

A Review on Development for Sterile Liquid Product Blow Fill Seal Pack

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ABSTRACT

which like pneumatic delivery, plastic ampoules are a medical specialty that are administered by sure ways in ampoules offers several advantages over glass ampoules, vials, or syringes. Plastic ampoules are a unit manufacture victimisation blow-fill-seal (BFS) technology. within the BFS method plastic extrusion, molding, antiseptic filling in one line operation. The in operation conditions for a BFS method and therefore the nature of plastic ampoules provides several issues to the steadiness and integrity of biological drug product. Blow-Fill-Seal (BFS) technology is an advanced aseptic manufacturing process widely used in the pharmaceutical, healthcare, cosmetic, and food industries for the production of sterile liquid products. The BFS machine integrates container formation, product filling, and container sealing into a single continuous automated operation, minimizing human intervention and reducing the risk of contamination. In this process, thermoplastic resin is extruded into a container, which is immediately filled with the product and hermetically sealed under sterile conditions. BFS technology is recognized as an advanced aseptic processing method because it provides high sterility assurance, operational efficiency, and cost-effective production

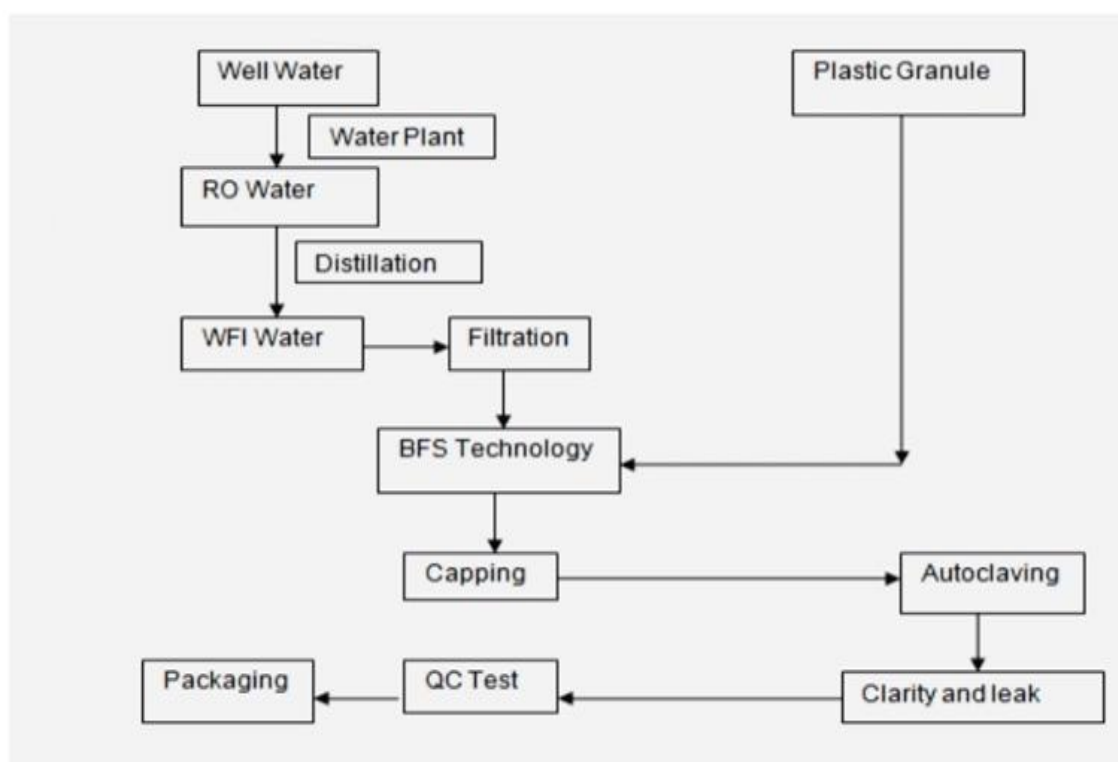
Keywords: BFS technology, Blow-Fill-Seal machine, Aseptic packaging machinery, Automatic forming filling sealing, Parison extrusion, Liquid filling mandrel

INTRODUCTION

The BFS method involves plastic extrusion, molding, sterile filling, and tight protection in one consecutive operation, as illustrated in Figure one. The organic compound material for primary containers is usually received as plastic granules (e.g., low-density synthetic resin [LDPE] or polypropylene [PP]). within the extrusion step, plastic granules are fed through Associate in Nursing extruder, wherever they're molten at temperatures on top of one hundred sixty °C. The molten plastic is ironed Associate in Nursing extruded through an opening, leading to an eternal hollow tube of melted plastic, cited as a parison. The metal mould then moves to surround the parison and forms the plastic instrumentation of desired form, assisted by either application of vacuum to the mould cavity through little orifices or by processing sterile air into the instrumentation afterwards, a parison die cut can cut the parison at the highest, and also the mould carrying the unclosed plastic instrumentation (at this stage cited as Associate in Nursing ampul) can move to the filling cupboard. within the filling step, the filling needle is inserted into the highest gap and answer is discharged into the phial. The filling needle retracts when the fill completion. the highest portion of the mould then comes along to press the plastic and to create hermetically sealed ampuls. The mould then opens and also the ampuls are discharged from the BFS machine and sent to the scrutiny station. Water for Injection^[1,2] is water of fresh top quality that is employed for product of parenterals (e.g. infusion answer for endovenous medical aid or answer for injection) and water- predicated ophthalmic product harmonious with aggregation. Water for Injection is employed within the product of conduit product and necessary specifics wherever product bane content should be controlled, and in necessary medicinal operations, like amnesty of sure instrumentation and conduit product- contact rudiments. As per WHO, The water is minimum amount limit of force of raw water for product of WFI^[3]. This force water could also be pre- treated therefore it applicable for distillation and water

