Improving Process Quality for Pharmaceutical Liquids

Aseptic blow/fill/seal vs. traditional aseptic processing

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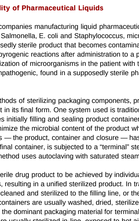
Since its introduction into the North American pharmaceutical market more than 40 years ago, blow/fill/seal (B/F/S) aseptic processing has established itself as a highly efficient and safe system for the filling and packaging of sterile pharmaceutical liquids and other healthcare products, such as creams and ointments. B/F/S product usage has been widely established in the ophthalmic and respiratory therapy markets for some time, and B/F/S technology has lately been gaining worldwide acceptance in the parenteral drug marketplace, replacing traditional glass vial processing in a growing number of applications.



B/F/S enables a container to be molded from plastic, aseptically filled and then hermetically sealed in one continuous, integrated and automatic operation, without human manipulation. The process provides flexibility in container design and system changeovers, high volume product output, low operational costs and a high assurance of product sterility. The inherent safety of the process — packaging sterile products under aseptic conditions without human intervention — has led the FDA and the United States Pharmacopoeia to characterize B/F/S technology as an "advanced aseptic process," indicating its use as a preferred technology.

New advances in drug delivery, the desire to improve convenience in handling pharmaceutical products, growing emphasis on combination products, the increasing focus on protein-based drugs and other biologics, and tighter regulatory criteria on product safety, have focused more attention on B/F/S technology over traditional aseptic methods as a better solution for the sterile, aseptic processing of pharmaceutical liquids.

Traditional Aseptic Processing and Sterility of Pharmaceutical Liquids

Microbial contamination is a serious issue for companies manufacturing liquid pharmaceutical formulations. Such liquids are ideal growth areas for bacteria like Salmonella, E. coli and Staphylococcus, microbes that have been found in various liquid drug products. A supposedly sterile product that becomes contaminated may result in deterioration of the drug and loss of potency, pyrogenic reactions after administration to a patient (particularly in parenterals), infection of the patient and colonization of microorganisms in the patient with the risk of a secondary infection. Any microorganism, pathogen or nonpathogenic, found in a supposedly sterile pharmaceutical product is dangerous.

Drug manufacturers have pursued various methods of sterilizing packaging components, product ingredients and equipment in order to achieve a sterile product in its final form. One system used is traditional processing, followed by terminal sterilization, which involves initially filling and sealing product containers within a cleanroom environment. The environment is set up to minimize the microbial content of the product while it is being manufactured. Each component of the process — the product, container and closure — has a low bioburden, but may or may not be sterile. The product, in the final container, is subjected to a "terminal" sterilization process, such as heat or radiation. The most common method uses autoclaving with saturated steam under pressure.

Traditional aseptic processing allows a final sterile drug product to be achieved by individually sterilizing the containers, material and equipment in-process, resulting in a unified sterilized product. In traditional aseptic processing, the containers are either supplied cleaned and sterilized to the filling line, or they are cleaned and sterilized within the aseptic filling line. Plastic containers are usually washed, dried, sterilized and cooled before filling. Glassware containers, which have been the dominant packaging material for terminally sterilized and traditionally sterilized pharmaceutical liquids, are usually sterilized in-line, exposed to hot air at 350° C while being passed through a Class 100 tunnel. A glass container temperature of 180 to 200° C is adequate for achieving sterility.

Methods of sterilization used in aseptic processing include filtering the solution by dissolving it in a solvent, such as Water For Injection (WFI), where the solution is passed through a sterilizing filter or membrane. Filter sterilization is used where the component is soluble and likely to be adversely affected by heat. A variation of this method includes subjecting the filtered solution to sterile crystallization and precipitation (lyophilization) of the component as a sterile powder.Dry heat sterilization is another effective method for sterilizing components that are heat stable and insoluble. Irradiation can also be used to sterilize some components.

Aseptic processing handles components, materials and equipment in such a manner that foreign microbial and endotoxin contaminents that exceed pre-determined acceptable levels are not introduced to the product stream. To this end, it is critical that all storage, conveying, filling and container-sealing stages be carefully controlled at each step of the process to maintain sterility of the product. Traditional aseptic processing, involving filling open glass bottles or vials, requires that the manufacturer maintain aseptic conditions in critical processing areas at all times. Unfortunately, the majority of liquid drug product contamination during the past several decades has come about from products produced in traditional aseptic processing facilities.

Personnel Intervention in Traditional Aseptic Critical Areas

Traditional aseptic sterilization involves handling and manipulation of the material, containers, and sterilization filling processes with human intervention, and therefore has a higher potential for contamination during processing. The FDA's 2004 Guidance for Industry Sterile Drug Products Produced by Aseptic Processing states that the design of equipment used in aseptic processing should limit the number and the complexity of aseptic interventions by personnel. Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures or the surrounding environment.

The act of walking by a person emits roughly 10,000 skin particles per minute. Such particles can and do hold microbial contamination. A rip in a worker's uniform, a momentary exposed wrist, a mask placed too low on the nose or physical contact with an open fill port will increase microbial contamination within a critical area.

