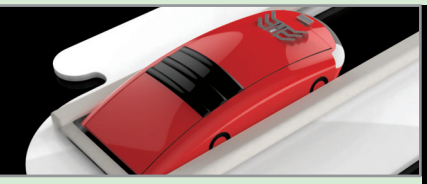
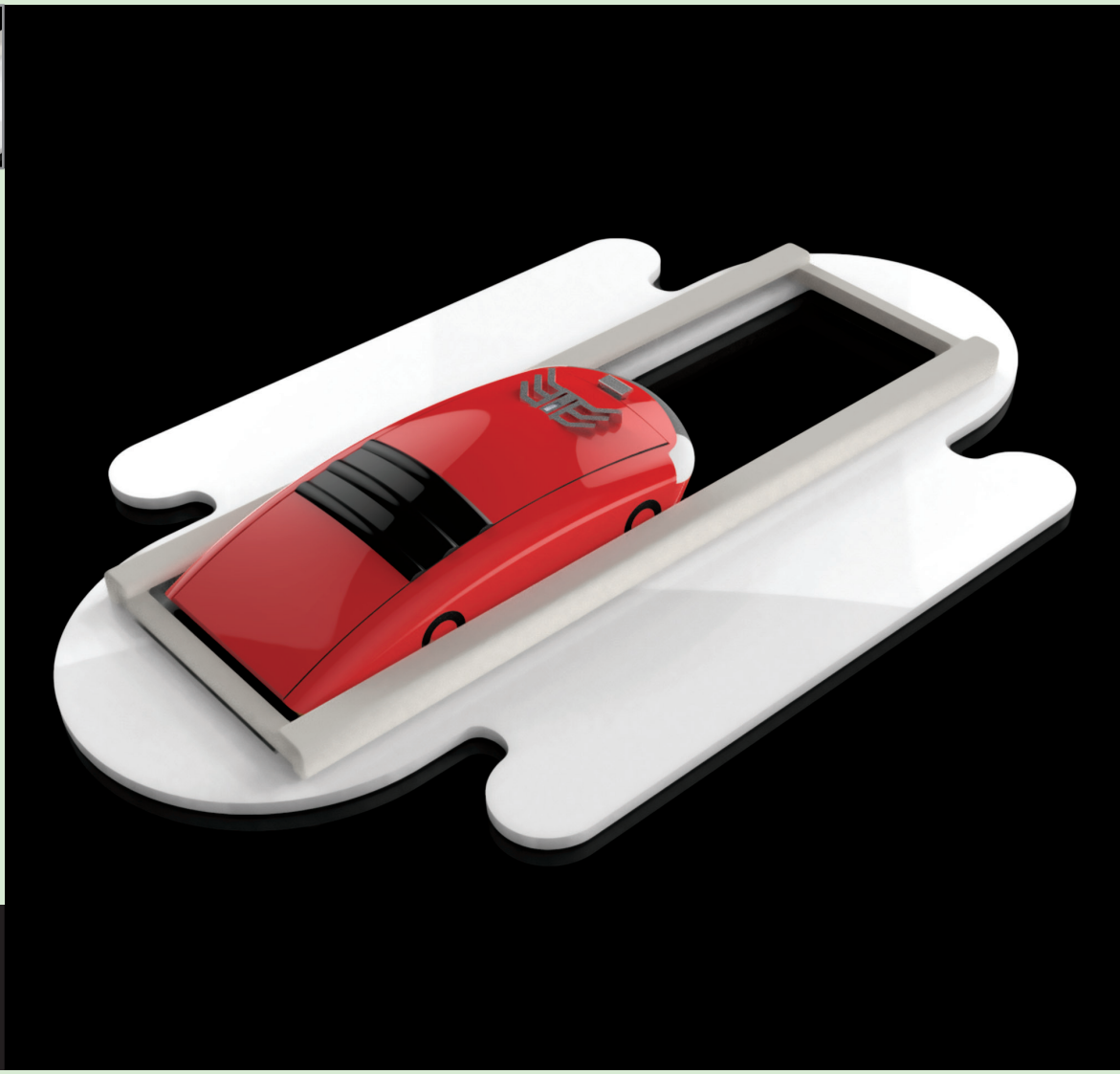
INJECTABLE DRUG DELIVERY 2012:
FORMULATIONS FOCUS



ONdrugDelivery
JUNE 2012
ISSUE NO 32
ISSN-2049-145X



ONdrugDELIVERY
niche information & intelligence

www.ondrugdelivery.com

Battelle

DEBIOTECH S.A. Switzerland
Innovative Medical Systems

np Nemaura PHARMA

novozymes®
Rethink Tomorrow

SEPPIC

ONdrugDelivery Issue No 32, June 2012

"Injectable Drug Delivery 2012: Formulations Focus"

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR 2H 2012:

Jun	Injectable Drug Delivery : Devices Focus
Jul	Oral Drug Delivery
Aug	CDMOs & CROs Offering Drug Delivery Solutions & Services
Sep	Drug Delivery in Diabetes
Oct	Prefilled Syringes
Nov	Pulmonary & Nasal Delivery (OINDP)
Dec	Delivering Biotherapeutics

SUBSCRIPTIONS:
To arrange your **FREE** subscription (pdf or print) to ONdrugDelivery, contact: Guy Furness, Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

SPONSORSHIP/ADVERTISING:
Contact: Guy Furness, Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:
Frederick Furness Publishing
48, Albany Villas, Hove, East Sussex, BN3 2RW
United Kingdom

PRODUCTION/DESIGN:
Mark Frost
www.frostmark.co.uk

ONdrugDelivery is published by Frederick Furness Publishing.
(ISSN 2049-145X print / ISSN 2049-1468 pdf)

Front cover image: ""Vaccine Delivery Made Child's Play", a Micropatch microneedle delivery device with racing car design, from Nemaura Pharma Ltd. Reproduced with kind permission.

CONTENTS

SCRIP
Insights

NEW REPORT

Drug Delivery Partnership Strategies

Case studies in effective licensing, collaboration, and therapeutic differentiation

About the Report

How is drug delivery partnering changing, and how will this affect your future deal-making?

Innovative drug delivery technologies are playing an increasingly important role in extending lifecycles, differentiating me-too products and unlocking the value of new compounds with challenging delivery requirements.

This report builds on interviews with industry executives, case studies, and analysis of deal and market data to set out strategies to help you optimally partner for enhanced drug delivery products.

Learn from interviews with senior drug delivery partnering executives.

Develop effective partnering strategies based on case studies and analysis of market data.

Unlock therapeutic value of new biopharmaceutical developments by strategic collaborations for innovative drug delivery technologies.

Optimize value from drug delivery partnerships to deliver successful differentiation from novel drug delivery applications.

Understand current and future trends in drug delivery deal-making in order to plan effective partnering strategy.

Visit **www.research-store.com/ondrugdelivery** to order now

novozymes®
Rethink Tomorrow

IMPROVING BIOTHERAPEUTICS FORMULATION: ALTERNATIVES TO HUMAN- AND ANIMAL-DERIVED EXCIPIENTS

In this article, Mark Perkins, PhD, Customer Solution Specialist, Novozymes Biopharma, describes the role of excipients in biotherapeutics, possible disadvantages from the use of animal-derived excipients, and the advantages, including ethical, regulatory, time and cost benefits, of using recombinant versions.

The term "excipient" describes a raw material that is added to a drug to provide suitable consistency or form. Ultimately designed to aid in the preparation of a stable drug formulation that has a particular shelf-life and bioavailability, it is an inactive material that can perform a variety of functions. These functions significantly differ between small-molecule pharmaceuticals and large-molecule biotherapeutic formulations.

Excipients can assist tablet formulation in small-molecule pharmaceuticals in a number of ways, for example, by affecting compressibility or performing the role of lubricant, glider, filler or disintegrant. However, in biotherapeutics (proteins, peptides and vaccines) although the goal of a stable, safe formulation is still essential, the process of formulation creates different challenges.

Proteins can be made inactive by heat, denaturation from liquid shear or denaturation at air-liquid interfaces. In addition, solution pH and buffer components can also inactivate these molecules. As well as the usual drug degradation pathways such as oxidation, racemisation and hydrolosis, biotherapeutics are further subject to disulphide exchange, beta elimination, aggregation and deamidation. As with small molecules, while there is no typical formulation for biotherapeutics, some generalities can be considered.

"THIS SIMPLE APPROACH OF ADDING ANIMAL- OR HUMAN-DERIVED PROTEINS TO FORMULATIONS HAS BEEN THE SUBJECT OF CLOSE SCRUTINY OVER RECENT YEARS. MANY FORMULATION SCIENTISTS HAVE MOVED AWAY FROM USING THESE PROTEINS"

CONSIDERATIONS IN THE FORMULATION OF BIOTHERAPEUTICS

The formulation of a biotherapeutic will contain salts and have an optimal solution pH. The pH of the formulation has two significant effects; the obvious one being that the pH has to be within a range in which the protein is stable and active. The second is that deviation from physiological pH will result in the patient suffering injection site pain during administration of the drug. The salts present are often targeted to physiological level or isotonicity. Therefore, if the protein is

Dr Mark Perkins
Customer Solution Specialist
T: +44 115 955 3355
E: mrpk@novozymes.com

Contact
Niklas Andersson
Global Communications Manager
T: +44 115 955 3355
E: NLAN@novozymes.com

Novozymes Biopharma US Inc
One Broadway, 14th Floor
Cambridge
MA 02142
United States

T: +1 617 401 2500
(US Sales Office)

T: +45 4446 2896
(EU Sales Office)

E: biopharma@novozymes.com

www.biopharma.novozymes.com

Sugars	Trehalose	**Amino Acids**	Histidine
	Mannose		Aspartic Acid
	Sucrose		Alanine
	Dextrose		Glutamic Acid
Polyols	Sorbitol	**Polymers**	Polysorbate
	Mannitol		Albumin
	Glycerol		Gelatin

Table 1: Commonly used excipients in biotherapeutic formulations.

not stable under these conditions, it is necessary to find further excipients to create stability. Some commonly used excipients are listed in Table 1.

These excipients can help to achieve the reconstitution of a protein, stabilisation of the product in solution and can aid lyophilisation. One specific challenge associated with proteins in liquid formulations is denaturation at the air-liquid interface. To minimise this problem, detergents, usually of a non-ionic nature, are generally used. A typical non-iconic detergent used in many protein formulations is polysorbate. This family of detergents is based on a polyoxyethylene backbone with a side chain containing sorbitan and a fatty acid, polysorbate 20, 40 and 80, having laurate, palmitate or oleate, respectively, as the side chain.

