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DRUG DELIVERY EVENTS
Provided by Christoph Blümmer

The 39th Annual Meeting & Exposition of the Controlled Release Society
July 15 - 18, 2012, Quebec, Canada

9th Central European Symposium on Pharmaceutical Technology
September 20 – 22, 2012, Dubrovnik, Croatia

NanoDDS'12 - 10th INTERNATIONAL NANO MEDICINE AND DRUG DELIVERY SYMPOSIUM
October 29-30, 2012, Atlantic City, NJ, USA

Oral Multiparticulate Dosage Forms – What's new?
November 13 – 14 2012, Prague, Czech Republic

New APV Course “Drug Delivery Strategies for Poorly Water Soluble Drugs - Established Platform Technologies & Recent Innovations”
November 29-30, 2012, Braunschweig, Germany

Despite one decade of intensive scientific discussion and global conferences on the subject of poorly soluble compounds, today there is still a strong need to understand better the principles underlying special types of formulation, their preparation and screening, variant selection based on biopharmaceutical criteria, stability prediction and in-depth material science aspects.

The new APV course, which will be held in Braunschweig on November 29-30, will be chaired by Dr. Oskar Kalb and Dr. Carsten Timpe from Hoffmann-La Roche AG, Basel, Switzerland. In addition to nanotechnology aspects (nanomilling, screening tools for stable nanosuspensions and downstream processing), it will focus on the parenteral drug delivery of poorly soluble drugs and also on other new technologies and innovative analytical approaches to prepare and characterize these systems in order to improve the biopharmaceutical properties of challenging new compounds. One course highlight will be a visit to the innovative nanomilling facility at the Institute for Particle Technology (Technical University Braunschweig, Prof. Arno Kwade).
**Sancuso® Transdermal Patch (ProStrakan Ltd)**

On 16 February 2012 the European Medicines Agency’s Committee on Medicinal Products for Human Use recommended ProStrakan’s Sancuso for approval by the EMA [1]. The product subsequently received marketing authorization in late April [2]. This acrylate-vinylacetate copolymer matrix-based patch delivers 3.1mg granisetron over 24 hours [3]. It is indicated for the prevention of nausea and vomiting caused by moderately to highly emetogenic chemotherapy for a planned duration of 3 to 5 consecutive days. The patch is placed on the skin 24 to 48 hours prior to chemotherapy to allow a build-up of drug levels in the plasma before administration of the first chemotherapeutic dose. The rate of this build-up can be such that lower plasma concentrations than those achieved with 2mg granisetron tablets may be observed at the start of anti-cancer therapy, resulting in an increased time to the onset of anti-emetic activity. As a result, the use of the patch is only indicated in patients with swallowing difficulties. The patch can remain on the skin for up to 7 days depending on the length of treatment. It should not be removed until a minimum of 24 hours has passed following administration of the last dose.

Granisetron has been shown to exert its anti-emetic activity by antagonizing the action of 5-hydroxytryptamine (5HT) at 5HT3 receptors, while having almost negligible affinity for other 5HT receptor sub-types (5HT1, 5HT2, 5HT4) or dopamine D2 binding sites. Approval was based on data on the existing oral product plus the outcome of a double-blind, double-dummy, multinational Phase III clinical study in 641 patients receiving multi-day chemotherapy. This showed that Sancuso was non-inferior to 2 mg oral granisetron in the prevention of chemotherapy-induced nausea and vomiting.

**Janumet® XR (Merck, Sharp & Dohme)**

In February the FDA approved Janumet XR (sitagliptin and metformin HCl extended release) tablets as an adjunct to diet and exercise in the treatment of adults with type 2 diabetes [4]. The product is indicated when treatment with the dipeptidyl peptidase-4 inhibitor, sitagliptin and extended release metformin HCl is deemed appropriate. These compounds improve blood glucose control by two different mechanisms: Sitagliptin inhibits dipeptidyl peptidase 4 which is responsible for the breakdown of incretin hormones including glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. Incretins are involved in glucose homeostasis and are released during the day and in response to a meal. Sitagliptin, by inhibiting the breakdown of these compounds, results in increased insulin release and decreased glucagon levels in the blood in a glucose-dependent manner. Metformin HCl is a biguanide that improves glycemic control by decreasing both hepatic glucose production and intestinal absorption of glucose, and by increasing peripheral glucose uptake and utilization.

Janumet XR is available in three strengths (50mg sitagliptin/500 mg metformin HCl, 50mg sitagliptin/1000mg metformin HCl and 100mg sitagliptin/1000mg metformin HCl). The tablets consist of an extended release core coated with an immediate release layer of sitagliptin. The immediate release layer is coated with a soluble polymer film containing hydroxypropylmethylcellulose and hydroxypropylcellulose.

