Pain-free, blunt-needle injection technology

Surprisingly, blunt needle injections have not only been found to be virtually pain-free - they also offer a host of other advantages for parenteral drug delivery.

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The offer of “pain-free” injections is a very attractive proposition indeed. But imagine a drug delivery system that could also eliminate needle stick injury, leakage and bleeding; could dose precisely to any depth from intradermal to intramuscular; could accommodate highly viscous or particulate-loaded compounds; could penetrate difficult-to-inject sites where ointments fail; and could be used by almost anyone. Now that would represent a major breakthrough!

Current drug delivery technologies have their own individual strengths and shortcomings. Hypodermic needles, for example, are problematic when used in large sizes, on sensitive areas or for multiple injections. They can leak or cause bleeding at the injection site, can accidentally injure patients or medical professionals, and have been known unintentionally to penetrate veins and arteries.

A new “blunt needle” approach being developed by a team of medical device specialists based in Oxford, UK, is poised to change this situation in the very near future. The technology features a closed-end needle that emerges from its actuator for just long enough to penetrate the skin, deliver its dose and withdraw almost without sensation, and - with minor modifications - accurately dose a wide array of compounds to a variably controllable depth. These features would suggest a safe, almost painless way to administer a host of currently-available drug therapies, as well as some that have so far proven to be “undeliverable”.

The case for a new drug delivery option

Beyond the clinical motivators, there are also compelling commercial reasons to intensify the search for new ways to deliver drugs. Many compounds are known to have therapeutic value but cannot be commercialised because they cannot be injected, ingested or otherwise effectively assimilated by the body. A good example is a compound that cannot be made soluble. The value of these “undeliverables” represents many hundreds of millions of pounds annually in terms of non-productive R&D investment. In addition, the value of lost sales of unused compounds is estimated at £3 billion per year; dozens of these could become viable with the right injection system. Also, each year the patents of dozens of drugs reach their expiry date; over the next five years, an estimated £20 billion of drug sales will involve drugs that are due to lose their patents (1). Unless patent-holders can add value to these drugs by expanding their use in a unique way, sales revenue from them will drop steeply as generic versions emerge. Blunt needle technology could be an important factor in these cases.

Meeting these needs is the focus of Imprint
Pharmaceuticals Ltd, a private company set up in 1999 to develop drug delivery technologies for pharmaceutical manufacturers. The blunt needle injector is the company's most promising new development.

How the blunt needle works

In this context “blunt” means that, compared with a hypodermic, the Imprint needle tip is smooth, streamlined, non-cutting and has a relatively blunt end with a non-coring aperture at the side where the drug is actually released. This design allows the needle to enter the skin very quickly without trauma. The needle is mounted in a handheld device, pre-charged with a small actuator that accelerates the needle from 0 to 60 mph in 1/20,000th of a second, rapidly delivers the dose and then automatically retracts into the unit as the needle is withdrawn.

A conventional hypodermic injection device - the type widely used with syringes and auto-injectors - has five razor sharp edges that slice their way into the skin, cutting tissue in the process. The sharp, open-end acts like an apple corer, often piercing nerves, capillaries and muscle on the way in. The Imprint needle, by contrast, stretches and displaces tissue in a manner similar to blunt dissection; this reduces the release of inflammatory cytokines which activate pain receptors.

As a result, trauma and bruising are greatly reduced, and healing at the site is more rapid. Because of the natural elasticity of the tissue and the fact that it has not been cut, the dermis moves back into place when the needle is removed. This results in much less drug leakage though the opening - and virtually no bleeding: the effect is that a more consistent, more precise dose is actually delivered. This could be of interest in those situations where repeated under-medication is a problem, or where delivery of skin-sensitising drugs too close to the epidermis can cause skin irritation - as would be the case with needle-free and topical delivery approaches.

The effective operation of the blunt needle lies in the design of the needle and associated components, and parameters such as needle entry velocity and acceleration profiles, angle of entry, repeat entry at high rates and precise depth control. Also of relevance are the needle actuator design and liquid injector concepts.

Potential applications

In the short term, three key categories of application for the technology are envisaged. Each is intended to expand the portfolio of drugs that can be safely, effectively and conveniently injected.

