APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER ISSUE 2/2018 - JUNE

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DRUG DELIVERY EVENTS

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+ **Skin Forum 2018 Annual Meeting Skin health and topical formulation - new insights and perspectives**
June 20-21, 2018 | Tallinn, Estonia (Course no. 6727) — Details

Controlled Release Society Annual Meeting & Exposition, 2018
July 22-24, 2018 | New York, USA — Details

+ **10th conference of the European Paediatric Formulation Initiative**
September 11.-13, 2018 | London, UK (Course no. 6729) — Details

17th Annual Congress on Pharmaceutics & Drug Delivery Systems
September 20-22, 2018 | Prague, Czech Republic — Details

AAPS PharmSci 360
November 04-07, 2018 | Washington, DC, USA — Details

Suggest a meeting to be announced!

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

AMGLIDIA™

On 22nd Feb the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended that Amglidia™ (an oral suspension containing glibenclamide) should receive marketing authorisation in the European Union (EU) [1, 2]. This medicine is a new formulation of this sulphonylurea drug suitable for dosing to newborns, neonates and children for the treatment of neonatal diabetes mellitus (NDM).

NDM is an exceptionally rare type of diabetes found in children 6 months old or less which results in dangerously high blood sugar levels and the risk of ketoacidosis as ketones start to accumulate in the body. Estimates of its incidence vary from 1 in 12,000 to 1 in 100-300,000 live births [3, 4]. There are a number different sub-groups of the disease which has a genetic origin. It is known that NDM caused by genetic mutations in the KCNJ11 and ABCC8 genes, which encode the two subunits of the adenosine triphosphate - sensitive potassium channel found on pancreatic β-cell membranes, are sensitive to treatment with sulphonylurea drugs like glibenclamide; as is the transient type of NDM caused by chromosome 6q24-related mutations. Defects in the KCNJ11 and ABCC8 genes affect around 42% of NDM patients [3]). Typically children with mutations in these genes produce insulin but cannot release it. Glibenclamide works to restore blood sugar control in NDM by inhibiting the ATP-sensitive potassium (KATP) channel to result in insulin

release and improved blood sugar control. This improvement in metabolic control may be sufficient to reduce or eradicate the need to inject insulin.

To date NDM has been treated with insulin which must be injected or commercially-available glibenclamide tablets, crushed before suspension in water and administered via an oral syringe. The latter is an off-label use of glibenclamide tablets which are licensed for the treatment of Type 2 diabetes in adults, Amglidia's suspension formulation is designed to enable accurate dosing of glibenclamide to these very young patients and avoid issues of under-dosing/over-dosing that could occur with the crushed tablet formulations. It is available as 0.6 mg/ml and 6 mg/ml dose strengths.

The CHMP's recommendation for the marketing approval for Amglidia™ was based on literature data, a bioavailability study and the results of the NEOGLI study, a tolerance and acceptability study which included only 10 patients due to the rarity of the disease [4]. The NEOGLi study showed that glycaemic control remained stable after switching from a crushed tablet formulation to the oral suspension.

Amglidia™ was granted an orphan designation in January 2016, which in line with European Orphan Drug legislation, will be reviewed again at the time of approval by the EMA's Committee for Orphan Medicinal Products (COMP) to confirm Amglidia's orphan status and enable the granting the product ten years of market exclusivity. The product was developed by AMMTeK, France.

AIMOVIG™

In May the CHMP adopted a positive opinion on Aimovig™ (erenumab) which, if approved, will be the first specifically designed therapy for the prevention of migraine [5, 6, 7] licensed in Europe. Around 15% of Europeans suffer from this condition whose symptoms include bouts of severe, throbbing headache, typically restricted to one part of the head, nausea, vomiting and increased light and auditory sensitivity. Sometimes a migraine attack is heralded by an "aura" which is a set of visual and auditory disturbances

Migraine sufferers are three times more likely to be women rather than men, with attacks often triggered by factors such as stress, hormonal changes, flashing lights, lack of food or sleep or by ingestion of certain foods. Migraine is known to be strongly influenced by genetics; however, its exact cause is not yet understood. It is thought to be a neurovascular disorder involving dilation of blood vessels both in the brain and the head due to the release of inflammatory substances. Current treatments for the condition target symptom control or aim to reduce the frequency of attacks but to date the options for prophylaxis are mainly re-purposed drugs developed for other indications whose efficacy is often variable. As a result of this and the side-effects associated with these therapies, patient adherence can be poor [8].

Aimovig™ is a monoclonal antibody developed by Novartis and Amgen specifically for migraine propylaxis. It antagonizes the actions of calcitonin gene-related peptide by binding to its receptors. It is available as a 70 mg solution for injection and is indicated in adult migraine sufferers who have a minimum of 4 migraine days per month. The solution is self-administered every four weeks sub-cutaneously using an auto-injector pen. The standard dose is 70 mg per month with the possibility to increase this to 140 mg if required.
The CHMP's recommendation was based on the results of two pivotal studies involving 667 patients with chronic migraine and 955 with episodic migraine [6] plus other studies. Both pivotal studies compared the use of Aimovig™ to placebo. In patients with chronic migraine three months of treatment with Aimovig™ resulted in an average reduction of 2.5 monthly migraine days compared to placebo. In patients with the episodic version of the condition the reduction was either 1.3 or 1.8 days, depending on the dose administered. The most frequent side-effects recorded were injection site reactions, constipation, muscle spasms and pruritus.

The product was also approved by the FDA in May [9] and is the part of a collaboration between Amgen and Novartis to bring new treatments for migraine and Alzheimer's disease to market. Amgen and Novartis will co-commercialize Aimovig™ in the USA. With respect to other markets Amgen has sole rights to the product in Japan while Novartis is responsible for its commercialization in Europe, Canada and the rest of the world [7].

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DRUG DELIVERY PEOPLE

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Provided by Dr. Lea Ann Dailey

For this issue of the Newsletter, we would like to introduce **PATRICK AUGUSTIJNS** as our featured Drug Delivery Scientist. Patrick Augustijns has a Pharmacy degree, a Master in Medical Sciences and a Ph.D. in Pharmaceutical Sciences. Prior to becoming a professor at the University of Leuven (Belgium), he spent time as a postdoctoral researcher at the University of Kansas and worked at GlaxoSmithKline (North Carolina). In 2003, Patrick Augustijns became chairman of the Drug Delivery and Disposition laboratory at the University of Leuven.

