APV Focus Group Drug Delivery

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

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DRUG DELIVERY EVENTS

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- **APV Workshop on Protein Aggregation and Immunogenicity | CN 6845** Details
  08.02. - 11.02.2022 | Munich, Germany
- **13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology CN 1022** | 28.03. - 31.03.2022 | Rotterdam, The Netherlands Details

Suggest a meeting to be announced!

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosemayr-Templeton

Trudhesa™ Nasal Spray (Impel NeuroPharma)

On 2nd Sept 2021 the FDA approved Trudhesa™ Nasal Spray which delivers 0.725 mg dihydroergotamine mesylate (DHE) per spray for the acute management of migraine with or without aura in adults [1-2]. The dose is one spray in each nostril which may be repeated after 1 hour. Administration is limited to 2 doses in 24 hours or 3 doses over 7 days due to the ergotamine derivative's vasoconstrictive effects which can result in ischaemia. The potential for ischaemic events is also the reason why it is recommended that patients are evaluated for cardiovascular risks before initiating DHE therapy, and that those still considered suitable despite certain risk factors receive their first dose in conjunction with electrocardiography in an appropriately equipped clinical facility.

The product contains DHE solution at a concentration of 4 mg/mL (equivalent to 3.43 mg dihydroergotamine), together with anhydrous caffeine (10.0 mg/mL), carbon dioxide (q.s.), anhydrous dextrose (50.0 mg/mL), and water (q.s. to 1.0 mL). This is the same composition used for the Migranal® (DHE) Nasal Spray which has been on the US market since 1997 [3]. However, the Trudhesa™ dose is lower (total 1.45 mg = 1 spray/nostril). In comparison the total dose of Migranal® is 2 mg, administered as 1 spray containing 0.5 mg of DHE per nostril, followed 15 minutes later by repeat

dosing. Both products are supplied as a DHE solution in amber glass vials, the difference between the two medicines is the product's co-supplied nasal spray device.

The Impel NeuroPharma product delivers DHE using the company's proprietary Precision Olfactory Delivery (POD®) technology. The device is designed to target delivery to the upper olfactory region of the nose which is rich in blood vessels employing hydrofluoroalkane-134a as the propellant. In contrast most other nasal delivery systems result in drug deposition predominantly in the lower part of the nasal cavity. Delivery of medicines to the lower nasal area can be variable as a result of loss of active due to "dripping" from the nares and swallowing, mucociliary clearance and depending on the exact device design, sub-optimal delivery caused by poor administration technique. The POD® device technology, which can also be applied to the nasal delivery of powders, has been shown using a radiolabelled tracer to deliver a higher percentage of drug to the target upper area compared to a conventional pump system [4].
The device is manually activated following four priming actions to produce a narrow plume of liquid capable of passing the nasal valve to reach the upper and middle turbinates and the olfactory epithelium. Activation of the device results in a biphasic release of propellant, the first phase atomises the liquid, the second propels it into the target upper nasal region. The device has also the advantage that delivery is not breath-actuated and therefore the patient is not required to co-ordinate breathing with device activation or adopt a specific head position. It can be operated by the patient or a care-giver.

Proof of improved DHE bioavailability with the POD® device was obtained in an open-label, randomized, three-period, three-way crossover clinical trial (STOP 101) [5]. This study involving 38 healthy volunteers, compared the bioavailability of INP104 (development code for Trudhesa™) 1.45 mg with commercially available intravenous (IV) DHE 1.0 mg and DHE nasal spray (Migranal®) 2.0 mg. The results showed that INP104 achieved comparable plasma levels to the IV formulation after 20 minutes and had similar bioavailability based on area under the curve (AUC). However, its use had the advantage of avoiding the initial high C_{max} obtained with intravenous delivery with a lower incidence of adverse events (19.8% for INP104 versus 34.4% with the injectable product).

The pharmacokinetic comparison between INP104 and Migranal® illustrated the differences in delivery achieved using the two devices. The C_{max} obtained with the POD® device was four-fold that of the commercially available nasal product with the AUC being 3-fold greater. This was despite the reduction in dose by just over 25%. In addition, INP104 administration resulted in less variability in the C_{max} and AUC obtained. Overall, the reported side-effects were 19.8% for INP104 and 11.8% for Migranal®. Mild nasal discomfort occurred in one subject each with INP104 and the comparator DHE nasal spray. As would be anticipated, nasal drug leakage either from the nares or into the nasopharynx was less for INP104 than Migranal® at 32.3% and 76.5% respectively.

Data to support Trudhesa's filing was also obtained from the STOP 301 safety and tolerability study [1, 6]. Other trial goals were an exploratory assessment of efficacy against pre-defined measures and an evaluation of patients' acceptability of the product. In total 354 patients started treatment in the first six-month part of the study, of which 262 (74%) completed therapy. Reasons for discontinuation included withdrawal by subject (25 patients/7.1%), adverse effects (24 patients/6.8%) and lack of efficacy (21 patients/5.9%). A 73-patient cohort continued on the trial extension to give 52 weeks of data on the 66 participants who completed the study. In total greater than 5,650 migraine attacks were treated in the study, with 5099 doses being administered in the first 24 weeks. In general, Trudhesa™ was well tolerated with mainly mild side-effects which resolved quickly. Over the 52-week period the most commonly reported treatment-related adverse events were nasal congestion (17.8%), nausea (6.8%), nasal discomfort (6.8%), abnormal olfactory test (6.8%) and vomiting (2.7%). In addition, long-term treatment did not induce changes to the nasal mucosa as assessed by nasal endoscopy, and olfactory function was shown to be maintained.

