APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER ISSUE 3/2015

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DRUG DELIVERY EVENTS

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DDL26 - drug delivery to the lungs 26
09.-11. Dec. 2015, Edinburgh, Scotland, UK — Details

◇ **APV course: ODx and MBx - Orodispersible and Mucoadhesive Buccal Formulations (CN 6621)**
28.-29. Jan. 2016, Innsbruck, Austria — Details

10th WORLD MEETING on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology
04.-07 Apr. 2016, Glasgow, Scotland, UK — Details

Suggest a meeting to be announced!

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

IMLYGIC®

Imlygic® (talimogene laherparepvec) from Amgen is the first oncolytic virus immunostimulant product to receive regulatory approval in the USA [1, 2]. It also received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 22 October 2015 [3, 4] and regulatory approval in Europe is expected imminently. Imlygic® is used for the treatment of malignant melanoma, a disease which in 2012 affected 100,000 people in Europe alone and was the cause of 22,000 deaths [4]. Although Imlygic® is not a typical drug delivery product, its approval will potentially impact on the development, funding and regulatory acceptance of other similar products and viral delivery systems in general. This makes the granting of its product license significant.

The product contains talimogene laherparepvec, a genetically modified herpes simplex virus -1 (HSV-1) capable of infecting melanoma cells, replicating within them and producing the immune stimulatory protein, human granulocyte-macrophage colony-stimulating factor (GM-CSF). The effect is self-perpetuating as when infected tumour cells lyse after being overwhelmed by the virus, viral copies are released into the patient's bloodstream to infect even more tumour cells. In addition, to direct tumour cell-killing through viral infection, the GM-CSF produced promotes a systemic anti-tumour immune and an effector T-cell response. Cell lysis also releases tumour antigens which will further stimulate the immune system. Although talimogene laherparepvec can enter healthy cells, Imlygic® is tumour-cell specific in that it is not able to replicate within healthy cells and hence cannot kill them.

Imlygic® is indicated for the treatment of melanoma in adults with unresectable disease that has spread but has not yet affected the bones, brain, lung or other internal organs. It is available as a liquid injection containing 1x 10^6 PFU/ml and 1x 10^8 PFU/ml. It is injected directly into the melanoma. Approval was based on one randomised controlled clinical trial in which 436 adults with regionally or distantly metastatic melanoma were either injected with Imlygic® (295 patients) or GM-CSF (141 patients). Imlygic® treatment resulted in a durable response rate (defined as disappearance of the

tumours or at least 50% reduction of tumours lasting at least six months) of 25% compared with 1% with GM-CSF treatment in a sub-set of trial patients whose disease had not spread to the lung or other internal organs [3, 4]. Imlygic® has not been shown to improve overall survival or have an effect on visceral metastases. The most frequently reported side effects were fatigue, chills, pyrexia, nausea, influenza-like illness and injection site pain.

Imlygic® has already been launched on the US market. Amgen anticipates the average cost of Imlygic® therapy to be approximately $65,000 in the US [2]. Analysts have estimated that maximum sales will be only around $200 million a year in the US [5]. This is because the clinical data showed that the product was most effective in a sub-set of patients with inoperable melanoma. The product is also likely to face competition from Yervoy (ipilimumab) and Opdivo (nivolumab) from Bristol-Myers Squibb and Keytruda (pembrolizumab) from Merck&Co which have been shown to extend survival times in patients with melanoma.

BELBUCA™ (BUPRENORPHINE) BUCCAL FILM

Belbuca™ buccal film from Endo Pharmaceuticals containing the partial mu opioid receptor agonist, buprenorphine, was approved by the FDA on 23 October 2015 [6, 7]. The product is indicated for the relief of severe pain requiring round-the-clock treatment. It is not for breakthrough pain. The product is available in the following strengths: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg. Opioid-naïve patients should be initiated on a dose of 75 mcg once or twice daily for 4 days before increasing the dose to 150 mcg twice daily.

The product was developed using BioDelivery Sciences International's BioErodible MucoAdhesive (BEMA®) technology [8] and will be marketed by Endo Pharmaceuticals [9] in accordance with the global licensing and development agreement between the two companies. Approval triggers a $50 million payment to BioDelivery Sciences International from Endo and the company will also be eligible for further milestones payments after launch if certain sales milestones are met [10]. The company may also be entitled to tiered royalties on net sales. The technology allows drug release to occur only from the mucoadhesive layer that is placed onto the buccal mucosa and not into oral cavity.

Approval of Belbuca™ was based on two double-blind, randomized, placebo-controlled, enriched-enrollment Phase 3 studies in patients with moderate to severe chronic low back pain. In the BUP-307 study the product was studied in opioid-experienced patients and in BUP-308 in opioid-naïve over a 12-week period. The trials included an open-label period in which patients were titrated to a tolerated, effective dose of Belbuca™ and then randomized to either Belbuca™ or placebo cohorts. In both studies, Belbuca™ demonstrated a consistent, statistically significant improvement in patient-reported pain relief at every week from baseline to week 12, compared to placebo.
Endo Pharmaceuticals plans to launch Belbuca™ in Q1 2016.

References and Further Information

[1] FDA approves first-of-its-kind product for the treatment of melanoma. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm469571.htm. (accessed 14.11.2015).

[2] FDA Approves IMLYGIC™ (Talimogene Laherparepvec) As First Oncolytic Viral Therapy In The US. http://www.amgen.com/media/news-releases/2015/10/fda-approves-imlygic-talimogene-laherparepvec-as-first-oncolytic-viral-therapy-in-the-us/ (accessed 14.11.2015).

[3] Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 19-22 October 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002416.jsp&mid=WC0b01ac058004d5c1 (accessed 14.11.2015).

[4] First oncolytic immunotherapy medicine recommended for approval. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002421.jsp&mid=WC0b01ac058004d5c1 (accessed on 14.11.2015).

[5] A. Weintraub. Amgen's Imlygic May Not Boost Earnings But It Will Change Cancer Care. http://www.forbes.com/sites/arleneweintraub/2015/10/28/amgens-imlygic-may-not-boost-earnings-but-it-will-change-cancer-care/ (accessed on 14.11.2015).

[6] Entry for BELBUCA on Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo (accessed on 14.11.2015).

[7] U.S. FDA Approves BELBUCA™ (buprenorphine) Buccal Film for Chronic Pain Management http://www.endo.com/news-events/press-releases (accessed on 14.11.2015).

[8] Biodelivery Sciences International website. http://www.bdsi.com/ (accessed on 14.11.2015).

[9] Endo Pharmaceuticals website http://www.endo.com/endopharma/home (accessed on 14.11.2015).