Patrick Augustijns' research is focussed on the biorelevant profiling of intestinal drug absorption, covering all underlying processes including dissolution, precipitation, degradation and permeation. One of his research interests involves the biorelevant and predictive evaluation of absorption-enabling strategies, including solubilization and supersaturation of poorly soluble drugs. In this respect, his lab has developed a ground-breaking approach for evaluating intraluminal drug and formulation behaviour in humans, which involves the aspiration and in-depth characterization of gastrointestinal fluids. Prof. Augustijns and his team contribute to the OrBiTo project (oral biopharmaceutics tools, an EU IMI project) involving leading partners from academia and industry, focusing on the development of innovative *in vitro* and *in silico* tools to simulate the intestinal behaviour of drugs. He was also coordinator of the FP7-ITN program ARIADME and is chair of EDAN (European Drug Absorption Network), GPEN (Globalization of Pharmaceutics Education Network) and ULLA (European University Consortium for Pharmaceutical Sciences). He is coordinator of the EU-COST action, UNGAP, with partners from 30 countries focusing on intestinal absorption. He is (co)author of over 290 papers in international journals and more than 300 presentations at scientific meetings. Since 2008, Patrick Augustijns is an AAPS-fellow, an honorary distinction by the American Association of Pharmaceutical Scientists.

DRUG DELIVERY COMPANIES

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Provided by Dr. Florian Unger/Dr. Karsten Cremer/Dr. Dieter Becker

SURFLAY NANOTEC GMBH (BERLIN, GERMANY)

Surflay Nanotec GmbH is a privately held nanotechnology and biotechnology company. It offers R&D services for surface modification and drug encapsulation/release/delivery systems using the Layer-by-Layer coating platform. The company also produces fluorescent polymers, sensor particles and biosensor systems.

Fact sheet:

Founded:	2008
Location:	Berlin, Germany
Ownership:	Privately founded
Employees:	11
Key technology:	Layer-by-Layer (LbL) coating/encapsulation and Whispering Gallery Modes based biosensor LbL is a surface modification and micro-encapsulation approach. Planar or colloidal surfaces are coated with cationic and anionic polymers subsequently. The result is a layered polymer coating, each layer having several nm of thickness. Surflay uses the LbL surface modification technology in order to control surface properties such as charge, hydrophobicity, bio-reactivity, etc. LbL approach helps also create micro-capsules carrying drugs and active

	compounds. These capsules are tools for targeted drug-delivery and triggered-release e.g. for perifollicular delivery of nanoscale capsules. A second key technology is a Whispering Gallery Modes (WGM) based biosensor. It gives similar results as Surface Plasmon Resonance but can be applied for multiplexing or use in the smallest cavities such as inside living cells. WGM approach helps detect biomolecules and monitor protein-protein interactions online.
Products:	• R&D as a service - tailored surface modification, LbL encapsulation for drug-delivery and release • DNA/RNA encapsulation and release e.g. control particles • Surflay fluorescent sensor particles - temperature, pH and gas sensors in the smallest volumes • WhisperSens - A WGM based biosensor for detection and monitoring of biomolecular interactions
Development status:	Fluorescent sensor particles - in market DNA control particles readily developed WhisperSens - routine in-house use. Production, shipping, guidance offered
Partnerships:	N/A
Website:	http://www.surflay.com
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FEATURED ARTICLE - I

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3D-PRINTING FOR DRUG DELIVERY

By Julian Quodbach, Ph.D., Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University Universitätsstraße 1, 40225 Düsseldorf, Germany; E-mail: julian.quodbach@hhu.de, Phone: +49 211 81-14385

1. Medical Challenges and the Current State of Dosage Form Manufacturing

Within the last decades and especially within the last few years, the perception of the magnitude of human heterogeneity and individuality has drastically changed. In many ways, this is due to cheaper and more readily available gene analysis. The National Human Genome Research Institute lists that the prices of a full genome sequencing dropped from 100.000.000 US$ in 2001 to around 1.000 US$ in 2015 [1]. Today, commercial providers offer genetic analyses starting at 99 US$ [2]. For 199 US $, some medical markers are screened additionally, e.g. for Parkinson's disease, late onset Alzheimer's disease, or sickle cell anemia. Even though these tests do not match the requirements of diagnostic tests, they provide individual insights regarding the patient's health. More thorough medical gene analyses allow, e.g., the determination of deficiencies or mutations that increase or decrease enzymatic activity and, thus, identify metabolic variations as well as the presence of specific receptors that are a prerequisite for drug action. These inter-individual variations explain at least in part the observations from medical studies. In 2015, Schork reported that the 10 highest grossing drugs in the United States fail to improve the conditions of 3 to 24 patients for every effective case [3]. At best, these drugs improve the lives of 25 % of patients and "only" put 75 % of patients at risk of adverse effects, in the worst case, only 4 % of patients benefit from the medications and 96 % are at risk of adverse effects. Genetic analysis revealed that the presence or lack of certain markers and mutations allows the prediction of therapy efficiency for some drugs. For other drugs the amount of body fat has a therapeutic influence on the distribution of the drug substance between blood, blood rich tissue and fat.

In consequence, the better understanding of human predispositions, metabolic singularities, and also age-related effects gave rise to the notion that in therapy with certain drug substance, only a few available doses do not provide the best balance of beneficial effect and risk. Whereas for some sub-groups and individuals common drug doses are suitable, some patients require deviating doses to ensure therapeutic success and safety.

Solid dosage forms usually show the highest drug stability, are widely accepted and are, therefore, the ideal candidates for dose individualization. However, the options to manufacture individual solid dosage forms are limited. Industrial and social development has been price-driven throughout industrialization, leading to the development of cheap manufacturing techniques for large product quantities. Until recently the manufacturing of low numbers of highly specialized goods has not been the focus of pharmaceutical development. Pharmacies around the world prepare thousands of extemporaneous products every day based on individual prescriptions. A large-scale individualization initiative, however, could not be answered with the current, limited resources of pharmacies. New technologies for the individual production of small batches are necessary. Ideally, the new technologies will also be applicable at decentralized locations, e.g. (hospital) pharmacies, to allow widespread manufacturing closer to the patients.

2. 3D-Printing

In recent years, 3D-printing, or additive manufacturing, has gained traction as a potential manufacturing technique to answer these needs. 3D-printing is a group of techniques that was mainly developed in the 1980s and early 1990s. With 3D-printing it is possible to print virtually every three-dimensional object from a computer aided design (CAD) file. The basic procedure is the same for all technologies. The CAD objects (Figure 1 A) are not simply fabricated in one step but are built up layer-wise until the desired object is obtained. These thin layers are created by a specialized computer program, which *slices* the CAD object into layers of predefined height (Figure 1 B). During the slicing process, the tool paths of the print heads and other movable parts, e.g. print platforms, are also automatically calculated. The newly created file containing the layer data is then transferred to the 3D-printer. The actual printing process is the solidification and creation of the sliced layers. After the first layer is (sufficiently) solidified, the printing of the second layer begins and so forth (Figure 1 C). The available technologies all rely on this principle but differ in the mechanism of layer creation.