No clinical efficacy studies were carried out on Janumet XR due to the presence of existing clinical data on the two compounds administered separately and co-administered (metformin HCL dosed as an immediate release tablet). However, studies in healthy adults were carried out. The 100mg/1000mg Janumet XR tablet and the 50mg/500mg strength were found to be bioequivalent to corresponding doses of co-administered sitagliptin and extended release metformin HCl. They were also found to be bioequivalent to each other when administered in equivalent doses (2 tablets 50mg/500mg versus 1 tablet 100mg/1000mg). With respect to time to achieve steady state plasma levels of both compounds, these were achieved for sitagliptin and metformin by Day 4 and 5, respectively, when two Janumet XR 50mg/1000mg tablets were dosed once daily in the evening for 7 days.

**References and Further Information**

[1] Summary of Opinion on Sancso  

[2] ProStrakan’s Sancuso Approved in Europe  


[4] Entry for Janumet XR on Drugs@FDA  
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202270s000lbl.pdf  
**ARISGEN SA (Geneva, Switzerland)**

ArisGen is striving to tackle the current pharmaceutical delivery and administration challenges of peptides to achieve (i) non-invasive peptide delivery and (ii) intracellular peptide delivery.

| Founded: | 2006 |
| Location: | Geneva, Switzerland |
| Ownership: | Privately founded |
| Employees: | 8 |
| Key technology: | **ArisCrown and ArisTarget**

**ArisCrown** is a breakthrough technology for oral and buccal (sub-lingual and gingival) peptide delivery. ArisCrown is based on a new approach to mask the functional groups of the active molecules by means of precision polymers, and combine them with the appropriate formulation excipients to provide controlled non-invasive drug absorption. Proof-of-concept studies generating successful PD and PK data have been performed using ArisCrown with a variety of peptides.

**ArisTarget** allows the intracellular delivery via reversible attachment of biocompatible polymers and specific bio-functional moieties to the peptide. Once in the cytosol, the cell’s naturally present esterases release the original active compound. In a variety of proof-of-concept experiments, ArisTarget showed significantly superior delivery properties compared to Cell Penetrating Peptides in vitro and in vivo.

| Products: | (i) Exenatide (exendin-4) oral and sub-lingual formulations. 
|           | (ii) Peptides to treat fibrocontractive diseases. |
| Development status: | Preclinical |
| Partnerships: | ArisGen is currently in partnership with 3 undisclosed large Pharma. |
| Website: | [http://arisgen.com](http://arisgen.com) |
| Contact: | Dr. Paolo Botti (CSO) 
|           | 14, Chemin des Aulx 
|           | CH-1228 Plan les Ouates, Geneva 
|           | Phone: +41 (0)22 8801015 
|           | Fax: +41 (0)22 8801013 
|           | e-mail: paolo.botti@arisgen.com |

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**KAREL ULBRICH** obtained his MS at the Institute of Chemical Technology, Prague in 1970. He completed his PhD under the supervision of Henry Kopeček at the Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic in 1975. Although he had already impressive results as a young scientist, his promotion at the Academy was restricted for political reasons. He completed his Dr. Sc. (similar to habilitation) at the Academy of Sciences of the Czech Republic after the political system changed.

Karel Ulbrich was appointed as Assistant (2000) and Full (2005) Professor at the Institute of Chemical Technology in Prague. He is Head of the Department of Biomedical Polymers at the Academy of Sciences of the Czech Republic. Between 1998 and 2007 he was Director of the Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic.

The most significant research interest of Professor Ulbrich is the development of synthetic polymeric carriers of biologically active compounds and their use as targetable drug delivery systems. Professor Ulbrich’s research is focused on the design, synthesis and characterization of water-soluble polymers and their conjugates with biologically active compounds, synthesis of thermoresponsive polymers and hydrogels designed for the controlled release of drugs and synthesis of polymers for the development of polymer-modified viral and nonviral gene delivery vectors. Professor Ulbrich contributed to the development of the polymer conjugates of doxorubicin based on N-(2-hydroxypropyl)methacrylamide copolymers (PK1 and PK2), the first polymer drug conjugates to enter clinical trials.

Professor Ulbrich has published more than 260 scientific articles, authored or co-authored 35 patents and he is the recipient of many awards. These include the Award of the Learned Society of the Czech Republic (1996), the Award of
the Ministry of Education, Youth and Sports of the Czech Republic (2002), Czech Head, award for Invention in polymer nanomedicines research (2005). He was also awarded “Præmium Academiae” from the Academy of Sciences (2008) and the Award of the Academy of Sciences of the Czech Republic for achievements in research (2011). He is a vice-chairman of the Scientific Board of the Academy of Sciences, a member of Scientific Councils of five Czech universities and a member of other scientific bodies.