The action of the amphipathic detergent's molecules gathering at the air-liquid interface, combined with the hydrophobic moiety in the air and the hydrophilic tail in the aqueous environment, is considered to prevent the denaturation at this interface. However, the combinations of pH, detergent and low-molecular-weight excipients may still not be enough to produce an optimal formulation for many protein-based biotherapeutics, which are most often required in very small therapeutic doses and can be denatured by surface adsorption to glass containers or container closures such as butyl septa.

As a result, many formulations require a bulking agent; the two proteins that have been widely used are human serum albumin (HSA) and gelatin. These can be added in large excess over the active protein and therefore reduce the risk of denaturation by surface absorption, as well as contribute to the reconstitution of lyophilised products. Compared with expensive biotherapeutics, which are prepared via cell culture, cell separation and downstream processing, gelatin and HSA are relatively inexpensive and commercially available in large quantities.

CONCERNS REGARDING GELATIN AND HSA

Approximately 50,000 metric tonnes of gelatin, chemically extracted from animal hides and bones, is produced annually for medical use. It is mostly used in oral drug delivery, such as capsule format.[1] Due to the differences in extraction procedures from company-to-company and the relatively crude nature of the extraction procedure, there is significant source and batch-to-batch variability that can affect the physiochemical properties of the gelatin. This can in turn affect the product in which the gelatin is used.

HSA is the most abundant protein in blood, present at a concentration of approximately 42g/l.[2] Since 1940, albumin has been fractionated from blood plasma[3] for use as a blood volume replacement and to treat burns victims. Today, HSA can be considered as a low-cost side-fraction generated when purifying expensive blood components such as IgG and factor VIII.

HSA has been widely used as an excipient to stabilise a number of therapeutic proteins (see Table 2). Additionally, as it is a human-derived protein and there are instances of allergic response to animal-derived gelatins, it can be regarded as the stabiliser of choice, immunologically speaking.[4,5] However, this simple approach of adding animal- or human-derived proteins to formulations has been the subject of close scrutiny over recent years. Many formulation scientists have moved away from using these proteins due to concerns that blood-borne contaminants such as mycoplasma, prions or viruses may potentially contaminate the final drug product.

RECOMBINANT PROTEIN EXCIPIENTS

The potential for prion and viral contamination of these excipients and the fact that gelatin and HSA are heterogeneous protein preparations and relatively impure, have driven the development of recombinant versions. Gelatin is a heterogeneous mixture of polypeptides, whilst HSA has a pharmocopoeial purity of only 96% (USP), the rest of the protein present being a mixture of polymers of HSA and other plasma proteins that remain from the purification. Additionally, these other proteins are denatured during the pasteurisation process that HSA final product undergoes. Given the very high purity of recombinant DNA-derived biotherapeutics, it seems somewhat illogical to adulterate them with relatively poorly defined excipients.

In comparison, animal-free components offer an ethical, safe solution for the production of ingredients that form the basis of biological products. These ingredients are gaining popularity as regulatory authorities begin to implement strict quality control measures on products to improve safety, particularly with potential contamination risks. The development and application of animal-free solutions for the production of biopharmaceuticals has many safety and regulatory advantages, and in addition is economically viable and commercially scalable.

BENEFITS OF RECOMBINANT PROTEIN EXCIPIENTS

An alternative solution to the costly and time-consuming search for a new formulation for a product containing a protein excipient has emerged from the same source as the biotherapeutics, namely recombinant DNA technology. Using genetically modified yeast it has been possible to express and purify recombinant gelatin and recombinant human albumin for use as excipients.

FibroGen (San Francisco, CA, US) has engineered human gelatins from specific segments of human collagen genes. They are expressed in the methylotrophic yeast Pichia pastoris and manufactured avoiding the use of animal- or human-derived materials. FibroGen's proprietary technology allows the production of discrete, reproducible batches of gelatin fragments

Protein	Trade Name
Erythropoietin	Epogen™ and Procrit™ (Amgen Inc)
Interferon alfa-2b	Intron A™ (Schering Corporation)
Antihaemophilic factor (FVIII)	Bioclate™ (Baxter Healthcare Corporation)
Tissue necrosis factor alpha-1a	Beromun ™ (Boehringer Ingelheim GmbH)
Interferon beta-1a	Avonex™ (Biogen BV)

Table 2: A selection of therapeutic proteins containing HSA as an excipient.

"BY INCLUDING rALBUMIN IN THE FORMULATION STRATEGY, DRUG MANUFACTURERS CAN REDUCE DEVELOPMENT TIMELINES, GETTING THE FINAL PRODUCT TO MARKET SOONER"

with specific molecular weights, providing customers with the ability to select a product optimised for specific applications.[2]

In response to industry demands, Novozymes Biopharma has developed a range of high-quality, animal-free recombinant human albumins (rAlbumins) specifically for use in drug delivery and formulation. Developed from a proprietary Saccharomyces cerevisae yeast strain, Novozymes' Recombumin® and Albucult® rAlbumins are manufactured to cGMP quality standards and have been shown to stabilise proteins by preventing aggregation, especially amyloid-like fibril products, while also acting as an antioxidant in preventing protein oxidation and as a blocking agent to prevent nonspecific adsorption to surfaces. The products offer security of supply and batch-to-batch consistency, while providing increased efficiency for companies looking for a compliant albumin alternative.

rAlbumins are structurally identical to HSA but significantly purer and can act as multifunctional excipients. Their use reduces the requirement for multiple excipients, such as sugars, amino acids and detergents (SADs) in a formulation and delivers a safe and consistent ingredient that enhances the stability and performance of the manufacturer's finished drug product.

In addition, Novozymes rAlbumins have unprecedented technical and regulatory support. Manufactured in large-scale facilities, USP-NF compliant and supported by a strongly documented safety package and drug master file (DMF), they reduce registration and regulatory issues. By including rAlbumin in the formulation strategy, drug manufacturers can reduce development timelines, getting the final product to market sooner.

CONCLUSION

Over recent years, the demand for animal-free ingredients has increased, with regulatory authorities enforcing more stringent controls on pharmaceutical products to improve safety, particularly with potential contamination risks from animal-derived ingredients.

rAlbumins offer the industry a viable alternative to HSA, providing the potential to improve both the safety and performance of new drugs. These innovative products have been designed to deliver a more consistent source of albumin, while decreasing regulatory burden. As a result, manufacturers are able to optimise the safety, functionality and quality of their formulations, with the potential to offer significant benefits for patients.

REFERENCES

1. *Cohn EJ, "The Properties and Functions of the Plasma Proteins, with a Consideration of the Methods for their Separation and Purification". Chem Rev, 1941, 28, pp 395-417.*
2. *Olsen D, Yang C, Bodo M, Chang R, Leigh S, Baez J, Carmichael D, Perälä M, Hämäläinen ER, Jarvinen M and Polarek J, "Recombinant collagen and gelatin for drug delivery". Advanced Drug Delivery Reviews, 2003, 55, pp 1547-1567.*
3. *Peters T, "All About Albumin". Academic Press, 1996, ISBN 0-12 552110-3,*
4. *Cooperman, L and Michaeli D, "The immunogenicity of injectable collagen". J Am Acad Dermatol, 1984, 10, pp 638-651.*
5. *Sakaguchi M and Inouye S, "Systemic allergic reactions to gelatin included in vaccines as a stabilizer". Jpn J Infect Dis, 2000, 53, pp 189-195.*

ABOUT NOVOZYMES

Novozymes Biopharma develops and manufactures high-quality, animal-free, and regulatory-compliant recombinant ingredients and technologies to provide pharmaceutical and medical device manufacturers the knowledge-based solutions needed to address the challenges in developing innovative, safer, and more consistent products. The company's large-scale manufacturing facilities worldwide are run to cGMP Q7 quality standards, ensuring customers the highest level of product quality and consistency, as well as the security of long-term supply. Novozymes' customer-integrated approach combines the company's scientific know-how and the specific needs of customers to deliver improved products and performance.

With >25 years' experience in the pharma industry, Novozymes is the world leader in the supply of recombinant products and technologies to the medical device and drug delivery market. Currently, 14% of the company's revenue is spent on R&D, demonstrating a commitment to scientific innovation.

By combining Novozymes' unique knowledge around our biological solutions such as recombinant albumin and hyaluronic acid with the specific application knowledge of our customers, we work with companies to deliver improved performance and safety for next- generation medical device and pharma products.

ABOUT THE AUTHOR

Mark Perkins is a formulation chemist with a PhD in Pharmaceutical Sciences from the University of Nottingham. He joined Novozymes Biopharma in 2010 as a customer solutions specialist. In this role he works with partners that are evaluating Novozymes' recombinant albumin products and technologies in the areas of biopharmaceutical formulation and half-life extension. Prior to this position, Mark worked as a materials specialist at an inhaled drug development company and as a project manager at an analytical consultancy.

MES STABILITY BIO

IS OUR MIDDLE NAME

Recombinant albumin USP-NF* - An ideal drug stabilizer

Novozymes' high quality recombinant albumins (rAlbumin) are developed and optimized for drug delivery and formulation. Manufactured to cGMP quality standards in large-scale facilities, our rAlbumins are supported by a comprehensive drug master file.

Ideal for stabilization, Novozymes' rAlbumins can help:

- **Acheive liquid formulations of protein therapeutics**
- **Limit protein loss due to non-specific adsorption**
- **Prevent functional or structural changes caused by oxidation**
- **Reduce aggregation/sub-visible particle formation and therefore potential immunogenicity concerns**

Find out more about how our rAlbumins can help you stabilize your drug by visiting our website or email us at **biopharma@novozymes.com**

*Meets National Formulary (NF) standards as published by United States Pharmacopeia (USP).

MAKING PRODUCTS BETTER TOGETHER

www.stabilizeyourformulation.com

novozymes®
Rethink Tomorrow

The Forefront of Delivery Science and Technology

The 39th Annual Meeting & Exposition of the Controlled Release Society

July 15–18, 2012
Centre des congrès de Québec
Québec City, Canada

Smart Materials—From Innovation to Translation

The Controlled Release Society (CRS) is the premier international, multi-disciplinary society dedicated to delivery science and technology. The Annual Meeting & Exposition gathers scientists from around the world and showcases:

- World-renowned plenary speakers, sessions, mini-symposia, and roundtables covering mucosal, oral, transdermal, and DNA and RNAi delivery; drug delivery to the brain; and much more
- CRS Innovation Sunday, connecting you with people, companies, novel technologies, and research that address challenges in delivery
- Premier research delivered through 200 presentations and 400 posters
- An exhibition giving you direct contact to more than 100 companies in delivery science and technology

Registration and Housing Now Open
Exhibit Space Currently Available

Fountaine de Tourny (Fountain) in front of the Parliament. La Maison Simons

CRS
Leading Delivery Science and Technology

www.controlledreleasesociety.org/meeting

COMPANY PROFILE – SEPPIC

"SEPPIC HAS BEEN DEVELOPING A NEW RANGE OF POWERFUL AND PATENTED SOLUBILISERS COMING FROM OUR RESEARCH IN LIPOAMINOACID TECHNOLOGY. THEY ARE DESIGNED TO DISSOLVE VERY POORLY SOLUBLE ACTIVES, PEPTIDES OR PROTEINS IN WATER FOR ORAL, TOPICAL AND PARENTERAL APPLICATIONS"

For more than 60 years, SEPPIC has created, developed and supplied innovative specialty chemicals and natural ingredients for various markets including cosmetics, pharmaceuticals, nutrition and industry.

