GAZETTE

Information days

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"Deadline for abstract submission: 15 November 2018!"

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2018
N°33

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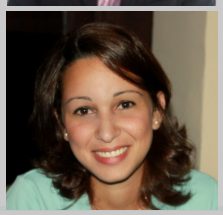

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APGI Thesis Award 2018

SANOFI

The "APGI YOUNG INVESTIGATOR AWARD" (sponsored by Sanofi and delivered jointly by SANOFI and APGI) recognizes the most outstanding doctoral thesis in the field of Pharmaceutical Technology each year.

If you defended your PhD thesis between 15 November 2017 and 14 November 2018, you can candidate for the 2018 "APGI YOUNG INVESTIGATOR AWARD". ***(page 16)***

Editorial

Dear Colleagues,

So far, 2018 has already been a very successful year for our society, with the **11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology,** which was held in **March in Granada:** More than 1300 participants from all over the world attended this conference, and a new record of exhibitors was achieved at the accompanying exhibition: "ResearchPharm".

Please note that the **15 November 2018 is the deadline for abstract submission** for the next meeting that we will jointly organize together with our German and Italian friends (the APV and ADRITELF): The **3rd Conference on Pharmaceutics**, which will be organized in **Bologna**, Italy, on **25-26 March 2019**. It is the continuation of the very successful new series of biannual meetings, which are held in all the uneven years. The first conference of this type was held in Reims, France, in 2015; the second in Krakow, Poland, last year. It is a 2 days meeting (Monday and Tuesday), including invited lectures, short talks selected from submitted abstracts, poster presentations and an industrial exhibition. Selected hot topics in Bologna include "*Manufacturing equipment and technologies*", "*Nanomedicines*", "*Arising new manufacturing technologies*", and "*Advances in oral drug delivery*".

On **27 November** we will organize an **APGI Information Day with Evonik** on **Oral solid dosage forms** - Formulation strategies and manufacturing approaches for challenging drugs at the CNAM in downtown **Paris**. Experts in the field will talk about their experience on functional polymers for targeted drug delivery, poorly soluble drugs, biopharmaceuticals and many other interesting topics.
Please note that the APGI Information Days are free of charge for APGI members. Also, if you subscribe now to the APGI, your subscription will also be valid in 2019. This means that you can benefit from reduced registration fees for events organized (or co-organized) next year.

The next year will start with a new type of event: For the first time, we will co-organize a **conference on "Advances in Formulation of Active Ingredients" with the Formulation Group of the French Chemical Society (SCF).** The meeting will be held on **10-11 January 2019 in Lyon**. It will be a perfect occasion for experts from industry and academia working in the field of pharmaceutical or cosmetic formulation development to meet and discuss. Specific focusses include: Materials/ Biomaterials; Formulations for cutaneous or mucosal administration; Nanoparticles: nanomedicine, toxicology and regulation; Process Engineering, characterization & modelling.

In 2019, we will also organize a ***Skin and Formulation & Skin Forum Meeting*** **on 23-24 September 2019 in Reims**, together with our English friends. The conference will be jointly organized by the APGI and "Skin Forum", following up the great success of this type of event in 2009. The meeting will be a perfect occasion for scientists in the pharmaceutical and cosmetic fields to exchange and get an update on the most recent developments from an industrial and academic perspective.

And please already safe the date for the **12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology**, which will be held in **Vienna, Austria** on **23-26 March 2020**!

Looking forward to seeing you at one of our upcoming events!

Prof. Juergen Siepmann
President of APGI

3rd European Conference on Pharmaceutics

25-26 March 2019, Bologna, Italy

Three years ago, we decided to create a new series of international, biannual meetings with our German and Italian friends (the APV and ADRITELF). The idea was to "fill the gaps" between the World Meetings on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, which are held in all the even years.

The first meeting of this new series of events was the 1st European Conference on Pharmaceutics, which was held in Reims, and which was a great success with more than 600 participants from all over the world. This was followed by another great success in Krakow, Poland, for the 2nd European Conference on Pharmaceutics. The next meeting of this type will be held in the lovely town of Bologna, in Italy, which is easy to reach by plane and train from all over the world.

Intentionally the European Conferences on Pharmaceutics are different from the World Meetings on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology: They are held on only 2 days (Monday and Tuesday) and all breaks and lunches are included. They are served in the exhibition and poster presentation area to allow for facilitated exchanges between scientists from industry, academia and regulatory authorities. And this includes the next generation: PhD students and post-docs.

The overall programme structure is as follows:

Very interesting hot topics will be treated in Bologna, namely:

Manufacturing equipment and technologies
Nanomedicines
Arising new manufacturing technologies
Advances in oral drug delivery.

Outstanding scientists from all over the world will give cutting edge presentations, including:

Stefaan de Smedt, University of Ghent, Belgium: Cytosolic delivery of biotherapeutics: the struggle with biological barriers goes on
Giustino di Pretoro, Johnson & Johnson, Germany: Continuous processing – what does the future of pharmaceutical manufacturing look like?
Iris Ziegler, Corden Pharma, Germany: Containment/High-potent drugs
Odra Pinato/Annalisa del Nevo, Stevanato Group, Italy: Innovative packaging
Julien Nicolas, University of Paris-Sud, France: New polymer-based drug delivery systems for cancer therapy
Paolo Gatti, Aptuit, Italy: Drug product nanotechnologies: formulation and process aspects from laboratory to production plant
Maria José Blanco-Prieto, University of Navarra, Spain: Nanotargeting of the heart

Monday, 25 March 2019

09:00 – 09:15	Opening		Posters	Exhibition
09:15 – 10:15	Plenary lecture			
10:15 – 10:45	Coffee break			
10:45 – 12:45	Invited talks	Short talks		
12:45 – 15:00	Lunch			
15:00 – 17:00	Invited talks	Short talks		
17:00 – 19:00	Welcome reception			

Tuesday, 26 March 2018

09:00 – 11:00	Invited talks	Short talks	Posters	Exhibition
11:00 – 11:30	Coffee break			
11:30 – 11:45	Awards			
11:45 – 12:45	Plenary lecture			
12:45 – 15:00	Lunch			
15:00 – 17:00	Invited talks	Short talks		

3rd European Conference on Pharmaceutics

25-26 March 2019, Bologna, Italy

Romána Zelkó, Semmelweis University, Hungary: Electrospinning and its applications in pharmaceutics
Guy van den Mooter, University of Leuven, Belgium: Electrospraying in drug formulation
Alice Melocchi, University of Milan, Italy: Drug printing technologies
Paola Minghetti, Univeristy of Milan, Italy: From the idea to the bedside: is the regulatory path coherent with patients' expectations?
Werner Weitschies, University of Greifswald, Germany: Novel in vitro test methods for predicting the performance of oral dosage forms in the gastrointestinal tract
Axel Zeitler, University of Cambridge, United Kingdom: New insights into tablet porosity and its critical role in oral drug delivery
Marc Schiller, Gruenenthal, Germany: Innovation in solid oral dosage forms - an industrial view

As in the past, the conference will be accompanied by an industrial exhibition, giving the opportunity to learn about the most recent advances in the broad field of pharmaceutics.

For more detailed information, please have a look at the meeting's website

www.europeanmeeting.org

and download the most recent announcement.

Looking forward to meeting you in Bologna!

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Silver Sponsor

BOSCH
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11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

19-22 March 2018, *Granada, Spain*

Report

The conference was jointly organized by APV (German "International Association for Pharmaceutical Technology"), A.D.R.I.T.E.L.F. (Italian "Associazione Docenti Ricercatori Italiani di Tecnologie e Legislazione farmaceutiche") and APGI (French "International Society of Drug Delivery Sciences and Technology). The opening ceremony started on Monday evening with the participation of Prof. Joerg Breitkreutz (President of APV), Prof. Anna Maria Fadda (President of A.D.R.I.T.E.L.F) and Prof. Juergen Siepmann (President of APGI) who welcomed the participants amongst others at Frederico Garcia Lorca. Afterwards, a coffee break included in the registration fees was organized at the industrial exhibition area which allowed doing networking with participants and industrial partners.

