

APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY NEWSLETTER ISSUE 3/2021 - December

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Fyarro™ (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

On 22 Nov the FDA approved Fyarro[™] (sirolimus protein-bound particles for injectable suspension) from AADI Bioscience Inc. (CA, USA) [1, 2]. Fyarro[™] is a lyophilised nanoparticulate formulation of the mTOR inhibitor, sirolimus, in which the active is bound to albumin. mTOR is a serine threonine kinase whose regulation is often found to be defective in a number of types of cancer. Fyarro[™] is the first medicine for the specific treatment of locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumour (PEComa). This very rare and aggressive form of sarcoma is thought to occur in 100 to 300 US patients annually. Little is known about this malignancy. However, it is thought to be associated with mutations in the TSC1 and/or TSC2 genes which result in the activation of the mTOR pathway. It affects women predominately and has a poor prognosis (average survival time of 12 -16 months following diagnosis of advanced disease) with existing chemotherapy being in the main ineffective. Fyarro[™] is formulated using the nab technology which is also used in Abraxane® (paclitaxol albumin bound nanoparticles). Use of this technology has been shown to promote the accumulation of sirolimus within solid tumours and result in greater tumour suppression and improved survival times over free drug [3]. This improvement is thought to be promoted by albumin which has been previously shown to accumulate in tumour tissue by passive and/or active mechanisms. In addition, albumin has been shown to be taken up by cancer cells for use as a food source by the dividing cells following its breakdown in lysosomes [3].

Fyarro[™] is marketed in vials containing 100 mg sirolimus, approximately 850 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). It is reconstituted with 20 mL 0.9%w/v sodium chloride prior to intravenous infusion over 30 min on Day 1 and Day 8 of every 21-day cycle, with treatment ceasing following disease progression or as a result of toxicity. Dosing is on a surface area basis with the recommended dose being 100 mg/m2. This dose can be reduced three times based on tolerability or modified in the case of patients with mild to moderate liver disease or in those on medication with weak to moderate cytochrome P-450 3A4 (CYP3A4) inhibitor activity. Co-administration of strong CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors and inducers is not advised.

Approval was based on the results from a multicenter, single-arm study involving 31 patients, 5 of whom had locally advanced unresectable PEComa and 26 were suffering from metastatic disease. Almost all had previously undergone surgery, while 6 had received radiation therapy and 4 patients had been treated with chemotherapy. Success was determined based on overall response rate (ORR) and duration of response (DOR) which was evaluated by blinded independent central review. The study results showed an ORR of 39% (12 patients) based on partial response with two patients deemed to have a Complete Response during follow-up. At the time of approval, the median follow-up period was 36 months (5.6 months to 55 months). Of the 12 patients who had responded to treatment, 11 had done so for at least 6 months, 8 had a DOR of one year or more, while 7 achieved a response lasting 2 years or more. Adverse events most often reported (≥55.5%) were stomatitis, fatigue, rash, infection, nausea, oedema, diarrhoea, musculoskeletal pain, weight loss, loss of appetite, cough, vomiting, and taste disturbances. The medicine is also associated with certain abnormalities in laboratory values.

US Product launch is planned in Q1 2022 with the wholesale acquisition price likely to be around US\$39,000 a month, or US\$468,000 a year [4]. The company is also investigating Fyarro's potential in other cancers associated with TSC1 or TSC2 mutations with a pivotal trial planned for late 2021/early 2022 [3].

Lonapegsomatropin

Lonapegsomatropin Injection from Ascendis Pharma (Hellerup, Denmark) received a positive recommendation for EU approval at the EMA's Committee for Medicinal Products for Human Use's November meeting [5, 6]. Lonapegsomatropin is indicated for the once weekly treatment of growth hormone deficiency in adolescents and children of 3 years and up to 18 years via subcutaneous injection. The recommended dose is 0.24 mg/kg expressed as a somatotropin equivalent. The product, which is already marketed in the USA under the tradename, Skytrofa® [7], consists of lyophilised powder for reconstitution and water for injection in a dual-chamber cartridge for injection using a product-specific autoinjector. The autoinjector enacts automatic reconstitution of the lyophilized drug product. This is followed by a manual mixing step which is controlled by the device. Lonapegsomatropin is available in a variety of dosage strengths (3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg and 13.3 mg).

The product is based on Ascendis' TransCon[™] prodrug technology by which a parent compound is bound through a proprietary linker to an inert carrier molecule, thus, inactivating it and protecting it from clearance [8]. The design of the linker is tailored based on the chemistry of the parent molecule and the desired release profile. Following administration, the transient conjugate releases the active parent molecule at a predetermined rate based on pH and temperature. As its name suggests Lonapegsomatropin is bound through a TransCon[™] linker to methoxypolyethylene glycol (4 x 10 kD). This conjugate is broken down under physiological conditions to release native somatotropin (minimum potency of NLT 2.5 IU/mg). Other excipients present are succinic acid, trehalose dihydrate and tromethamine for pH adjustment [7].

