

Pushing the Boundaries of Needle-free Injection

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Dr Simon Bennett has over 16 years' experience in life sciences in three successful start-up companies, including business development director roles at Solexa, a public company pioneering novel systems for genomics, and Oxagen, where he established and led the Women's Health Programme. Dr Bennett has a degree in Biology from the University of London, a DPhil from the University of Oxford and is the co-author of over 100 scientific articles and four patent applications. He has been involved in over 40 commercial deals and has also played a pivotal role in several venture capital led funding rounds.



Dr Charles Potter is the inventor of the Glide technology and founder and CEO of Glide Pharma. He holds an engineering degree and PhD from Cambridge University. Dr Potter spent six years undertaking research within the Transplant Unit at Papworth Hospital, Cambridge, UK, a specialist cardiothoracic centre, where he gained extensive medical experience. He has worked in four other successful start-up companies, including nearly six years at PowderJect Pharmaceuticals where he saw the company grow from just five employees to over 1000.

Introduction

Many medicines cannot be taken orally because the structure and chemistry of the digestive system makes it difficult and, in some cases impossible, for these drugs to enter the bloodstream. For these, a range of alternative routes for administration exists, including topical (skin, nose, lung, nail and other mucosal membranes), transdermal patches, sprays, gels and ointments, as well as injections. Methods of delivering drugs across the skin such as transdermal patches, creams and lotions have been on the market for many years but are limited in the number of drugs for which these are suitable due to the size of molecule that can pass passively across the skin. Various alternative approaches are being developed that involve transient alteration of the structure of the *stratum corneum* of skin using chemicals, ultrasound or electric currents, thus allowing temporary entry of the drug (Singh, 2005). Where the typical oral route is not an option, or where quick release of the drug or vaccine is essential, injection remains a very common administration route. To undertake an injection, the drug or vaccine can be formulated in either a liquid or a solid dosage form. These drugs or vaccines can be injected with devices that either incorporate a needle or which are needle-free.

Needle-based Delivery Systems

The best known and most common method of injecting drugs in solution through the skin is to use a standard needle and syringe. Alternative formats for this technology include auto-injectors, to enable users to self-administer with a spring powered device, and safety needles which

have been developed to try and prevent needle-stick injuries, such as those being developed by **BD Medical-Pharmaceutical Systems**, **King Pharmaceuticals** and **Ypsomed**. Recent legislation in the US has meant that safety needles are being used more routinely in healthcare. While it is not a requirement that pharmaceutical companies must deliver their injectable products with safety needle devices, there is a clear move towards alternative approaches, for example using needle-free systems, as a value-added feature in product life-cycle management.

Some pharmaceutical products are manufactured as solid implants. This is normally to provide a slow release formulation for the therapeutic agent over a period of weeks or even months. Examples include female contraceptives, such as Implanon® marketed by **Organon**, treatment of prostate cancer, such as Zoladex® from **AstraZeneca**, and drugs to control opiate addiction, such as that being developed by **Titan Pharmaceuticals**. These implants are currently inserted during a surgical procedure or are delivered through a wide bore needle into the skin. The procedure is slow and uncomfortable and often involves revisiting the clinic to have the implant removed, and so these systems have not received widespread use other than for very specific applications.

Needle-free Injections

Needle-free injection technology has been in development for over 150 years. H. Galante et Compagnie of Paris manufactured a device that was presented to the Imperial Academy of Medicine by A. Béclard in December 1866. Similar devices, best described as jet injectors,

were instrumental in vaccinating very large numbers of individuals after World War II. But it has been only in the past 20 years or so that we have seen major technological advances as the need for needle-free drug delivery has become more widely recognised. Yet, despite a lot of investment in research and development, the promise of needle-free injection technologies remains to be fully realised.

The benefits of needle-free injections are obvious. People on the whole do not like needles; 10% of the population are pathologically scared of needles. Needle stick injuries are painful and, importantly, increase the risk of spreading blood-borne infections. Also, disposing of used needles is burdensome and expensive. Furthermore, the need to use needles and syringes means that some drugs – other than life-dependent medicines such as insulin – are less likely to be self-injected. Having to have a medical practitioner, rather than the patient, administer an injectable drug further increases the workload on local healthcare services. Moreover, because many people are reluctant to use needles, treatment is often delayed or ignored. Invariably, the condition worsens, with the consequential impact on both the patient and the healthcare system. That all said, compared with needle-free alternatives to date, in many circumstances reduced costs, convenience and reliability of administration have contributed to the fact that the traditional needle and syringe has been a hard habit to break. With an increasing number of biopharmaceutical drugs and vaccines that cannot be delivered orally and, with the introduction of stricter regulations – particularly in the US – to avoid the needle-stick injuries, the need for safe, reliable, yet cost-effective alternatives to the traditional needle and syringe is set to rise.

