

DRUG DELIVERY & FORMULATION

SOLUTIONS & SERVICES

ONdrugDelivery
SEPTEMBER 2013
ISSUE N° 44
ISSN-2049-145X



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ONdrugDelivery Issue N° 44, September 2013
"Drug Delivery & Formulation
Solutions & Services"

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Jan: Ophthalmic Drug Delivery
Feb: Prefilled Syringes
Mar: Transdermal Patches, Microneedles & Needle-Free Injectors
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ISSN 2049-1468 pdf
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Front cover image "MEMS pumping unit of the Debiotech NanoPUMP™ device" supplied by Debiotech SA. Reproduced with kind permission. Debiotech's feature article appears in this issue, page 16.

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KEEPING UP WITH THE BIOPHARMACEUTICAL MARKET

In this article, **Hans Ole Klingenberg, Director, Global Marketing, Novozymes Biopharma,** shares how the company is helping its clients meet changing industry demands.

The pharmaceutical biologics market is a significant and rapidly developing field, populated with a range of players, from large companies to fast-growing start-ups. Exciting technology and impressive growth predictions characterise the market. The market for biologics is moving increasingly towards the use of these kinds of medical products as blockbuster treatments, assisting in the treatment of chronic conditions, such as arthritis and diabetes, and

significant challenges. Increasingly, companies are being asked to look into creating 'more for less' – safer, more tailored therapies on smaller budgets and in quicker timeframes. Manufacturers must improve and streamline their processes in order to get the most from this increasingly competitive field. Doing so can ensure their success in a market which is evolving and growing, fuelling the development of a greater number of more innovative therapies

that can make a real impact on healthcare around the world.

"INCREASINGLY, COMPANIES ARE BEING ASKED TO LOOK INTO CREATING 'MORE FOR LESS' – SAFER, MORE TAILORED THERAPIES ON SMALLER BUDGETS AND IN QUICKER TIMEFRAMES. MANUFACTURERS MUST IMPROVE AND STREAMLINE THEIR PROCESSES IN ORDER TO GET THE MOST FROM THIS INCREASINGLY COMPETITIVE FIELD"

CHALLENGES OF AN EVOLVING MARKET

Safety has always been a top priority within the biologics market, especially with some studies suggesting these types of therapies pose a heightened risk of adverse effects compared with other treatments.² Under this scrutiny, and after several high-profile product recalls, the safety record and testing of proposed treatments is being

this step forwards is reflected in some exciting market predictions. At the end of 2012, one estimate puts the global biologics market at US\$176.4 billion (£110 billion), with expected CAGRs of over 9.5%.¹

In a market this size, there are huge opportunities – both financial and in solving unmet clinical needs – in fields such as oncology, infectious and inflammatory diseases, and paediatric vaccines. But there are also

exposed to even greater examination from governments and regulatory agencies.

This tight monitoring of safety levels is a trend that is likely to continue, and manufacturers are encouraged to do everything possible to ensure the purity and safety of their end products right from the initial formulation stages. This involves knowing the sources of components, being certain of their purity and quality and, when scaling-up from laboratory



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formulation to manufacturing, ensuring batch-to-batch consistency.

A second, related challenge becoming increasingly important in the formulation stages of therapies is the stability of manufactured molecules. Not only does this impact on the safety of the end product – stable therapies remain within the therapeutic range in a patient's system for longer, increasing the patient's tolerance to the drug and reducing side effects – but by creating molecules which remain active for longer, lower and less frequent dosage levels for patients can be achieved, resulting in increased patient adherence.

This is an issue which is particularly prevalent when working with manufactured peptides and proteins, often hampered by their characteristically short half-lives. While natural antibodies have a recirculation half-life of around 250-300 hours, engineered antibodies struggle to reach 25% of this level. It is therefore unsurprising that many companies and regulatory agencies are pushing for technologies to assist in the creation of more stable therapies with longer half-lives and dosage extension.

By creating these, there is also hope that an increased number of treatments with tuneable half-lives can be developed, allowing therapies to be fine-tuned to suit patients' needs without the requirement of a complicated dosing regime. Achieving more control over drug release would mean that dosing frequency could be reduced and stable levels maintained in the body, increasing patient safety and adherence. This is therefore another ideal that is being pushed for by companies throughout the pharmaceutical industry, and is sure to play a major role in the development of the market.

However, it must not be forgotten that all of these obstacles – safety, stability and flexibility – need to be overcome in a manufacturing environment. As previously stated, methods must be easy to scale-up to industry-level manufacturing once they have gone through a laboratory setting. Companies are aiming to make their processes cost-efficient and reduce the time to market, and even then it often takes several years for a potential therapy to reach clinical trials. The main challenge to be found is achieving all of these goals simultaneously.

ENSURING PURITY AND SAFETY

In order to develop safer and more innovative products, there are several techniques available to formulators. One such solution is to remove as many animal-derived components as possible from product formulations. Quality control on products is becoming subject to stricter governing from regulatory bodies, aiming to

improve safety and minimise risk by encouraging the use of animal-free treatment components. For example, traditional sources of hyaluronic acid (HA) – often used in applications such as trabeculectomy, retinal reattachment and trauma surgery – include rooster comb extract and various attenuated strains of *Streptococcus*

“IT MUST NOT BE FORGOTTEN THAT ALL OF THESE OBSTACLES – SAFETY, STABILITY AND FLEXIBILITY – NEED TO BE OVERCOME IN A MANUFACTURING ENVIRONMENT ... METHODS MUST BE EASY TO SCALE-UP TO INDUSTRY-LEVEL MANUFACTURING”

bacteria. These are further purified using harsh organic solvents, and could potentially result in contamination risks from animal-derived proteins, viruses or endotoxins.

In order to assist its clients and help them to provide purer, safer treatment therapies, Novozymes Biopharma provides an alternative to the traditional animal-derived sources of HA. This has been achieved through the development of a *Bacillus* fermentation process. *Bacillus subtilis* is a non-pathogenic host whose products are categorised as “Generally Recognized as Safe” (GRAS) by the US FDA. HA derived in this manner shows low amounts of nucleic acids, proteins, bacterial endotoxins, exotoxins and microbial contamination, and hypersensitivity reactions in patients are therefore reduced.

The use of *Bacillus*-derived HA is just one method by which Novozymes Biopharma is helping the industry move towards the production of safer, more sustainable product formulations.

STABILISING DRUG FORMULATIONS

The importance of producing a stable molecule for treatment therapies has already been recognised in this article. Optimising the product formulation, for example by adding stabilising excipients, provides a valuable solution for formulators who wish to stabilise their protein-based treatment and vaccine formulations.

However, many methods for stabilisation require multiple excipients, leading to a large amount of time and resources being dedicated to this by developers. Combinations of human serum albumin (HSA) and a variety of sugars, amino acids and detergents (SADs) have been found to be useful in stabilising both protein-based treatments and vaccine formulations, but a method to reduce the number of excipients needed to stabilise therapeutic proteins is highly sought after.

rAlbumin from Novozymes Biopharma, has been shown to stabilise such formulations by protecting against surface adsorption, inhibiting aggregation and also functioning as an antioxidant. This combination reduces the amount of treatment molecule lost throughout the body before it reaches its therapeutic target,

leading to an increased efficiency and improved results at lower dosage. Using rAlbumin, formulation scientists can simplify their strategies and reduce the number of excipients needed to stabilise a protein-based treatment or vaccination candidate. The knock-on effect is less time spent refining combinations of excipients and therefore streamlining of the formulation and manufacturing processes.

SUSTAINED-RELEASE AND FLEXIBLE HALF-LIVES

Half-life extension is an area that has captured the attention of many formulators within the biopharmaceutical market. Peptide and proteins, especially, do not have sufficient half-lives to allow their use as effective treatments in a clinical setting. In these cases the frequency and high doses that would be required to achieve a therapeutic effect are likely to make them intolerable to patients. Extending the half-lives of manufactured molecules, and acquiring technologies that will facilitate greater control of the therapeutic half-life of drug candidates, is therefore an important goal of many pharmaceutical companies.

In response to this, Novozymes Biopharma has created a tuneable half-life extension technology in the form of Albufuse® Flex and Recombumin® Flex (currently in pivotal Phase III trials with GSK and TEVA) based on a series of engineered human albumins with modified binding to the human FcRn receptor. The combination of these engineered albumins with a drug candidate offers the potential for tuneable control of the therapeutic half-life in a manner previously unachievable with native human albumin and other HLE technologies, such as PEGylation and Fc and albumin fusion proteins. Together with reducing dosing frequencies from days to weeks, this is the only technology using natural functioning, animal-free recombinant albumin.

“MANY METHODS FOR STABILISATION REQUIRE MULTIPLE EXCIPIENTS, LEADING TO A LARGE AMOUNT OF TIME AND RESOURCES BEING DEDICATED TO THIS BY DEVELOPERS ... A METHOD TO REDUCE THE NUMBER OF EXCIPIENTS NEEDED TO STABILISE THERAPEUTIC PROTEINS IS HIGHLY SOUGHT AFTER”

EFFICIENT, SCALABLE MANUFACTURING

By including Novozymes Biopharma components in formulations, pharmaceutical manufacturers have access to a sustainable supply of components at a large scale. This ready supply should allow them to continue with production in an efficient and streamlined fashion.

With 25 years' worth of experience in industrial-scale manufacturing, Novozymes Biopharma ensures that its facilities can provide a ready supply of high-quality, standardised product, delivering completely scalable product manufacture to clients. Its large-scale manufacturing plant has the capacity for fermentation of volumes from 5-27,000 litres. This ready supply ensures clients can achieve a streamlined process that gets their potential therapies towards clinical trials, and eventually to market, as quickly as possible.

CONCLUSION

With ever more innovative products coming onto the market, and more emphasis being placed on providing tailored, safe therapies in a shorter timeframe, it is an exciting and challenging time to be part of the biopharmaceutical arena. Novozymes Biopharma has developed some unique and innovative technologies to help its clients meet the needs of a rapidly evolving market, and work to provide them with additional regulatory support and security of supply.

Many challenges and obstacles need to be overcome, but it is generally agreed that biologics will be one of the cornerstones of

future therapies, and will play a role in treatment of several major diseases. Consequently, creating safe, stable therapies is the aim of many scientists within drug formulation, half-life extension and medical device applications. Novozymes Biopharma's solutions and expertise are tailored to match the needs of this highly driven market.

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Hans Ole Klingenberg is Director for the Global Marketing group in Novozymes Biopharma. Hans Ole has been with Novozymes for more

than ten years and has through his time at Novozymes held various positions in the area of corporate business development, with a focus on the establishing new business entities for Novozymes in the biopharmaceutical industry. Hans Ole has since 2007 been working in Novozymes' Biopharma business with a focus on marketing, and is commercially responsible for establishment of Novozymes' new Hyaluronic Acid business franchise. Hans Ole has a background from Copenhagen University, with a bachelor in chemistry and master in Economics. He is based in Denmark.