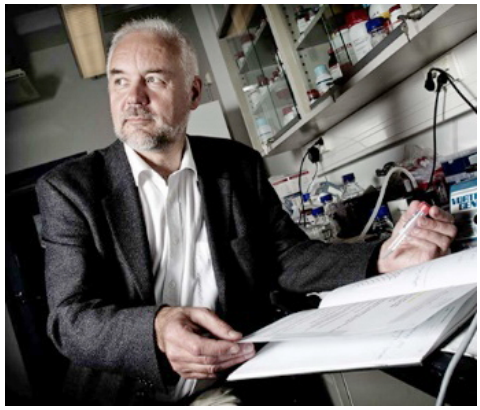
[10] FDA Approval of BELBUCA™ (CIII) (Buprenorphine HCl) Buccal Film for Chronic Pain Triggers Milestone Payment of $50 Million to BioDelivery Sciences from Partner Endo Pharmaceuticals. http://bdsi.investorroom.com/2015-10-26-FDA-Approval-of-BELBUCA-CIII-Buprenorphine-HCl-Buccal-Film-for-Chronic-Pain-Triggers-Milestone-Payment-of-50-Million-to-BioDelivery-Sciences-from-Partner-Endo-Pharmaceuticals (accessed on 14.11.2015).

EGALET CORPORATION (Værløse, Denmark)

Egalet, a fully integrated specialty pharmaceutical company, is focused on developing and commercializing medicines for patients with moderate to severe pain. The company markets OXAYDO™ (oxycodone HCl, USP) Tablets for oral use only – CII, the first and only approved immediate-release oxycodone product formulated to deter abuse via snorting. It is indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. The company also markets SPRIX® (ketorolac tromethamine) Nasal Spray, a non-steroidal anti-inflammatory drug (NSAID) indicated in adult patients for the short-term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level. Egalet's Guardian Technology platform, which combines abuse-deterrent features and precision delivery, can be applied broadly across different classes of pharmaceutical products and be used to develop combination products that include multiple active pharmaceutical ingredients with similar or different release profiles.

Fact sheet:

Founded:	Unknown
Location:	Værløse , Denmark (R&D Center), with headquarters in Wayne, PA, USA
Ownership:	Unknown
Employees:	Unknown
Key technology:	Egalet Guardian™ Technology utilizes injection molding to create a hard matrix and shell that is designed to be difficult to crush, grind, chew, or dissolve and that turns to gel when exposed to water.
Products:	OXAYDO™ Acute and chronic severe and moderate pain SPRIX® moderate to moderately severe pain
Development status:	Egalet is developing a pipeline of late-stage opioid-based product candidates that are specifically designed to deter abuse by physical and chemical manipulation. Egalet's lead programs, Egalet-001, an abuse-deterrent, extended-release, oral morphine formulation, and Egalet-002, an abuse-deterrent, extended-release, oral oxycodone formulation, are in phase 3 clinical development for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate.
Partnerships:	Unknown
Website:	http://www.egalet.com
Contact:	Egalet Headquarters 460 E. Swedesford Road Suite 1050 Wayne, PA 19087, USA Tel: +1 610 833 4200 Research and Development Lejrvej 37-39 , 3500 Værløse , Denmark Tel: +45 44 47 80 80 Fax: +45 44 47 24 25



ARTO URTTI, PhD, is a Professor in Biopharmaceutics at the University of Helsinki, Finland, and has been the Director of the University's Centre for Drug Research since 2005. He is currently also part-time professor of biopharmacy at the University of Eastern Finland.

In 1986, Prof. Urtti received his Ph.D. degree from the University of Kuopio, Finland, after working as a postdoctoral fellow in the Dept. of Pharmaceutical Chemistry, University of Kansas (USA). He subsequently took up a post as Associate Professor of Pharmaceutical Technology and Professor of Biopharmaceutics at the University of Kuopio. He has also spent time as a post-doctoral fellow and as a visiting professor at the Dept. of Bio-Pharmaceutical Sciences at the University of California, San Francisco and the Department of Pharmaceutics, University of Wisconsin, respectively.

Professor Urtti's main research fields are drug delivery (controlled release, computational and cell-based methods for ADME research) and nanotechnology (biomaterial structures for drug and gene targeting). Particular interest in the

research program is focused on ocular drug delivery. He has published over 280 peer-reviewed articles in the field and has filed over 20 patent applications.

In recognition of his research achievements, Prof. Urtti has been awarded the American Association of Pharmaceutical Scientists Fellowship, Honorary Membership of the Finnish Pharmacists' Association, the Albert Wuokko Prize, as well as the Millennium Distinction Award. He was also the editor-in-chief of European Journal of Pharmaceutical Sciences for 10 years and serves as editorial board member in many other journals.

DRUG DELIVERY GROUPS

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ACADEMIC RESEARCH GROUPS: PHARMACEUTICAL POLYMERS

Provided by Dr. Ferdinand Brandl and Manuel Gregoritza, University of Regensburg, Germany

Austria:

Institute	University of Innsbruck, Austria
Department/Lab	Pharmaceutical Technology, Drug Delivery and Powder Technology
Contact	Prof. Dr. Andreas Bernkop-Schnürch
Website	http://www.uibk.ac.at/pharmazie/phtech/drugdelivery
E-Mail	Andreas.Bernkop@uibk.ac.at
Research Areas	• Development of drug delivery systems for the non-invasive administration of poorly absorbed drugs • Development of novel excipients with enzyme inhibitory, permeation enhancing, mucoadhesive, and efflux pump inhibitory properties • Development of mucoadhesive polymers and polymer–enzyme inhibitor conjugates

Belgium:

Institute	Ghent University, Belgium
Department/Lab	Department of Pharmaceutics, Laboratory of Pharmaceutical Technology
Contact	Prof. Dr. Jean Paul Remon
Website	http://www.ugent.be/fw/pharmaceutics/en/research/farmtech
E-Mail	jeanpaul.remon@ugent.be
Research Areas	• Development of innovative drug dosage forms (mainly solid dosage forms) for human application and veterinary use • Pharmaceutical excipients to modify the drug release properties (*e.g.*, immediate, controlled, or sustained release) • The applied technologies include granulation, tableting, extrusion/spheronization, and freeze-drying

Czech Republic:

Institute	The Czech Academy of Sciences, Prague, Czech Republic
Department/Lab	Institute of Macromolecular Chemistry, Biomedical Polymers
Contact	Prof. Dr. Karel Ulbrich
Website	http://www.imc.cas.cz/en/umch/o_biomed.html
E-Mail	ulbrich@imc.cas.cz
Research Areas	• Polymers and polymer systems for targeted drug delivery, and polymers for combined therapy and diagnosis • Polymer gene delivery systems • Hybrid macromolecular stimuli-responsive systems

France:

Institute	Université Angers, France
Department/Lab	UFR Sciences pharmaceutiques et ingénierie de la santé, Micro et nanomédecines en biomimétiques (UMR-S 1066)
Contact	Prof. Dr. Jean-Pierre Benoit
Website	http://mint.univ-angers.fr/fr/index.html
E-Mail	jean-pierre.benoit@univ-angers.fr
Research Areas	No information provided on website; check the publications of the group.