The hot topic session starts with a first talk on "Oral delivery of peptides for gastrointestinal targets" by Prof. Jean-Christophe Leroux from ETH Zurich in Switzerland. After that Prof. Abdul Basit (University of London in the United Kingdom) gives a very interesting talk about "colon targeting" entitled: "Translating pharmaceutics into oral therapeutics". The session ended with a last talk given by Maria José Alonso (University of Santizgo de Compostela, Spain) on "Transmucosal drug delivery (Nasal, Oral, Ocular)". On the next day, the conference started by the morning session at Frederico Garcia Lorca with new manufacturing technologies symposium including: "Technologies to enhance delivery of poorly water soluble drugs" given by Prof. Bill Williams (University of Texas, Austin, USA), and "3D printing for pharmaceutical applications" presented by Alvaro Goyanes (University of London, UK). Furthermore, Prof. Andrea Dietzel (University of Technology Braunschweing, Germany) gives a very interesting presentation on Microfluidics for pharmaceutical technology. After the coffee break, AVP awards were given to the winners and then followed by a plenary lecture given by Dr. Arzu Selen from the FDA entitled: "Pediatric formulations and dosage forms: Appli-

The afternoon session included short talks on nanoparticles including: Josef Mesek from Veterinary Institute in Czech Republic on “Nanofibre-based mucoadhesive film for oromucosal delivery of therapeutic nanoparticles”, Angela Fabiano (University of Pisa, Italy) on “Impact of mucoadhesive polymeric nanoparticulate systems on oral bioavailability of a protein model drug”, Ana Luisa Martinez-Lopez (University of Navarra, Spain) on “Zein nanoparticles for oral insulin delivery: In vivo evaluation in Caenorhabditis elegans”, Alexander Biehl from Helmeholzt Institute for pharmaceutical Research in Germany on “Applying multiple particle tracking to pharmaceutical research: A computational toolbox to address the transport and diffusion of nanoparticules through mucus”, Nunzio Denora (University of Bari, Aldo Moro, Italy) on “Sorafenib laoded SLN magnetically targeting hepatoma” and last but not least, Myriam Shetab Boushehri (University of Bonn, Germany) reported a very interesting talk on “Potential role of ammonio methacrylate nanoparticles as effective anticancer immunotherapeutics.

In the parallel session in the Manuella de Falla auditorium short talks were given on Controlled drug delivery including: Viktoria Planz (University of Franckfurt, Gernamy) on “Protein delivery to the oral cavity using electrospun fibers – fabrication strategies for high loading delivery systems with controlled release kinetics, Claire-Helene Brachais (ICMUB, France) on “Formulation of soft thin films based on low methoxyl pectin: A compromise between mechanical and in vitro release properties of indomethacin”, Isabell Speed (University of Dusseldorf, Germany) on “Prolonged release properties realized for orodispersible films by incorporation of drug-loaded micropellets”, Priyanka Thipsay (University of Mississippi USA) on “Impact of formulation and process parameters in twin screw hot-melt granulation coupled with in-line particle size analysis of sustained release HPMC granules”, Elien De Coninck (University of Ghent, Belgium) on “Prilling of fatty acid-API suspensions: Processabilty and characterization” and finally, Karsten Mader (University of Halle, Germany) on “Injectable oleogels for parenteral controlled release: Concept, in vivo performance and clinical potential”.

In the afternoon session, short talks were presented about Technical innovations – printing technologies including: Presentations of Carlos A. Garcia-Gonzalez (University of Santiago de Compostela, Spain) on “Inkjet bio printing of aerogel microspheres for pulmonary administration of salbutamol sulfate”, Diego Lopes (RCPE GmbH, Austria) on “Industrial inkjet printing for on-demand manufacturing of film-in-capsule dosage forms”, Tim Feuerbach (University of Dortmund, Germany) on “Development of filaments for fused deposition modeling 3D printing with medical grade PLGA”, Aleksandra Dominik (Wroclaw Medical University, Poland) on “Knowledge based design fabrication of fast dissolving tablets using drop-on-demand 3D printing technologies”, and Ilas El Aita (University of Düsseldorf, Germany) on “Extrusion based 3D printing of immediate release levetiracetam tablets”. The last presentation of the session was given by Wiebke Kempin from University of Greifswald in Germany, entitled: “3D printing of rapid release tablets based on polyethylene glycol for thermosensitive drugs”. In the parallel session in the Albeniz Machuca auditorium, invited talks on Dermal and transdermal drug delivery started with a very interesting talk given by Prof. José Louis Jorcano (University Carlos III, Madrid, Spain) on “3D printing of human skin”, followed by a talk given by Sebastian Kerski (tesa Labtec, Germany) entitled: “Permeation models for transdermal drug delivery”, and finally Dr. Begona Delgado Charro from University of Bath in the United Kingdom on “Topical treatment of nail diseases: Can we get on with it?”. In the afternoon session, invited speakers talked on Peptide and protein formulation including: Prof. Véronique Préat (University of Louvain, Belgium) on “Recent advances in protein delivery”, Prof. Wolfgang Friess (University of Munich, Germany) on “Lipid formulations for protein and peptide delivery” and to conclude the session Flora Felsovalyi from Roche in Switzerland talked about “Protein stability and compatibility for combination product development of biologics”.

International Conferences and Workshops

In the parallel session in the Machado Picasso auditorium, short talks on Peptide and protein formulation including: Christina Haeuser from University of Basel in Switzerland, “Collapse temperature modifiers and their effect on cake appearance – imaging techniques for lyophilisates”, Hristo Svilenov from University of Munich in Germany “Isothermal chemical denaturation for formulation studies of a mab: effect of formulation ph, denaturant choice and incubation time”, Panna Vass from university of Budapest in Hungary “Solid formulation of β-galactosidase by electrospinning”, Maarten Batens from University of Leuven in Belgium “Electrospraying fully aqueous protein solutions: A feasibility assessment”, Roland Brock, from Radboud University Medical Center in Netherland “Requirement of peptide polyplexes for efficient oligonucleotide delivery” and finally, Teresa Kraus from University of Munich in Germany “The evaluation of immunogenicity of protein aggregates in a human artificial lymph node model”.

In the afternoon session, talks from invited speakers on new challenges in oral delivery have been presnted. Prof. Clive Wilson from University of Strathclyde in the United Kingdom gave a very interesting talk about “Ethanol-sensitive dosage forms”, followed by Dr. Klaus Wening from Gruenenthal in Germany who talked about “Abuse deterrent dosage forms – needs, technologies and test characterization”. Furthermore, Dr. Ajit Narang from Genentech in the United States presented the Precipitation and excipient interactions of poorly soluble drugs impacting oral and IV pharmacokinetics.

On Wednesday, in Frederico Garcia Lorca auditorium short talks on Pediatric and geriatric drug delivery were given including: Anna Kira Adam from University of Dusseldorf in Germany “Direct compressible enteric-coated pellets for multi-unit mini-tablets”, Lourdes Contreras from Pfizer in the United Kingdom “Development of multiparticulate systems platform, flexibility for patients”, Nicolas Thurin from Catalent Pharma Solutions in Belgium “Pediatric formulation development of epinephrine injection: A child’s play”, Marzia Cirri from University of Florence in Italy “Development and characterization of thermosensitive gels for the treatment of oral pediatric mucositis”, Sven Stegemann from Lonza in Austria “Closing the gaps in medicine development for the older population – Outcomes and actions from an APV workshop” and last but not least for this session, Fabrice Ruiz from ClinSearch in France “Acceptability of formulations in older patients with swallowing disorders”.