The application of this transient pro-drug approach improves the product's pharmacokinetic profile compared with the parent compound enabling reduced frequency of injections. In the case of Lonapegsomatropin this results in a weekly subcutaneous injection compared to the daily administration required by the current standard of care with somatropin.

The recommendation for EU approval was based on results from the Phase 3 heiGHt, fliGHt and enliGHten clinical studies [5]. The heiGHt trial was a non-inferiority study versus daily Genotropin® in treatment-naïve patients, the fliGHt study was designed to provide data to support switching from daily somatropin to Lonapegsomatropin and the enlighten trial, is a long-term safety study which at the time of writing this article is still ongoing [9, 10].

The heiGHt trial was an international multi-site randomized, open-label, active-controlled study over 52 weeks involving 161 treatment-naïve, paediatric patients suffering from growth hormone deficiency [9]. Randomisation was 2:1 Lonapegsomatropin 0.24 mg/kg/week versus the equivalent dose of daily somatropin (0.034 mg hGH/kg/day). The primary endpoint of the non-inferiority trial was annualized height velocity (AVS) at 52 weeks, while the secondary endpoints included change from baseline in height SD scores (SDS). At 52 weeks the Lonapegsomatropin cohort achieved a least squares mean AVS of 11.2 cm/year with a standard error (SE) of 0.2 cm/year. This compared with 10.3 (0.3 SE) cm/year for daily somatropin (P = 0.009). The trial results therefore showed that Lonapegsomatropin was both non-inferior and superior to daily administration of somatropin itself. In the same time period SDS improved in the lonapegsomatropin group from baseline by 1.10 (0.04) versus 0.96 (0.05) for daily somatropin (P = 0.01). Other factors including adverse effects were similar between the two groups.

References and Further Information

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DRUG DELIVERY COMPANY

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

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CUTANOS (VIENNA, AUSTRIA)

Fact sheet:

Founded:	Early 2021		
Location:	Vienna, Austria (EU)		
Ownership:	Founded in early 2021 by Prof. Dr. Christoph Rademacher, a biotechnologist and Dr. Robert Wawrzinek, an organic chemist in biomedicine, as a spin-off of the Max Planck Institute of Colloids and Interfaces.		
Employees:	2 - 10		
Key technology:	LC-TDS (Langerhans Cell Targeted Delivery System): The technology is based on a modular antigen/drug delivery platform to "Langerhans cells", a subset of dendritic cells in the skin (epidermis). It utilizes an artificially produced ligand that specifically binds to the surface receptor Langerin. The antigen/drug (mRNA, small molecules, peptides, proteins) can be delivered to Langerhans cells using carriers like lipid nanoparticles, liposomes, proteins or microparticles. Benefit of this novel approach would be an immune cell-specific and minimally-invasive vaccination and/or immunotherapy approach via the skin to treat infectious diseases, cancer or autoimmune diseases.		
Products:	Minimally-invasive immunmodulating products for intradermal administration based upon specific immune cell targeting.		
Development status:	Early start-up with long-term experiences from Max Planck institute of Colloids and Interfaces.		
Partnerships:	Max Planck Innovation (as the technology transfer organization of MPG). Investors are KHAN TECHNOLOGY Transfer Fund I (KHAN-I), High-Tech Gründerfonds III, IST cube and a private investor. Cutanos also secured a AWS Seedfinancing (funded by the federal Austrian bodies BMDW and BMK).		
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ORAL DELIVERY OF OLIGONUCLEOTIDES: CAN THE IMPOSSIBLE BECOME POSSIBLE?

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1. Development of nucleic acid therapeutics

Oligonucleotides are short single or double stranded synthetic deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) that have gained significant interest as therapeutics due to their potential for one time only treatment or management of a wide range of diseases including orphan genetic alterations, cancer and diabetes. The understanding of biological mechanisms has led to the first targeted therapies, such as hormone-based treatments or monoclonal antibodies, but the identification of the genetic alterations responsible for diseases has opened a new era by the development of oligonucleotides (1). The sequence of oligonucleotides is complementary to that of their target. It adjusts to the genetic, molecular, and phenotypic characterizations of the disease and patient, a property that provides high selectivity. Therefore, the disease shapes the oligonucleotide sequence making the concept of personalized medicine approachable and possible.

