400
300
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100

Missing the Point

Dr Simon Bennett and Dr Charles Potter of Glide Pharma discuss the advantages of needle-free injection technologies – an area of science in which its promise outweighs its achievements to date

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. Simon 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 as well as Founder and CEO of Glide Pharma. He holds an Engineering degree and PhD from Cambridge University. Charles 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 1,000.

The benefits of needle-free injection have been recognised for over 150 years. H Galante et Compagnie of Paris manufactured a formative 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 only in the past 20 years have we seen major technological advances as the need for needle-free drug delivery has become more widely recognised. Yet, despite much investment in research and development, the promise of needle-free injection technologies remains to be fully realised.

The benefits of needle-free injection are obvious; people on the whole do not like needles. Needles increase the risk of spreading blood-borne infections and 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 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 a consequential impact on both the patient and the healthcare system. That said, compared with needle-free alternatives to date, in many circumstances the convenience, reliability and reduced costs of administration afforded by traditional injections have contributed to the fact that the 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

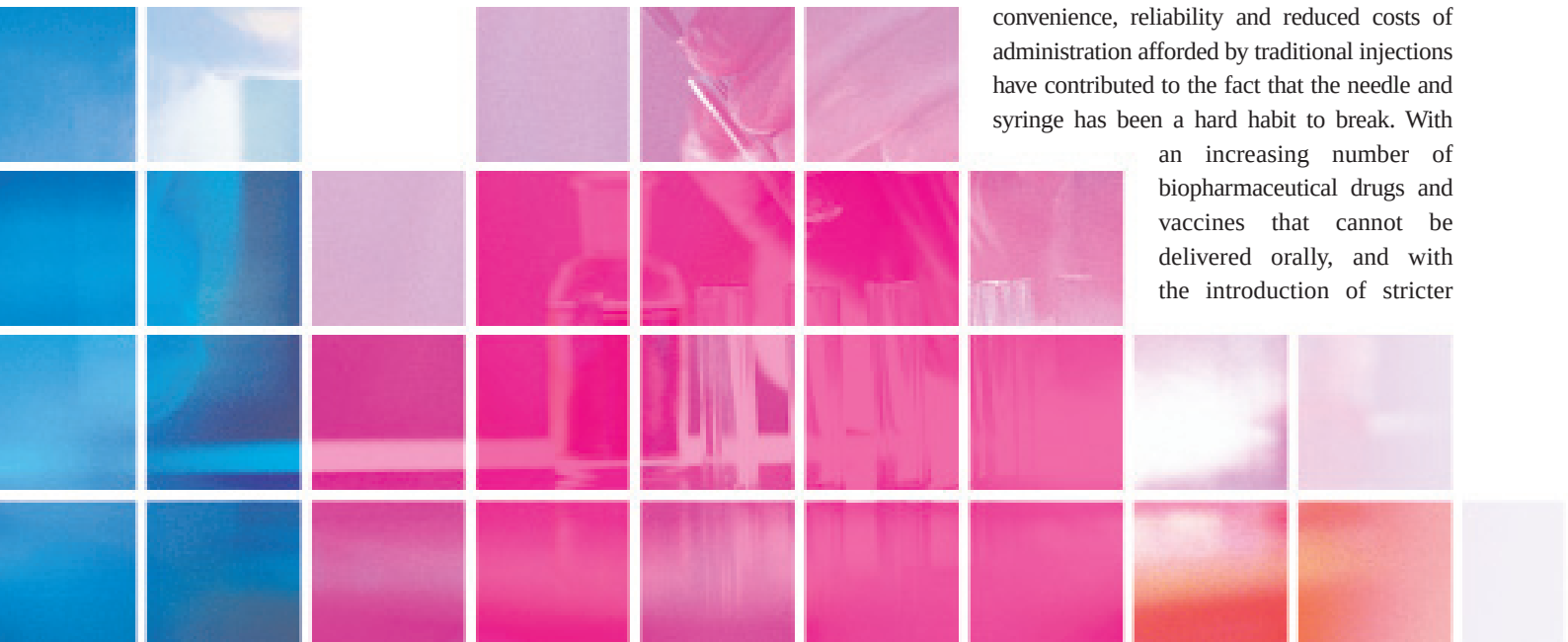


Table 1: Transdermal Delivery of Liquids and Solids		
	Liquid dosage form	**Solid dosage form**
High velocity (firing)	Liquid jet injectors	Powder injectors
Low velocity (pushing)	Needle and syringe and auto-injectors	Solid dose injectors

regulations – particularly in the US – to avoid the needle-stick injuries, the need for safe, reliable, yet cost-effective alternatives to traditional injections is set to rise.

INJECTIONS IN PERSPECTIVE

Many medicines cannot be taken orally because of difficulties due to the structure and chemistry of the digestive system; in some cases it is impossible for these drugs to enter the bloodstream. 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. Liquids and solids can be delivered either with a needle (in other words, traditional needles with a syringe or trocar) or without a needle (that is, needle-free technologies) to penetrate the skin.

Another way to classify the systems that delivers liquids and solids through the skin is to differentiate between high velocity (firing) and low velocity (pushing) of the drug into the body (see Table 1).

