APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

International Association for Pharmaceutical Technology

Newsletter ISSUE 1/2021 - May

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DRUG DELIVERY EVENTS

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- **Skin Forum 2021 Annual Meeting | CN 6833** Details
  14.09. - 15.09.2021 | Bratislava, Slovakia
- **13th EuPFI Conference 2021 -** Formulating better medicines for children **| CN 6841** Details
  22.09. - 23.09.2021 | virtual event platform

Suggest a meeting to be announced!

APV NEWS

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Provided by Dr. Peter van Hoogevest, PHARMANOVATION Consulting

Webinar on "The Importance of Drug Delivery in the Combat of COVID-19"

On Tuesday, February 9, 2021, from 13.00 -18.30 CET, the APV Focus Group Drug Delivery organised a webinar on "The Importance of Drug Delivery in the Combat of COVID-19". The purpose was to highlight the impact of enabling innovative drug delivery technologies on the effectiveness and the applicability of APIs or vaccines in the fight against Covid-19 infection. One focus was given to different vaccines types and their requirements and options for delivery. The opportunities and challenges of the lipid nanoparticle technology for vaccine delivery were shown. Furthermore, a critical consideration of stability and cold chain supply requirements for mRNA and vector-based vaccines were presented. The opportunities to treat COVID-19 infection by inhaled therapies were reviewed. Finally, attention was paid to the development of antiviral therapies by means of the antiviral Remdesivir. Six reputed scientists in the area were invited to give lectures of ca. 45 min each.

After the welcome address made by Peter van Hoogevest, PhD (Head Scientific Department, Lipoid GmbH,

Ludwigshafen, Germany), Prof. Gerrit Borchard, PhD (Section of Pharmaceutical Sciences, Institute of Pharmaceutical Sciences of Western Switzerland – ISPSO, University of Geneva, Switzerland) gave an excellent introduction to the topic with the title "Our only hope: Vaccines, an introduction" on the development of vaccines and their action mechanisms. Then Prof. Daan Crommelin, PhD (Emeritus Professor, Pharmaceutics University of Utrecht, Netherlands) gave an interesting seminar on "Addressing the cold reality of mRNA and viral vector based COVID-19 vaccine stability". He highlighted the stability issues of the current delivery systems and mRNA and gave examples of how the stability, by using especially freeze-drying, could be improved and the logistical difficulties of cold-chain supplies avoided. Dominik Witzigmann, PhD (Nano Medicines Innovation Network (NMIN), Canada), gave a seminar on "Lipid nanoparticle technology enabling therapeutics and vaccines for COVID-19". He reviewed the research and development of the lipid particles used nowadays for the COVID-19 vaccines of BioNtech and Moderna and the product Onpattro and related (phospho)lipid excipients. The production aspects of lipid particles and liposomes were addressed in more detail by David Jung (Manager - Process Equipment Design, Evonik Canada, Inc, Canada) in his seminar on "Overcoming challenges of manufacturing and fill/finish of lipid nanoparticles for mRNA delivery". Since COVID-19 is mainly related to the occurrence of lung infections, the search for an inhalation therapy could make sense. David Cipolla, PhD; MS (Chemical Engineering, Vice President of Research, Insmed Incorporated, USA) reviewed the ongoing R&D efforts in this area extensively. The course was concluded by the seminar of Laura Bauer (Research Scientist II, Gilead Sciences Inc, USA) on "Remdesivir drug product manufacturing response to the COVID-19 pandemic", describing the challenges of the formulation development and scale-up of a parenteral formulation for this poorly water soluble compound.

The event was well received and gave a very good overview on the role and impact of drug delivery on the prophylaxis and treatment modalities of COVID-19. About 32 participants from all over the world attended the webinar. Especially the format of a limited number of reviewing seminars and the possibility of simultaneously connecting many scientists in many time zones was highly appreciated. The APV Focus Group Drug Delivery thanks the speakers for their valuable contributions.

Interested in Hearing More?
If this article has whet your appetite for more information on this topic, the next webinar on "The Importance of Drug Delivery in the Combat of COVID-19" will be held on 24 June 2021. You can register online at www.apv-mainz.de.

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosemayr-Templeton

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Covid-19) have been at the forefront of the news over the past few months. However, despite the plethora of information and discussion in the mainstream media concerning the vaccines themselves and the challenges posed by their mass production and roll-out, little had been said about the critical role drug delivery plays in leveraging the effectiveness of those based on messenger RNA (mRNA). In this short review of recently approved drug delivery products, the focus is on the first three vaccines approved by the EMA (Comirnaty® from Pfizer/BioNTech and the Covid-19 vaccines from Moderna and AstraZeneca (now known as Vaxzevria™).
These are the most commonly administered in Europe and offer so much hope for ending the human suffering and economic damage brought about by the Covid-19 pandemic and the measures taken to control it.

Introduction

All three of the Covid-19 vaccines, which will be discussed, function by stimulating an immune response against the spike protein which decorates the surface of SARS-CoV-2 [1-3]. The spike protein is responsible for giving the virus its characteristic halo or corona which is common to all members of this virus family. This transmembrane glycoprotein plays a critical role in viral infection as viral entry to cells begins with its binding to angiotensin-converting enzyme 2 (ACE2) receptors present on the surface of many cell types including those in the respiratory tract and deep lung. Once inside the cell the virus replicates using the cell's own systems, thus, enabling the formation and release of new virus particles capable of causing further infection [4-5].
The vaccines are all nanoparticulate dispersions injected intra-muscularly. They contain either lipid nanoparticles loaded with mRNA coding for the spike protein or an adenoviral vector containing the DNA code for the same protein. The nanoparticles/vectors are taken up by endocytosis into macrophages and dendritic cells at or close to the injection site and in the associated lymph nodes. Once inside the cell the mRNA/or viral vector escapes the endosome into the cytoplasm and translation of the genetic information into the spike protein occurs.
The presence of the spike protein initiates a chain of events which results in both the production of neutralising antibodies and a targeted T-cell response. This response furnishes the body with the ability to recognise and mount a rapid defence against SARS-CoV-2 infection through the induction of memory T-cells, and memory B-cells capable of producing neutralising antibodies [6-7].

In the remainder of the article the three vaccines are discussed in detail.

Comirnaty®

On 21.12.2020 the European Commission awarded a conditional marketing authorisation for Comirnaty®, the first vaccine against Covid-19 approved in the EU, thus, paving the way for the start of a massive vaccination effort to inoculate the around 440 million people in the EU [1]. Comirnaty®, a mRNA vaccine developed by BioNTech SE (Mainz, Germany) in collaboration with Pfizer, is currently approved for use in those aged 16 years and over [7, 8], although an application has been recently submitted to the EMA for its use in children in the 12-15 years age range [9]. Two doses are administered with a recommended interval of three weeks between doses and a maximum interval of 42 days based on the clinical data submitted to the EMA [8, 10]. However, this interval was extended to up to 12 weeks in the UK in order to maximise the number of people inoculated with the limited vaccine supplies initially available [11].