Karel Ulbrich likes travelling and sports like skiing, cycling and hiking.

On the occasion of his 65th birthday, the Prague Meeting on Macromolecules: Polymers in Medicine 2012, which takes place from July 1st to 5th, will be dedicated to him. He certainly deserves this acknowledgement. Karel Ulbrich combines scientific excellence with friendliness, openness and kindness. At this conference, Ruth Duncan will give a talk entitled “Polymer therapeutics as Nanomedicines: the end of the beginning”. Karel is certainly one of the key scientists amongst the beginners, but we are sure that he will also contribute to the next steps in the science and translation of polymer therapeutics.

FEATURED ARTICLE

REDEFINING THE LIMITS OF TRANSDERMAL DRUG DELIVERY: NEW TECHNOLOGIES FOR THE NON- AND MINIMALLY-INVASIVE DELIVERY OF PEPTIDES AND PROTEINS INTO THE SKIN

By Maria Lapteva, Ingo Alberti, Yong Chen, Taïs Gratieri, Dhaval R. Kalaria, and Yogeshvar N. Kalia
School of Pharmaceutical Sciences, University of Geneva & University of Lausanne, Geneva, Switzerland

1. Introduction

Transdermal delivery is convenient, shows high patient compliance and, in certain cases, can provide therapeutic advantages over oral administration. However, its scope is limited to a select group of therapeutic agents that possess (i) the balance of physicochemical properties required to traverse the stratum corneum, viable epidermis and enter the dermal capillaries and (ii) the necessary potency, so that the small amount of drug that reaches the target is able to elicit the desired pharmacological effect. As such, conventional wisdom has long held that the transdermal route is only useful for the administration of moderately lipophilic (log Ko/w ~2-4), low molecular weight (< 500 Da) compounds. Although it is certainly true that the drugs approved to-date by the regulatory authorities tend to fall in this category, the advent of new delivery technologies means that horizons can be broadened and molecules that were previously considered “non-starters” for the transdermal route – namely, peptides and proteins – can be viewed in a different light. Here, we present a brief overview of these methods: these range from non-invasive techniques where transport across intact skin is enhanced through the use of either an additional driving force or of energy to compromise the skin barrier, to minimally-invasive methods designed to create transport conduits in the stratum corneum that facilitate passive diffusion into the underlying viable tissue.

2. Iontophoresis

As a general rule, the transport of polar or ionized molecules across the skin is severely limited by both the structure and the composition of the stratum corneum. The lipid-rich intercellular space offers a rather inhospitable – i.e., thermodynamically unfavorable – environment to hydrophilic molecules. However, good aqueous solubility and the presence of ionized groups at physiological pH are distinct advantages for iontophoretic delivery which uses the application of a mild electric potential gradient across the skin to facilitate transport. Thus, poor candidates for passive delivery – i.e., hydrophilic, charged species – are often ideal for electrically-assisted transport into the skin [1]. In its simplest form, an iontophoretic system comprises two electrodes – the anode (positive electrode) and the cathode (negative electrode) – a microprocessor, a battery or a power supply and a drug reservoir. The application of an electric field results in a flow of current generated by the ordered movement of ions present in the formulation and in the skin. This is referred to as electromigration (EM) and is usually the dominant electrotransport mechanism. The ionization, under physiological conditions (isoelectric point of ~ 4-4.5 [2]), of fixed carboxylic groups in the skin means that when the electric field is applied, a convective solvent flow is generated in the direction of counter-ion flow motion to neutralize membrane charge – that is, in the anode-to-cathode direction. This solvent flow is referred to as electroosmosis (EO) and provides a second (minor) mechanism for the permeation of cations and also enables the electrotransport of neutral molecules from the anode. Anions are delivered exclusively by electromigration from the cathode.