Half a century ago, antisense oligonucleotides (ASOs) (synthetic single stranded DNA of ~18-30 nucleotides) successfully inhibited viral replication (cytomegalovirus-CMV) in vitro which led to the FDA approval of the first drug product (Vitravene) in 1998 for the treatment of CMV-retinitis. Second generation ASOs were developed with improved chemical and enzymatic stability, limited unintended off-target activity as well as increased affinity to the gene target (2). These efforts led to the market launch of the first DNA aptamer (Macugen) in 2004, siRNA (Onpattro) in 2018 and the GalNAc-siRNA conjugate (Gilvaari) in 2019. Comparing the size of the different modalities to ASOs, siRNA has 21-30 nucleotides while aptamers are much larger with 56-120 nucleotides (34- 72 kDa) (3, 4). To date, all approved oligonucleotide therapeutics (Table 1) are administered via injection locally to either the eye and spinal cord (Macugen, Spiranza) or parenterally aiming at liver targeting (Defitelio, Givlaari) (4-6).

2. Why Oral delivery of Oligonucleotides?

The most recent advances in the oral delivery of peptides have offered an optimistic perspective for the potential of orally administered oligonucleotides to reach the systemic circulation. The market introduction of the peptide formulations, Rybelsus (semaglutide, Novo Nordisk, for type 2 diabetes (FDA approved, 2019) and MyCapssa (octreotide, Chiasma) for acromegaly (FDA approved, 2020), demonstrated that oral delivery of macromolecules is a tangible therapeutic goal. Both formulations achieved comparable efficacy to that of subcutaneous and intravenous dosing, respectively (7, 8). On the same note, AstraZeneca in collaboration with Ionis Pharmaceuticals recently published the promising in vivo activity of an orally administered GalNAc ASO in rat, dog and cynomolgus monkeys (9).

Oral delivery of oligonucleotides can be considered an attractive option when therapeutic equivalence to the injectable counterpart (10) is demonstrated and if commercially viable. The high potency of these new modalities may balance the possible limited bioavailability when administered orally. This option favours patient centricity with better compliance with the therapeutic scheme due to better convenience because the pain, discomfort and side effects associated with injection are eliminated which is even more relevant for chronic treatments. Additionally, lower production costs in comparison to sterile injectables, reduced healthcare expenditures by elimination of the need for trained professionals and specialized equipment further strengthen the pursuit of oral delivery alternatives.

Product Name (Company)	Туре	Authority approval	Date of approval	Indication	Administration route/target organ
Vitravene (Ionis Pharma/ Novartis)	ASO	FDA	1998	Cytomegalovirus (CMV)	IVI/ Eye
Macugen (NeXstar Pharmaceuticals /Eyetech Pharmaceuticals)	Aptamer	FDA	2004	Age-related macular degeneration (AMD)	IVI/ Eye
Kynamro (Ionis Pharmaceuticals/ Genzyme/ Kastle Therapeutics)	ASO	FDA	2013	ApoB - Homozygous familial hypercholesterolemia (HoFH)	SQ/ Liver

Table 1: Oligonucleotide products approved by FDA and/or EMA (4-6, 11, 12)

Product Name (Company)	Туре	Authority approval	Date of approval	Indication	Administration route/target organ
Defitelio (Jazz Pharmaceuticals)	Mixture of PO ssDNA and dsDNA	EMA	2013	Hepatic Veno- occlusive disease (hVOD)	IV/ Liver
Exondys 51 (Sarepta Therapeutics)	SSO (Splice Switching Oligonucleotide)	FDA	2016	Duchenne muscular dystrophy (DMD)	IV/ Skeletal muscle
Spiranza (Ionis Pharmaceuticals/ Biogen)	SSO	FDA	2016	Spinal muscular atrophy (SMA)	IT/ Spinal cord
Onpattro (Anylam Pharmaceutics)	siRNA	FDA	FDA 2018 Heredia fDA 2018 media (hTTR) amy polyneuro		IV/ Liver
Tegsedi (Ionis Pharma/ Akcea Therapeutics)	ASO	FDA	2018	hTTR	SQ/ Liver
Waylivra (Ionis Pharma, Akcea Therapeutics)	ASO	EMA	2019	Familial chylomicronaemia syndrome (FCS)	SQ/ Liver
Givlaari (Anylam Pharmaceutics)	GalNAc-siRNA	EMA	2019	Acute Hepatic Porphyria (AHP)	SQ/ Liver
Vyondys 53 (Sarepta Therapeutics)	SSO	FDA	2019	DMD	IV/ Skeletal muscle
Oxlumo (Anylam Pharmaceutics)	GalNAc-siRNA	FDA & EMA	Primary 2020 hyperoxaluria type 1 (PH1)		SQ/ Liver
Leqvio (Novartis/ Anylam Pharmaceutics)	GalNAc-siRNA	EMA	Hypercholesterolemi2020a or mixeddyslipidemia		SQ/ Liver
Amondys 45 (Sarepta Therapeutics)	ASO	FDA	2021	DMD	IV/ Skeletal muscle