Institute	University of Lille, France
Department/Lab	Faculty of Pharmaceutical Sciences, Controlled Drug Delivery Systems and Biomaterials
Contact	Prof. Dr. Jürgen Siepmann
Website	http://u1008.univ-lille2.fr
E-Mail	juergen.siepmann@univ-lille2.fr
Research Areas	• Preparation of drug delivery systems and biomaterials by direct compression of drug–polymer blends, fluidized bed coating, extrusion, and freeze drying • Physicochemical characterization of drug delivery systems, *e.g.*, by differential scanning calorimetry, size exclusion chromatography, and mechanical analysis • Development of mathematical theories to predict the effects of formulation and processing parameters on the resulting release kinetics

Institute	Université de Lorraine
Department/Lab	Faculté de Pharmacie de Nancy
Contact	Prof. Dr. Philippe Maincent
Website	http://pharma.univ-lorraine.fr
E-Mail	philippe.maincent@univ-lorraine.fr
Research Areas	No information provided on website; check the publications of the group.

Institute	University of Paris-Sud, Orsay, France
Department/Lab	Institute of Pharmaceutical Sciences, Department of Physical Chemistry, Pharmaceutical Technology and Biopharmacy (UMR CNRS 8612)
Contact	Prof. Dr. Patrick Couvreur
Website	http://www.umr-cnrs8612.u-psud.fr/pres_eq7-uk.php
E-Mail	patrick-couvreur@u-psud.fr
Research Areas	• Organic synthesis; polymer chemistry; chemistry of materials; chemistry of bioconjugation; physical chemistry; pharmaceutical technology and drug delivery; cellular and molecular biology; pharmacology; *in vitro* and *in vivo* imaging • Development of targeted nanocarriers; development of nanotheranostics (*i.e.*, nanoparticles possessing therapeutic and diagnostic functions); overcoming drug resistance • Elaboration of new treatments toward severe diseases (*e.g.*, cancer, neurodegenerative diseases, or intracellular infections)

Germany:

Institute	Free University of Berlin, Germany
Department/Lab	Institute of Pharmacy, Department of Pharmaceutical Technology
Contact	Prof. Dr. Roland Bodmeier
Website	http://www.bcp.fu-berlin.de/en/pharmazie/pharmazeutische_ technologie/bodmeier/index.html
E-Mail	bodmeier@zedat.fu-berlin.de
Research Areas	• Multiparticulate, pulsatile, and gastroretentive drug delivery systems; matrix tablets; fast dissolving dosage forms; delivery of poorly soluble drugs; formulation of moisture-sensitive drugs • Coating with aqueous polymer dispersions, aqueous/organic polymer solutions; coating with natural polymers; coating of pellets, tablets, capsules; polymer powder coating • Production of micro- and nanoparticles; incorporation of micro- and nanoparticles in dosage forms • Biodegradable implants and microparticles; liquid drug delivery systems; delivery systems for peptides, proteins, and oligonucleotides; mucoadhesive drug delivery systems

Institute	Free University of Berlin, Germany
Department/Lab	Institute of Pharmacy Pharmaceutical Technology, Nanotechnology and Cosmetics
Contact	Prof. Dr. Rainer H. Müller
Website	http://muller-berlin.com
E-Mail	rainer.mueller@fu-berlin.de
Research Areas	No information provided on website; check the publications of the group.

Institute	Martin Luther University of Halle-Wittenberg, Germany
Department/Lab	Pharmaceutical Technology and Biopharmaceutics
Contact	Prof. Dr. Karsten Mäder
Website	http://pharmtech.pharmazie.uni-halle.de/ag-tech/
E-Mail	karsten.maeder@pharmazie.uni-halle.de
Research Areas	• Development of novel polymers as drug delivery systems • Production, characterization and optimization of polymeric micro- and nanoparticles as drug delivery systems • *In situ* forming implants • Development of coated drug delivery systems • Physicochemical characterization of drug delivery systems using EPR spectroscopy, EPR imaging, NMR spectroscopy, MRI, DSC, FFF, and other methods

Institute	Ludwig Maximilian University of Munich, Germany
Department/Lab	Pharmaceutical Biotechnology
Contact	Prof. Dr. Ernst Wagner
Website	http://www.cup.lmu.de/pb/aks/ewagner/
E-Mail	ernst.wagner@cup.uni-muenchen.de
Research Areas	• Development of non-viral gene transfer vectors (biodegradable polycations, purification of polyplexes, bioresponsive polyplexes, intracellular fate of polyplexes) • Investigation of targeting strategies (receptor-ligand interaction, transcriptional targeting, physical targeting) • Novel strategies for cancer treatment, overcoming chemoresistance, and preventing metastasis

Institute	University of Regensburg
Department/Lab	Department of Pharmaceutical Technology
Contact	Prof. Dr. Achim Göpferich
Website	http://pharmtech.ur.de
E-Mail	achim.goepferich@ur.de
Research Areas	• Synthesis and characterization of polymeric hydrogels for controlled protein delivery • Synthesis of block copolymers, preparation of polymeric nanoparticles, targeted drug delivery • Development of novel vectors for nucleic acid delivery

Institute	Saarland University, Saarbrücken, Germany
Department/Lab	Biopharmaceutics and Pharmaceutical Technology
Contact	Prof. Dr. Claus-Michael Lehr
Website	http://www.uni-saarland.de/lehrstuhl/lehr-lab.html
E-Mail	lehr@mx.uni-saarland.de
Research Areas	• Production of nanoparticulate carrier systems based on biodegradable starch derivatives for targeted drug delivery into tumor cells (NanoSTARCH) • Studying the interactions of biological systems with nanoparticles and nanoparticle coated surfaces used for pharmaceutical purposes (NanoBIOComp)

Italy:

Institute	Università di Pavia, Italy
Department/Lab	Dipartimento di Scienze del Farmaco
Contact	Prof. Dr. Carla Caramella
Website	http://dipsf.unipv.eu/
E-Mail	carla.caramella@unipv.it
Research Areas	No information provided on website; check the publications of the group.