The vaccine is a frozen concentrate for dispersion in a multidose vial which, following dilution with 1.8 mL of 0.9% saline, provides five or six 0.3 mL doses of 30 µg single-stranded, 5'-capped mRNA for the surface spike protein of the SARS-CoV-2 virus. The protein produced differs from that of the native spike protein by two mutations involving exchange of the natural amino acids for proline. The inclusion of proline at these two points in the spike protein structure is key as it constrains the protein into a pre-fusion conformation which boosts it antigenicity [8, 13]. The mRNA is manufactured by transcription from DNA templates in an in vitro cell-free environment. Its structure is optimised for chemical stability and for efficient translation in order to enable sufficient spike protein expression to establish the specific immune response before the mRNA is broken down. These modifications include replacement of uridine by modified N1- methylpseudouridine (m1ΨTP) and capping of the 5' prime end. These changes ameliorate the destructive response of the innate immune system to the mRNA itself [8, 13].

In order to deliver mRNA vaccines intracellularly and protect the mRNA from degradation by ribonucleases, the mRNA is embedded within lipid nanoparticles. These non-viral vectors contain a cationic or pH sensitive lipid to bind, condense and protect the mRNA through the interaction of the positive charge on the lipid with the negative charge on the molecule's phosphate groups. The lipid:mRNA complexes form the electron dense centre of the nanoparticles. The nanoparticles also typically contain a helper phospholipid, cholesterol and a lipid-polyethylene glycol (PEG) conjugate. The PEG-lipid conjugate is included to reduce non-specific protein adsorption on the nanoparticle surface and to increase nanoparticle stability. The PEG content has to be optimised as too much reduces the ability of the nanoparticles to interact with the cell and endosomal membranes. The role of the helper lipid and cholesterol in the nanoparticle formulation is to improve lipid bilayer formation and nanoparticle stability. Their presence has been demonstrated to impact positively on transfection, with the overall transfection efficiency being influenced by the ratios of the different lipids in the formulation [14-15].

In the case of Comirnaty® the nanoparticles contain the cationic lipid, ALC-0315, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) to complex the mRNA and facilitate its release under the acidic conditions within the endosome. The lipid-PEG conjugate is ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide. Both of these lipids have not been previously used in approved products in Europe and are considered novel excipients. The other two components of the nanoparticles are the zwitterionic phospholipid, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol. The DSPC readily forms lipid bilayers and, together with cholesterol, facilitates stable bilayer formation in formulations containing the cationic, ALC-0315. The other excipients include buffer salts and sucrose for pH control and cryoprotection [8, 13]. The lipid nanoparticle manufacturing process and analytical methods were developed by Polymun GmbH, Austria and the company is also involved in the vaccine's GMP manufacture [16].

The vaccine is packed in glass vials. The ability to extract six doses from the vial following dilution is dependent on the use of a syringe/needle with a dead-space of not more than 35 microlitres. Otherwise only 5 doses can be successfully extracted. The product (unopened vial) is stored at -90 °C to -60 °C but for transport/storage purposes it can be kept at -20°C±5°C for a one-time period of up to 2 weeks prior to being returned to -90 °C to -60 °C conditions. Once thawed the shelf-life has been recently increased from 5 days to 1 month at 2 °C to 8 °C, with up to 12 hours allowed for transportation and up to 2 hours when the unopened vial is stored at not more than 30 °C. Once diluted the vaccine is stable at 2°C to 30°C for 6 hours from a physical and chemical stand-point [8].

Comirnaty® was assessed in two clinical studies. The second of these, Study 2, is an ongoing Phase 1/2/3 randomised, placebo-controlled, observer-blinded trial conducted in various countries. In order to compress timelines, it was designed to achieve multiple goals: to investigate the impact of different doses, enable candidate selection and determine vaccine efficacy. Approximately 44,000 participants were involved in the Phase 2/3 part of the study. They were randomised to receive two doses of either the vaccine or a placebo injection 3 weeks apart. Data from 18,242 volunteers in the vaccine cohort and 18,379 in the placebo cohort were included in the analysis. The dose interval ranged from 19 to 42 days, with over 93% receiving the vaccine between 19 and 23 days after the first dose. These participants had not displayed symptoms or serological evidence of Covid-19 prior to Day 7 after administration of the second dose. The cohort also included a significant number of volunteers aged 65 years and above [8, 13].

The first primary assessment was COVID-19 infection after 7 days from the second dose in participants who had tested negative up until that point. Diagnosis of Covid-19 was based on at least the presence of one symptom and testing by reverse transcription-polymerase chain reaction (RT PCR). The surveillance time at the time of the analysis was 2,214 person-years for Comirnaty® and 2,222 person-years for the placebo injection.

The data showed that Comirnaty® displayed a 95% vaccine efficacy (95%, confidence interval (CI): 90.0, 97.9) when all subjects meeting the criteria were included. This did not decrease significantly if all participants over 16 years including those with previous Covid-19 infection were assessed: 94.6% (95% credible interval of 89.9% to 97.3%). The vaccine was also shown to be highly effective in volunteers likely to develop severe disease such as those with asthma, diabetes and/or a body mass index (BMI) ≥ 30 kg/m2. Typically, adverse reactions to Comirnaty® were mild or

moderate and short-lived. They included injection site pain, fatigue, headache, muscle pain and chills, joint pain, pyrexia and injection site swelling. Rare anaphylactic reactions have also been reported [8].
The clinical trial data is supported by information from a recent real-world observational study in Israel which matched almost 600,000 vaccinated individuals to the same number of non-vaccinated controls based on similar demographics and medical history. This study showed that 7 days after the second dose, vaccine effectiveness was judged to be 94% in preventing mild Covid-19 disease and 92% for severe Covid-19, thus, demonstrating that Comirnaty® works in real life situations [17].

