

WHITEPAPER

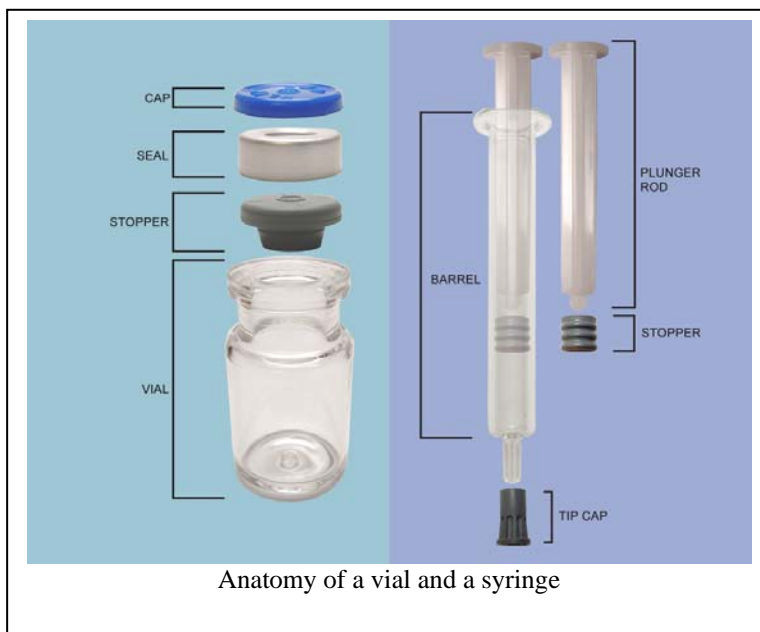
Hyaluron Contract Manufacturing

Solutions for All Your Aseptic Parenteral Drug Formulation/Filling Needs

BUBBLE-FREE FILLING®: A New Option in Prefilled Syringe Filling

Introduction

The advent of bubble elimination in a prefilled syringe offers many advantages worth exploring prior to deciding how a product is to be packaged for clinical studies or commercial distribution. This technique further enhances the benefits of prefilled syringes. Prefilled syringes vs. vials have become the container of choice for parenteral drug delivery. The increase in their use is directly correlated to changes in the healthcare industry. Some of the main advantages of prefilled syringes are safety in administration, ease of use for both healthcare professionals and end users; reduced risk of contamination of product, less waste of costly or scarce API, ease of manufacturing, improved dosing accuracy and enhanced product differentiation. The growth in this mode of administering therapeutics has led to innovative solutions in filling and stoppering methods.



In a number of studies, Hyaluron Contract Manufacturing (HCM) of Burlington, Massachusetts, found that the advantages of prefilled syringes can be further enhanced by reducing the size of the air (gas) bubble inside the syringe or better yet, eliminating it totally. After a series of tests and validated studies a new and innovative method has been developed to fill syringes that will eliminate the air bubble. Patented and trademarked, BUBBLE-FREE FILLING® is now available as an option for those in need of fill/finish services.

This whitepaper presents the pros and cons of traditional filling methods and highlights the findings of studies that led to the development of BUBBLE-FREE FILLING®. The purpose of this information is to assist decision-makers in choosing the best filling and stoppering method for any given drug product. This decision can be just as important as choosing the right container / closure packaging system. Understanding all options available, prior to filling a product into a syringe, is beneficial to the overall drug development process.

Traditional Filling Methods Background

Syringe filling and stoppering can be completed in various ways. The following are three conventional methods:

1) Traditional filling and stoppering (online filling followed by online stopper placement):

Traditional filling and stoppering methods use conventional filling equipment. First, a needle is placed into the syringe and the product is expelled; then the stopper is forced inside an insertion tube (which is narrower than the syringe); next the insertion tube is placed inside the syringe above

the liquid level line and a rod pushes the stopper out of the insertion tube into the syringe. The two main advantages of this conventional method are minimal operator intervention, and a quick filling speed that makes it less costly and more time-efficient. One of the disadvantages is this method leaves a large air bubble.