Institute	University of Sassari, Italy
Department/Lab	Department of Chemistry and Pharmacy
Contact	Prof. Dr. Paolo Giunchedi
Website	http://dcf.uniss.it/ws.php?lang=en
E-Mail	pgiunc@uniss.it
Research Areas	No information provided on website; check the publications of the group.

Netherlands:

Institute	Utrecht University, Netherlands
Department/Lab	Utrecht Institute for Pharmaceutical Sciences, Department of Pharmaceutics
Contact	Prof. Dr. Wim E. Hennink
Website	http://www.uu.nl/en/research/pharmaceutics
E-Mail	w.e.hennink@uu.nl
Research Areas	• Recombinant and semi-synthetic drug delivery systems, artificial microbes for vaccination, biomimetic vectors for gene delivery, cost-effectiveness of biopharmaceuticals • Nanogels for peptide and protein delivery, polymeric and mixed micelles for delivery of hydrophobic drugs and photosensitizers, polyester nanoparticles, polymeric absorbents • Hydrogels for regenerative medicine, hydrogels for cartilage regeneration by 3D-printing, hydrogels that release drug-loaded micelles for tumor therapy, polysaccharide-based nanogels

Switzerland:

Institute	University of Geneva, Switzerland
Department/Lab	Biopharmaceuticals and Pharmaceutical Technogy
Contact	Prof. Dr. Éric Allémann
Website	http://www.unige.ch/sciences/pharm/fagal/index.html
E-Mail	eric.allemann@unige.ch
Research Areas	• Biomaterials • Polymeric nanoparticles • Formulation of proteins • Photodynamic therapy • Hot-melt extrusion of polymers

Institute	ETH Zurich, Switzerland
Department/Lab	Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, Drug Formulation and Delivery
Contact	Prof. Dr. Jean-Christophe Leroux
Website	http://www.galenik.ethz.ch
E-Mail	jean-christophe.leroux@pharma.ethz.ch
Research Areas	• Design of polyion complex micelles for antisense oligonucleotides and siRNA delivery • Novel strategies for the treatment of celiac disease • Functionalized amphiphilic biodegradable polymers for drug targeting applications • Colloidal vesicles for the treatment of drug overdose

Disclaimer:

This list has been compiled by Dr. Ferdinand Brandl and Manuel Gregoritza, University of Regensburg, Germany. The selection is based on the number of publications, which has been retrieved by using the Scopus search string TITLE-ABS-KEY(polymer) AND (LIMIT-TO(SUBJAREA, "PHAR")). Whilst every effort has been made to ensure the correctness and completeness of the information provided, there may be some inaccuracies and/or omissions. If you feel that your workgroup should be listed here, please e-mail Ferdinand.Brandl@ur.de.

FEATURED ARTICLE

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Application of numerical simulations in pharmaceutical tableting

By Claudia Hildebrandt [1], Srikanth R. Gopireddy [2] and Nora A. Urbanetz [2]
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[2] Daiichi-Sankyo Europe GmbH, Pharmaceutical Development, Luitpoldstrasse 1, 85276 Pfaffenhofen, Germany

1. Introduction to drug delivery product quality control by numerical simulations

Numerical simulations are widely used in the automotive, aerospace and chemical industries whereas in the pharmaceutical industry, simulations are still rarely applied. This is although they can be used as powerful tools in process and product understanding which forms part of the increasing requirements of the authorities. In 2009 the ICH adopted the Quality by Design (QbD) paradigm for process development by introducing the ICH guideline Q8 [1]. There are several options on how the QbD approach can be implemented in the pharmaceutical development (PD) of drug products. As illustrated in Fig. 1 *[see section "Figures"]*, science-based manufacturing of pharmaceuticals involves not only process analytical tools, but also the implementation of a risk management strategy, the design of experiments, advanced data analysis techniques, material characterization and eventually process modeling and control via numerical simulations [2, 3]. Additionally, in January 2014 the FDA issued a draft guidance on implementing computational modeling and simulation for "Studies in Medical Device Submissions" [4].

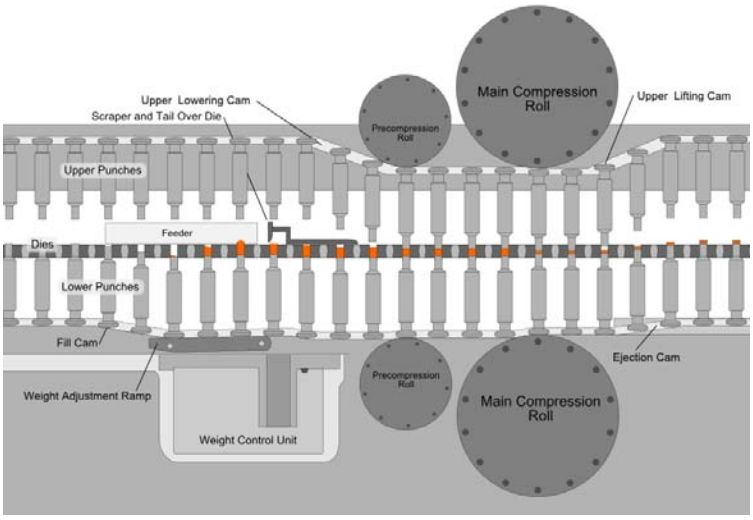

Fig. 2: Schematical illustration of a rotary tablet press (side view) [Wikipedia]

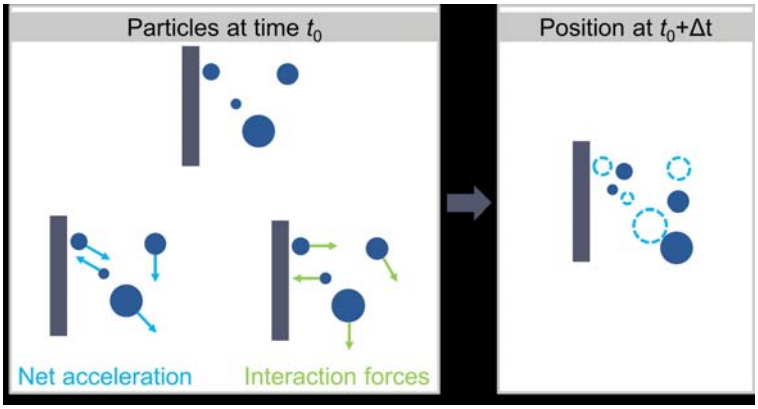

Fig. 3: Computational procedure of DEM

Tablets as drug delivery systems were first described in ancient times by the Greeks. The first industrial tablet production dates back to 1877 and today this dosage form covers 80% of all available drug delivery systems (according to the International Association of Pharmaceutical Technology) [5].