COVID-19 Vaccine Moderna® Dispersion for Injection

This vaccine obtained an EU conditional marketing authorisation on 06.01.2021 [2]. It was developed by Moderna Inc. (MA, USA) [18]. Like Comirnaty®, its active moiety is a single-stranded, 5'-capped mRNA for the production of the SARS-CoV-2 viral spike protein. The mRNA is manufactured by cell-free in vitro transcription from DNA. The mRNA is translated in human cells into the full-length spike protein in its pre-fusion conformation. The conformation is constrained due to the presence of two proline substitutions in the heptad repeat 1 domain of the protein [19-20].
The mRNA is formulated in a lipid nanoparticle dispersion which is stored frozen. Each dose (0.5 mL) contains 100 µg of mRNA. The nanoparticles consist of SM-102, (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate), a proprietary ionisable lipid which interacts with the mRNA. They also contain the pegylated lipid, 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG), cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC). Other excipients include buffer salts, sucrose and water for injections [19].
The vaccine is approved for adults 18 years of age and over. The posology is two doses of 0.5 mL by intramuscular injection recommended to be separated by 28 days. The vaccine is more stable than the Pfizer/BioNTech one. Current stability data enables the unopened vials to be stored in a freezer (-15°C to -25°C) for 7 months, at 2°-8°C for 30 days and at 8°C to 25°C for up to 12 hours following removal from the fridge. In-use stability data shows that the vaccine is chemically and physically stable for 6 hours between 2°C and 25°C once the vial has been punctured. Each multi-dose vial contains 10 doses ready for administration [19].
Approval was based on the results of a placebo-controlled, observer-blind Phase 3 trial involving 30,351 volunteers who had previously not suffered from Covid-19. Exclusion criteria included pregnancy, previous Covid 19 infection, immunocompromised individuals or those who had received immunosuppressant therapy in the last 6 months. The participants were evaluated for the development of the disease for a median time-period of 92 days with the interval ranging from 1 day to 122. Disease development was assessed by RT PCR and by a Clinical Adjudication Committee.
The efficacy analysis consisted of 14134 trial participants who had received COVID-19 Vaccine Moderna and 14073 who had received the placebo injection. They were administered the second dose 25 to 35 days after the first. The participants were aged between 18 and 94 years old (median 53). The study showed that the vaccine had an overall vaccine efficacy of 94.1 % (95% CI: 89.3, 96.8) with an incidence rate of SARS-CoV-2 infection per 1000 person years of 3.328. In those of 65 years and older the efficacy fell slightly to 86.4% (CI: 61.4, 95.2). The main side-effects reported in the Phase 3 trial were injection site pain, tiredness, headache, muscle and joint pain, chills, nausea/vomiting, axillary swelling/tenderness, fever, injection site swelling and redness. Rare anaphylactic reactions have also been reported [19].
The effectiveness of the Moderna vaccine has been demonstrated in a US Centers for Disease Control and Prevention (CDC) real-life study in healthcare employees [21]. The study monitored the effectiveness of both the Moderna and Pfizer/BioNTech vaccine in preventing SARS-CoV-2 infection, both symptomatic and asymptomatic, in 3950 volunteers over a 13-week period. The study showed that two doses of either vaccine reduced the risk of infection (as measured by nasal swab tests and RT PCR) by 90% at least two weeks after vaccination, while two or more weeks after the first dose the risk fell by 80%.

Vaxzevria™

The third Covid 19 vaccine approved in the EU was COVID-19 Vaccine AstraZeneca suspension for injection, now known under the tradename, Vaxzevria™. This vaccine, which was granted a conditional marketing authorisation on 29.01.2021 [3], was developed and commercialised through a collaboration between the Jenner Institute and Oxford Vaccine Group of Oxford University, UK and AstraZeneca. The collaboration is unusual in that it was agreed that the vaccine is sold not-for-profit during the pandemic, making it affordable for low to middle income countries [22].
The vaccine differs from the Pfizer/BioNTech and Moderna vaccines in that delivery and spike protein expression is effected through a replication-deficient viral vector. Each 0.5 mL dose contains not less than 2.5 × 108 infectious units (Inf.U) of replication-deficient chimpanzee adenovirus containing the code for SARS-CoV-2 Spike glycoprotein (ChAdOx1-S). This viral vector encodes for the spike protein fused to a tissue plasminogen activator (tPA) leader sequence. The viral vector particles each contain a single copy of the double-stranded DNA including the spike protein code and are between 80 and 100 nm in size [23-24].

The virus vector is manufactured in T-REx-293 cells. These are immortalised primary human embryonic kidney cells that have been modified with sheared human adenovirus serotype 5 (HAdV5) so that they can support production of the replication-deficient adenovirus. The protein produced is in the trimeric pre-fusion conformation. However, it is not stabilised in this form. The vaccine also contains L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate (dihydrate) and water for

injections. The vaccine posology is two 0.5 mL doses administered intramuscularly to adults 18 years and over, 4 weeks to 12 weeks apart [23-24].
The advantage with the AstraZeneca vaccine over its mRNA counterparts is that the unopened vials can be stored in a refrigerator which significantly simplifies the logistics of a mass vaccination program. Once opened the vaccine is stable for 48 hours at 2°C to 8°C. Within that period, it can kept at below 30°C for a maximum of 6 hours.

Efficacy data was calculated on the pooled results of an ongoing Phase 2/3 trial in the UK and a ongoing Phase 3 study in Brazil. Exclusion criteria included severe cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic and neurological disease, immunosuppression, pregnancy and those previously infected with the virus. The vaccine cohort were injected with two doses of 5 × 1010 viral particles (equates to not less than 2.5 × 108 infectious units per dose). The control in the trials was either saline or meningococcal vaccine. The dosing interval for 86.1% of the trial participants was 28 to 84 days.

In the efficacy analysis data from 6,106 subjects in the vaccine cohort and 6,090 in the control cohort was evaluated. Vaccine efficacy was assessed to be 62.6% (95% CI: 50.9; 71.5) following two doses administered 3 to 23 weeks apart. In those who received the second dose within 4 to 12 weeks, the vaccine efficacy was 59.5% (95% CI: 45.8, 69.7). This latter group consisted of 87% of participants in the 18-to-64-year-old age group. Unfortunately, the trials yielded insufficient data to evaluate the ability of the vaccine to protect older groups. Nevertheless, the EMA experts recommended the use of the vaccine in adults of 18 years and older based on the aforementioned efficacy data in younger people, the immune response and good safety profile observed in trial participants over 55 years and previous experience with other vaccines [3]. Despite this, a number of EU countries e.g., Germany and Austria, initially restricted its use to adults under 65 years.
The most side-effects experienced in the clinical studies resolved quickly and were of a mild to moderate nature. They included injection site tenderness (63.7%), injection site pain (54.2%), headache (52.6%), fatigue (53.1%), myalgia (44.0%), malaise (44.2%), pyrexia (includes feverishness (33.6%) and fever >38°C (7.9%)), chills (31.9%), arthralgia (26.4%) and nausea (21.9%). In general, the frequency and severity of the adverse reactions were less with the second dose.
The vaccine has been the subject of both positive and negative headlines pre-approval and post-approval. Firstly, pre-approval there was a dosing issue which resulted in around 3000 patients in the clinical studies receiving the first dose at 50% potency (with better vaccine efficacy results) and controversy over the use of this data in the initially released pooled results [25]. Secondly, there have been well-publicised issues with supply of this vaccine to EU countries. Most recently there has been concern about rare incidences of embolic and thrombotic incidents associated with thrombocytopenia being related to vaccine administration. So far analysis of this data by the EMA has concluded that the benefits of the vaccine still outweigh the risks. However, additional advice has been added to the product information [26] and since these rare events appear to more prevalent in younger women, some EU countries have restricted the vaccine to older age groups or have stopped its use [27].
On the positive side a study, conducted by the University of Edinburgh, UK and Public Health Scotland on Covid vaccine effectiveness showed that receiving the first dose of Vaxzevria™ reduced the need for in-patient treatment by 94% 28 to 34 days post-vaccination. At the time of the analysis around 490,000 people in Scotland had received the first dose of the AstraZeneca vaccine out of a total of 1.14 million vaccinated with a Covid-19 vaccine. In vaccinated adults of 80 years and above the vaccine effectiveness was 81% (95% CI: 65 to 90) which was also the same for the Pfizer/BioNTech vaccine [28].