**Current “undeliverables”** First on Imprint’s list of priorities is an improved method for delivering multiple microinjections (0.01 to 100µl) at a sub-dermal level (0.5 to 5mm deep). This system, called the Imprinter™, enables better drug delivery to sites such as the sole of the foot, the fingernail, the palm or scalp. It is ideally suited for compounds not suitable for formulation as ointments, creams or gels.

Applications include the treatment of skin cancer, fungating breast cancers, nail-bed fungal diseases, baldness and delivery of anaesthetics. Tablets and topicals represent well-established, simple and inexpensive delivery methods; however, both can have serious limitations when it comes to getting the correct amount of active drug to the sub-dermis.

Tablets can produce undesirable side effects at drug concentrations high enough to provide the required effect, while many topicals simply cannot penetrate the skin’s barrier. In addition, injection of, for example, infected foot ulcers can be problematic using a hypodermic: the sharp point can split the tissue on the foot, weakening the protective role of the skin and risking spread of the infection. The Imprint needle safely penetrates this type of site without splitting the skin.

Another “undeliverable” is the type of drug that requires multiple, consecutive injections. A modified prototype of the Imprinter combines a fine needle with a liquid delivery system and a dose regulator to give pulsed microdoses of drug over wide areas. Such a device is known to be of great interest to those who treat a variety of skin disorders, as well as baldness. The potential also exists for this...
approach to be used to deliver large molecule antibodies - reducing the need for patient-unfriendly therapies such as iv treatments.

**Patient-administered drugs** Imprint is also developing a simple pen injector that can be loaded and administered by the patient, as directed by their doctor. Called the Painless Precision Pen™, this device is seen as an alternative for frequent self-administration conditions such as diabetes. The pen is intended to inject volumes of 0.1 to 1 ml, and to a depth of 5 to 15 mm. In addition to being relatively pain-free, the pen also promises minimal leakage and a level of simplicity that a child could learn.

**Intra-muscular injections** The Imprint technology is also being adapted to offer the first large needle auto-injector for single intramuscular or subcutaneous injections of long-acting viscous or microparticulate-laden formulations. Called Depotject™, its possible clinical uses include hormonal treatments for conditions such as gigantism and the administration of psychotropic drugs. Once fully developed, Depotject is expected to be able to carry needles of 16 gauge and above - again with the low pain and trauma profile of Imprint's fine needle range.

Administration of depot-forming drugs currently requires a large needle injected by a skilled nurse, and often one with specialist knowledge of Z-track or air-bubble techniques. The injection is generally done in hospitals because of the serious risk of intravenous injection or other complications. Because of a greatly reduced profile for trauma, it is anticipated that Depotject will enable such injections to be performed in less formal, more cost-effective settings - in the GP clinic or possibly in the patient’s home.

The safe, consistent, deep placement of drugs is ideally suited to patients who might forget or are unable to medicate on schedule. Depot-forming medicines can provide a gradual release of the

Because of the natural elasticity of the tissue and the fact that it has not been cut, the dermis moves back into place when the needle is removed.

Figure 2. The Imprinter prototype being held by Peter Crocker, Chief Executive Officer.

Figure 3. The smaller Imprinter prototype showing its various working parts.
active chemical agent over a period of several months. Human growth hormone administration is viewed as being an ideal use for DepotJect.

Comparison with other delivery systems

The drug delivery market is currently estimated at about $18 billion worldwide, representing 15 percent of the total pharmaceutical market. Industry sources are clear that improved drug delivery is an increasingly important aspect of every pharmaceutical manufacturer’s business. Needle-free options are seen to represent a growing market, but they tend to be focused on simple, fixed-dose, single shot, low-dose medicines with the viscosity of saline; there is also concern that some can be non-precise.

Both powder jet and liquid jet technologies necessitate some re-engineering of drugs previously delivered by other methods; in addition, unlike needle delivery systems, jet systems must be injected through soft skin and only to sub-cutaneous depth. Liquid jet also has limits as to the viscosity of the drug that can be injected and is unable to deal with anything of a particulate nature.

Needle-based injectors can deal with depth, allowing for intramuscular injection. However, the shortcomings of hypodermic needles persist. Small-bore needles are less painful, but they don’t work for viscous or particulate drugs. Short needles are less painful, but are prone to leakage. Large bore needles are unacceptably painful without anaesthetic. And virtually all hypodermic needles can cause needle-stick injury. This is an issue that currently costs the medical profession billions of dollars annually, and is the subject of new legislation around the world.