After the coffee break, APGI Awards was given this year to Dr. Ranhua Xiong and then followed by a plenary lecture “Tackling physological resistances to drug delivery” from Prof. Elias Fattal (University of Paris-sud, France), the winner of Maurice-Marie JANOT Award sponsored by Sanofi.

The afternoon session on Personalized medicines/ pediatrics/geriatric started by a very interesting talk by Maren Preis from Abo Akademi University in Finland about personalizing medicines by drug printing, followed by Karin Bracht from Medicines and Healthcare products Regulary Agency in the United Kingdom who talked about “Acceptability and palatability studies in PIPs and MAA” and finally, Diana van Riet-Nales from Medicines Evaluation Board in Netherlands presented “New reflection paper for drug delivery to older people: similarities and differences with the EU’s pediatric legislation and quality guideline”.

In the parallel session in the Manuella de Falla auditorium, invited talks were given in a symposium on Data integrity including: Ib Alstrup from Danish Medicines Agency in Denmark “Data integrity and governance in GxP enviornments - a regulatory perspective”, Alessandro Regola from Bayer Quality Assurance Corporate in Italy “Data integrity in manufacturing and analytics: Form a challenge to an opportunity for the industry” and Bernd Rinn from ETH Zürich in Switzerland “Are your data on fire? Science between, “Fake Data” and “Open Data“.

The afternoon session started with short talks on Pharmaceutical manufacturing and engineering which were given by: Madeleine Witting from AbbVie in Germany "Predictive models of lyophilization process for development, scale-up/tech transfer and manufacturing", Julian H. Gitter from University of Munich in Germany "Accelerating the freeze drying process of a monoclonal antibody by addition of tertbutyl alcohol", Raphael Paus from Janssen (J&J) in Belgium "A model-based approach to scale up pharmaceutical roller compaction processes for continuous manufacturing", Hannah Lou Reimer from University of Düsseldorf in Germany "Improved predictability of ribblet solid fraction in roll compaction simulation", Jan Hendrik Finke from University of Braunschweig in Germany "Scalability from compaction simulator to production rotary press: Check compression profiles and mind the feeding" and finally, Christoph Portier from University of Ghent in Belgium "Robustness of low-dosed lactose/MCC based formulations in continuous twin screw granulation".

In the parallel session in Albeniz Machuca auditorium, invited speakers talked on Biopharmaceutics including: Jennifer Dressman from University of Frankfurt in Germany "The OrBiTo decision tree for product performance testing", followed by Stéphane Beilles from Sanofi in France who talked about "IVIVC, in silico modeling". Furthermore, David B. Turner from Simcyp Ltd in United Kingdom gave a talk about Applications of population PBPK in the development of oral drug products.

Invited talks continued in the afternoon with a symposium entitled: Advanced characterization techniques including: Jean Doucet from CNRS and Novitom in France "Synchrotron X-ray computed microtomography (SR-µCT) for pharmaceutics", Jens Frahm, Max Planck from Institute for Biophysical Chemistry in Germany "Real-time MRI - an unexpected adventure" and the last talk given by Anette Larsson from Chalmers University of Technology in Sweden on "Methods for characterization of the drug release mechanism from coated extended release pellets".

In the auditorium of Machado Picasso, the morning session started with a very interesting talk on "Nanofibers as delivery system for a new probiotic strain isolated from oral microbiota" presented by Spela Zupancic from University of Ljubljana in Slovenia followed by Naoual Dahmana from University of Geneva in Switzerland who presented "Topical delivery of spironolactone nanocarriers prevents dexamethasone induced delayed corneal wound healing" and Kazuo Maruyama from University of Teikyo in Japan who talked about "Enhancement of ERP effect by the combination of lipid bubbles and ultrasound". In the afternoon, short talks on Dermal and transdermal included: Dominique Lunter from University of Tuebingen in Germany "Confocal Raman microscopy (CRM) - a versatile tool to characterize semisolid formulation inner structure and skin penetration", Stuart Jones from King's College London in United Kingdom "Topical hypobaric pressure: A novel means to enhance the delivery of nanosized drug aggregates into the skin", Hasan Akbaba from Ege University in Turkey "shRNA-encoding plasmid loaded solid lipid nanoparticles against 5-o reductase activity for the treatment of androgenic alopecia: Topical delivery and in vitro evaluation", Evi Christodoulou from Aristotle University of Thessaoniki in Greece "Porous dressings of chitosan/modified chitosan blends for topical and transdermal delivery of chloramphenicol", Michael Herbing from Almirall Hermal GmbH in Germany "Topical film-forming systems for enhanced dermal delivery of tazarotene" and Ryan Donelly from Queen's University of Belfast in United Kingdom "Microarray patches for HIV prevention and treatment".

At the end of the day, a gala dinner included in the registration fees took place at la Mamunia restaurant.

The last day of the conference started at Frederico Garcia Lorca auditorium with invited talks on Continuous manufacturing including: Thomas de Beer from University of Ghent in Belgium “PAT for model based design, optimization, monitoring and control of continuous manufacturing”, Dejan Djuric from Bayer in Germany “Continuous processing of solid dosage form” and last but not least, Hirofumi Takeuchi from Gifu Pharmaceutical University in Japan “Continuous pharmaceutical process in Japan: Our challenges in characterizing pharmaceutical processes including continuous granulation and tableting”.

After the coffee break, the ADRITELF award lecture was given and followed by a very interesting talk given by Sébastien Lecommandoux from ENSCBP-Bordeaux-LCPO in France on “Innovative biomaterials polymer-based Biomaterials”.

The afternoon session started with short talks on nanoparticles and liposomes including: Léna Guyon from MINT in France “Nanoassemblies formed by cell-penetrating peptides and ferrocifens for lung cancer treatment”, Barbara Tessier from Institute Galien Paris Sud in France “Synthesis and formulation of poly(malic acid)-budesonide nanoprodrugs for lung administration”, Francesca Ungaro from University of Napoli Federico II in Italy “Inhalable mucus-penetrating nanocrystals for lung delivery of a new anti-Burkholderia agent in cystic fibrosis”, Alessandro Dalpiaz from University of Ferrara in Italy “Bile acids modulation of nanoparticle macrophage uptake”, Sarah Kindgen from ETH Zurich at Switzerland “A liposomal melanoma peptide vaccine induces antigen-specific CD8 T cells with potentially anti-tumor propertiesn” and Christophe Chassaing from Ipsen in France “Stealth pH-sensitive liposomal formulations for intracellular delivery of therapeutic peptides”.

In the parallel session in Manuella de Falla auditorium , the morning session started with short talks on Oral delivery including: Cornelus van Nostrum from University of Utrecht in Netherlands “PEGylated mixed micelles for oral delivery of vitamin K”, Caroline Twarog from Institut Galien Paris Sud in France “Understanding physicochemical interactions between intestinal permeation enhancers and exenatide to improve oral peptide formulation”, Svenja Niese from University of Düsseldorf in Germany “Development of a continuously produced orodispersible film for individual dosing of warfarin sodium”, Daniel Markl from University of Cambridge in United Kingdom “Analysis of anisotropic pore structures of pharmaceutical tablets”, Maximilian Sager from University of Greifswald in Germany “Biorelevant dissolution testing of IR dosage forms under fasted state conditions using the GastroDuo” and Pauric Bannigan from University of Limerick in Ireland “The role of biorelevant dissolution media in the selection of optimal salt forms of oral drugs: Maximising the gastrointestinal solubility and in vitro activity of the antimicrobial molecule, clofazimine” and in the afternoon with three invited talks on new materials including: Carmen Alvarez Lorenzo from University of Santiago de Compostela in Spain “Cyclodextrin networks in drug delivery and regenerative medicine”, Jan Hendrik Schattka from Evonik in Germany “New functional polymers for oral drug delivery” and finally, Francesco Puoci from University of Calabria in Italy “Molecularly imprinted polymers in drug targeting”.