As a subsidiary of AIR LIQUIDE Group since 1986, fully integrated in the Healthcare World Operations division, SEPPIC combines the organisational skills and energy of a medium-sized company with the strength of a large international group. Our policy of partnerships together with a strong financial capacity has enabled us to bring leading-edge technologies to the Health and Beauty markets.

Our ambition is to be a global supplier of first-class specialty ingredients to improve overall efficacy and safety to our customers' formulations.

Thanks to a strong expertise in galenic, emulsion, biology and immunology, SEPPIC provides a large range of actives and excipients for manufacturing drugs and vaccines. Among our areas of expertise, we provide adjuvants for therapeutic vaccines and non ionic surfactants dedicated to sterile drug formulations.

Heloise Imbault
Account Manager, Vaccine Adjuvants & Injectables
T: +1 973 882 5597
F: +1 973 882 5178
E: heloise.imbault@airliquide.com

SEPPIC, Inc
30 Two Bridges Road, Suite 210
Fairfield, NJ 07004
United States

www.seppic.com

Our R&D Technical Centres are fully dedicated to our customers' projects; we provide technical assistance, regulatory support and training courses in the US, Europe & Asia.

STERILE DOSAGE FORM EXPERTISE

SEPPIC continuously designs and expands its range of excipients to meet customers' needs.

We have developed a specific range of surfactants, solubilisers and emulsifiers dedicated to parenteral and ophthalmic formulations. These products are manufactured under the most stringent quality standards and comply with current pharmacopoeias. The PPI range contains high quality grade Polysorbates (MONTANOX™ PPI line) and Sorbitan Esters (MONTANE™ PPI line).

SEPPIC controls every step of the manufacturing process from the raw materials (conducting regular audits of suppliers, using GMO free materials, TSE-BSE free certified raw materials supplied in drums) to the release of finished product. SEPPIC follows GMP part II guidelines for all its PPI range manufacturing process, using dedicated vessels, validating cleaning procedures, a final filtration step and packing the products under nitrogen in air controlled environment.

SEPPIC ensures low peroxides value, very low limits for residual solvents, microbiologic and endotoxin tests for each batch and by controlling raw materials, intermediates and finished products.

SEPPIC offers a wide range of documents, statements and studies in order to help you in registering your drugs. Drug Master Files (DMFs) and Common Technical Document (CTD) references are available on demand.

SEPPIC can select the best product for you and provide assistance in the formulation of emulsions or in the solubilisation of poorly soluble APIs. SEPPIC offers enhanced specifications or specific requirements on request.

R&D CONTINUOUS DEVELOPMENT

SEPPIC has been developing a new range of powerful and patented solubilisers coming from our research in lipoaminoacid technology. They are designed to dissolve very poorly soluble actives, peptides or proteins in water for oral, topical and parenteral applications.

SEPICLEAR™ 01 PPI is a pure lipoaminoacid. It has excellent solubilising properties (see Figure 1) and is very easy to disperse in water at pH 7. SEPICLEAR™ 01 PPI has been developed to be used into parenteral drugs and the production follows GMP part II standards.

This new excipient offers a new alternative to solubiliser technologies and can be used at very low percentage.

SERVICES & TECHNICAL SUPPORT

Our ambition is to make our customers' lives easier, for a healthier future. Our most exciting challenge is helping you formulate, manufacture and launch your products. To achieve this, SEPPIC offers assistance at every step of customer's development. Our team of experts in chemical synthesis, formulation and analysis is available to assist throughout your drug development process.

SEPPIC guides you in selecting the product best fitted for your development. We can provide assistance in the formulation of emulsions or in solubilisation of challenging compounds.

For each specific development, SEPPIC can offer a customised product. Thanks to its knowledge in surfactant synthesis, SEPPIC can manufacture products in order to meet specific requirements including enhanced specifications, process or formulation dosage. We can also offer new technologies espe cially dedicated to customers' needs.

SEPPIC offers its analytical experience to provide a better support and better characterisation of its products. We can implement and provide new analysis techniques in order to comply with our customers' requirements.

SEPPIC also has three training centres (in the US, France and China) where we organise workshops for our customers. Training can also be organised at your location to teach your technicians how best to use SEPPIC's products.

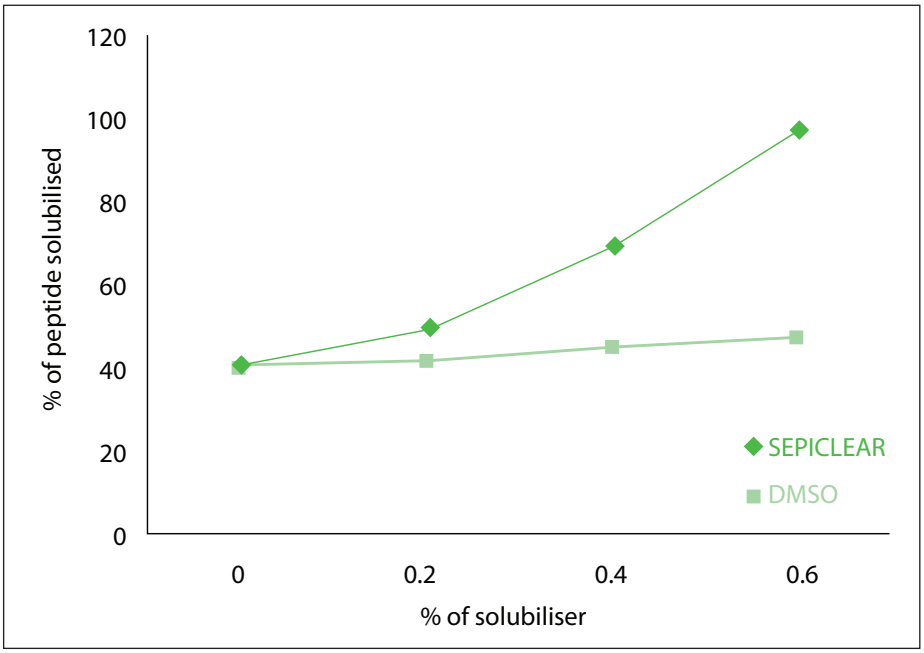


Figure 1: In an experiment to solubilise 1mg of a peptide in water, with SEPICLEAR 0.6% 100% was solubilised compared with only 50% of the peptide being solubilised with DMSO 0.6%.

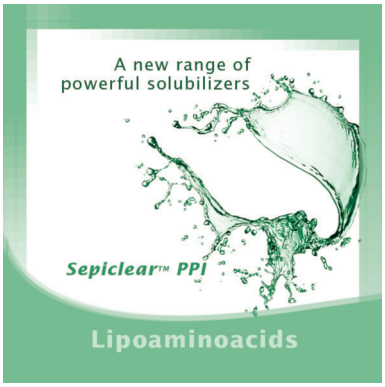
From formulation to commercialisation, SEPPIC provides full support to make your parenteral drug development a success.

Excipients for injection

Injectable Surfactants

High quality solubilizers for parenteral use

As for all its product ranges dedicated to human health, SEPPIC produces its high quality injectable surfactants under GMP PartII standard.



Lipoaminoacids

New range of powerful solubilizers

SEPPIC research has developed new powerful solubilizers based on lipoaminoacid technology. SEPICLEAR 01 PPI is your solution for drug solubilization.

Services

Your partner for parenteral dosage form

SEPPIC proposes customized services in formulation and assistance at every step of your product development.

SEPPIC S.A.
FRANCE
Tel. : +33 (0) 1 42 91 40 00

Head Office
75, quai d'Orsay
75007 Paris
FRANCE

www.seppic.com

SEPPIC Pologne Office
POLAND
Tel. : +(48) 22 690 68 73

SEPPIC Colombia SAS
COLOMBIA
Tel. : (571) 746 00 25

SEPPIC Asia Singapore
SINGAPORE
Tel. : +65 62 78 67 11

SEPPIC ITALIA Srl
ITALY
Tel. : +39 02 38009110

SEPPIC Inc.
USA
Tel. : +1 973 882 5597

SEPPIC Dubaï Office
UAE
Tel. : + 971 4 299 3444

SEPPIC Mumbai
INDIA
Tel. : 912242664387 (D)

SEPPIC GmbH
GERMANY
Tel. : +49(0)2203-89830-20

SEPPIC Brasil
BRAZIL
Tel. : +55 11 3242 3911

SEPPIC Japan Office
JAPAN
Tel. : 81 3 6414 6725

SEPPIC China
CHINA
Tel. : +86 (21) 64 66 01 49

SKIN DRUG DELIVERY: IMPROVING QUALITY OF LIFE

In this article, Nemaura Pharma Limited, describes two of the company's key technologies – the Memspatch® microneedle system and the Micropatch™ skin insertion platform.

Nemaura Pharma provides end-to-end turnkey solutions for drug delivery through the skin using its proprietary platform technologies. Its two lead technologies are the Memspatch® microneedle system and Micropatch™ skin insertion platform. In combination, these technologies offer versatile topical or transdermal delivery platforms for a large range of molecules, including biologics.

Improving patient compliance, reducing side-effects, and enhancing effectiveness of therapy by maintaining constant drug plasma levels are leading to an increasing number of drug companies turning to transdermal drug delivery platforms both for existing molecules as well as new chemical entities and biologics.

Nemaura Pharma has a portfolio of proprietary technologies including conventional matrix patches with enhanced physical stability, and simple microneedle based technologies for rapid and efficient delivery of a range of molecules. These technologies have all been developed to be cost effective alternatives to conventional modes of drug delivery, yet provide accurate, robust and reproducible dosing with minimal patient intervention.

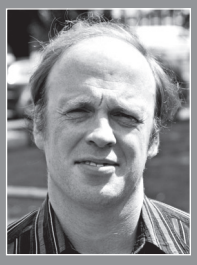
NEMAURA'S KEY OBJECTIVES:

- Improve patient compliance
- Remove operator dependence
- Make devices intuitive to use
- Simplify production processes
- Keep costs down
- Provide versatile platforms for small molecules through to biologics
- Provide efficient end to end turnkey solutions to clients

"THE PATCH COMPARTMENT IS SLID ACROSS THE SKIN, AND GENTLY GLIDES ACROSS, EASING THE MICRONEEDLES OVER THE SKIN ONE ROW AT A TIME, ENSURING 100% OF THE NEEDLES GRADUALLY EASE INTO THE SKIN WITH VIRTUALLY ZERO IMPACT FORCE AND WITHOUT THE INCONSISTENCIES OF HIGH IMPACT DEVICES."