Although iontophoresis is one of the more mature transdermal delivery techniques, much remains to be learned and pre-conceived notions challenged. Until recently, there was a general consensus that it could only be used for the delivery of small hydrophilic molecules or, at best, cationic peptides, which could benefit from EO for delivery into the skin under physiological conditions. Thus, in addition to numerous studies into the transdermal iontophoresis of low molecular weight drugs, the electrotransport of several cationic peptides - including gonadotropin releasing hormone and its analogues, somatostatin analogues, calcitonin and the N-terminal (1–34) fragment of human parathyroid hormone has also been reported [3]. Given the physicochemical properties of peptides and their constituent amino acids, it is clear that they are extremely poor candidates for partitioning into and passive diffusion through the lipid-rich intercellular space in the stratum corneum. Therefore, the non-invasive iontophoretic delivery of these molecules with so-called “undesirable” physicochemical properties represents a considerable achievement [3]. It should come as no surprise that the most studied peptide has been insulin [4, 5]. However, even though some studies showed reduction in blood glucose levels in small animals, drastic conditions were often required to disrupt skin barrier function and even then the results have not been reproduced in humans, where significantly greater quantities of the hormone are required for pharmacol-
The problem is that insulin is a poor candidate for iontophoretic delivery, based on its physicochemical properties, its pharmacokinetics and pharmacodynamics. Indeed, the quest to deliver insulin by transdermal iontophoresis should serve as an example (i) to highlight the need for a rational selection of candidates for a given delivery technology and (ii) to show that although new technologies may enable significant breakthroughs in delivery capability, they cannot be used for all drugs.

The perceived limits of iontophoresis were challenged in 2007, when it was shown that it was possible to deliver cytochrome c, a 12.4 kDa protein, non-invasively across intact skin [6]. Furthermore, contrary to previous assumptions, it was also demonstrated that EM was the dominant mechanism and that EO accounted for only 10% of transport. Subsequently, the successful delivery of enzymatically active ribonuclease A (13.6 kDa with a pI of 8.64) across porcine and human skin demonstrated that, in addition to structural integrity, biological activity was also retained post-iontophoresis [7]. Again, EM was the main electrotransport mechanism (>80% of the total flux). More recently, it was shown that transdermal iontophoresis was also able to deliver a biologically active negatively charged protein (ribonuclease T1; 11.1 kDa and a pI of 4.27) non-invasively across intact skin, meaning that cathodal electromigration of anionic macromolecules was sufficient to overcome opposition due to convective solvent flow in the anode-to-cathode direction [8]. The limits were further pushed back when the delivery of biologically active human basic fibroblast growth factor, a 17.4 kDa protein, was confirmed into and across the skin in therapeutically relevant amounts corresponding to those used in clinical trials and animal studies for the treatment of burns, incisional wounds, recalcitrant ulcers and peripheral arterial disease [9]. All of these results add to the body of evidence that iontophoresis can be used for the non-invasive transdermal delivery of both cationic and anionic proteins and refute the dogma that these molecules are too large to be delivered across intact skin by this technique. A summary of peptides and proteins studied and the experimental models used is shown in Table 1.

Table 1. List of relevant studies applying iontophoresis for delivery of therapeutic peptides and proteins in vitro and in vivo
Adapted from [3]

<table>
<thead>
<tr>
<th>Therapeutic agent</th>
<th>Approximate molecular mass (Da)</th>
<th>Model</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>6000</td>
<td>Diabetic rats</td>
<td>Monomeric human analogue (intact skin) and bovine insulin (impaired barrier) induced decrease in blood glucose level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porcine epidermis/in vitro and diabetic rats</td>
<td>Combination approach with permeation enhancers increased transport</td>
</tr>
<tr>
<td>Human calcitonin</td>
<td>3500</td>
<td>Rats</td>
<td>Hypocalcemia comparable to intravenous</td>
</tr>
<tr>
<td>Salmon calcitonin</td>
<td>3430</td>
<td>Rabbits</td>
<td>Therapeutic effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shaved rats</td>
<td>Therapeutic effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rats</td>
<td>Comparable to subcutaneous injection</td>
</tr>
<tr>
<td>hPTH</td>
<td>4117</td>
<td>Rats, hairless rats, beagle dogs</td>
<td>Absorption via hair follicles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovariectomized rats</td>
<td>Similar results to subcutaneous injection</td>
</tr>
<tr>
<td>LHRH</td>
<td>1182</td>
<td>Yorkshire pigs</td>
<td>Pharmacologically active LHRH delivered</td>
</tr>
<tr>
<td>Nafarelin</td>
<td>1322</td>
<td>Human skin in vitro</td>
<td>75 % pulsed DC current was most efficient in delivery</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>1210</td>
<td>Healthy males</td>
<td>Pharmacologically effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Healthy males</td>
<td>Comparable to subcutaneous injection</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>1311</td>
<td>Porcine skin in vitro</td>
<td>Therapeutic amounts delivered</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>1084</td>
<td>Human and rat skin in vitro</td>
<td>Therapeutic dose delivered</td>
</tr>
<tr>
<td>9-desglycinamide vasopressin</td>
<td>1028</td>
<td>Human skin in vitro</td>
<td>Transport achieved mainly by EO</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>1183</td>
<td>Diabetic rats</td>
<td>More effective than oral and nasal route</td>
</tr>
<tr>
<td>Octreotide</td>
<td>1019</td>
<td>Rabbits</td>
<td>Increased flux as function of current and concentration</td>
</tr>
<tr>
<td>Vapreotide</td>
<td>1131</td>
<td>Porcine skin in vitro</td>
<td>Peptide irreversible binds to skin but therapeutic concentrations can be achieved</td>
</tr>
</tbody>
</table>
### 3. Sonophoresis