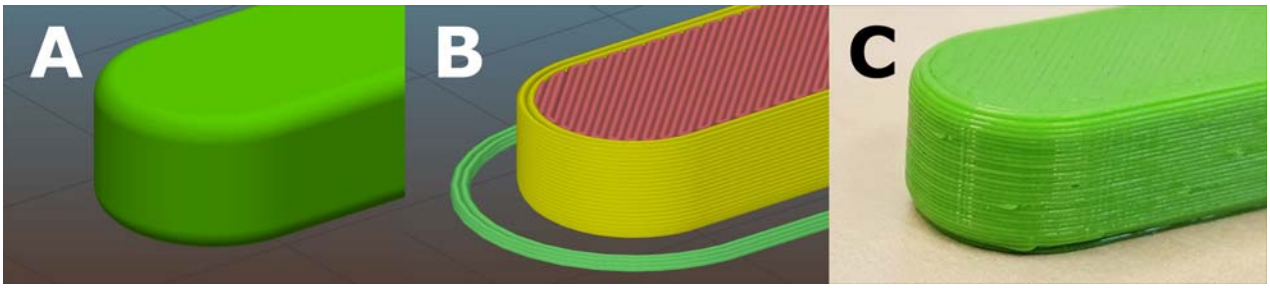

Figure 1: Depiction of the process flow. A: Computer designed dosage form, B: Dosage form sliced into thin layers with visible tool path, C: Printed object with visible layer structure

Opportunities of 3D-Printing

Unlike traditional manufacturing technologies, 3D-printing allows almost complete control over the size, shape, and internal structure of the product, leading to adjustable dosing and dissolution rates. These variations can be achieved by simple modifications of the desired objects in a 3D-design program. Approaches that were reported but not feasible to adapt can now be implemented without effort. For example, Reynolds et al. demonstrated that highly similar dissolution profiles could be achieved when tablets with the same specific surface areas (SSAs) but different size and, thereby, different doses were prepared [4]. This is easily transferred to 3D-printing [5, 6]. Furthermore, incompatible active pharmaceutical ingredients (APIs) can be combined in a single dosage form while also enabling different release kinetics because of compartmentalization [7]. Even periodic release profiles or individual bursts effects after predetermined time periods can be achieved by 3D-printing [8]. Another advantage of 3D-printing is that this kind of versatility can be achieved from a limited set of feedstock materials or intermediates and with basic training in CAD of 3D structures.

Whereas traditional manufacturing equipment was designed for industrial settings and scales, 3D-printers are mostly benchtop machines that can be set up in hospital pharmacies and community pharmacies. Thus, leading to a decrease in complexity of potential individualized therapy scenarios, as local manufacturing facilities lead to easier and quicker communication between medical practitioners, manufacturers, and patients.

2. 3D-Printing Technologies and their Application

The available technologies differ mostly in the mechanism of layer solidification, the printing speed, the applicable materials, the thermal load, and the achievable resolution of the print. Objects smaller than red blood cells [9] to complete houses can be printed. In pharmaceutical studies, only a handful of these techniques has been used. In the following, a selection of commonly used techniques is presented and their field of application discussed.

Fused Filament Fabrication (FFF)

The 3D-printing technique most widely used is Fused Filament Fabrication, also known as Fused Deposition Modeling™ (FDM). The feedstock material for FFF is a polymer filament that is fed into the print head. In the print head the polymer is plasticized, extruded through a nozzle and deposited on a heated print bed. The print bed and print head can move independently from each other to construct the desired layers. Lateral resolution is determined by the nozzle diameter (usually 250 µm to 400 µm in pharmaceutics) and the built-in kinematic. Depending on the printer, layer heights as low as 10 µm are possible. This resolution, however, leads to a drastic increase of the printing time. With layer heights of 100 µm to 200 µm, the printing of a tablet shaped dosage form requires several minutes. For FFF, the printing process itself does not pose the main challenge but the manufacturing of applicable filaments. Once a filament with suitable mechanical properties is available, the printing process itself should work as reliably as with commercial, non-pharma grade filaments.

Whereas initial studies used non-pharma grade filaments for the printing of dosage forms, a number of studies demonstrated the use of pharma grade polymers as raw materials for the manufacturing of filaments. Mostly, small scale conical twin-screw extruders were used [10-13]. Up to ~10 g of material was mixed and extruded to filaments that could be

printed. Melocchi et al. demonstrated that ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, methacrylic acid copolymer, polyethylene oxide, polyvinyl alcohol, alcohol-polyethylene glycol graft copolymer, and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer could be used extruded to filaments in combination with plasticizers and used to print simple disc geometries [13]. The extrusion temperatures ranged from 65 °C (polyethylene oxide) to 190 °C (polyvinyl alcohol), the print temperatures from 160 °C to 225 °C for the same polymers.

However, not all polymers are equally suitable for the manufacturing of filaments and 3D-printing. Pharmaceutical polymers were usually designed to achieve modifications of the dissolution rate or to improve processability. For FFF, the mechanical properties are much more important. Directly after the extrusion process, the filaments have to be wound up on spools, which is the intermediate transport form. After a given time, the filaments have to be un-wound and are mechanically fed into the print head. Two counter-rotating rolls or conveyer belts are used to force the filaments through the heating element and out of the nozzle. Thereby, axial and longitudinal forces are exerted on the polymer filaments that are not present in common pharmaceutical manufacturing processes. Zhang et al. introduced a structured approach to the formulation development of filaments based on basic mechanical testing [14]. The manufacturing of several 100s of meters of printable filament via co-rotating twin-screw extrusion was also demonstrated [15]. In several studies, new dosage form design to accelerate or modify drug release rates have been introduced, e.g. [6, 16, 17].

Powder Bed Printing

Powder bed printing is a drop-on-solid deposition technique. This technique was developed at the Massachusetts Institute of Technology and the first one to be used to print medical products and dosage forms [18, 19]. The printer creates a smooth, thin powder layer and uses an inkjet process to deposit a binder liquid on the powder bed. After the binder hardened, a new powder layer is created on top of the previous layer and the process is repeated. The layer height and print resolution are defined by the particle size of the powder. A big advantage of powder bed printing is that large scale machines allow the printing of dozens to thousands of dosage forms in parallel. For this purpose, the powder bed covers a large area and multiple print heads are used. Until now, no studies investigated commercial, large scale powder bed printers for their suitability to print dosage forms. Commonly, these printers are used to 3D-print molds that are later filled with a molten or hardening substrate. For this process type, a powder mixture with the desired properties as well as an ink for the inkjet process have to be developed.

This technology is also used for the production of the first FDA approved 3D-printed tablet Spritram by the company Aprecia. Spritram is a fast dispersing dosage form containing high doses of levetiracetam [20]. In this case, 3D-printing is not used to individualize the drug dose but to increase therapy adherence of patients with swallowing deficiencies.

