



Advances in Prefilled Syringe Technology

Developments in areas such as component materials, surface treatments and filling processes are continuing to boost the appeal of prefilled syringes and expand their use with many of today's parenteral products

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Prefilled syringes are a fast-growing alternative to vials for many of today's parenteral products. According to one recent estimate, the market for prefilled systems has grown by over 20 per cent in the last three years and is likely to see a sustained growth rate of between 10 and 15 per cent in the foreseeable future (1).

The increased interest in prefilled syringes is largely driven by the many advantages they offer relative to vials. These include greater ease of use, reduced waste, improved dosing accuracy and enhanced product differentiation. Recent advances in syringe technology promise to further enhance the benefits of a prefilled syringe. For example, there have been new developments in component materials, as well as surface treatments and filling/stoppering processes, which offer important advantages to both the manufacturer and the end-user.

Several studies conducted by a leading provider of aseptic manufacturing services to companies in the pharmaceutical and biotechnology sectors have found that the advantages of a prefilled syringe can be significantly improved by decreasing the size of the gas bubble inside the syringe. The gas bubble is not intrinsic to the syringe but is a by-product of sub-optimal filling processes. Reducing the gas bubble, these studies showed, offers greater assurance with regard to dosing accuracy and precision as well as product sterility. Additionally, removing the gas bubble entirely from a prefilled syringe can improve the stability of many oxygen-sensitive compounds, as well as proteins that rearrange due to the gas-liquid interface.

COMPONENT MATERIALS

Borosilicate glass has long been the industry standard for parenteral products in prefilled syringes. It is easy to

sterilise and offers better visibility as well as enhanced barrier properties; it also has low reactivity and its nature and content are better defined and understood. For companies moving their product from a vial to a prefilled syringe, this factor is important since they know what to expect and how to compensate for any challenges that might arise.

Glass, however, contains small amounts of alkali ions which can cause a pH shift in some sensitive products (2). It can also harbour residual traces of tungsten, a byproduct of the glass-forming process, which can cause protein aggregation (3). Furthermore, proteins and peptides adsorb to glass which can, potentially, lead to a decrease in potency of the drug (4). Additionally, glass is breakable and requires added care when filling and handling.

Plastic has been an alternative to glass in prefilled syringes since the early 1990s. The earliest plastics, however, were made of polypropylene which did not offer the clarity of glass, or many of its barrier properties and ease of sterilization. Polypropylene plastics also presented more challenges with regard to extractables and leachables than glass due to a lack of historic data.

Manufacturers have begun to develop new plastics – such as cyclic olefin copolymers – that are able to hold their own against glass. These plastics offer high

Figure 1: A prefillable syringe consists of a barrel, a plunger rod, stopper and tip cap. Advances in surface treatments used to facilitate the movement of the individual parts have decreased the amount of free silicone that could potentially interact with a drug product

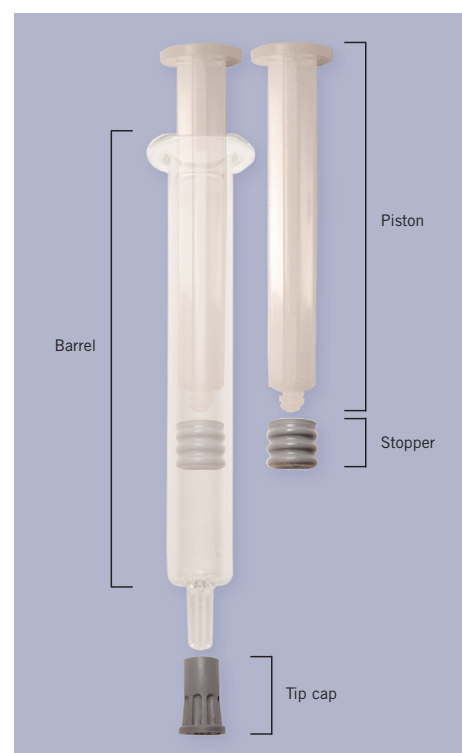
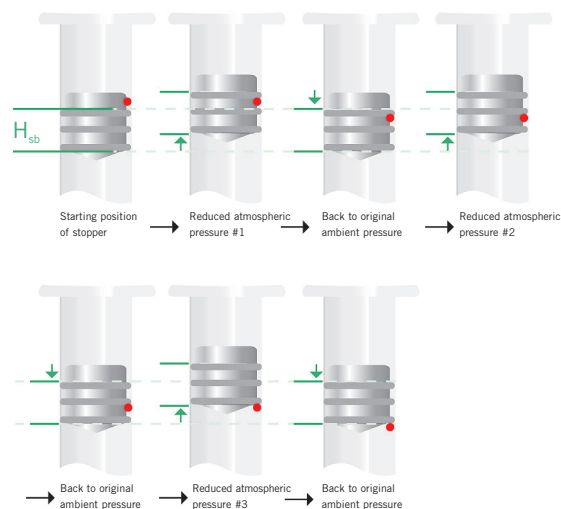