2) Online vacuum filling followed by online vacuum stoppering:

The online vacuum filling and online vacuum stoppering method first pulls a vacuum from the sterilized syringe and then fills it with the product (while still under vacuum). Next, a vacuum is applied, again, and the stopper is pulled into position using differential pressure. There is no compression of the stoppers and insertion rods are not required. The key advantage of this method is the reduction in the size of the bubble between the product and the stopper. However, there is still a bubble. This method works well with coated stoppers because the stopper is not forced into the syringe by the insertion rod thus limiting the tearing and / or wrinkling of the coating.

3) Online filling followed by offline vacuum stoppering:

This method is similar to No. 1. However, it differs by utilizing offline vacuum stoppering. After the syringe is filled it is placed into an offline vacuum chamber where the stopper is placed. The disadvantage with this method is there is additional operator intervention, which increases the risk of contamination. It also increases the time to complete the entire process, which adds to the cost.

The Problems

Although, there are many benefits to utilizing the traditional methods of filling syringes, there are some disadvantages. Traditional methods leave a large air bubble, minimally 2.5mm, left in the syringe. The air bubble is a by-product of traditional filling methods and is not intrinsic to the finished product. In some cases the air bubble can serve an advantageous purpose. However, in other situations it can lead to problems. After conducting testing, and under some specific circumstances, HCM suggests that reducing the size of the air bubble inside a prefilled syringe will increase product quality.

The air bubble associated with prefilled syringes can cause problems with dosing accuracy and precision; allows for stopper movement during shipping; and can influence the stability of oxygen-sensitive compounds and some proteins that rearrange as a result of the gas-liquid interface.

The Solutions

HCM, a leading provider of aseptic manufacturing services, has introduced another method for filling syringes that will alleviate the problems associated with the air bubble in prefilled syringes. This new method uses online vacuum filling and online vacuum stoppering, along with proprietary technology to eliminate the air bubble inside a syringe (for low viscosity liquids). This proprietary process was designed by re-engineering standard syringe filling equipment to create a unique fluid handling and transfer process. The United States Patent and Trademark Office has granted a patent and registration of trademark for this proprietary process.

The Advantages

Enhanced Dosing Accuracy and Precision

Challenge – Improving Dosing Accuracy:

A prefilled syringe is often administered in an upright position in which the air bubble is positioned near the stopper. During administration the stopper is pressed; then the product is expelled; and finally the air bubble is expelled. When the air bubble is being expelled it will actually move into the hub of the syringe and force any remaining product out of the barrel into the needle (then into the patient).

Alternately, when a prefilled syringe is administered in the inverted position the air bubble is positioned near the needle. Once again the stopper is pressed and in this scenario the air bubble is expelled first. This is significant because once the stopper reaches the hub of the syringe there is no air bubble to help expel the remaining product. This can result in “hold-up” which means some product is left behind in the syringe and is not being delivered to the patient. This can have a negative impact on a patient’s treatment if the exact dose of therapeutic prescribed is not injected. In addition, many of today’s potent drugs are administered in smaller volumes so patients need the full dose.

Solution:

To determine hold-up volumes HCM conducted tests with a 1ml syringe filled by traditional filling / stoppering methods. They also used various sizes of needles and administering positions. The results measured hold-up volumes of product and showed that as the size of the needle increased so did the hold-up volumes.

	<i>Hold-up volume</i>	<i>% of 0.30 ml dose</i>
1ml long syringe hub	0.0099 ml	3.3%
16 gauge 1”	0.0391 ml	13.0%
18 gauge 1.5”	0.0299 ml	10.0%
26 gauge 5/8”	0.0011 ml	0.4%

An HCM study measured the hold-up volumes in a 1ml syringe and three varying size needles. The study found that in a 1 ml syringe, the hold-up was 0.0099ml, or more than 3 percent of a 0.30ml dose. When the hold-up volume in a 26 gauge 5/8” needle was added to the hold-up volume of the 1ml syringe, a common configuration for pre-filled syringes, the hold-up volume was 0.0011ml or nearly 4 percent of a 0.30 ml dose.