system. The finished water should meet all of the chemical needs for sublimite Water also as an spare microorganism bane specification. Since endotoxins area unit made by microorganisms that area unit susceptible to inhabit water. The instrumentation and procedures should be designed to depress or stop microbic contamination and it should be take down bane from row water. Row water is use by the system Water for Injection systems should be use validate methodology and turn out. The intermediate product is submitted to Quality department to check the standard of water. The Water for Injection composition permits itto be packed in bulk for artificial use.^[4,5] the ultimate product demanded specifications include the test for Bacterial endotoxins, and those of the packaged water Sterile Purified Water,^[6] except for Labeling.^[7,8]Well Water and plastic grain is stuff. The H₂O is treated for oral communication of H₂O to artificial language water then WFI water. Then WFI water is store in tank in sterile conditions so water was offer to instrument that exploitation BFS technology. Instrument has 2 input one contain plastic and second contain water. BFS technology provides output product as WFI . Output of BFS technology product is goes for capping. Product goes for autoclaving and clarity & leak take a look at, QC testing, QC-QA Approval so it goes for packaging unit and market. WELL WATER TO RO WATER (UNIT OPERATIONS CONCERNS) :- The step of unit operation for story of H₂O to artificial language water:

1. Pre-filtration a pair of .Activated Carbon three Additives four Organic Scavengers
2. Softeners half-dozen. Deionization
3. Reverse diffusion eight. Ultra-filtration
4. Charge-Modified Filtration
5. Microbial Retentive Filtration
6. Ultraviolet Light
7. Distillation
8. Storage Tanks
9. Distribution Systems14. Distribution Systems



Pre – Filtration:

Pre-filtration is a preliminary process. Filtration is found to cast off strong contaminants right all the way down to a length of seven to 10 µm from the supply of uncooked water, and It is likewise protected downstream gadget additives from particulates which could inhibit device overall performance, and it can shorten their powerful life. This coarse filtration generation makes use of primarily sieve results for debris seize and an intensity of filtration medium that has a higher “dust load” capacity. Some filtration gadgets are to be had in a

specific variety of designs and Designs are use for specific applications. It is maximum relevant unit process. Removals efficiencies and capacities differ significantly, from granular mattress filters like multimedia or sand for huge water gadget, to intensity cartridge for smaller water gadget.

Designs and operating system can also additionally impact overall performance of intensity filters consists of channeling of the filtration media, blockages from silt, microbial growths, and filtration media loss for the duration of improperly returned wash. Control degree includes stress and float video display units for the duration of use and returned wash, sanitation, and changing filtration media. A vital design problem is sizing of the filters to save you channeling or media loss due to irrelevant water float charge, in addition to right sizing to reduce excessively common or rare returned wash or cartridge filter replacement.^[9]

Activated Carbon:

Granular activated carbon can take in low molecular weight natural cloth and a few oxidizing components, like chlorine and chlorine compounds. Activated carbon, need to use for getting rid of from the water. They are used to keeping excellent attributes, and it gives protections towards response with downstream stainless metallic surface, resin, and membrane. The activated carbon

beds are powerful for bacteria growth, hydraulic channeling, the natural adsorption capacity, incapacity to be regenerated in situ, shedding of bacteria, endotoxins natural chemicals, and satisfactory carbon particles. Control measures can also additionally require tracking water waft rates, pressures, sanitizing with warm water or steam, backwashing, trying out for adsorption capacity, and the maximum latest requirements is too alternative of the carbon bed.^[10]

Additives:

The intention of chemical components is defined below^[11] to manipulate microorganisms e.g. habitants such as chlorine compounds and ozone,^[12] to beautify the elimination of suspended solids e.g. flocculation agents, (three) to do away with chlorine compounds, to avoid scaling on opposite osmosis membranes, and to alter pH^[13] for extra powerful elimination of carbonate and ammonia compounds through opposite osmosis. These components do now no longer represent as an “introduced substances” and on the cease of technique it needs to be eliminated through next processing steps. The components are absent from the completed water.^[14]

Organic Scavenging:

gadgets base on primary anion-change resins. It is able to put off organic fabric and endotoxins^[15] from the water. The technique is found weakly as in step with protocol. This can regenerate through biocide caustic brine solutions. Operation technique are related to organic scavenging capacity, particulate, chemical and microbiological fouling of the reactive resin surface, float rate, regeneration frequency, and dropping of resin fragments.

Softeners:

Water softeners are used as a disinfectant or disinfectant elimination gadgets it can feasible either upstream or downstream of disinfectant. Softeners make use of sodium-primarily based totally cation-change resins to take away water-hardness ions, like calcium and magnesium that would intervene with the performance of downstream processing equipment, like reverse osmosis membranes, deionization gadgets, and distillation gadgets.

Deionization (DI):

Deionization (DI) and non-stop electrode ionization (CEDI) are powerful strategies of enhancing the chemical great attributes of water via way of means of removing cations and anions. DI structures are containing charged resins which require periodically regeneration with an acid and base. Cationic resins are regenerated with both hydrochloric or sulfuric acid that still update the captured fine ions with hydrogen ions. Anionic resins are

regenerated with sodium or potassium hydroxides, which additionally update captured bad ions with hydroxide ions. Because free endotoxin is negatively charged, there's some elimination of endotoxin gain via way of means of the anionic resin. Both regenerate chemical compounds are biocide and provide a degree of microbial control.