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Novozymes is the world leader in bioinnovation. Together with customers across a broad array of industries we create tomorrow's industrial biosolutions, improving our customers' business and the use of our planet's resources. With over 700 products used in 130 countries, Novozymes' bioinnovations improve industrial performance and safeguard the world's resources by offering superior and sustainable solutions for tomorrow's ever-changing marketplace. Novozymes' natural solutions enhance and promote everything from removing trans fats in cooking, to advancing biofuels to power the world tomorrow. Our never-ending exploration of nature's potential is evidenced by over 6,000 patents, showing what is possible when nature and technology join forces. Our 5,000+ employees working in research, production and sales around the world are committed to shaping business today and our world tomorrow.

“THE COMBINATION OF THESE ENGINEERED ALBUMINS WITH A DRUG CANDIDATE OFFERS THE POTENTIAL FOR TUNEABLE CONTROL OF THE THERAPEUTIC HALF-LIFE IN A MANNER PREVIOUSLY UNACHIEVABLE WITH NATIVE HUMAN ALBUMIN AND OTHER HLE TECHNOLOGIES, SUCH AS PEGYLATION AND FC AND ALBUMIN FUSION PROTEINS”

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TOPICAL & TRANSDERMAL DRUG DELIVERY – HAVE WE ONLY JUST SCRATCHED THE SURFACE?

ONdrugDelivery Magazine spoke with Professor Marc Brown, Chief Scientific Officer, Chief Operating Officer and Co-Founder of MedPharm, the topical and transdermal formulation development specialist, about how new drug delivery technologies may open yet more horizons for pharmaceutical companies in the near future. Here, he shares his insights on topical and transdermal drug delivery and presents one new platform technology, MedSpray, which was developed by MedPharm and is now available to clients under licence.

Q: What do you see as the key drivers that have fuelled the topical and transdermal space over the last decade?

According to BCC Research, the global dermatology market reached \$15.8 billion (£9.9 billion) in 2012, and is expected to reach \$18.5 billion by 2018, registering a compound annual growth rate (CAGR) of 2.8%.¹ IMS Health would have us believe we are there already with a market value of \$18bn in 2008. Vagaries aside as to what classifies as dermatology or cosmeceuticals, the area continues to grow thanks largely to the cross-fertilisation of biotherapeutics from other indications to treat psoriasis, such as the anti-TNF antibodies and new interleukin antibodies, such as Centocor's Stelara, and Amgen's brodalumab, which is due to start Phase III. Most dermatological diseases are common, chronic and costly, fulfilling the criteria that pharma like. Add to this the increasing use of transdermal delivery devices to deliver active compounds systemically via non-invasive patches, then you have burgeoning interest in both diseases of the skin and how drugs can be delivered to or across the skin. The North American drug delivery market is expected to register a CAGR of 8.9% between 2012 and 2017, and transdermal systems are expected to make up a significant percentage of this.²

Trends in pharmaceuticals over the recent past have rapidly changed the presentation of the

drugs we use today. There have been several shifts driven by patient and clinician choice and compliance. A drive in innovation with drug delivery devices themselves and improvements in primary packaging now form an integral part of the overall product, for example metered-dose inhalers, transdermal patches and nasal sprays. Formulations that target extended- or modified-release profiles have also become standard dosing options where the active may have a short plasma half-life, to avoid multiple daily dosing or where systemic exposure to smaller amounts of the drug over a longer period is desirable e.g. anti-infectives, NSAIDs and mental disorder drugs. New demands are being made of formulation scientists from marketing, compliance, lifecycle management and distribution departments that require new dosage forms that provide competitive differentials, convenience to the end user, enhanced safety, stability and efficacy or to reinvigorate mature drugs for new uses in other indications or in the same indication but with a different posology. As such the design and use of topical and transdermal dosage forms is now entering a new phase of innovation.

We have seen a large movement in the demand for new formulations for locally applied products driven by a number of factors.

Firstly, more actives are being promoted for local delivery as part of lifecycle management having originally started life as oral forms,

such as terbinafine. Secondly dermatology is becoming an interesting space for big pharma again due to the repositioning and success of such blockbuster drugs as the anti-TNF biologics for psoriasis. Humira, Embrel and Remicade now hold positions one, two and four in worldwide sales.³ Most of the important dermatological and inhaled drug indications are chronic and by their very nature need long-term repeated administration which usually means lifetime treatment; this can be a very lucrative business. Third, innovation in transdermal patches and devices has opened up a new multi-billion pound market for extended or modified drug release.

Finally, most companies do not have the internal topical and transdermal formulation and testing expertise needed to innovate their existing drug franchises. In order to develop more versatile dosage forms with improved delivery and aesthetics, which will be fundamental to their subsequent market success, these companies look to outsource. For example, in topically applied formulations in dermatology, patients obviously want a cure but they do not necessarily want to compromise their physical appearance to get one. Such locally applied formulations therefore have to meet criteria that other oral or parenteral formulations do not need to consider. The art of this area of formulation science is long dead in big pharma.

Q: So what is so different about the skin as a route for drug delivery as opposed to say the intestinal lining?

Where do I begin! The skin first and foremost is the primary barrier we have between our precious internal organs and our external environment. It's also a watertight container. We would not want to swell up to the size of a balloon every time we jumped into the bath or swimming pool. Like a lot of things in nature it is far more complex in terms of design than people think or understand. It's our largest organ and primary defence against invading pathogens, toxic chemicals and ionising radiation. The skin is crammed with sensors and responds to external humidity changes and insult or trauma. It has a complex homeostatic system to help us maintain a stable core temperature as well as maintain the integrity of the barrier function and repel invaders and repair damaged tissue. It has a highly efficient immune response system comprising both cell-mediated and innate immune responses. That is why it can at times be so sensitive to inflammation from an insect bite or other allergen. The skin can recruit T-cells and other inflammatory cells at the first sign of damage through incredibly fast chemotactic responses driven by local cytokine production. A lot of skin diseases such as psoriasis and cancers hijack this system.

Q: It seems a pretty impregnable fortress then?

Yes but having said that, it is permeable once you can penetrate the *stratum corneum* (SC). The main defence is the 'bricks and mortar' compacted design of flattened corneocytes surrounded by a lipid matrix in the SC (see Figure 1) which makes it very hydrophobic (Elias, 1983; Suhonen *et al.*, 1999). As such, certain chemicals under certain conditions such as primarily lipophilic compounds with a molecular weight <500 Da have the best chance of penetration. The potency of any drug also needs to be considered. However, we have developed some techniques and systems that can modify these established rules.

Methods for overcoming the barrier are generally considered to be either: chemical/passive, for example the use of penetration enhancers, prodrug and eutectic systems; or physical/active such as iontophoresis, electroporation, ultrasound, microneedles, application of local heat, needleless injection and combinations thereof. Both techniques change either or both of the diffusion rate of the active and/or the per-

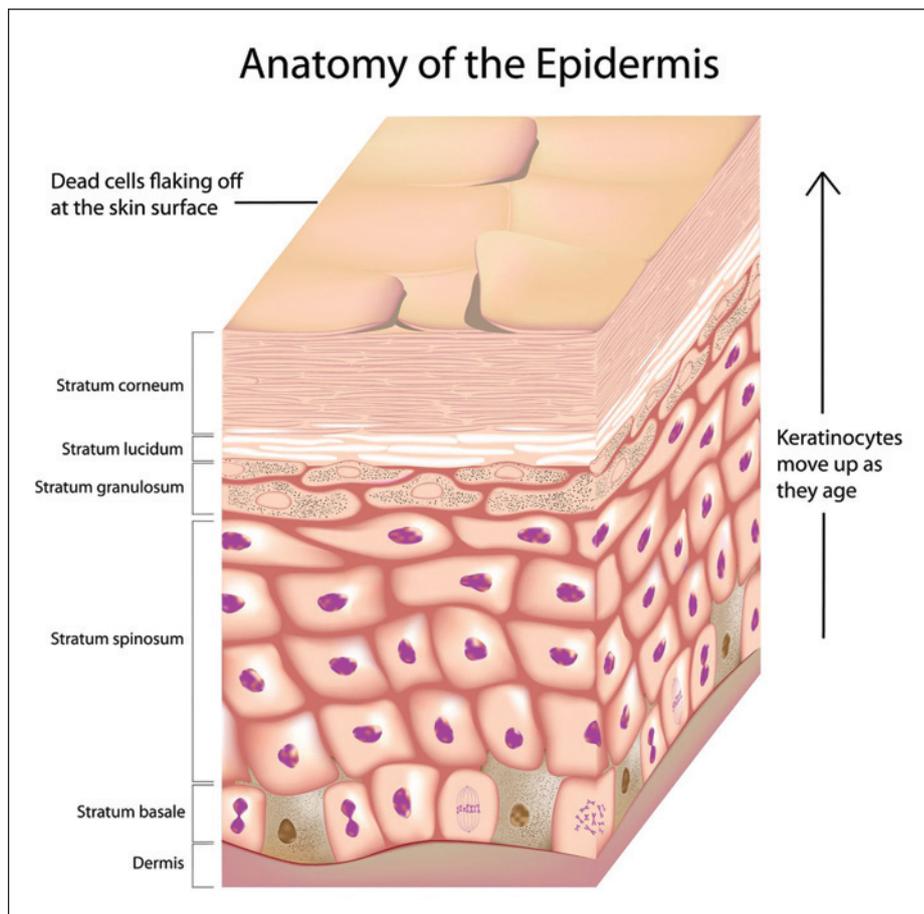


Figure 1: Anatomy of the epidermis.

meability of the SC. Up until relatively recently and despite this understanding, the actual efficiency of delivering an active to the skin from many traditional formulations such as creams/emulsions and ointments was very poor as typically a large proportion of the drug remains trapped in the vehicle (Barry, 1991; Shah *et al.*, 1989). However, technologies such as MedSpray[®] have improved things significantly.

If the barrier can be overcome there are unique advantages of delivering a drug to, and across, the skin when compared with oral and parenteral delivery. These include the avoidance of hepatic first-pass metabolism, improved patient compliance, reduced toxicity and ease of access to the affected site for locally acting drugs. Why deliver a drug to treat a skin condition orally? Why risk exposing delicate organs to the possible off-site toxicities and wasting the majority of the drug in circulation unless you really have to?

Q: What specific parameters do you need to address when optimising the delivery of a drug into and across the skin?

A chemical species will naturally diffuse across

a boundary or into an adjacent concentration of different chemical species by passive diffusion. Broadly speaking this is represented by a chemical's diffusion coefficient. When looking at systems that involve permeation across a membrane or into the skin, flux according to Fick's laws is most applicable as a theoretical modelling system, simplified to:

$$J = k_p \cdot c_{app}$$

(where, J is flux, k_p is the permeability coefficient, and C_{app} is the applied dose).

According to Fick's laws the most important factors that influence flux across the skin are the concentration gradient of the drug between the formulation and the skin, the partition coefficient of the permeate and the diffusion coefficient (Thomas and Finnin, 2004; Hadgraft, 2004).