To measure dosing accuracy, a second test was conducted. This study compared traditionally filled syringes (online filling and stoppering) to those using the BUBBLE-FREE FILLING® method. It was found that syringes filled with the BUBBLE-FREE FILLING® method expelled more of the product than those filled

by the traditional method. This occurred no matter what the orientation of the syringe. Therefore, concluding that BUBBLE-FREE FILLING® enables the patient to consistently receive the entire dose prescribed regardless of syringe orientation. Given the low concentration of protein drugs as well as the increased number of non-clinical uses for prefilled syringes, this is an important consideration.

Challenge – Improving Safety:

Studies showed that there is a greater probability for product to leak out of the tip of the needle of a prefilled syringe that has been filled via traditional filling methods. This is due to a vacuum being created when the tip cap is removed. This leakage will lead to less than accurate dosing and also exposes hazardous cytotoxic and potent compounds to the administrator. These discrepancies in the delivered dose can be significant seeing that today's products call for small volumes and are often self-administered by patients.



Figure 3. A bubble inside a syringe can cause product to drip from the needle when the tip cap is removed. A bubble-free syringe does not leak when the tip cap is removed, enhancing dosing accuracy and safety.

Solution:

HCM's studies showed that with BUBBLE-FREE FILLING® no product was observed leaking because there is no bubble to expand as the tip cap is removed. This leads to a greater assurance of safety for the administrator, and more accurate dosing for patients. In addition, drug sponsors will have additional certainty there will be less waste in manufacturing when filling via the BUBBLE-FREE FILLING® method.

Improved Sterility Assurance Due to Microbial Contamination

Challenge – Improving Sterility Assurance:

Within any cleanroom environment there is the risk of undetected accidental contamination by common microorganisms. In order to secure a sterile environment there are many controls and validations of the manufacturing process, the environment, and the equipment. However, there is always a risk of microbial growth.

Solution:

A study using trypticase soy broth, a media which supports the growth of several microorganisms, was challenged with three different microorganisms to determine microbial growth. Half of the samples were filled using traditional filling methods and the other half were filled using the BUBBLE-FREE FILLING® method. After 2 weeks in incubation the syringes were observed and compared.

The results are the following:

1. With the microorganism *Candida albicans*, a yeast, there was growth with the syringes filled traditionally and none with the syringes filled with the BUBBLE-FREE FILLING® method.
2. With the microorganism *Bacillus subtilis*, a bacteria, there was some cloudiness in the syringes filled traditionally (indicating growth) and none with the syringes with the BUBBLE-FREE FILLING® method.
3. With the microorganism *A. niger*, a mould, there was growth in both but less with the syringes filled with the BUBBLE-FREE FILLING® method. However, this was to be expected because *A. niger* prefers an aerobic environment to grow, yet, it will also grow under anaerobic conditions.

The study concluded that BUBBLE-FREE FILLING® inhibits and / or prohibits growth of aerobic microorganisms and slows down the growth of facultative microorganisms. BUBBLE-FREE FILLING® is not meant to be used in place of any of the controls, rigors or validations in a sterile manufacturing environment but it is an added level of security that can protect against low-level contaminations. When selecting a drug's packaging and mode of shipment it is advised to select the most rugged choice available to further protect the parenteral from unintentional contamination.

Challenge – Eliminating Stopper Movement:

Manufacturers producing parenterals aseptically are mandated by regulation to produce a product in an aseptic environment utilizing sterile processes. These processes are validated to assure the final product is sterile. However, once a product leaves the sterile manufacturing facility it can be exposed to contaminants. For instance, many drugs are shipped several times before they reach their final destination. An air bubble sealed inside a prefilled syringe acts like a spring, expanding and contracting with changes in external ambient pressure.