Over almost 150 years of tablet production and process development, nontrivial challenges still remain to ensure product quality. One major issue in tablet production and from a patient safety point of view is the accurate content and content uniformity of the active pharmaceutical ingredient (API). The tableting process on a high-speed rotary tableting press can be generally divided into three distinct stages: die filling, compaction and ejection. A schematic illustration of a rotary tablet press is presented in Fig. 2. The first stage, the die filling, represents the most crucial control variable since it specifies the mean and range of both the tablet mass and the mass of the API.

With exponentially increasing computational power and a better understanding of particle physics, numerical simulations can be applied to pharmaceutical process understanding. The computational fluid dynamics (CFD), the finite element method (FEM) and the discrete element method (DEM) are models which were developed to elucidate the fundamental physical processes underlying the manufacture, formulation and delivery of pharmaceutical dosage forms [6]. CFD is applicable in the analysis of gas-liquid systems whereas FEM is predominantly used in structural and mechanical analysis of materials. Similarly the DEM model is suitable for solid-based systems, in which particles are considered to be individual elements and collisional forces between the particles as well as with the geometry are estimated to compute the resulting particle trajectories (see Fig. 3) [2]. The details of DEM and its application to particle systems is comprehensively summarized by Zhou et al. [7, 8] and Ketterhagen et al. [9].

This article will focus on the use of DEM to study die filling in order to improve process understanding and will emphasize how DEM simulations are able to support experimental studies. It will tell the story of how simulations will be able to impact product quality by process understanding in a positive way.

2. Model die-shoe filling set-up to visualize the die filling process

Experimental set-up of the model-die shoe system

The story of investigating die filling started with the paper by Wu et al. in 2003 which reported the development of a model die-shoe filling system to facilitate visualization of the commercial die filling processes within the steel and cement industries. This was later adopted to pharmaceutics [10]. The system enables the interaction between a stationary die and a moving delivery system to be studied (see Fig. 4). The shoe, a rectangular box, is filled with powder and translates over a transparent die with a steady state velocity between 10 and 10000 mms^{-1}. The model provides a direct measure of flowability and quantitative results are obtained by measurement of the mass of powder in the die as a function of the shoe velocity. The entire die-filling system is located in a transparent vacuum chamber to determine the influence of air [11].

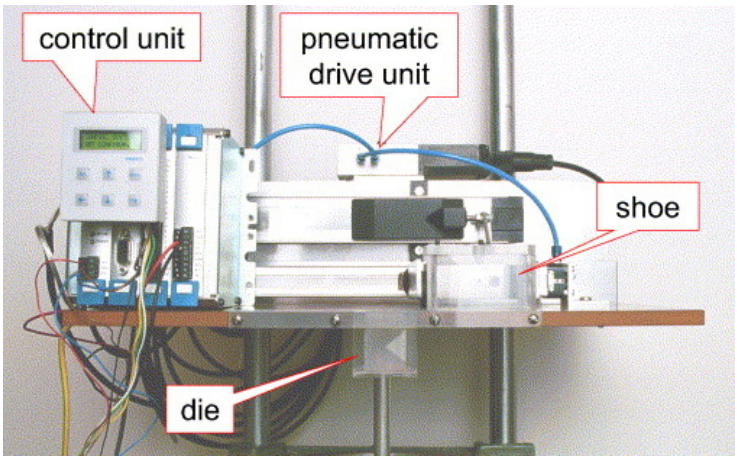

Fig. 4: Experimental set-up of the model die-shoe filling system [10]

High-speed videos have been employed to observe details of the flow process as the powder is delivered into the die. Three major types of flow have been identified: nose, bulk and

intermittent flow, which are schematically shown in Fig. 5. The nose flow dominates at low shoe speeds, whereas the bulk flow controls at high shoe speeds [10]. In comparison, pharmaceutical powders are more likely to flow intermittently, which is illustrated as the random detachment of individual particles [12].

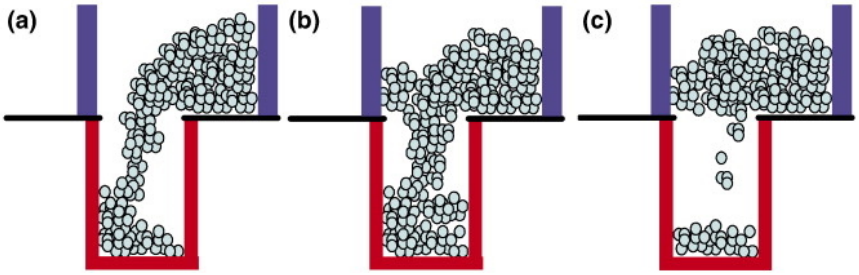

Fig. 5: Schematic representation of (a) nose, (b) bulk and (c) intermittent flow [12]

The latest experimental study was published in 2013 by Mills et al. [13] with the focus on the effect of particle size and density of microcrystalline cellulose on the flowability. The flowability was quantified using the concept of "critical velocity" which was first introduced by Wu et al. [10] and describes the maximum velocity of the shoe for which a given die is completely filled with powder after one pass. For example, the critical velocity correlated with the particle size, resulting in a higher critical velocity for larger particles [13].

All experimental studies supported the process understanding of powder delivery into a confined space with respect to the influence of particle size and density, of air and vacuum and of gravity and suction filling [10-16].

Numerical simulations of the model die-shoe system

Three years after the development of the model die-shoe filling system, numerical simulations started with the calculation of flowability metrics. The focus of these simulation studies include the identification of optimum process conditions, optimization of the powder formulation in terms of flowability and segregation and an increased understanding of the process under consideration.