Pressure Assisted Microsyringes (PAM)

The working principle of PAM is the simplest one. A semi-solid is extruded from a cartridge through a nozzle with a pressurized gas and deposited on a print bed. The semi-solid can be a thermoplastic polymer above the T_g or a solution or suspension of polymers and other appropriate materials. When a thermoplastic polymer is used for printing, the complete material supply is heated above the T_g to allow continuous printing. This might limit the number processable APIs. The advantage of this approach is that semi-solids over a relatively wide viscosity range can be used for the printing process, which greatly simplifies the formulation development process. The processable viscosity depends on the viscoelastic properties of the material, the nozzle diameter, and the available pressure of the propellant. Average nozzle diameters are between 300 µm to 600 µm.

This technique is also used for the printing of cell-containing suspensions as no heat is required for the printing of hydrogels and the shear rates are usually very low. Only few studies rely on this technique. It was used to construct complex dosage forms from DMSO and acetone containing semi-solids [7, 21]. Drawbacks of this method are the use of potentially toxic organic solvents and the long preparation and drying time (24 h each). However, the omission of filament preparation might prove this technique more versatile concerning processable polymers and substrates.

Inkjet Printing

Besides for the printing of 2D images, inkjet printing can be employed to create three dimensional structures. Multiple passes of the print head over the same place slowly buildup a 3D object. Until now, only one study was published that made use of this technique. Kyobula et al. used a hot melt chamber in combination with a hot melt print head to print dosage forms from molten bees' wax containing 5 % fenofibrate [22]. The high viscosity of bees' wax enables a quicker structural buildup that with low viscous inks. However, it has to be assumed that printing still requires a considerable amount of time. An advantage of 3D-inkjet printing is that the spacial resolution is high compared to the aforementioned systems. A generalization of the achievable resolution is not possible, because it is limited by the drop size and potential material coalescence after drop deposition. Similar to PAM, the molten material has to be kept above the T_g during the complete printing time, thereby limiting the processable APIs to thermostable materials.

Stereolithography (SLA)

SLA uses lasers to chemically crosslink a dissolved photo polymer. Thereby, solid layers can be produced with high precision. The first layer is created at the phase interface of the polymer solution and a holding structure that is either slightly submerged or lifted to create a new interface with the polymer that can be crosslinked. This method has been used in two studies. SLA was used to manufacture modified release dosage forms containing 4-aminosalicylic acid and

acetaminophen [23] and also to create hydrogels containing up to 10 % of ibuprofen [24]. In both studies polyethylene glycol diacrylate (PEGDA) was used as photo polymer. Due to the highly reactive character of PEGDA or any other photo polymer, analyses for residual monomers would have to be performed before any human application could be considered. However, no data on residual PEGDA was provided in these studies.

3D-printing: The future of manufacturing medicine?

This is the headline of an article by Katharine Sanderson in *The Pharmaceutical Journal* from 2015. Betteridge's law of headlines states that "any headline that ends in a questions mark can be answered by the word no". This is also true here. 3D-printing will not be "the future" but "part of the future" of manufacturing medicines. 3D-printing allows the automatized manufacturing of small quantities and batches of individualized medicines either in an industrial or a point-of-care setting. A sensible use of 3D-printing is dose individualization of APIs with narrow therapeutic indices, such as cytostatics, and of APIs that are not available in pediatric or geriatric doses and sizes, or the release modification of APIs that require varying release profiles because of chronopharmacodynamical considerations.

For 3D-printing to fulfill its promises, many hurdles still have to be overcome. Until now, only a few printers are available which adhere to pharmaceutical manufacturing standards. These are mostly bio-printers, used for the printing of cell-systems or scaffolds. Common 3D-printers are constructed for rapid prototyping of design parts and tools and not with the manufacturing of medicines in mind. No procedures exist, yet, to investigate and prevent cross contaminations, to ensure non-destructively that the correct doses are printed, or to guarantee that the shape of printed dosage form is within certain limits of the design file. Furthermore, no comprehensive regulatory framework governs the procedures for a widespread adaption of individualized medicines. However, history has proven that researchers and regulators have always caught up with pharmaceutical needs when opportunities arise. It is a near certainty that the remaining challenges and questions will be answered and that individualized medicine will become a reality for patients.

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FEATURED ARTICLE - II

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DRUG DELIVERY ACROSS THE BLOOD-BAIN BARRIER

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1. The blood-brain barrier as a challenge for drug delivery

Since its discovery by Paul Ehrlich and Edwin Goldman in the late 19th and early 20th centuries the blood brain barrier remains one of the biggest challenges in pharmacotherapy and has been object of intensive research over decades. The brain is the most sensitive organ of our body, which is highly susceptible to a large variety of chemicals, including potentially toxic metabolites or constituents of our daily food intake that are non-toxic to= other parts of the body. Therefore, it is particularly protected. The "firewall" is set up by the vascular wall of brain capillaries, the so called "blood-brain barrier" (BBB). This microvessel network operates as a dynamic regulator of ion balance, mediator of nutrient transport, and barrier to harmful molecules. However, at the same time it represents a major obstacle to the development of CNS-drugs. Approximately 98% of small molecule and all large molecule drugs are normally excluded from the central nervous system[1,2] by this barrier. Therefore, understanding its structural features including the mechanisms determining its function are an absolute prerequisite for successful drug delivery to the brain.

Major components of the barrier are microvessel endothelial cells, pericytes and foot processes of astrocytes. The endothelial cells and pericytes are embedded into and surrounded by a basal membrane and all these components are in close proximity to neurons, giving the whole ensemble the name "neurovascular unit". Brain microvessels exhibit some fundamental differences compared to peripheral capillaries. Whereas the latter are fenestrated, the endothelial cells of brain capillaries are very closely connected by tight junctions and zonulae occludentes. In addition, the number of mitochondria is about 5 to 10 times higher than in cells of peripheral microvessels, indicating a high metabolic activity. The capillaries pervade the brain with a total length of approx. 600 km, single branches have a mean distance of appr. 40 µm and a capillary surface area available for molecular transport of about 20 square meter[3].

Due to the very tight junctions the blood-brain barrier has to be passed via the transcellular route. Only few small polar compounds including water, glycerol and urea diffuse across tight junctions. Some cerebral nutrients like glucose or amino acids pass the BBB via carrier-mediated mechanisms such as the GLUT1 transporter or the large amino acid transporter LAT1. Other carrier proteins are the monocarboxylate transporters MCT-1 and MCT-2, which transport short-chain monocarboxylic acids (e.g. lactate, pyruvate or mevalonate). In mice 2 thyroid-transporters, a sulfate transporter, the L-ascorbic acid transporter and a folate transporter have been identified in the barrier[4].

Most interesting for drug availability in the brain are the ATP-dependent export proteins, which represent a major defense mechanism of the brain: P-Glycoprotein (P-gp, ABCB1), several MRP proteins (multidrug resistance related proteins, ABCCs) and BCRP (breast cancer resistance protein, ABCG2). They are of particular relevance, since they recognize a huge variety of diverse substrates and are subject of complex signaling cascades regulating their expression and function. One of these events involves activation of orphan or nuclear receptors including the pregnane xenobiotic receptor (PXR), the aryl hydrocarbon receptor (AhR), the glucocorticoid receptor (GR), and the constitutive androstane receptor (CAR) which results in an upregulation of the ABC transporters at exposure to xenobiotics[5].