In the auditorium of Albeniz Machuca, the symposium entitled: Nanotechnology/nanomaterials started with a very interesting talk of Elias Fattal from University of Paris-Sud in France on “Nanomedicine and inflammation triggering or treating”, after that Raymond Schiffelers from University of Utrecht in Netherlands talked about “Targeted RNA deliverys” and last, Fabio Beltram from Scuola Normale Superiore in Italy presented “Nanotechnology in biomedicine”.

In the afternoon, invited talks on Drug-device combinations/combination products included: Carla Marcella Caramella from University of Pavia in Italy “Combination products and innovation in drug delivery”, Paolo Mangiagalli from Sanofi in France “Holistic design and PFS components control plan for robust autoinjector delivery of biologic” and a speaker requested from the FDA in the United States “Regulatory aspects of drug-device combinations (EU & US)”.

International Conferences and Workshops

In Machado Picasso auditorium, short talks from selected abstracts included: Physical pharmacy and preformulation, Marc Descamps from University of Lille in France "Using Milling to explore the physical state of pharmaceuticals", Ainoha Coelho from University of Lisbon in Portugal "NIR and Raman spectroscopy as tools to assure olanzapine stability in formulations", Peter Ouma Okeyo from University of Copenhagen in Denmark "Chemical mapping of hydrate-anhydrate transformations at a single particle level using Raman line focusing", Carolin Auch from Merck in Germany "Melt-screening method with improved predictability regarding polymer selection for amorphous solid dispersions", Anna Nardi from University of Barcelona in Spain "SeDeM Diagram: An improved expert system tool for pre-formulation and formulation drug products" and PQuentin Ribeyre from GranuTools in Belgium "How to improve classical flowability/ rheology tests to fulfil pharmaceutical industries requirements".

In the afternoon, the conference ended with short talks on Bioavailability and intestinal absorption including: Fiona McCartney from University College Dublin in Ireland "Investigation of derivatives of Labrasol® as permeation enhancers across rat intestinal tissue mucosae ex vivo", Luca Casettari from University of Urbino in Italy "Ex-vivo evaluation of intestinal permeability enhancing effects of mono-esterified sugar based surfactants", Lasse Blaabjerg from University of Copenhagen in Denmark "Correlation between glass forming ability and supersaturation potential of poorly soluble drugs with and without polymers", Kohsaku Kawakami from the National Institute for Materials Science in Japan "Relevance of liquid-liquid phase separation of supersaturated solution to oral absorption of amorphous solid dispersion", Daniel J. Ellenberger from University of Texas at Austin in the United States "KinetiSol dispersing improves in vitro and in vivo dissolution of vemurafenib" and last, Yvonne E. Arnold from University of Geneva in Switzerland "Ex vivo porcine small intestine to investigate passive drug absorption".

Furthermore, poster presentations exhibiting during the whole conference gave the opportunity to get an update on the most recent research in Pharmaceutics and to personally exchange deeply with the authors. Also, an industrial exhibition accompanied the Conference and allowed the participants learning about the latest trends and newest products in the area of pharmaceutical ingredients, developing & processing equipment, analytical technologies, medicinal products & devices and many other fields.

We are looking forward to seeing you again in the next "12th World Meeting" in Vienna, Austria!


Fotografia: Javier Algarra

12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

23-26 March 2020, Vienna, Austria

In continuation of the very successful past meetings in Budapest, Paris, Berlin, Florence, Geneva, Barcelona, Malta, Istanbul, Lisbon, Glasgow and Granada, we will organize the 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology in Vienna, Austria, on 23-26 March 2020.

As in all the even years, we will jointly organize this largest event in our field in Europe jointly with our German and Italian friends: the APV and the ADRITELF, as well as with many other European sister societies. More than 1300 participants from all over the world are expected and close to 1000 abstracts. Various hot topics in our field will be addressed, and world-wide leading researchers will present overview talks on the current state of the art in their fields. In addition, short talks selected from submitted abstract will allow learning about cutting edge research findings.

As in the past, the accompanying exhibition "ResearchPharm" will provide a cross-disciplinary platform for pharmaceutical scientists working in all fields of drug development in industry, academia and regulatory bodies.

Roughly one third of the participants are expected to come from industry, one third from academia, and one third will be young scientists (PhD students and post-docs): the next generation.

In total, 7 plenary lectures, 32 invited lectures, 64 short talks and several hundreds of poster presentations will be held, covering the entire range of research and development in pharmaceutics, biopharmaceutics and pharmaceutical technology.

Please already safe the date and plan to join us!

"Skin and Formulation, 5th Symposium & 17th Skin Forum"

23-24 September, 2019, Reims, France

Organization Committee

Dr Vincent Faivre, University of Paris-Sud, France
Prof. Jonathan Hadgraft, University of London, United Kingdom
Dr Majella Lane, University of London, United Kingdom
Dr Anne-Marie Pensé-Lhéritier, EBI, France
Dr Anthony Rawling, AVR Consulting, United Kingdom
Dr Michel Sournac, Institut de Recherche Pierre Fabre, France

The *"Skin and Formulation 1st Symposium"* was organised in Paris in 2003, with more than 170 attendees. Three years later the *"Skin and Formulation 2nd Symposium"* was held in the "Palais des Congrès" in Versailles on 9-10 October, 2006. In the same prestigious location, the *"Skin and Formulation 3rd Symposium"* took place on 9-10 March, 2009. These symposia have provided a unique discussion forum between pharmacists, biologists, chemists and physicians on the interactions between the skin and formulations applied to it. The various aspects of the topical and transdermal applications of pharmacologically and cosmetically active compounds have been presented and discussed. In 2012, the *"Skin and Formulation 4th Symposium"* left the Ile de France region and relocated to Lyon on 4-5 June. In this symposium, important topics focused on *in silico*, *in vitro* and *in vivo* evaluations of skin products and formulation trends, especially in the field of powder technology.

We are now pleased to announce the upcoming ***"Skin and Formulation 5th Symposium"* on 23-24 September, 2019, in Reims (Reims Convention Centre – *Palais des Congrès*).** With direct express trains from Paris or its airports, Reims is the perfect city to live sparkling meetings among historical monuments and unique vineyards.

This time the Symposium will be co-organized with the *"17th Skin Forum".*

We would like to thank Dr Majella Lane, University of London, and Co-chair of the *"Skin and Formulation 5th Symposium",* for the following short presentation of *Skin Forum*:

"In 1999 Professor Jonathan Hadgraft received funding from the Engineering Physical Sciences and Research Council in the United Kingdom to establish a network of scientists whose research focuses on the mechanisms and modulation of skin permeation.

International Conferences and Workshops

The Skin Forum has evolved from this network and today represents more than 1000 chemists, pharmaceutical scientists, physicists and biologists who share a common interest in the physicochemical and biological properties of human skin. The annual Skin Forum conference brings together internationally recognised experts and provides an opportunity for research students to meet opinion leaders in a relaxed and informal manner. Because of the close research links with European colleagues Skin Forum has now come together with APGI to jointly organize the "Skin and Formulation 5th Symposium" in Reims in 2019.

Topics will again focus on the areas that encompass pharmaceuticals, cosmetics and dermatology and about products applied to the skin. The main objective of this symposium is to compare, to confront point of views in order to initiate discussions and exchanges between the different communities composing the audience.

The 5th Symposium programme will treat advances in topical formulations for improved skin delivery and will include the following topics:

- **Skin biology**. Skin is a complex and dynamic ecosystem that is colonized by bacteria, fungi and viruses. This skin microbiota is fundamental to skin physiology and immunity. This session will notably underline how cosmetics and pharmaceutics could act intelligently to preserve or eliminate this microbiome.
Confirmed speakers: Dr. Cécile Clavaud (L'Oréal); Pr. Matthew Hardman (University of Hull); Dr. Dominik Imfeld (DSM Ltd).