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DRUG DELIVERY GROUPS

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Provided by Prof. Olivia Merkel, Domizia Baldassi and Bettina Schwarz

ACADEMIC GROUPS WITH FORMULATION CAPABILITIES FOR INHALATION AND INTRANSAL DELIVERY

This newsletter section is intended to give a brief overview of academic groups working on the development of formulations for inhalation and intranasal administration. It is part of an occasional series giving brief details of research teams exploring different aspects of drug delivery research. It is not intended to be a comprehensive list of those involved in the area. As it is a living document, our readers are most welcome to suggest other research teams they are aware of for inclusion in our next edition.

The contact person given is the head of the department or working group.

University

AUSTRIA

Research Focus	Pulmonary delivery, nanotoxicology
Institution	University of Vienna
Address	Department of Pharmaceutical Technology and Biopharmacy, Althanstrasse 14 1090 Wien
Contact	Lea Ann Dailey
eMail	leaann.dailey@univie.ac.at
Web site	https://medienportal.univie.ac.at/uniview/professuren/cv/artikel/univ-prof-dr-rer-nat-lea-ann-dailey/

BELGIUM

Research Focus	Mucosal and pulmonary delivery
Institution	Ghent University
Address	Laboratory for General Biochemistry and Physical Phamracy, Ottergemsesteenweg 460, 9000 Ghent
Contact	Koen Raemdonck
eMail	koen.raemdonck@ugent.be

Research Focus	Mucosal and pulmonary delivery
Institution	Louvain Drug Research Institute, UC Louvain
Address	Avenue Mounier 73/B1.73.12, 1200 Woluwe-Saint-Lambert
Contact	Rita Vanbever
eMail	rita.vanbever@uclouvain.be
Web site	https://uclouvain.be/repertoires/rita.vanbever

CANADA

Research Focus	Inhaled pharmaceutical aerosols
Institution	University of Alberta
Address	Aerosol Research Laboratory, T6G 2G8 Edmonton, Alberta
Contact	Warren H. Finlay
eMail	warren.finlay@ualberta.ca
Web site	https://sites.ualberta.ca/~arla/warren_finlay.html

Research Focus	Particle design for pulmonary and intranasal administration
Institution	University of Alberta
Address	10-269 Donadeo Innovation Centre For Engineering, 9211-116 St, Edmonton AB
Contact	Reinhard Vehring
eMail	reinhard.vehring@ualberta.ca
Web site	https://apps.ualberta.ca/directory/person/vehring

Research Focus	Pulmonary drug delivery, Aerosols
Institution	McMaster University
Address	Health Sciences Centre, 1200 Main Street West, Hamilton, Ontario
Contact	Myrna B. Dolovich
eMail	mdolovic@mcmaster.ca
Web site	https://fhs.mcmaster.ca/medsci/faculty/dolovich_myrna.html

DENMARK

Research Focus	Mucosal and pulmonary delivery
Institution	University of Copenhagen
Address	Department of Pharmacy, Universitetsparken 2, 2100 København
Contact	Camilla Foged
eMail	camilla.foged@sund.ku.dk
Web site	https://pharmacy.ku.dk/research/vaccine-design-delivery/

FRANCE

Research Focus	Mucosal and pulmonary delivery
Institution	Institut Galien Paris-Sud
Address	School of Pharmacy, Rue Jean Baptiste Clément 5 92290 Châtenay-Malabry
Contact	Elias Fattal
eMail	elias.fattal@u-psud.fr
Web site	http://www.umr-cnrs8612.universite-paris-saclay.fr/presentation_pers.php?nom=fattal

GERMANY

Research Focus	Drug delivery across mucosal barriers
Institution	Department Drug Delivery, Helmholtz Institute for Pharmaceutical Research Saarland
Address	Universitätscampus E8 1, 66123 Saarbrücken
Contact	Claus-Michael Lehr
eMail	Claus-Michael.Lehr@helmholtz-hips.de
Web site	https://www.helmholtz-hips.de/en/research/people/person/prof-dr-claus-michael-lehr/

Research Focus	Mucosal and pulmonary delivery
Institution	Ludwig-Maximilians University of Munich
Address	Department of Pharmacy, Butenandtstr. 5-13, Haus B, 81377 Munich
Contact	Olivia Merkel
eMail	olivia.merkel@lmu.de
Web site	https://www.cup.lmu.de/pb/aks/merkel/

Research Focus	Mucosal and pulmonary delivery
Institution	Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes
Address	Klinik für Innere Medizin V, Gebäude 41, 66421-Homburg
Contact	Robert Bals
eMail	m5.sekr @uks.eu
Web site	http://www.uniklinikum-saarland.de/de/einrichtungen/kliniken_institute/medizinische_kliniken/innere_medizin_v/klinik_team/unser_team/
Research Focus	Pulmonary drug delivery
Institution	Institute for Lung Biology and Disease, Helmholtz Zentrum München
Address	Ingolstädter Landstraße 1, 85764 Neuherberg
Contact	Otmar Schmid
eMail	otmar.schmid@helmholtz-muenchen.de
Web site	https://www.helmholtz-muenchen.de/ilbd/research/ilbdcpc-research-groups/pulmonary-aerosol-delivery-schmid-lab/scientific-focus/index.html

Research Focus	Pulmonary drug delivery, 3D in vitro models
Institution	Technische Universität Braunschweig
Address	Institut für Pharmazeutische Technologie und Biopharmazie, Mendelssohnstraße 1, 38106 Braunschweig
Contact	Stephan Reichl
eMail	s.reichl@tu-braunschweig.de
Web site	https://www.tu-braunschweig.de/pharmtech/institut/arbeitsgruppen/reichl/reichl

Research Focus	Pulmonary drug delivery, nasal, delivery, mucosal delivery
Institution	Christian-Albrechts-Universität zu Kiel
Address	Abteilung Pharmazeutische, Technologie und Biopharmazie, Grasweg 9a, R. T 202, 24118 Kiel
Contact	Regina Scherließ
eMail	rscherliess@pharmazie.uni-kiel.de
Web site	https://www.pharmazie.uni-kiel.de/de/pharmazeutische-technologie-und-biopharmazie

HONG KONG

Research Focus	Pulmonary delivery, RNA inhalation
Institution	University of Hong Kong
Address	Faculty of Medicine, 21 Sassoon Road, Pokfulam, Hong Kong SAR
Contact	Jenny K.W. Lam
eMail	jkwlam@hku.hk
Web site	https://www.jlamlab.hku.hk/