In addition to the aforementioned carrier proteins, the blood-brain barrier contains several receptors responsible for the passage of large molecules, such as the transferrin receptor (TfR), the insulin receptor (IR), the insulin-like growth factor 1 receptor (IGF1R), the LDL-receptor, the leptin receptor (OBR), the low-density lipoprotein-related receptor 1 (LRP1), and the receptor of advanced glycation end products (RAGE). In general, these receptors provide targets for brain directed delivery of drugs, which under normal circumstances do not cross the blood-brain barrier, including large biopharmaceuticals. Recombinant proteins, enzymes, and monoclonal antibodies can be re-engineered for transport across the human BBB with molecular Trojan horse technology either by direct coupling to antibodies against a distinct receptor or by packing them into a colloidal carrier, such as nanoparticles or liposomes, which are surface modified with receptor-directed antibodies or antibody fragments.

Two other pathways across the BBB are mediated by caveolae or plasmalemmal vesicles and clathrin-coated pits/vesicles[6]. The caveolae-mediated permeation across endothelial cells is also known as bulk-phase or fluid-phase transcytosis, being independent from interactions between the transported molecules and the caveolar vesicle membrane. Because of the negative surface charge of the clathrin-coated pits this pathway is of interest for the transport of positively charged molecules including artificially cationized proteins, such as albumin, when electrostatic interactions occur between the positively charged moieties of the proteins and negatively charged membrane surface regions on the endothelial cells.

2. Chemical modification of drugs to overcome the barrier

The substrate selectivity of transport proteins within the barrier as well as the use of charged molecules complicate the passage across the barrier. Therefore, several techniques have been suggested to modify the structure of molecules in order for them to be transported. One of the best-known proposals is the so-called retro-metabolic drug design, which involves two approaches: soft drugs and targeted chemical delivery systems (CDS)[7]. These systems provide site-specific traffic properties by sequential metabolic conversions and make use of site-specific enzyme-activation. For example, administration of lipophilic dihydrotrigonelline–drug constructs enabled entrapment of hydrophilic trigonelline^{+}–drugs in the brain. The positively charged oxidized drug precursor accumulates beyond the blood brain barrier and then the active drug is split off. Drugs delivered to the brain by this approach include steroids, peptide hormones, neurotransmitters, anticonvulsants, antibiotics, antiviral, anticancer, antidementia drugs and others[8] A similar idea based on a dihydroquinoline/quinolinium targeting system has been used for delivery of GABA to the brain[9]. Furthermore, a 1-malonyl-1,4-dihydropyridine/pyridinium moiety was successfully used for brain targeting and tested derivatives showed remarkable antidepressant activity comparable to imipramine[10].

3. Manipulation of efflux transporters

Considering the important role of ABC transporters as a defense system for the CNS their direct blockade becomes an obvious way to improve drug delivery. Several inhibitors of P-gp have been developed including Valspodar (PSC-833, a cyclosporin derivative), Elacridar (GF 120918, a substituted isoquinolinyl acridoecarboxamide), Biricodar (VX-710, an amino-keto-pipecolinate derivative), Dexniguldipine (a dihydropyridine derivative), ONT-093 (a diarylimidazol compound), Zosuquidar (LY335 979; a difluorocyclopropyl dibenzosuberane), Tariquidar (XR9576, an anthranilic acid derivative) and Laniquidar (R101933, a benzacepine-3-carboxylate derivative). However, although some of these proved to be very effective *in vitro* and in animal trials in blocking ABC transporters and allowing substrates to get into the brain at rather high concentrations (e.g.[11], Figures 1 and 2), none of them have been marketed. Thereby it has to be noted, that direct inhibition of ABC transporters may be of therapeutic benefit in situations where acute dosing is indicated. However, it is uncertain whether chronic administration of blocking agents is feasible given the protective role of ABC transporters not only in the blood-brain barrier but also in other organs.

Another strategy to modify ABC transporters is manipulate the regulatory pathways underlying their expression and function. It would clearly be advantageous to modulate p-glycoprotein function over a short time interval, while maintaining continuous long-term protection. For example, it was shown that Endothelin-1 (ET-1) regulates p-glycoprotein at the blood-brain barrier. In intact rat brain capillaries, sub-nanomolar to nanomolar concentrations of ET-1 rapidly and reversibly decreased p-glycoprotein-mediated drug efflux in a similar way to PSC-833, suggesting almost complete loss of function. It remains to be seen whether signaling can be manipulated in such a way as to make it useful in the clinic. Beside this fast-functional regulation ABC-transporters may also be affected by transcriptional modulation. Ligand-activated transcription factors, so-called orphan receptors including the pregnane-X receptor (PXR) or the aryl-hydrocarbon receptor (AHR) are able to upregulate the expression of ABC transporters in the blood brain barrier. For example, PXR can be activated by natural steroids such as pregnenolone and progesterone, but also by synthetic glucocorticoids, anti-glucocorticoids, diverse dietary compounds, a large number of commonly prescribed drugs and environmental toxins such as DDT or TCDD. Thus, this gives another example by which the activity of ABC transporters is modulated and points to selective tightening of the blood-brain barrier and to enhanced neuroprotection in patients exposed to the wide range of xenobiotics that are PXR ligands. However, since many p-glycoprotein substrates are used to treat CNS disorders increased pump expression so implies reduced access of such drugs to their site of action inside the CNS (for review of the signaling pathways see[12]).

4. Opening of tight junctions at the blood brain barrier

In 1970 Stanley Rapoport postulated for the first time that drug penetration across the blood-brain barrier could be transiently increased by intra-arterial infusion of concentrated solutions[13]. Thereby, the mechanism responsible for this barrier opening seems simple: intracarotid infusion of hypertonic solutions increases osmolarity within the capillary lumen, drawing water out of the endothelial cells. Subsequent shrinkage then opens intercellular tight junctions. The effect lasts 20-30 minutes, during which drugs that normally do not cross the blood-brain barrier enter the brain. However, detailed cellular mechanisms responsible for blood-brain barrier opening may well be more complex, since osmotic stress is known to affect second messenger systems as well as the cytoskeleton. Today, intracarotid infusion of a hypertonic mannitol solution is the most commonly used method in preclinical and clinical studies. In animal studies osmotic disruption of the blood-brain barrier increases drug delivery to the brain by 10- to 100-fold[14].

Tight junction permeability can also be increased non-osmotically. Alkylglycerols have been used to open the blood-brain barrier in rats with implanted brain tumors to deliver methotrexate to the brain[15]. The use of alkylglycerols looks promising, considering their potential for exact regulation of barrier opening and lack of long-term toxicity. However, their exact mechanism of barrier opening remains to be determined.