With respect to the patient-reported efficacy assessment, 38% of patients reported they were pain-free after 2 hours of administration, 66% had pain-relief and 52% were free from their most bothersome migraine symptom. Of the 38% of those whose pain was completely resolved at 2 hours, 93% and 86% still were pain-free at 24 hours and two days respectively. Study participants also reported faster and more consistent onset of therapeutic effect compared with their previous best usual treatment. In addition, 84% found Trudhesa™ easy to use and preferred it to their current therapy.

Market entry for Trudhesa™ is anticipated in late September 2021 [4].

Paediatric Formulations for Children with Hepatitis C or Venous Thromboembolic Events

In June of this year, the FDA approved three oral pellet formulations of previously approved medicines designed to serve the paediatric market. These age-appropriate medicines, together with the clinical data generated, enable the on-label use of these life-saving medicines to treat younger age groups, and widen the options available to clinicians to treat paediatric patients suffering from either Hepatitis C infection or Venous Thromboembolic Events. The products are as follows:

Epclusa® Oral Pellets

Epclusa® contains sofosbuvir, a hepatitis C (HCV) virus nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor in a fixed dose combination [7-8]. Administration is once daily and the treatment duration is 12

weeks for both adults and children. Dosing for paediatric patients is based on weight with the dose rising from sofosbuvir 150 mg/velpatasvir 37.5 mg for those 3 years and over weighing less than 17 kg, to sofosbuvir 200 mg/velpatasvir 50 mg in children with a body weight between 17 kg and 30 kg. Children weighing 30 kg and above receive the adult dose of 400 mg sofosbuvir and 100 mg velpatasvir.

A tablet formulation of Epclusa® containing 400 mg sofosbuvir and 100 mg velpatasvir was approved in the US in 2016 for adults with HCV (genotype 1 to 6) with/without compensated cirrhosis, and for administration in conjunction with ribavirin therapy for HCV patients with decompensated cirrhosis. This was followed in 2020 by approval of a 200 mg/50mg tablet and the extension of Epclusa's use to children aged 6 years and above or those weighing at least 17 kg.

Clinical data using the recently approved oral pellet formulation has enabled a further lowering in the patient age range from 6 years to 3 years with no weight limit. The pellet formulation is available in two strengths: sofosbuvir 200 mg/velpatasvir 50 mg and sofosbuvir 150 mg/velpatasvir 37.5 mg. The lower strength covers the dose required for children 3 years of age and above, weighing less than 17 kg. The higher strength provides a child-orientated dosage form option for those weighing 17 kg and over in addition to the tablet formulations. The film-coated pellets can be taken with or without food. Mixing the pellets with non-acidic foods at room temperature or below e.g., with ice-cream, is advised for young children to improve palatability as vomiting and spitting out of the pellets was an issue in a clinical study of Epclusa® in children under 6 years. This Phase 2 open-label study, involving 41 HCV patients aged 3 to less than 6 years, showed that 12 weeks' treatment with Epclusa® resulted in a long-lasting virologic response (SVR12) or cure rate of 83% (34/41) among all patients. The remaining 7 patients discontinued treatment within 3 weeks of starting therapy.

Mavyret® Oral Pellets

Mavyret® was first approved in the USA in 2017 for adult patients infected with HCV genotype 1, 2, 3, 4, 5 or 6 without cirrhosis or with compensated cirrhosis [9]. It was also approved as a second-line treatment for those with HCV genotype 1 infection, who had first received therapy containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The product contains both glecaprevir, a HCV NS3/4A protease inhibitor, and pibrentasvir, a HCV NS5A inhibitor. The adult dose is three tablets once daily (3 x glecaprevir 100 mg/ pibrentasvir 40 mg) administered with food. In 2019 the adult dose and existing tablet formulation received FDA approval for administration to children of 12 years or older or those weighing 45 kg or more.

The newly approved pellet formulation and associated clinical data enable dosing to children in the age range 3 years to less than 12 years based on weight. Each child-resistant packet contains sufficient pellets for a 50 mg glecaprevir and 20 mg pibrentasvir dose. Children weighing less than 20 kg are administered 3 sachets of pellets (150 mg glecaprevir and 60 mg pibrentasvir) daily with the dose increasing step-wise with the weight of the child until this reaches 45 kg. Children of 12 years of age and above or weighing 45 kg or more can be administered pellets if they find the tablets difficult to swallow. Treatment duration for both adults and children is 8 weeks in treatment-naïve patients and 12 weeks in the case of liver or kidney transplant patients. Up to 16 weeks' treatment is recommended when Mavyret® is used as second-line therapy, with the exact length of therapy being dependent on the HCV genotype, the previous medication received and the presence or absence of compensated cirrhosis. The oral pellets are administered after the entire dose has been sprinkled on a small amount of viscous food with low water content e.g., chocolate spread.

