

Pre-fillable Syringes for the Biotechnological Requirements of the Present and Future



Abstract

Pre-fillable syringes are both pharmaceutical primary packaging and drug delivery devices. End users, drug administration agencies and the pharmaceutical industry are imposing increasingly stringent quality requirements on pre-fillable syringes in both these functions. Optimised production and inspection processes ensure that the syringes can meet these requirements. Although siliconisation is crucial as lubricant to the proper function of the plunger in the syringe body, it has to be reduced to the minimum in syringes used for innovative biotech drugs. A long-term study investigated the factors that affect break loose and gliding forces in syringes during the injection process. The findings make a valuable contribution to establishing certainty that syringes in auto-injectors, which are often stored for lengthy periods of time, will still reliably administer the required dosage.

1. Pre-fillable Syringes

Pre-fillable syringes are still one of the strongest growth segments in the global primary packaging materials market. In 2015, approximately 3 billion pre-fillable syringes were sold worldwide. Pre-fillable syringes must fulfill the most varied requirements, both as the lowest interaction primary packaging material possible, and on the other hand as a secure delivery system ("drug delivery device"). Special requirements for purity are presented by innovative medications originating from biotechnological research. The classical application areas for medications in pre-fillable syringes (heparin as a thrombosis prophylaxis and vaccines) have today been supplemented by many additional illnesses that can be treated with the help of pre-filled syringes. Ophthalmological applications, the treatment of arthritis, growth hormones, various forms of cancer or applications for neurological conditions – every therapy requires adjustments and further developments that initially seem minor, but have very different syringe designs as a consequence when considered in detail (Fig. 1).



Figure 1

Pre-filled Syringe as Primary Packaging Material

The number of biotechnologically manufactured medications is increasing constantly. Many of these are filled and stored in syringes for the benefit of the user (pre-filled syringes). However, under certain circumstances proteins can react to components of the syringe that are not part of a classic vial. In addition to the packaging material glass (pharmaceutical glass, type I glass in accordance with Ph. Eur.), syringes contain the following "components": silicone oil as a lubricant for the plunger stopper, traces of tungsten from the production process of the glass syringes, stainless steel of the cannulas, as well as the glue used to fix the cannulas. As with the vial, these new sources for leachables and extractables (L&E) are supplemented by the elastomer-based sealing components. In the case of the syringe, one differentiates between halobutyl-based rubber types for plunger stoppers and synthetic isoprene blends for sealing caps (tip caps and, in the case of needle syringes, so-called needle shields, Fig. 2). Other components such as the plunger rod and, e.g., the backstop, are not primary packaging materials, as they have no contact with the product's primary packaging. The pre-filled syringe primarily protects the medication against oxidation and microbial contamination¹. It should interact with the solution or contaminate this with L&E and particles to the least extent possible. This is especially important for the primary packaging of protein-based medications and for ophthalmological applications. In the context of stability studies, pharmaceutical companies are obliged to examine the possible interactions between packaging materials and medication. The drug stability must thereby be ensured until the

expiration of the drug shelf-life.

Actual Syringe Function

End users such as doctors, nursing staff and increasingly patients themselves ("home use") expect and wish that injections can be administered as seldom as possible, meaning at long intervals, as simply as possible and with a minimum of pain. The syringe thus needs to be adapted not only to the medication, but also to the users. This means that pre-fillable syringes are increasingly being integrated into auto-injectors for use at home. Failure-free function, even with highly viscous solutions or low dosages, must thus also be ensured. Protection from needle stick injuries is another aspect that is increasing in importance. In the USA, "needle safety systems" have already been federally regulated to manufacturers since 1999 in the form of the "Needle Stick Safety and Prevention Act". Needle injuries ultimately represent a potential source of infections with life-threatening diseases like hepatitis or HIV for nursing staff. Auto-injectors also offer these properties, but are not normally used in hospitals or by specialist personnel. Most needle safety systems work by a spring-driven mechanism that shields the needle after the injection has been carried out. Packaging material



Figure 2

development departments thus face a variety of challenges in coordinating automatic injectors, needle protection, syringe and medication with one another. In the biotech sector, the 1 ml long needle syringe is the most frequently used format for subcutaneous injections. The current trend toward larger dosage volumes also brings with it an increasing demand for 2.25 ml needle syringes. In ophthalmology, primarily Luer lock types are used, as special cannulas are needed.