ICELAND

Research Focus	Intranasal drug and vaccine delivery
Institution	University of Iceland
Address	Faculty of Pharmaceutical Sciences, Hofsvallagata 53, 107 Reykjavík
Contact	Sveinbjörn Gizurarson
eMail	sveinbj@hi.is
Web site	https://uni.hi.is/sveinbj/

IRELAND

Research Focus	Pulmonary Biopharmaceutics
Institution	Trinity College Dublin
Address	Department of Pharmacy, College Green, Dublin 2
Contact	Carsten Ehrhardt
eMail	carsten.ehrhardt@tcd.ie
Web site	https://www.tcd.ie/research/profiles/?profile=ehrhardc

ITALY

Research Focus	Pulmonary delivery, inhalation
Institution	University of Naples Federico II
Address	Department of Pharmacy, Via D. Montesano 49, Studio C31 - IV piano
Contact	Francesca Ungaro
eMail	francesca.ungaro@unina.it
Web site	https://www.docenti.unina.it/francesca.ungaro

Research Focus	Intranasal and pulmonary drug delivery
Institution	University of Parma
Address	Department of Pharmacy, Parco Area delle Scienze 27/a, I° Piano, Corpo C Nord, 43124, Parma
Contact	Fabio Sonvico
eMail	fabio.sonvico@unipr.it
Web site	https://personale.unipr.it/en/ugovdocenti/person/15144

NETHERLANDS

Research Focus	Pulmonary drug delivery
Institution	University of Groningen
Address	Faculty of Science and Engineering, Nijenborgh 4, 9747 AG Groningen
Contact	Henderik Willem Frijlink
eMail	h.w.frijlink@rug.nl
Web site	https://www.rug.nl/staff/h.w.frijlink/

SPAIN

Research Focus	Nose-to-brain delivery, mucosal delivery
Institution	University of Santiago de Compostela
Address	CIMUS Research Institute, Avda. de Barcelona s/n, Campus Vida s/n, 15782, Santiago de Compostela, Spain
Contact	Maria Jose Alonso
eMail	mariaj.alonso@usc.es
Web site	https://www.usc.es/grupos/mjalonsolab/

SWITZERLAND

Research Focus	Pulmonary delivery, in vitro lung models, nanotoxicology
Institution	University of Fribourg
Address	Adolphe Merkle Institute, Chemin des Verdiers 4 CH-1700 Fribourg
Contact	Barbara Rothen-Rutishäuser
eMail	barbara.rothen@unifr.ch
Web site	http://www.am-institute.ch/about/people/staff/barbara-rothen

UNITED KINGDOM

Research Focus	Inhalation Biopharmaceutics
Institution	King's College London
Address	Franklin-Wilkins Building, Stamford Street London, SE1 9NH
Contact	Ben Forbes
eMail	ben.forbes@kcl.ac.uk
Web site	https://www.kcl.ac.uk/people/ben-forbes

USA

Research Focus	Mucosal delivery
Institution	John Hopkins University
Address	400 N. Broadway Baltimore, MD 21287
Contact	Justin Scot Hanes
eMail	hanes@jhmi.edu
Web site	https://www.hopkinsmedicine.org/profiles/results/directory/profile/4706886/justin-hanes

Research Focus	Inhaled therapeutics
Institution	UNC Eshelman School of Pharmacy
Address	120 Mason Farm Road, , CB# 7356, Chapel Hill, NC, 27599
Contact	Anthony Hickey
eMail	ahickey@unc.edu
Web site	https://pharmacy.unc.edu/directory/ahickey/

Research Focus	Development of inhalation drugs
Institution	University of Florida
Address	College of Pharmacy, 1225 Center Drive, Gainesville, FL 32610
Contact	Günther Hochhaus
eMail	hochhaus@cop.ufl.edu
Web site	https://pharmacy.ufl.edu/profile/hochhaus-guenther/

Research Focus	Pulmonary pharmaceutics and drug delivery
Institution	Virginia Commonwealth University
Address	School of Pharmacy, 410 N 12th Street, P.O. Box 980533
Contact	Sandro R.P. da Rocha
eMail	srdarocha@vcu.edu
Web site	https://app.pharmacy.vcu.edu/srdarocha

Research Focus	Intranasal drug delivery to the brain
Institution	University of Minnesota
Address	151 Oyster Point Boulevard, South San Francisco, CA 94080
Contact	Robert Thorne
eMail	thorne@dnli.com
Web site	https://www.pharmacy.umn.edu/bio/cop-experts/robert-thorne

Technologies

Pulmonary delivery is a drug administration route based on the inhalation of a drug formulation through the mouth. This allows a direct application of the therapeutic agent within the lungs.
Nasal delivery is a drug administration route for local and systemic delivery. A special application is the intranasal delivery from nose to the brain to bypass the blood brain barrier.

QUALITY BY DESIGN AND ITS APPLICATIONS IN BASIC (NANOMEDICINE) RESEARCH: A PHD STUDENT PERSPECTIVE

[1]Department of Pharmaceutical Technology and Biopharmaceutics Martin-Luther-University Halle-Wittenberg 06120, Halle (Saale), Germany. E-mail: paul.neumann@pharmazie.uni-halle.de
[2]Department of Pharmaceutical Technology and Biopharmacy University of Vienna, Vienna, 1090 Austria.
E-mail: leaann.dailey@univie.ac.at

1. Quality by design: Historical development

Quality has manifold definitions, for example it can be understood as excellence, value, conformity to specifications, conformity to requirements, fitness for purpose, loss prevention and meeting and/or exceeding customer expectations [1]. Quality gurus such as Philip Bayard Crosby, Joseph M. Juran and W. Edwards Deming began to shape the foundations and establishment of quality management systems, which were first applied in the steel and automotive industries before also finding application in the pharmaceutical industry. Until the uncovering of the serious and dramatic undesirable side effects of Elixir Sulfanilamide (1937) and thalidomide (1957), the pharmaceutical market was minimally regulated [2]. As a result of these tragedies, a number of regulations were successively introduced. However, the modern era in terms of product quality in the pharmaceutical industry did not really begin until 2004 with a FDA concept paper entitled "Pharmaceutical cGMP for 21st Century". Subsequently, the ICH established basic regulatory guidelines, namely Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality Systems) [4], which in combination form the basis for the quality by design concept for the production of high-quality medicinal products.

The term 'Quality by Design' was first used by Juran in 1985, when the first draft of his book was made available to some industry representatives; while access to the wider public was provided in 1992 through publication of his book [3]. The fact that increased testing does not necessarily improve product quality led to the philosophy: "quality cannot be tested into products but it should be built in or should be designed". According to ICH Q8 (R2), QbD is "a systematic approach to drug development that emphasizes the need to start with predefined goals and understand the product and process based on sound science and quality risk management" [4]. Thus, this philosophy can be seen as an experimental design philosophy that emphasizes the value of thorough intellectual planning before starting laboratory studies. Additionally, QbD principles extend beyond development into the product lifecycle, providing a solid framework for the transfer of product knowledge and process understanding from drug development to commercial manufacturing processes, as well as for changes and optimizations after the development phase [5].

