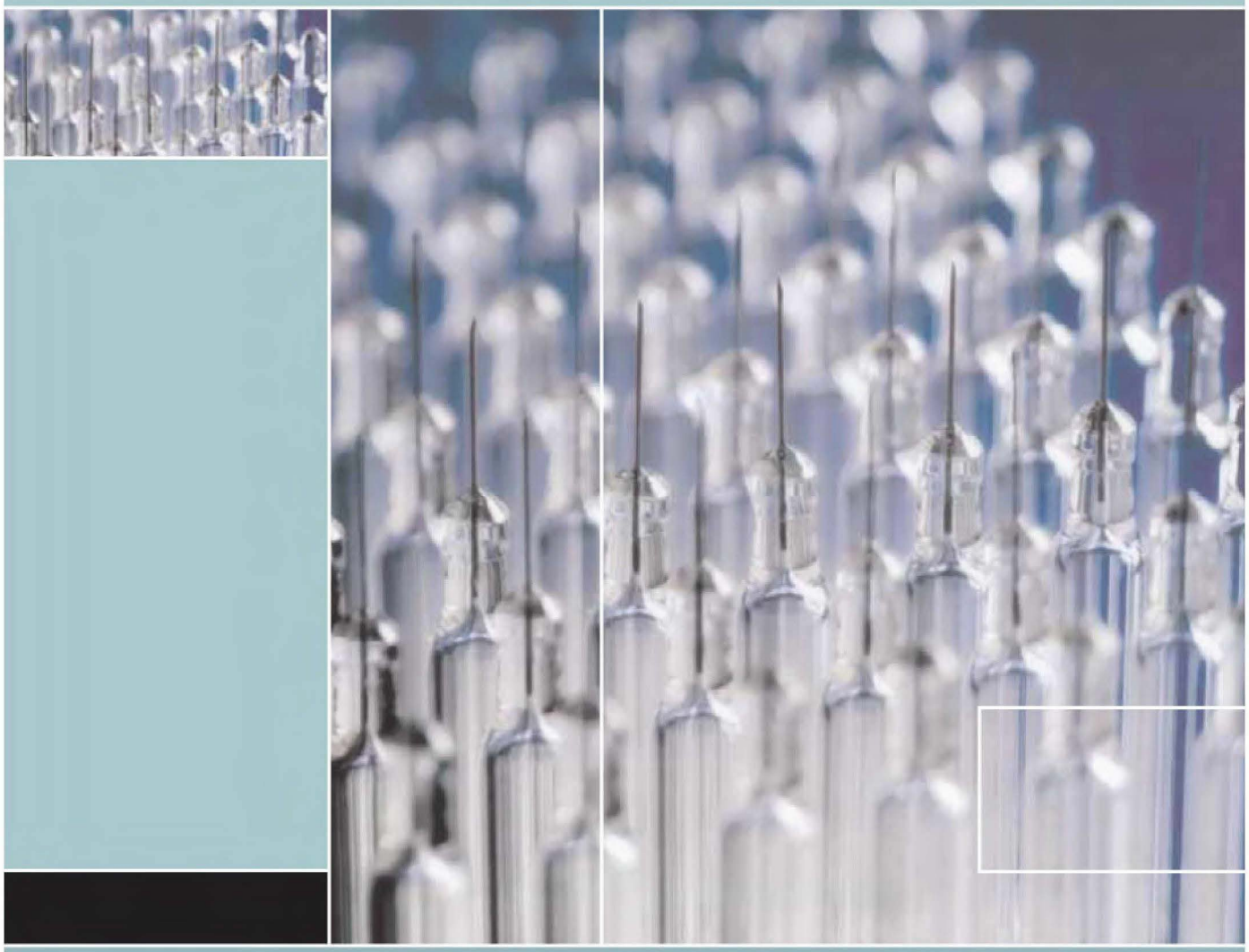
PREFILLED SYRINGES

INNOVATIONS THAT MEET THE GROWING DEMAND



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"Prefilled syringes: innovations that meet the growing demand"

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Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

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PREFILLED SYRINGES:

WHY NEW DEVELOPMENTS ARE IMPORTANT IN INJECTABLE DELIVERY TODAY

Within the almost $100 billion injectables market, one such injection format – the prefilled syringe – is becoming increasingly popular. But, as prefilled syringe manufacturers and fillers are required to deal with an ever-growing number of new types of compounds in new therapeutic classes, they encounter new obstacles, and must devise methods of overcoming them. In this piece, Dr Thomas Brachtendorf and Mathias Romacker, Directors of Business Development at Buender Glas (a division of Gerresheimer pharmaSystems), outline some of the advances and innovations that have enabled the prefilled syringes sector to keep ahead of rapid changes and growing demand.