Needle-free Delivery of Liquids

Needle-free injectors have the obvious advantages that they avoid those issues relating to needle phobia, needle disposal and the potential for cross contamination of blood-borne diseases. Probably the most well-known needle-free technologies involve liquid jet injection. Liquid jet injector technology was first developed many decades ago and yet it is still not widely used although there are products based on some of these technologies on the market (Ajmani, 2006; Dubin, 2006; Sinha *et al.*, 2005). One of the main attributes of the liquid jet injectors is that these use the drug in a liquid form which therefore does not typically require re-formulation from standard needle and syringe formats. Space does not permit a description of all the needle-free, liquid jet injector technologies that are currently available or in development. Some of the major companies include **Antares**, **BioJect**, **BioValve Technologies**, **CrossJect Medical Technology**, **Injex** (formerly **Equidyne**), **PenJet** and **Zogenix** (formerly **Aradigm**).

The jet injectors have been developed as both single-use devices and multi-use systems. All require a power source that provides a very high peak pressure behind the liquid

in order that it can 'drill' a hole in the skin, without the use of a needle, followed by a reduced pressure profile to force the rest of the liquid into the skin. This requires careful control over the power source to ensure accurate and reliable delivery of the drug to different skin types or even different skin locations on the same person. A variety of power sources has been developed for these liquid jet injectors, including:

- **Springs** (e.g. *VitaJect* and *BioJector 2000* from BioJect, *AdvantaJet* from Activa Systems, *MediJect VISION* from Antares, *Injex 30* from Injex-Equidyne and *Mhi-500* from Medical House Products *MediJect VALEO* from Antares and *LectraJet* from DCJI)
- **Compressed gas** (e.g. *IntraJect* that was recently acquired from Aradigm by Zogenix and *Iject* from BioJect)
- **Controlled chemical reactions** (e.g. *CrossJect* from CrossJect)

The requirement for control is one of the main reasons why the liquid jet injectors are not more commonly used today. Furthermore, some of these power sources have cost implications that are not insignificant, and thus, for some applications and scenarios, the cost to benefit ratio is difficult to argue.

Needle-free Delivery of Solid Formulations

As well as the obvious advantages for liquid formulations, such as needle phobia etc. described above, delivering the drug or vaccine in a solid dosage form has the additional advantages that the therapeutic agent will typically be more stable and may not require cold chain storage. In addition, a solid formulation presents the opportunity to combine fast-acting and delayed-release forms such as for vaccines so that the 'prime' and 'boost' shots can be given together in a single administration.

PowderJect developed one of the better known needle-free technologies for the delivery of solid formulations. The PowderJect technology was invented in 1993. The technology fires powders at supersonic velocities into the outer layers of the skin using a helium powered device. In use, the device is held against the skin and when the helium micro-cylinder is actuated, the pressurised gas entrains the drug particles and accelerates them to a sufficient velocity such that they are able to penetrate the skin. This technology is in development by **Corgentech** to deliver a local anaesthetic agent and by **PowderMed**, which it was announced will soon be acquired by Pfizer, for the delivery of DNA vaccines on gold carrier particles.

In general, the systems that fire the drugs into the skin at high velocity are more complex than those that push the drug into the skin and therefore these tend to be more expensive. Furthermore, as human skin varies across different ages, races and even between different parts of an individual it is also difficult to fix a velocity that will work accurately and reliably for all patients.

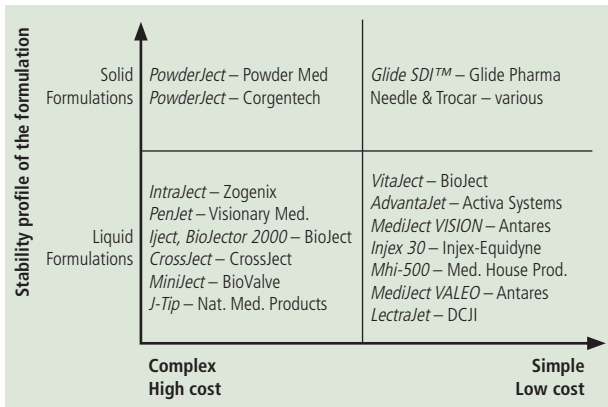


Figure 1 – The Competitive Landscape of Needle-Free Injectors. A number of technologies exist that deliver liquid formulations. Few exist that are capable of delivering solid formulations. Needle and trocar are simple but involve a surgical procedure that can be uncomfortable. Only the Glide SDI™ combines the benefits of solid dose with a simple, easy to use and cheap to manufacture device.

