Glass: applications in pharmaceutical packaging

A review of how glass is treated for use in pharmaceutical applications and how it is then used in the production of injection systems.

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Essential requirements in the parenteral field are high hydrolytic resistance to the drug, high neutrality and chemical resistance.

As new applications are developed, so the demands on pharmaceutical glass for use as a packaging material and in injection systems also increase. While syringe shapes must be practical for machine-handling reasons, there is now the additional requirement for precise compatibility with other system components. In this article, we review how glass is treated for use in pharmaceutical applications and how it is then used in the production of injection systems.

Basic glass requirements and surface treatment

Essential requirements in the parenteral field are high hydrolytic resistance to the drug, high neutrality and chemical resistance. Sometimes the glass may also require surface treatment, either at the manufacturer or the processor.

Disponil® is used to protect glass surfaces from scratching during transit and processing, and the inner surface of glass containers is sprayed with an ammonium sulphate solution to increase hydrolytic resistance, primarily for unbuffered systems (WFI, isotonic salt solution).

Coating glass with silicone (siliconisation) facilitates efficient emptying of the contents and eliminates dosage errors or wastage. It is also important for the lubricity of the closure system. There are three different types of siliconisation process: immersion, silicone swabbing and silicone spraying.

With the immersion process, the glass barrel is immersed in a silicone bath and subsequently passed through a drying tunnel to bind the coating. The amount of silicone oil on the glass is critical – not only because of the potential

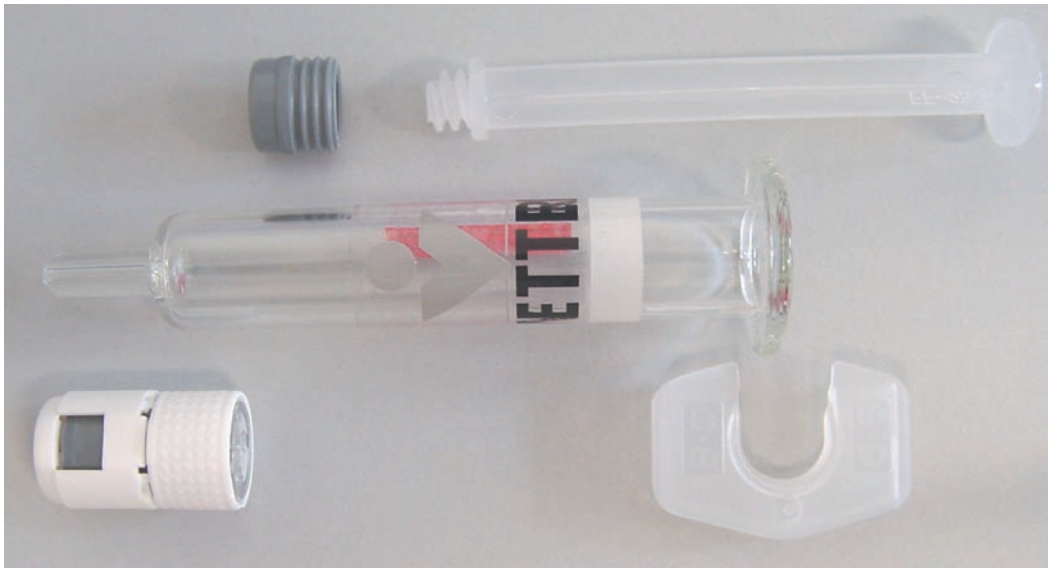

Figure 1. Syringe with cone.

interaction with the drug, but also for the exact physical adjustment and correct functioning of the closure system used.

Glass processors mostly do not perform silicone immersion, so siliconisation must be performed during the washing process by the filler. It is the final washing process and can be done in two different ways. Silicone swabbing involves putting pure silicone oil into the syringe via a special swabbing pin, ensuring an even distribution over the surface. The glass barrel is then transferred via the autoclave to the clean-room, where it is filled. Silicone spraying involves spraying an O/W emulsion onto the barrel via a fine spray nozzle. The barrel is baked – and also depyrogenised – in a dry heat tunnel. Spray siliconisation uses only small quantities of silicone and provides an even distribution over the surface but, because of the temperatures, it is not suitable for syringes with staked needles.

As biotechnology-based medicines become more sophisticated, sensitivity to silicone becomes more crucial.