Another option to open tight junctions is the application of focussed ultrasound[16]. At low frequencies magnetic resonance imaging guided focused ultrasound can be used together with injected microbubbles to open the blood-brain barrier. By the microbubbles the acoustic energy is concentrated inside the blood vessel. The stable expansion and contraction of the bubbles leads to a mechanical stimulation of the microvesels and results in a transient, reproducible opening. First clinical trials in patients with glioblastoma yielded promising intermediate results without any ultrasound related side effects.

Nevertheless, this therapeutic approach needs carefully to be evaluated further. Tight junctional disruption is non-selective and may thus enhance entry of blood-borne substances, such as albumin, which may well lead to unwanted side effects. Opening the barrier leaves the CNS unprotected. In addition, increased blood-brain barrier permeability may be limited spatially, thus complicating drug delivery to the whole organ or specific loci.

5. Receptor mediated transport and colloidal carriers

Besides membrane carrier proteins with their selective substrate recognition, membrane receptors undergoing endocytosis and transcytosis across the barrier are favourite targets for brain drug delivery. Receptors of interest include the transferrin receptor, the insulin receptor, the LDL/LRP receptors, the leptin receptor and the receptor of advanced glycation end products (RAGE). They offer the option to bypass the export proteins without direct inhibition. Small molecules can be coupled to their physiological ligands and they can also be targeted by surface-modified colloidal carriers such as liposomes, solid lipid nanoparticles, albumin nanoparticles or polymeric nanoparticles.

The transferrin receptor moves apotransferrin in the brain-to-blood direction and holotransferrin from blood to brain. One of the first studies involving this receptor used immunoliposomes with anti-receptor antibodies for CNS-delivery of antineoplastic daunomycin in rodents. The study impressively demonstrated that the immunoliposomes are able to host ≥ 10.000 drug molecules[17]. This approach was later successfully extended to the CNS delivery of a biological in an experimental model of Parkinson's disease in order to normalize tyrosine hydroxylase activity in the striatum of adult rats[18]. Thus, the striatal tyrosine hydroxylase activity ipsilateral to the intracerebral injection of the neurotoxin could be normalized. Similar results could be obtained with an antibody against the mouse transferrin receptor. An interesting drug delivery system for chemotherapy of glioblastoma consists of transferrin and cell-penetrating peptide dual-functionalized liposomes, Tf/TAT-lip[19], which had been loaded with doxorubicin (DOX) as a model drug. *In vivo* experiments in an orthotopic rat brain tumor model revealed significantly prolonged survival times after administration of these liposomes compared to treatment with non-surface decorated liposomes. In another dual targeting study[20] a cyclic arginine-glycine-aspartic acid (RGD) peptide and transferrin (TF) were utilized as targeting ligands for paclitaxel loaded liposomes for glioblastoma treatment. *In vivo* imaging demonstrated brain distribution of these RGD/TF-liposomes. A further approach used a dual mechanism, receptor mediation across endothelial cells via transferrin receptor combined with external non-invasive magnetic force, by ferrous magnet-based liposomes for BBB transmigration enhancement[21]. Compared to magnetic force- or transferrin receptor-mediated transportation alone, the synergy of this combined approach resulted in 50-100% increased transmigration without affecting the BBB integrity.

The insulin receptor was targeted in an approach for successful nonviral gene transfer (plasmids encoding either luciferase or ß-galactosidase) to primate brain after encapsulation of plasmids into PEGylated immunoliposomes, coupled to a monoclonal antibody to the human insulin receptor. Neuronal expression of the ß-galactosidase gene in brain was demonstrated by histochemistry and confocal microscopy[22].

LDL (low density lipoprotein receptor) and low-density lipoprotein receptor related receptor have also been targeted, either by liposomes surface-modified with ApoE or fragments thereof[23] or by modified albumin nanoparticles or polymeric nanoparticles. For the latter these receptors are of particular interest: Preparation of nanoparticles in presence of surfactants such as Tween-80 or Pluronic F68 results in subsequent binding of apolipoproteins (mainly ApoE) to the surface of the nanoparticles in the blood circulation and then in recognition by the LDL or LRP receptors in the blood brain barrier. Polymers used for that purpose are predominantly made from polylactide/glycolide or

poly(alkyl-cyanoacrylate), both being biodegradable polymers. Thus, only approved excipients can be used, and no covalent linkage of the targeting moiety is required. Successful brain delivery using this approach has been shown for a variety of drugs including different peptides, antiviral drugs, cytostatics, nucleic acid constructs and others. For a review of this topic see[24,25].

The peptide hormone leptin is a major regulator of body weight, and controls together with the peptide hormone ghrelin hunger and satiety. Fat induced leptin crosses the BBB by transcytosis and interacts with leptin receptors in the arcuate nucleus to inhibit feeding and increase thermogenesis, which decreases fat mass. Absent or impaired leptin receptors are discussed to be a cause of obesity in humans. Recent *in vitro* studies[26] demonstrated the uptake of liposomes surface modified with a leptin analog. However, it was not absolutely clear whether the leptin receptor was directly involved in liposomal transfer across the cells and it was suggested that macropinocytosis largely contributed to the cellular uptake of the liposomes.

The Receptor for Advanced Glycation Endproducts is a transmembrane receptor of the immunoglobulin super family[27]. This multi-ligand receptor is involved in inflammatory disorders, diabetic complications, tumor growth, and Alzheimer's disease. RAGE appears to interact with amyloid ß resulting in transport of amyloid ß across the blood-brain barrier and anti-Aβ-MAb (Aβ-MAb)-decorated immunoliposomes (LIP) had been used to target RAGE[28]. Uptake of these liposomes into human brain endothelial hCMEC/ D3 cells was measured and it was shown that transcytosis of Aβ-MAb-Liposomes through monolayers was 2.5 times higher when monolayers were pre-incubated with Aβ1-42.

As mentioned earlier caveolae-mediated permeation and the clathrin-coated pit-pathway are 2 additional options to cross the blood-brain barrier. The latter can be targeted when cationized albumin is used as the surface ligand of colloidal drug carriers[29].

Another option for drug delivery to the CNS are cell-penetrating peptides, which are quite heterogeneous in size (10–27 amino acid residues), but they all possess positive charges. Cell penetrating peptides derived from natural proteins include the transcription-activating factor Tat, penetratin, and the so-called Syn-B vectors as well as engineered short peptides like the homoarginine vectors, transportan or sequence signal-based peptide (SBP) and the fusion sequence-based peptide (FBP). The exact mechanisms, by which these peptides are internalized and carry their payload, are still under discussion and may be different for the distinct peptides, but several studies indicate a crucial role of basic residues in the translocating ability of these molecules, which can either be directly coupled to drugs of interest or be attached to nanoscaled drug carriers[30,31].