In addition, the flux of a molecule across a membrane should increase linearly with concentration until c_{app} (applied dose) reaches the solubility limit; the point of saturation (i.e. a thermodynamic activity (TA) of 1). Diffusion rates are also routinely faster for low-

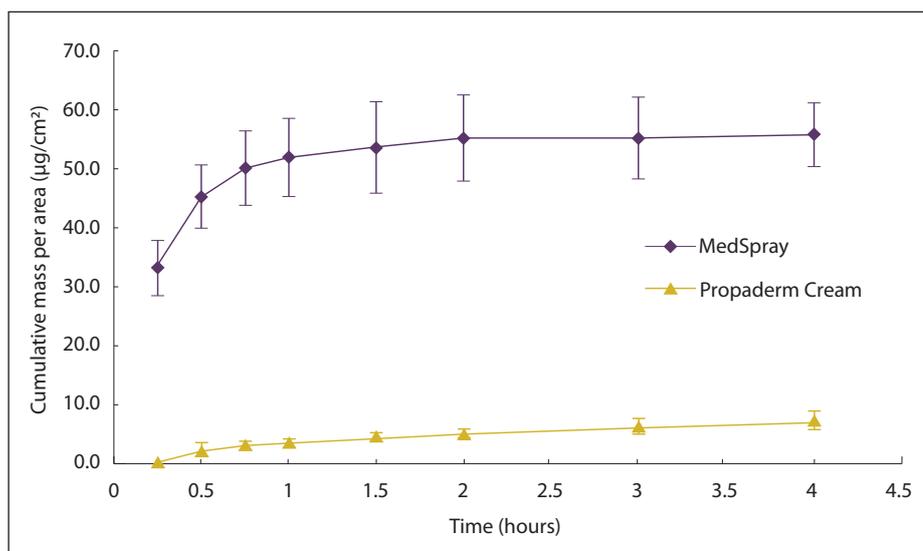


Figure 2: Comparison of BDP release from MedSpray with a marketed cream using a synthetic membrane (mean ± standard deviation, n=5).

melting-point compounds. In the past, these laws were often forgotten and hence resulted in the poor efficiency of delivery from such formulations that limits the efficacy of many topical products.

In summary, the higher the thermodynamic activity of the active within the formulation (upon application), the more efficient the delivery. This is the case for all such formulations applied to the skin. This approach (originally theoretically conceived by Higuchi) has been used in the development of supersaturated systems where the thermodynamic activity of the drug in the formulation exceeds unity ($TA > 1$) by using non-solvents and/or antinucleating polymers. However, such approaches have failed in the past because of the inherent chemical and physical instability of the drug (i.e. it crashes out).

Our MedSpray technology uses a different approach. It is an aerosolised spray that upon actuation and evaporation of the propellant and various co-solvents produces a film on the skin surface containing the drug in a high or supersaturated activity state, thus overcoming the instability issues observed previously. It also contains a clever combination of commonly used enhancers which improves the delivery even further.

Q: What are the potential applications of MedSpray?

As we have already shown, MedSpray is a fundamental advance in how actives can be delivered topically for application locally to treat dermal infections, inflammation, pain, psoriasis, atopic dermatitis, acne etc, and for transdermal delivery. The parameters in the drug-release profile can be changed according to drug release and penetration requirements.

Basically, MedSpray is a new hybrid between an aerosol dosage form and a transdermal patch or film. We term this technology Patch-in-a-can™. It is sprayed on to the surface of the skin and forms a microfilm, where it can deliver the drug over a short or long time (extended or modified release) depending on the preferred profile. The properties of the film can be designed according to the disease being treated, e.g. occlusive and hydrating for psoriasis. In addition, the fact that MedSpray can be sprayed directly onto the skin means it does not have to be rubbed in or manipulated and thus there is no chance of an infection being spread or of cross contamination, a problem common with the more traditional dosage forms. In addition, MedSpray can also be designed so that the patient feels cooling upon application which can help in the relief of certain symptoms such as itch and pain.

As such, MedPharm has currently tested MedSpray up to and including Phase II trials using a number of actives including ibuprofen, diclofenac and a number of other NSAIDs, terbinafine and other antimicrobials, antihistamines, anaesthetics, methylphenidate, testosterone and other steroids, fentanyl and buprenorphine, to name but a few.

Q: How did MedPharm get involved in the development of novel delivery technologies?

It was always in our plan. MedSpray was our first idea which is now patented throughout the world including the US and Europe, and we have continued to refine and adapt its versatility to a wider variety of actives as it has been licensed or as we have had the means internally. A recent development is MedRo, where MedSpray has been adapted to deliver drugs locally or systemically via the oral mucosa.

Another delivery technology, MedTherm®, is in its infancy but is as equally exciting. All such technologies are available to our clients, with the knowledge that they will have a patentable product.

Q: Why did you see a need for these innovations?

Over the past 14 years at MedPharm we have been given some challenging actives to formulate. It stands to reason that a new client would give us candidates that they have found difficult to formulate themselves. This is great as it tests our mettle and forces us to expand the accepted boundaries. We found that the existing arsenal of formulation approaches, even with penetration enhancers, was simply not enough and we needed new approaches to give the patient/consumer what they want whilst increasing delivery and efficacy. There is also a desire to move away from potential irritants, greasy and impractical ointments and creams along with cumbersome and expensive delivery devices such as large inefficient transdermal patches, needleless injectors and proactive delivery devices such as iontophoresis and electrophoresis which have proven too impractical for routine use.

Q: Why would a drug manufacturer choose MedSpray to deliver their drug?

The advantages are pretty clear I think. Primarily it's a more effective vehicle for increasing delivery. Less of a reservoir of drug remains in the vehicle on the skin unlike creams or ointments. It's also easier for the patient to apply as they don't have to touch the affected area with their fingers and the resultant microfilm doesn't leave an obvious greasy residue. Patients also like it since the evaporation of the volatiles has a cooling effect on application. Finally it's ideal for extended drug release where the active is delivered over time. That's why we developed a terbinafine version and went all the way into a clinical trial to show it provided cure after only one administration. I might add that all the excipients are pharmaceutically acceptable and are approvable in the EU and US and since we now have clinical exposure in 120 patients we know there are no skin-irritation or other toxicity issues.

Q: What other data have you got on the efficacy?

We have been working on this technology for a number of years now and have acquired plenty of drug release data in our models using different actives. Some of it is still proprietary for clients but we have shown the system to be both

robust and versatile. For transdermal delivery we have shown improvements in methylphenidate uptake over Noven Therapeutics' methylphenidate patch, Daytrana®. Choosing hydrofluoroalkane (HFA) as a propellant was a critical point in the development as this, unlike other propellants previously used, is environmentally friendly and non-flammable. We used a co-solvent system to enhance drug solubility and anti-nucleating agents which was another important step in the development. We have data in our *in vitro* performance testing models to show that we can improve the release of betamethasone valerate and beclomethasone dipropionate (BDP) from their original cream or mousse forms (see Figure 2). At each of the time-points taken, the quantity of drug released across the membrane by the spray was significantly greater compared to the cream (<0.05 ANOVA). For instance, the flux of the BDP MedSpray formulation was 30-fold higher than the equivalent BDP cream

So in conclusion, there are many parameters to consider when formulating a drug for application to the skin that are not relevant to oral or parenteral forms. However, the benefits in patient compliance, ease of use and targeted action outweigh the difficulties and with the new delivery technologies that are advancing, drug companies may be following this route of administration with a closer eye in the future.

Q: You also talked about MedTherm. How does this compare?

In addition to the saturation principle we have also looked at active methods of boosting diffusion through the application of locally raised temperatures. This has resulted in an ongoing development we call MedTherm. We apply the drug in a device or formulation that self-generates local heat on application (similar to the heat patches you can buy) but that also contains a combination of enhancers. These thermogenic formulations enhance delivery through the skin through a synergistic effect of thermophoresis on the enhancers which in combination increases the passive diffusion kinetics of the drug and disrupts the lipid lamellae in the SC causing the layer to become more fluid (Silva *et al*, 2006). It has also been postulated that the heat increases local blood flow through dilation of the blood vessels which aids absorption (Hull, 2002; Osigo *et al*, 1998). In our *ex vivo* performance-testing models we have already shown a 75-fold increase in the delivery of lidocaine into human skin and are now following this up with a comprehensive project to develop a MedTherm topical version of methotrexate, a notoriously difficult compound to formulate.

Temperatures of just over 40°C are achievable and effective, and this is actually fairly pleasant on the affected skin, producing a soothing anti-pruritic effect.

Q: You have mentioned your *in vitro* / *ex vivo* models a couple of times. Why are these models so important to MedPharm?

At MedPharm we have developed and validated a versatile range of performance testing models, a lot using human tissue, that help us to optimise our formulations and also to demonstrate how the formulations are going to perform when they enter clinical evaluation. This provides our clients with some confidence that when they spend vast sums of money for the necessary clinical trials, the projects will not fail; it reduces risk. In addition, for skin indications it is probably easier and more pertinent to use *in vitro* / *ex vivo* human skin models, such as the Franz cell, than testing on animals, whose skin is very different to that of humans. MedPharm has also developed human skin models of disease which our clients use to select the right drug to progress and to get an indication of formulation efficacy. Our toxicity models provide our clients with the knowledge of any potential risk of toxicity, e.g. irritation, when they enter the clinic. Again, such models also minimise any animal testing that may have to be performed; something critical for MedPharm. I believe MedPharm has become one of the world leaders in developing these models and in some cases our models have provided competent authorities with enough evidence to circumvent the need for extended bioequivalence trials for certain formulations. As such MedPharm's performance testing facility which includes all these models has just doubled in size and capacity to accommodate our clients' requirements.

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ABOUT MEDPHARM

MedPharm, based in Guildford, Surrey, UK, has worked with more than 150 clients in the design and development of topical formulations and medical devices for drug delivery, including both transdermal patches and metered-dose inhalers. The company has contributed to the development of numerous new and generic products including 15 products that have since gained market approval. Its expertise has always been in the design and performance testing of topically and transdermally delivered drugs.

MedPharm has carved a niche amongst the worldwide contract research providers in this field contributing to formulations for application to the skin, nail, eye, airway and mucosal surfaces and covering all semi-solid dosage forms, foams, sprays, patches, aerosols, and many other devices. MedPharm's experience over the past decade in topical and transdermal formulation design has highlighted new opportunities in today's competitive market for such routes as an alternative to parenteral and oral drug delivery.

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Professor Marc Brown, PhD, CChem, FRSC, co-founded MedPharm, the contract development and manufacturing organisation (CDMO) in 1999 as a spin-out of King's College London, where he had previously been a Senior Lecturer in the School of Pharmacy. He maintains his links with academia with professorial positions at the UK Universities of Hertfordshire, Reading and Dundee. Previously he had worked in the pharmaceutical industry in North America where he managed the development and approval of several topical formulations. To date he has been involved in the pharmaceutical development of 20 products that are now on the market in Europe, America and Japan including, Solaraze®, Zyclara® and Picato®. It has been during the creation and growth of MedPharm that he has witnessed most acutely the changes in formulation design, drug delivery and regulatory aspects for topically (locally acting) and transdermally (systemic) delivered drugs.