The gadget may be designed in order that the cation and anion resins are in separate or "twin" beds, or they may be blended together to shape a blended bed. Twin beds are without problems regenerated, however deionize water much less correctly than blended beds, that have an extensively greater complex regeneration process. Rechargeable resin canisters can additionally be used for this purpose.

Stress throughout the membrane have an effect on the selectivity of this permeation. With the right controls, RO membranes can reap chemical, microbial, and endotoxin exceptional improvement.^[16] The procedure streams include deliver water, product water (permeate), and waste water (reject). Depending on supply water, pretreatment and system configuration versions and chemical components may be essential to reap favored overall performance and reliability. A most important issue affecting RO overall performance is the permeate restoration rate, that is, the quantity of the water passing via the membrane in comparison to the quantity rejected. This is stimulated through the several factors, however most importantly through the pump stress. Recoveries of 75% are typical, and might accomplish a 1 to two log purification of maximum impurities. For maximum feed waters, that is typically now no longer sufficient to meet Purified Water conductivity specifications.^[17]

Reverse Diffusion (RO):

Semipermeable membranes square measure employed in rear prolixity(RO) machines. Ro membranes"" pores" are literally intersegmental gaps between emulsionsegments.molecules. they are massive enough to permitpenetration.water motes, nonetheless they're inadequate to undergo.chemical ions that are hydrous but, there square measure different aspects tocontemplate.pH, temperature, and discriminational pressure square measure all factors tocontemplate.The property of a membrane is littered with the pressure acrossit.this generality Ro is doable with the proper will perform chemical, microbiological, and naturalfunctions.Improvements in poison quality.^[18]

THE DEVELOPMENT AND MANUFACTURE OF BIOLOGICAL MERCHANDISE VICTIMIZATION BFS

BFS Steps In Biological Producing:

Fill – finish operations of natural medicine wares, significantly proteins or organism antibodies, occasionally begin with medicine substance(or targeted bulk) handed either cold at 2 – 8 °C for temporary storehouse, or firmed at expression buffer can be added and mixed together with the medicine substance in a mixing tank, to reach the target attention as final medicine product. The result is also transferred into a holding tank through a sludge to cut back bioburden position. The holding tank containing advanced product will be used to store the wares for associate degree extended quantum of your time to accommodate producing programming. These operation way, as well as thawing, dilution, mixing, and filtration area unit generally conducted during a Grade C space. Figure two illustrates the system in flow.

Utmost factors of the BFS machine area unit settled during a Grade C room; solely the filling cupboard is controlled underneath a Grade A condition. Time- pressure stuffing, wherever a pinch stopcock is employed to manage the filler volume, is generally employed in the filling operation. The inflow is decided by the pressure applied to the liquid force(or swell tank), and thus the pinch stopcock gap time determines the ultimate filler volume. throughout the stuffing system, resolution sterilization is achieved by altering- grade pollutants.

The cooperation of the BFS machine with filling needles, swell tank, and altering sludge generally takes place during a Grade C surroundings. The BFS machine is 1st assembled and sanctified through clean in- place(CIP) procedures. It also gets connected to the altering sludge, and thus the entire cooperation is castrated underneath

a valid brume- in- place(draft) cycle, from the filling needle, all the thanks to the purpose of reference to the wares tank.

Aseptic process needs contamination management and sterilization of 3 main aspects: drug-product resolution, primary instrumentality elements, and operation surroundings. The sterilization technique for drug product resolution during a BFS method is analogous to a traditional fill–finish method, wherever typical sterilizing grade filters area unit used. not like the element process steps within the standard fill–finish method (i.e., washing, depyrogenation, and siliconization of vials, syringes, and stoppers), the first instrumentality is made within the BFS method, and therefore the molding of plastic rosin at elevated temperature provides a instrumentality "free" of viable microorganisms and with acceptable toxin levels. the flexibility for a BFS extrusion method to yield product with acceptable quality has been incontestible by controlled challenges studies, wherever LDPE granulates were contaminated with characterised levels of microorganism spores and endotoxins, then pressed through a BFS machine victimisation Tropton Soy Broth and Water for Injection because the filling media ^[19]. Higher fractions of contaminated units were discovered with augmented challenge level (or quantity of spores and toxin within the plastic granulates). The higher than study incontestible it's important to determine applicable acceptance limits for bioburden and toxin levels on plastic granulates to assure final product quality.

The overall extrusion and molding method of the BFS operation is conducted in an exceedingly Grade C space. However, the air shower for the filling shroud of the BFS machine ought to give a Grade A condition. international organization pointers state that, "The condition ought to adjust to the viable and dead limits at rest and viable limit only in operation" ^[20]. there's potential risk for mobile contamination before the mildew moves to the filling shroud space, wherever the air shower maintains a Grade A setting. Recent studies have shown that almost all of the mobile contamination happens between the time once the highest is cut from shaped containers and once they pass underneath the air shower . The microorganism and particulate controls area unit extremely instrumentality and website specific. Therefore, a media fill should be conducted for every specific machine, process, or instrumentation sort. A recent survey of the BFS business provides a superb summary of this practices in antiseptic BFS technology, showing that the BFS method includes a lot of lower frequency (about one-tenth) of contaminated media fills compared with standard processes ^[21]