Sonophoresis, or the application of ultrasound to facilitate transdermal delivery, has been studied for more than half a century [10]. Although both low and high frequency sonophoresis (LFS and HFS) have been investigated to enhance skin permeability using various frequencies ranging from 20 kHz to 16 MHz, only low-frequency ultrasound (20-100 kHz) has been demonstrated to produce appreciable enhancement of transdermal transport [11, 12]. As a result, much of the more recent work has focused exclusively on LFS [13]. Over the past decade, research on LFS can be classified into two categories: (i) simultaneous application of drug and ultrasound to the skin or (ii) a short application of ultrasound to pre-treat the skin in order to increase its permeability prior to application of the drug formulation [14].

Ultrasound is a mechanical vibration and is produced by converting electrical energy into mechanical energy by a piezoelectric crystal, thereby generating acoustic waves. The mechanisms behind sonophoretic enhancement are not very clear, though acoustic cavitation, the formation and oscillation of microbubbles in the coupling medium, is believed to have a major role [15, 16]. Although it was previously suggested that cavitation within the skin resulted in disruption of the permeability barrier, it has now been proposed that the collapse of cavitation bubbles and formation of a microjet at the surface of the stratum corneum (i.e., outside the skin) gives rise to shock waves that can perturb the skin barrier and render it more permeable [17].

Delivery of macromolecules by LFS into and across the skin has been a topic of extensive research during the last two decades since Tachibana and Tachibana [18] reported in 1991 that the application of LFS at 48 kHz enhanced the transport of insulin across the skin of hairless mice fasted overnight and partially immersed in an aqueous solution of insulin (20 U/ml). After exposure to ultrasound at 48 kHz for 5 min, the blood glucose level of the mice fell rapidly to 34 ± 11.9% of control values in 120 min. Moreover, the blood glucose levels remained low for 240 min (the duration of the experiment) [18]. Mitragotri et al. [11, 19] showed that application of LFS at even lower frequency (20 kHz) was able to induce significant transdermal transport of large molecules including insulin, v-interferon and erythropoietin across human cadaver epidermis in a Franz diffusion cell. It was also reported that a decrease in the blood glucose concentration of hairless rat induced by LFS-mediated insulin delivery at intensities of 62.5 and 225 mW/cm² for 1 h was similar to that induced by single subcutaneous injection of 100 µU and 1 U insulin, respectively [11, 19]. The feasibility of LFS-mediated skin vaccination has also been investigated [20]; the delivery of tetanus toxoid (150 kDa) into mouse skin following pre-treatment with 20 kHz LFS and 1% SLS not only elicited an enhanced immune response, but also activated Langerhans cells.

### 4. Microneedles

Micrometer-scale needles, or "microneedles", provide a minimally invasive, safe [21] and painless disruption of the skin barrier [22] and, in principle, enable the delivery of macromolecules into the viable epidermis. Microneedles can be defined as thin, short, solid or hollow cannulae, which up on application can penetrate the epidermis without reaching the dermis and its pain sensitive nerve endings [23]. They can be classified in three categories: solid, degradable and hollow. Different materials have been used to produce microneedles: metal or silicon [24, 25], biodegradable [26-28] and non-biodegradable synthetic polymers [29, 30], sugars [31, 32] and natural polymers [33, 34]. In early research, solid needles were simply used to pierce the skin and a drug containing patch was then placed on the treated area. Insulin was one of the first macromolecules successfully delivered in vivo using this method [35, 36]. Transdermal insulin delivery was increased, resulting in a significant reduction in glucose blood levels in diabetic rats; however, as with other transdermal delivery methods, the scale-up to humans remains problematic.