Approval for use in children is based on the results of the two-part DORA open-label study in HCV-infected patients without cirrhosis. Part 1 evaluated the efficacy of the adult dose of Mavyret® in 47 children aged 12 to 17 years old, around 75% of whom were treatment-naïve. All participants achieved the primary endpoint of no detectable viral RNA at 12 weeks following treatment (SVR12). In Part II Mavyret® was assessed in 80 younger patients aged 3 to 11 years. Dosing was carried out on a weight basis for 8, 12 or 16 weeks in 62 of these patients, with 18 receiving a lower dose. Of the 62 patients included in the efficacy analysis, 61 were cured of the infection based on the SVR12. The remaining one patient discontinued treatment early as a result of an adverse reaction.

Pradaxa® Oral Pellets

Pradaxa®, containing the direct thrombin inhibitor, dabigatran etexilate as the mesylate salt, first gained US approval as a capsule formulation in 2010 [10]. The only indication at launch was to reduce the risk of stroke and systemic embolism in adults with non-valvular atrial fibrillation. However, since then it has been approved for several other indications e.g., the treatment and prevention of recurrence of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have undergone parenteral anticoagulant administration for 5-10 days.

In 2021 the FDA approved both Pradaxa® capsules and a new oral pellet formulation of dabigatran etexilate mesylate for use in paediatric medicine to treat and prevent recurrence of venous thromboembolic events (VTE) in patients administered parenteral anti-coagulants for at least 5 days. The capsule formulation is indicated for children of at least 8 years of age and the oral pellets are for children at least 3 months old to less than 12 years of age. Pradaxa® is administered twice daily and dosing in children of 2 years and above is based on weight and on weight and age for those in the 3-month to 2-year age range. The pellets are available in a variety of strengths (20 mg, 30 mg, 40 mg, 50

mg, 110 mg and 150 mg dabigatran etexilate) to enable exact dosing to the different age and weight ranges. They can be swallowed with apple juice or mixed with certain soft foods e.g., mashed banana and should not be taken with milk or milk products. It should be noted that the oral bioavailability of dabigatran etexilate is formulation dependent and age dependent. Therefore, the two formulations are not interchangeable on a mg for mg basis.

Clinical efficacy in paediatric patients was established in two clinical trials. The DIVERSITY study evaluated Pradaxa® against standard of care (SOC) (low molecular weight heparins or vitamin K antagonists or fondaparinux) for the treatment of VTE in children less than 18 years of age. The open-label, parallel group, non-inferiority study involved 267 patients randomized 2:1 to Pradaxa® or to SOC. 168 patients were in the 12 to less than 18 years age range, 64 patients were aged between 2 and 12 years and 35 were less than two years old.

Dabigatran etexilate mesylate was administered in an age-appropriate formulation (capsules, oral pellets, or oral solution) with the dose adjusted for age and weight. All patients had previously received a parenteral anti-coagulant for at least 5 days. After 6 doses, blood from those on Pradaxa® was analysed for drug concentration and a single dose adjustment allowed to achieve target levels of the active of 50 – 250 ng/ml. The median duration of the treatment period was 85 days.

Efficacy was based on a composite primary endpoint of patients with complete thrombus resolution, no recurrent venous thromboembolic event, and no mortality related to a venous thromboembolic event. The study showed that Pradaxa® was non-inferior to SOC with 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group meeting the composite endpoint criteria.

The second study (Study 2) was an open-label, single-arm safety study to assess Pradaxa® for the prevention of recurrent VTE in children from birth to less than 18 years. 214 patients were enrolled in Study 2 who required further anticoagulation as result of a clinical risk factor following initial VTE treatment for a minimum of 3 months or after completing the DIVERSITY trial. They received age- and weight-adjusted doses of Pradaxa® in either capsule or pellet form until either there was no further clinical risk or up to a maximum of 12 months. Primary study endpoints included recurrence of VTE, bleeding events, and mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. No deaths occurred in the treatment period and the overall probability of no recurrence of VTE during therapy was 0.990 (95% CI: 0.960, 0.997) at 3 months, 0.984 (95% CI: 0.950, 0.995) at 6 months, and 0.984 (95% CI: 0.950, 0.995) at 12 months. With respect to freedom from bleeding events, the probability was 0.849 (95% CI: 0.792, 0.891) at 3 months, 0.785 (95% CI: 0.718, 0.838) at 6 months, and 0.723 (95% CI: 0.645, 0.787) at 12 months.