ASO, antisense oligonucleotide; ssDNA, single stranded DNA; dsDNA, double stranded DNA; SSO, splice switching oligonucleotides; GalNAc, N-acetylgalactosamine; IT, intrathecal; IV, intravenous; IVI, intravitreal injections; SQ, subcutaneous

3. Challenges presented by the gastrointestinal tract

The key challenge for oral delivery of oligonucleotide-based therapeutics is to deliver the active compound to its intracellular site of action, i.e. cytosol or nucleus. Oligonucleotides are typically highly charged (negative charges) hydrophilic large molecules, with size ranging from 4-10 kDa for single-stranded ASOs to ~14 kDa for double-stranded siRNAs to 34-72 kDa for aptamers to 700-7000 kDa for self-replicating mRNAs (2-4). These properties make them poorly permeable through the intestinal epithelium and can lead to low oral bioavailability. Orally administered oligonucleotides have additional obstacles to tackle over the conventional parenterally administered compounds, with most challenging being the permeation through the intestinal biological barriers. They must also resist the chemical degradation due to the acidic conditions of the stomach and enzymatic degradation in the extracellular space throughout the gastrointestinal (GI) tract.

Biological Barriers

The intestinal epithelium comprises a mucus layer, a single layer of epithelial cells tightly bound together and the vascular endothelium, located at the basolateral side (Figure 1). Epithelial cells line the intestinal lumen and are connected by the tight junctions (TJs) while endothelial cells line the interior surface of blood vessels and lymphatic vessels forming the endothelium and are also connected to each other by tight, adherence, and gap junctions (13).

The mucus layer is a first line of protective barrier composed of water (95%) and mucin which is an O-linked glycoprotein with oligosaccharide side chains and terminal sialic acid and sulfate groups giving it a net negative charge (14). Mucus as a biological hydrogel possesses two strategies to trap molecules: (a) size filtering and (b) interaction filtering (15). Size filtering allows molecules smaller than the cut-off size (20nm), such as ASOs and siRNAs (~16nm), to pass through the layer (15), while molecules above the threshold of the mucus mesh space (200nm) are trapped. Through interaction filtering the negative charge of pligonucleotides could enhance permeation through the mucus because they interact with the mucin polymers via repulsive forces. However, high negative charge may increase the repulsion between the oligonucleotides and the mucus network resulting in impaired diffusion through the mucus layer (16). Trapped molecules and particles are rapidly eliminated because the mucus layer is renewed every 4-6 hours (14).

Once a molecule has been transported through the mucus, there are 4 available pathways for its absorption across the intestinal and vascular epithelium (Figure 1):

- transcellular diffusion through the epithelial cell,
- paracellular permeation via the tight junctions (TJ) of adjacent cells,
- transcytosis
- carrier-mediated endocytosis.

The degree of lipophilicity and size plays a crucial role on a drug's passive transport. A minimum level of lipophilicity is required for a molecule to partition into epithelial cell membranes and be absorbed transcellularly. Passive absorption is not possible, if those requirements are not met. TJs are transcellular proteins that monitor the transport of water, ions and nutrients; and the absorption of proteins and bacterial antigens (17). Therefore, paracellular transport is an alternative pathway but it is restricted to hydrophilic molecules with a cutoff molecular weight of 100-200 Da (18) leading to a built-in limited passive absorption of oligonucleotides through tight junctions.



Figure 1: Schematic representation of drug absorption pathways

It has been reported that the majority of oligonucleotides enter cells by carrier-mediated endocytosis. Synergy of endocytosis, intracellular vesicular trafficking and endosomal release is required for the delivery of the macromolecules at the ultimate site of action (19, 20). Although oligonucleotides are taken up by the cells, they are trapped in the lipid bilayer of endosomes and thus they are not exposed to the cytoplasm and nucleus (2). Alternatively, they fuse into lysosomes and undergo degradation (21). Their large size and/or high charge make them unable to passively diffuse through the cell membrane or the endosomal lipid bilayers leading to their inherent low oral bioavailability. Small molecules, such as chloroquine, and peptides conjugated to the RNA, such as melitin, have been investigated as endosomolytic agents that disrupt or lyse the lipid bilayer (22). The latter was developed as a two-molecular dynamic polyconjugate (DPC) by Arrowhead Pharmaceuticals (CA, USA) but the clinical trials were rejected by the FDA due to toxicity derived possibly from melitin (2). Chloroquine presented high toxicity and a very small therapeutic index for clinical use (2).

4. Chemical and Enzymatic barrier of GI tract

Oligonucleotides are stable in solution at 2–8 °C around neutral pH and with common excipients, such as sodium chloride. They have poor stability throughout the GI tract due to pH gradient and luminal fluid composition.