Innovative solid microneedles (ZP Patch Technology, formerly, "Macroflux®") coated with bioactive molecules were developed by Zosano Pharma, Inc. (USA). Application of a titanium microprojection array coated with ovalbumin, used as a model protein antigen, triggered a 50-fold greater immune response than that following s.c. and i.m. injection [37]. Desmopressin, a potent synthetic peptide for the treatment of enuresis in young patients, suffers from poor and variable bioavailability when administered orally and intranasally (0.1 and 3.4 % respectively), while conventional injectable forms are unsuitable for routine use in children. The systemic bioavailability of desmopressin achieved using the

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<table>
<thead>
<tr>
<th>Therapeutic agent</th>
<th>Approximate molecular mass (Da)</th>
<th>Model</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatotropin</td>
<td>3929</td>
<td>Hairless porcine skin in vitro</td>
<td>Linear increase in flux with current density but independent of type of current and frequency</td>
</tr>
<tr>
<td>Hairless guinea pig</td>
<td>Steady state levels similar to subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHRP</td>
<td>817</td>
<td>Rats</td>
<td>Therapeutic levels achieved</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>150,000</td>
<td>Humans with hyperhidrosis</td>
<td>Amelioration of symptoms</td>
</tr>
<tr>
<td></td>
<td>Rats</td>
<td>Toxin found in hair roots, sebaceous glands and arrector pili muscles fibres</td>
<td></td>
</tr>
</tbody>
</table>

GHRP: Growth hormone-releasing peptide; hPTH: Human parathyroid hormone; LHRH: Luteinizing hormone-releasing hormone
The delivery of several other biopharmaceuticals including brain natriuretic peptide (BNP), insulin, luteinizing hormone-releasing hormone (LHRH), erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF) and influenza vaccine using the coated microneedle array is currently under Phase 1 investigation, whereas a human parathyroid hormone (1-34)-coated microneedle patch system for the treatment of severe osteoporosis is moving towards Phase 3 studies [39]. Earlier studies have demonstrated superior pharmacokinetics and pharmacodynamic responses as compared to subcutaneous injection of hPTH(1-34). Other studies with solid microneedles have shown that the stability of microneedles coated with inactivated influenza virus was improved by the addition of trehalose and this also resulted in increased immunogenicity in vivo [40-42].

The use of novel materials has enabled the design of degradable or dissolvable devices. Upon insertion into the skin, the microneedles rapidly dissolve and hence release drug directly into the skin [32]. This strategy was used to deliver human IgG [32], recombinant human growth hormone and desmopressin [43], heparin [31], EPO [44] and insulin [34]. Biodegradable polymeric microneedles have been fabricated to encapsulate and to deliver calcine and bovine serum albumin. These were shown to possess the appropriate mechanical proprieties to pierce the skin, provide a good encapsulation efficiency and to enable controlled release of both compounds [27, 45].

Obviously, a limitation of coated microneedles is the quantity of drug that can be deposited on the surface and, hence, the amount that can be delivered. Hollow microneedles combined with a drug reservoir enable much larger amounts of drug to be administered. In this case the drug diffuses freely inside the needle before reaching deeper skin tissue. Flavivirus [46, 47] and a combination of anthrax, botulism, plague and staphylococcal toxins [48] have been delivered using this technology. After microneedle application, Rhesus monkeys were entirely protected from a lethal challenge by *Bacillus anthracis* spores, botulinum neurotoxin A, or staphylococcal enterotoxin B. It should also be noted that the combination of microneedles with other transdermal delivery technologies including iontophoresis and sonophoresis can yield synergistic effects [23]. In terms of safety, microneedles induced lower microbial penetration [49] and faster skin healing [50] than hypodermic needles and in general no adverse reactions or pain were reported to be observed following their use [21, 51].

Several companies – e.g., Theraject Inc. (USA) [52], Valeritas Inc. (USA) [53], Debiotech S.A. (Switzerland) [54] to name but a few – have developed technologies and/or have submitted or been issued patents. However, few systems are in advanced clinically studies [23], except for, as mentioned before, the ZP Patch product developed by Zosano Pharma Inc. (USA) which is poised to enter into Phase 3. Although microneedles seem to be a promising technology for the delivery of macromolecules into and across the skin, no products have been marketed to date and they will face stiff competition from intradermal injection systems that have needles that are only slightly longer (1-1.5 mm – most microneedles are typically in the 0.5-0.7 mm range). For example, Intanza®/IDflu® was the first intradermal-injection based influenza vaccine marketed in Europe by Sanofi Pasteur using the BD Soluvia™ microinjection system (Becton Dickinson, USA) [55].

### 5. Thermal and radiofrequency ablation

As an alternative to mechanical perforation of the epidermis, thermal and radiofrequency-induced ablation techniques involve the use of microelectrode arrays to apply short pulses of thermal or radiofrequency energy that “burn away” discrete regions of the SC and so create transport pathways. Although the high temperatures employed (> 100 °C) may appear too aggressive, heating is normally restricted to very small superficial areas and is applied for only short time intervals (< 1s) [56], creating micropores with a definite shape and size corresponding to the geometry of the ablation elements; e.g., (i) circular micropores of 30 μm diameter and 70 μm depth without any necrosis of the surrounding tissue [57] and (ii) micropores with an elliptical geometry of 80 μm width, 300 μm length and 40–50 μm depth, have been described [58].