According to the FDA's guide, airborne contamination is directly related to the number of people working in a cleanroom and the level of congregation by personnel in areas where critical aseptic manipulations are performed. Isolation of personnel from these critical areas would eliminate the major source of contamination in traditional aseptic processing.

In traditional aseptic processing, changing or adjusting filling nozzles and heads necessitates the shutdown of the filling operation and requires re-sterilization of the entire equipment. This increases manual intervention in this critical area. Cleaning and sterilization, which is carried out by personnel, opens the door to breaching of established procedures for microbial decontamination and potential introduction of other particulates like dirt, oil and chemicals.

Mold is common flora found on floors, walls and ceilings of buildings. Contamination occurs due to the retention of water in cracks, edges and joints that are susceptible because of inadequate sealing. Brooms, mops and anything used for cleaning can become contaminated and increase atmospheric contamination because of raised dust or splashing water. In traditional aseptic processing, significant manual intervention is required in critical areas to maintain compliance with established sterile mandates.

Advanced blow/fill/seal Aseptic Technology

In advanced aseptic B/F/S processing, containers are formed from a thermoplastic granulate, filled with a liquid pharmaceutical product and then sealed within a continuous, integrated and automatic operation without human intervention. Bulk solution prepared under low bioburden or sterile conditions is delivered to the machine through a product delivery system that has been previously sterilized using an automated steam-in-place process.

Modern B/F/S machines are fully automated, designed to require minimum human access and operate in a classified environment using the following steps:

1. granules of a polymer resin, according to a predetermined set of specifications, such as polyethylene, poly-propylene, co-polymers or other blow moldable resins, are pneumatically conveyed from a non-classified area into the hopper of the B/F/S machine, from which the plastic is fed into a multi-zone rotating screw extruder which produces a sterile homogenous polymer melt (160-250° C);
2. then to a parison head which produces a sterile tubular forms of the hot resin (called parisons). The parisons are prevented from collapsing by a stream of sterile filtered support air. Some high-speed B/F/S machines have as many as 16 parisons being formed simultaneously;
3. container mold(s) close around the parisons, and the bottom of the parison is pinched closed, while the top is held open in a molten state;
4. the container is formed in the mold by blowing sterile air or creating a vacuum;
5. filling needles deposit the stipulated volume of product into the container;
6. the filling needles are withdrawn, and the upper part of the mold closes to form and seal the upper part of the B/F/S container;
7. the mold is opened and the completed, filled containers are conveyed out of the B/F/S machine to a remote station where excess plastic is removed and the finished product is then conveyed to final packaging.

Various in-process control parameters, such as container weight, fill weight, wall thickness and visual defects provide information that is monitored and facilitates ongoing process control.

The forming, filling and sealing steps are achieved in one unit operation; the cycle is completed within seconds. Automation of B/F/S process steps eliminates manual intervention and reduces risk to the product. No production personnel are present in the filling room during normal operation.

Microbial and Particulate Integrity in the Aseptic blow/fill/seal System

Sterility of B/F/S polymeric containers, materials and processes is validated by verifying that time and temperature conditions of the extrusion, filling and sealing processes are effective against endotoxins and spores.

Challenge studies have been conducted on the sterility levels of advanced B/F/S technology, which demonstrate a uniform capability of achieving contamination rates not exceeding 0.001% throughout the entire process. Even higher sterility assurance levels, approaching 0.0000001%, have been achieved using high levels of airborne microbiological challenge particles.

Endotoxins are a potential pyrogenic contaminant, essentially dead bacterial cellular matter. They can lead to serious reactions in patients, particularly with those receiving injections, ranging from fever to death. A critical aspect of B/F/S technology is its pyrogen-free molding of containers and ampoules. Extensive experiments confirming the efficacy of the B/F/S extrusion process have been performed using high levels of spores and endotoxin-contaminated polymer granules. The typical B/F/S extruders have demonstrated spore contamination rates of 0.000001%, and 0.00001% for endotoxins.

Control of air quality is critical for sterile drug product manufacture. B/F/S equipment design typically employs the use of specialized measures to reduce microbial contamination and particle levels that can contaminate the exposed product. The B/F/S process inherently produces a very low level of particulate matter and much of potential B/F/S microbial contamination (viable) in the air is mitigated by the absence of manual intervention in its critical areas. Non-viable particles generated during the plastic extrusion, cutting, and sealing processes are controlled. Provisions for carefully controlled airflow protect the product by forcing created particles outward while preventing any inflow from the adjacent environment. These "zones of protection" can also incorporate designs that separate them from the surrounding environment, providing additional product protection.

The B/F/S critical processing zone is continually supplied with HEPA-filtered air by an air shower device (shroud). The B/F/S critical zone is the area where the containers are exposed during filling. Air in the critical zone meets Class 100 (ISO 5) microbiological standards during operations. The critical zone is continuously monitored to ensure a positive differential pressure is maintained between the shroud and the adjacent cleanroom.