Depurination of DNA starts in the highly acidic gastric environment of the stomach (pH 1.5-2 in fasted state which can increase to 3-6 in the fed state) (14, 23). Moreover, oligonucleotides are vulnerable to proteolytic degradation throughout the GI tract starting with pepsin, the most prominent peptidase secreted in the stomach (23) and following with intestinal peptidases secreted by the pancreas, such as trypsin, chymotrypsin, intestinal brush border peptidases, such as carboxypeptidases and aminopeptidases, and nucleases.

Starting from single stranded antisense oligonucleotides (ASO), which are more prone to degradation, advances in medicinal chemistry have led to successful chemical modifications increasing the stability and binding affinity to the target site (4) (Figure 2). Several modifications in the backbone, such as phosphorothioate and phosphoroamidate, reduce oligonucleotide degradation by nucleases in the blood and tissues. The first product with a phosphothioate backbone was approved in 1998 (Vitravene). In addition, modifications in the sugar unit, using the 2'-O-Me and 2'-O-(2-methoxyethyl) (MOE) groups, have been widely used to enhance nuclease resistance along with increased binding affinity to RNA (4). The same effect on stability and efficacy results was achieved by introducing either locked nucleic acids (LNAs) or constrained ethyl (cEt) in the sugar unit because both groups bridge the sugar units forming conformationally restricted nucleotides (4, 24). Moreover, changes in the nucleobase, such as pyrimidine methylation, lead to an increase of the melting point by 0.5 °C per substitution, which increases the overall physicochemical stability of the compounds. Kynamro, an FDA approved ASO drug product, includes in its structure all three modifications described previously.



Figure 2: Evolution of oligonucleotide modification to tackle chemical and enzymatic degradation.

In case oligonucleotides cannot be chemically engineered to resist enzymatic degradation in the gastrointestinal tract, formulation efforts are required. Enzymatic degradation may be controlled by either administering enzyme inhibitors, chelating agents or by modulating the pH to a non-favorable environment for the enzyme and/or using a delivery system. Co-formulation of oligonucleotides with enzyme inhibitors alone has shown limited success because it can increase the amount of drug at the site of action but may not promote drug permeation (25). If the major site of degradation is the stomach, enteric coatings may be used to prevent release in the stomach and allow release when the target pH is reached in the intestinal region of interest (18).

5. How to overcome the challenges: Permeation Enhancers

In 2003, the first oral administered oligonucleotide (ISIS 104038), developed by Ionis Pharmaceuticals, reached Phase I clinical trials. Sugar and backbone modifications were introduced in the ISIS 104838 ASO, i.e. 2'-MOE in the ribose sugar units and phosphorothioate in the backbone, which increased its resistance to nucleases. The drug product was manufactured as a solid dosage form (26) and resulted in an average of 9.2% plasma bioavailability after oral delivery across four formulations (27). In addition, Ionis in collaboration with AstraZeneca, recently published promising in vivo data showing the high accumulation of GalNAc ASO (AZD8233, also known as ION-863633) in the liver after oral administration (9). A 7% liver bioavailability was achieved in cynomolgus monkeys, which was 5-fold higher than that measured in plasma (~1.8%). For both oligonucleotides, permeation enhancers (PE) were used to improve cellular uptake. Moreover, the recent approved peptide formulations for oral delivery, i.e. Rybelsus® (semaglutide - Novo Nordisk) and MyCappsa (octreotide - Chiasma, Inc), use PE technology The oral bioavailability in humans of semaglutide varied between 0.4% and 1% and of octreotide was around 0.7%. All these achievements have raised the hopes towards the oral delivery of oligonucleotides. Depending on the Cost-of-Goods (COGs) and potency of the API a low oral bioavailability may still meet the criteria for a successful commercial drug product development.

Permeation enhancers (PEs) are compounds capable of promoting membrane permeation of orally administered compounds and are intentionally included in oral formulations. Although the mechanism of action is not clear for all

PEs, they are divided into two categories: those that enhance transcellular permeation and those that target the paracellular route via the tight junctions. The commonly used permeation enhancers in preclinical and clinical development are presented in (Table 2). The most extensively studied permeation enhancers include the acylated amino acid, salcaprozate sodium (SNAC), and medium-chain fatty acid, sodium caprate (C10). SNAC is well known from the groundbreaking Eligen™ technology (Emisphere Technologies, now part of NovoNordisk), which was used initially to promote Vitamin B12 passing through the intestinal barriers and reach blood circulation (28). as a medical food supplement and more recently from the approved semaglutide oral formulation (Rybelsus) for Type II diabetes (8). SNAC has an unclear mechanism of action and is possibly compound specific. It was first hypothesized that SNAC improves passive trancellular permeation via hydrophobization (dipole-dipole interactions). New findings from Rybelsus® suggested that SNAC improves permeation over the gastric barrier via membrane perturbation (transcellular) and protection from enzymatic degradation via neutralization of the low gastric pH (28, 29).