More Safety with Backstops

In addition to the needle, the finger

flange is also an element of the syringe of relevance for safety. The exertion of force during an injection increases depending upon the viscosity of the solution. A backstop on the finger flange enlarges the contact area and in this way improves the ergonomics (Fig. 3).



Figure 3

The backstop also functions as a locking element. It prevents accidental leaking of product when pulling back the plunger by stopping the plunger before the end of the syringe body (Fig. 4).

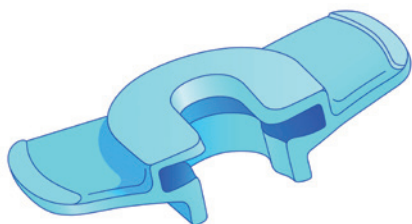


Figure 4

2. Product Quality and Modern Production

Added to this complex situation of the syringe between technical and pharmaceutical requirements are the high standards of pharmaceutical customers with regard to consistent product quality with low reject rates, problem-free processability on the filling lines and a secure, uninterrupted product supply². The required quality therefore requires continuous further development of production processes.

New challenges arise due to the assembly of glass syringes into plastic devices, like in auto-injectors or needle safety systems. Here the important thing is to avoid potential glass breakage with an adapted design of the syringe body and/or of the plastic device.

Camera Technology in Glass-forming

Using high-resolution camera technology, the glass syringes in production today can be checked 100 % for so-called cosmetic defects (like air lines, inclusions, scratches, cracks, particles) (Figs. 5 and 6).

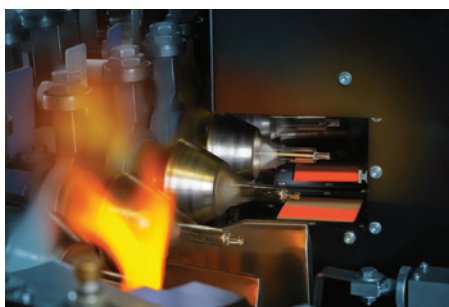


Figure 5



Figure 6

The dimensional accuracy of the syringe body from the cone over the shoulder and the syringe body to the finger flange is also controlled. Several cameras are used on a production line to record and differentiate the individual defects. The technology is so sophisticated in high resolution that individual defect types can be differentiated. This makes it possible to define and check customer-specific product properties. Depending upon the application, narrower dimensional requirements are important, e.g., for use in auto-injectors, while Japanese customers attach extremely great importance to minimising cosmetic defects. The exact shoulder and cone shape in combination with precise positioning of the graduation supported by the camera technology also enables unprecedented precision when emptying

the syringes. This is especially decisive for smaller filling volumes. The newest camera technology allows for 360° inspection, which significantly improves the quality control of the manufactured syringes.

Cleanrooms and RTF® Production

Following the forming of the syringe, the needles are glued in at the so-called "cold end" of production in the cleanroom (so-called staked-in needle syringes). Further steps and packaging then take place in the ready-to-fill (RTF®) process. The RTF process consists of washing, siliconisation and positioning of the tip cap or needle shield with subsequent packaging in the nest and tub (Fig. 7).



Figure 7

Following ethylene oxide (EO) sterilisation, the product is "ready-to-fill", meaning that the syringes can be filled at the pharmaceutical or biotech company directly without additional process steps. Syringe processing, of course, takes place in appropriately classified cleanrooms. Like modern glass-forming lines, modern assembly lines also avoid defect-prone glass-to-glass or glass-to-metal contact; optimised washing and siliconisation processes ensure the observance of increasingly strict regulatory requirements. After being put into pouches, the syringes are transported into a cleanroom ISO class 8 for end packaging in polypropylene (PP) boxes and final EO gas sterilisation.