MEMSPATCH® MICRONEEDLE SKIN DELIVERY PLATFORM

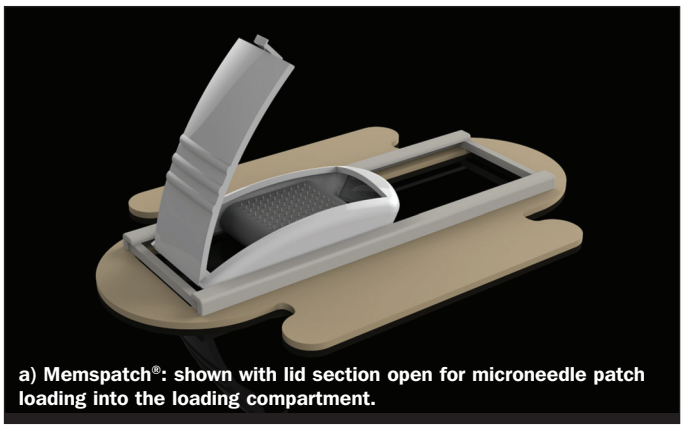
The memspatch® is a versatile platform for the delivery of small molecules as well as biologics in a reproducible, almost operator independent manner. The platform includes a device that acts as an applicator for administering almost any microneedle type patch to the skin. Microneedles are needles whose length is in the hundreds-of-microns range, which are produced from a wide variety of materials including polymers, metals, and the drug formulation itself.



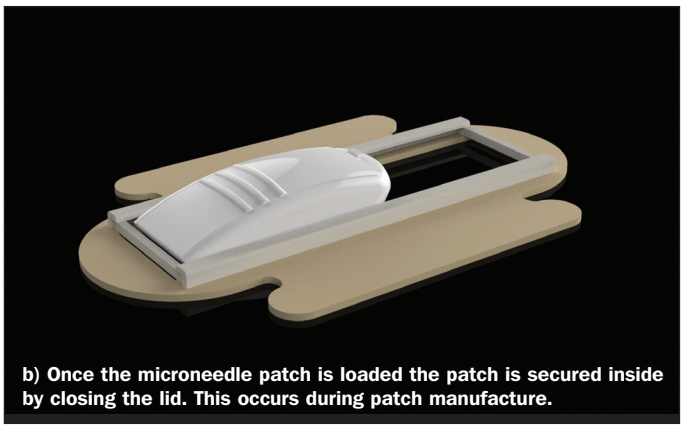
Dr Richard Toon
Technical and Business Development Manager
E: rctoon@nemaura.co.uk

Nemaura Pharma Limited
Holywell Park
Ashby Road
Loughborough
Leicestershire, LE11 3AQ
United Kingdom

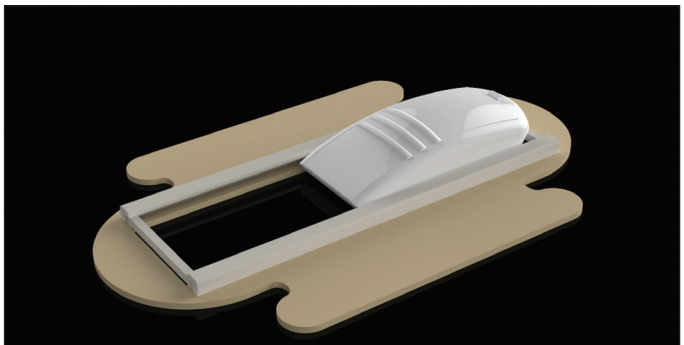
www.nemaura.co.uk



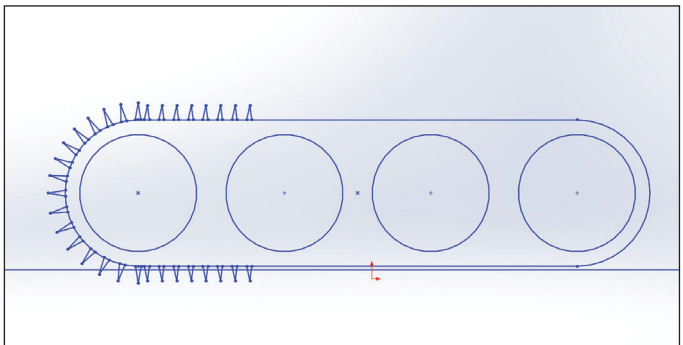
a) Memspatch®: shown with lid section open for microneedle patch loading into the loading compartment.



b) Once the microneedle patch is loaded the patch is secured inside by closing the lid. This occurs during patch manufacture.



c) After the surrounding adhesive patch is applied to the skin, the microneedle patch chamber is gently pushed across the skin, causing the needles to insert into the skin by rolling over a belt and roller, one row at a time, ensuring 100% of the needles are inserted into the skin.



d) Schematic of the Memspatch® internal belt-and-roller mechanism, which gently inserts the needles into the skin, one row at a time.

Figure 1: Memspatch® allows 'zero-impact' application of microneedles to the skin for topical or transdermal application.

Microneedles are traditionally inserted into the skin either using high impact mechanical or pneumatic actuator devices, or by depressing into the skin using the thumb. These methods suffer from the issues of operator training and person-to-person variability in dosing due to inaccurate operation or uneven pressure being applied to the patch. Furthermore the high impact devices can potentially lead to trauma of the skin, and breakage of the tips of the needles, maintaining the sharpness of which is crucial to ensure painless skin penetration. Moreover these are generally large devices that are bulky to carry around and complex thus costly to produce and supply.

The Memspatch® is unique and possibly the most effective means of obtaining reproducible and consistent dosing with microneedles, using a minimal-impact or 'zero-impact' technique.

As shown in Figure 1a, the applicator device consists of a patch that may be self-adhesive with a compartment that retains the drug-loaded microneedle patch. The drug-loaded patch is loaded into the device during manufacture and sealed away from the patient (Figure 1b), thus preventing any possibility of breakage of the needles or accidental injury to the patient.

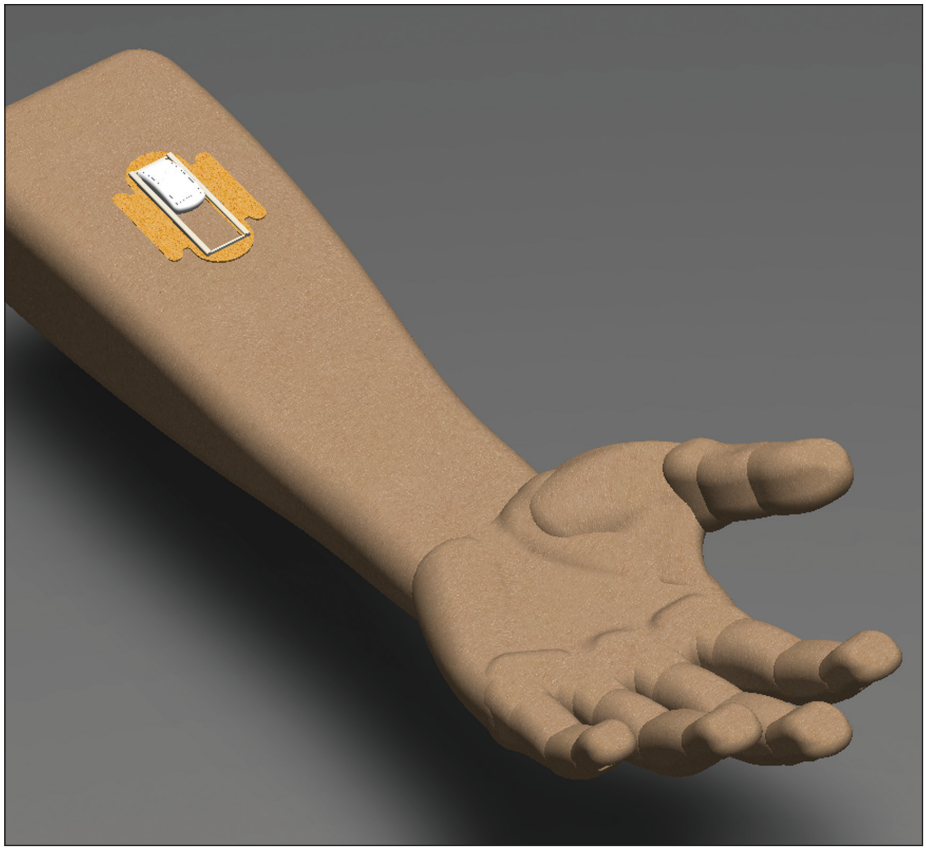


Figure 2: Memspatch® in place, applied on the forearm.

Figure 3: Micropatch® single-use particle-insertion devices shown in two colours. The recess in the centre is where the patient applies pressure using the thumb to activate the device.

Once the Memspatch® is applied, the patch compartment is slid across the skin, and gently glides across (Figure 1c). As it glides, the internal mechanism of the Memspatch® (schematic shown in Figure 1d) eases the microneedles over the skin one row at a time, ensuring 100% of the needles gradually ease into the skin with virtually zero impact force and without the inconsistencies of high impact devices.

Figure 2 shows the patch in place on the arm.

Nemaura offers this system either as a platform for use with microneedle patches produced by their clients, or with Nemaura's own microneedle formulation produced using a readily scalable process that does not require costly installations.

"THE MICROPATCH™ OVERCOMES THESE LIMITATIONS ALLOWING ALMOST ANY MOLECULE IN SOLID OR SEMISOLID FORM TO BE GENTLY INSERTED INTO THE SKIN TO THE DESIRED DEPTH."

This particular formulation may be used for both topical administration as well as some systemic products. The patch may be retained on the skin for minutes or several hours where required and is produced cost-effectively using conventional patch manufacture facilities.

Skin permeation studies using diclofenac sodium in Nemaura's formulation showed a 40-fold increase in the amount of drug administered compared with a market leading gel, without leaving any visible signs of skin irritation, and an administration/patch skin application time of less than one minute; that is, the patch was removed immediately after administration in this instance.