From the medium-chain fatty acids, sodium caprate (C10) and sodium caprylate (C8) have received the most attention. Sodium caprate was originally used as the main excipient of an oral solid-dosage form (GIPETTM). Gastro-Intestinal Permeation Enhancement Technology) by Elan Pharma (Dublin, Ireland). Later Merrion Pharmaceuticals (Dublin, Ireland) licensed the technology and used C8 and/or C10 for oral peptide delivery (30, 31). Ionis Pharmaceuticals (Carlsbad, CA, USA) and AstraZeneca have used the GIPET[™] technology to facilitate the permeation of ISIS104838 and AZD8233 compounds respectively (9, 27). Sodium caprylate was also used as an excipient in the Transient Permeation Enhancer (TPE[™]) technology developed by Chiasma Inc. (Ness Ziona, Israel). TPE[™] is an oil suspension composed of C8, as the driver of the permeation, and PVP forming a hydrophilic powder suspended in a lipophilic medium of glyceryl mono- or tricaprylate (11). TPETM was applied to Mycappsa[®], which is the FDA approved product of the cyclic octa-peptide, octreotide (32). C10 at low concentration (2.5-8 mM) acts on TJs, promoting paracellular permeation (33) while at higher concentrations (8-13 mM) acts via transcellular perturbation due to its surfactant-like effect (28, 34).

So far, a number of clinical studies have been performed using alternative permeation enhancers for oral delivery of peptides and proteins. Acyl carnitines such as lauroyl carnitine or taurodeoxycholate have been used to enhance trancellular permeation since 1980 (11, 35). The Peptiligence[™] technology has been used for peptide formulations and consists of an enteric-coated tablet containing citric acid, standard excipients, and acyl carnitines. FDA recently approved KORSUVA[™] (difelikalin, Enteris BioPharma, NJ, USA) to treat atopic dermatitis and additional two peptide formulations, i.e. TBRIA[™] and Ovarest[®], based on the same technology, are in Phase II clinical trials.

Class	Class Examples/Technology-Strategies		Clinical stage (Market name)	
Acylated Amino Acids	ccylated Amino C8 derivatives (SNAC) ccids Eligen™ (SNAC, 5-CNAC, 4-CNAB)		Y (Rybelsus® FDA approved 2019)	
Anionic Surfactants Medium Fatty Acid Chains	Sodium caprate (C10), sodium caprylate (C8) GIPET® (enteric coated solid dosage form Transient Permeability Enhancer - TPE®	Transcellular & Paracellular	Y (C10/ISIS104838 Phase I discontinued, GIPET® Insulin Phase II) Y (MyCappsa™ FDA approved 2020)	
Amphoteric surfactants (acyl carnitine)	C12- or C16-carnitine chloride Peptilligence™	Transcellular	Y (Tbria™ Phase II, Ovarest® Phase II, KORSUVA™ Phase II)	
Chelating Agents	EDTA POD™ (EDTA, bile salts and omega-3 fatty acids - oil suspension of peptide)	Paracellular: Chelating calcium opens tight junctions (TJs)	Y	
Taurodeoxycholate, ursodeoxycholate, Bile Salts taurocholate and chenodeoxycholate NOD formulation NOD formulation		Transcellular	Ν	
Ionic Liquids	Choline Geranate (CAGE)	Opens TJs	Ν	
Cell Penetrating Peptides (CPP) Polyarginine, Penetratin		Membrane perturbation, endocytosis, complexation	Y (PsorBan [®] - CyA- polyArg conjugates- Phase IIa Interrupted)	

Table 2: Permeation enhancer technologies for biotherapeutics and their clinical status

Chelating agents such as EDTA, have been the key component of the POD[™] technology (Oramed Pharmaceuticals, Jerusalem, Israel). Compared to the Peptiligence[™] technology, POD[™] is an oil suspension composed of EDTA, bile salts, omega-3 fatty acids and protease inhibitors, i.e. soybean trypsin inhibitor and aprotinin. It has been used to promote paracellular permeation of peptides and insulin by disrupting the integrity of tight junctions. Insulin has been formulated using the POD[™] technology and is in Phase II clinical trial (11). Bile salts have also been investigated to enhance intestinal permeability of insulin when incorporated into enteric coated nanoparticles (NOD Pharmaceuticals, China) (35).