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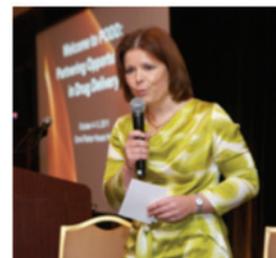
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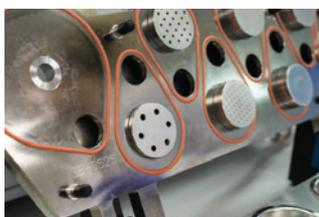
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DISPOSABLE PATCH PUMP FOR ACCURATE DELIVERY

Here, Laurent-Dominique Piveteau, PhD, MBA (INSEAD), Business Development Director, Debiotech, describes the application of the company's NanoPUMP™ technology in the design and development of JewelPUMP™, a wearable device for the continuous infusion of insulin, comprising a micro-engineered delivery system with advanced failsafe and safety features, a touchscreen patient interface, and mobile phone technology. Already in clinical trials as a delivery system, development of JewelPUMP™ is also being taken forward for incorporation with a continuous glucose monitor into an artificial pancreas technology. Beyond insulin, this disposable patch pump can be used in other areas such as patient-controlled analgesia, Parkinson's disease and parenteral delivery of high-dose biopharmaceuticals.

Pumps are commonly used today in many therapeutic areas for the injection of active drug substances. They can be found in the hospital setting, in the emergency and operating rooms, and at the bedside, but also increasingly at home

form. Development of such products is more challenging than it seems at first, in particular to provide a smaller, more convenient disposable product – to remove all maintenance work by the patient – while maintaining the same levels

of safety and accuracy as those available with large precision electro-mechanical systems. In addition, such new drug delivery systems should also provide a record of patient compliance, preferably in real-time or over the cloud.

**“COST EFFICIENCY IS ALSO OF ESSENCE
IN THE MEMS INDUSTRY. AS AN
EXAMPLE, ON AN EIGHT-INCH WAFER
THERE ARE UP TO 375 NANOPUMPS
PRODUCED AT ONCE. THE STANDARD
SIZE OF A PRODUCTION BATCH IS
25 WAFERS, REPRESENTING A TOTAL
AMOUNT OF 9,375 PUMPS”**

SAFETY, ACCURACY, CONVENIENCE

Debiotech has been developing innovative drug delivery systems for more than 23 years. One of its proprietary

platforms, the NanoPUMP™, is particularly suited for this type of applications because of its unique precision integration and miniaturisation. Based on a microfabricated silicon chip, so called Micro Electro Mechanical System (MEMS), it is currently used as the engine for a device targeting complex Continuous Subcutaneous Infusion of Insulin (CSII): the JewelPUMP™. This product is currently subject to further development for other drug applications.

with patients managing their own treatment daily. In this context, the quest for smaller pumps, able to provide specific administration profiles while being easy to use and comfortable for the patient, is growing. These pumps are used for chronic, long-term therapies, such as infusion of insulin for diabetes, or apomorphine for Parkinson's disease, but also for acute single or infrequent injections, for example, of peptides, or biopharmaceutical drugs that cannot be made available in sustained-release



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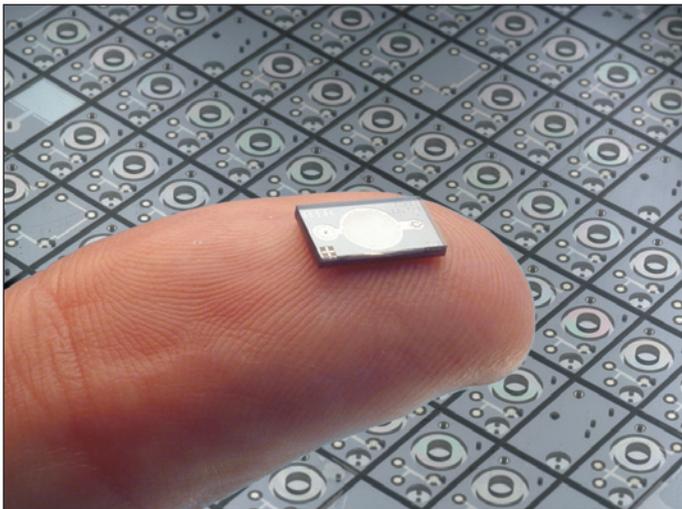


Figure 1: The MEMS pumping unit: 10x6 mm².

The pumping mechanism of the NanoPUMP™ comprises a miniaturised MEMS membrane pump (10x6 mm²) (see Figure 1). This pump, comprising a pump chamber having a stroke volume of 200 nl, two valves located on both sides of the pumping chamber, and two strain gauge sensors, is mounted on a ceramic substrate and is driven by a bending low power consumption piezo-electric actuator (see Figure 2). This component weighs less than 2g and is made out of silicon, a highly biocompatible material. It can, in its current design, pump fluids of various viscosities at rates up to 2.5 ml/h with an accuracy better than 5% at all delivery rates (Figure 3).

This pumping mechanism is connected to a disposable container with enough capacity for several days of therapy and an electronics containing all the elements necessary to drive and control the injection profile with all required information and alarm means. This assembly forms a completely sealed, waterproof, miniaturised device within an optimal physiological shape, which can be placed directly on the patient's skin (Figure 4). The drug is injected into the intradermal space through a flexible cannula directly connected to the pump.

The reservoir is a semi-rigid element made of a plastic component acting as a sort of backbone on which the pumping mechanism is attached together with a welded thermoformed membrane constituting the drug reservoir. It contains a patented membrane filter ensuring the automatic priming of the pump as well as the retention of any air bubble in the reservoir. The plastic component contains the entire fluidic path: access to fill the reservoir, passage between the reservoir and the pumping mechanism and connection of the pump to the injection site. This path is design to minimise dead volume. Thanks to the resulting high compression ratio, the device can pump compressible fluids such as air, and is therefore self-priming. This high degree of integration also allows for both a more compact pump packaging, and a major simplification of the assembly process and thus a reduction of production costs.

Constant and accurate flow-rate is guaranteed through the control of the displacement of the pumping membrane. The movement occurs between two mechanical stops defined by the construction of the chip: the flow rate is linear with actuation frequency and virtually insensitive to inlet and outlet pressure, actuation voltage, temperature, viscosity and aging. The outlet valve is equipped with a safety device – an anti free-flow valve – that blocks the outlet under abnormal pressure conditions in the reservoir. Thanks to a drug reservoir always maintained at normal ambient pressure, the pump is protected against any potential harmful over-delivery. Additionally the pump is equipped with two built-in

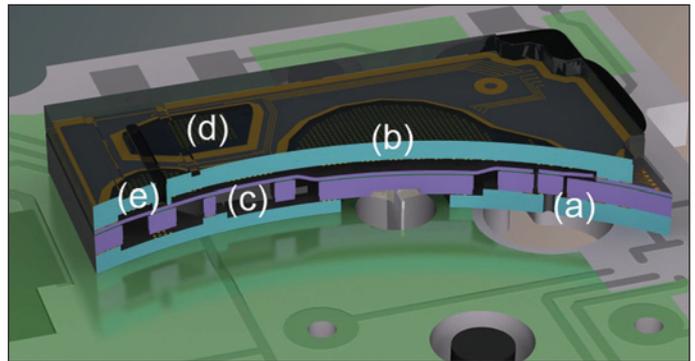


Figure 2: Cross section of the MEMS chip of the NanoPUMP™ showing the inlet valve (a), the pumping chamber (b), the first (c) and second (d) detectors and the outlet valve (e). The MEMS chip is attached to a ceramic substrate on which electrical connections are printed.

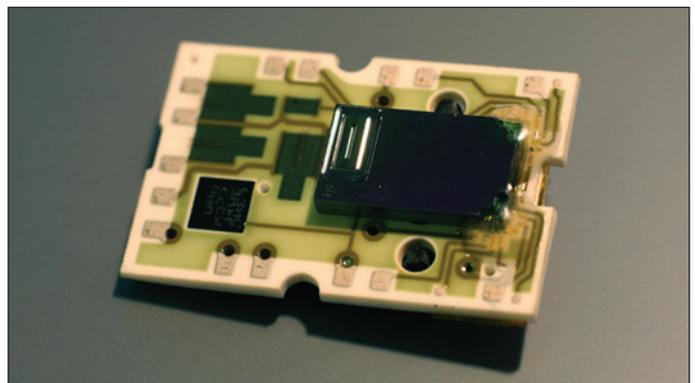


Figure 3: The MEMS pumping mechanism mounted on a ceramic substrate: the heart of the NanoPUMP™.



Figure 4: The NanoPUMP™ applied on a patient's body.



Figure 5: The JewelpUMP™ and its remote control.



Figure 6: The remote control of the JewelPUMP™.

“THE STUDY, WHICH INVOLVES SEVEN RESEARCH CENTRES IN FRANCE, IS AIMED AT DEVELOPING NEW ALGORITHMS FOR A CLOSED-LOOP SYSTEM, ALSO CALLED AN ARTIFICIAL PANCREAS. IN SUCH A CLOSED-LOOP SYSTEM, THE INFUSION PUMP IS CONNECTED TO A CONTINUOUS GLUCOSE METER (CGM) THAT REGULARLY MEASURES THE PATIENT’S BLOOD-GLUCOSE CONCENTRATION”

sensors monitoring the pumping at each stroke level. Abnormal conditions such as occlusion, presence of air, end of reservoir, anomalous leaks are immediately detected and reported, allowing for fast action. The pump is also designed to be waterproof for as little interference as possible with the patient’s normal life.

The pumping mechanism is manufactured in close partnership with ST Microelectronics in its state-of-the-art facilities located in Italy and Malta. Each single pump is fully tested: in few seconds, the stroke volume is measured and the integrity and tightness of the entire pump is verified. The complete system is covered by twenty five families of patents that ensure exclusivity for Debiotech until 2033.

THE JEWELPUMP™: AN IMPLEMENTATION OF THE NANOPUMP™

The NanoPUMP™ is the heart of the JewelPUMP™, a medical device currently being developed by Debiotech to be used for the treatment of Type 1 diabetes (another version targeting Type 2 diabetes is currently in development). Type 1 diabetes is an autoimmune disease in which the islets of Langerhans present in the pancreas and producing insulin have become nonfunctional. Insulin is an essential element for the proper functioning of cells metabolism as it governs their ability to absorb glucose from the blood and use it as source of energy.

The standard treatment for these patients is the replacement injection of insulin. A typical delivery profile comprises a basal rate, covering the necessary requirements for the vital functions and representing about the half of total daily dose, and several times a day larger bolus injected over a short period to cover the needs generated by sugar intake and meals. A pump designed for insulin delivery shall therefore be able to inject over a very broad range of rates, from less than 5 μ l/h up to 200 μ l in a few minutes. In addition, the profile will vary between patients and for a given patient it must be adapted from one day to the next, depending on his health, his physical activity, the content of his meals ... These adjustments are made by the patient himself. It is therefore necessary to provide the user with a very easy and ergonomic programming interface. Finally, insulin is a very potent drug and its plasma concentration must be maintained within a very narrow window; over-delivery as well as under-delivery can lead to very serious conditions, sometimes to death.

The JewelPUMP™ (shown in Figure 5) is based on the NanoPUMP™ construction. A disposable reservoir including the pumping mechanism is connected to a reusable controller. The reservoir has a volume of 5 ml and can contain 500 U of insulin, an amount sufficient



Figure 7: Screenshots of the remote control.