Some view the injectables market as the traditional, more conventional side of drug delivery. As such, they do not tend to associate it with the level of cutting-edge science and technology that is readily linked with other delivery methods, such as advanced inhalers.

In reality though, the experience of anyone close to the injectables sector would lead them to take a quite different view. The number of injectable products is rocketing – not least because injection is currently the only viable way of delivering many of them. As a consequence, demand for technologies that improve the production, administration, and the experience of receiving injectable products, is strong.

The first products presented in prefilled-syringes were heparins, launched in Europe by Sanofi and Rhône Poulenc-Rorer in the early 1980s. At that time, the prefilled-syringes market was viewed as a relatively insignificant niche area within the huge injectables market. Therapeutically, prefilled syringes were limited to a narrow range of applications in a few vaccines and anticoagulant products. Their use was also limited geographically to Europe.

Initial interest, during the 1980s and 1990s, was sparked primarily by the clear advantages prefilled syringes have over traditional vials and ampoules. The procedure for using a prefilled-syringe product often involves nothing more than removing the syringe from the packaging and injecting the formulation. In contrast, anyone administering a traditional injection from a vial might typically have to: read the required dose from the physician's dosing directions, withdraw from the vial slightly more formulation than is required, invert the syringe to allow any air bubbles to reach the top, depress the plunger slightly to expel any air and, finally, depress the plunger slightly further still to leave precisely the required dose, which they measure using the scale along the syringe barrel.

Prefilled syringes, with their single-use, disposable format, together with the fact that they eliminate several of the procedures required prior to administering a formulation presented in a vial, are significantly quicker and more convenient. Ease of use, in addition to simply making them more convenient, means that prefilled syringes are safer.

The major safety benefit is the reduced likelihood of dosing errors – which can occur at each of the steps in the vial/ampoule procedure. The fixed dose in a prefilled syringe is filled mechanically and is checked electronically during quality control.

As well as reducing errors in the dose quantity, prefilled syringes reduce the risk of administering the wrong product because the syringe and packaging are clearly labelled with the drug name. For syringes filled at the point of administration, there is a period – between filling and giving the dose – when the syringe can be left full of drug but completely unmarked, on a tray ready to use. This is a danger period since the identity of the drug in the syringe is typically known only to

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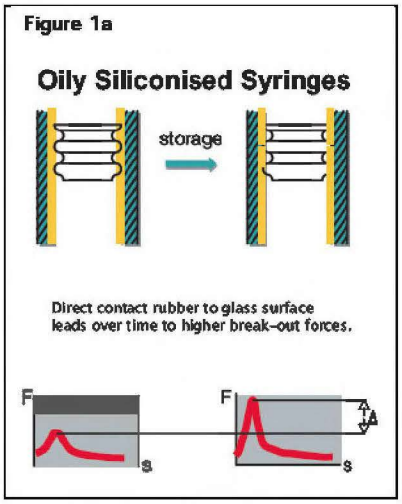

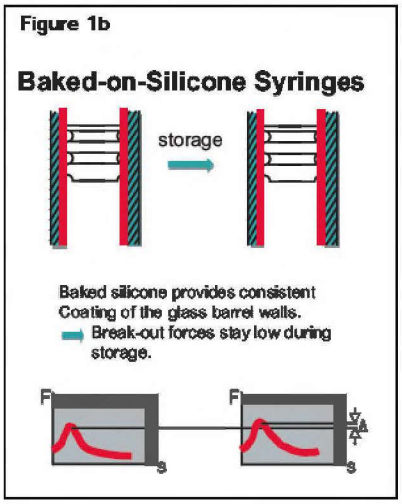

Figures 1a and 1b: the break loose effect

the person who filled it and the information only exists in the memory of that person. If they are distracted during the danger period, or are perhaps called away to an emergency and have to hand over to another person the job of giving the injection, there is a real risk of a mistake occurring.

Another safety benefit is the reduced risk of needle-stick injury. Accidents are more likely with traditional formats because the user is required to expose the needle tip for longer, while performing a series of actions requiring dexterity and concentration. The fact that prefilled syringes are single-use devices also eliminates the possibility of cross-infection arising from needle re-use.

Prefilled syringes contain the precise amount of drug that is to be injected, but vials and ampoules have to contain more liquid than the actual dose in order for the correct amount to be withdrawn. The excess formulation is wasted and, especially with expensive biotech products, elimination of wastage allows the manufacturer to make significant cost savings

As demand increased, and the range of viable applications of prefilled syringes broadened, the market began to grow. Notably, the US market, with its shorter history of prefilled syringes, was particularly keen on the advantages this format gave, to the extent that it is now exclusively an RTF syringe market.