PE content in commercially available solid dosage formulations is relatively high, such as 300mg SNAC in Rybelsus and more than 500mg C10 in tablets using GIPET® technology, which raises questions regarding their safety. Despite the high doses required, due to their rapid absorption and elimination and low potency in the small intestine, both SNAC and C10 are considered safe to use, as there is no evidence of infection from pathogens' absorption (36) and no impact on tight junction structure and functionality (37). Membrane perturbations and the opening of tight junctions are claimed to be temporary and reversible for TPE® technology. The membrane damage caused by two bile salts, sodium taurocholate and sodium taurodeoxycholate, in an intestinal single pass perfusion model, was reversible within 1-3h after removal of the surfactants

Ionic liquids are another promising emerging technology that is being explored to improve intestinal permeability. Choline geranate (CAGE) has been included in Insulin oral formulations. The pharmacodynamic bioavailability reached 66% when 5 insulin Units/kg were administered orally relative to the 2 Units/kg of subcutaneous injection in rat (38).

Permeation enhancer technology is promising but also challenging. Successful PE activity depends on the drug release kinetics from the PE-based dosage form, the degree of permeation enhancement and safety, particularly for chronic treatments. There are four examples of release kinetics, which affect the onset of action and thus drug bioavailability (10). Immediate- and complete release of both the PE and active agent, initial burst release of the both followed by a second release phase for the PE. In the latter case, co-localization of active ingredients and PE might not occur. The third example is asynchronous release by pre-exposure of the intestinal barrier to the PE and lastly sustained synchronous release, which involves co-release of the active agent and PE over ~60 min. The difference between immediate and sustained release is the larger contact area of PE with the small intestine that occurs in the latter.

6. Conclusions

Oral delivery of oligonucleotides has the potential to improve patient's quality of life but there are many obstacles and challenges yet to overcome. The harsh environment of the GI tract and the intestinal epithelial barriers may contribute to degradation of oligonucleotides and limit their absorption leading to low bioavailability and variable plasma concentrations. The development of new technologies using permeation enhancers and the recent FDA approval of oral peptide formulations provide undisputed examples of the success of the oral delivery of macromolecules. Although there are still gaps in our knowledge in what concerns safety of PEs, the administration of oligonucleotides via the oral route is gaining traction in academia and in the pharmaceutical industry.

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DRUG DELIVERY LITERATURE

Provided by Dr. Carsten Timpe

RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

Brain delivery

Overview of Current Drug Delivery Methods Across the Blood-Brain Barrier for the Treatment of Primary Brain Tumors

Haumann R, Videira JC, Kaspers GJL, van Vuurden DG, Hulleman E. CNS Drugs. 2020 Nov;34(11):1121-1131. *The review gives an overview about the status quo regarding treatment of brain tumors.*

Polymeric Nanoparticles for Brain Drug Delivery - A Review

Raman S, Mahmood S, Hilles AR, Javed MN, Azmana M, Al-Japairai KAS. Curr Drug Metab.2020;21(9):649-660.

A non-systematic review was carried out, and the literature searched in Google, Science Direct and PubMed. An overview is provided for the formulation of polymeric nanoparticles using different methods, the effect of surface modification on the nanoparticle properties with types of polymeric nanoparticles and preparation methods. An account is given of different nanomedicines employed with therapeutic agent to cross the BBB plus the biodistribution of the drugs.

Peptide, Protein-based Drug Delivery

Brain penetrating peptides and peptide-drug conjugates to overcome the blood-brain barrier and target CNS diseases

Zhou X, Smith QR, Liu X. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2021 Jul;13(4):e1695.

This review examines the latest development of brain-penetrating peptide shuttles and brain-permeable peptide-drug conjugates (PDCs) as molecular vectors to deliver small molecule drug payloads across the BBB to reach the brain parenchyma. Emerging knowledge of the contribution of the peptides and their specific receptors expressed on the brain endothelial cells, choice of drug payloads, the design of PDCs, brain entry mechanisms, and delivery efficiency to the brain are highlighted.

Oral Delivery

Nanoemulsion as Oral Drug Delivery - A Review

Sabjan KB, Munawar SM, Rajendiran D, Vinoji SK, Kasinathan K. Curr Drug Res Rev. 2020;12(1):4-15. *This review gives an overview about nanoemulsions as oral drug delivery systems.*

Oral Modified Drug Release Solid Dosage Form with Special Reference to Design; An Overview

Murugesan S, Gowramma B, Lakshmanan K, Reddy Karri VVS, Radhakrishnan A.

Curr Drug Res Rev. 2020;12(1):16-25.

This review describes basic information regarding modified release dosage forms designed to release their medication in a controlled manner, criteria for selecting modified release dosage forms and factors influencing the dosage and release pattern.

Oral Disintegrating Tablets - An Updated Patent Perspective

Sharma S, Singh K. Recent Pat Drug Deliv Formul. 2020;14(3):166-190.

The present study focused on non-patent and patent citations concerning ODT along with active ingredients, techniques used and results of the innovations.

Oral drug delivery with nanoparticles into the gastrointestinal mucosa

Liu J, Leng P, Liu Y. Fundam Clin Pharmacol. 2021 Feb;35(1):86-96.