Needle-free injection methods, such as powder jet and liquid jet, have solved some of the pain and safety problems but - beyond the delivery of DNA, common vaccines and insulin - their effectiveness is limited, and their suitability for insulin therapy is questioned by some. Inhaled insulin is problematic and cannot yet replace injectable formulations. An orally administered insulin is on the distant horizon, but is unlikely to become available for at least ten years.

The Imprint blunt needle technology is designed to eliminate many of the limits now encountered by drug formulators, allowing them to choose the most effective physical and chemical formulation parameters - without injection technique (or lack of one) being an issue.

The relative strengths and weaknesses of blunt needle technology compared with the major injection technologies currently available are shown in Table 1.

Future prospects

The prototype blunt needle injector currently involved in trials is slightly larger than a mobile phone; the ultimate size of the Imprinter will be closer to that of a large, felt-tipped highlighter. The development of new prototypes is ongoing.

Table 1. The characteristics of Imprint compared with other drug delivery systems.

<table>
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<tr>
<th>Imprint</th>
<th>Hypodermic</th>
<th>Liquid jet</th>
<th>Powder jet</th>
<th>Patch/Gel</th>
<th>Tablet</th>
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<tbody>
<tr>
<td>100mg-plus</td>
<td>10μl-5ml</td>
<td>&lt; 1 ml load</td>
<td>Max 2mg load</td>
<td>Few mg</td>
<td>100mg-plus</td>
</tr>
<tr>
<td>1μl to 5ml</td>
<td>Single</td>
<td>Single</td>
<td>Single</td>
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<td>Active chemical</td>
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<td>period of several months. Human growth hormone administration is viewed as being an ideal use for DepotJect.</td>
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Of those (patients) receiving an injection of saline solution with the Imprinter, a significant proportion were unable to tell whether they had, or had not, been injected at all.

Innovations in Pharmaceutical Technology
The main clinical trial conducted to date was carried out at the Pain Relief Unit of the John Radcliffe Hospital, Oxford, UK. In the study, led by Dr Chris Glynn, senior consultant, 14 volunteers were injected with either the blunt needle or a hypodermic, and then asked to rate pain levels. The blunt needle group reported significantly less pain - logging a score of 8 for the Imprinter versus 19 for the hypodermic.

Also, 21 per cent of the needle and syringe injections bled, compared with only two per cent of the blunt needle injections. Of those receiving an injection of saline solution with the Imprinter, a significant proportion were unable to tell whether they had, or had not, been injected at all. A typical comment from participants was that they felt “pressure rather than pain”.

Two pharmaceutical manufacturers have engaged Imprint to undertake feasibility and development studies; several others are discussing proof-of-principle studies with selected compounds; and two international patents are progressing though the approval system. Experienced development and manufacturing teams at Chelsea Instruments and Plasro Ltd have made major contributions to the development of clinical prototype design and manufacturing processes. Production costs are expected to be in line with other auto-injectors.

The discovery has also earned for Imprint the status of “Inventor of the Year” for 2001 from the award sponsors, Hewlett Packard and the UK BBC television programme “Tomorrow’s World”; the company has also received two Smart Awards from the UK Department of Trade and Industry (DTI). Patent reports commissioned by the DTI before granting each of these awards confirmed that Imprint’s patents are novel and do not conflict with any existing patents, and that no patents have been found that would inhibit Imprint from developing its products as planned.

Imprint’s board, management team, consultants and advisors include more than a dozen highly experienced professionals from mechanical and fluidic engineering, physics, biochemistry, finance, medicine, pharmaceuticals, regulatory affairs, patents and licensing, and other disciplines. The route to regulatory approval is expected to be a direct one; in brief, blunt needle products could be in use within the next two to four years.

**Conclusion**

As the technology develops and advances, additional opportunities are likely to arise for the partnership of individual drugs with specific, tailored delivery systems. This type of collaboration could help to dramatically improve treatment of many difficult or untreatable conditions. Blunt-needle technology has the clear potential to produce - in time - injection systems capable of delivering to different depths from intradermal to intramuscular, handling high viscosity and particulate content, and improving topical treatment with high drug penetration (even in highly sensitive areas) - all leading to greatly expanded uses for existing medicines.

The benefits for medical care will be improved safety and efficacy, better patient compliance through pain-free precision and ease of use.

**Reference**