When Shove Comes to Push for Solid Doses – the Glide SDI™

Achieving a constant, reliable delivery of a solid dosage form with the simplicity of low velocity administration is a challenge that has been overcome by Glide Pharma (Figure 1). **Glide Pharma**, previously known as **Caretek Medical Ltd**, is an Oxford, UK-based speciality pharmaceutical company that has developed its revolutionary Glide™ Solid Dose Injector (*Glide SDI™*) platform technology. The *Glide SDI™* is a novel, needle-free drug delivery system that avoids all the obvious issues associated with needles, such as needle phobia, injury, cross contamination and needle disposal. Yet, unlike most transdermal, needle-free technologies, *Glide SDI™* delivers the drug in a solid dosage form. Moreover, it is easy to use, cheap to manufacture and can be used for self-administering drugs with the minimum of training. The basic principle of operation of the *Glide SDI™* is that the pharmaceutical material is pushed against, pierces and penetrates the skin in a fraction of a second with a very simple to use, spring-powered, hand held actuator delivery device, which is the size of a marker pen. The pharmaceutical material is formed as a tiny solid rod with a point, which is fashioned during the manufacturing process, at one end (Figure 2).

The Glide™ drug cassette contains the active drug mixed with excipients. The formulation may contain one or more active drug components and may be formulated to provide immediate and/or sustained release of the drug to achieve the desired release kinetics of the drug to the systemic circulation. The drug cassette contains no sharps so it can be safely thrown away with normal household waste following use. The Glide™ actuator is triggered by pushing the end of the drug cassette against the target tissue. The pushing of the Glide™ actuator against the skin compresses the main driving spring and when the preset spring force is achieved the Glide™ actuator automatically triggers and pushes the drug from the drug cassette into the skin. The

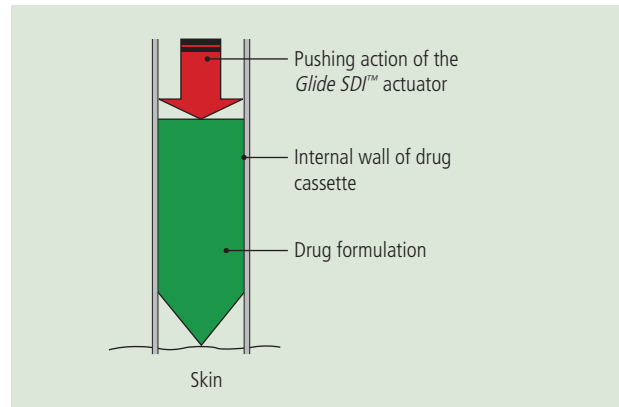


Figure 2 – Using Glide Pharma’s system the pharmaceutical material is pushed against, pierces and penetrates the skin using a simple, spring-powered, handheld actuator.

pushing action is important because it means that the drug is delivered in a controlled manner to the same depth in the skin every delivery regardless of the skin type or location on the body. The actuator can be configured as a fully disposable system (Figure 3), although if a course of treatments is required then the reusable actuator would be retained and a number of preloaded drug cassettes (Figure 4) would be supplied.

Glide SDI™ is suitable for use by a healthcare professional or for self administration by a patient, and requires minimal training. Many individuals can be trained to use the device very quickly, for instance in scenarios such as a mass vaccination in the third world or for biodefence applications.



Figure 3 – *Glide SDI™* can be configured as a single disposable unit.



Figure 4 – *Glide SDI™* can be configured as a reusable actuator with a number of disposal cassettes that can be thrown away in the household rubbish. No sharps, no needle injuries, no cross-contamination and safe, easy disposal.

Conclusion

A need for alternative ways to deliver the growing list of new biopharmaceutical and molecular entities, such as vaccines, DNA-based therapies, peptides and proteins that cannot be administered orally has provided renewed focus on needle-free injections. The benefits of needle-free injection are clear and obvious yet, despite a 150-year history, relatively few products have made it on to the market, perhaps owing, amongst other factors, to the complexity of some of technologies that have been developed to date. The challenge now is to develop technologies that not only will ensure patient compliance and trust but also are simple and cheap to manufacture. Needle-free technologies that provide cost-effective solutions for safe, reliable and controlled delivery of pharmaceutical materials in a range of different scenarios, including for self-administration with the minimum of training, such as that offered by the *Glide SDI™*, are those most likely to have the greatest impact on healthcare and thus the industry.

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