References and Further Information

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6. Smith TR, Winner P, Aurora SK et al. STOP 301: A Phase 3, open-label study of safety, tolerability, and exploratory efficacy of INP104, Precision Olfactory Delivery (POD®) of dihydroergotamine mesylate, over 24/52 weeks in acute treatment of migraine attacks in adult patients. Headache (2021), 61(8):1214-1226.
7. U.S. Food and Drug Administration Approves New Formulation of Epclusa®, Expanding Pediatric Indication to Treat Children Ages 3 and Older With Chronic Hepatitis C. U.S. Food and Drug Administration Approves New Formulation of Epclusa®, Expanding Pediatric Indication to Treat Children Ages 3 and Older With Chronic Hepatitis C (gilead.com).
8. Entry for Epclusa on Drugs@FDA. Drugs@FDA: FDA-Approved Drugs.
9. Entry for Mavyret on Drugs@FDA Drugs@FDA: FDA-Approved Drugs.
10. Entry for Pradaxa on Drugs@FDA Drugs@FDA: FDA-Approved Drugs.

DRUG DELIVERY COMPANY

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Provided by Dr. Carsten Timpe, Dr. Florian Unger, Dr. Karsten Cremer

PRECISION NANOSYSTEMS (VANCOUVER, CANADA)

PNI is a global leader ushering in the next wave of genetic medicines in infectious diseases, cancer and rare diseases. We work with the world's leading drug developers to understand disease and create the therapeutics and vaccines

that will define the future of medicine. PNI offers proprietary technology platforms and comprehensive expertise to enable researchers to translate disease biology insights into non-viral genetic medicines.

Fact sheet:

Founded:	2010
Location:	Vancouver, Canada
Ownership:	Private
Employees:	150+
Key technology:	• NxGen™ Scalable Microfluidic Technology • GenVoy Delivery Platform The NxGen microfluidic mixer at the heart of the NanoAssemblr is uniquely capable of enabling all scales, from µL to 50 L scales, through a single mixing element while maintaining controllable and reproducible particle formation conditions that ensure reproducible results for a wide range of particle types. The GenVoy Delivery Platform comprises off-the-shelf Research-use only (RUO) reagents such as GenVoy-ILM™ that can prepare RNA lipid nanoparticles (LNP) for discovery and proof-of-concept studies, and a proprietary LNP Library designed to take your genetic medicine to the clinic.
Products:	• NanoAssemblr® Suite (Spark™, Ignite™, Blaze™, GMP System) — A manufacturing platform using NxGen microfluidic technology to generate nanoparticles from preclinical to commercial manufacturing scales. • GenVoy-ILM — An RUO ionizable lipid mix that enables the rapid and easy production of RNA-LNP for gene delivery using the NanoAssemblr Platform. • GenVoy-ILM T Cell Kit for mRNA — An RUO LNP reagent mix optimized for the delivery of mRNA into activated primary human T cells using LNP formulated on the Spark. • Clinical Lipid Library — Proprietary lipids and nanoparticle formulations available for clinical use with seamless translation from GenVoy-ILM reagent kits for mRNA-based vaccines, gene therapies and cell therapies. • Contract Services — Custom genetic medicine formulation and manufacturing process development solutions leveraging PNI's research facilities, technical team and platforms. Projects range from aid with lipid nanoparticle formulation development, screening, and validation to assistance with downstream processing, tech transfer and CMC needs.
Development status:	Currently supporting customers from preclinical to commercial manufacturing stages
Partnerships:	Many industrial partners including Daiichi-Sankyo and Fujifilm
Website:	https://www.precisionnanosystems.com/
Contact:	Martin Rabel Field Application Scientist, Precision NanoSystems mrabel@precision-nano.com Precision NanoSystems 655 W Kent Ave N #50 Vancouver, BC V6P 6T7 Canada Tel: **+1 888-618-0031** Email: info@precision-nano.com

ORAL PEPTIDES - PRODUCTS, PIPELINE & TECHNOLOGIES - A SHORT REPORT

[1]PharmaCircle LLC, Sunny Isles Beach, Florida, USA., T: +1.800.439.5130, E: info@pharmacircle.com, www.pharmacircle.com

1. Introduction

This featured article provides an overview of oral peptide products, both approved and in development, and the technologies underpinning them. The data are sourced from proprietary databases from PharmaCircle, an information provider to the pharmaceutical industry, providing business prospecting and analysis tools, pipeline and products intelligence, regulatory data, and other information solutions to clients.

2. Overview

The oral delivery of peptides and small proteins, let's arbitrarily cap at 5,000 Daltons or less, has been a target of Drug Delivery for at least a couple of decades promising the substitution of an oral tablet for injections. The potential patient benefits include patient convenience and ultimately greater compliance. For the pharmaceutical industry high performance oral delivery of peptides and smaller proteins would open up new therapeutic indications and 'rehabilitate' generic products and markets.

Until the recent approval of Novo Nordisk's Rybelsus oral peptide (semaglutide, 4.1 kDa), peptide and small protein delivery have been limited to products for non-systemic indications, typically antibiotics, and systemic therapies with peptides smaller than 1,500 Da. The Eligen technology underlying Rybelsus, while effective, is still not ideal with a delivery efficiency of less than 1% for semaglutide. Earlier attempts to apply Eligen, possibly an earlier generation of the technology, to insulin (~5.8 kDA), heprin (~15 kDa), LMWH (~4.5kDa), teriparatide (4.2 kDa), and hGH (~22 kDa) did not support further development or approval.