Figure 2: The expansion and contraction of a bubble inside a syringe can cause the stopper to rise into non-sterile areas of the barrel, potentially pulling silicone and other contaminants into the product



heat resistance and a low level of extractables and leachables, and are less permeable to water (5). They are also more transparent, lightweight and shatter-resistant, enhancing visibility and facilitating filling operations as well as ease of use.

SURFACE TREATMENTS

In addition to making enhancements to the component materials of a container/closure system, syringe manufacturers are finding ways to mitigate the effects of silicone on sensitive biopharmaceuticals. Unlike a vial, the various parts of a syringe must be free to move in order to facilitate administration of the product. In the past, syringe manufacturers have used silicone to lubricate the stopper and plunger, enabling these parts to move freely. However, silicone, which is used in both glass and plastic syringes, can cause issues with product stability.

More recently, some syringe manufacturers have started baking the silicone onto the syringe to limit the amount of free silicone that is available, thus decreasing the potential for interaction with the product (3). Others have developed barrier films to aid in lubricating the components, while protecting the drug product from contaminants that could potentially be leached from the elastomeric stopper which, in a syringe, is in constant contact with the product. West Pharmaceuticals, for example, has introduced FluroTec, a fluoropolymer barrier film used on syringe components to facilitate administration of the product and to guard against extractables and leachables. This syringe system provides a silicone-free container which is advantageous to silicone-sensitive products.

FILLING/STOPPERING PROCESSES

Until recently, there were three principal methods for filling and stoppering syringes, each with its own advantages and challenges.

The most common filling and stoppering process uses high-speed equipment to expel the product into the syringe and force the stopper – which is first compressed in a narrow insertion tube – into place. The advantages of this method include minimal operator intervention and high-throughput, making it less costly and faster. A significant disadvantage is the large air bubble – 2.5mm minimum – which is left in the syringe. This bubble can increase the risk of stopper movement during shipping, and cause loss of product during expulsion activities prior to administration. It can also cause stability issues for some proteins and oxygen-sensitive compounds. Additionally, online stopper placement does not work well with coated stoppers since the compression of the stopper in the insertion tube and the force of the insertion rod can cause the coating to wrinkle and tear.

The second most common method for filling and stoppering syringes is online high-speed filling followed by offline vacuum stoppering. With this method, syringes that have been filled online are manually moved from the filling machine and placed into a vacuum chamber. The advantage of this method is that it is effective in removing over 99 per cent of the air bubble, resulting in a bubble that is significantly smaller than that left by traditional online stoppering methods. One disadvantage, however, is that this method requires additional operator handling and significantly reduces throughput.

Online vacuum filling followed by online vacuum stoppering was recently introduced by fill equipment manufacturers and is becoming increasingly popular. With this method, a vacuum is applied both before and after filling, and vacuum stoppering is done online. The primary advantage of this method is reduced operator handling and the ability to obtain bubble-free filling of viscous liquids. Online vacuum stoppering also works well with coated stoppers, as there is no compression of the stopper via the insertion rod.

