APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

International Association for Pharmaceutical Technology

Newsletter ISSUE 1/2022 - September

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Suggest a meeting to be announced!

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosemayr-Templeton

Amvuttra™ Injection

Amvuttra™ Injection for subcutaneous use contains 25 mg/0.5 mL of vutrisiran, a small interfering RNA which blocks translation of the transthyretin gene. On 13 June 2022 it was approved by the FDA for the therapy of polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (hATTR) in adults [1, 2]. Around one month later it received a positive opinion from the EMA's Committee of Human Medicinal Products (CHMP) for its use in hATTR amyloidosis patients with Stage 1 or Stage 2 polyneuropathy, making its authorisation in Europe imminent [3, 4]. In both regulatory jurisdictions the compound has orphan drug status.

hATTR is a rare, autosomal dominant disease caused by defects in the gene encoding for transthyretin, a 55 kDa protein. Transthyretin is manufactured mainly in the liver and circulates as a tetramer in blood and cerebrospinal fluid. Its role in the body is to transport thyroxine (T4) and, in a complex with retinol-binding protein, Vitamin A [5]. Greater than 120 genetic variants of transthyretin have been identified, most of which are associated with disease. However, the most common is the p.Val30Met mutation where valine is replaced by methionine at position 30. hATTR is a protein misfolding disease in which insoluble TTR amyloid fibrils gradually deposit in various organs. This slow build-up results in a variety of clinical symptoms presenting in adulthood typically in patients less than 50 years old (early onset disease). However, in a sub-set of patients, symptoms may only develop in old age (late-onset disease). hATTR is a progressive, debilitating disease which results in significantly reduced life expectancy. Clinical manifestations, age of onset and rate

of disease progression may vary depending on the causative genetic variant, geographical location, whether the mutation was inherited from the maternal or paternal line plus other factors. However, polyneuropathy is the most common symptom which, as it worsens, can lead to issues such as postural hypotension, and digestion and bladder problems. Other organs such as the heart, eyes and kidney can also be affected with cardiomyopathy being diagnosed in around 50% of patients.

Vutrisiran was developed by Alnylam Pharmaceuticals, Inc. (MA, USA) [6]. It is a double-stranded small interfering RNA that reduces production of both mutant and wild-type transthyretin (TTR) in the liver through the targeted destruction of TTR mRNA. Vutrisiran has been shown to reduce TTR human serum levels by 83% at steady state. Chemical modification using Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery technology enables increased compound stability and targeting to liver cells. The conjugate technology consists of siRNA covalently bound via a linker to three N-acetylgalactosamine (GalNAc) residues. The trivalent sugar conjugate has high affinity for the asialoglycoprotein receptor on the surface of hepatocytes, promoting uptake into the cells which are the site of transthyretin production [1]. Amvuttra™ is administered subcutaneously once every three months as the sodium salt in a sterile buffered solution. It therefore affords more clinician and patient-friendly administration than the previously approved Onpattro® (patisiran) which is dosed intravenously every three weeks.

US approval was based on the 9-month results of the HELIOS-A Phase 3 open-label study in hATTR patients with neuropathy [1, 2], and the positive CHMP opinion on data from the same trial at 18-months [3, 4]. The 164 study participants (randomised 3:1) either received 25 mg of Amvuttra™ subcutaneously once every 3 months, or the previously approved patisiran 0.3 mg/kg intravenously every 3 weeks.

Efficacy assessments involved comparing the results of those administered Amvuttra™ versus those obtained from a similar patient population administered placebo in the Apollo study, a placebo-controlled Phase 3 study of patisiran in the treatment of hATTR amyloidosis associated polyneuropathy. Efficacy was assessed using the difference in the modified Neuropathy Impairment Score +7 (mNIS+7) at baseline and after 9-months' and following 18 months' of treatment (primary end-point). In particular, cranial nerve function, muscle strength, and reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology were evaluated using this objective methodology. The mNIS+7 scale ranges from 0 to 304 points, with the larger scores indicating more severe disease. The benefits of Amvuttra™ treatment were also assessed at the same time-points using a patient-reported evaluation known as the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score (main secondary end-point). Additional secondary endpoints included speed of walking over 10 metres and changes in body mass index. The study results showed that Amvuttra™ therapy achieved the primary and all secondary trial end-points at both Month 9 and Month 18. At 9 months over 50% of participants showed either no further disease progression or an improvement in symptoms and this effect was still present at 18 months with the effect of treatment increasing with time [7]. The most common side-effects of Amvuttra™ include arthralgia, pain in the arms and legs, dyspnea and injection site reactions. Due to transthyretin's role in Vitamin A transport, supplementation is required during therapy. The product is now launched on the US market [6].