MICROPATCH™ SOLID DOSE SKIN INSERTION PLATFORM

The Memspatch® technology described above provides an avenue for the delivery of a range of molecules primarily intended for deliv-

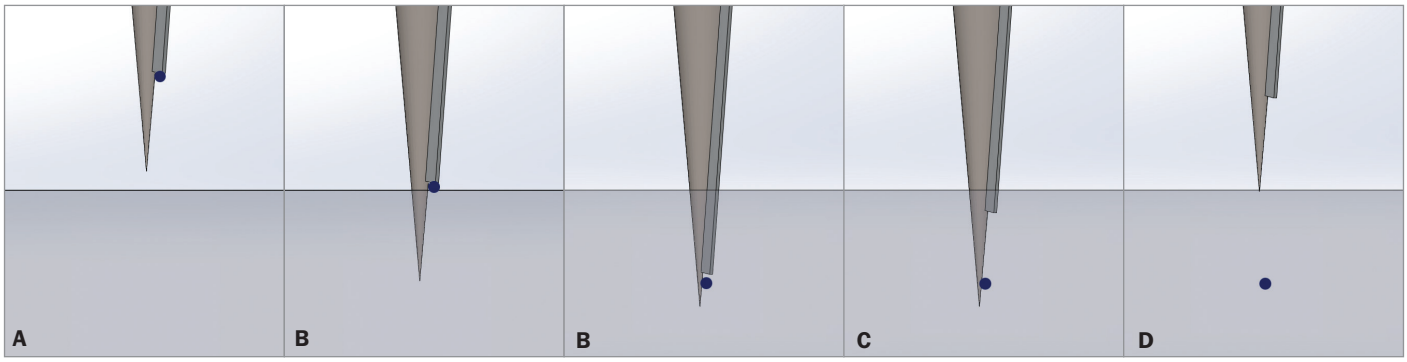


Figure 4: Sequence of microneedle delivery via the Micropatch™.

A) Microneedle or needle with adjacent drug loaded carrier.
B) The needle is inserted into the skin, engineered to insert to the desired depth.
C) Drug carrier slides down the side of the needle inserting the drug into the skin and then
D) retracting.
E) The needle is retracted from the skin with the drug remaining inside the skin.

ery over a sustained period of time. One of its key limitations is that many molecules requiring skin delivery will not have the correct physicochemical properties that allow them to be formulated into microneedles with the required physical strength, or allow them to be coated on to the surface of microneedles for delivery to or via the skin.

Micropatch™ overcomes these limitations allowing almost any molecule in solid or semi-solid form to be gently inserted into the skin to the desired depth – in conjunction with super-sharp stainless steel needles.

The actuator is a single-component produced by injection molding a single piece of plastic, thus cost effective to produce as a single use disposable unit (see Figure 3).

Micropatch™ can be used for a single drug or multiple drugs simultaneously using multiple needles on a single device. This is achieved using a single pressing motion and a disposable device.

Needle length can be varied from hundreds of microns, that would be pain free, or several millimeters in length for deeper depot delivery of drug 'packages'. The drug packages may be formulated as spheres in the diameter range of tens to hundreds of microns, making it easy to administer precise doses, effortlessly and mostly painlessly.

The device works on the principle of the microneedle, in that sharp small diameter stainless steel needles effortlessly pierce the skin, and can be pain free depending on the depth of penetration. This insertion is then followed by the insertion of a defined dose of the drug in a microsphere, or other structure with defined dose, ensuring 100% of the dose loaded is delivered instantly. The sequence of steps for drug delivery are shown in Figure 4.

Formulations can be adjusted to provide very rapid onset of absorption and action, or sustained delivery over hours, and days, or weeks where required. The needles can automatically retract within the device thus preventing sharps injuries or damage to the device on storage and transport.

"DRUG PACKAGES MAY BE FORMULATED AS SPHERES IN THE DIAMETER RANGE OF TENS TO HUNDREDS OF MICRONS, MAKING IT EASY TO ADMINISTER PRECISE DOSES, EFFORTLESSLY AND MOSTLY PAINLESSLY."

The applications of these technologies are broad and range from small molecules to peptides and proteins, and vaccines. They provide means for enhancing stability by eliminating the cold chain, and improving patient compliance. They enable self-administration and provide a robust means for minimally invasive instant delivery of drugs via the skin.

Nemaura Pharma already has global license agreements with pharmaceutical companies for some of its technology platforms. Nemaura is actively seeking to broaden the list of partnerships and collaborations where molecules, which may otherwise suffer from inadequate dosing or dosing methods to which patients are averse, can be simply and effectively delivered by gently gliding solid and semi-solid micro-doses accurately and consistently into the skin.

EXHIBITOR CASE STUDY

Gerresheimer enjoys the complete package at InnoPack

Gerresheimer, a world leader in pharmaceutical packaging, is a regular exhibitor at InnoPack. We caught up with Jens Kuerten, Director of Corporate Communications and Marketing, to hear how Gerresheimer realizes maximum value from InnoPack with active, across-the-board participation in the show and related events.

GERRESHEIMER

Q. Please tell us a little about Gerresheimer

A. We are an international leader in solutions for the pharma and healthcare industry, focusing on primary packaging and drug delivery. We're a global, publicly listed company with operations in 45 countries around the world, 10,000 employees and sales of more than €1bn.

Our roots are in glass packaging, but over the last 15 years we've added plastic packaging solutions to our portfolio. We make a huge variety of products including vials, ampoules, bottles, all types of containers, and drug-delivery devices such as prefillable syringes, inhalers, auto-injectors, insulin pens, and so on.

> **"We expect to meet most our global customers at the fair!"**

Q. How did you first get involved with InnoPack?

A. We've actually exhibited for several years with a positive ROI, so it was an easy decision to come back for 2011.

> **"Many other events have a narrow focus, either geographically commercially, but InnoPack's broad focus makes it very important for us."**

Q. What sort of presence do you have at InnoPack?

A. Our presence has steadily increased in size over the years. We try to balance three aims:

- build our global group brand
- demonstrate our portfolio of solutions
- meet new and existing customers

InnoPack offers great potential for media work, well-attended speaking opportunities and other side events. For example, we took part in the CPhI Innovation Award 2011, making it through to the final round with our high-performance multilayer plastic vial for parenteral products. Attending fairs is always complex, but the practical side works out pretty well at InnoPack.

Q. What were your hopes & expectations of InnoPack?

A. We are present at almost 40 global fairs and conferences every year. When a new platform emerges, we usually attend as visitors before deciding whether to exhibit the following year. InnoPack, which I regard as part of a package along with ICSE and CPhI, is one of the few strategic pharmaceutical events most important and valuable for us

By 'strategic' I mean that we expect to meet most of our global customers at the fair – not just nationally or regionally but Europe-wide – and that we present all our divisions and products when we exhibit. Many other events have a narrower focus, either geographically or commercially, but InnoPack's broad focus makes it very important for us.

“We are present at almost 40 global fairs. InnoPack is the most important and valuable for us.”

Q. What benefits do you realize from InnoPack?

A. The key benefit for us is meeting all our current and potential customers under one roof. We can also meet new potential partners.

There’s also an opportunity to extend business with existing customers. For example, if a customer only buys vials from us, we can show them additional items from our portfolio.

The presence of the other shows (ICSE, CPhI, and P-MEC) makes for a broader range of exhibitors and visitors, and lots of conference and speaking opportunities.

With ROI we look at the number of leads gained and also the quality of meetings. For us, InnoPack and CPhI develop our customer relationships and gain new leads.

“InnoPack is by far the most important fair.”

Q. Overall, how would you rate your experience?

A. It’s very good. For us, InnoPack is by far the most important fair.

DEBIOTECH S.A. Switzerland
Innovative Medical Systems

NanoJect™

SIMPLE AND RELIABLE INTRA-DERMAL INJECTIONS

Intradermal injections have historically been difficult to administer successfully yet they have numerous advantages. Here, Astrid Cachemaille, Project Manager & Clinical Affairs Manager, and Laurent-Dominique Piveteau, PhD, Director, Business Development, both of Debiotech SA, describe some of the benefits of the intradermal delivery route, and a microneedle device which makes intradermal delivery a viable clinical option.

Debiotech's NanoJect™ device was conceived in order to overcome the problems encountered with classical intradermal delivery techniques. Convenient, precise, well controlled and reproducible intradermal injection of drugs – from small molecules to large peptides – have become possible thanks to an original design of microneedles combined with a specifically developed insertion/infusion system (see Figure 1).

For the patient, this is now a pain-free procedure. It also satisfies clinicians, since they can very easily inject up to 500 µL in three seconds, while precisely controlling the injection depth of the drug.

"TREATMENTS THAT WERE TURNED DOWN BEFOREHAND BECAUSE OF THE COMPLEXITY OF THEIR IMPLEMENTATION WILL BECOME STANDARD APPROACHES"

The NanoJect™ device is easy to use and requires only a short training. It could therefore be widely used for diverse applications across the world (see Figure 2).

THE CHALLENGE OF INTRADERMAL INJECTIONS

Interest in intradermal immunisations began in the early 20th Century with the work of Charles Mantoux. This French physician developed an approach for the intradermal injection of tuberculin as a diagnostic skin test for tuberculosis disease. Two decades later, a study conducted by Louis Tuft showed that a smaller dose of typhoid vaccine injected intradermally had an equivalent immune response and an improved adverse event profile compared to the full dose injected subcutaneously. Subsequently, several studies aiming at evaluating the efficiency and utility of intradermal delivery route such as vaccine dose reduction were conducted using different commercially available vaccines including, amongst others, influenza, measles, cholera, rabies, hepatitis B and polio.

Today it is well documented that the immune response after intradermal administration of one-tenth of an intramuscular dose for rabies is equivalent to the full dose given intramuscularly. For influenza, a recent study demonstrated a much better immunisation of the older population – which is most at risk – with an intradermal injection than if done by a subcutaneous injection when using the same dose of vaccine.

The routine use of intradermal injection has however been limited by the complexity of applying Charles Mantoux's method – where a standard needle (Figure 3) is inserted at a grazing angle into the skin. In particular, success is known to be highly dependent upon the experience and technique of the healthcare worker. Control of injection depth is very poor and reproducibility is low.

Astrid Cachemaille
Project Manager & Clinical Affairs Manager

Dr Laurent-Dominique Piveteau
Director, Business Development

Debiotech SA
"Le Portique"
28, avenue de Sévelin
CH-1004 Lausanne
Switzerland

T: +41 21 623 60 00
F: +41 21 623 60 01
E : debiotech@debiotech.com

www.nanoject.net
www.debiotech.com

Figure 1: The Nanoject™ assembled with an example syringe.

The introduction of a device that deeply simplifies this type of injection will undoubtedly open several new avenues in intradermal drug therapy. Treatments that were turned down beforehand because of the complexity of their implementation will become standard approaches.

NANOJECT™: THE SOLUTION FOR SUCCESSFUL INTRADERMAL DELIVERY

The NanoJect™ device consists of short (less than 1mm), sharp and hollow microneedles produced using Micro-Electro Mechanical System (MEMS) techniques (see boxed text, p 20).