Plastic vs. Glass Containers

Injectables, ophthalmics, biologicals and vaccines are produced in a number of different types of containers, including bottles, vials and ampoules that are made from glass and plastic. Protecting the contents of these aseptic liquid drugs through filling, packaging and transportation, and allowing for safe and easy administration are critical objectives in the aseptic process. The industry is infused with a strong emphasis on quality control. Raw materials, and in-process and finished products are continually checked for approval and rejection.

The packaging needs for pharmaceutical liquids are quite demanding. It is not unusual for degradation of the product to occur during processing or while in transit. The physical properties of liquids can be altered with inadequate packaging components. For aseptic filling, the package must be produced, stored, filled and sealed under conditions that preserve sterility. Likewise, the appearance of particulates in sterile solutions is equally undesirable.

Glass, although a standard in the aseptic pharmaceutical liquids industry, is not without its limitations. There is the safety issue; glass vials are subject to breakage, both in transit and while being administered. Handling glass containers always involves a certain amount of risk of lacerations and glass splinters. Glass ampoules, for example, generate a fine array of small glass particles during opening.

Manufacturers using glass containers are also subjected to design limitations when the designs become somewhat complex. With glass containers, as design complexity increases so does the cost. Once glass containers are produced, they need to be transported to the aseptic facility. Glass is typically transported in cardboard boxes, which can contain mold spores such as Penicillin sp. and Aspergillus sp., as well as bacteria like Bacillus sp. Paper, also used in the shipping of glass, can contain mold spores, too. The rubber closures used on the glass containers may have mold contamination.

Domestic drug companies have been slow to change to plastic, primarily due to the existing installed base of glass production of small-volume parenteral drugs in the U.S. However, the same is not the case with new drugs that are coming onto the market. These are more frequently being looked at, and submitted for FDA approval, in plastic containers produced by advanced B/F/S aseptic processing. Supporting this move is that the B/F/S processing resins, polyethylene and polypropylene, are generally considered inert by the FDA. Many of the blow molding resins used in B/F/S processing have received international acceptance as suitable for food and drug applications, and many of the drug products produced outside of the U.S. can be found packaged with these resins.

With the continued refinement of B/F/S technology, its acknowledgment by the FDA as a preferred technology for aseptic processing, and its growing acceptance by drug companies, the migration from glass to plastic containers used for aseptic pharmaceutical liquids is growing rapidly. It has become more cost effective to use plastic containers for aseptic liquids, which effectively means manufacturers one-third of the cost of glass. Plastic is less expensive to ship because the containers are lighter. For small-volume parenterals, the use of plastic is inevitable, and increasingly being considered for these reasons.

Although many B/F/S systems make available only a limited number of container choices within each container category, some B/F/S machines do allow for broad versatility in container design. Advanced B/F/S machines can design virtually any container mold through the use of sophisticated CAD/CAM technology and 3-D modeling. These design systems, when interfaced with the latest in CNC and EDM machinery, ensure fabrication of key components to precise tolerances.

B/F/S machine designs also allow for mounting of separate sterile items (inserts) within the B/F/S container, and in-mold coding and engraving, which provide further opportunities for innovative design over that of glass products.

Changeover Flexibility for Shorter Runs, Increased Uptime, Maximized Throughput

Modern B/F/S system design is focused on simplicity and flexibility. Many B/F/S machines are configured to produce more than one bottle shape or format. This makes it easy to change over from one container size to another. A B/F/S machine might produce a family of 2, 3 and 5ml, then switch to a family of 5, 10 and 15ml, or to one of 10, 15 and 20ml, moving from one to the other with relative ease of machine set-up. This is ideal for manufacturers performing contract packaging of aseptic liquid pharmaceutical solutions, because of their need for changeover flexibility.

The growing usage of biologics demands different formats of packaging. They usually require smaller process runs and are typically heat sensitive. Many of these new biotechnological drugs do not withstand steam sterilization or irradiation and so are best treated aseptically. More advanced B/F/S machines have been designed so they can handle these heat sensitive products.

Machine models are available that can produce containers ranging in size from 0.1mL to 1000mL at production rates of 15,000 units per hour, depending on container configuration. B/F/S machine efficiency is very high. More advanced B/F/S machines can approach 99% uptime efficiency, significantly higher than traditional aseptic processing, which is plagued with slow-downs due in part to manual interventions. To further minimize potential process downtime, some manufacturers are now segmenting their high-volume process lines into more short-run lines, so that if one of the lines goes down for maintenance or repair, it will not stop the entire production throughput.

When aseptic throughput is interrupted, or not running because of downtime, the entire process line is affected, which represents a significant production loss to the manufacturer.

An Aseptic Technology Destined to Prevail

More rapid container closure processing, elimination of aseptic critical-area personnel interventions, increased system uptime over traditional processing, pyrogen-free molding of containers and ampoules, more flexibility with container design, and an increased capability to capitalize on short runs: these are some of the benefits for manufacturers inherent in advanced blow/fill/seal aseptic technology. And for the consumer, increased safety and confidence in their drug products are strong additional benefits.

These are advances that are significant, if not fully realized yet within the aseptic liquid pharmaceutical marketplace. But it is apparent that advanced B/F/S aseptic technology is destined to become a major player in this arena.

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