Adlarity® Transdermal System

On 11 Mar 2022 the FDA approved Adlarity® (donepezil transdermal system) from Corium Inc. (MI, USA) [8, 9]. Donepezil is a reversible acetylcholinesterase inhibitor, which has been approved since 1996 in the US for the therapy of mild to severe dementia caused by Alzheimer's Disease. The dose is 5 mg per day. This can be increased after 4 to 6 weeks of initiation of treatment to a maximum of 10 mg. Since its initial approval as 5 mg and 10 mg tablets (Aricept®), the compound has been marketed as an oral solution, oral disintegrating tablets and in combination with the N-methyl D-aspartate (NMDA) receptor antagonist, memantine, as an extended release capsule (Namzaric®). This is the first time it has reached the US market as a transdermal formulation.

The Adlarity® transdermal patch is based on Corium's proprietary CORPLEX™ transdermal technology which has been previously used in several US over-the-counter products, e.g., Procter & Gamble's Crest® Whitestrips [10]. The company website states that the technology can be used for products with high drug loading and can be modified to achieve immediate-to-slow-transdermal release profiles, including potentially combinations of both. It enables the production of products with good adherence to both wet and dry skin surfaces and is not only applicable to patches but other types of formulations as well. For examples, the technology has been applied to liquids, semi-solid and solid formulations such as sprays, dry and wet films, gels, creams, cream and powders.

The Adlarity® transdermal patch contains donepezil both as the base and as the hydrocholoride salt. It enables the delivery of 5 mg donepezil per day or 10 mg per day for 7 days. The transdermal system is a rectangular 6-layer laminate. It is composed of an overlay backing/adhesive layer, separating layer, drug containing-matrix, porous membrane, contact adhesive, and a release liner which is removed immediately prior to application. The 5 mg/day patch (dimensions 8.3 cm by 10.8 cm) contains 88.4 mg of donepezil and the larger (10.8 cm by 14.4 cm) 10 mg/day system, 176.7 mg of active. The drug-matrix contains a mixture of donepezil base (15% to 35%) and the corresponding HCL salt (65% to 85%) to deliver donepezil base across the skin. The patch also contains acrylate copolymer, ascorbyl palmitate,

crospovidone, glycerol, lauryl lactate, polypropylene membrane, sodium bicarbonate, sorbitan monolaurate, and triethyl citrate.

The relative biovailability from the Adlarity® system was assessed in 60 healthy volunteers. In the initial titration stage of the study the participants were given the 5 mg/day patch for 5 weeks. In the second and third stages of the trial, the volunteers were randomised into two cohorts in a cross-over design, one group received the 10 mg/day patch and the other a donepezil tablet 10 mg/day, both for 5 weeks.

Drug exposure in terms of AUCtau and Cmax at steady state compared well to that of 10 mg tablets administered orally. Unsurprisingly, there was a delay in drug absorption following application of the 5mg/day patch for the first time, with maximum plasma concentrations being first reached later in the 7-day period. However, steady state was achieved within 22 days of multiple administration. The site of patch application affected donepezil absorption to a limited extent with the back (avoiding the spine) being the recommend application site, with the thighs or buttocks as a secondary option.

In general, the side-effects experienced by the volunteers when using the Adlarity® 10 mg/day transdermal patch were similar to those reported in previous clinical trials of oral donepezil in Alzheimer's patients and included headache (15%), application site pruritus (9%), muscle spasms (9%), insomnia (7%), abdominal pain (6%), application site dermatitis (6%) and constipation (6%). All of the dermal adverse effects were evaluated by a physician using a skin irritation scale and considered mild.

Corium relied on the extensive existing clinical database on donepezil to demonstrate the efficacy and safety of this compound in the treatment of dementia associated with Alzheimer's. Approval of the Adlarity® patch was based on the aforementioned relative bioavailability data plus other data e.g., from clinical studies investigating its adhesion to skin and potential of the patch to cause skin sensitisation.

Approval of the Adlarity® transdermal system will increase Alzheimer patient choice, especially for those with swallowing difficulties. The transdermal delivery of donepezil and the steady drug plasma concentrations that it affords, will avoid the drug plasma concentration fluctuations observed with oral formulations and result in a low likelihood of the GI side-effects associated with this compound. In addition, administration of donepezil via a patch allows carers to check if the medication has been administered, which is crucial for those suffering from a disease that impairs memory.