BLOW- FILLER- SEAL TECHNOLOGY:

Aseptic blow- filler- seal(BFS) technology is the process by plastic grains are comes under applicable heat which provides different size and shape, at a time products filled with paddings, sterile filtered product are seals in sequence of operations within the controlled sterile terrain of a single instrument of product. The blow- filler- seal process is sterile processing technology, which is accepted by worldwide in the allowed for the artificial engineering aseptic product. Blow- fill- seal systems are furnishing too important inflexibility for packaging and different-different design of product, low provident cost and a high sterility assurance.^[22]. Due to instruments, minimal number of operating labor force and small space can produce the large number of the product. A variety of polymers may be used in the process, low and high- viscosity polyethylene and polypropylene being the most popular. Low and highdensity polymer are use in difference types of packaging. The inner sides of packages(which interact with product) are made up of low viscosity polymer and external side is made up of high viscosity polymers. ^[23,24] product by BFS Technology

WHAT IS BLOW-FILL-SEAL (BFS)?

BFS is a specialized manufacturing process where pharmaceutical-grade plastic resin (typically polyethylene or polypropylene) is extruded, blown into a container shape, filled with sterile liquid product, and sealed hermetically in a single continuous operation.

Extruding:

The plastic parison, extruded from polymer, is accepted by the opened blow mould and cut below the bones of the parison head.^[25] Plastic polymer is convert liquid phase to solid phase, which is suitable for input polymer in blow mould and stop the inflow of polymer.

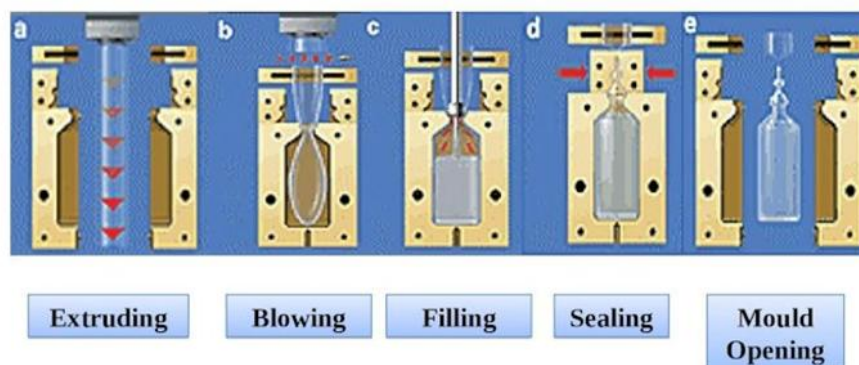
Moulding:

The main mould closes and contemporaneously seals the bottom. The special mandrel unit settles onto the neck area and forms the parison into a vessel, using compressed air. Small holders are formed by vacuum.3.1.3 Filling By way of the special mandrel unit, the product, precisely measured by the dosing unit, is filled into the vessel.

Sealing:

After the special mandrel unit retracts, the head mould closes and forms the required seal by vacuum. 3.1.5 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. [26,27]

Steps of Blow-Fill-Seal Technique



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BFS PROCESS CHARACTERIZATION AND VALIDATION

A natural manufacturing confirmation program encompasses outfit qualification, drawing confirmation, and process confirmation. The BFS outfit suppliers and manufacturers generally have well- established practices for performing outfit qualification and drawing confirmation. Process confirmation, still, could be a challenge for natural manufacturing using BFS technology.

The thing of process confirmation is to give a high degree of assurance that the specific manufacturing process will constantly produce product meeting destined acceptance criteria. ultramodern- day process confirmation programs correspond of process characterization studies and full- scale qualification lots produced under GMP conditions. Process characterization can be performed on each unit operation to estimate and characterize an respectable range of operating conditions that yields respectable product quality and process performance. A quality- by- design(QbD) approach, which totally uses threat assessments and multivariate characterization studies, is the current state of the art. Process characterization may be carried out at different scales, and it may also include engineering runs to mimic the overall process inflow.

Grounded on the outgrowth of process characterization, full scale GMP batches are manufactured under normal settings. Both physical attributes(similar as ampul appearance, integrity, fill volume, and wall consistence) and chemical attributes of the product are checked to insure that the process performs as anticipated.

It's important to fete the oneness of the BFS process when applying the below process characterization and

process- confirmation approach. The BFS machine is a custom- erected machine. The outfit setup and operation frequently involves both robotization control and primer adaptations. The driver experience or "know how" generally is veritably important to the proper operation of the BFS outfit. similar driver-dependent performance, to a certain extent, is in discrepancy to the QbD paradigm of pharmaceutical manufacturing, where critical process parameters(CPPs) are linked, understood, controlled, and covered to achieve a robust manufacturing process. The large number of controllable and willful parameters in the BFS process makes process characterization and process confirmation much more grueling than conventional natural stuffing processes. For case, the filling speed for a peristaltic or rotary piston pump is the typical process parameter that can be estimated during stage-alone process- characterization studies. The filling speed, still, for a BFS process is substantially fixed, due to constraints from accompanied movement of the extruder, earth, filling, and seal operations. Only minor adaptations can be made to the duration of each of the BFS way(banishing, putrefying, and stuffing), and similar adaptation may be necessary to achieve optimum product appearance.