3. Application Examples from Ophthalmology

Another therapeutic area in which pre-fillable syringes have made drug delivery more user-friendly and decreased risk is ophthalmology. The syringes are primarily used here for cataract operations in the anterior eye area and for the treatment of wet macular degeneration inside the eye. In the case of cataract operations, the injection of viscous hyaluronic acid prevents the collapse of the anterior

chamber and simplifies the insertion of artificial intraocular lenses. In the case of macular diseases, monoclonal antibodies (mAbs) injected into the vitreous body can inhibit the adverse growth of blood vessels and in this way maintain the sight of the patient. Both therapies are very different, although the eye is treated in both cases. The hyaluronic acids used for cataract operations are highly viscous, but are not especially sensitive to potential chemical interactions. RTF syringes can be equipped with backstops for enlarging the finger contact area for the injection. Luer lock syringes enabling free choice of needles are commonly used (Fig. 8a). Conversely, the monoclonal antibodies (mAbs) used for the therapy of retina removal are biotechnologically manufactured. In ophthalmology they are injected with fine needles repeatedly

thus very important, as this can be seen by the optometrist during the operation and be recognised as contamination ("droplets"). The droplets may also accumulate in the vitreous humour and possibly cause "seeing spots" with extended therapy. This phenomenon is harmless but bothersome. The use of heat-cured siliconised syringes is therefore recommended for critical application areas like ophthalmology, or for several silicone oil-sensitive³, biotechnologically manufactured formulations. These syringes, also known as baked-on RTF syringes, are not spray siliconised with pure silicone oil, but are instead sprayed with a silicone oil-water emulsion, which is baked onto the glass matrix surface using a dedicated oven at several hundred degrees [°C]. In the process, solid bonds between the glass matrix and the polydimethylsiloxane chains are formed, which results in a permanent, hydrophobic anti-friction coating. The number of free droplets later found in the filled syringes thereby decreases by about 90 % in comparison to conventional spray siliconisation (Fig. 9).

contamination⁵. By washing the syringe immediately following the forming of the cone and by using alternative forming pin materials, tungsten residue can already be reduced to an extent specified by the customer during production of the glass syringes, or even entirely avoided. Staked-in needle syringe bodies are generally less burdened with tungsten residue, as the UV-hardened glue seals the sensitive syringe area in addition to the even comparatively small bore diameter. There is no officially prescribed limit value for tungsten yet, but many syringe manufacturers have specified their own internal tungsten limits.

$$F = 8 Q \mu L / \pi R^4 * A$$

F = Frictionless travel force L = Needle length
 Q = Volumetric flow rate R = Needle inner diameter
 μ = Fluid viscosity A = Cross section area of syringe plunger

Figure 10

6. Alternatives to Glass Syringes

Although glass remains widely used as primary packaging for parenterals, cyclical olefins are increasingly asserting themselves as an alternative packaging material for pre-fillable syringes. Cyclical olefins (cyclo olefin polymer: COP, cyclo olefin copolymer: COC) are as clear as glass, but considerably less prone to breakage. The L&E profile of the material is very favourable. Containers can be produced extremely precisely on fully-automated lines by injection moulding. There are no potential tungsten or glue contaminants. There is no release of metal ions or an increase in the pH value of the solution due to hydrolysed sodium, a phenomenon especially known from glass vials. COP plastic syringes are exceptionally well-suited for the packaging of biotechnological, cytotoxic and/or viscous medications (Fig. 11).