The recently announced acquisition of Emisphere suggests that Novo Nordisk has plans to further improve the Eligen technology for the delivery of a next generation oral semaglutide, other peptide therapeutics, or even an oral insulin.

3. Search Summary

Tables 1-3 in this report summarize respectively the currently approved orally administered peptides and small proteins, the later stage (≧Phase 2) clinical pipeline, and selected leading drug delivery technologies that claim the potential to orally deliver peptides.

Among the approved oral peptides shown in Table 1, linaclotide and vancomycin are not intended for systemic uptake. Three approved peptides, octreotide, desmopressin, and cyclosporin are sufficiently well absorbed to provide for systemic action. All are relatively small, <1,300 kD, and with the exception of cyclosporin have minimal oral bioavailability. Cyclosporin, with a molecular weight of 1,202 Da, is very much an outlier with a bioavailability of 30%. Both octreotide and desmopressin with similar molecular weights have an oral bioavailability of less than 1%.

The Phase 3 pipeline, shown in Table 2, is mostly composed of smaller peptides, ≦1,000 Da. The Phase 2 pipeline consists of products indicated for both non-systemic indications, ulcerative colitis and irritable bowel, and systemic indications with peptides in the upper 1,000 Da range. A more ambitious product, Oshadi's Oshadi Icp, is taking a run at diabetes with an oral insulin formulation.

Table 3 lists 32 selected oral peptide delivery technologies. This is just a fraction of the 311 recorded on PharmaCircle's Drug Delivery Analyzer module, of which 208 are considered by the company's analysts to be active.

4. Reflections

Novo Nordisk's decision to acquire Emisphere appears to be a sound technology investment. There seems to be little in the product development and technology development pipeline to directly challenge Rybelsus and Eligen. When a company finds itself in a leadership position, it is always wise to invest in reinforcing that position.

Table 1: Approved & Marketed Oral Peptides

Product	Active	Company	Associated Technology	Molecular Weight (Da)	Oral Bioavailability
Mycapssa	Octreotide	Chiasma	TPE Technology	1,019	**B**0.5%
DDAVP	Desmopressin	Ferring	None	1,069	~0.12%
Neoral	Cyclosporin	Novartis	Oral Lipid & SEDDS	1,202	30%
Vancocin	Vancomycin	ANI	None	1,449	~0%
Linzess	Linaclotide	Ironwood	Colonic Release	1,527	~0%
Rybelsus	Semaglutide	Novo Nordisk	Eligen	4,114	0.4-1%

Source: PharmaCircle Pipeline & Products Intelligence Module (2020-11-26)

Table 2: Late Stage Pipeline Oral Peptides

Product /Phase	Active	Company	Indication	Molecular Weight (Da)	Oral Bioavailability
Phase 3					
Trofinetide	Trofinetide	Neuren	Rett Syndrome	315	Unknown
Korsuva	Difelikefalin	Cara	Pruritus	739	10-16%
Larazotide	Larazotide	9 Meters	Celiac Disease	786	Unknown
PRL001	Cyclosporin. Omeprazole	Perle	Diabetes, Type 1	1,202, 345	30% (Cyclosporin)
Phase 2					
Apo805K1	Orilotimod	ApoPharma	Psoriasis	371	Unknown
LH-025	KdPT	Dr. August Wolff	Ulcerative Colitis	386	Unknown
Ovarest	Leuprolide	Enteris	Endometriosis	1,209	Unknown
Linaclotide CR	Linaclotide	Ironwood	Irritable Bowel	1,527	Unknown
SP-333	Dolcanatide	Bausch	Opioid Constipation	1,682	Unknown
LAT8881	LAT8881	Lateral	Migraine	1,815	Unknown
EB612 & 613	Teriparatide	Entera	Osteoporosis	4,117	Unknown
Oshadi Icp	Insulin (Others)	Oshadi	Diabetes, Type 1	5,778	Unknown
gpASIT+	gpSIT	ASIT Biotech	Allergic Rhinitis	Unknown	Unknown
BBT-401	BBT-401	Bridge Biotherapeutics	Ulcerative Colitis	Unknown	Unknown
PN-943	PN-943	Protagonist	Crohn’s Disease	Unknown	Unknown
PGT-200	PGT-200	Protagonist	Crohn’s Disease	Unknown	Unknown
OptiquelT	T B27PD	Enzo	Uveitis	Unknown	Unknown

Source: PharmaCircle Pipeline & Products Intelligence Module (2020-11-26)