Another illustration of manually acclimated parameters is the plastic- resin weight. The resin weight determines how important plastic is extruded to form the vessel and directly correlates with the vessel wall consistence. Too important resin may affect in holders with "big" appearance or problems with deflash while too little resin may beget issues for vessel integrity or ampoule leakage. The applicable quantum(or range) of resin is generally determined from outfit qualification. It can only be manually acclimated through a many mechanical corridor at the morning of each product run. thus, the process and product development for BFS process needs to balance an empirical approach and a methodical approach. The natural manufacturer needs to unite nearly with the BFS outfit supplier or contract manufacturer to design a robust program for process characterization and confirmation.

The implicit roadmap for process characterization and process confirmation. threat assessments are largely recommended for each unit operation as well as for each of the way from the BFS operation in order to identify implicit failure modes from outfit and mechanics, as well as product- impact aspects. The affair from the threat assessments would be a list of process parameters that could affect the overall process or product quality. farther development and characterization studies should be designed for these parameters either as stage-alone studies or overall engineering runs. CPPs are named grounded on the outgrowth of process characterization. Eventually, full- scale qualification lots should be produced(generally at target settings of the process parameters) to demonstrate the validated state of the end- to- end process.^[28]

Blow-Fill-Seal, also spelled as Blow/Fill/Seal, in this article abbreviated as BFS, is an automated manufacturing process by which plastic containers, such as bottles or ampoules are, in a continuous operation, blow-formed, filled, and sealed.^[29] It takes place in a sterile, enclosed area inside a machine, without human intervention, and thus can be used to aseptically manufacture sterile pharmaceutical or non-pharmaceutical liquid/semiliquid unit-dosage forms.^[30] BFS is an advanced aseptic processing technology that is typically used for filling and packaging of certain sterile liquid formulations like liquid ophthalmics, inhalational anesthetics, or lavaging agents, but can also be used for injectables,^[31] parenteral medicines^[32] and several other liquid or semiliquid medications,^[32] with fill volumes ranging from 0.1...1000 cm³.^[33,34,35] Compared against traditional glass ampoules, BFS ampoules are inexpensive, lightweight, and shatterproof.^[36]

BFS material

The materials used in BFS packaging are usually polyolefins, mainly polyethylene (LDPE^[37,38] or HDPE),^[39] and polypropylene^[40] (PP). These materials are robust and inert to ensure sterility and tightness during the product's shelf life.^[41] Diffusion tendencies can be reduced by using virgin polymers, but diffusion cannot be prevented entirely. This is due to the nature of polyolefins and their additives, if present.^[42] Several polyethylene suppliers have developed special EP or USP grade resin for BFS containers. Permeation into BFS containers and water loss may be an issue with some BFS resin. Therefore, in some applications, secondary packaging methods (lamine pouches) are used.^[43]

BFS process:

Sterile compressed air is then introduced through the filling mandrel to inflate and form the container. In the

BFS process for smaller ampoules the compressed air system is avoided by using vacuum forming the container instead. After the BFS container has been formed, the desired liquid is filled into the container through the filling mandrel unit. Then, the filling mandrel unit is lifted off, and the head mold hermetically seals the container. Simultaneously, the head contour is formed by vacuum. In the last step, the mold opens and the finished container leaves the mold.^[49]

One process cycle takes a few seconds.^[50] The process speed and thus process output largely depends upon the BFS container size and the BFS machinery dimensioning. For instance, in the early 2000s, Rommelag's 3012, 305, and 4010 M machines had outputs of approximately 4000, 8000, or 20,000 containers per hour.^[51] These machines have been succeeded by the Rommelag 312, 321, 360, 364 and 460 machines with output ranges of up to 35,000 containers per hour.

Sterility requirements:

The BFS processes is an aseptic filling process, which produces sterile products and thus needs to be sterile.^[52] Aseptic BFS machines must be designed in a way that prevents extraneous contamination.^[53] Thus, rotary-type BFS machines are placed in classified areas same as shuttle-type BFS machines (open parison), which have a cleanroom shroud grade-A-compliant provided with sterilised air and kept under overpressure. Automatic SIP programs are used to sterilise the BFS equipment and this avoids human interventions. Due to automatic start up and filling processes BFS machines require no human interaction during the actual BFS process. However, certain adjustments or interventions need to be carried out by personnel. Both particle and microbiological contamination monitoring are required in a BFS machine environment, as well as routine CIP/SIP processes.^[54] BFS machines are typically fitted with several different sterilising air filtration systems for the buffer air, support parison air and air shroud grade A air (if needed for shuttle machines, e. g. open parison type ones).^[55] Typically, the air is sterilised by filtration systems that have automatic filter integrity testing installed (i. e. automatic water intrusion or particle testing). The air systems are typically integrated into the SIP cycle of the BFS machine.^[56]

BFS allows many different container designs, a consistent high process quality, a high process output,^[57] and is, compared against other packaging processes, inexpensive.^[58] In addition to that, BFS containers are lighter than glass containers, and shatterproof, which eases their transport.^[59,60] Due to the single-dose nature of BFS containers, they are more convenient to use for patients.^[61] BFS technology assures high levels of sterility, especially

compared against conventional filling,^[62] which is mainly achieved by the absence of human contact/interventions – a major source of contamination.^[62]



Eye drops sold in blow fill seal packaging

HISTORY

BFS was developed in the early 1960s^[63] at Rommelag.^[64] In 1963, Gerhard Hansen applied for a patent on the BFS process.^[65] Originally, it was used for packaging of non-sterile products, such as non-sterile medical devices, food, and cosmetics.^[65] In the early 1970s, Rommelag's Bottelpack system was first used for packing large volume pharmaceutical solutions.^[66] By the late 1980s, BFS had been well-established in the packaging industry, especially for packaging pharmaceutical and healthcare products.^[67] During the 1980s and 1990s, BFS came into use for the now common small volume unit-dosage forms.^[68] Since the early 2000s, BFS has been emerging as the preferred packaging process for parenteral products.