2. Where does quality by design fit into an academic research setting?

Technological advances and newer, sometimes more complex therapeutic approaches are changing the landscape of drug delivery. Especially basic research in drug delivery is becoming more interdisciplinary and many new drug delivery platforms are coming from chemistry, physics, biology, biotechnology, and engineering labs. This changing environment has injected fresh ideas and exciting new technologies into basic drug delivery research however the challenges of translation remain the same. In many cases, new technologies bring an even higher level of complexity which makes translation an even greater challenge. When working in a highly interdisciplinary research team, one important role of the pharmaceutical scientist is to provide input to team members without a background in pharmaceutical development on how to address the challenges related to research translation.

However, even pharmaceutical scientists in academia, especially young researchers, sometimes have incomplete knowledge of how QbD is implemented in the pharmaceutical industry. There are also very few detailed practical examples published in the wider literature, which can be used as a guidance for academic researchers wanting to learn more about QbD and its advantages for pharmaceutical research. One excellent exception is the detailed commentary published by Troiano et al [6] in 2016 entitled “A Quality by Design Approach to Developing and Manufacturing Polymeric Nanoparticle Drug Products”. This excellent overview provides a detailed but clear description of how quality by design was implemented in the development of a relatively complex nanomedicine formulation, the main elements of which are shown in simplified form in Figure 1.

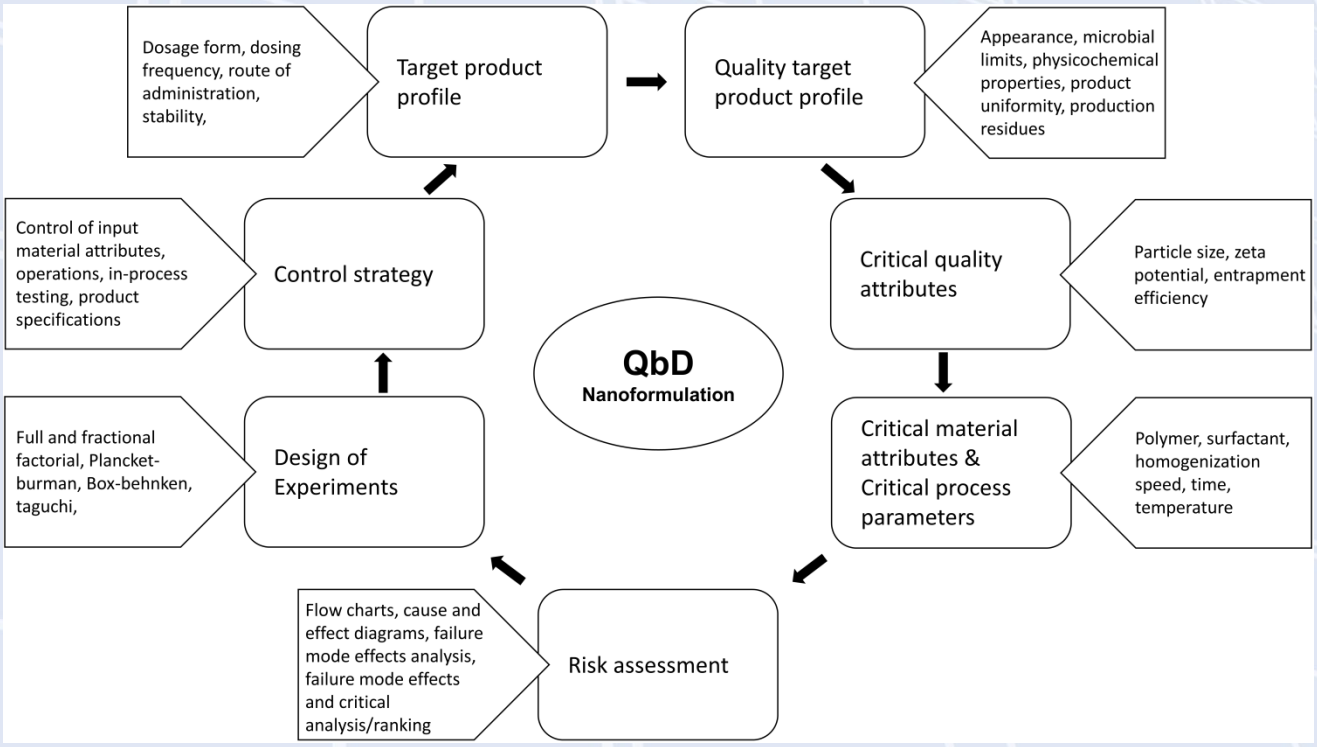

Figure 1: Main elements of the QbD concept in simplified form as applied to a nanomedicine [6,7].

An early application of selected QbD concepts from Figure 1 in the academic research setting can be a useful teaching tool for early career researchers, can save time and financial resources as well as enhance the value proposition of the work, especially if translation towards clinical applications is the goal [8]. These aspects will be briefly discussed.

- **A teaching tool for early career researchers**

One useful application of QbD in academic pharmaceutical research lies in the training of young researchers, who often have little experience of both the pharmaceutical industry and general scientific study design. QbD can help PhD students to learn the basics of good study design by providing an established and validated experimental design framework that can be readily adopted by young researchers to structure their own projects [8].

The learning process begins with the theoretical development of a putative target product profile (TPP) for a given research project, for example a nanomedicine. A prospective summary of the ideal product requirements is reflected in the target product profile (TPP), which will be the main project driver. Based on the TPP of the theoretical formulation and patient needs, a summary of the essential product characteristics needed to ensure the desired quality in terms of product safety and efficacy is compiled, the quality target product profile (QTPP). For the development of the QTPP, a comprehensive knowledge of the quality standards of the pharmacopoeias with regard to the planned dosage form/administration form is required. The QTTP can be seen as a link between the biological performance and the physicochemical characteristics of the formulation. In a subsequent step, young researchers can use their QTTP to identify the critical quality attributes (CQA), which can be physical, chemical, biological or microbiological properties or characteristics of a drug product, which should be within a defined specification range to ensure the desired product quality. Since CQAs are usually closely related to the materials and processes used, critical material attributes (CMA) and critical process parameters (CPP) can also be derived [1-5].

Although this process of conceptualization has become second nature to pharmaceutical scientists in the industry, it has not yet embedded itself as the norm in academia, as is illustrated by the relatively unstructured approach to the assessment of CQAs in research publications investigating novel drug delivery platforms. If we use the example of nanomedicine formulations, as depicted in Figure 1, the majority of nanomedicine research publications include common CQAs such as nanoparticle size, zeta potential and entrapment efficiency, but omit other important quality attributes such as sterility and endotoxin content (in platforms that would obviously be classified as parenteral products), product yield, content uniformity, residual solvents or reaction products, stability studies, etc. Furthermore, when the results of physicochemical characterisation studies are reported, they are rarely interpreted in the context of defined acceptance criteria and pharmacopeial quality standards for a particular product type or application route, such as a parenteral product for intravenous injection. It can be admittedly quite challenging to determine theoretical product specifications and acceptance criteria for new technologies at the early research stage, yet the understanding gained from this intellectual exercise is a further important teaching tool for young researchers.