Table 3: Selected Oral Peptide Delivery Technologies

Technology	Company	Suggested Applications
Transint	Applied Molecular Transport	Proteins, peptides, oligonucleotides
Biocon Prodrug	Biocon	Peptides, proteins, small molecules
NanoArmored Protein Engineering	BioHybrid Solutions	Proteins, antibodies
CSSR	BioLingus	Proteins, peptides, cytokines, nucleotides, domain antibodies, immunotherapies, enzymes, probiotics, vaccines
GI-MAPS	BioSerenTach	Peptides, proteins, small molecules
ArisCrown	Capsugel	Peptide, protein, antibody, small molecule, siRNA
TPE	Chiasma, Inc.	Peptides, proteins, small molecules
HDV	Diasome Pharmaceuticals	Large proteins such as insulin and interferon, peptides, small molecules, diagnostic imaging agents, nutraceuticals
Eligen	Emisphere Technologies	peptides, proteins, carbohydrates, small molecules, oligosaccharides, oligonucleotides
Peptelligence	Enteris BioPharma, Inc.	Peptides, proteins, small molecules
Entrega Oral Hydrogel	Entrega, Inc.	Peptides, proteins, small molecules
Accordion GR Pill	Intec Pharma	Absorption challenged drugs
Soteria	Intract Pharma	Peptide, protein, antibody, oligonucleotide
Ionis Oral Macromolecule Delivery	Ionis Pharmaceuticals	Peptides, proteins, small molecules, oligonucleotides
MIT Foldable Oral Microneedle Delivery	Massachusetts Institute of Technology	Macromolecules
MIT Self-Orienting Millimeter-Scale Actuator	Massachusetts Institute of Technology	Peptides, proteins, vaccines, nucleic acids
LNC Technology	Matinas BioPharma	Peptides, proteins, oligonucleotides, small molecules
NanoMega	NanoMega Medical	Peptides, proteins
Molecular Envelope	Nanomerics	Peptides, proteins, small molecules
POD Technology	Oramed Pharmaceuticals	Peptides, proteins
Progenity Ingestible Electronic Capsule	Progenity	Biologicals, small molecules
Axcess	Proxima Concepts	Small molecules, peptides, proteins, oligonucleotides
Calix	PureTech Health	Peptides, proteins, oligonucleotides, small molecules
Extreme Diversity	Ra Pharmaceuticals	Synthetic macrocyclic polypeptides
RaniPill	Rani Therapeutics	Peptides, proteins, antibodies, RNAi therapies and select vaccine
NOD	Shanghai Anbo Biomedical	Small molecules, peptides, proteins, oligonucleotides, carbohydrate
Thiomers	ThioMatrix	Peptides, proteins, small molecules

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 Christoph Rademacher as our featured Drug Delivery Scientist. Christoph studied Molecular Biotechnology at the University of Lübeck, Germany, followed by a PhD in Biophysical Chemistry at the same institution, where his research focussed on glycobiology. He spent two years at the Scripps Research Institute in La Jolla, USA as a postdoctoral research associate followed by the award of an Emmy Noether Fellowship and position as Group Leader at the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany. Since September 2020 he has joined the Department of Pharmaceutical Sciences at the University of Vienna, Austria, as a Professor of Molecular Drug Targeting, where his research interests focus on the interface between fundamental glycobiology research and targeted drug delivery.

In 2021 Prof. Rademacher founded Cutanos, a dermal drug delivery company based in Vienna which is developing targeted delivery systems for vaccine and immunotherapies for auto-immune diseases. The proprietary targeting strategy is based on synthetic small molecules with a high specificity and ideal affinity to the Langerin receptor on the surface of Langerhans cells located within the epidermis. Microinjection technologies will be used to provide a minimally invasive administration route for the dermal application of immunotherapeutics.

DRUG DELIVERY LITERATURE

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Provided by Dr. Carsten Timpe

RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

Transdermal Delivery

Current trends in polymer microneedle for transdermal drug delivery

Ahmed Saeed Al-Japairai K, Mahmood S, Hamed Almurisi S, Reddy Venugopal J, Rebhi Hilles A, Azmana M, Raman S., Int J Pharm. 2020 Sep 25;587:119673.

The review summarizes the importance of polymeric microneedles and discusses some of the most important therapeutic drugs being studied in microneedle research, mainly protein drugs, vaccines and small molecule drugs in regenerative medicine.

Recent progress of 3D-printed microneedles for transdermal drug delivery

Yang Q, Zhong W, Xu L, Li H, Yan Q, She Y, Yang G. Int J Pharm. 2021 Jan 25;593:120106.

This review aims to summarize the numerous recently reported studies utilizing a 3D-printing process to fabricate transdermal drug delivery systems, not only adopting versatile printing methodologies, but also employing different formulation strategies, to fabricate both artificial cargo delivery systems and sophisticated bio-inspired microneedles. In addition, the article attempts to elaborate their advantages and limitations, discussing promising potential applications as novel drug delivery systems.

Thermoresponsive gating membranes embedded with liquid crystal(s) for pulsatile transdermal drug delivery: An overview and perspectives

Lin SY, J Control Release. 2020 Mar10;319:450-474.

This review article focuses on thermoresponsive gating membranes embedded with liquid crystals (LCs) for transdermal drug delivery using pulsatile drug delivery system (PDDS) technology. In addition, the article reviews and discusses the principal rationale and the advanced approaches for the use of PDDSs, the marketed products of chronotherapeutic DDSs with pulsatile function designed by various PDDS technologies, pulsatile drug delivery designed with thermoresponsive polymers, challenges and opportunities of transdermal drug delivery, and novel approaches of LC systems for drug delivery.