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ESOCAP (BASEL, SWITZERLAND)

Effective topical treatment of the esophagus is difficult to achieve with the current standard of care, due to the short drug contact time of a few seconds from the mouth to the stomach. Based on its proprietary drug delivery technology, EsoCap develops drug products for esophageal diseases such as eosinophilic esophagitis (EoE), GERD (gastrointestinal reflux disease) and Barrett's Syndrome. Its clinical stage lead product is a new formulation of mometasone for EoE. EsoCap is also open to partnerships with other pharmaceutical companies interested in developing products for esophageal diseases.

Fact sheet:

Founded:	2017
Location:	Basel, Switzerland
Ownership:	Privately funded company
Employees:	< 10
Key technology:	EsoCap's technology is for selective drug delivery to the esophagus, allowing the topical application of drug substances for targeted treatment of diseases affecting the esophagus. It includes a capsule containing a thin film loaded with a drug. Upon drinking the capsule from a specially designed drinking cup, the film unrolls and sticks to the patient's esophageal mucosa, where it dissolves slowly while releasing the drug substance.
Products:	EsoCap's lead product, ESO-101, is a hard gelatin capsule comprising a film formulation of mometasone furoate (800 µg) for once daily use. The administration is facilitated by a customised drinking cup with an applicator which holds the capsule. The actuation of the applicator causes the piercing of the capsule and the release of the film, which is then ingested by the patient along with liquid.
Development status:	EsoCap is currently conducting a Phase II clinical study of ESO-101 in adult patients with active eosinophilic esophagitis.
Partnerships:	The company has a well-established partnership with scientific team of Prof. Weitschies at the University of Greifswald, Germany, where the EsoCap technology was originally invented.
Website:	www.esocapbiotech.com
Contact:	EsoCap AG Malzgasse 9 4052 Basel, Switzerland e-mail: isabelle.racamier@esocapbiotech.com

DRUG DELIVERY PEOPLE

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Provided by Prof. Dr. Lea Ann Dailey

For this issue of the Newsletter, we would like to introduce Simona Mura as our featured Drug Delivery Scientist. After graduating as a Pharmacist (University of Cagliari, Italy), Simona obtained her PhD in Chemistry and Technology of Drug in 2009 at the same university (under the direction of Prof. Anna Maria Fadda) working on the design and in vitro evaluation of novel vesicular systems for the topical delivery of drugs. In 2008, she joined the group of Pr Elias Fattal (Faculty of Pharmacy, Institut Galien, UMR CNRS 8612) at the University Paris-Sud (France) as a post-doctoral research assistant to study the lung toxicity of biodegradable nanoparticles designed for the pulmonary administration of drugs. In 2011 she was appointed Associate Professor in the same University within the framework of the « CNRS-Higher Education chairs » program and she joined the group of Prof. Patrick Couvreur at Institut Galien Paris-Sud. In 2015, became Visiting professor at the Osaka University (Group of Pr Mitsuru Akashi) and in 2017 had the honour of being selected to join the prestigious Institut Universitaire de France (IUF) as a Junior member. She was awarded her HDR (accreditation to conduct research) in 2018.

Simona's research is carried out at the interface between chemistry, physical-chemistry and biology. She focuses on the design of biomimetic drug delivery systems and the understanding of the behaviour of nanomedicines in the complex biological milieu encountered in the human body from the site of administration to the site of action by combining 3D culture methodologies, microfluidic technology and advanced characterization techniques.

To date, she has authored/co-authored 60 peer-reviewed articles and co-authored 4 book chapters and edited one.

FEATURED ARTICLE

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Provided by Carsten Timpe, Louise Rosenmayr-Templeton

THOUGHTS ON THE PAST, PRESENT AND FUTURE OF DRUG DELIVERY: AN INTERVIEW WITH DR. CARSTEN TIMPE

Introduction

Dr Carsten Timpe has been a member of the APV Drug Delivery Focus Group for many years. Earlier this year Carsten informed the group that he would not only be retiring from his role as Technical R&D Expert Scientist at Roche, but also leaving our group at the end of the year. His leaving is of great sadness to the group and we will miss his enthusiasm, ideas and contributions to the Focus Group's numerous activities. Carsten has helped organise and acted as chair/co-chair and/or presented at numerous APV events including those focusing on poorly soluble compounds and paediatric medicine. I particularly appreciate his input and support for the Newsletter. Carsten made regular contributions to the Newsletter in the form of the Drug Delivery Literature Section and organised in conjunction with Karsten Cremer and Florian Unger, the Drug Delivery Company section. He contributed articles on nanoparticulate formulation and solid dispersion approaches to enabling oral delivery of poorly soluble drugs, reports on APV events in which he was involved and facilitated many more articles through his ideas and contact network. I would like to thank Carsten and just before he leaves for a well-deserved and based on his extensive list of interests, very active retirement, I asked him for his thoughts on the past, present and future of drug delivery.