Figure 11

Cataract surgery

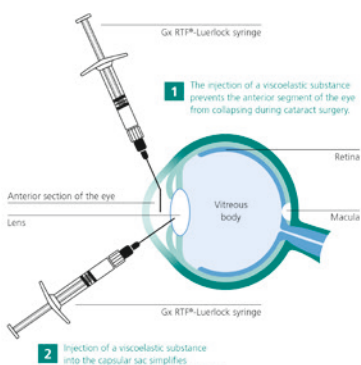


Figure 8a

Injection into the vitreous body

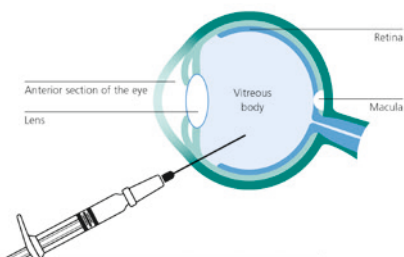


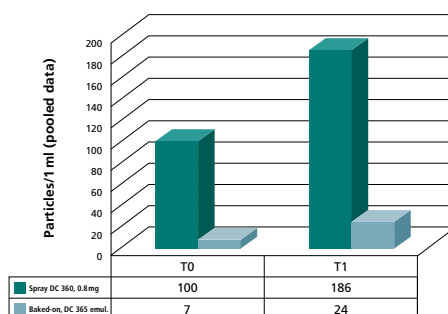
Figure 8b

at intervals of several weeks directly into the interior of the eye (Fig. 8b). In these cases low dosage volume requires highly precise syringe dimensions and scaling. Both treatment areas are subject to strict requirements with regard to the allowed particle load.

4. Baked-on Siliconisation for Special Cases

The reduction of free silicone oil (sub-visible particles) in the drug solution is

Figure 9



Baked-on siliconised syringes are thus also highly suitable as packaging materials for solutions sensitive to silicone oil⁴. First concepts of a completely silicone oil-free glass syringe exist but are not commercialised in glass syringes yet.

5. What is Tungsten Doing in the Syringe?

Apart from silicone oil, additional substances can interact with the active ingredient or formulation components. For example, a tungsten pin is used to create the syringe bore (Fig. 10). When traces of tungsten or tungsten oxides remain in the bore area, protein-based medications can react sensitively in rare cases. For example, protein aggregates were found under particular circumstances in pre-filled syringes that can be traced back to tungsten

7. Syringe Functionality

In order for a syringe to function optimally, the interplay of syringe body and plunger must be coordinated. Criteria here are the so-called break loose force that needs to be overcome upon commencement of emptying the syringe, and the gliding force exercised via the plunger rod during the injection itself. Important are simple and safe operation, complete emptying and precise dosage. Typical for the activation of a syringe are two phases with differing force progressions on the final break loose and gliding behaviour.

Typical curve for empty syringes

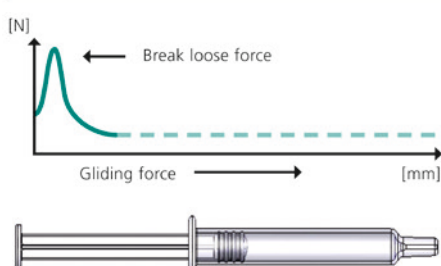


Figure 12

Siliconisation of syringe bodies and plungers

Pre-fillable glass syringes are either siliconised inside with pure silicone oil as described or subjected to baked-on siliconisation. Both procedures result in differing gliding properties of the plunger stopper, as the quantity, distribution and type of the silicone oil have a great influence here. In the case of spray siliconisation, the quantity and the distribution profile of the oil in the syringe can also be varied⁶. The system is completed by plunger stoppers from various manufacturers, which in turn consist of various rubber formulations (bromobutyl or chlorobutyl rubber), have different respective dimensions, are for the most part also siliconised (differing quantities and processes) or have been treated with a special coating of fluoropolymers.

Setting the plunger

The syringe diameter and the way in which the plunger stopper is brought into the syringe influence the behaviour when emptying a syringe. The manufacturers of filling machinery offer two plunger stopper placement techniques here: The plunger can be placed in the filled syringe by means of a vented tube. To this purpose the rubber stopper must be briefly compressed in a tube and

positioned at the correct position in the syringe. When the tube is pulled out, a rod fixes the plunger at the desired position. This procedure results in slight mechanical stress on the plunger. The alternative vacuum placement method generates a vacuum within the interior of the syringe and hence pulls the plunger stopper inside the barrel until it is just above the surface of the liquid. The plunger thus moves a distance along the interior surface of the glass. The choice of either method has a varying influence on the final break loose and gliding behaviour.