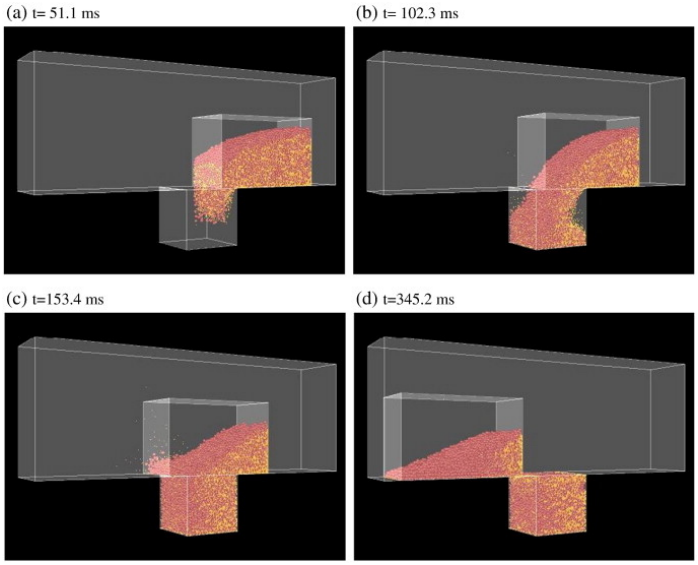

Fig. 6: Die filling in air with a moving shoe [22]

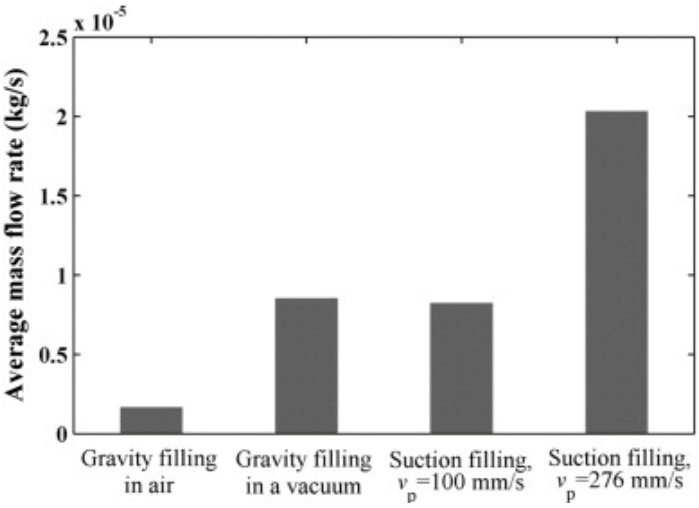

Fig. 7: Average mass flow rates under various filling conditions (v_p = punch velocity) [23]

The first studies in 2006 [14] and 2008 [17] by Wu et al. were limited by computational resources to a 2D model and a very small number of simulated particles (2000 and 3000, respectively). The first 3D model was published in 2009 (Bierwisch et al. [16, 18]). However this study deals with metallurgical materials where the particle-particle and particle-wall interactions are quite different compared to pharmaceutical powders. Furthermore, the effect of air was not included.

On the way to more realistic simulations, the effect of air was included by coupling the DEM with the CFD model. This early work suffered from 2D simulations and few particles with a large particle size [19-21]. Guo et al. were the first who studied the influence of different particle sizes (binary mixture, 120,000 particles in total) on the segregation behavior within a 3D air model (see Fig. 6) [22]. In their follow-up study they included the effect of suction filling, which models the downward motion of the lower punch in a rotary tablet press. They concluded that the downward motion of the punch in suction filling created a pressure gradient across the powder bed, which augmented the flow of powder into a die. As a result the mass flow rate and the critical shoe velocity were significantly increased compared to gravity filling in air (see Fig. 7). This study underlines that suction filling can be employed to improve the process efficiency of the die filling [23].

A more comprehensive and realistic 3D DEM numerical work studied powder flow from a fixed shoe to the moving die, the same as in a rotary tablet press. The

effect of process conditions, i.e. the turntable rotational speed and particle size as well as size distribution (mono-disperse vs poly-disperse) on the die filling were investigated [24]. A follow-up study showed the die filling process from an open feeder system, which can be also used in tablet presses. Particles were filled continuously into a chute and discharged into a rotating die table (40 rpm) (see Fig. 8, unpublished data).

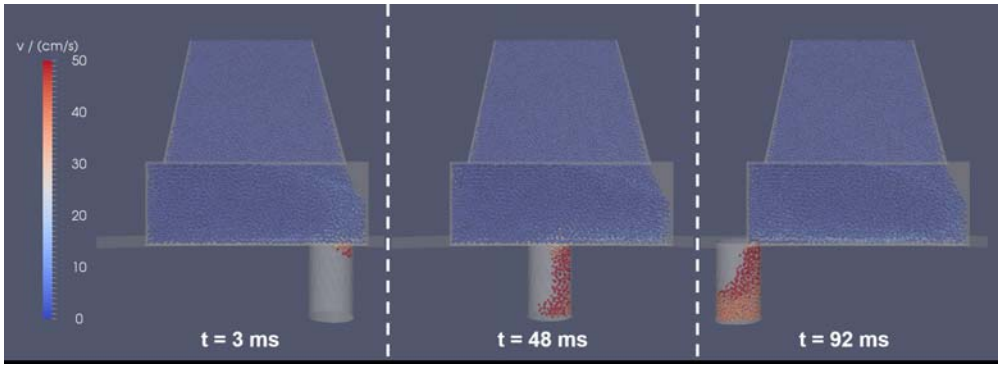

Fig. 8: Powder discharge from an open feeder system into a rotating die table

However, most of these experimental and numerical studies investigated the powder flow from a rectangular shaped shoe compared to the very complex die filling with an advanced feeding system which is present in rotary tablet presses.

3. Die filling in rotary tablet presses

Experimental powder die filling in rotary tablet presses

In rotary tablet presses the feed frame facilitates even filling of the dies and contributes significantly to the final tablet quality in terms of weight variation and content uniformity. Feed frames are mechanical devices which force the powder to fill into the dies of a rotary tablet press. Typically, a feed frame is a box containing one or more paddles. Powder enters through the top, the paddles force the powder to exit through a slit at the bottom, pushing it into the dies.
Different designs of the feed frames in terms of number, dimensions, and shapes of the paddles, number of chambers and heights exist [25]. One example of the feed frame for a MODUL™ P tablet press is depicted in Fig. 9.

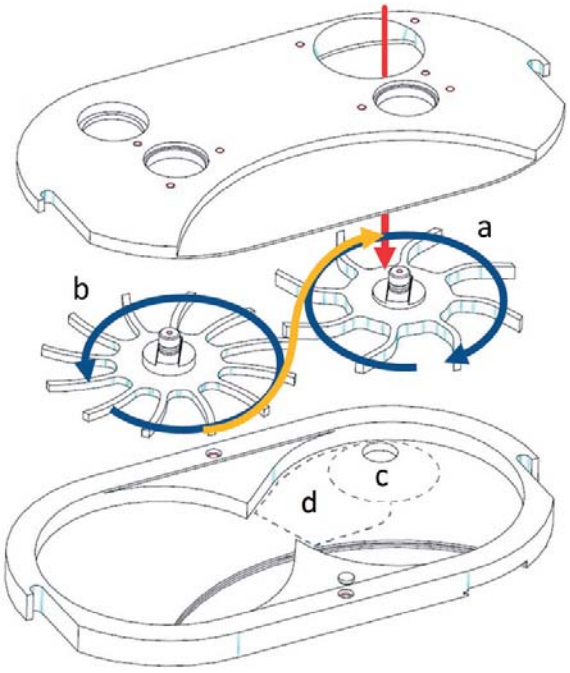

Fig. 9: Schematic overview of the feed frame with two paddles:
(a) feeding paddle (b) metering paddle (c) infeed (d) recirculation area of the feeding paddle. Arrows depict schematically the movement of the powder through the feed frame [26]

From 2010 on, four studies investigated different process parameters within the feed frame. Mendez et al. systematically focused on the effects of blend composition, feed frame parameters (blade speed, residence time), rotary die disk parameters (die disk speed, die diameter), uniformity of die filling, applied shear and finally the flow properties of pharmaceutical blends [25].