- **Re-enforcing the concepts of knowledge and design space in research publications**

The pressure from journal editors and reviewers to publish only the most novel and interesting observations from a research study has contributed to the trend that many scientific articles in higher impact journal contain only a very narrowly focused and highly selective set of data. This form of “cherry picking” within data sets results has been linked to the difficulties in translating novel academic findings into the clinic, because it often results in a less than complete picture of the strengths and limitations of a new discovery or technology [9,10].

In the academic sector of drug delivery related research, there is still a strong prevalence of “one factor at a time” experimental designs, which provide the advantage that they are straightforward to understand, especially for young researchers, but can also result in a random selection of experimental conditions, which fail to create a comprehensive understanding of process and material characteristics as well as the interactions between variables. In contrast, the QbD experimental philosophy promotes factorial design-based approaches (i.e. Design of Experiments) that can account for both multiple variables as well as their interactions [1]. These considerations date back to the 1920s, when Ronald Aylmer Fisher introduced basic procedures in the design of experiments in the field of agricultural research, such as repetitions, random sequences, block formation and blending. DOE helps to determine the relationship between the process influencing factors, and the properties of the product. Using computer-aided process design and process simulation, simultaneous evaluation of different factors can be realized in a systematic way with a minimum of experiments. This comprehensive knowledge allows the identification of variables over a wide experimental range, the region of operability, also known as knowledge space. The area within the knowledge space where consistent quality can be achieved is called the design space. (Figure 2) [2,4]. Since many PhD programmes do not always include a formal training component, DoE and other multivariate experimental design methodologies are not always taught in a formal way to early career researchers. Inclusion of advanced experimental design methodologies in doctoral training schools could therefore benefit early career researchers [8].

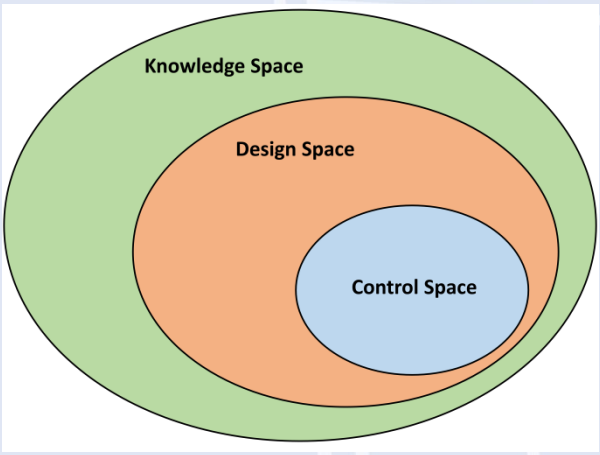

Figure 2: QbD interdependencies. Schematic representation of the relationship between knowledge, design, and control space.

3. Selected examples of QbD inspired approaches in basic (nanomedicine) research

While examples of QbD have been continually present in academic research publications focusing on more conventional dosage forms, there are fewer explicit examples in publications of newer technology platforms, for example in the nanomedicine or immunotherapy fields (see Table 1 for selected examples where QbD was usefully implemented). Organizations such as the Nanotechnology Characterization Laboratory [11] and the European Nanomedicine Translational Hub [12] have been instrumental in provided guidance in the form of standard operating procedures and one-on-one consulting services, but often this information reaches many academic researchers only after a proof-of-concept stage has been reached and they are now focused more on translation. At this point, however, testing pharmaceutical quality into a new drug delivery platform may be too late. Instead, instilling a wider awareness about QbD-inspired approaches to experimental design in academic research might address some of the challenges in translating academic research towards viable products.

Table 1:

Selected recent publications applying a QbD inspired approach	Ref.
Improving the oral bioavailability of multi-kinase inhibitor loaded nanoparticles	[13]
Optimisation of PEG-PLGA nanomicelles for targeted cancer therapy	[14]
Optimization of the spray drying process for the drying of risperidone nanosuspension	[15]
Optimization of estrogen functionalized chitosan nanoparticles loaded with doxorubicin-estrone conjugates	[16]
Fabrication of nanostructured lipid carrier to encapsulating efavirenz	[17]
Production process optimization of electrosprayed nanoparticles and electrospun fibers for coating of microneedles	[18]
Conjugated polymer nanoparticles as fluorescent/photoacoustic contrast agent for cancer diagnostics	[19, 20]

4. How can industry help academia?

One of the difficulties facing academic researchers with regard to implementation of QbD principles in their work is the lack of detailed and relevant examples from industry across a wide range of different formulation types. As Jesus Zurdo and colleagues have stated [21], “The definition of a relevant QTPP is not a simple task. It does require the involvement of technical experts from multiple disciplines and areas of development (discovery, manufacturing, and clinical development), supply chain, distribution, and so forth. Most importantly, it should also incorporate key input needs and requirements from end-users or what in QbD nomenclature is known as the ‘voice of the customer’.” In basic pharmaceutical research many of these inputs are not available. However, it can also be postulated that the more academic researchers understand about the real-world challenges of drug product development, the better the chances of designing novel technologies with better chances of successful translation. Researchers involved in industrial drug product development can help academic researchers embed QbD inspired experimental design in one or more of the following ways:

- **Publish more examples** of TPP, QTPPs, CQAs, CMAs and CPPs for a variety of formulation types in scientific journals, especially those with an interdisciplinary emphasis. In our own field of research, we have found the commentary paper by Troiano et al [6] to be an exceptionally useful example, due to the high level of detail provided as well as the clear explanations of the QbD process in an industrial nanomedicine development project.
- **Participate in doctoral training.** Many companies collaborate with a wide range of academic research institutes and can become involved in training young researchers. Development of an interactive course on QbD-inspired experimental design for doctoral training programmes could be one way to rapidly engage young researchers with the benefits of QbD in an academic research setting.
- **Influence the peer-review process**. Although many industrial researchers are not routinely involved in the scientific peer-review process, it is a powerful tool to engage in culture change within publication practices. Scientific peer-review offers a direct opportunity to communicate with researchers directly and discuss the merits of a more comprehensive experimental design process with an emphasis on pharmaceutical quality, if not necessarily for the study under review, then at least for future studies.

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DRUG DELIVERY PEOPLE

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Provided by Prof. Dr. Lea Ann Dailey

For this issue of the Newsletter, we would like to introduce Peter Kleinebudde as our featured Drug Delivery Scientist. Peter is a pharmacist by training and completed his PhD in Pharmaceutical Sciences at the University Kiel in 1987. He then worked for Glaxo GmbH in Germany in the area of pharmaceutical development and bulk manufacturing. He later returned to the University of Kiel for his habilitation after which he was offered the position of associate professor at the University Halle-Wittenberg in 1998. From 2002 to 2003 he was the Dean of the School of Pharmacy in Halle before being offered a chair in Pharmaceutics and Biopharmaceutics at the Heinrich-Heine-University Duesseldorf in 2003. Since 2019 he is Dean of the Faculty of Mathematics and Natural Sciences.