Blow-Fill-Seal, also spelled as **Blow/Fill/Seal**, in this article abbreviated as **BFS**, is an automated manufacturing process by which plastic containers, such as bottles or ampoules are, in a continuous operation, blow-formed, filled, and sealed. It takes place in a sterile, enclosed area inside a machine, without human intervention, and thus can be used to aseptically manufacture sterile pharmaceutical or non-pharmaceutical liquid/semiliquid unit-dosage forms. BFS is an advanced aseptic processing technology that is typically used for filling and packaging of certain sterile liquid formulations like liquid ophthalmics, inhalational anesthetics, or lavaging agents, but can also be used for injectables,¹ parenteral medicines and several other liquid or semiliquid medications with fill volumes ranging from 0.1...1000 cm³ Compared against traditional glass ampoules, BFS ampoules are inexpensive, lightweight, and shatterproof

- **Ultimate Sterility:** The entire process happens inside a sterile, Class A (ISO 5) localized environment without human intervention, drastically reducing the risk of microbial contamination.
- **Preservative-Free Formulations:** Because the process ensures absolute sterility, manufacturers can produce single-dose eye drops and nasal sprays without harsh preservatives, reducing patient irritation.
- **Cost-Efficient Production:** Combining container forming, filling, and sealing into one machine reduces required cleanroom footprint, cuts down on component inventory, and lowers shipping costs compared to glass.
- **Shatterproof & Safe:** Plastic BFS ampoules are highly durable, shatter-resistant, and eliminate the risk of glass-shard contamination during opening.
- **Design Flexibility:** Single-dose vials, multi-dose bottles, and custom ergonomic shapes can all be engineered seamlessly on standard BFS machinery.

CONS & LIMITATIONS:

- **High Heat Exposure:** The plastic extrusion process involves high temperatures, making BFS challenging for highly heat-sensitive or thermolabile biological molecules.
- **Large Initial Capital:** Purchasing high-speed BFS machinery and setting up the required cleanroom infrastructure demands a significant upfront investment.
- **Material Permeability:** Plastics are generally more permeable to gases and water vapor than glass, which can affect the shelf life of highly volatile formulas.
- **Common Uses & Applications**
 - **Ophthalmics :** Single-use, preservative-free artificial tears and medicated eye drops.
 - **Respiratory:** Unit-dose inhalation solutions used in nebulizers.
 - **Biologics & Injectables:** Sterile water for injection, vaccines, and certain stable intravenous solutions.

TECHNIQUES

1. Parison Extrusion Techniques:

The process begins by converting raw plastic granules into a molten tube called a **parison**.

- **Thermal Plasticization:** Extruders heat pharmaceutical-grade resins (like LDPE or Polypropylene) to precisely 170°C – 230°C to kill structural microbes while making the material malleable.
- **Continuous vs. Shuttle Extrusion:** In continuous systems, the molten parison flows non-stop, and molds move into place mechanically to clip it. In shuttle systems, the mold remains fixed under a dosing station, and a mechanical arm moves the cut parison into position.

2. Container Shaping & Blowing Techniques

Once the mold clamps around the hot plastic tube, specific pneumatic techniques shape the container.

- **Positive Pressure Blowing:** A multi-functional mandrel (needle) lowers into the neck of the parison and injects sterile, micro-filtered compressed air at high pressure to force the plastic against the mold geometry.
- **Vacuum-Assisted Molding:** For highly intricate container designs (like calibrated squeeze ampoules or targeted twist-off tabs), external vacuum lines suction the hot plastic from the outside of the mold simultaneously, ensuring clean definition.

3. Precision Sterile Dosing Techniques

The mechanism responsible for dispensing the liquid product requires intense speed and measurement control.

- **Time-Pressure Dosing:** A highly accurate technique where a computer-controlled valve opens for a microsecond-exact duration. Under constant, steady pressure from an intermediate buffer tank, the precise dose volume flows out.
- **Active Mandrel Cooling:** To safeguard heat-sensitive liquid formulations (like biological proteins) from the adjacent hot plastic walls, a continuous loop of cooling fluid circulates inside the mandrel walls to act as a thermal buffer.

4. Hermetic Sealing Techniques

As soon as the filling nozzles pull backward, the top section of the container is closed.

- **Heat Fusion Sealing:** The primary technique takes advantage of the remaining latent heat (170°C+) in the upper parison ribbon. A secondary set of sealing molds compresses this semi-molten head section to weld the plastic shut into a single solid piece.
- **Ultrasonic Welding:** Used selectively for advanced component insertions (such as embedding a preformed rubber puncture cap into a multi-dose bottle), using high-frequency vibrations to instantly fuse two separate parts.

5. Micro-Environment Sterility Techniques

Because humans are kept away from the open containers, the machinery depends on specialized barrier physics.

- **Aseptic Air Showering:** A continuous stream of HEPA-filtered, sterile air creates an overpressure "air shroud" directly above the filling mandrels. This micro-zone pushes microscopic ambient particles outward, creating an active barrier.

- **Automated CIP/SIP Cycles:** Clean-In-Place (CIP) and Steam-In-Place (SIP) techniques clean the fluid lines internally with pressurized water and high-temperature steam (121°C) before every new production run, ensuring absolute systemic decontamination.