Altegra Therapeutics has developed a system based on resistive energy ablation that consists of a single use disposable patch (PassPort™) and a reusable handheld applicator. The patch contains an array of electrically resistive filaments and application of a short controlled pulse of electric current causes them to heat up and ablate the stratum corneum – the formulation is applied in a second step. Gene expression for adenovirus-based vaccines following topical immunization via PassPort™ was reported to be 100-fold higher following application to microporated skin as compared to intact skin [57]. The same system has been used for the delivery of interferon α-2b [59] and clinical studies are reported to be underway for the delivery of basal insulin [60].

TransPharma Medical has developed an ablation system based on the application of an electric current in the radiofrequency range (100 – 500 kHz) [61]. The ViaDor™ technology consists of a reusable battery-operated handheld electronic control unit and a disposable microelectrode array that is employed in conjunction with a drug-containing patch. The microelectrode array can generate 144 microchannels over a 1.4 cm² area with each microchannel being about 50 μm in length and 30–50 μm at its widest aperture. Application of the radiofrequency electrical current causes the ions present in the tissue to vibrate. This results in local frictional heating of the neighboring tissue and the rapid obliteration of cells close to the energy source [62]. After microporation, a patch is applied and drug is released from the reservoir. The ViaDor™ system has been used to deliver human growth hormone (hGH; 22 kDa) in rats and guinea pigs. Creation of micropores in the outer layers of the skin enabled efficient delivery of hGH, with a bioavailability of 75% (rats) or 33% (guinea pigs) relative to subcutaneous (s.c.) injection with plasma profiles resembling that of s.c. injection. Elevated levels of systemic insulin-like growth factor-1 (IGF-I) were observed after transdermal delivery of hGH to hypophysectomised rats, indicative of the bioactivity of the transdermally delivered hGH in vivo [63]. The technique has also been used for DNA delivery resulting in gene expression within the epidermis and dermis [62]. A number of human clinical studies have been reported using the ViaDor™ system – e.g., for human growth hormone and calcitonin [64].
6. Laser ablation

In this technique, cutaneous micropores are created by removing tissue through the use of laser-generated energy. The lasers are derived from systems that are in routine use as safe and efficient devices for the local treatment of medical conditions (e.g., keloids or warts) or in aesthetic dermatology for superficial skin ablation (e.g., wrinkle reduction or removal of age spots). Many different types of laser system have been used for dermatological [65] or aesthetic [66] applications; each one has unique characteristics (wavelength, power, and length of pulse duration) that can be tailored for an optimal treatment.

The solid-state erbium-doped (Er:YAG) lasers used for cutaneous microporation in drug delivery are derived from devices developed for aesthetic skin resurfacing treatments. They emit near-infrared light at 2940 nm. The particular feature of this wavelength is that it is specifically absorbed by water, which instantly vaporizes resulting in epidermal ablation with minimal heat generation and coagulation [67]. Lasers can be used to produce an array of micropores; this can be done by splitting the beam (however, this reduces the applied energy) or by using a scanning device that focuses the full beam energy at each point to create the micropore. This is followed in a second step by the application of the drug-containing formulation. Since healthy skin is left between the pores, this allows a faster recovery of the treated area [68]. As for thermal and radiofrequency ablation, the size and depth of the micropores can be controlled, so as to control the rate and extent of drug delivery [69]. The procedure is minimally invasive and almost painless (only a slight pricking is perceived), if the laser energy is set so that the penetration depth is limited to the upper dermal layer, just skimming the nociceptive nerve endings.

Laser microporation for drug delivery is a relatively recent application and only a limited number of studies have been published to date. Attempts to deliver peptides and proteins are even less common, which leaves room for potential innovation. In an exploratory in vitro study attempting to determine the macromolecular cutoff of transdermal delivery across laser-porated skin, hexameric insulin (36 kDa) showed significantly higher permeation (>2.6-fold higher after 12 h contact) across excised porcine skin than dextran with similar molecular weight (38 kDa), following Er:YAG laser pre-treatment (Continuum Biomedicals, CA, USA). Output energies of 0.45–1.35 Joule (J) per pulse with a beam spot size of 7 mm in diameter achieved fluences of 1.2–3.5 J/cm² [70]. It was concluded that molecular weight was not the only parameter determining permeation, but macromolecular conformation might also be involved (insulin is globular, whereas dextran is linear and might be more hindered). The same Er:YAG laser (but with output energies of 0.45–0.65 J, and fluences of 1.2–1.7 J/cm²) was used to demonstrate the feasibility of delivering lysozyme in mice in vivo [71]. Serum samples were assayed for the anti-lysozyme antibody 1 month after the first treatment. Titers of immunoglobulin G (IgG) were significantly enhanced in the serum by 3-fold. The immunization levels for 1.4 and 1.7 J/cm² were equivalent (p>0.05).