Peter's main research interests focus on solid dosage form design and developing pharmaceutical process technology in areas such as roll compaction/ dry granulation, extrusion and coating. As an expert in these technologies, he has published over 280 peer-reviewed papers and has given more than 250 invited lectures. He is an active member of several scientific societies including the AAPS, APV, DPhG, Dechema and VDI. He was president of the International Association for Pharmaceutical Technology (APV) from 2002 to 2010 and chair of the APV focus group Solid Dosage Forms from 2010 to 2016. He is a member of the editorial boards of the AAPS PharmSciTech, Acta Pharm Hung, Eur J Pharm Biopharm, Int J Pharm, J Pharm Sci and Pharm Dev Tech. He was a founding member of the Pharmaceutical Solid State Research Cluster in 2006. From 2004 to 2020 he was a (deputy/full) member of the German Pharmacopoeia Commission and worked for the expert group Pharmaceutical Technology, the last five years as chair. For ten years, the last three as chair, he was also a member of the Powder Working Party and for six years a member of Group 12 of the European Pharmacopoeia.

RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

Amorphous Systems, Co-salts, Solid dispersions

Systematic screening of pharmaceutical polymers for hot melt extrusion processing: a comprehensive review

Thakkar R, Thakkar R, Pillai A, Ashour EA, Repka MA Int J Pharm. 2020 Feb 25;576

In this review, a stepwise discussion of techniques useful to screen and select polymers suitable for hot melt extrusion processing is explored and reported.

Intrathecal/Intracranial delivery

Current Nanoparticle Approaches in Nose to Brain Drug Delivery and Anticancer Therapy - A Review

Ansari MA, Chung IM, Rajakumar G, Alzohairy MA, Alomary MN, Thiruvengadam M, Pottoo FH, Ahmad N. Curr Pharm Des. 2020;26(11):1128-1137

By using nanotechnology-based nanoparticles (NPs) targeted drug delivery can be improved across blood-brain barrier (BBB) with discharge drugs in a controlled manner. NPs confer safe from degradation phenomenon. Several kinds of NPs are used for nose to the brain (N2B) enroute, such as lipidemic nanoparticles, polymeric nanoparticles, inorganic NPs, solid lipid NPs, dendrimers. Among them, popular lipidemic and polymeric NPs are discussed, and their participation in anti-cancer activity has also been highlighted in this review.

New modalities (siRNAs, LNAs, Oligonucleotides etc.)

Nanocarrier Mediated siRNA Delivery Targeting Stem Cell Differentiation

Fernandes F, Kotharkar P, Chakravorty A, Kowshik M, Talukdar I. Curr Stem Cell Res Ther. 2020;15(2):155-172

Stem cell-based regenerative medicine holds exceptional therapeutic potential and hence the development of efficient techniques to enhance control over the rate of differentiation has been the focus of active research. One of the strategies to achieve this involves delivering siRNA into stem cells and exploiting the RNA interference (RNAi) mechanism. The various nanomaterials that are currently being explored and discussed in this review include liposomes, carbon nanotubes, quantum dots, protein and peptide nanocarriers, magnetic nanoparticles, polymeric nanoparticles, etc. This review also includes discussion on siRNA co-delivery with imaging agents, plasmid DNA, drugs etc. to achieve combined diagnostic and enhanced therapeutic functionality, both for in vitro and in vivo applications.

Nanosystem-based Drug Delivery

Role of Nanobiotechnology in Drug Delivery

Jain KK. Role of Nanobiotechnology in Drug Delivery. Methods Mol Biol.

2020;2059:55-73

The paper gives a brief overview of the use of nanobiotechnology in drug delivery.

Stimuli-responsive charge-reversal nano drug delivery system: The promising targeted carriers for tumor therapy

Fang Z, Pan S, Gao P, Sheng H, Li L, Shi L, Zhang Y, Cai X. Int J Pharm. 2020 Feb 15;575

This paper discussed the recent advances in the study of charge-reversal nanocarriers that could control the distribution of drugs in response to specific stimuli, such as pH, reduced glutathione (GSH) concentration, enzyme concentration, light and thermal stimulation. The applications of CRNDDS (charge-reversal nano drug delivery system) in the tumor treatment was also analyzed and summarized.

Pulmonary Drug Delivery

Respiratory Tract: Structure and Attractions for Drug Delivery Using Dry Powder Inhalers

ElKasabgy NA, Adel IM, Elmeligy MF. Respiratory Tract: Structure and Attractions for Drug Delivery Using Dry Powder Inhalers. AAPS PharmSciTech. 2020 Aug 21;21(7):238.

In this review, different types of inhaler devices are illustrated like metered dose inhalers (MDIs), dry powder inhalers (DPIs), nebulizers, and the new soft mist inhalers (SMIs).

Oral Drug Delivery

Trends in the production methods of orodispersible films

Musazzi UM, Khalid GM, Selmin F, Minghetti P, Cilurzo F. Int J Pharm. 2020 Feb 25;576

This review critically discusses current trends in the technology platforms proposed to manufacture ODF, including the innovation and opportunities to produce very small batches in a pharmacy setting.

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

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

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

Emerging Applications of Drug Delivery Systems in Oral Infectious Diseases Prevention and Treatment. Molecules

Liang J, Peng X, Zhou X, Zou J, Cheng L.Molecules. 2020 Jan 24;25(3):516

In the review, emerging recent applications of DDS in the treatment for oral infectious diseases have been summarized, including dental caries, periodontitis, peri-implantitis and oral candidiasis. Furthermore, oral stimuli-responsive DDS, also known as "smart" DDS, have been reported recently, which could react to oral environment and provide more accurate drug delivery or release. In this article, oral smart DDS have also been reviewed. The limits have been discussed, and the research potential demonstrates good prospects.

ABOUT THE FOCUS GROUP

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

COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

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

Our mission includes in particular the following tasks:

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

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

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

MEMBERS OF THE APV DRUG DELVIERY FOCUS GROUP:

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

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

Martin Bornhöft, PhD
APV Office, Mainz (D)

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

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

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

Bernd Riebesehl, PhD
Novartis Pharma, Basel (CH)

Lea Ann Dailey, PhD
University of Vienna (A)

Andrea Engel, PhD
Evonik Corporation, (US)

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

Karsten Cremer, PhD
Pharma Patents, Basel (CH)

Florian Unger, PhD
Bayer, Wuppertal (D)

Peter van Hoogevest, PhD
PHARMANOVATION Consulting (D)

Simone Wengner, PhD
Catalent, Eberbach (D)

Uwe Hanenberg, PhD
Catalent, Schorndorf (D)

EDITORIAL GROUP OF THE NEWSLETTER

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

contact us: drug_delivery@apv-mainz.de