Would you like to analyze the **process parameters for an automated visual inspection** of finished BFS containers, or look into the differences between **LDPE and Polypropylene** molding settings

PRODUCT TEMPERATURE IN A BFS PROCESS

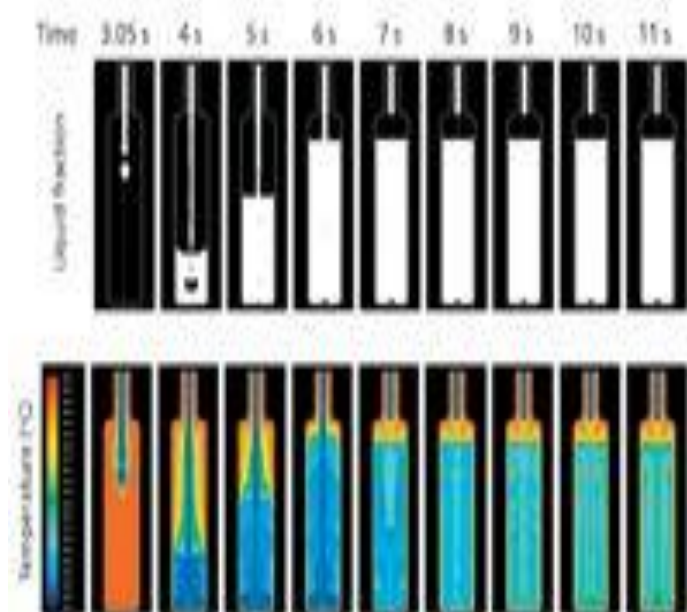
One of the major challenges for the BFS operation compared with a conventional filling process is the high temperature involved in the plastic extrusion step. As illustrated in Figure 1, the plastic granules are melted and extruded at temperature in excess of 160 °C. The hot parison will come into contact with a metal mold, be transported to the filling shroud, and be filled with drug product. Cool water circulating inside the mold helps to lower the ampul temperature. The cooling process, however, is limited by the contact time between the ampul and the mold (a total of about 10 s). In addition, the ampul cooling is restricted by the minimum temperature needed to form a hermetic seal at the end of the filling step. The ampul temperature near the neck area has to remain high enough to ensure an appropriate seal at the end of the filling process.

In the development phase of a biological drug product, when using a plastic ampul as the primary container, it is important to understand the temperature to which the product could be exposed. The folded conformations of proteins are only marginally stable, and a rise in temperature can denature the molecule leading to loss of activity. Elucidating the temperature profile during the BFS process will enable formulation scientists to develop more robust formulations.

In a BFS manufacturing process, product temperature during the filling process is not an easily controlled parameter, and it cannot be directly measured. Instead, the controllable parameters are the starting-product solution temperature in the bulk tank, plastic extrusion temperature, mold-cooling water temperature, and the cycle time for each BFS step (e.g., molding, filling, and sealing).

The authors have used a computational fluid dynamic (CFD) model (ANSYS Fluent 12) to simulate the BFS process using the Pulmozyme ampul as a model. Initial simulation results (not shown) showed that ampul-wall temperature reaches mold temperature quickly (within 1 s) during If the actual mold temperature is at cooling-water temperature (usually near room temperature of ~ 25 °C), the finished ampuls at the end of BFS process should not be significantly hotter than the mold cavity. It is the authors' experience, however, that product ampuls usually feel warm right after the BFS process. This observation suggests that the actual mold temperature is much higher than the cooling-water temperature (the actual mold temperature during BFS production is not usually measured).

For the purpose of the CFD simulation, the authors adjusted the mold temperature to different settings. Figure 3 illustrates the product-temperature profile when the mold temperature was set at 60 °C. The simulation assumes that it takes approximately 11 s for the entire BFS process including ~3 s for the molding step, ~3 s for filling, and ~5 s for forming a hermetic seal. The upper portion of Figure 3 shows the liquid volume in the ampul, as it is being filled (from time = 3 s). The temperature profiles of the entire ampul (including wall, solution, and air) throughout the filling and sealing step are shown in the bottom sequence of Figure 3. It should be noted that in the actual manufacturing process, the filling nozzle is retracted from the ampoule after filling is complete to allow for sealing. Since this is a nonproduct contact part the current CFD simulation simply turns off the solution flow from the inlet nozzle, instead of modeling the actual nozzle retraction.



Simulation of product temperature in a blow fill seal process.

The simulation revealed that the ampul is cooled from the initial extrusion temperature of $\sim 160\text{ }^{\circ}\text{C}$ to $60\text{ }^{\circ}\text{C}$ (assumed actual mold temperature) in less than 2 s. Forced convection dominates heat transfer during filling from 3 s to 6 s, thereafter natural convection becomes more prominent. By the time the filled ampul was ejected from the mold 11 s only the fluid layer near the ampul walls had been heated to within $10\text{ }^{\circ}\text{C}$ of the mold temperature. The majority of the liquid remains considerably cooler.

In the current simulation the authors assumed a worst-case scenario of liquid being filled at $\sim 25\text{ }^{\circ}\text{C}$. In the actual production process, the drug substance is typically maintained at $2\text{--}8\text{ }^{\circ}\text{C}$ and would be introduced in the ampoule close to these temperatures. Therefore, in a production BFS process, it is expected that the drug substance would experience temperatures that are lower than these shown in the CFD simulation results.