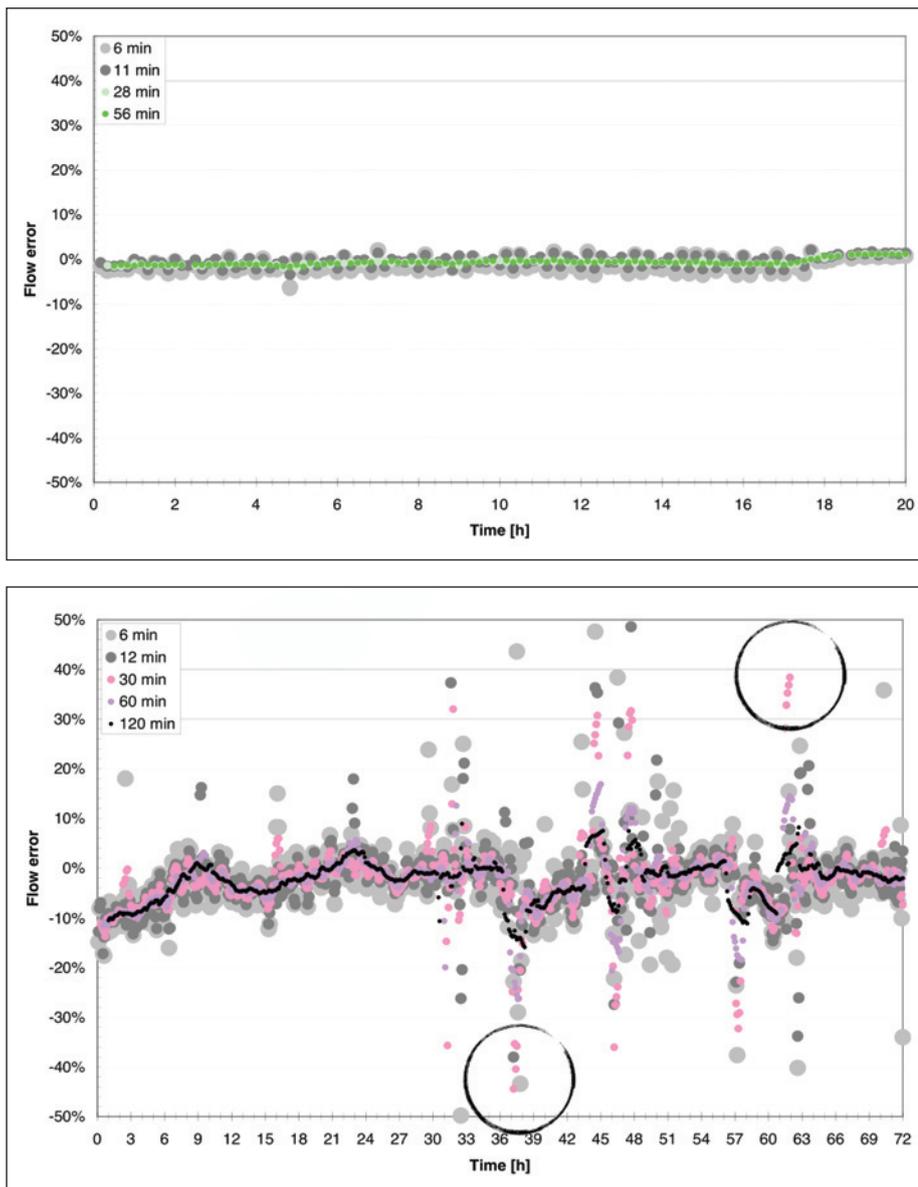


Figure 8: Graphs showing the deviation of the “real delivery rate” from the programmed rate for the JeweIPUMP™ (a) and a durable syringe drive pump (b). As can be seen, the JeweIPUMP™ always remains within $\pm 5\%$ from the programmed rate, while the syringe drive system presents under delivery of 45% over 30 minutes and over deliveries of nearly 40% over 30 minutes.

for a week’s treatment. This represents more than twice the capacity of existing pumps. The controller can be used for two years. It comes in different colours which can be adapted by discretion to the colour of the patient’s skin or, on the contrary, be chosen as a fashion accessory. The entire pump has an external volume of approximately $60 \times 40 \times 14 \text{ mm}^3$ and a total weight of less than 25g.

The pump contains a first sensor that monitors the temperature of the insulin present in the reservoir and advises the patient in case of over exposure to heat (for example, being left in the sun), as well as a second activity and position sensor for potential automatic treatment adjustments. It can be freely attached and detached during treatment,

according to patient needs. The patient just has to slide the pump onto a patch adapter that is connected to the flexible cannula. The system will automatically detect that is has been disconnected and then reconnected, and as such will stop and then resume the infusion. The pump also integrates an alarm system combining both sound and vibration. This combination allows for discreet information for low-priority messages, while ensuring that the patient is alerted in case of an emergency.

The pump is programmed with a remote control (Figure 6) incorporating a large colour touchscreen and communicating through a Bluetooth BLE protocol with the pump. Particular attention was paid to the development of the graphical user interface and

the technological capabilities of the touchscreen were used to their fullest (Figure 7). Based on an Android OS platform, the programming of the pump is very intuitive. The software includes functionalities to assist the patient in determining his insulin needs and to send relevant information to the caregiver. To avoid any confusion, fonts of different sizes were used to discriminate units from subunits and each submenu has a specific colour; the patient knows immediately in what submenu he is. The security of data exchange has also been pushed to its maximum by integrating into the pump electronics a unique SIM card that will create an almost inviolable communication link between the pump and the remote controller.

CLINICAL RELEVANCE

The JeweIPUMP™ has been tested by many diabetic patients in both Europe and the US. These patients were already using pumps or had refused to, or stopped, using pumps following a negative experience. They were given the opportunity to wear, manipulate and program the pump. The general feedback was very positive with more than 85% of patients wanting to switch immediately to the JeweIPUMP™.

The pump is also in a multicentre clinical study with more than 50 patients to date. The study, which involves seven research centres in France, is aimed at developing new algorithms for a closed-loop system, also called an artificial pancreas. In such a closed-loop system, the infusion pump is connected to a continuous glucose meter (CGM) that regularly measures the patient’s blood-glucose concentration. In response to variations in this concentration the system will adapt the quantity of delivered insulin: the amount is increased in case of growing

glucose concentration or stopped to avoid hypoglycaemia. The ability of such a closed-loop system to deliver a treatment safely lies in the accuracy of each of its elements. It is essential that the exact dose of insulin is delivered in response to the measured glucose level otherwise this could lead to a subsequent wrong decision by the algorithm.

“BEYOND INSULIN, THE PUMP COULD BE USED, FOR EXAMPLE, IN PATIENT CONTROLLED ANALGESIA (PCA), IN PARKINSON’S DISEASE THROUGH INFUSION OF APOMORPHINE, TO CONDUCT VARIOUS HORMONAL TREATMENTS OR ALSO FOR THE PARENTERAL DELIVERY OF SOME HIGH-DOSE BIOPHARMACEUTICALS”

While on average, over 24 hours, current wearable pumps can infuse a drug precisely, events of more than 30 minutes with over- or under-delivery of more than 30% occur regularly (see Figure 8). Unfortunately, this 30-minute window corresponds to the reaction time of current closed-loop systems. A poor accuracy in the delivery method will lead to dramatic instabilities. Closing the loop with accurate pumps should therefore lead to a significant improvement in the quality and reliability of these systems.

Diabetic patients consider undetected occlusions as one of the most dramatic types of events that may occur during CSII. If handled in a wrong way, this may lead to coma and potentially to death. With its integrated detector placed within the pumping element, the JewelPUMP™ can detect occlusion after just one pump-stroke, i.e. after only 200 nl or 0.02 units of insulin have been missed. It becomes possible to give an early and unambiguous alarm to the patient, allowing him to take any action to liberate the occlusion in a safe way.

CONCLUSION

Drug infusion pumps are still often cumbersome and complex devices. They are adapted for involved and motivated patients and can be used only after a long training. This has limited drastically their use for therapies outside of Type 1 diabetes and this despite a growing number of studies showing much better outcomes when treatments are conducted with pumps compared with classical methods. The disposable NanoPUMP™ with

its small size, low cost, ease of use and convenience is offering a real solution to democratize the use of pumps in a large number of therapies, with simple or complex delivery profiles, and potentially improving compliance. The most evident application is certainly Type 2 diabetes, a form of the disease hitting an older population that often

refuses its condition and looks for therapies perceived as noninvasive.

Beyond insulin, the pump could be used for example in the management of pain in patient controlled analgesia (PCA), in the treatment of Parkinson’s disease through infusion of apomorphine, to conduct various hormonal treatments or also for the parenteral delivery of some high-dose biopharmaceutical

formulations. Even a prefilled drug option could be considered, based on highly biocompatible material used. For all these markets and several others, the NanoPUMP™ has a great potential for success.

ABOUT DEBIOTECH

Debiotech SA is a Swiss Company with more than 20 years’ experience in developing highly innovative medical devices, based on micro- and nanotechnology, micro-electronics, and innovative materials. The company concentrates on implantable and non-implantable systems, in particular for drug delivery and diagnostics, with a demonstrated competence lying in the identification of breakthrough technologies and their integration into novel medical devices.

Devices developed by Debiotech are eventually licensed to major international pharmaceutical and medical device companies, with a track record of over 40 license agreements worldwide. Examples of products in addition to the JewelPUMP™ for diabetes care include the I-Vantage™ IV pump for hospital and home-care, the CT Express™ Contrast Media injector for CT-Diagnostic Imaging (recently acquired by Bracco Imaging), the NanoJect™ microneedles for intradermal injections, the DialEase™ home-care miniaturised dialysis equipment, and others under development.

MICRO-ELECTRO MECHANICAL SYSTEM (MEMS)

MEMS is a manufacturing method that uses technologies developed by the semiconductor industry to create mechanical and electrical structures in wafers made of single-crystal silicon. A combination of photolithography, etching and deposition processes is used to create structures in the sub-micrometre range in a highly reproducible manner and in very high volumes. All these processes are conducted in an ISO class 5 cleanroom environment. At this scale silicon is both mechanically resistant and elastic. It is therefore possible to create structures such as flexible membranes that will support millions of actuations without showing signs of fatigue. Cost efficiency is also of essence in the MEMS industry. As an example, on an eight-inch (20 mm) wafer (Figure 9) there are up to 375 NanoPUMPs produced at once. The standard size of a production batch is 25 wafers, representing a total amount of 9,375 pumps. Thanks to this very high parallelization in the manufacturing process, it is possible to reach high cost effectiveness.

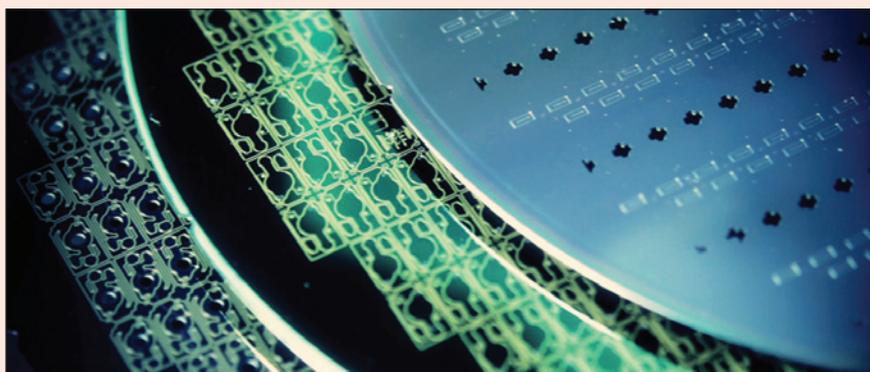


Figure 9: The different wafers forming a NanoPUMP™.