- Please can you give the readers some brief biographical details.

I studied Pharmacy at the Technical University of Braunschweig from 1978 to 1982. After approbation as a registered pharmacist and completing civilian service, I worked for 3 years in a retail pharmacy in Hannover. Soon I realised that working as retail pharmacist did not fully address my interests in science, technologies and further education, so I began in 1988 a Ph.D. in pharmaceutical chemistry at the Philipps University in Marburg under the supervision of Prof. Klaus Hartke. After my Ph.D. In 1992 I started my industrial career at Jenapharm GmbH in Erfurt/Weimar as head of an experienced team in charge of solid oral dosage form development including GMP manufacture of clinical supplies and evaluation of new technologies for poorly soluble drugs. During that time, I joined the APV and for several years was a member of the focus group "Pharmatechnik". In 2000 I took the next step in my career when I joined Lilly Forschung as a Research Scientist with responsibilities for setting up a new early phase formulation team at the Hamburg site and transferring new formulations to the GMP manufacturing site in Indianapolis. Due to closure of the Lilly development sites in Europe, I moved to Novartis Pharma in Basel in 2007, working as a Fellow in the special drug delivery area focusing on poorly water-soluble drug candidates. After promotion to Senior Fellow, I moved in 2012 to Hoffmann La Roche Pharma in Basel where I am now working as a Technical R&D Expert Scientist and member of the pharmaceutical development department leadership team.

- What/Who inspired you to become involved in drug delivery science?

I first came into contact with drug delivery at Jenapharm working on pellets, solid dispersions, pulsatile and also bioadhesive buccal drug delivery. We filed patents in these areas and, e.g., for pulsatile delivery we bought and installed a tailor-made capsule filling machine within my group [1].
Following that initial inspiration to bring medicines successfully to the patient (e.g., see [2],[3]), my interest in drug delivery grew further at Lilly with the department in Hamburg getting more and more involved in the development of an increasing number of poorly soluble drugs [4]. During that time, we collaborated with external technology providers, i.e., in the field of melt extrusion, in addition to using internal delivery approaches such as the use of mesoporous silica.

At Novartis one of my first projects was the drug product development of a solid dispersion, prepared by spray granulation layering. The special delivery group also had strong expertise in developing SEDDS/SMEDDS formulations and later I worked together with my colleague, Dr. Michael Juhnke, on nanoformulations and became a member of the Novartis technology platform network at that time [5], [6], [7], [8].

My time at Roche began in 2012 with early phase development work, followed 2 years later by important global filing activities e.g., for Alecensa™, an oncology product against non-small cell lung cancer. In 2014 I also took over the Chair of the Roche paediatric-geriatric formulation working group (PG-FWG) from Rainer Alex, a role I still hold. In the following years the Working Group developed an internal paediatric drug delivery strategy and created a couple of guidance documents [9], [10]. In addition, the PG-FWG has been and continues to be engaged in the European Paediatric Formulation Initiative (EuPFI) organisation together with numerous other pharmaceutical companies and universities [12]. Throughout all these years at Lilly, Novartis and Roche I gave several talks at conferences and webinars about the delivery of poorly soluble drugs and paediatric development. In addition, I proposed and moderated or co-moderated several APV seminars in my role as a member of the focus group “Drug Delivery”.

- What do you think were the most significant developments in drug delivery which occurred during your career?

When I started my career, proposals to deliver a poorly soluble drug as a solid dispersion were rejected by management with the argument that these systems would be metastable and manufacture would be impossible e.g., due to the requirement for large amounts of solvent. Over the last 2-3 decades, scientific understanding of these systems has dramatically increased facilitated by the availability of new analytical technologies (i.e. Raman microscopy, XRPD including more sophisticated analysis such as like pair distribution function etc.) and the arrival of new polymers in the excipients portfolio (i.e. HPMC-AS). In the meantime, a number solid dispersion formulations have been commercialised successfully including products for the treatment of life-threatening diseases such as HIV infections (e.g., Ritonavir/Lopinavir melt extruded formulations).