Manufactured as single needles or as arrays of three needles in a row, their channel opens on the side (Figure 4) at a depth in the skin between 300 µm and 600 µm, allowing the delivery of small boluses up to 500 µl in only three seconds.

The opening can be orientated at will to control the orientation of the liquid distribution into the skin The device also comprises an inserter which plays an important role in facilitating

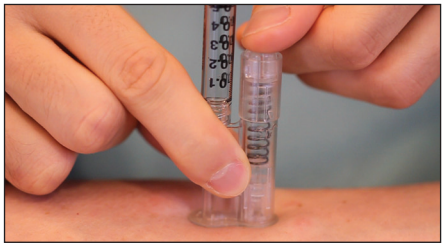


Figure 2: The Nanoject™ device is easy to use.

Figure 3: The microneedle's length in comparison with a 25G needle.

the use of the device, while guaranteeing the success of the injection. The whole system is disposable, that is, for single use only, thus avoiding any cross-contamination issues.

The extremely sharp tip and the limited length of the microneedles (see Figure 5) ensure very gentle penetration while avoiding most pain receptors in the skin. The presence of the

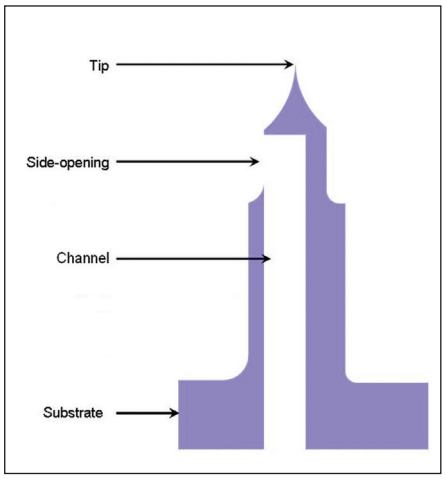


Figure 4: Schematic cross-section of the needle, showing fluidic channel and side-opening.

controlled dimensions of the microneedles guaranteed by the MEMS technology, the depth of injection is also very precise and reproducible.

Compression of tissue as well as high hydrostatic pressure within the tissue is known to be a limiting factor for the diffusion of fluids. The side positioning of the opening therefore permits the delivery of the fluid in a region that is not compressed during the insertion of the needle (as is the case at the tip of the needle).

"DURING THE DEVELOPMENT OF THE DEVICE, OVER 500 INJECTIONS IN HEALTHY VOLUNTEERS HAVE BEEN CONDUCTED"

hole on the side of the needle limits the risk of coring and consequent clogging of the fluidic channel. It also potentially permits faster healing of the skin thanks to the absence of tissue removal. Because of the extremely well

The force required to push the liquid is therefore minimised, limiting the risk of needle dislodgment and consequent leaks.

The microneedles are mounted on a single-use inserter on which any type of luer lock syringe can be attached. The role of this inserter is to guarantee the perfect and easy placement of

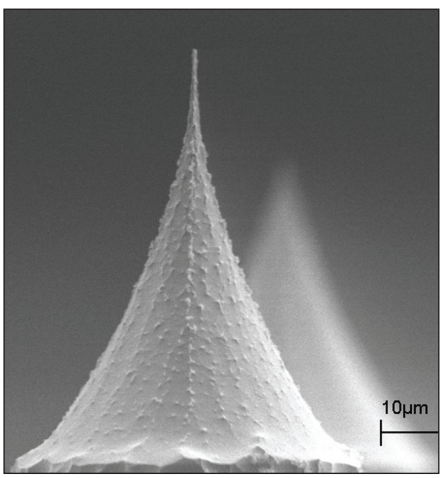


Figure 5: SEM images of (left) the microneedle and (right) the needle tip.

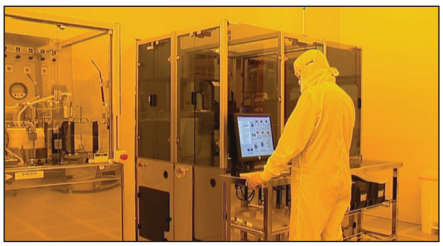


Figure 6: Nanoject™ manufacture and assembly takes place in ISO class 5 down to ISO class 3 clean rooms.

the microneedles within the upper layer of the skin and to maintain the ideal conditions for a reproducible and successful injection, avoiding any possible leak during injection. The entire system (microneedles plus inserter) is covered by six families of patents that ensure exclusivity for Debiotech until 2032.

The manufacture and assembly process of the NanoJect™ devices take place in a clean and controlled environment – ISO class 5 down to ISO class 3 clean rooms (see Figure 6). The production is now an established and GMP-compliant industrial process delivering substantial amounts of devices for various trials and CE marking is in progress.

CLINICAL INVESTIGATIONS UNDERWAY

During the development of the device, over 500 injections in healthy volunteers have been performed in addition to *in vitro* and *in vivo* experiments conducted in animal models. An in-depth analysis of the interactions between the skin, the needles and the injected fluid has been conducted using computed tomography, optical coherence microscopy as well as histological cross-sections. Mouse, rat, pig and human skin models have been used to understand the key mechanisms of intradermal injection with microneedles – the importance of the skin elasticity, the role of the pressure applied onto the skin before, during and after injection, the behaviour of the fluid once injected or the influence of the device design on the final success of the injection –and to optimise the penetration-injection process.

A successful injection is characterised by a bleb formation at the skin surface, with the absence of any leak. The bleb disappears within a few minutes, as the injected fluid is drained within the tissues (see Figure 7).

"THE MOST INTERESTING AND PROMISING APPLICATIONS OF MICRONEEDLES ARE PROBABLY THOSE WHERE THE INTRADERMAL ROUTE PRESENTS A DIFFERENT PHARMACOLOGICAL RESPONSE THAT COULD BE BENEFICIAL FOR THE TREATMENT"

The pain was assessed (and its absence during insertion confirmed) by comparing, on the same patient, different types of injections: various volumes (from 100-500 μl) and various sites (forearm, deltoid and abdomen), taking the established Mantoux method as a reference.

Repeatability and ease of use were tested with assistance of different external clinicians. After a short training session, they were able to perform several intradermal administrations appropriately. All these experiments confirmed the ease of use of the device as well as the speed and the efficiency of the injection.

Based on these successful results, the Nanoject™ device has entered into a clinical trial in collaboration with the Vaccine and Immunotherapy Centre of CHUV (Centre Hospitalier Universitaire Vaudois; Lausanne, Switzerland). The study is a single-centre, randomised, double-blind, placebo-controlled, comparative Phase I first-in-man to assess the safety and tolerability of rabies vaccine "Vaccin rabique Pasteur®" injected using NanoJect™, and the non-inferior immune response, compared with classical intradermal or intramuscular injection using a syringe. This study is the first in a series of clinical trials.

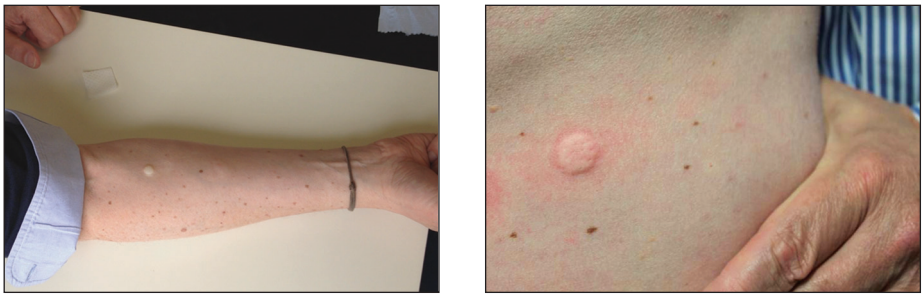
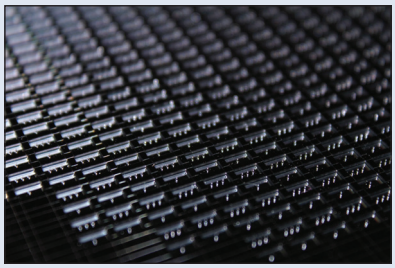


Figure 7: Photos following NanoJect™ intradermal injections of 200μL on the forearm (left) and 500μL on the abdomen (right). A successful injection is characterised by a bleb formation, which disappears within a few minutes, as the injected fluid is drained within the tissues.

TOWARDS NEW APPLICATIONS

A great variety of applications can be envisaged for intradermal delivery using microneedles. The goal sought is, in some cases, to avoid

MICRO-ELECTRO MECHANICAL SYSTEM



Partial view of an eight-inch wafer, with chips of one and three microneedles.

MEMS (Micro-Electro Mechanical Systems) is a manufacturing technology that uses the same processes as those developed for the integrated circuit industry. Mechanical and electrical structures are created in a mono-crystalline silicon wafer by a combination of etching and deposition processes. The precision of this method is such that sub-micron structures can easily be obtained at very high volumes. On a single silicon wafer, hundreds of chips can be manufactured. As an example, on an eight-inch wafer (see image inset), there are no less than 1,500 microneedle chips produced at once, part of a batch of 25 wafers representing 37,500 microneedles. Thanks to this high parallelisation, MEMS technology allows the delivery of highly cost effective products.

the pain induced by needles during their insertion into the skin. Microneedles are also seen as an excellent solution against needle phobia and therefore should encourage a better compliance with treatments that require regular injections. But the most interesting and promising applications of microneedles are probably those where the intradermal route presents a different pharmacological response that could be beneficial for the treatment.

The potential of dose reduction (or increased efficacy) with some vaccine formulations has been identified quite early. More recently, a change in the pharmacokinetics of several drugs, such as insulin, for example, has been reported following intradermal injection.

On one hand, reduced doses of vaccines are of particular interest for regions where vaccination campaigns are difficult to conduct, for diseases presenting a fast evolution and that require regular new formulations or for pandemics that require extremely fast response. On the other, faster peak values of insulin may fundamentally change the treatment of diabetes, greatly facilitating the realisation of an artificial pancreas.

While, in industrialised countries, human rabies is close to being eradicated, it is still responsible for about 55,000 deaths every year in territories where access to the vaccine is difficult. For several years, the WHO has been conducting extensive studies aimed at reducing the dose needed for efficient protection, and today WHO recommends the use of intradermal injections with a fifth of the dose that is used intramuscularly. A device guaranteeing an easy and successful injection of the vaccine dose is a key enabling factor for the implementation of this strategy.

Influenza presents a different challenge: the virus is mutating extremely rapidly and a complete new immunisation of the population is needed every year. The time between the moment the WHO provides its guidance about the strains to introduce in the new vaccine and the beginning of the vaccination campaign is relatively short, putting a lot of pressure on the manufacturers. In particular, there is a risk of shortage in supply if for any reason the supply chain of one of these manufacturers is disrupted. In fact this very situation arose within the last few years, and prompted a demand from the authorities to identify new ways to reduce the required dose. In addition, following the recent events around avian flu (2004) and swine flu (2009), growing concern is expressed about the threat of pandemic resulting from a virulent strain. Under these circumstances, the need for rapid vaccination of a large population in an efficient manner is critical. Here again the need for methods requiring smaller doses has been expressed.