As biotechnology-based medicines become more sophisticated, sensitivity to silicone becomes more crucial. Accordingly, siliconising processes must be further optimised to ensure minimal amounts of silicone on surfaces or stoppers. However, the functional lubricity required within the packaging system must be maintained beyond the prescribed storage duration and temperature. The possible chemical interaction between the treated surface of the primary packaging and the closure parts must be checked by stability studies according to the various pharmacopoeia (Ph Eur, USP, JP).

Syringes

The standard-sized syringes with staked needles are 1 ml and 0.5 ml models; these are widely used for medications such as vaccines, growth hormones and heparins. There are different types of needle with different bevels (cut angles). The most common are the 3-bevel needle, the MG (MGlas) V-bevel needle and the BD (Becton Dickinson) Hypak™ 5-bevel needle. The different bevel angles facilitate the insertion and removal of the needle.

Tapered syringes are either small- (<1ml), medium- (>3ml) or large-volume (>5ml). In contrast to syringes with pre-attached needles, tapered syringes cannot be directly administered. A transfer device or application system is needed – for example, a needle, 3-way tap and so on. Owing to the way in which the glass is shaped (warm moulding), length tolerances of up to +/- 0.75mm are required.

A distinction is made between single chamber cartridges (SCC) and dual chamber with a round or square-shaped bypass (DCC). This bypass allows the diluent to flow from the distal chamber via the stopper to the proximal chamber at the time when the freeze-dried drug is to be reconstituted. As with tapered syringes, the precise shape and tolerance of the head of the cylinder is crucial for interaction with the closure system.

Specifications of syringes and cartridge systems

The needle is attached to the tapered syringe with a Luer connection. Development and testing are based on current DIN standards (ISO 594, DIN-EN 1707, DIN-EN 11608 or DIN-ISO 13926). The connection between the standard barrel and the closure system, needle or stopper determines the impermeability of the system and has to be extensively tested. Pharmaceutical impermeability (mechanical and microbiological) has to be proven.

The head must be shaped to withstand the forces exerted when a subsequent application is

Figure 2. Vetter's V-OVS NS® closure system.

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attached. For this reason, Vetter has specified a load test for this part of the barrel. The pre-processing quality requirements demanded are laid down in specifications, and regular tests of incoming goods or conformity certificates are necessary. Specified criteria are compared – using harmonised methods or agreed specimen volumes – either in-line or off-line (In-Process-Control). The Acceptance Quality Level (AQL – the number of defective parts permissible for batch acceptance) is statistically decisive for each defect class (lethal, highly critical, cosmetic, and so on). DIN-ISO 2859 defines the test parameters and levels. If a batch fails an initial test, a second more extensive test can be ordered. If successful, the batch can then be approved.

Closure systems

The closure parts are a critical feature of injection systems. The proximal sealing element is always made of a soft elastomer. By assembling a variety of components, the sealing quality of the elastomer parts can be combined with the stiffness of the plastic parts – and a more convenient system obtained. The soft component in tapered syringes is a tip cap – that is, a single component in various shapes (for example, ribbed) or as a component in a closure system (for example, a V-OVS® system). The Vetter V-OVS® system is designed for Luer tapers; the system facilitates the removal of tip cap and cap simultaneously. The pre-attachment of the V-OVS® system should take place in a separate aseptic area prior to the filling line. The pre-assembled closure system (V-OVS®) enters the clean-room via the autoclave and is used to seal the filled syringe. This makes the pharmaceutical filling process safer and its efficiency higher.

Syringes with staked needles are sealed with a needle shield. To improve stiffness, standard needle shields have a rigid needle shield (RNS). The disadvantage of shields is that steam-permeable types of elastomer must be used (either natural or synthetic rubber). Natural rubber types harbour some allergenic potential, while some alternative types tend to become sticky during sterilisation.

Vetter supplies a system combining the advantages of a rigid cap with the sealing qualities of the needle shield and a tamper-free closure – the V-OVS NS® (Figure 2). This enables a free choice of the type of rubber used. The closure system – pre-assembled in a clean-room atmosphere – is placed into the glass barrel in a sterile environment by a special steam process that ensures that all surfaces are sterilised. Only after the autoclave process is the V-OVS NS® attached in the final sealing position.

This process shows the increasing importance of functional, handling and processing aspects in the development process. The integration of the packaging system into pharmaceutical process development is increasingly becoming a competitive factor. This is how delivery systems – such as Becton Dickinson's SCF System or Vetter's Lyco-Ject® or V-OVS® System – came about in the first place.