- **Biophysical tools**. Fine tools are needed to investigate the skin and its interaction with topical formulations. Recent progress in imaging and characterization techniques will be described.
Confirmed speakers: Pr. Malcolm Clench (Sheffield Hallam University); Dr. Jean Doucet (Novitom).

- **Rheology of skin products**. An important area of the applied physics for the scientists, crucial process parameters for industrial, textures for the consumers. Rheology is a complex area which will be addressed during this symposium.
Confirmed speakers: Pr. Florence Agnely (University of Paris-Sud); Dr. Pascal Brochette (Atellane); Dr. Valentine Ibekwe (MHRA).

- **Skin product development**. From concept to final product, skin product development significantly depends on the context. New active ingredients or reformulation? Pharmaceutical application or cosmetic product? Through case studies, this session will illustrate the key-concepts of such developments.
Confirmed speakers: Pr. Jonathan Hadgraft (University of London); Dr. Milica Lukic (University of Belgrade); Pr. Mauricio Camargo and Dr. Javier-Andres Arrieta Escobar (University of Lorraine).

- **Man and Machines**. A large spectrum of data invades our lives, artificial intelligence excite our minds. From the detection of pathologies to the selection of ingredients for topical products, this session will give some trends in the use of digital technologies in skin area.

International Conferences and Workshops

Skin Forum
international skin science network

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Suppliers will again be invited to display their latest technologies.

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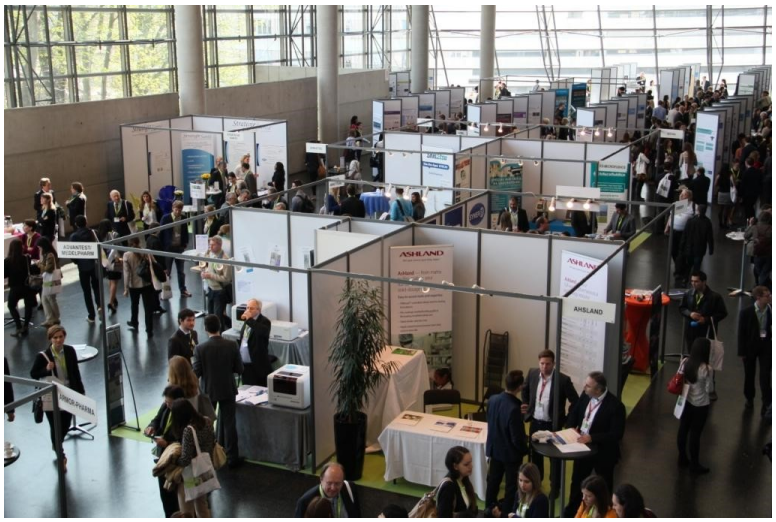

APGI YOUNG INVESTIGATOR AWARD

Dear all,

The "APGI YOUNG INVESTIGATOR AWARD" (sponsored by Sanofi) recognizes the most outstanding doctoral thesis in the field of Pharmaceutical Technology each year.

If you defended your PhD thesis between 15 November 2017 and 14 November 2018, you can candidate for the 2018 "APGI YOUNG INVESTIGATOR AWARD".

Please send a pdf file of your thesis (in French or English) and a short curriculum vitae, by 24 November 2018, to APGI (apgi.asso@u-psud.fr) and Géraldine Piel (geraldine.piel@ulg.ac.be).

The file can also be sent by We Transfer (a compressed version would be appreciated).

Thanks to the supervisors to forward this information to potentially interested current and former PhD students.

The price (accompanied by a check) will be officially awarded at the 3rd European Conference on Pharmaceutics**,** 25-26 March 2019 in Bologna, Italy

APGI thesis award 2017/2018

Dr. M.S. Ranhua Xiong

The promotor:
Prof. dr. Kevin Braeckmans
The co-promotors:
Prof.dr.apr. Stefaan De Smedt
Prof. dr. Andre G. Skirtach

has been awarded for his Ph.D. thesis entitled:

Intracellular delivery of biopharmaceuticals and contrast agents by VNB photoporation and sizing nanomaterials in bio-fluids by FRAP

Summary
This thesis consists of two parts, which summarized separately below.
Part I INTRACELLULAR DELIVERY OF BIOPHARMACEUTICALS AND CONTRAST AGENTS BY VAPOR NANOBUBBLE (VNB) PHOTOPORATION Cytosolic delivery of foreign materials into live cells is an important step for many applications in cell biology and pharmacy. For instance, intracellular delivery of DNA is required for studying gene expression, mutation analysis, and gene therapy. Similarly, mRNA delivery into live cells enables assessing cell biological functions, while small interfering RNA (siRNA) is introduced for sequence-specific gene silencing. Apart from biological molecules there is an equal interest in the intracellular delivery of contrast agents. Recently, the use of inorganic particles as imaging contrast labels is being investigated, such as superparamagnetic iron oxide nanoparticles (SPIONs) and Gadolinium complexes for MRI, and quantum dots (QD) and upconversion nanoparticles for fluorescence imaging. Some of those exogenous nanomaterials could be introduced into cells via a viral vector. But immunogenicity and toxicity are major concerns. On the other hand, the nanomaterials could be formulated into non-viral carriers, typically lipid or polymer based. As these are generally internalized by cells through endocytosis, escape from the endosomes into the cytosol is typically needed. Up to date, endosomal escape remains one of the major bottlenecks hampering safe and efficient delivery of nanomaterals into the cytosol. Physical approaches have been developed as well to deliver nanomaterials into the cytosol of cells by transient permeabilization of the cell membrane. Such physical methods have attracted considerable interest as they typically offer generic applicability to a variety of cell types and enable direct delivery of the exogenous materials into cytosol. Micro-injection, electroporation and sonoporation are typical examples of physical delivery methods. Laserassisted photoporation is an alternative promising physical technique that is receiving increasing attention in the last decade. Especially in combination with enhancing nanoparticles like plasmonic NPs it seems to be a promising technology. By attaching plasmonic NPs such as gold nanoparticles (AuNPs), to the cell membrane, the photoporation effect can be achieved at lower laser intensities. This means that throughput can be increased since non-focused laser light can be used to illuminate a large amount of cells, leading to distinct phenomena such as heating of the cell membrane, acoustic shockwaves, and formation of water vapor nanobubbles (VNBs). Recently, it has been shown that VNBs can be used to permeate the plasma membrane and deliver cell impermeable compounds into the cytosol by the mechanical force induced by their expansion and collapse. A particular feature of VNB photoporation is that there is no neat heat transfer to the surrounding tissue as all energy is converted to mechanical energy. As VNB photoporation is still fairly new, the aim in Part I is to explore its usefulness for a number of applications, as detailed below. Summary 238 In Chapter 1, an in-depth introduction is provided on photoporation to explain its fundamentals as well as its current applications. The various forms of laser-assisted photoporation are explained, with the two major classes being direct laser-induced photoporation and nanoparticle sensitized photoporation. The mechanisms responsible for cell membrane permeabilization are discussed, alongside technological advances and biological applications. This review chapter should give the reader the necessary background for a good understanding of the subsequent experimental chapters. In Chapter 2, we report on a systematic comparison of AuNP mediated photoporation for delivering macromolecules in cells by heating of the membrane and VNB generation. While it has been shown that both heating of AuNPs and VNBs can be used to permeate the plasma membrane and deliver cell-impermeable compounds into the cytosol, it remains unclear which of both mechanisms are the most efficient. Despite the fact that it requires higher laser energies, surprisingly we find that VNBs allow more efficient cellular uptake of compounds with little or no cytotoxicity as compared to direct heating. This is attributed to the fact that bigger pores can be formed with VNB photoporation, allowing better entry of molecules that are present in the cell medium. Furthermore, we successfully show that VNB photoporation can transfect cells with siRNA more efficiently as compared to direct heating, resulting in enhanced gene silencing. Finally, we show that pores of different sizes can be created with VNB photoporation depending on the laser intensity, thus enabling sizeselective delivery of macromolecules in cells. In Chapter 3, we explore the use of VNB photoporation for the cytosolic delivery of contrast agents in a fast and non-toxic manner.
Long-term in vivo imaging of cells is crucial for the understanding of cellular fate in biological processes in cancer research, immunology or in cell-based therapies such as beta cell transplantation in type I diabetes or stem cell therapy. Traditionally, cell labeling with the desired contrast agent occurs ex vivo via spontaneous endocytosis, which is a variable and slow process that requires optimization for each particular label-cell type combination. Following endocytic uptake, the contrast agents mostly remain entrapped in the endolysosomal compartment, which leads to label degradation, cytotoxicity and asymmetric inheritance of the labels upon cell division. We hypothesize that direct delivery of contrast agents into the cytosol by VNB photoporation can alleviate the many difficulties related to endocytic cell labeling.