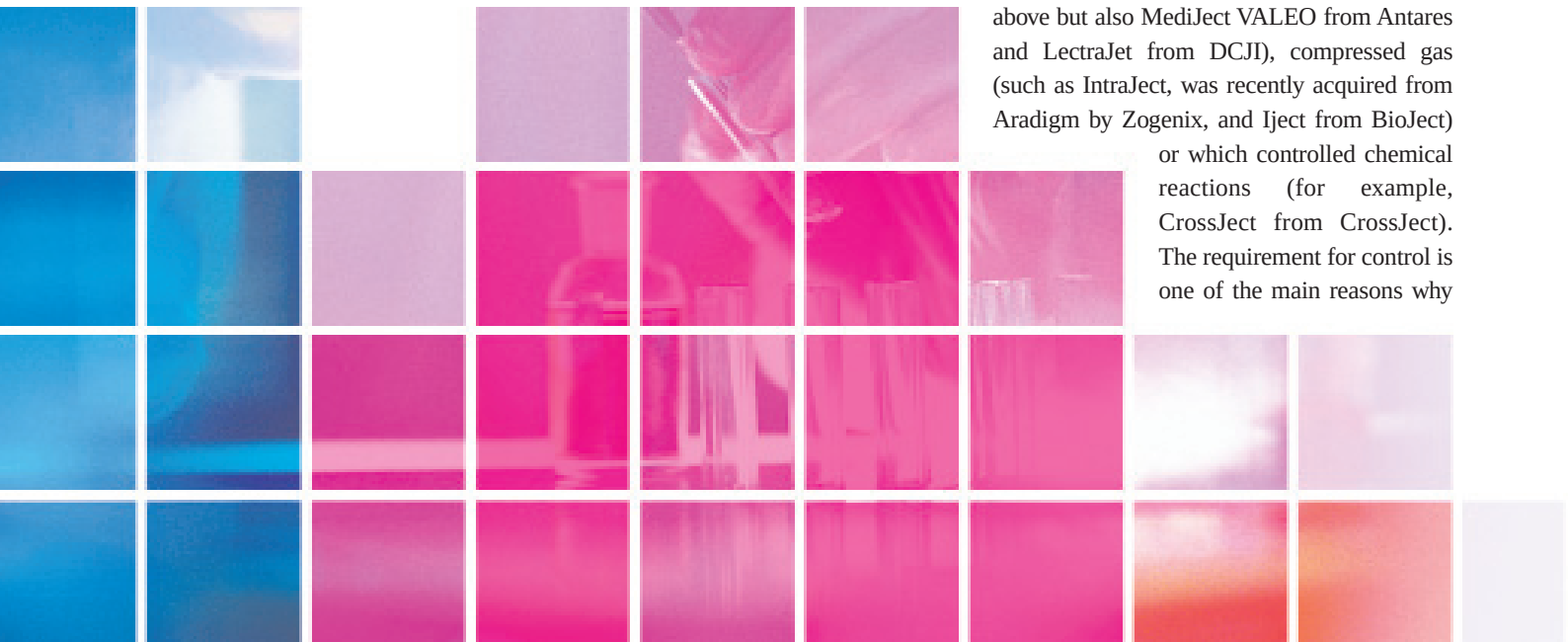
The best known and most common method of injecting drugs through the skin is to use a standard needle and syringe. Alternative formats for this technology include auto-injectors, to enable users to self-administer with a spring powered device, and safety needles which have been developed to prevent needle-stick injuries. Such technology is 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 lifecycle 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, for example Implanon® marketed by Organon, treatments for 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 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. There are, however, a few products based on some of these technologies on the market; the 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. One of the main attributes of the liquid jet injectors is that they use the drug in a liquid form, which therefore does not typically require re-formulation from standard needle and syringe formats.

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 to '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 (for example those on the market as above but also MediJect VALEO from Antares and LectraJet from DCJI), compressed gas (such as IntraJect, was recently acquired from Aradigm by Zogenix, and Iject from BioJect) or which controlled chemical reactions (for example, CrossJect from CrossJect). The requirement for control is one of the main reasons why



Delivering the drug or vaccine in a solid dosage form has several advantages – 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.

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 with.

Figure 1: The system can be configured as a reusable actuator with a number of disposal cassettes that can be thrown away in the household rubbish

NEEDLE-FREE DELIVERY OF SOLID FORMULATIONS

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PowderJect has developed one of the better known 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. 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 for the delivery of DNA vaccines on gold carrier particles.

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

COMBINING THE BENEFITS OF SOLID DOSAGE FORM WITH LOW VELOCITY ADMINISTRATION

Achieving constant, reliable delivery of a solid dosage form with the simplicity of low velocity administration is a challenge that is being addressed. One novel, needle-free drug delivery system (the Glide SDI™) seeks to avoids the obvious issues associated with needles – such as needle phobia, injury, cross contamination and needle disposal – by delivering the drug in solid dosage form. This makes it is easy to use, cheap to manufacture and can be used for self-administration with the minimum of training. The basic principle of the technology 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.

A 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 actuator is triggered by pushing the end of the drug cassette against the target tissue. The pushing of the actuator against the skin compresses the main driving spring, and when the preset spring force is achieved the actuator automatically triggers and pushes the drug from the drug cassette into the skin. The pushing action is important; 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, although, if a course of treatments is required, the reusable actuator would be retained and a number of preloaded drug cassettes would be supplied (see Figure 1).

CONCLUSION

A need for alternative methods 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 the focus today has been sharper than it has ever been. Despite a 150-year history, the challenge now is to develop technologies that will not only ensure patient compliance but that are also 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 are those most likely to have the greatest impact. ◆

The authors can be contacted at
simon.bennett@glidepharma.com
and charles.potter@glidepharma.com