Influences of storage

An important aspect for pre-filled syringes is of course their long-term performance. The pre-filled syringe has to remain fully functional even after several years of storage. Storage can influence the performance of the syringe system and is, among other factors, dependent upon the filling material and the temperature. Various time points as well as different plunger stoppers show varying results here.

Other aspects

Manufacturers of pre-fillable syringes provide an intermediate product for pharmaceutical companies and are thus not responsible for the final functional properties of the filled syringe. The break loose and gliding forces of empty syringes are therefore collected as a base measurement. However, their significance with regard to the subsequent behaviour of the filled syringes is limited. Product viscosity, needle length, interior diameter of the needle and diameter of the plunger stopper also have a significant influence here (Fig. 13).

$$F = 8 Q \mu L / \pi R^4 * A$$

F = Frictionless travel force	L = Needle length
Q = Volumetric flow rate	R = Needle inner diameter
μ = Fluid viscosity	A = Cross section area of syringe plunger

Figure 13

With the help of special thin-wall cannulas, highly viscous liquids can also be injected using larger interior diameters. These relationships are expressed with the Hagen-Poiseuille formula and are recorded under the keyword "syringeability"⁷.

8. Gliding Force Study

The understanding of the syringe as an injection system is of great importance for manufacturers and users of syringes. A long-term study from 2011 to 2015 therefore examined how parameters named above influence the break loose and gliding forces, and what the decisive criteria for simple and problem-free usage are. The syringes were tested empty or filled with water for injection (WFI) and equipped with various plunger stoppers. In the process, only needle syringes with the most frequently used cannulas with 25 G, 5/8" and 27 G, 1/2" diameters or lengths were used. The syringes were subsequently emptied on a force measurement device at various points in time and the corresponding force curves were noted. The measurement data from approximately 20,000 syringes collected over the course of the study enable an optimised selection of suitable syringe components. Study parameters:

Syringe shape:

1 ml short, 25 G needle, 5/8"
1 ml long, 27 G needle, 1/2"

Siliconisation process:

RTF spray siliconisation with pure silicone oil (0.8 mg per syringe)
RTF baked-on siliconisation with silicone emulsion

Filling material:

Empty
Water for injection

Plunger assembly:

Vacuum stoppering
Vent tube stoppering

Plunger:

Manufacturer
Shape
Material
Coating
Siliconisation

Storage period:

0, 3, 6, 12, 24, 36 months at room temperature
Accelerated aging 3, 6 months at increased room temperature and air humidity (40 °C, 75 % rH).

Results of Gliding Force Study

Most syringes function throughout the entire testing period, but some demonstrate peculiar features and are therefore not suited for all applications. A properly functioning system is shown in Fig. 14.

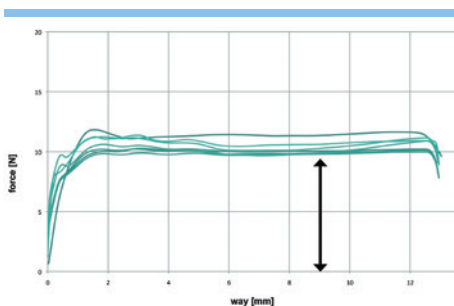


Figure 14

Several force-deflection graphs of sub-optimal systems are described as examples in the following:

- Extremely high breakaway forces and a strong drop of the breakaway to the gliding force can cause considerable problems for the syringe user when the syringe suddenly empties rapidly after initial high pressure. Here it is conceivable that the syringe content might be lost or that the patient might suffer pain during the injection (Fig. 15a).