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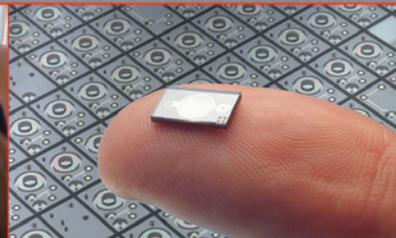
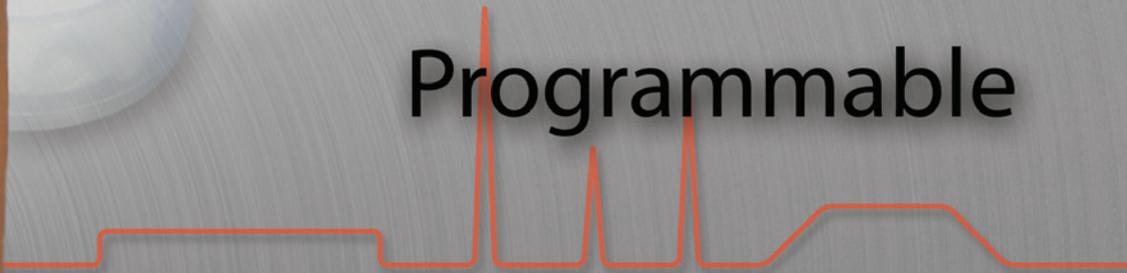


Intuitive

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GREAT INVENTIONS THAT TRICK NATURE – NEW DELIVERY SYSTEM OPTIMISES BLADDER CANCER TREATMENT BY INCREASING DWELL TIME

In this article, Sari Prutchi Sagiv, PhD, Marketing Director at TheraCoat, explains why longer chemotherapy dwell-time is critical for the optimal treatment of bladder cancer, and how this can be achieved via a simple yet sophisticated drug delivery system.

INTRODUCTION

TheraCoat's Internal Cavity Drug Retention (ICDR) system allows for controlled and highly effective delivery of therapeutic agents into the bladder without being voided and diluted by the urine, overcoming the major drawbacks of instilled therapies. ICDR defies some natural norms regarding the behaviour of materials. Normally, gels become liquid with heat, not the other way around. Based on advanced materials technologies, the novel ICDR system stays liquid outside the body when cooled,

non-invasive disease with a high survival rate but high recurrence rates mean lifelong treatment and monitoring.

Around 35% of the non-muscle invasive bladder cancer (NMIBC) tumours recur within one year after surgical removal. As a consequence, NMIBC patients have to undergo periodical and expensive follow-up, making NMIBC the most expensive cancer to treat on a lifetime basis.¹ The cost per patient from diagnosis to death can reach US\$120,000 (£75,000), translating to a \$3.8 billion annual spend in the US.

treating bladder cancer have largely proven to be insufficient since after intravesical instillation, drug concentration is immediately reduced and washed out due to continuous urine creation and voiding. Therefore, the cancerous tissue is not optimally exposed to the drug, allowing tumour reseeding and migration.

The improved efficacy of chemotherapy following increase in tissue exposure time (dwell time) was established by numerous *in vitro* models,²⁻⁴ *in vivo* studies,⁵ and computer simulations.⁶ Schmittgen showed that tumour sensitivity increases with increasing Mitomycin

“AFTER TRADITIONAL INTRAVESICAL INSTILLATION, THE DRUG CONCENTRATION IS IMMEDIATELY REDUCED AND WASHED OUT DUE TO CONTINUOUS URINE CREATION AND VOIDING”

and becomes a muco-adhesive gel only once inside the bladder. The use of the ICDR system increases drug exposure and reduces toxicity, significantly enhancing treatment potential, safety and compliance.

BLADDER CANCER

Bladder cancer is the fourth most frequent solid tumour cancer in men and the seventh in women, with more than 350,000 new cases diagnosed worldwide annually with a prevalence of 840,000 patients in Europe and 530,000 in the US. Most patients suffer from a

The initial treatment of this cancer is surgical removal of the tumour, commonly known as transurethral resection of the bladder tumour (TURBT) followed by a series of periodic intravesical chemotherapy instillations which the patient is required to retain for approximately 60 minutes. Intravesical chemotherapy is used either as an adjuvant to TURBT, to delay tumour recurrence, or to control widespread disease not manageable by surgical methods.² The rationale is to expose tumours to high local drug concentrations while minimising systemic exposure, enhancing treatment efficacy and reducing drug toxicity. But these traditional approaches to



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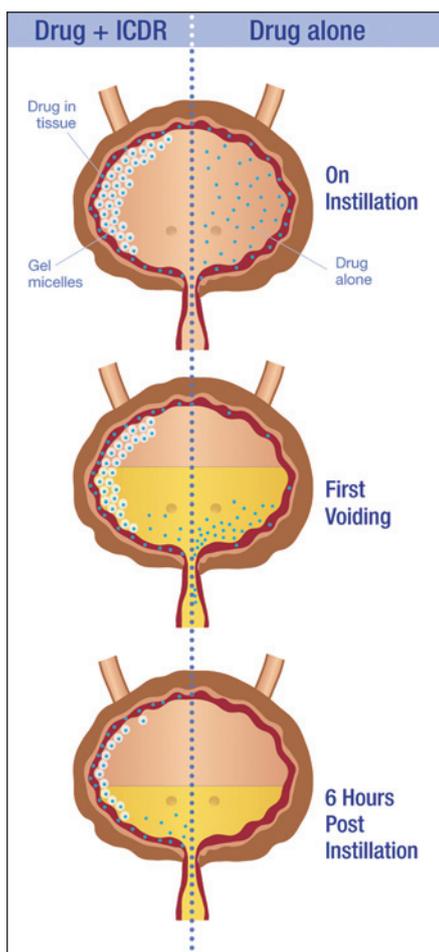


Figure 1: Drug intravesical instillations with and without ICDR. With ICDR, the drug concentration is kept for longer.

C (MMC) exposure time.⁴ De Bruijn treated bladder cancer patients with intravesical MMC using 30- and 60-minute dwelling times.⁵ He demonstrated that recurrence was significantly lower in the 60-minute treatment group. No recurrences were found in patients with low grade tumours when the 60-minute dwelling time was used. These results were supported by numerous studies conducted by Barlogie *et al*, Slee *et al*, Ozawa *et al* and Perry *et al*.⁷⁻¹⁰

Based on this data, Badalament's suggestion for optimisation of the efficacy of intravesical chemotherapy included holding the dosing solution as long as possible ("Have the patient hold the intravesical therapy in his bladder as long as possible") and dehydration of patient for reducing urine production ("Dehydrate patients prior to intravesical therapy").¹¹

Prolongation of intravesical treatment dwell time is imperative for enhancing the anti-tumour effect of the instilled chemotherapy.

PROLONGING DWELL TIME

The novel ICDR system addresses these current treatment drawbacks. The system employs a novel hydrogel with unique thermo-sensitive

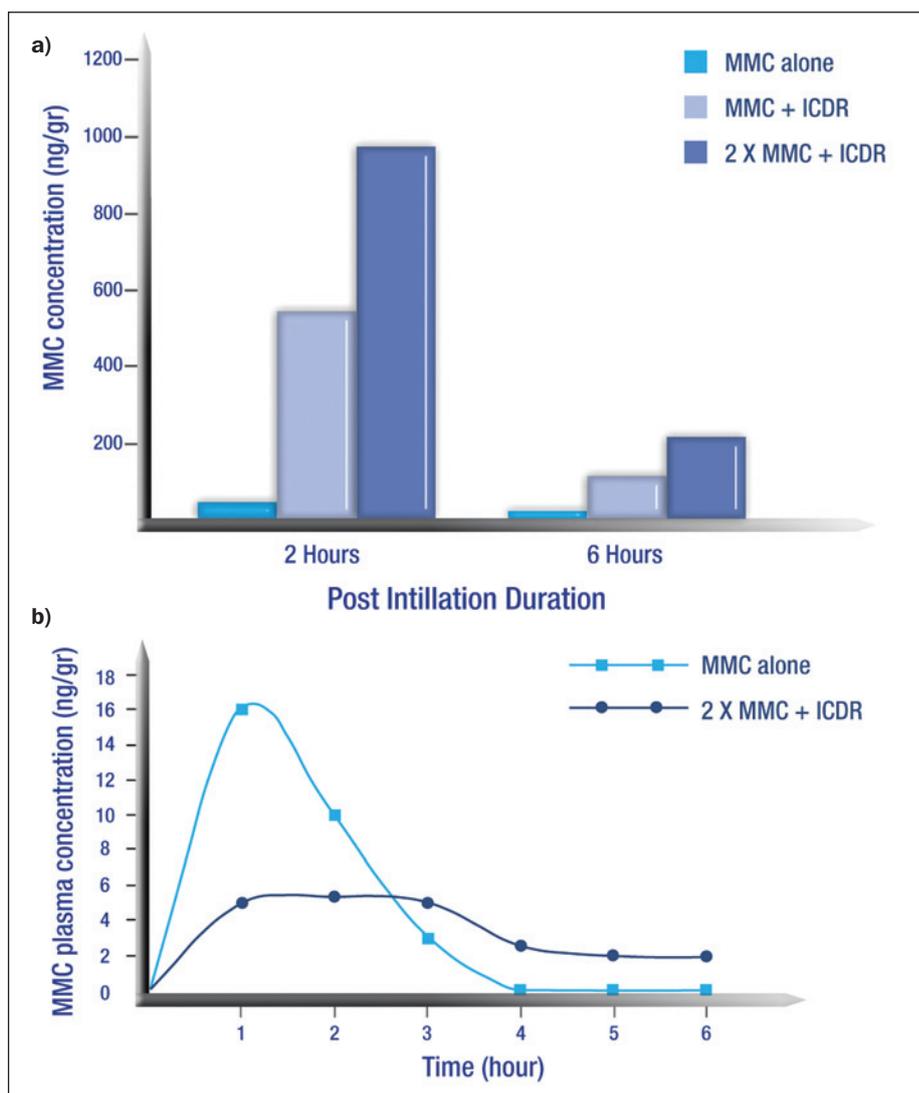


Figure 2: When used with ICDR a) the level of Mitomycin C (MMC) in the tissue two and six hours following instillation was 11-13 fold higher compared with drug alone (same total dosage), and b) the levels of MMC in the plasma were significantly lower than drug instilled alone.

properties which enable it to convert from a liquid state when cold into a gel at body temperature. In its liquid state, ICDR can easily be mixed with a specific drug for convenient cath-

eter delivery into the bladder (as performed in the standard intravesical chemotherapy). Once inside the bladder, it solidifies, adheres to the mucosal layer and forms a drug reservoir. Upon contact with urine the gel reservoir dissolves and gel micelles entrapping the drug adhere to the mucosal layer of the bladder.