APGI thesis award 2017/2018

First, we demonstrate efficient and safe loading of fluorescent dextran and QD in different cell types by photoporation. Compared to endocytic uptake, cell loading with photoporation was 50 and 3 times more efficient for FD and QD, respectively. Combined with reduced toxicity, this enabled extended cell visualization in vitro over 10 cell generations for FD and 3 generations for QD. This shows that old-school labeled dextrans are excellent inexpensive and biocompatible labels for cell tracking when delivered by photoporation as compared to much more expensive and often toxic QDs. We demonstrate for the first time that asymmetric Summary 239 inheritance of fluorescent labels can be avoided by cytosolic delivery via photoporation. As a result, the cell intensity polydispersity remains identical over multiple cell divisions, while it rapidly increases for endocytic loading (already factor 10 after 6 divisions). Finally, we show extended in vivo imaging of an insulin producing cell line (INS-1E cell line) labeled with Cy5.5-dextran by photoporation. Cells labeled by photoporation could be imaged up to two months instead of only two weeks in case of endocytic labeling. In Chapter 4, VNB photoporation is applied to deliver antibody funcationlized QDs in living cells for subcellular labeling. The application of QDs as subcellular labels for microscopic investigation of living cells remained virtually impossible until now due to a lack of means to deliver QDs unambiguously into the cytosol of cells. We first confirmed highly efficient delivery of PEG-coated QDs into living cells. We obtained more than 80% of positive cells while the cell viability remained as high as ~85%. As a first proof-of-concept, we delivered antibody functionalized QDs in HeLa cells targeted at the microtubules. Successful labeling of the microtubules was achieved, although the contrast was rather limited likely due to the presence of too many unbound QDs in the cytosol. Although further work is needed to get better control on the quantity of QDs that are delivered into the cells, it shows that photoporation has the long-awaited capability to deliver antibody-targeted QDs into living cells for live cell microscopic visualization. In Chapter 5 we explored one of the most unique features of photoporation, which is to deliver exogenous materials into selected cells within a large population of cells. We developed the soft- and hardware to perform cell-selective intracellular delivery by spatially resolved nanoparticle enhanced photoporation (SNAP). Cells can be photoporated according to pre-defined patterns or in an interactive image-guided manner. The unique technological capability to deliver compounds quickly and flexibly into selected cells was applied to two challenging application. Applying SNAP to cell-selective photoporation of single neurons in automated image-guided mode, we labeled and highlighted single neurons for accurate morphological analysis. On the other hand, we used SNAP to deliver a non-toxic fluorescent marker into morphologically distinct primary normal human epidermal keratinocytes. In particular, polynucleated or mononucleated senescent cells are separately targeted so that they can be purified for further downstream molecular and functional analysis in relation to cancer research. Part II SIZING NANOMATERIALS IN BIO-FLUIDS BY FLUORESCENCE RECOVERY AFTER PHOTOPOBLEACHING (FRAP) FRAP is advanced well-known fluorescence microscopy method for measuring molecular mobility in biomaterials, cells and tissues. FRAP has been widely applied in the biophysical, Summary 240 pharmaceutical and material sciences. In a FRAP experiment, the sample is placed on a microscope and the fluorescently labeled molecules or nanoparticles are photobleached in a micron sized area by a powerful excitation pulse. The fluorescence inside the bleach area will subsequently recover at a rate that is proportional to the diffusional rate of the fluorescent species. Typically the average fluorescence intensity inside the bleach area is quantified as a function of time. A suitable mathematical model is used to fit the fluorescence recovery data, from which an average local diffusion coefficient follows. However, by calculating the average fluorescence in the bleach area, the special information is effectively lost and only the time-progression of the average intensity is taken into account. Instead, by also analyzing the spatial diffusion profile in function of time one can expect much better precision of FRAP experiments. In Part II we develop such a new and improved tempo-spatial FRAP model and show that it can be used for diffusion analysis of polydisperse systems. In particular the method is used to measure the hydrodynamic size of molecules in biological fluids, as explained below. In Chapter 6, we describe the improved FRAP methodology that enables the measurement of continuous distributions of diffusion coefficients (cFRAP). A rectangular area is photobleached and the full tempo-spatial information available in the confocal recovery images is exploited using a dedicated theoretical recovery model to extract a continuous distribution of diffusion coefficients. It is found from simulations that cFRAP can distinguish two subpopulations if their diffusion coefficient differs by as small as a factor 3 in comparison with at least a factor of 8 for traditional FRAP methods which only consider the average fluorescence as a function of time. It is confirmed through simulations that cFRAP can correctly analyze polydisperse systems with a broad range of diffusion coefficients. The performance of cFRAP was compared experimentally to DLS as a standard technique for measuring the size distribution of polydisperse nanomaterial dispersions. Thanks to including spatial, information in the cFRAP model, the PDI of the distributions was significantly less compared to the apparent PDI measured by DLS. In Chapter 7, we demonstrate the strength and versatility of cFRAP in a number of challenging sizing applications. As a first application, we used cFRAP-sizing to analyze protein aggregates in the sub 0.1 μm range in full serum. This is of current interest since protein aggregation has emerged as a key issue underlying multiple deleterious effects in the use of protein therapeutics, including loss of efficacy, altered pharmacokinetics, reduced stability and shelf life, and induction of unwanted immunogenicity. Fluorescently labeled BSA was used as a model protein, which could be analyzed by cFRAP down to a concentration of 4 μg/ml (60 nM). cFRAP-sizing could discriminate both monomers and aggregates in a single measurement, not only in buffer but also in undiluted serum. As a second application cFRAP was used to study the permeability of the intestinal and vascular barriers in mice in unprecedented detail. The classic protocol requires the separate Summary 241 administration of dextrans of different molecular weights, each time in a different animal. The leakiness of the barrier is then evaluated by quantifying the fluorescence intensity for each dextran size in the relevant fluid (prepared from the receptor tissue). Instead, by intravenous administration of a mixture of five FDs covering a broad range of sizes from about 1-100 nm, here we demonstrate that a single experiment is sufficient when combined with cFRAP-sizing. This results in 5 times less animals compared with the classic fluorimetry method. At the same time unprecedented detailed information is obtained on the continuous size range of probes that can leak through the barrier. Using cFRAP-sizing we even succeeded in analyzing FD leakage in microliter samples of cerebrospinal fluid, notwithstanding that the fluorescence was very weak. Both applications show that cFRAP is a promising new method to measure the size distribution of molecules and nanomaterials in undiluted biological fluids.

Information days

APGI Information Day 2018 with EVONIK:

ORAL SOLID DOSAGE FORMS: Formulation Strategies and Manufacturing Approaches for Challenging Drugs

27 November 2018, Paris

The new chemical entities entering drug development nowadays often come along with specific challenges for formulators. With respect to maximum therapeutic effects and reliable functionality, the preferred dosage forms are multiparticulates with controlled drug release. However, poor solubility and / or limited permeability may not allow for sufficient bioavailability of APIs that are supposed to be administered via the oral route. Although biopharmaceuticals offer amazing therapeutic advantages, the challenges are often rather high to design drug products that allow for therapeutic efficacy through oral administration. At patient's side, a growing number of consumers have difficulties to swallow solid dosage forms; thus, there is a need for alternatives such as liquids while keeping the option to control drug release.