The emergence of biotechnology drugs in the early 1990s gave demand for prefilled syringes a colossal boost worldwide and this product class today still represents the highest potential for future growth. In Europe, new drugs that have been presented in prefilled syringes include: erythropoietins such as Recormon and Eprex; interferons like Betaferon, Avonex, Copaxone and Rebif; and rheumatoid arthritis drugs like Enbrel and Humira, to name just a few.

Crucially, biotech provided a late but very profound entry into the previously untapped US market, where many of the aforementioned products, and many other biotech products, were developed and launched first – often in prefilled syringes.

RECENT INNOVATIONS

The continually increasing demand for prefilled syringes has maintained pressure on manufacturers to devise methods for increasing production capacity and driving down costs. Alongside these ongoing advances, which focus on improving the overall efficiency of the production process, recent trends in the industry, and in the healthcare environment generally, have given rise to several specific innovations that improve the quality of prefilled syringes.

Like many manufacturers, Buender Glas has experienced a rapid expansion in the number of therapeutic classes its prefilled syringe products must serve, and foresees a continuation of this trend. Its novel technologies broaden the range of products that can be presented in prefilled syringes and, crucially, increase the acceptability of prefilled syringes among the patients and medical professionals that use them.

BAKED-ON SILICONE

Among the most important innovations are those that have overcome the compatibility and stability issues that arise when dealing with biotechnology formulations. One particularly common problem has been that such products can react with the oily form of silicone, which is used as a lubricant to coat the sliding components of the syringe.

The propensity for silicone to react with the formulation is dependent on the concentration of silicone in the syringe and its chemical activity. The latter is determined by the number of terminal hydroxyl groups, which is greater the shorter the silicone polymer chain length..

Baking-on the silicone – which involves heating the silicone-coated syringe to a specific temperature for an appropriate time – results in longer chains that are more closely adhered to the surfaces they coat. Thus the concentration of silicone in the syringe and its chemical reactivity are both reduced and the product's stability is increased.

The second benefit of baked-on silicone is that it reduces the frequency of the "break loose" effect. The effect can occur during storage when the rubber closure, inside the syringe barrel, expands outwards so that eventually it displaces the low-friction silicone coating and comes into direct contact with the inner glass surface (see figure 1a).

The user cannot detect the problem until the point of administration when they try to depress the plunger. Because the rubber closure is essentially stuck to the inside surface of the syringe, a high initial force is needed to shift it. The needle has already penetrated the patient's skin and the tip is positioned in their tissue at this point, so the lack of control as the extra force is applied, and the potential for a sudden movement as the rubber closure is freed up, is clearly undesirable.

As shown in figure 1b, baked-on silicone provides a more consistent coating of the syringe walls, which prevents the expanding rubber closure from touching the glass wall. Lubrication is maintained so that the initial force required to inject using prefilled syringes with baked-on silicone remains consistently low before and after storage.

Syringes with staked-in needles have yet another advantage from the baked-on siliconisation process. Until now, baked-on silicone was not available with staked-in needle syringes since a needle could not be glued into the channel of a syringe after baking process or the baking process itself would soften the glue in the channel, resulting in a bad fixation of the needle.

The key to producing staked-in needle syringes with baked-on silicone lies in the inactivation of silicone located in the channel where the needle will be glued in. For this purpose Buender Glas had developed a patented process.

AVOIDING PH CHANGES

Another challenge has been to prevent the undesirable pH change that sometimes occurs in liquids stored in prefilled syringes. It has been observed in solvent syringes containing water for injection (WFI) or saline solution, in diluent prefilled syringes, which contain WFI for reconstituting lyophilised products, and in syringes con-

taining non-buffered drug solutions. For WFI, the upper pH limit specified in the USP is 7.

The shift in pH occurs because the USP Type 1 glass used in prefilled syringe manufacture is a borosilicate glass, which must be subjected to various temperature changes during the glass tube production process (see Figure 2). Around the beginning of the cooling phase, at 580 C, sodium oxide forms and remains in the glass. During storage, sodium ions are released into the WFI and, as shown in figure 3, increase the concentration of hydroxide ions, thus increasing alkalinity

Sodium oxide is transported during the tempering process to the surface of the syringe glass barrel. Over time, the ions on the inside of the syringe are released into the WFI. This results finally in an increase of the concentration of hydroxide ions, yielding a change in the pH.

Buender Glas has developed an ammonium sulfate pre-treatment process that solves this problem. Ammonium sulphate is sprayed into the glass barrel before the tempering process of the formed syringe is started. During the following heating process, the formed sodium oxide reacts with the ammonium sulphate by forming highly soluble sodium sulphate plus water and ammonia.

A study compared the pH increase in bi-distilled water in an untreated glass syringe with that of water in an ammonium sulfate treated syringe. After being heated to 121 C for one hour, the pH of the water in the untreated syringe increased from 5.5 to 6.6 while the pH of the liquid inside the treated syringe increased from 5.5 to 5 9. This effect was checked in stability studies and long-term data is expected soon.