"PROLONGATION OF INTRAVESICAL TREATMENT DWELL TIME IS IMPERATIVE FOR ENHANCING THE ANTI-TUMOUR EFFECT OF THE INSTILLED CHEMOTHERAPY"

eter delivery into the bladder (as performed in the standard intravesical chemotherapy). Once inside the bladder, it solidifies, adheres to the mucosal layer and forms a drug reservoir. Upon contact with urine the gel reservoir dissolves and gel micelles entrapping the drug adhere to the mucosal layer of the bladder.

The drug is slowly released, keeping high and effective tissue drug concentration for a longer period of time (approximately 6-8 hours). During the release of the drug, the gel

is slowly dissolved and no traces of the gel are present after the treatment period. Since the gel dissolution is gradual, the gel delays the voiding of the drug from the bladder once the first uri-

ICDR CHARACTERISTICS

nation occurs (in contrast to the standard intravesical chemotherapy) as well as decreases drug dilution by the ongoing produced urine which continuously enters the bladder (Figure 1).

ICDR is a thermo-sensitive hydrogel with reverse thermal gelation (RTG) properties: it has high viscosity at body temperature and very low viscosity (fluid like) at 5°C. This temper-

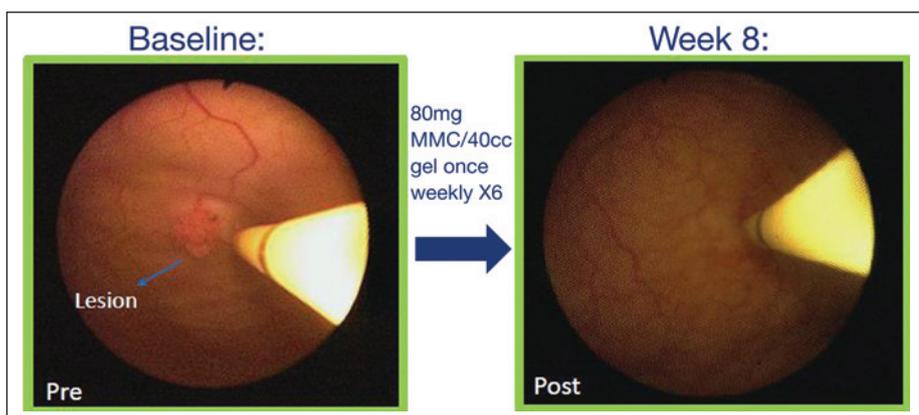


Figure 3: After six weekly instillations of MMC mixed with ICDR, the tumours were completely removed in a patient with superficial bladder cancer.

Photo courtesy of Dr Sudhir K Rawal, Director Surgical Oncology & Chief of Surgical Gynae Uro-Oncology, Rajiv Gandhi Cancer Institute and Research Centre, India.

ature-dependent viscosity characteristic allows for simple instillation of the cooled liquid gel into the bladder.

The hydrogel is formulated solely with well-known ingredients, approved by the US FDA as inactive ingredients and widely used as excipients in numerous commercial formulations. The hydrogel is 100% biocompatible.

Following mixing with a drug, the gel is capable of storing the drug without changing the drug structure and activity. It is considered inert with no expected chemically modifying interaction within the gel and between the gel and its loaded drug. The gel formulation can be easily adjusted and tailored for retention of various drugs and delivery rates ranging from 3-24 hours.

The amphiphilic nature of ICDR facilitates incorporation of both hydrophilic and hydrophobic drugs.

It is water soluble, insensitive to pH, and also muco-adhesive and flexible, complying with the natural volume and shape changes of the internal cavity under treatment

PRECLINICAL & CLINICAL STUDIES

ICDR was shown to cause no damage to the bladder, ureter or urethral tissues (preclinical results) and had no significant effect on instillation safety (preclinical and clinical results).

Studies in large animals (pigs) testing intravesical instillation of MMC in ICDR demonstrated a lower systematic exposure to MMC in comparison with standard treatment. MMC plasma levels were far below the blood toxic MMC levels. The lower systematic exposure of TheraCoat's treatment suggests that TheraCoat's treatment has the potential to lower adverse event rate and lower side effects leading to higher patient compliance. In addition, gel residues with MMC were detected in the pig bladder six hours following instillation, supporting the retention capabilities of the TheraCoat system.

Thus, the preclinical results demonstrate that ICDR increases the availability of MMC to the tissue and prolong its exposure duration (Figure 2a) while decreasing MMC exposure to the systemic circulation (Figure 2b).

Clinical safety studies with patients following single or multiple instillations with ICDR with and without MMC showed:

- Smooth injection of gel through catheter
- Catheter removal five minutes post instillation
- No bladder contraction due to gel instillation
- Free urination and no obstructive symptoms
- No study-related adverse events.

Preliminary results from ongoing clinical studies show efficacy of the delivery system in tumour ablation in low-grade bladder cancer patients. Figure 3 demonstrates a complete response to treatment (tumours were completely removed) in a patient after six weekly instillations of MMC with TheraCoat's ICDR.

FUTURE DIRECTIONS

Current treatments for bladder diseases, including bladder cancer, comprise local intravesical drug instillations, but these treatments have largely proven to be insufficient. Scientific literature strongly supports that the longer the tumour tissue is exposed to chemotherapy the more effective it is to kill cancer cells, but once a drug is delivered into the bladder, it is quickly diluted and excreted due to continuous urine creation and voiding. Thereby, a clear unmet need exists for means to prolong drug retention and tissue exposure in order to improve efficacy.

TheraCoat effectively overcomes current treatment drawbacks and has developed a new proprietary drug delivery system for local treatment of bladder diseases. The novel hydrogel-based system enables controlled and longer exposure of bladder tissue to therapeutic agents as

compared with standard intravesical instillations.

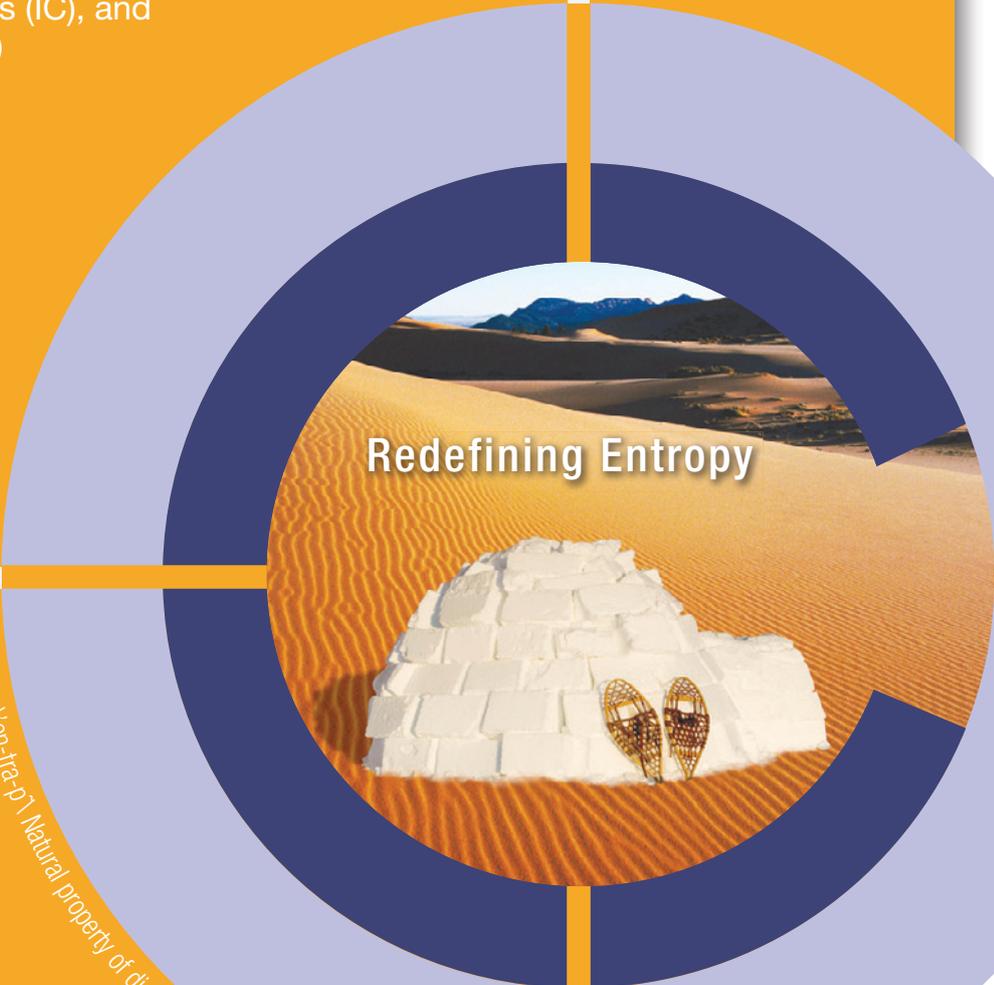
In addition to bladder cancer, TheraCoat is currently developing improved delivery modes for a number of bladder diseases including upper tract urothelial carcinoma, interstitial cystitis and overactive bladder.

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Novel drug delivery solutions for the optimal treatment of bladder diseases

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Publication Month	Issue Topic	Materials Deadline
October 2013	Prefilled Syringes	Issue now closed
November 2013	Pulmonary & Nasal Drug Delivery (OINDP)	Extended
December 2013	Delivering Biotherapeutics	November 4th
January 2014	Ophthalmic Drug Delivery	December 9th
February 2014	Prefilled Syringes	January 13th
March 2014	Transdermal Patches, Microneedles & Needle-Free Injection	February 10th
April 2014	Pulmonary & Nasal Drug Delivery	March 10th
May 2014	Injectable Drug Delivery 2014: Devices Focus	April 14th
June 2014	Injectable Drug Delivery 2014: Pharmaceuticals Focus	May 12th
July 2014	Novel Oral Delivery Systems	June 9th
September 2014	Drug Formulation & Delivery, Services & Solutions 2014	August 4th

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PREFILLED SYRINGES FOR VISCOUS FORMULATIONS

In this article, Mahesh Chaubal, PhD, Senior Director, Drug Development, R&D Medical Products, Baxter Healthcare Corporation, provides a glimpse of some of the challenges faced during the development of viscous formulations of biopharmaceutical products for injection, from a formulator's perspective, especially when the finished product is filled in a prefilled syringe.

Prefilled syringes represent a patient-friendly and compliant way to administer drugs in an alternate setting such as the home. This makes them an appropriate device for drugs that are administered chronically.

Prefilled syringes have gained popularity over last two decades due to the emergence of biologics as a major class of injectable therapeutics.¹ Today, biologics are used for the treatment of various acute and chronic conditions. For chronic conditions, the final dosage form should be patient friendly, such that the patient can self-administer and avoid the costs of using a healthcare provider. However, a downside of chronically administered drugs is the frequency of injections. In an effort to reduce the frequency of injections, formulators often try to load a significant dose in a single injection that must then be delivered. High-dose formulations pose significant challenges from a formulation and fill-finish perspective.