Intrathecal/Intracranial /Intervertebral Delivery

Drug delivery in intervertebral disc degeneration (IVDD) and osteoarthritis (OA): Selecting the optimal platform for the delivery of disease-modifying agents

Colella F, Garcia JP, Sorbona M, Lolli A, Antunes B, D'Atri D, Barré FPY, Oieni J, Vainieri ML, Zerrillo L, Capar S, Häckel S, Cai Y, Creemers LB, J Control Release. 2020 Dec 10;328:985-999.

This review provides a comprehensive overview of the currently most promising disease-modifying drugs as well as potential drug delivery systems for OA and IVDD therapy.

New modalities (siRNAs, LNAs, Oligonucleotides, Gene Delivery etc.)

In vivo gene delivery mediated by non-viral vectors for cancer therapy

Mohammadinejad R, Dehshahri A, Sagar Madamsetty V, Zahmatkeshan M, Tavakol S, Makvandi P, Khorsandi D, Pardakhty A, Ashrafizadeh M, Ghasemipour Afshar E, Zarrabi A. J Control Release. 2020 Sep 10;325:249-275.

In this review, the recent discoveries on non-viral gene delivery systems are discussed. The in vivo gene delivery mediated by non-viral vectors to treat cancer in different tissue and organs including brain, breast, lung, liver, stomach, and prostate is also highlighted. Finally, the state-of-the-art and promising perspective of in vivo gene editing using non-viral nano-vectors is delineated.

Nucleic acid-based drug delivery strategies

Tan X, Jia F, Wang P, Zhang K. Nucleic acid-based drug delivery strategies. J Control Release. 2020 Jul 10;323:240-252.

In this review, recent progress in nucleic acid-based drug delivery strategies is discussed, including their potential, unique use cases, and risks that must be overcome or avoided.

Nanosystem-based Drug Delivery

Development of High-Drug-Loading Nanoparticles.

Liu Y, Yang G, Jin S, Xu L, Zhao CX. Development of High-Drug-Loading Nanoparticles. Chempluschem. 2020 Sep;85(9):2143-2157.

This minireview presents an overview of recent research on developing nanoparticles with high drug loading (>10 wt%) from the perspective of synthesis strategies, including post-loading, co-loading, and pre-loading.

Drug delivery systems based on nanoparticles and related nanostructures

Nikezić AVV, Bondžić AM, Vasić VM. Drug delivery systems based on nanoparticles and related nanostructures. Eur J Pharm Sci. 2020 Aug 1;151:105412.

This review emphasizes recent advances in the usage of various types of nanoparticles and similar nanostructures for drug delivery, aiming to provide a critical review of less toxic and more effective treatment.

Ocular Drug Delivery

Advances and limitations of drug delivery systems formulated as eye drops

Jumelle C, Gholizadeh S, Annabi N, Dana R., J Control Release. 2020 May 10;321:1-22.

This review article focuses on the recent advances in the development of ocular drug delivery systems. In addition, the potential challenges for commercialization of new DDS are presented.

Advances in ocular drug delivery systems

Kang-Mieler JJ, Rudeen KM, Liu W, Mieler WF. Advances in ocular drug delivery systems. Eye (Lond). 2020 Aug;34(8):1371-1379.

This review highlights the advantages and limitations of selected drug delivery systems of novel biomaterial implants and depots. The main emphasis is on less invasive, longer acting, sustained release formulations for the treatment of retinal disorders.

Intravitreal hydrogels for sustained release of therapeutic proteins

Ilochonwu BC, Urtti A, Hennink WE, Vermonden T. J Control Release. 2020 Oct 10;326:419-441.

This review highlights how hydrogel formulations can improve intravitreal protein delivery to the posterior segment of the eye in order to increase therapeutic outcome and patient compliance.

Pulmonary Drug Delivery

Inhaled nanoparticles-An updated review

Praphawatvet T, Peters JI, Williams RO 3rd. Inhaled nanoparticles-An updated review. Int J Pharm. 2020 Sep 25;587:119671.

This article presents an updated review of delivery systems, process technologies, and the potential of inhaled nanoparticles for local and systemic therapies administered to the lungs.

Parenteral Drug Delivery

Cyclodextrins (CD) in Parenteral Formulations

Loftsson T. Cyclodextrins in Parenteral Formulations. J Pharm Sci. 2021. Feb;110(2):654-664.

This review focuses on the physiochemical and biological properties of CDs as well as their pharmacokinetics after intravenous administration. Their regulatory status is briefly reviewed and their tendency to self-assemble to form clusters or aggregates

discussed. Finally, some examples are given of how CDs are applied in aqueous parenteral formulations, how their solubilizing effect has been enhanced and how their target concentration is determined.

Oral Drug Delivery

Recent advances in colon drug delivery systems

Arévalo-Pérez R, Maderuelo C, Lanao JM. Recent advances in colon drug delivery systems. J Control Release. 2020 Nov 10;327:703-724.