INCREASING FOCUS ON THE PATIENT

The general trend in the wider healthcare sector, increasingly to place the patient more at the centre of treatment strategies, rather than focusing purely on their disease, is having a considerable impact on the prefilled syringes sector and prompting new thinking.

The requirement from consumers for more convenient treatments is one of the factors driving the prefilled syringe market en masse. However, this demand for convenience also gives companies within the sector an opportunity to differentiate themselves.

Uppermost in the thoughts of many patients receiving injections are pain and discomfort. The needle is clearly the main component that determines how pleasant or unpleasant a patient finds the injection. Buender Glas has identified three parameter sets that exert the greatest influence.

The first are the basic needle-quality characteristics, such as the requirement for a hook-free needle tip and smooth surfaces. These are achieved through a validated, reliable production process. Secondly, there are less critical, subtler factors such as the number of bevels at the needle tip, the angle of the bevels and the bevel length. Thirdly, the coating substance and method of application, for example siliconisation, have been recognised as key in determining the pain of injection.

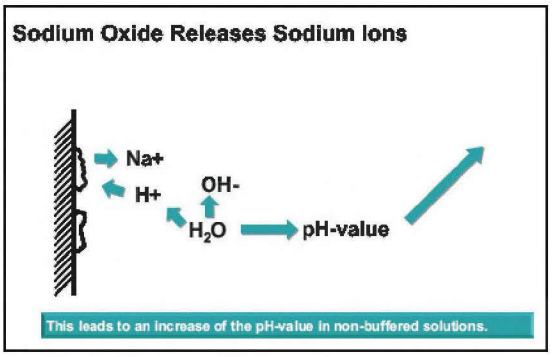

Figure 2: pH shift in all-glass syringes

The increase in the number of prefilled syringes being used to self-inject, often at home, is in part a reflection of the trend towards more patient-centred treatments, but equally due to the application of prefilled syringes in new indications, such as rheumatoid arthritis and multiple sclerosis.

Prefilled syringe manufacturers are developing design features that take into account that in diseases such as these, the self-injecting patient is likely to be physically impaired in terms of the force they can apply and their degree of manual control. Relatively simple, though important, new features include a larger finger flange on the syringe barrel and a larger thumb plate on the plunger, to make the device easier to handle.

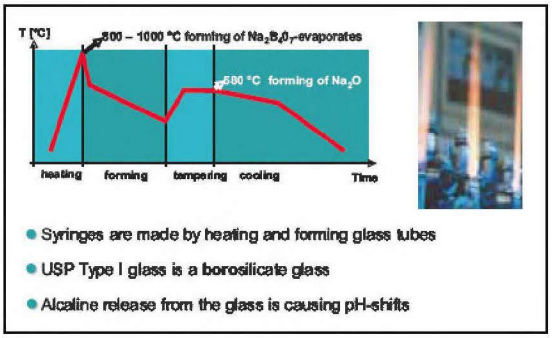

Figure 3: Sodium oxide releases sodium ions

LONG-TERM VIEW

Looking ahead, the continual progress towards ever cheaper and quicker production processes, which has been underway from the first days of prefilled syringe manufacture, will no doubt continue in the background.

One specific development predicted in the coming years is an increased interest in the use of plastics, instead of glass, for the syringe body. Plastic is already widely used in syringes, but its application has hitherto been limited to large-volume (20-50 ml) syringes for delivering contrast media, for example.

For smaller volume syringes (0.5-2.0 ml) glass is the material of choice. However, prefilled syringe manufacturers are investigating the potential of plastic in their products perhaps for use in certain niche areas yet to be identified. Buender Glas, for example, has a plastic product ready for initial testing.

Finally, the predictions made in the 1990s that invasive drug delivery was nearing its end were clearly somewhat premature. However, those involved in the production of invasive delivery systems such as prefilled syringes are perhaps mindful that, one day, the predictions are likely to be fulfilled. Like its peers, Buender Glas is forging links and building expertise outside prefilled syringes. Indeed, specific applications of its core technologies in the areas of needle-free injection and nasal delivery are already being explored internally and with partners.

CONCLUSION

The examples of innovations given above are just a few among many new technologies and processes that have been adopted in prefilled syringe production. Others involve, for example, increasing further the sterility of the finished product and decreasing the number of particulates found in the formulation; optimising the design, composition and coatings for elastomeric components such as plungers and needle shields; and even ingenious advanced labelling technologies, including peel-off tabs and radio frequency transmitters, to increase product safety and security.

The need for prefilled syringe producers to innovate and make real breakthroughs has never been greater than in recent years. With the market for prefilled syringes estimated to have grown by more than 20% annually in the US since 1999, to reach its current size of $200 million, and by around 8% annually in Europe to reach $1 billion, we appear to be rising to the challenge.