"FASTER PEAK VALUES OF INSULIN MAY FUNDAMENTALLY CHANGE THE TREATMENT OF DIABETES"

CONCLUSION

Intradermal injection is a delivery route that has for a long time been neglected due to the lack of user-friendly, reliable and efficient devices. Nonetheless, several studies had emphasised its advantages for certain types of treatments compared with the conventional subcutaneous and intramuscular routes.

Until now, all of the intradermal solutions proposed lacked the ease of use, the reproducibility, the reliability, or the absence of leakage, or were strongly limited in the type of molecules that could be delivered. Microneedles have, since their appearance, been seen as an excellent way to solve all these issues. However, the interaction of these short and fine structures with an elastic structure such as skin has been underestimated. Driving the needle into the skin and keeping it at a given depth, and applying and maintaining the right pressure before, during and after the drug administration, will also determine the final success of the procedure.

The NanoJect™ device, as shown by all the data collected on its efficacy, repeatability and usability, is offering a real solution to tackle this very promising area of drug delivery.

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.

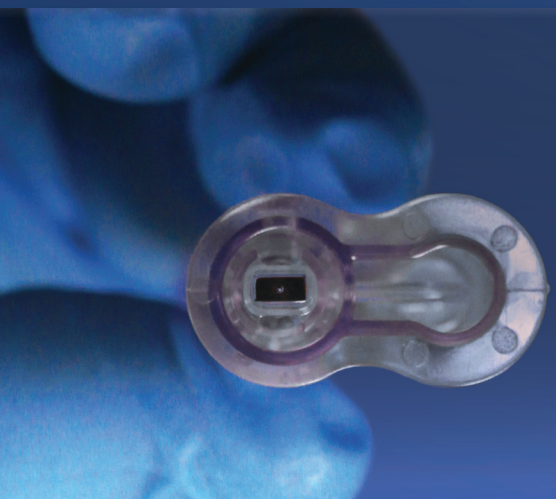
Devices developed by Debiotech are eventually licensed to major international pharmaceutical and medical device companies, with a track record of over 40 license agreements worldwide. Examples of products include the I-Vantage™ IV pump for hospital and home-care, the CT Expres™ Contrast Media injector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

NanoJect™

Microneedle Intra-Dermal Injection

Simple and Reliable ID System

- easy to use and reproducible
- painless injection
- automatic insertion
- precise depth control
- up to 500 µl in 3 seconds



www.nanoject.net

DEBIOTECH S.A. Switzerland

Innovative Medical Systems

ONdrugDELIVERY
niche information & intelligence

The leading topic-targeted sponsored drug delivery publication.

www.ondrugdelivery.com

Battelle

DECREASING RISK THROUGH TRUE INNOVATION: CROSS-DISCIPLINARY SOLUTIONS FOR DIFFICULT CHALLENGES IN DRUG DELIVERY

With protein-device combination products coming through development in increasing numbers, Battelle has developed a cross-disciplinary approach for de-risking device innovation, and overcoming the challenges for delivering viscous formulations. Here, Amy Heintz, PhD, Senior Research Scientist, and Reade Harpham, Manager of Human Centric Design, both of Battelle, provide examples of how this approach delivers results and can save pharma and biotech companies time and money. Battelle's emphasis on innovative device development, as exemplified by its alliance with Zogenix for the development of DosePro®, is also highlighted here.

The lack of novel technologies in the delivery of highly viscous biologics and the costly development of new devices is stifling innovation in the drug delivery industry. The inevitable evolution of biologics, the high cost of device development and the fear of patient and physician rejection create risks that are inhibiting innovation by pharmaceutical and device companies. In today's cautious economic climate, pharmaceutical and medical device companies are leery of investing too much time and money in a product that requires a robust and costly development process if the outcome is unpredictable.

At Battelle, de-risking innovation through a controlled process that incorporates a cross-disciplinary approach to drug delivery enhances development and can potentially save pharmaceutical companies significant time and money.

PROTEIN-DEVICE COMBINATIONS & HEALTHCARE'S CHANGING NEEDS

While the 1980s and 1990s was the era of the small-molecule, blockbuster drug, we are now entering the era of the protein-device combination product. Therapeutic proteins can be designed with specificity that allows unprecedented ability to target disease mechanisms with fewer side effects. Furthermore, the complex and unique structure of proteins enables a broad range of patent protection.

> "WHILE THE 1980S AND 1990S WAS THE ERA OF THE SMALL-MOLECULE, BLOCKBUSTER DRUG, WE ARE NOW ENTERING THE ERA OF THE PROTEIN-DEVICE COMBINATION PRODUCT"

Biologics are predicted to generate 60% of biopharma growth this decade. There are more than 100 therapeutic proteins available for the treatment of diseases such as auto-immune disorders, cancer, infertility and osteoporosis. Of all the biologics, monoclonal antibodies are predicted to show the most growth.

Because of their large size and limited stability, proteins cannot be readily delivered by oral or transdermal delivery. Biologics are delivered by drug-device combinations like infusion pumps, injectors or syringes.

For patients suffering from chronic diseases that require regular treatment, the trend

Dr Amy Heintz
Senior Research Scientist

Mr Reade Harpham
Manager of Human Centric Design

T: +1 614 424 6424
E: healthlifesciences@battelle.org

Battelle
505, King Avenue
Columbus, OH 43201-2696
United States

www.battelle.org

is towards self-administration. This trend is driven by patient preference, as well as reduction of costs associated with visits to healthcare facilities. Commercial injection devices are on the market for the treatment of diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS) and Crohn's disease.

The spectrum of delivery devices for proteins spans from short to long delivery time and from small to large volume. Standard devices include syringes, pen injectors, auto-injectors and infusion pumps. Emerging devices such as patch pumps and needle-free injectors enable self-administration of high-dosage formulations that cannot easily be met with auto-injectors. Some of the key performance indicators for selection of an appropriate device include dose volume, drug viscosity, delivery time, injection site, injection depth, target population requirements and product cost target. In addition, the device cannot introduce any instability issues. For example, silicone and tungsten have been linked to protein aggregation.

The development of protein injection devices poses significant challenges – both technical and regulatory. The US FDA expects usability engineering to be performed throughout a device's design and development lifecycle, using methods such as those described in IEC 62366, an FDA-recognised consensus standard. Pharmaceutical companies once focused only on obtaining clinical approval for a drug. Now, they are also responsible for minimising the device's risk in regard to potential misuse, including documentation of the severity of failure and a focus on the users' perception, cognition and ability.

A SMARTER APPROACH – HUMAN CENTRIC DESIGN

In addition to integrated science, technology and engineering innovation, Battelle's Human Centric Design service features formative and summative usability studies that have determined the most common use errors for highly viscous therapies delivered via auto-injectors. These include inversion of the device, improper angle of insertion and incomplete dose due to failure to hold for the required amount of time. Compounding the issue, many of the patients suffering from chronic illnesses have impaired ability that creates unique usability challenges. While we know that physical strength increases during childhood and adolescence, it remains relatively constant over adulthood and then decreases with age.

However, the manner in which the behaviour changes for disabled or diseased populations is not well-characterised. We find that some diseases cause a general weakening, while others such as RA, make specific body movements, like pinching or twisting, more difficult. The limited strength and dexterity can cause significant user-related risks for injection devices. These issues must be addressed at the beginning of development activities in order to provide patients with safe and effective therapy.

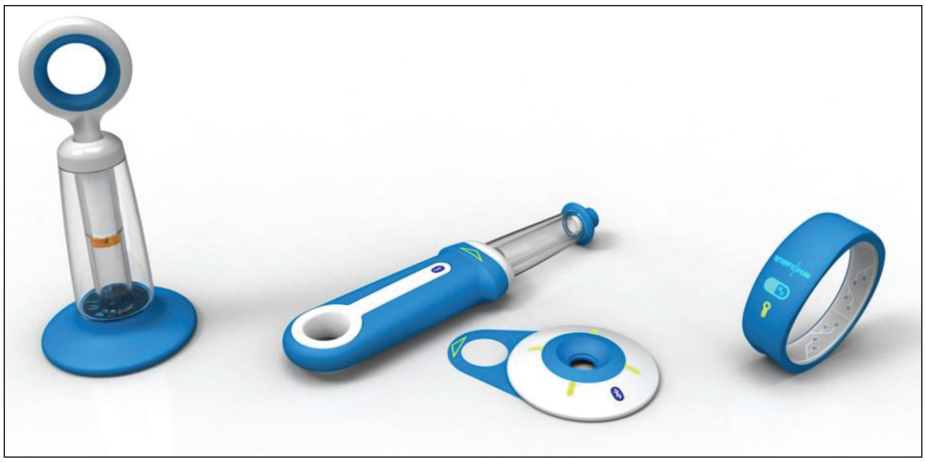


Figure 1: Syringe device enhancement that addresses stability and device feedback requirements.

Proper device design begins by integrating traceability to user needs at concept inception. Understanding the user population's unique characteristics is elemental to our design philosophy. This human centric design philosophy greatly accelerates the time it takes to bring safe and effective devices to market.

Therefore, Battelle is developing low-risk user interfaces for patients with RA and MS. The initial research phase used contextual research to understand user perception, cognition and abilities. Observation of patients performing hands-on activities provided an opportunity to understand participants' hand and finger capabilities and limitations. In addition, social media outlets including online patient forums and communities were leveraged to provide large amounts of information not only about specific issues or problems people encounter, but also potential aids and solutions as they share their experiences managing their health. The contextual research leads to the definition of high-level requirements in which traceability is integrated prior to design controls.

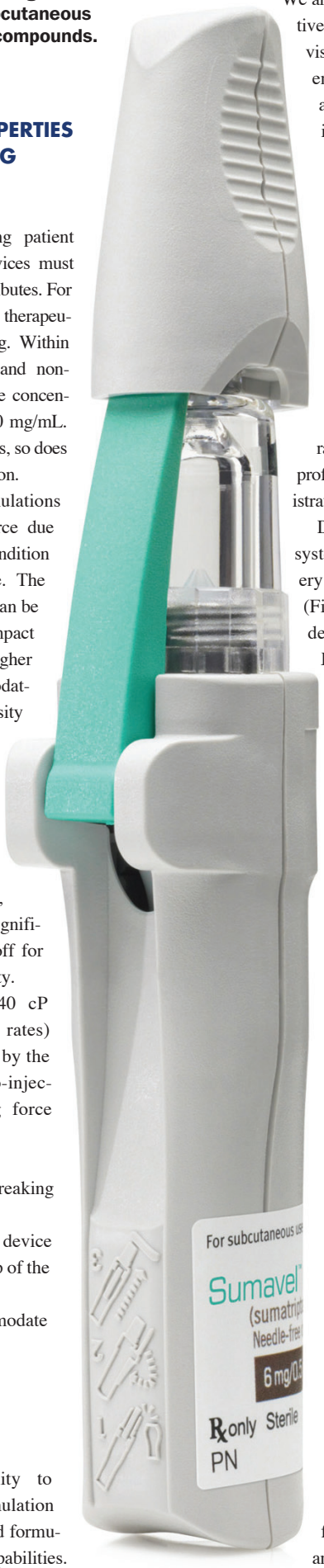
For example, patients with RA have physical limitations that require a device to maintain stability during injections. Cognition risks related to inadequate device feedback point to the need to gather obvious and accessible device feedback.