The latest innovation in filling and stoppering syringes uses online vacuum filling and stoppering in conjunction with other proprietary technology to produce a syringe that is bubble-free. This method, known as bubble-free filling, is most advantageous for non-viscous products, since viscous products can be

filled without bubbles using online vacuum filling and stoppering alone.

The advantages of bubble-free filling include:

Enhanced Dosing Accuracy

Studies show that reducing or eliminating the bubble inside a prefilled syringe assures the same dose will be delivered regardless of syringe orientation, ensuring the end-user receives the entire deliverable dose.

Improved Product Sterility

A gas bubble inside a syringe can cause the stopper to move into non-sterile areas of the syringe when the syringe is exposed to changes in atmospheric pressure, potentially pulling contaminants and/or silicone oil into the product. Reducing the size of the gas bubble limits stopper movement, offering greater assurance with regard to package integrity and product sterility. Further, decreasing the size of the bubble inside a prefilled syringe prevents the growth of aerobic microorganisms and inhibits the growth of facultative microorganisms.

Decreased Waste/Greater Safety

The expansion of a gas bubble inside a syringe can result in a drip from the needle when the tip cap is removed. Decreasing the size of the bubble – or eliminating it altogether – ensures that less product will be wasted as a result of the drip and reduces the likelihood of administrator exposure to cytotoxic compounds.

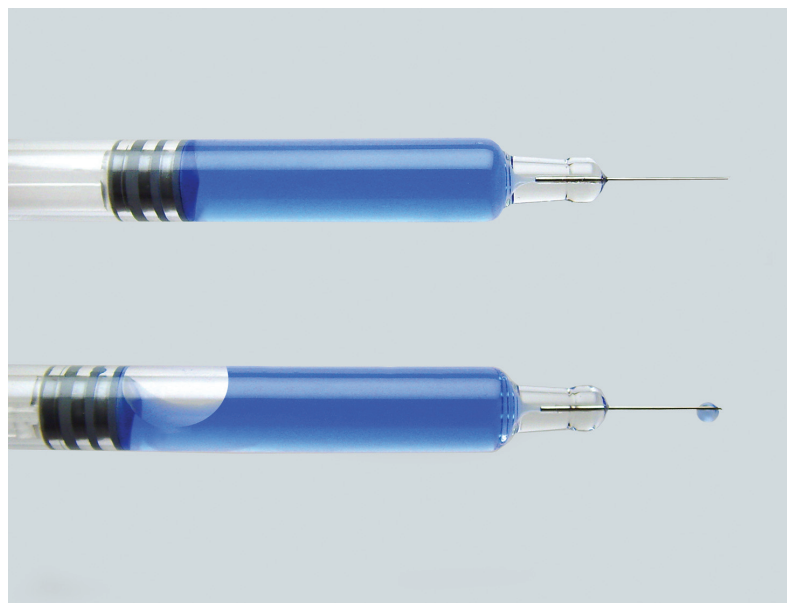
Increased Product Stability

The liquid-gas interface inside a prefilled syringe can cause molecular rearrangement in some proteins, while air bubbles, in conjunction with silicone, may lead to protein aggregation. Eliminating the liquid-gas interface increases the stability of these products. In addition, removing the air from a prefilled syringe enhances the stability of oxygen-sensitive compounds.

CONCLUSION

As prefilled syringes continue to find favour as an alternative to vials for many drug products, advances in prefilled syringe technology will continue to provide added benefits. These advances include developments in component materials, surface treatments and filling processes.

One new filling process, bubble-free filling, offers improved dosing accuracy and greater assurance with regard to product sterility and stability in a prefilled syringe. These benefits, together with others – including



enhanced ease-of-use and reduced waste, as well as the potential to one day lyophilise products in standard, commercially available syringes – will continue to boost the appeal of prefilled syringes and expand their use with many of today's parenteral products.

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Acknowledgement

The author would like to thank Kelly Jenkins Lin at Hyaluron Contract Manufacturing for her assistance in the preparation of this article.

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Figure 3: A bubble inside a syringe can cause the 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