With respect to processing and production of controlled release multiparticulates, the challenges which need to be addressed include process optimization, reasonable application of the Quality by Design (QBD) guidelines, and smart scale up strategies – whereby the costs and efforts should be kept on a minimum level to stay competitive. Additionally, another process option that has gained awareness in the recent past is the application of continuous manufacturing to enhance production processes, going along with reduced costs and manufacturing times.

All of these aspects plus the question of advanced, highly efficient equipment cleaning are discussed in the upcoming APGI Information Day on 27 November, 2018. Experts from industry and academia present various approaches to overcome these challenges and make ongoing and future drug product development projects a success. APGI and Evonik invite all formulation scientists, lab heads, process engineers, scale up experts and production managers to join this one-day event, gather new insights and take home valuable approaches for direct implementation into their daily work.

For more information and registration, click here.

Please note that the APGI Information Days are free of charge for APGI members. Also, if you subscribe now to the APGI, your subscription will also be valid in 2019. This means that you can benefit from reduced registration fees for events organized (or co-organized) next year.

Information days

Formulation Days 2019

Advances in Formulation of Active Ingredients

10-11 January, 2019, Lyon, France

Dear Madam, Dear Sir, We are pleased to announce that the Conference Formulation Days 2019 – "Advances in Formulation of Active Ingredients", will be held on 10 & 11 January, 2019 in Lyon, France. It will be the first joint Conference of the International Society of Drug Delivery and Pharmaceutical Technology (APGI) and the Formulation Group of the French Chemical Society (SCF). The aim of this conference is to be a forum where experts from industry and academia working in the wide field of formulations dedicated to pharmaceutical or cosmetic applications can meet for cross-sector discussions. For this edition, the scientific program will cover four main topics:

- Materials, Biomaterials
- Formulations for cutaneous or mucosal administration
- Nanoparticles: nanomedicine, toxicology and regulation
- Process Engineering, characterization, modelling

For more details, please visit our website http://formulationdays2019.univ-lyon1.fr/

Deadline for abstract submission extended to 15 November

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Pharmaceutical Twin-Screw Processes – a continuous approach to drug manufacturing

Authors: Dr.-Ing. Margarethe Richter, Dirk Leister, Thermo Fisher Scientific, Karlsruhe, Germany

INTRODUCTION

Since the mid of the 1980's twin-screw extruders are established tools in the pharmaceutical industry for formulation and manufacturing of new drugs. In general, the two different processes can be performed using parallel co-rotating twin-screws (Figure 1). If a die is placed at the end of an extruder barrel, and material is compacted and pressed through this die, then the process is called extrusion. By omitting the die the material can be kneaded and agglomerated in the barrel without an increase in pressure. This process is called granulation. Both processes can be performed with and without water.

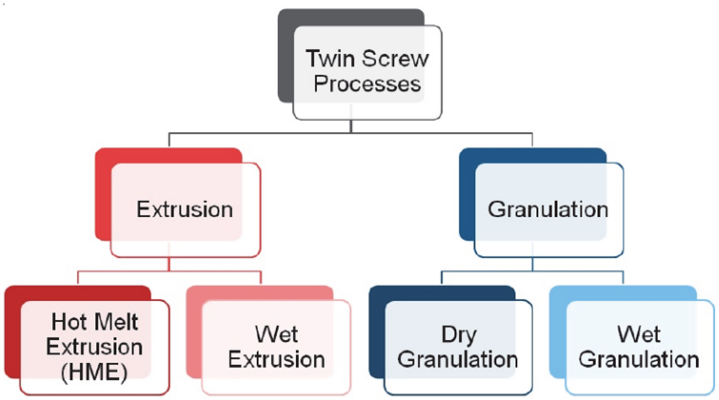


Fig. 1: Overview of twin-screw processes

Hot melt extrusion (HME) was, and most probably still is, the most important technique to produce solid dispersions for solid oral dosage forms and several commercial products are produced with this technology [1]. In the past two decades the area of extruder utilization has grown significantly and other drug delivery systems are now produced successfully using an extruder e.g. films, implants, co-extrudates, capsules and granules.

Twin-screw granulation (TSG) gained attention in the recent years. In most cases this relates to a wet granulation where water is used to perform the granulation. But the twin-screw technology enables the operator to perform a variety of processes. A dry or melt granulation can be done as well as wet-extrusion spheronization. Thus, using one machine, different types of granulation processes can be tested to find the optimum for a given formulation.

CONTINUOUS MANUFACTURING (CM) USING TWIN-SCREW EXTRUDERS

It is increasingly recognized that the future of pharmaceutical manufacturing will continue towards the development and adoption of continuous manufacturing techniques. This is in part due to lower operating costs, smaller footprint and increased flexibility that continuous manufacturing offers. TSG has emerged as a popular continuous manufacturing technology for consistent, repeatable high-quality production of both standard and complex dosage forms.

This article will introduce case studies of dry/melt and wet granulation using TSG to show how it is possible to tailor particle properties. Some important process parameters are introduced and how they are used for a successful process design. The work presented here is meant to give an overview on the possibilities using TSG. More in-depth material on all aspects presented are available and can be requested from the authors.

DRY/MELT GRANULATION

Some active pharmaceutical ingredients are very sensitive to hydration or to heat, requiring alternative granulation techniques to be investigated.

Dry granulation requires high mechanical forces for compaction. Using a thermoplastic binder however, thermally activated dry granulation can be performed on parallel twin-screws [2]. Then, the drying step is not needed.
In comparison to hot melt extrusion (HME) dry granulation is performed above the glass transition temperature of the polymeric binder, but below the melting temperature of the API. Furthermore, in case of dry granulation low binder contents of approx. 10% can be used, allowing the production of high-dose formulations.

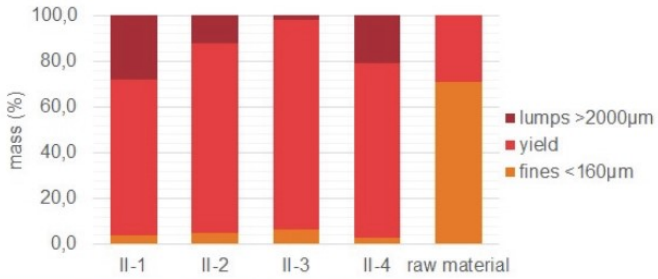
MATERIALS AND METHODS

Dry granulation is tested using the Thermo Scientific ™ Pharma 11 Twin-Screw Extruder with the granulation kit and a gravimetric Twin Screw feeder (Figure 2). As a formulation the binder Soluplus® (BASF) with a low glass transition temperature was chosen. Furthermore, the process temperature was set to 130 °C or 150 °C and comparatively low throughputs and screw speeds were realized. A sieve analysis was performed for the starting and resulting materials. Lactose was used a as a substitute for an API.

Fig. 2: Pharma 11 extruder with granulation kit

RESULTS

Figure 3 summarizes the results from sieve analysis for the different process conditions indicated in the table (Trial II-1 to II-4). The right-hand side of the graph shows that the raw material consists of mostly fine particles (smaller than 160 µm). All samples from the trials show an increase in particle size, resulting in at least 70% yield -size particles. In experiments II-1 to II-3 the screw speed was varied, showing that the particle size distribution is very sensitive to this parameter.
A change in barrel temperature from 150 °C to 130 °C (II-3 and II-4) results in a larger amount of oversize particles and less fines. This can be explained by the increase of viscosity of the polymeric binder. The resulting torque during the granulation seems to be a good indicator for the quality of the process. Experiment II-1 and II-4 exhibited the same torque and a similar particle size distribution.