Narang et al. introduced a dimensionless shear number which is defined as a function of shear rate, shear frequency and residence time of the powder in the feed frame. This number would provide guidance to the scale-up and interchangeability of tablet presses and to estimate the total shear imparted by the force feeder on the granules [27]. Another study investigated the effect of the feed frame design and operating parameters on the powder hydrophobicity and flow properties [28]. The latest comprehensive work in 2015 examined the influence of paddle speeds and fill depth at different tableting speeds on the weight and weight variability of tablets [26]. This study could help to predict the optimum combination of the studied process parameters yielding the minimum tablet weight variability.

All in all, the experimental work came to the following conclusions:

- The powder weight in the dies increases for faster feed frame speeds and decreases for higher die disc speeds [25].
- A higher die table and force feeder speed reduces the tablet tensile strength and the tabletability. The force feeder speed attributes to the shearing of the granules, leading to its over-lubrication [27, 28].
- Paddle speeds in the force feeder are of minor importance for tablet weight variability in case of powders with excellent flowability but are when the powders have flow properties classed as fair. [26].

These studies can support the understanding of die filling within the tableting unit operation however they are limited by:

- The very high number of different experiments, that have to be conducted, i.e. the Design of Experiments (DoE) setup in [26].
- The large quantity of material and amount of time required.
- The residence time of the particles within the feed frame, that is difficult to track and which requires the coloring of the particles and subsequent particle detection, i.e. via Near Infrared technique [25].

These limitations of experimental studies can be overcome by the support of numerical simulations which will be discussed in the next section.

Numerical powder die filling in rotary tablet presses

Compared to the higher number of publications dealing with the simulation of the model die-shoe filling system, the interest into simulations of the force feeder system just started in 2014. Mateo-Ortiz et al. studied the particle size segregation phenomena in a Manesty Beta Press. They could show that the particles segregated inside the feed frame at low paddle wheel speeds (see Fig. 10). By plotting velocity profiles and particle vectors, the percolation phenomenon was identified as the most significant segregation mechanism (see Fig. 11 *[in section "Figures"]*) [29]. Another study by Ketterhagen in 2015 focused on the effect of different paddle wheel shapes (see Fig. 12 *[in section "Figures"]*) in a single paddle wheel force feeder setup and the particle residence time distribution within the feed frame. He could show that a faster paddle wheel speed can generally lead to more uniform tablet masses (see Fig. 13 *[in section "Figures"]*) [30]. However the material characteristics of the analyzed particles corresponded to those of large (0.9 mm radius) glass beads rather than pharmaceutical powders.

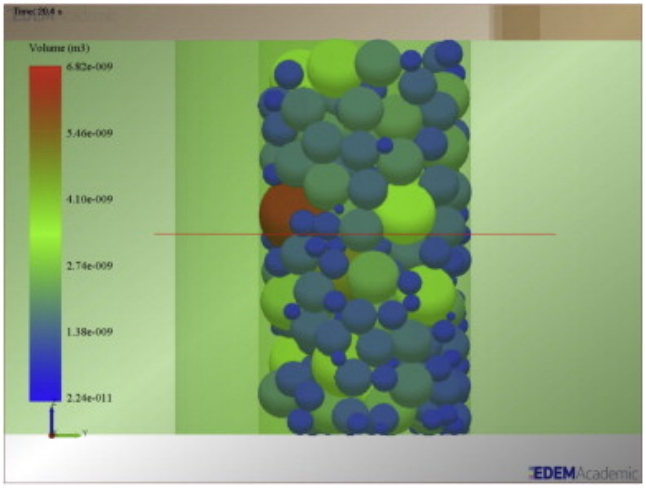

Fig. 10: Example of top to bottom segregation in a die [29]

Just recently, we were able to investigate a more realistic force feeder setup with microcrystalline cellulose, a commonly used excipient in tablet formulations, with a poly-disperse particle size distribution. The smallest particles (radius of 167.5 µm) were assumed to represent the active pharmaceutical ingredient (API) (see Fig. 14 *[in section "Figures"]*). By using simulations we could easily calculate the content uniformity and weight variation according to the Ph. Eur. Monograph 2.9.40 (see Fig. 15 *[in section "Figures"]*) [31].

Since die filling within production tablet presses represents a major quality attribute, simulations can support the process understanding in a positive way:

- Particle velocities and residence time distributions can be easily calculated and help in measuring the work done on the particles and the resulting effects such as particle attrition and powder lubrication.
- Different particle sizes and materials can be simulated to get an idea of the critical process parameters such as paddle wheel and die table speed where experiments would take quite long and require a lot of material.
- A deep insight into the instrument design and process variables can be easily obtained where experiments are limited.

With the help of increased numerical resources, simulations will allow the system studied to get more and more complex with respect to number of analyzed particles and different material characteristics. By this, simulations will represent a powerful tool in formulation and process design and support product quality control concurrently with established means of pharmaceutical development.

4. Summary and Conclusion

This article tells the story of research related to die filling from its beginning in 2003 to the state-of-the art in 2015. The first experiments were performed with a model die-shoe filling system and established a frame work for the discharge of powder from a moving into a stationary box. The experiments could be well reproduced by numerical simulations; however, this model system could not be simply converted to the complexity within the tableting unit operation. Just in 2010, the first force feeder experiments were conducted and were supported four years later by numerical simulations. To date simulations of this unit operation of the pharmaceutical industry have just started but will grow in the near future.

The major benefits of numerical simulations are the low costs and the vast array of process parameters which can be easily analyzed. In line with the regulatory requirements and the QbD approach, simulations provide an effective instrument for process understanding and can help in identifying the critical attributes of the tableting unit operation whereas experimental and analytical approaches are limited. The simulation of the die filling process in tablet presses is one approach to get a better understanding of the production of this dosage form, but with the increasing innovations in drug delivery, simulations will be considered from the very beginning of process development in the future.