Based on the observation of higher actual mold temperature compared with that of the cooling water from the simulation results, it is highly recommended to monitor the actual mold temperature during the development or characterization phase of the BFS process. Monitoring could potentially be achieved by attaching thermocouples to the mold or by infrared temperature measurement of the mold surface.

LEAK DETECTION IN PLASTIC AMPULS

The formation of the primary container is an integral part of the BFS operation and container-closure defects can be a major problem. US regulatory authorities require that "as a final measure, the inspection of each unit of a batch should include a reliable, sensitive, final product examination that is capable of identifying defective units (e.g. "leakers")" (8). It is also stated in the EU guidelines that "containers closed by fusions, e.g., glass or plastic ampoules should be subject to 100% integrity testing"^[69]

There are multiple leak-detection technologies available, such as the vacuum-decay method, high-voltage leak detector, or near infrared leak detection. Among these methods, the vacuum-decay method is often selected for biological manufacturing because it has no product quality impact (even though there is no documented product quality impact from other methods to the authors' knowledge). During vacuum decay leak detection, the test article is placed inside a chamber, which is then evacuated to a known pressure. If the product container exhibits a leak, the chamber pressure will rise at a rate greater than a predetermined baseline value.

The qualification of a leak-detection machine can be achieved by challenging the system with calibrated needle valves, or by means of "leaky" samples, created by either laser microdrilling or capillary tube insertion into ampuls. In the authors' experience, creation of "leaky" samples of ampuls is not reproducible, and needle valve

is a preferred method to qualify the leak detection machine. Leaky samples created by laser microdrilling or capillary tube insertion in plastic materials have many challenges. Most plastic resins, such as LDPE, do not have the required material characteristics (too soft and poor adhesion) to support reliable mounting of a capillary or to maintain a consistent hole size. The drilling process with LDPE yields a conical-shaped orifice that results in flow rates that are difficult to predict. Furthermore, the verification process is destructive in that the flow rate is measured under vacuum, which can result in obstruction of the orifice by the product. Therefore, the actual test sample used cannot be verified prior to testing. The variables of shipping, handling, and pressure as a result of air transportation could also result in inconsistent results.

Alternatively, the needle valves can be calibrated with a flow meter to a specific flow rate corresponding to a specific orifice size. Calibrated needle valves represent a suitable qualification approach to the system that will demonstrate the system's ability to detect an actual leaking sample with a known hole size and flow rate.

Another main challenge with in-line leak detection operation is the high false rejection rate. Due to the high temperature required for plastic extrusion, the ampuls, immediately after BFS process, are notably warmer than room temperature. When the products are immediately placed in a vacuum-detection chamber, the heat from the ampul can cause a slight increase in pressure which the instrument may interpret as a leaky sample, which will trigger a false rejection signal. Therefore, it is highly advisable to have the product equilibrated to room temperature prior to subjecting the product to vacuum leak detection

PACKAGING REQUIREMENTS, EXTRACTABLES AND LEACHABLES

The primary containers of ampuls manufactured using BFS process are plastic materials, such as LDPE or PP, which are gas-permeable to some degree. During long-term storage, water vapor may diffuse out of the ampul resulting in alterations in drug concentration. Conversely, oxygen permeation could cause protein oxidation. Gas permeation can be minimized by sealing the plastic ampuls inside laminated foil pouches (as a secondary packaging layer). For example, in the development of the Pulmozyme drug product, studies showed that protein concentration increased by more than 30% due to water loss when the naked product was stored at 37 °C for ~700 days ^[70]. Such water loss was prevented by adding an aluminum foil pouch as a secondary packaging layer. In addition, the aluminum foil pouch protects the drug product from light-induced degradation. Furthermore, oxygen-sensitive products can be sealed into pouches under a nitrogen blanket (overlay) to provide additional protection against oxidation.

Secondary packaging materials are typically comprised of multiple layers of polymers (i.e., polyester, PP, or polyethylene), inks, adhesives, as well as possibly unreacted monomers and oligomers derived from adhesive materials. When in direct contact with primary containers, these materials have the potential to penetrate through plastic ampuls. In addition, the direct contact between the liquid product and the primary container (even though the primary container material is typically made of much cleaner polymers) could lead to extraction of chemicals. These chemical extracts and leachates from plastic packaging materials could act as adjuvants in stimulating an immune response in the patient ^[71]. Leachates would especially be of concern if the product is to be injected subcutaneously, as the localized concentration of product and adjuvant is more likely to stimulate the production of neutralizing antibodies than intravenous injection or inhalation ^[72]. Therefore, it is imperative that the extractable and leachable program for plastic ampul products be conducted with both pouched and unpouched samples to understand the respective extracts and leachates from both the primary and the secondary packaging materials ^[73,74]

CONCLUSION

BFS technology has great potential in the field of biopharmaceutics because of reduced human intervention during the production process, convenience, and ease of use offered by its final product in plastic ampul form. The operating conditions of the BFS process and the nature of plastic ampuls pose many challenges to the stability of biopharmaceutical drug products. 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.

Finally, the BFS process may not be suitable for many proteins, especially large, complex proteins with multiple sites for activity and proteins that are highly temperature-sensitive. In addition, chemical extracts or leachates from the direct contact between the product and the primary container, as well as volatile chemicals from secondary packaging layers could act as adjuvants in stimulating an immune response in the patient, which would be of particular concern if the product were to be injected subcutaneously. These factors should be evaluated and addressed in the early-development phase if plastic ampuls are selected as the product containers.

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