When discussing the use of colloidal carriers, it has to be kept in mind, that only a minor amount (< 5%) of an i.v. administered dose reaches the enteral nervous system. Reasons for that are the turnover capacity of the targeted receptors as well as the fact, that they are not exclusively localized at the blood-brain barrier. Most of them can also be found in other organs, e.g. liver, spleen, kidney, lungs. Nevertheless, significant therapeutic effects of brain-targeted colloidal carrier systems have been observed in animal studies and in the meantime first clinical trials have been started[32].

6. Nasal drug delivery and brain targeting

Delivering drugs to the brain via the olfactory region of the nose and the bulbus olfactorius is emerging as a new option for the delivery of drugs, since the distance between the site of administration and the site of action is relatively short thus allowing enhanced brain targeting and reduced systemic side effects. However, the amount of drug reaching the brain via that pathway is again relatively low (normally < 0.5% of the dose): Parts of it may be lost locally due to mucociliary clearance or enzymatic degradation and some might be absorbed into the systemic circulation, be distributed to non-target tissues, and finally be eliminated. In addition, it has to be kept in mind, that the anatomy of the nasal cavity exhibits some important species differences. The respiratory component of the nasal epithelium dominates the olfactory component in humans, in contrast to rats and dogs. However, from a patient's perspective intranasal drug administration is attractive: The nasal cavity has a relatively large surface area of ca 150 cm^2, first pass metabolism is substantially avoided, drug administration requires little training and carries little risk of injury and - due to its noninvasive nature - it results in relatively high compliance particularly in children and elderly people. A variety of nasal formulations has been used in the clinics, but it is not clear from these studies, whether there was direct passage from nose to brain or via the systemic circulation. Delivery systems administered include various types of (micro/nano) emulsions, polymeric or solid lipid nanoparticles, diverse liposomes and others. From all these studies it can be concluded that even more fundamental mechanistic investigations are necessary. In addition to their therapeutic efficacy the toxic potential of intranasal drug formulations must be carefully evaluated. Particularly, colloidal carriers may cause cellular and subcellular damage. Inflammation, necrosis, allergenicity, immunogenicity, and even carcinogenicity represent potential areas to be considered. Potential benefit and drawbacks of brain-directed nasal drug delivery systems are summarized in [33,34]

7. Concluding remarks

Drug targeting to the central nervous system has recently received remarkable interest. Whereas administration of normal colloidal carriers such as liposomes and nanoparticles yielded more or less disillusioning results within the last 25 years, the above discussed surface modifications and vector technologies offer promising tools for new therapeutic areas. Modified carriers have shown first positive clinical results. Even if broader use of the mentioned systems and their

validation in *in vivo* models will require some time, the continuously ongoing optimisation of carrier systems by use of new excipients, of enzymatically cleavable bonds and improved targeting vectors will lead to novel biodegradable systems, offering new possibilities of drug delivery to the central nervous system.

8. Figures

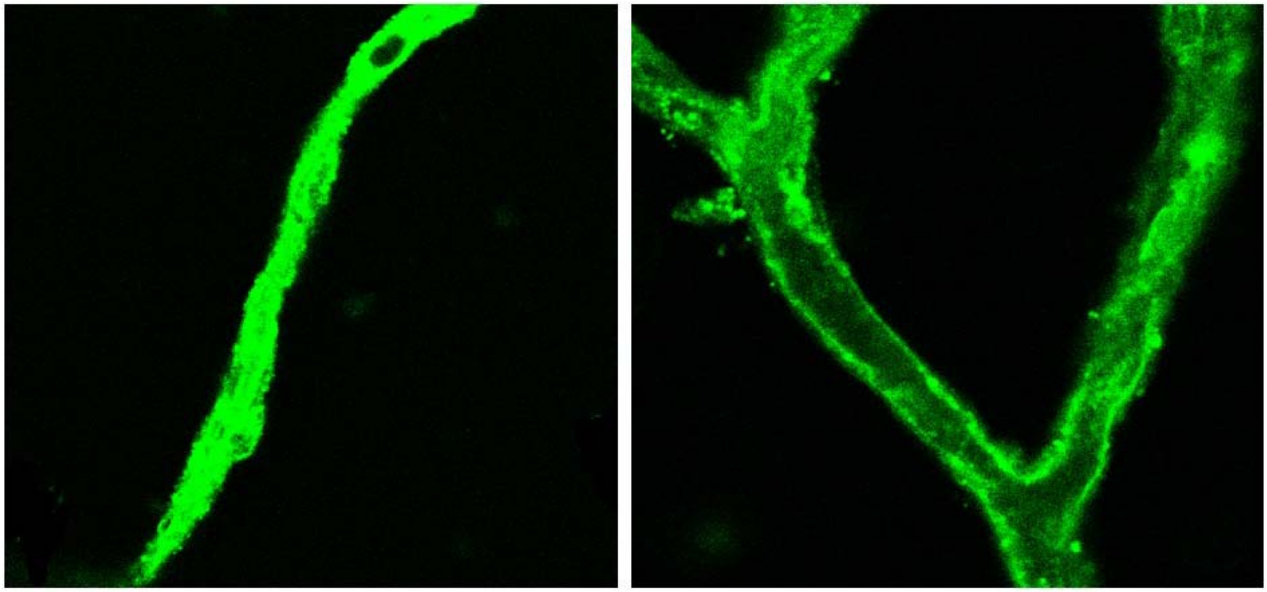

Figure 1:
Excretion of fluorescent labelled rapamycin, a P-gp substrate, into the lumen of isolated porcine brain capillaries in the absence and in the presence of 0,5 µM PSC-833, a potent P-gp blocker. Excretion is almost totally blocked after P-gp inhibition.

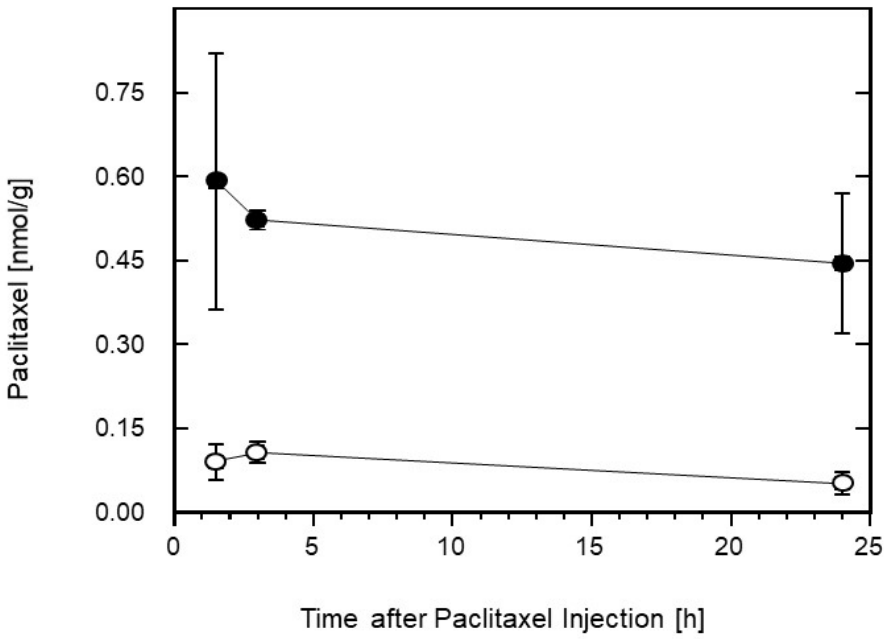

Figure 2:
Effect of P-gp inhibitor PSC-833 on paclitaxel brain levels in nude mice after intravenous injection of 8 mg/kg paclitaxel. Four hours before intravenous application the animals were treated with 50 mg/kg PSC-833 by mouth (PSC-833 group, filled squares). Means ± SEM, n = 3–4. Compared with the respective controls, all values in the PSC-833 group were significantly ($P \leq 0.05$) higher indicating potent inhibition of P-gp. Figure modified from [11]