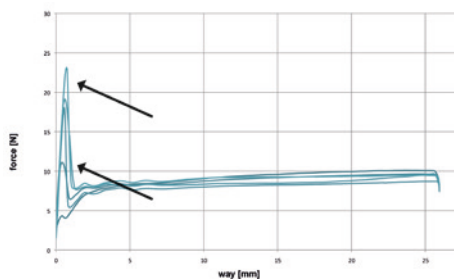


Figure 15a

- The parallel samples should demonstrate the lowest possible fluctuations with reference to one another. Figure 15b

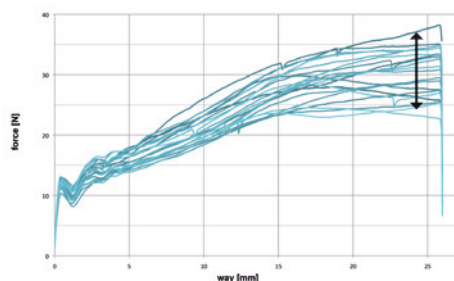


Figure 15b

shows an unfavourable example.

- Also unsuitable are combinations of syringe and plunger stopper with which the gliding force rapidly increases between the beginning and the end of the injection. It may be possible that the complete dosage will not be administered

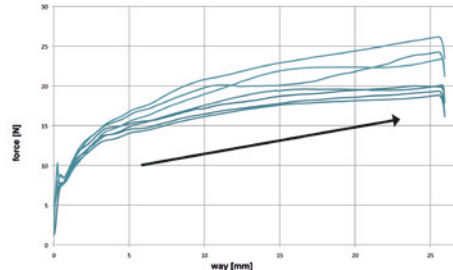


Figure 15c

if the required force increases when pressing out (Fig. 15c).

- Even an excessive increase of the forces in the course of the storage period is critical, as this has a negative effect on reliability for the user. Syringes with high variability would not function with auto-injectors.

Summary

The results of the study contribute to providing a clearer picture of the influence factors of decisive importance for syringe function. A series of hypotheses could be confirmed, and others were revised. When designing the study it could be confirmed that the accelerated storage of syringes at an increased ambient temperature and air humidity is a reliable instrument for measuring the effects of storage in an accelerated process.

- The advantage of baked-on as opposed to spray siliconisation brings a considerable reduction of the free silicone oil in the solution, whereas the gliding forces are slightly higher than with spray siliconisation.
- The assumption that the break loose forces for syringes with spray siliconisation increase more during storage than for syringes with baked-on siliconisation could not be generally confirmed for all plungers.
- The influence of the storage duration on break loose and gliding forces is generally rather moderate.
- In contrast, the plunger stopper is of decisive importance. Here the selection of its shape, the material, the coating and the siliconisation have a considerable influence on the ultimate functional capability of the syringe.
- The matter of whether the plunger stopper was assembled using vacuum or vent tube stoppering only had significant effects for some plunger stopper types.

The choice of the right syringe is as important for a successful therapy as the medication itself. Only reliable syringe systems lead to acceptance and trust with medical specialists and to increased compliance among patients.

9. Outlook

There will most likely never be an all-purpose solution for pre-fillable syringes. Thanks to the available range of syringe sizes, types and materials, of graduations, plunger stopper shapes and rubber formulations, as well as siliconisation processes and needle types, there is instead a comprehensive kit available, from which specific solutions can be compiled or modified for the respective application area. For subcutaneous delivery, a highly viscous biotechnological medication in an auto-injector involves other requirements of the syringe than does an aqueous solution that is administered once annually in the form of a vaccination. With manual administering of injections, medical specialists or patients can react unconsciously to fluctuating force requirements. The case is different for the use of pre-fillable syringes in auto-injectors, which play an increasingly important role in the treatment of chronic illnesses. In this case, the available forces are defined by the spring force. The siliconisation of the syringe must therefore be set in such a way that complete emptying of the syringe is reliably ensured with these forces, even after longer storage. An interior diameter of the needle used that is adapted to the viscosity is also important for the period of administering (around 10 s is usually desirable). It is thereby expected of the syringe manufacturer to understand the needs of his customers and work closely together with the pharmaceutical customer during product development. Increasingly individualised medicine, the increasing importance of innovative medications and the increasingly frequent usage of automatic injectors will in future further increase the trend toward highly developed, pre-fillable syringes.

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