This review focuses on the latest research progress of nanoparticles to penetrate the mucosal barrier, including the delivery methods of nanoparticles on the surface of gastrointestinal mucosa, and aims to summarize how successful oral nanoparticle delivery systems can overcome this biological barrier in the human body. In addition different types of drug delivery systems and their advantages and disadvantages in design and potential applications are discussed including a review and summary of various methods for evaluating oral nanoparticles in in vitro and in vivo models.

Dermal and Transdermal Drug Delivery

Recent Approaches on Novel Topical Delivery Systems for Atopic Dermatitis Treatment

Kahraman E, Aydilek N, Güngör S. Recent Pat Drug Deliv Formul.2020;14(3):191-200.

This review focuses on the mechanism of disease and development of nanocarrier based novel drug release systems in the management of atopic dermatitis.

Lipid vesicles: A versatile drug delivery platform for dermal and transdermal applications

Chacko IA, Ghate VM, Dsouza L, Lewis SA. Lipid vesicles: A versatile drug delivery platform for dermal and transdermal applications. Colloids Surf B Biointerfaces. 2020 Nov;195:111262.

This review article describes the various vesicular systems reported for skin delivery of actives with relevant case studies. The vesicular systems presented here are in the order of their advent, from conventional systems to the advanced lipid vesicles. The design and development of drugs in vesicular systems have brought a new dimension to the treatment of disease conditions by overcoming the permeation limiting barriers, thus improving its efficacy.

Gene Drug Delivery, Gene Therapy, siRNAs, ASOs, Oligonucleotides

Overcoming the delivery- barrier of oligonucleotide drugs and enhancing nucleoside drug efficiency: The use of nucleolipids

Zhou X, Wang S, Zhu Y, Pan Y, Zhang L, Yang Z. Med Res Rev. 2020 Jul;40(4):1178-1199.

This review introduces the progress of nucleolipids and provides new strategies for improving the delivery efficiency of nucleic acid-based drugs, as well as lipophilic prodrugs of nucleosides or nucleotides for antiviral or anticancer therapies.

Progress on ocular siRNA gene-silencing therapy and drug delivery systems

Jiang J, Zhang X, Tang Y, Li S, Chen J. Fundam Clin Pharmacol. 2021Feb;35(1):4-24.

This review summarizes the progress of the ocular siRNA gene-silencing therapy by focusing on siRNA drugs for age-related macular degeneration (AMD) and glaucoma already used in clinical research, the main routes of drug delivery and the non-viral vectors for siRNA drugs.

Nanosystem-based Drug Delivery

Chitosan Nanoparticles as a Novel Drug Delivery System: A Review Article Matalqah SM, Aiedeh K, Mhaidat NM, Alzoubi KH, Bustanji Y, Hamad I.

Curr Drug Targets. 2020;21(15):1613-1624.

In this review, the importance of chitosan and its derivatives in drug delivery is illustrated, different methods of preparation of chitosan and chitosan derivatives NPs and their physio- chemical properties are addressed. Moreover, the desirable characteristics of successful NPs based drug delivery systems, as well as the pharmaceutical applications of these NPs are also clearly explored.

Preparation and Surface Modification of Polymeric Nanoparticles for Drug Delivery: State of the Art

Joshi G, Patel M, Chaudhary D, Sawant K. Recent Pat Drug Deliv Formul. 2020;14(3):201-213.

This review focuses on the techniques used for the fabrication of polymeric nanoparticles, the material used for surface modification and their applications.

Nanocontainers for drug delivery systems: A review of Halloysite nanotubes and their properties

Hasani M, Abdouss M, Shojaei S. Int J Artif Organs. 2021 Jun;44(6):426-433.

In this review, the emphasis is on the main properties of Halloysite nanotubes (HNTs) to manage and develop effective drug delivery tools in the biomedical and pharmaceutical fields.

Recent advances in ultrasound-triggered drug delivery through lipid-based nanomaterials

Ahmadi A, Hosseini-Nami S, Abed Z, Beik J, Aranda-Lara L, Samadian H, Morales-Avila E, Jaymand M, Shakeri-Zadeh A. Drug Discov Today.2020 Dec;25(12):2182-2200.

The review highlights the potential role of ultrasound in combination with lipid-based carriers to achieve a targeted conventional chemotherapy (CTP) strategy using engineered smart drug delivery systems.

Ocular Drug Delivery

New ophthalmic drug delivery systems

Castro-Balado A, Mondelo-García C, Zarra-Ferro I, Fernández-Ferreiro A. New

ophthalmic drug delivery systems. Farm Hosp. 2020 Jul 1;44(4):149-157.

This review includes current developments in ophthalmic topical and intravitreal drug administration routes as well as those under investigation.

ABOUT THE FOCUS GROUP

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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