Quantitative anthropometric data can also be useful, but is not readily available for motions encountered in medical-device use such as auto-injectors or syringes for healthy adult populations or users with limited strength. To meet this need, Battelle has designed and built a set of ergonomic test fixtures to collect force and torque data for 20 different movements related to medical device use. This data can be used to develop appropriate and detailed design guidelines. While these design guidelines do not eliminate the need for formative user testing, they can provide early-stage recommendations for device use by intended users with physical limitations.

"HIGHER VISCOSITY CAN BE ACCOMMODATED WITHIN A LIMITED VISCOSITY RANGE BY INCREASING THE DIAMETER OF THE NEEDLE OR INCREASING THE INJECTION TIME. HOWEVER, WE FIND THAT THESE MODIFICATIONS GENERALLY OPPOSE PATIENT NEEDS"

The results of our research have led to product concepts that are now being tested in formative usability studies. For example, a simple device enhancement for a syringe (see Figure 1) addresses stability and device feedback requirements by including a wide base for stability and a plunger ring that provides obvious tactile and visual status indication. Formative testing of this concept and others will provide iterative testing to reduce risk and document mitigation strategies.

Figure 2: The DosePro®, Zogenix' novel injection system for subcutaneous delivery of therapeutic compounds.



FORMULATION PROPERTIES IMPOSE CONFLICTING DEMANDS

In addition to satisfying patient attributes, drug delivery devices must comply with formulation attributes. For instance, dosages for protein therapeutics range from 40-1000 mg. Within the limit of stable, active and non-aggregating formulations, the concentration can vary from 10-300 mg/mL. As the concentration increases, so does the viscosity of the formulation.

Higher viscosity formulations require higher injection force due to the no-slip boundary condition at the walls of the needle. The Hagen–Poiseuille equation can be used to approximate the impact of viscosity on injectors. Higher viscosity can be accommodated within a limited viscosity range by increasing the diameter of the needle or increasing the injection time. However, we find that these modifications generally oppose patient needs. For example, long injection times pose significant risk of premature lift-off for patients with limited dexterity.

Viscosities above 20-40 cP (measured at high shear rates) become difficult to deliver by the typical spring driven auto-injector. Increasing the spring force also increases:

- The risk of the syringe breaking during impact
- The risk of damage to the device during storage due to creep of the plastic parts
- The device size to accommodate the larger spring

A NEW WAY OF THINKING

Battelle has the ability to address design and formulation issues through our integrated formulation and engineering capabilities. We are actively researching alternative approaches to deliver high-viscosity formulations, including emerging devices, modifying auto-injector design and creating new formulations.

One solution to the challenges of drug delivery lies in emerging device technology. Delivery time increases with increasing viscosity due to viscous dissipation in the needle. Viscous dissipation can be substantially reduced by injection through an orifice rather than injection through a needle, using a rapid biphasic delivery pressure profile to achieve selective administration to subcutaneous tissue.

DosePro® is a novel injection system for subcutaneous delivery of therapeutic compounds (Figure 2). The product was developed by Zogenix (San Diego, CA, US), and Battelle is seeking opportunities to advance the technology for the delivery of multiple biologics. In vitro studies have demonstrated DosePro's potential to deliver highly viscous formulations up to 2000 cP through an orifice in the device rather than a standard needle. In addition, the device provides almost instantaneous injection – less than 100 milliseconds – which may minimise premature injection for patients with limited dexterity (Figure 3). The DosePro® is available as a 0.5 mL, and Battelle is seeking partners to design a 1.2-mL device that utilises standard filling.

Battelle's wide range of R&D capabilities in multiple industries also impacts the way we think about medical device development. For example, our experience in the oil and gas industry has inspired us to explore modifications to auto-injectors that enable delivery of viscous formulations by leveraging an approach frequently used to transport highly viscous oils through pipelines. By eliminating the no-slip boundary condition, the force can be substantially reduced. The approach is called core annular flow, in which a low-viscosity annulus, such as the formulation buffer, is used to lubricate a high-viscosity core, the protein formulation. A pressure reduction of 2- to 10-fold can be achieved with a protein core and buffer annulus depending on the fraction of annular fluid introduced and the viscosity ratio of the core/annulus. Device design incorporating core annular flow is in the early stages of development, and an early product concept and benchtop model is available.

Changes to formulation can also enable injection of viscous formulations. Suspension-based formulations are known to provide reduced viscosity relative to solution-based formulations of equivalent protein concentration. In a suspension, the protein particles are suspended in a non-solvent. This approach has been shown to work for crystalline monoclonal antibodies and milled proteins.

However, few processes exist that can be used to efficiently prepare protein suspensions with the appropriate particle characteristics, high activity and bioavailability. Battelle has developed an approach that generates highly active, dense, spheroid protein microparticles and differs from traditional protein microparticle preparations that inherently exhibit significant losses in biological activity from thermal, interfacial and shear stresses. In model proteins, 95% active protein was recovered. This approach should be useful for creating high-concentration suspensions suitable for use with auto-injectors.

SKIN CHARACTERISTICS

Finally, in addition to usability and formulation concerns, the skin characteristics of the patient population must also be considered. Effective delivery depends on the release of the drug to the proper tissue depth. During injection, the skin deflects (or "trampolines") as the needle enters, changing the depth of penetration. Traditional needle-syringe injection devices rely on the patient or caregiver to compensate by pushing the needle further into the skin.

By the nature of their design, auto-injectors remove the user from controlling the needle insertion depth. Skin trampolining can prevent the needle from reaching the intended depth, especially in patients with lax skin.

Battelle has created a Finite Element model to evaluate the effects of injection parameters and tissue characteristics on the amount of skin deflection during needle penetration. Ultimately, use of this model, combined with measurements from human subjects, will allow

device developers to evaluate the ability of an autoinjector to reach the proper delivery depth for the intended patient population earlier in the device development cycle.

CONCLUSION

Transitioning protein formulations to injection devices requires the addressing of challenges associated with delivering high concentrations of sensitive, high-molecular-weight molecules in a manner that is easy, reliable and acceptable to the patient. Integrating traceability to user requirements at the inception of research is critical to designing marketable devices, particularly devices for use outside clinical settings.

The delivery of viscous protein formulations is a critical challenge. Battelle is taking a systems approach to addressing this challenge with a cross-disciplinary process that creates innovation from the intersection of our specialised science, engineering and technology capabilities. The collaboration of device design, formulation and usability considerations into our development process makes Battelle a unique partner in translating technology from the concept stage to commercial product and fulfills the distinct, dynamic and vital needs of the drug delivery market.

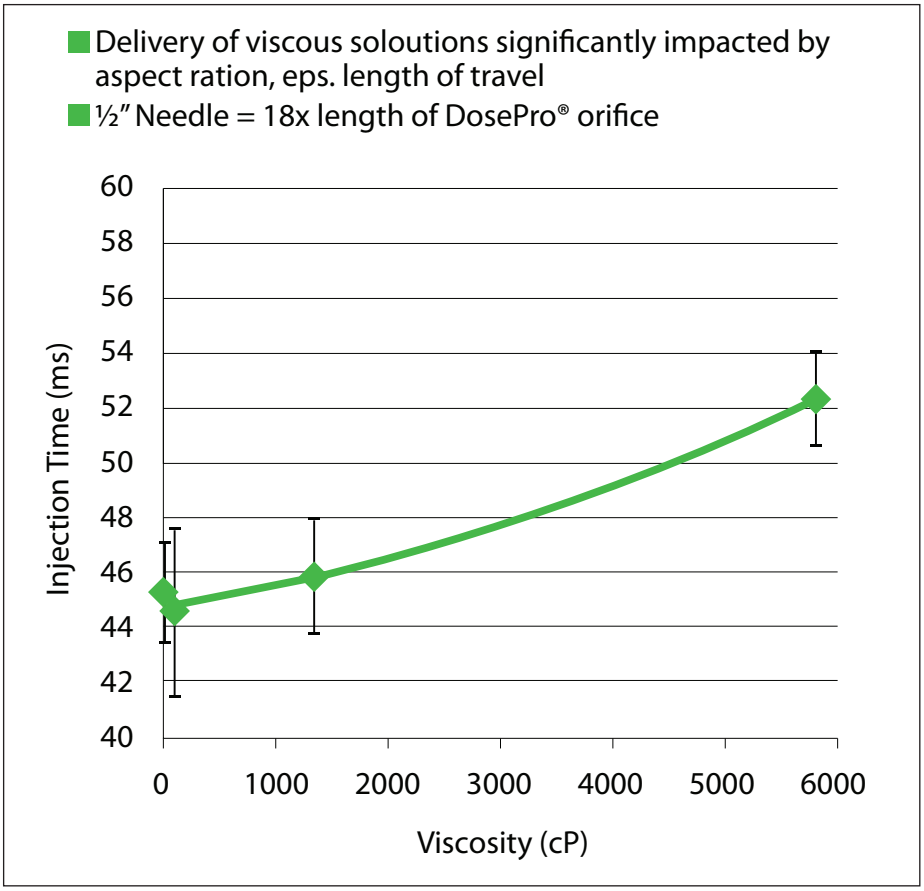


Figure 3: Rapid delivery of viscous formulation by DosePro®.

DosePro®

LESS**is**MORE

Simplicity is key when it comes to self-injection. **DosePro®** makes it simpler without the needle.

- ***Less*** time to inject so the dose is fully delivered
- ***More*** acceptance and adherence by patient
- ***Less*** time to train patients on self-injection
- ***More*** differentiation for injectable products
- ***Less*** difficulty in the delivery of viscous formulations

Choose **DosePro®** as your injection technology – the only pre-filled, needle-free, disposable injection technology on the market.

*Contact **Battelle Today***

Zogenix® Battelle

NEEDLE FREE INJECTION | DRUG DELIVERY TECHNOLOGY

206.588.9827 | healthlifesciences@battelle.org