This review aims to bring together knowledge regarding the materials and processes used in the development of pharmaceutical formulations capable of reaching the colon, as well as to highlight recent advances in the field.

Bile acid transporter-mediated oral drug delivery

Deng F, Bae YH. Bile acid transporter-mediated oral drug delivery. J Control Release. 2020 Nov 10;327:100-116.

This review introduces the key factors in enterohepatic recycling, especially the mechanism of bile acid uptake by the apical sodium-dependent bile acid transporter (ASBT), and the development of bile acid-based oral drug delivery for ASBT-targeting, including bile acid-based prodrugs, bile acid/drug electrostatic complexation and bile acid-containing nanocarriers. Furthermore, the specific transport pathways of bile acid in enterocytes are described and the recent finding of lymphatic delivery of bile acid-containing nanocarriers is discussed.

Orally administered self-emulsifying drug delivery system in disease management: advancement and patents

Mishra V, Nayak P, Yadav N, Singh M, Tambuwala MM, Aljabali AAA., Expert Opin Drug Deliv. 2021 Mar;18(3):315-332.

This review provides updated information regarding the types of SEDDS, their preparation techniques, drug delivery and related recent patents along with marketed formulations.

Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist

Bucheit JD, Pamulapati LG, Carter N, Malloy K, Dixon DL, Sisson EM Diabetes Technol Ther. 2020 Jan;22(1):10-18.

The article describes a new coformulation of semaglutide with sodium N-[8-(2-hydroxybenzoyl) amino caprylate (SNAC) which is the first oral GLP-1 RA reviewed by the U.S. Food and Drug Administration (FDA). The SNAC technology prevents destruction of semaglutide in the stomach and facilitates transcellular absorption through the gastric membrane enabling semaglutide to reach the systemic circulation intact.

Brain Delivery

Recent strategies and advances in the fabrication of nano lipid carriers (NLC) and their application towards brain targeting

Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Patel RJ, Ajazuddin, Ravichandiran V, Murty US, Alexander A., J Control Release. 2020 May 10;321:372-415.

This review highlights recent progress towards the development of NLC for brain targeting of bioactives with particular reference to surface modifications, formulation aspects, pharmacokinetic behavior and efficacy with respect to the treatment of various neurological disorders like Alzheimer's Disease, Parkinson's Disease, schizophrenia, epilepsy, brain cancer, CNS infection (viral and fungal), multiple sclerosis, cerebral ischemia, and cerebral malaria.

Carbon nanostructures: The drug and the delivery system for brain disorders

Henna TK, Raphey VR, Sankar R, Ameena Shirin VK, Gangadharappa HV, Pramod K. Int. J Pharm. 2020 Sep 25;587:119701.

This review focuses on different carbon nanostructures for brain-targeted drug delivery and their CNS activities. As a carrier and CNS therapeutic agent, carbon nanostructures can revolutionize the treatment of brain disorders.

Other Administration Routes (e.g. Vaginal, Rectal)

Design, fabrication and characterisation of drug-loaded vaginal films: State-of-the-art

Notario-Pérez F, Cazorla-Luna R, Martín-Illana A, Galante J, Ruiz-Caro R, das Neves J, Veiga MD., J Control Release. 2020 Nov 10;327:477-499.

The aim of this review was to highlight the most recent research directions and indicate challenges related to vaginal drug administration. Intravaginal products still gain enormous scientific attention, and novel polymers and formulations continue to be explored. However, there are research areas that require more extensive studies in order to prove the safety of novel vaginal products.

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 de-livered 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 bi-ological 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.

MEMBERS OF THE APV DRUG DELVIERY FOCUS GROUP:

Georg Böck, PhD
Focus Group Chairman Boehringer Ingelheim Pharma, Biberach (D)

Johannes Bartholomäus, PhD
APV Liaison Officer
Pharmakreativ Consulting, Aachen (D)

Martin Bornhöft, PhD
APV Office, Mainz (D)

Rainer Alex, PhD
F. Hoffmann-La Roche, Basel (CH)

Carsten Timpe, PhD
F. Hoffmann-La Roche, Basel (CH)

Louise Rosenmayr-Templeton, PhD
Tower Pharma Consulting, Berndorf (A)

Bernd Riebesehl, PhD
Novartis Pharma, Basel (CH)

Lea Ann Dailey, PhD
University of Vienna (A)

Andrea Engel, PhD
Evonik Corporation, (US)

Simon Geißler, PhD
Merck Serono, Darmstadt, (D)

Karsten Cremer, PhD
Pharma Patents, Basel (CH)

Florian Unger, PhD
Bayer, Wuppertal (D)

Peter van Hoogevest, PhD
PHARMANOVATION Consulting (D)

Simone Wengner, PhD
Catalent, Eberbach (D)

Uwe Hanenberg, PhD
Catalent, Schorndorf (D)

EDITORIAL GROUP OF THE NEWSLETTER

Editor: Dr. Louise Rosenmayr-Templeton, Tower Pharma Consulting, Berndorf (A)
Layout: Anna-Maria Pötzl, APV e.V., Mainz (D)

contact us: drug_delivery@apv-mainz.de