The feasibility of delivering antithymocyte globulin (ATG, 155 kDa; Thymoglobulin®, Genzyme Corp), an FDA-approved therapeutic for the induction of immunosuppression, across porcine and human skin in vitro and in mice in vivo was demonstrated following skin pretreatment by another Er:YAG laser (P.L.E.A.S.E.®, Pantec Biosolutions, Ruggell, Liechtenstein) [72]. The structural integrity and biological activity of the antibody post-delivery were confirmed by Western blot and a human lymphocyte cytotoxicity assay, respectively. The laser was a scanning device that was able to generate an array of several hundred identical pores created sequentially. Increasing laser fluence by 2 and 6 times (from 22.7 to 45.3 and 135.9 J/cm²) increased total ATG delivery by almost 3- and 5-fold (from 1.70±0.65 to 4.97±0.83 and 8.70±1.55 μg/cm²). Another antibody, approved for the induction of immunosuppression, basiliximab (144 kDa; Simulect®, Novartis Pharmaceuticals, Basel, Switzerland) was also tested in the same study. It was delivered in vitro across porcine skin with the same protocol as for ATG. A three-fold increase in laser fluence from 45.3 to 135.9 J/cm² resulted in a two-fold increase in basiliximab delivery from 6.74±0.66 to 12.36±1.62 μg/cm² (P=0.0007). Both ATG and basiliximab studies demonstrated that laser microporation was able to deliver antibodies locally into the skin at levels sufficient for pharmacological effect.

The same laser has also been used in a clinical setting to deliver a biopharmaceutical protein, follicle stimulating hormone (FSH, 32 kDa). This was the first relevant phase I clinical study performed in patients, demonstrating the feasibility of protein delivery by laser microporation [73]. FSH is commonly used in infertility treatment with daily subcutaneous injections of 150 to 300 I.U. over 10-12 days with the goal to stimulate egg cell (oocyte) maturation. The purpose of the study was to investigate the primary pharmacodynamic characteristics as well as the safety and tolerability of the newly developed FSH protein patch in 10 oocyte donors and to compare it with the effects of subcutaneous injections of Fostimon® (IBSA, Lugano, Switzerland) in another 10 oocyte donors. At least two follicles of 15-27 mm diameter were retrieved in six out of ten P.L.E.A.S.E.® / patch patients and nine out of ten injection patients. One of the subjects in the patch group even reported a pregnancy, thereby confirming suitability and efficacy of the method.

7. Conclusion

The "rule-of-thumb" of only considering drugs of modest molecular weight and moderate lipophilicity for administration across the skin needs to be revisited in the light of the development of new transdermal delivery techniques. These permit the transport of hydrophilic molecules, peptides and even proteins into and across the skin. The challenge is to translate these demonstrations of feasibility into successful products. It is to be hoped that the identification of appropriate drug candidates and indications coupled with further technological advances and cost-effective production strategies can combine to make this a reality.
Literature/References


**DRUG DELIVERY LITERATURE**

Provided by Dr. Carsten Timpe

**RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY**

**Recent advances in brain tumor-targeted nano-drug delivery systems.**

**Recent advances in predicting skin permeability of hydrophilic solutes.**

**Modelling of pecturnaneous drug permeation and investigation of penetration enhancer effect.**

**Emulsion forming drug delivery system for lipophilic drugs.**

**Nano cancer therapy strategies.**

**Nanofibers: effective generation by electrospinning and their applications.**

**Pseudomonas sp. as a Source of Medium Chain Length Polyhydroxyalkanoates for Controlled Drug Delivery: Perspective.**

**Nanostructures as promising tools for delivery of antimicrobial peptides.**
Brandelli A.; Mini Rev Med Chem. 2012 Apr 17. (Epub ahead of print)

**Aerosol device selection for spontaneously breathing patients: 2012.**

**Antibody therapy of cancer.**

**Nanoscale drug delivery systems for enhanced drug penetration into solid tumors: current progress and opportunities.**

**Halloysite clay nanotubes for controlled release of protective agents.**

**An update in options for the treatment of pain: a review of new opioid formulations.**
Microsystem technologies for medical applications.

Delivery of molecular and nanoscale medicine to tumors: transport barriers and strategies.

Polymers for drug delivery systems.
The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceutics.

**OUR MISSION STATEMENT:**
Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nanotechnology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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