In the field of nanoformulation we are witnessing a real flood of publications, patents and delivery ideas, of course mainly in the parenteral area. The interest in treating difficult diseases like cancer more successfully or delivering drugs to the brain by overcoming the blood-brain barrier, opening tight junctions etc. demonstrates the need to invest in drug delivery to a much greater extent than before. Such investment will hopefully lead to more efficacious drugs in the near future for the benefit of patients.

Nowadays the world of oral drug delivery also has to deal with the delivery of macromolecules (peptides, oligonucleotides). For example, the recent successful launch of the GLP-1 analog semaglutide (RybelsusTM) with a molecular weight of 4113 Da has demonstrated that for medium--size large molecules oral absorption can be feasible. Of course, the gastric and intestinal stability of macromolecule drug candidates against proteases and nucleases has to be taken into consideration, as well as how to improve their permeation across the mucosa.

Tremendous progress has been achieved in the field of paediatric drug delivery in the last 10 to 20 years: while decades ago the general thinking was not to conduct clinical trials with children, nowadays the significant regulatory pressure on pharmaceutical companies to develop medicines for children had led to a paradigm shift from which millions of young patients benefit. For example, Roche has recently launched Evrysdi ™ (risdiplam) which is a treatment for the devastating disease, Spinal Muscular Atrophy (SMA). The medicine can be administered at home and is approved for use both in children and in adults. It is impressive to see how such medications can help improve the life of severely ill young patients and their families as well.

- Looking to the future, what aspects/developments in drug delivery do you find the most exciting?

Delivery of Macromolecules

As previously mentioned, the oral delivery of medium-sized large molecules like peptides and oligonucleotides is an exciting field of innovation. The successful oral delivery of larger molecules could result in improved medication adherence by patients by allowing them to just swallow their “pills” versus having to go to a hospital or to the physician to have the drug administered intravenously. This will be challenging for sure and probably requires the integration of different delivery approaches, from using suitable permeation enhancers to the application of device systems that operate using a kind of injection-like principle in the gut (e.g. “Rani-Pill” and others).

Paediatric Medicine

Regarding paediatric drug delivery, the pharmaceutical industry has learned its lesson quite well and overall, more and more progress can be seen on a global level. For example, China has now established a paediatric guidance document which integrates all the learnings made in Europe and in the USA so far. Nevertheless, a better understanding of devices, and how to improve taste and palatability in general still remain fields where more research is required.

Geriatric Medicine

In order to improve the delivery of medicines to geriatric patients, the pharmaceutical industry probably has to do more than before as elderly people represent a dramatically growing patient population worldwide. For example, the industry will need to focus more on aspects like the ease of drug administration, human factor considerations, multi-morbidity, parallel use of several drugs by a patient and the readability and comprehensibility of leaflets. Further thoughts on this topic can be found e.g., in reference [11].

- Patient-centric medicine has the potential to be disruptive for the pharmaceutical industry, regulatory and the traditional way medicines have been produced, tested and released e.g, the 3D printer in the hospital pharmacy. What are your thoughts on how developments in patient-centric medicine can be implemented to drive the goal of personalised medicines?

As already mentioned above, patient-centric drug development is a complete paradigm shift which requires a much better understanding of diseases, the medical requirements of patients and the social environment in which the patients live. Taking care of a patient in a third world country, who is surrounded by family members, could be a different story to that of an elderly patient in our Western world who lives alone and has problems to get medical assistance and support on a daily basis. In addition, we need to take into consideration the economic aspects of improved patient centricity, e.g., can we expect that patients have access to fancy digital technologies that would monitor important physiological or organ functions? Therefore, I assume that industry would develop strategies for these different scenarios. Probably these could range from rather simple to more complex solutions which would also involve more sophisticated technical features (e.g., sending signals from an electronic capsule to a cell phone).

- On a personal note – have you any special plans/goals for your retirement?

I belong to a very problematic group of curious persons who unfortunately have interests in too many things. These span from searching for minerals in quarries to playing music on period string instruments from the Renaissance and Baroque periods, learning new languages, writing stories etc.

Honestly I am afraid that pharmaceutical topics will consequently play a smaller role in my life than in the last 30 years - as "*tempus fugit*" and our lives are rather short - according to Seneca (☺)….

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ABOUT THE FOCUS GROUP

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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.

COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

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, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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