9. References

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DRUG DELIVERY LITERATURE

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RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

Structural modifications of DS for solubility enhancement (Amorphous Drug Delivery Systems, Cocrystals, Polymorphism)

Application of various polymers and polymer-based techniques used to improve the solubility of poorly water soluble drugs: A review, Acta Pol Pharm. 2017 Mar;74(2):347-356, Muhammad Sarfraz R, Bashir S, Mahmood A, Ahsan H, Riaz H, Raza H, Rashid Z, Atif Raza S, Asad Abrar M, Abbas K, Yasmeen T

Different techniques are being used to enhance the solubility of water insoluble drugs. These techniques include variety of polymers to enhance solubility of these drugs like polyethylene glycol 300, polyvinyl pyrrolidone, chitosan, β-cyclodextrins etc.

Peptide, Protein-based Drug Delivery

Molecular engineering solutions for therapeutic peptide delivery, Acar H, Ting JM, Srivastava S, LaBelle JL, Tirrell MV, Chem Soc Rev. 2017 Oct 30;46(21):6553-6569

In this review, the authors focus on self-assembled vehicles as nanoparticles to carry and protect therapeutic peptides and deliver them to the desired tissue

Dermal and Transdermal Drug Delivery

Subcutaneous drug delivery: An evolving enterprise, Jones GB, Collins DS, Harrison MW, Thyagarajapuram NR, Wright JM., Sci Transl Med. 2017 Aug 30;9(405)

Recent advances in subcutaneous drug delivery and device design are transforming the biopharmaceutical sector and improving patient care.

Dissolving microneedles for transdermal drug delivery: Advances and challenges, Ita K, Biomed Pharmacother. 2017 Sep;93:1116-1127

Over the last number of years, a significant body of evidence has shown the benefit of using dissolving microneedles (DMNs) for transdermal drug delivery. These devices are prepared from a wide range of materials such as sugars and polymers. In this review, the authors have focused on the advances made in the field in recent years using a representative set of studies. DMNs can be used to delivery low molecular drugs as well as peptides, proteins and other high molecular weight compounds.

Gene Drug Delivery, Gene Therapy, siRNAs

Physical Methods for Drug and Gene Delivery Through the Cell Plasma Membrane, Jakutavičiūtė M, Ruzgys P, Tamošiūnas M, Maciulevičius M, Šatkauskas S., Adv Anat Embryol Cell Biol. 2017;227:73-92

One method for membrane permeabilization, electroporation, has already been translated to clinical practice for localized anti-cancer drug delivery and is termed "electrochemotherapy". Clinical trials for gene delivery using electroporation as well as drug delivery using another cell permeabilization method, sonoporation, are also underway. This review focuses on these two methods, including their fundamental principles and state-of-the-art applications. Other techniques, such as microinjection, magnetoporation, photoporation, electrospray, and hydrodynamic and ballistic gene delivery, are also discussed

Nanosystem-based Drug Delivery

Recent biomedical applications of gold nanoparticles: A review, Elahi N, Kamali M, Baghersad MH, Talanta. 2018 Jul 1;184:537-556

This article reviews the popular gold nanoparticles synthesis methods and mentioned their established applications in various demands, especially in biological sensing.

Nanotechnology based approaches for anti-diabetic drugs delivery. Kesharwani P, Gorain B, Low SY, Tan SA, Ling ECS, Lim YK, Chin CM, Lee PY, Lee CM, Ooi CH, Choudhury H, Pandey M, Diabetes Res Clin Pract. 2018 Feb;136:52-77

In this review, the authors provide an overview on distinctive features of each nano-based drug delivery system for diabetic treatment and current NPs applications in diabetes management.

Strategies in the design of gold nanoparticles for intracellular targeting: opportunities and challenges, Yang Y, Ren L, Wang H, Ther Deliv. 2017 Oct;8(10):879-897

In this review, we summarized recent advances in designing Au NPs with the capabilities of cellular penetration and internalization, endosomal escape, intracellular trafficking and subcellular localization via various approaches including physical injection, tuning the physiochemical parameters of Au NPs, and surface modification with targeting ligands. Strategies for delivering Au NPs to specific subcellular destinations including the nucleus, mitochondria, endoplasmic reticulum, lysosomes are also discussed. Moreover, current challenges associated with intracellular targeting of Au NPs are discussed with future perspectives proposed.

Oral Drug Delivery

Formulation possibilities of self-emulsifying drug delivery systems, microemulsions and nanoemulsions, Jakab G, Fülöp V, Santha K, Szeröczei D, Balogh E, Antal L. Ismail R, Csóka I. ,Acta Pharm Hung. 2017;87(1):27-34

The aim of this review is to introduce the self-emulsifying drug delivery systems which can be used to improve the bioavailability of poorly water soluble drug substances

Pulmonary drug delivery

Misuse and/or treatment delivery failure of inhalers among patients with asthma or COPD: A review and recommendations for the conduct of future research., Mahon J, Fitzgerald A, Glanville J, Dekhuijzen R, Glatte J, Glanemann S, Torvinen S., Respir Med. 2017 Aug;129:98-116

There is evidence for all identified inhalers that some people may be using them incorrectly, but it is unclear which inhalers have higher rates of misuse or which steps within the inhaler technique are most difficult for patients. The optimal techniques for using inhalers are not standardised. Researchers undertaking future inhaler studies are respectfully directed to recommendations of the authors for future research.

Alternative application routes (e.g. intrathecal, brain delivery etc.)

Designing and developing suppository formulations for anti-HIV drug delivery, Ham AS, Buckheit RW Jr , Ther Deliv. 2017 Aug;8(9):805-817

Despite a long history of use for rectal and vaginal drug delivery, the current worldwide market for suppositories is limited primarily due to a lack of user acceptability. Therefore, virtually no rational pharmaceutical development of antiviral suppositories has been performed. However, suppositories offer several advantages over other antiviral dosage forms. With continuing research into rational suppository design and development, there is significant potential for antiretroviral suppository drug delivery.

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.

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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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