T (°C)	150	150	150	130
screw speed (rpm)	100	70	130	130
torque (%)	50	70	38	50

Fig. 3: Overview on dry/melt granulation results

WET GRANULATION

Even though dry granulation has some unique advantages over liquid based granulation processes, wet granulation using water as a binder liquid is currently the most wide spread used method when it comes to particle agglomeration.

The principle of TSG is shown in Figure 4. The solid powder is automatically fed into the twin-screw extruder. This can be done in a so called split feed: feeding API and excipients separately or as a powder blend. A pump adds the liquid binder separately. Within the barrel the material is mixed, kneaded and tempered to target temperature (cooling or heating). Agglomeration takes place during this process. The granules exit the barrel through an open discharge and are transferred to the next process step (e.g. drying).

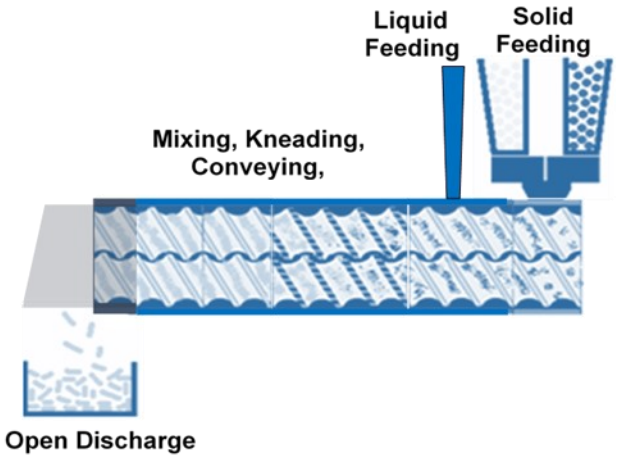


Fig. 4: Principle of wet TSG

There are several process parameters that can be changed independently: the liquid to solid ratio (L/S), the total throughput of material that is fed into the barrel, the screw speed of the extruder, the screw configuration and the temperature of the granulation process. All of these influence the granule quality and hence the final tablet hardness and the release profile of the API.

All results presented here were obtained using the Thermo Scientific™ Pharma 11 Twin-Screw Extruder in wet granulation configuration. For the trials a placebo formulation of 62.8% lactose, 32% corn starch, 5% PVP 30 and 0.2% talcum has been granulated using water. The granules have been analyzed for particle size distribution (PSD) in-line using the Eyecon$_2$ Particle Analyzer (InnopharmaTechnology, Dublin).

PARAMETERS IN WET TSG

As published by several other authors, e.g. Thompson [3], Keleb [4] and Beer [5], the liquid-to-solid ratio (L/S) has a significant influence on the granule quality. Fig. 5 shows the particle size distribution for varying L/S between 18% and 28%. The curve shifts to the right, thus, to higher particle size for rising L/S. Consequently, increasing L/S increases the mean mass diameter, the size and the amount of oversize particles and reduces the amount of fines.

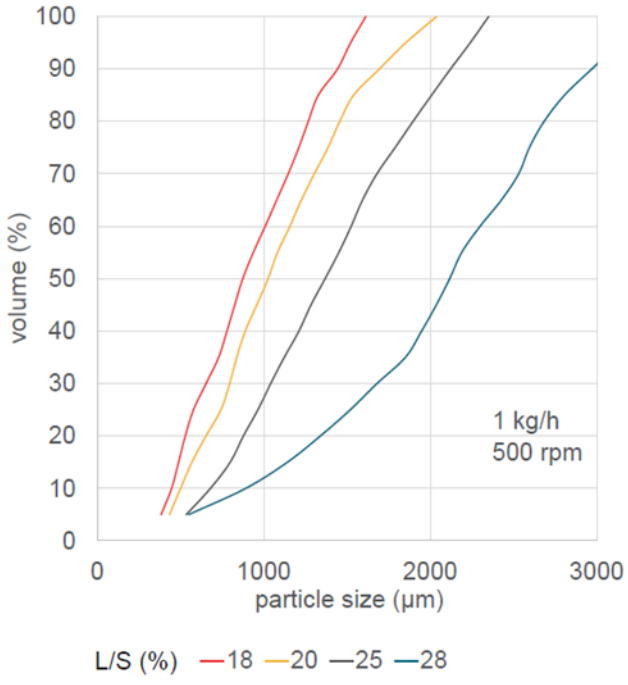


Fig. 5: PSD in dependence of L/S ratio

In contrast to a batch process in continuous operation the amount of material per time [kg/h] is a significant process parameter. Combined with the screw speed this parameter influences the filling level of the TSG. This filling level influences the mean mass diameter (d_{50}) and porosity of granules to a large extend. Figure 6 summarizes this effect.

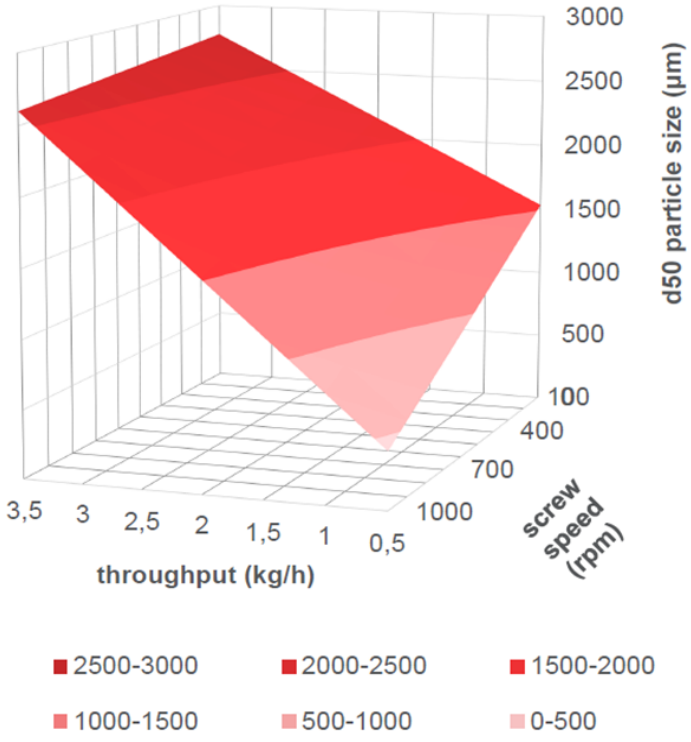


Fig. 6: Influence of filling level on granule size

If the screws are filled with more material (larger throughput and lower screw speed), the material is compressed more which results in larger particles. If the screws are comparatively empty (high screw speeds and low throughputs), there is only a little compression and the granules are smaller.

CONCLUSION

Twin-Screw Granulation (TSG) is a very versatile technique for particle agglomeration. Not only is it possible to formulate actives that are sensitive towards hydration and/or heat with a water-free process (melt/dry granulation). But the understanding of process parameters and their influence on granule properties allow also for a tailored particle size (Figure 7).

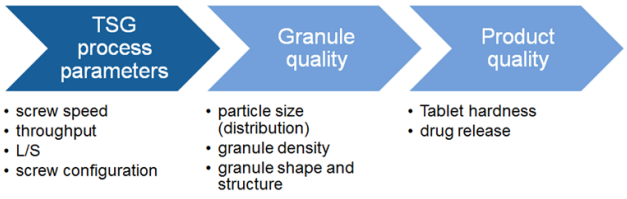


Fig. 7: From process parameters to product quality

Beside that wide range of possible applications, twin-screw extruders make sense as tools for continuous manufacturing, as by design they facilitate the 24/7 operation. The possibility of continuous manufacturing allows the user to speed up research and development, be flexible on production, and produce in high and constant quality. A deep process understanding is the key to take the advantage of fast development.

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Agenda

APGI events

3nd European Conference on Pharmaceutics
25-26 March 2019
Boulogne, Italy

Skin & Formulation
23-24 September 2019
Reims, France

12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
23-26 March 2020
Vienna, Austria

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