygen sensitive products, filled units can be placed in foil pouches or other secondary packaging. Inert gases can be used in these secondary packages to lessen risk for oxygen permeation. Process development and product stability studies using products filled using the B/F/S process, container, and packaging can provide evidence of product compatibility. Companies considering the use of B/F/S should take steps to assure that the heat and permeation issues do not have an adverse effect on product quality.

4. Moving forward:

The Blow-Fill-Seal International Operators Association (BFSIOA) and the Parenteral Drug Association (PDA) have been working together to create a comprehensive technical report containing practical and scientific information regarding the use of B/F/S for aseptic manufacturing of sterile products. The report will be based on BFSIOA's "Points to Consider" document, dialogue with industry, and input from the newly-created PDA B/F/S Industry Group. This guidance on best practices, as well as scientific rationale and data to support those practices, will help the B/F/S industry continue to improve its technology for advanced aseptic processing[13,14].

APPLICATION

BFS vials and bottles are ideally suited for unit dose applications of liquids for the pharmaceutical and medical device industries. The unit does applications are typically used in ophthalmic products (eye drops), inhalation solutions (nebulized solutions or suspensions), and in the application of topical or orally dispensed material (gel, cream, ointment, or aqueous liquid).

- **Pharmaceutical**
  - •OTC and Rx unit dose eye drops
  - •Inhalation solutions
  - •Injectable products
  - •Biotechnology products
  - •Topical liquids, creams, gels, and ointments
  - •Oral liquids
- **Medical**
  - •Components to medical devices
- **Diagnostics**
  - •Components in diagnostic kits
  - •Reagents in diagnostic products[15]

CONCLUSION

Blow–fill seal technology is recognized as an efficient, advanced aseptic processing technology for liquid pharmaceutical products .It provides far higher levels of quality assurance, together with definite cost advantages, compared with traditional aseptic filling techniques. The technology has been well established in the field of ophthalmic product for a long period of time, and has shown an excellent record of successful launches of new products and designs benefit to the patient. Worldwide acceptance in the market has confirmed the particular suitability of this form packaging for ophthalmic applications BFS technology has great potential in the field of biopharmaceutics because of reduced human intervention. The operating conditions of the BFS process and the nature of plastic ampoules pose many challenges to the during the production process, convenience, and ease of use offered by its final product in plastic ampoules form. Biopharmaceuticals may experience elevated temperature during the BFS process. CFD could be a useful tool for better understanding the temperature dynamics during the BFS operation. The unique aspects of BFS operation call for a balanced empirical and systematic approach during process development and process validation.

FUTURE TRENDS

In the era of globalization, it would be a challenge for the packaging industry, as the years ahead would witness the opening of the global channels, and to match the international standards and quality, it is necessary that packaging industry upgrades more in research to have a holistic approach to packaging that would go beyond functional aspect of packaging. Presently, very few pharmaceutical industries spend time and money on R and D in packaging. The conventional packages available do not serve the purpose of providing protection against counterfeiting and quality, and the industry seems to be sluggish in adopting the technical advances in the packaging, probably on account of the prohibitive cost factor. As packaging industry is directly or indirectly involved in the drug manufacturing process, it becomes ethically mandatory to understand and incorporate scientific methods in packaging. The pharmaceutical packaging trends are on the verge of innovative rapid growth provided the needs of the product, its security, cost and patient convenience is taken into consideration to build brand identity.

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