The design and functionality of the prefilled syringe must allow for stopper movement for the drug to be administered properly. However, this movement (combined with the air bubble) can expose the drug to contaminants. HCM's tests have proven that when syringes filled with traditional filling / stoppering methods are exposed to reduced atmospheric pressure the stopper rises into non-sterile territory (in the barrel of the syringe). This is a result of the expansion of the air bubble. It has been found that the larger the air bubble - the greater the movement. If the stopper moves just once during transport the probability of its sterility being compromised are minimal. However, there are occasions when a product will be transported on more than one flight allowing the stopper to move several times. This increases the chances of violating the product's sterile validation.

Solution

HCM conducted tests to simulate changes in atmospheric pressure to determine if these conditions impact product sterility. Syringes were filled traditionally with air bubbles the size of 2.5mm and 5mm. They were placed inside a vacuum chamber and a vacuum was pulled to reduce atmospheric pressure. Then the vacuum was released to restore ambient pressure. This action was repeated several times to simulate pressure changes that might occur during shipping. The study showed that as the pressure decreased, the bubble expanded and the stopper rose into non-sterile areas of the barrel where it could pick up contaminants. When pressure returned to the original levels the stopper moved to its original position. The problem is, after viewing the syringes being tested, there was no visible indication that the stopper had ever moved into non-sterile areas. This makes it difficult for the end user to detect if sterility has been violated. Further, it was determined that syringes with larger sized air bubbles showed greater movement at any elevation. The syringes with the smaller bubbles only entered non-sterile areas of the barrel at much higher elevations. Syringes that were filled with the BUBBLE-FREE FILLING® method did not move when pressure changes were simulated.

Stability of Oxygen-sensitive Compounds Improved

Challenge – increasing stability of protein products:

Air bubbles can have a negative impact on the stability of some drug solutions. Also, the liquid-gas interaction can lead to molecules rearranging themselves in the traditionally filled syringes. For example, proteins are sensitive to both air and

silicon. At the air and silicon interface, i.e. bubble within the syringe, protein aggregation can occur.

Reduced product stability can also be seen with protein and peptide based products. They are sensitive to their packaging and can precipitate due to the liquid / gas interface thus decreasing stability. Many drug developers are forced to lyophilize their products due to this issue. Lyophilizing a product not only increases the aseptic handling and risk but is also requires additional end user work. This could result in poor administration or drug compliance.

Solution:

BUBBLE-FREE FILLING® eliminates the gas / liquid interface inside a prefilled syringe and can have a significantly positive effect on products that have container sensitivity such as protein and peptide based drugs. This could give the user more choices and increase stability with regard to container systems.

Summary

Today's innovative high-speed filling equipment is currently able to fill prefilled syringes with "almost" no bubble. Only HCM can offer "no" bubble through their BUBBLE-FREE FILLING® technology. HCM has conducted a number of studies to confirm and better understand the advantages of eliminating the bubble inside a prefilled syringe. Patients have a better chance for a successful therapeutic treatment when dosing accuracy is improved. The goal

and commitment is to make it possible for parenterals to reach patients safely and efficiently. BUBBLE-FREE FILLING® also provides additional assurances of sterility by reducing stopper movement as well as creating an unfavorable environment for the growth of aerobic and anaerobic microorganisms. To read more about the studies conducted visit HCM's website at www.hyaluron.com; click on the "News" tab and find an article titled, *A Better Fill for Prefilled Syringes: Applications & Advantages of BUBBLE-FREE FILLING for Today's Parenteral Products.*

Contact Informations:

Jeanne Lawson, Editor/Writer

jlawson@hyaluron.com

Hyaluron Contract Manufacturing

99 South Bedford Street

Burlington, MA 01803