Cartridge systems

Cartridges are generally sealed with a straight or tapered stopper. Vetter's Lyo-Ject® closure system has several components with multiple functions. It is a syringe system, although the glass barrel itself is a cartridge (apart from a reshaped, plastic finger grip which is fitted separately). The tapered stopper in the glass barrel and the tip cap seal the system; the bump stopper is both a tip-cap mounting and a taper stopper, as well as the compatible connection between the closure part and the head. The tamper-free seal fixes the lower part of the bump stopper in the head of the cartridge with the V-OVS® ring. In an initial step (lyophilisation), the closure system is attached to the head and is finally pressed into position after freeze-drying. DCCs are filled and treated in a similar way. Characteristic parts are the crimp closure or the Vetter Lyo-Cartridge System V-LK®.

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Closure systems must satisfy high demands throughout the product life-cycle; they must be washable, sterilisable and easily compatible with processing conveyance systems. Components in contact with the drug must fulfil the stringent demands of the various pharmacopoeia (Ph Eur, USP, JP) and must pass the regulatory authorities' compatibility examinations.

Closure parts are made of elastomer and common plastics, but interesting new developments in plastics are constantly being evaluated. A prerequisite for application in primary packaging is long-term availability in an unchanged form. A drug master file must also be submitted to the regulatory authorities.

Sterilisation of primary packaging

Closure-parts produced in a non-controlled environment must be machine-washed to remove particles, bacterial spores and endotoxins, prior to assembly and sterilisation. Elastomer parts have silicone added to the WFI in the last washing stage to lubricate stoppers.

Autoclaving ensures that all the closure parts are thoroughly sterilised. Plastics suffer shrinkage from washing or autoclaving, which can affect their tolerances. Accordingly, individual process specifications and steps must be respected and checked very accurately during manufacture. The autoclaving of primary packaging is usually performed using saturated steam – much like a pressure cooker. Closure parts must be safe from contamination prior to and after sterilisation. The sterilisation of filled barrels or cartridges is often performed under pressure (equivalent to that inside the container) with a sterile, compressed air and steam mixture.

Radiation sterilisation (β or γ rays) is also performed. This may affect some closure parts (polymers age more quickly) and has implications for the choice of materials. Ethylene oxide (EtO) is also used for sterilisation. This is highly aggressive, and evidence must be provided after gassing that no EtO remains in the system.

Impermeability of the packaging system

To gain certification, a new packaging system must demonstrate impermeability under different pressure conditions. This can be done with a dye test under sub-atmospheric pressure for packaging systems without needles, and under atmospheric and supra-atmospheric pressures for packaging systems with needles. Packaging is also subjected to a microbiological impermeability test which involves a pre-test incubation period and, subsequently, various pressure tests in a germ-infested environment. If the test object displays no contamination after a prescribed period, then the system is deemed to be impermeable.

Claudia Roth studied chemical/ process engineering at the University of Erlangen (Germany). She undertook her PhD thesis (freeze-drying) at Roche Diagnostics (Mannheim, Germany). Since 2000, she has worked for Vetter Pharma-Fertigung (Ravensburg, Germany). Starting within aseptic production as Assistant to the Head of Production, she took over responsibility for a newly created group within the R&D department (process development and process implementation). The focus of the group is on pharmaceutical process development for prefilled systems (liquid/freeze-dried) and implementation within aseptic production.

Jochen Alberstetter obtained a degree in packaging technology at the University of Applied Sciences (Stuttgart, Germany). After graduating in 1999, he worked as a Project Engineer in the field of packaging development for baby-care products with a major producer of consumer-care products. His responsibilities include planning, design and realisation of packaging systems made of plastic injection moulding and flexible packaging systems, to be produced in adherence with technical and health-related requirements. In March 2001, he joined Vetter Pharma-Fertigung as Head of Packaging Development. Key responsibilities include the development of aseptically prefilled syringe systems (that is, tamper-evident systems, syringe and cartridge barrels, rubber components) and all of the production-related processes.

Note: Vetter (Ravensburg, Germany) is an innovative and experienced 'full service partner' for the biopharmaceutical and pharmaceutical industry; it has extensive experience in handling aseptic-filled systems in accordance with GMP guidelines and is an approved FDA site. Vetter offers a comprehensive range of services focused on aseptic pre-filled application systems, such as injection syringes and cartridges – for example, packaging and process development including freeze-drying, pharma process scale-up, regulatory expertise, laboratory services, aseptic filling and technology transfer.