Typically, drug stability over the duration of the product's shelf-life is a formulator's main focus. However, when developing dosage forms for self-administration, additional factors have to be taken into consideration. These include performance of the device over the shelf-life, and the human factor aspects of the device usability. The importance of the latter is visible in the US FDA's guidance on using human factors for medical devices.²

For viscous formulations, device performance and human factors become even more important, given that a viscous formulation may be harder to administer via a prefilled syringe. The interplay between these various factors is demonstrated in this brief case study for developing a viscous formulation in a prefilled syringe format.

FORMULATOR PERSPECTIVE

High-concentration drugs that are administered chronically are formulated to provide sustained release. This can be achieved via either the use of a release rate modifier or intrinsically long half-life of the drug. Release-rate modifiers include polymers formulated as microspheres or gels, as well as oily depots wherein the drug is dissolved in pharmaceutically acceptable oil. In each case, the release-rate modifier (or high concentration of the drug) result in a formulation that has high viscosity.³ Figure 1 lists some of the potential drug formulations that involve high viscosity.

When dealing with highly viscous formulations, the end-user perspective is important upfront at the formulation development stage. Highly viscous formulations cause challenges during various process steps, such as transfer operations (pumping) and

Type of viscous formulation	Example product
Polymer-solvent gels	Eligard
Polymer solutions	Hyalgan
Oily formulations	Faslodex
Microspheres	Lupron depot
High concentration MABs	Kineret (150 mg/mL)

Figure 1: Table listing examples of marketed high viscosity formulations available in prefilled syringes.

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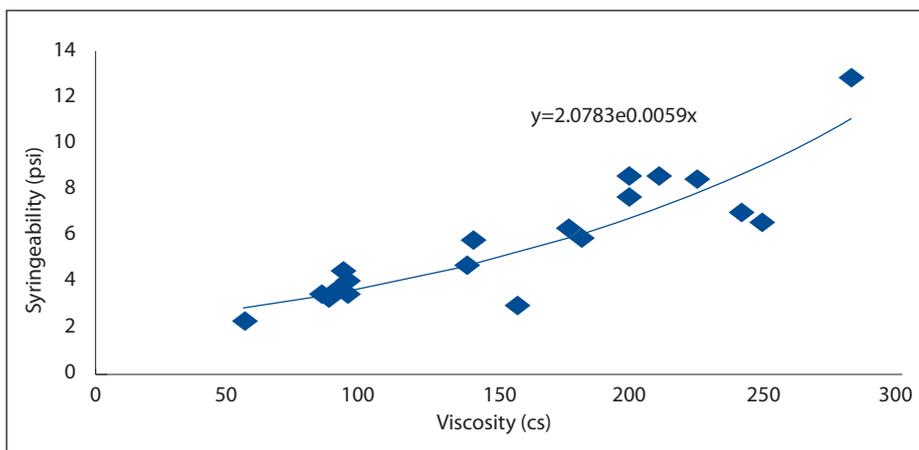


Figure 2: Relationship between viscosity and syringeability for an oily formulation injected using a glass prefilled syringe.

filtration, among others. If the final container closure is a prefilled syringe, then high viscosity can also cause problems with the syringeability of the final formulation.

Syringeability or injectability is the ability/ease by which a formulation can be dispensed out of a syringe. Currently, no harmonised approach exists for testing the syringeability of a drug. Limited literature data is available that describes various approaches for evaluating syringeability.^{4,6} Formulators often mistakenly assume a direct correlation between syringeability and viscosity and hence use viscosity of the drug solution as a surrogate measure of syringeability.

In this study, syringeability from a BD Hypak glass prefilled syringe was measured directly using the Hagen-Poiseuille equation, which is used to assess the pressure differential across a pipe during flow. In this case, flow through a needle as the formulation is pushed out is analogous and hence justifies the use of this equation:

$$\Delta P = 8QL\mu/\pi r^4$$

where P is the pressure across the needle, Q is the injection speed, μ is the viscosity of the formulation, L is the length of the needle and r is the radius of the needle.

As can be seen in Figure 2, during formulation optimisation studies for an oily depot formulation, a direct correlation could be obtained between the viscosity of the formulation and the respective syringeability of the product from a prefilled syringe.

In order to assess the viability of syringing

this viscous formulation, the viscosity of the formulation was compared with other viscous products. Figure 3 shows that when the viscosity of the formulation was compared with another commercially available viscous product, Hyalgan (sodium hyaluronate; Fida, Italy), it was observed that while the two formulations had similar viscosity, there was a significant difference in their syringeability. Hyalgan is a formulation of hyaluronic acid which is a thixotropic polymer gel.⁷ Hence viscosity of the formulation decreases during the syringing process. Another product listed in Figure 1, Eligard (leuprolide acetate; Sanofi, France), utilises the shear thinning property of poly(lactic-co-glycolic acid) (PLGA) solutions to reduce the viscosity of the formulation prior to administration.⁸ This demonstrates that while viscosity is an important formulation parameter, it is not always indicative of the syringeability of the product and hence specific studies are required in the prefilled syringe of choice.

Given the high syringeability forces required for the test article, the formulation was modified by changing the oil-drug ratio and also by adding a solvent to reduce viscosity. This resulted in a formulation that demonstrated acceptable forces for syringeability of the product through a typical BD Hypak glass syringe.

SUMMARY

Prefilled syringes are a preferred container closure system for delivery of chronically delivered formulations, due to ease of

administration in an alternate setting, such as at home. However, this format adds complexities, compared with the conventional vial format. This report provides a case study of the interplay between formulation development and fill-finish configuration development. It is essential for the two activities to occur simultaneously to develop an effective product. In this specific case, an effective formulation in prefilled syringe was developed by manipulating the oil-to-cosolvent ratio of the oily depot formulation.

Use of the appropriate fill-finish partner is important in developing such complex formulations. Baxter's BioPharma Solutions business has in-house capability to support formulation development and fill-finish aspects of viscous formulations in prefilled syringes.

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Formulation	Viscosity	Syringe DP	Instron Force Measurement (N)	
			Mean force, 1 mL	Mean force 3mL
	Cp	psi	Mean force, 1 mL	Mean force 3mL
Hyalgan	284	3.94	2.3	NP
Castor oil	912	25.1	NP	90.9
Test article	283	12.85	6.9	37.8

Figure 3: Comparison of viscosity and syringeability of an oily depot formulation with a commercial viscous product.



PROTEIN SOLUBILITY CAN BE ENHANCED AT VARIOUS POINTS ALONG THE PRODUCTION PIPELINE

In this short article, Michelle Amaral, PhD, Science Writer/PR Consultant, Soluble Therapeutics, summarises some of the techniques available for the generation of different formulations of recombinant protein therapeutics, and high-throughput technologies that reduce the time required to screen for the optimal formulation.

A revolutionary moment for the pharmaceutical industry occurred with the advent of recombinant technologies, which enabled proteins to be manufactured and then delivered to humans or animals for the purpose of treating illness and disease. As a result, a wide range of therapeutic approaches opened up: aberrant proteins causing a disease state could be replaced; novel proteins combatting a particular disease could be introduced; and delivery of small-molecule pharmaceuticals could be enhanced through conjugation to a protein or antibody.

In the late 1970s, insulin was the first human protein to be produced using genetic engineering technologies and became commercially available in 1982, greatly advancing the treatment of diabetes. However, the use of proteins in therapeutic strategies presents a number of challenges, namely the requirement that a protein be highly concentrated, stable, and active in solution when delivered.

Fresh, innovative approaches are now providing valuable solutions for protein pharmaceuticals. The aforementioned challenges can be confronted at various points along the path of protein production. In the early stages of development, a protein's solubility can be affected by the choice of expression vector and the option of adding a fusion tag to the protein of interest. Further downstream, self-interaction chromatography (SIC) is being used as a fast

and effective method for determining the most optimal formulation of a protein solution.

The selection of a high-performance expression vector is a must when creating a strategy for recombinant protein production, as it can play an integral role in promoting a soluble product in addition to an optimal yield. In many cases, these vectors encode for extra amino acids that are then attached, or fused, to the protein of interest upon expression. The result is a fusion protein with greater solubility than that of the native macromolecule expressed alone. Oftentimes, the fusion partner even contains a region of histidine "tags" that enable quick, efficient purification with affinity chromatography and a cleavage site that allows its subsequent removal using a specific protease treatment.

A fusion partner can range in size from a few amino acids to approximately 25 kDa. The added residues create disorder, allowing greater distance between each protein molecule and thus giving the protein of interest "space" to fold properly. This process enhances solubility of the target protein and prevents aggregation. Activity assays have been performed on numerous representative proteins, demonstrating that functionality is preserved.

Protein solubility can also be enhanced after its production by formulating a buffer solution with conditions that are optimal for proper folding and stability. This is an important step along



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the pipeline, as protein pharmaceuticals must be highly concentrated so efficacious levels can be reached when delivered to a patient. At such high concentrations, however, proteins have a tendency to precipitate out of solution, aggregate, or form a highly viscous phase - all of which are not amenable to storage or delivery of the drug, since the protein's activity becomes compromised. Unfortunately, standard recipes for these formulations do not exist, and the conditions for each protein can vary greatly. Each component must be determined empirically, varying such characteristics as pH, additives, and salt concentration. But with such an array of components from which to choose, finding optimal formulations can prove to be a monumental task requiring upwards of one year to complete.

Self-interaction chromatography has been recently introduced as a powerful method for developing highly concentrated protein formulations - and in just a matter of weeks. SIC is a technique that measures the extent of a protein's interaction with itself, and its applicability is generally unaffected by the vast array of additives available to the typical formulation professional.

Other methods of measuring protein-protein interactions are sometimes limited because of

the light scattering effects of some additives. SIC requires a small amount of protein that is covalently attached to beads and packed into a microcapillary HPLC column. The mobile phase of the SIC experiments consists of the formulation being tested, along with a 1 μ l bolus injection of the protein of interest. The elution of the protein injected in the mobile phase is measured via UV detection and the retention time is used to evaluate whether or not the formulation or additive of interest is causing attraction or repulsion between the protein molecules.

Data collected via SIC enables the calculation of a parameter that quantitatively describes the protein's interaction with itself; this is the second virial coefficient, or B value. The B value is the sum of all potential forces between two proteins including ionic, dipole, hydrophobic, and van der Waals forces; it is a measure of protein flexibility in all orientations and distances. In general, positive B values indicate a net repulsion between two protein molecules while negative B values indicate a net attraction. When additives are introduced into solutions, the B value is altered such that the protein molecules display mild attraction to each other, which is conducive to crystallisation, or enhanced repulsion, which increases the

protein's physical stability and solubility.

Experimentally determined B values can be used to predict the B value of a protein in over 12,000 other formulations using an artificial neural network. This is a wealth of information for groups that are developing a new biopharmaceutical. Differential scanning calorimetry and other biophysical techniques are performed to confirm a complete characterization profile on the final solutions.

Treatments for disease have drastically improved since the advent of protein therapeutics. In order to be successful, though, a protein must be highly concentrated, stable, and active in solution without aggregation or other phase changes that are detrimental to the drug delivery process and the patient. Solubility can be enhanced at several points along the protein production pipeline. Creating disorder by fusing extra amino acid residues to the protein of interest generates distance between each molecule, enhancing the ability of the protein to fold correctly. An optimal formulation for the protein of interest is crucial for protein performance as well.

High-throughput methods that screen components of the solution save time and money for a company developing a promising drug.



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