Figures:

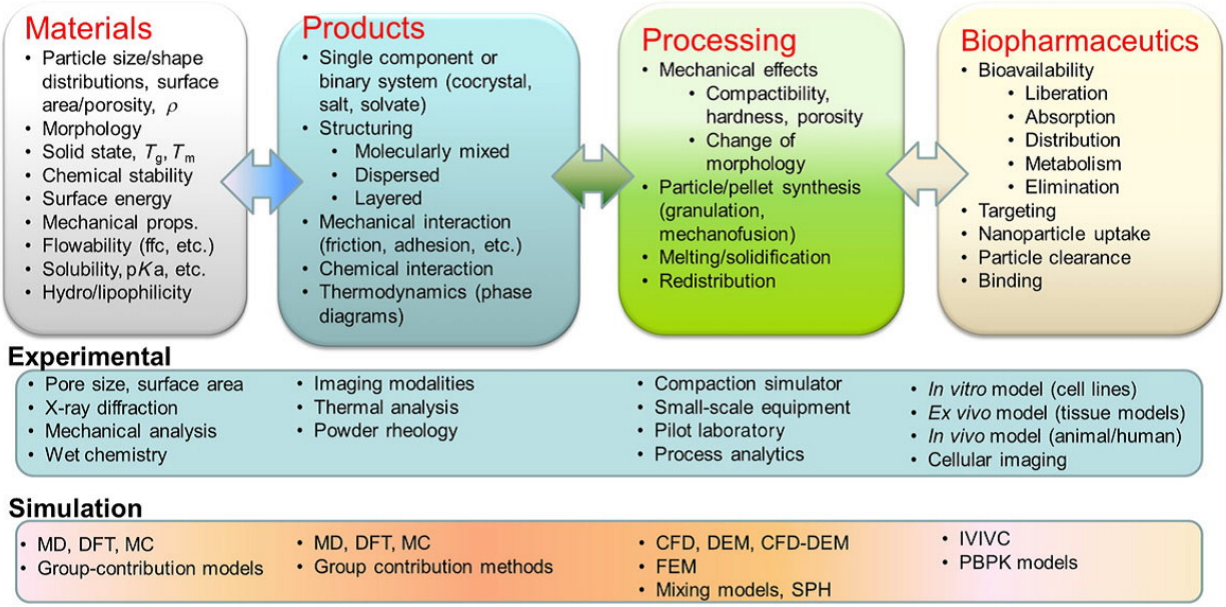

Fig. 1: Product quality control options of pharmaceutical development [2]

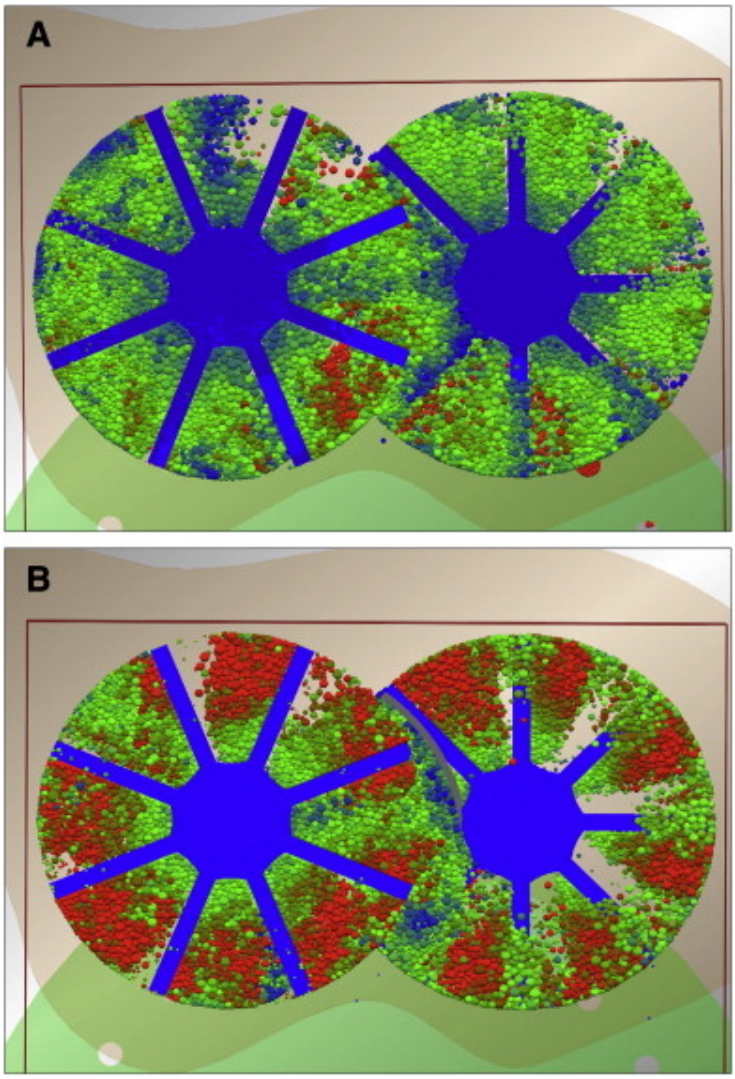

Fig. 11: Particle velocity profile at 24 rpm (A) and 72 rpm (B) paddle wheel speed [29]

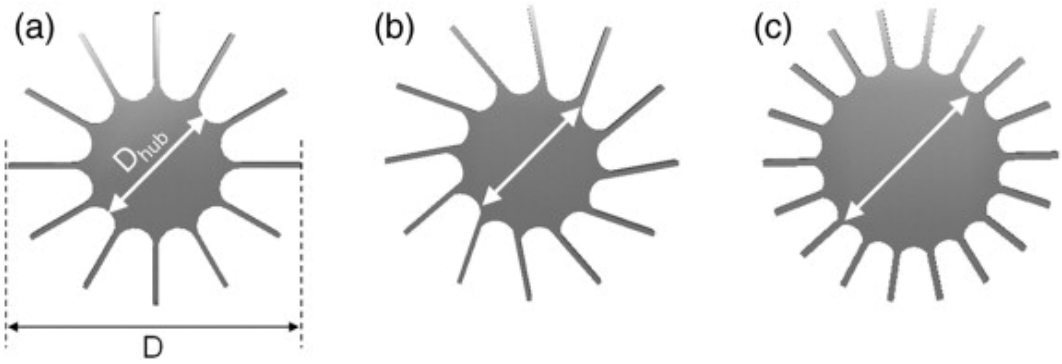

Fig. 12: Paddle wheel shapes investigated: (a) standard, (b) angled and (c) large hub wheel [30]

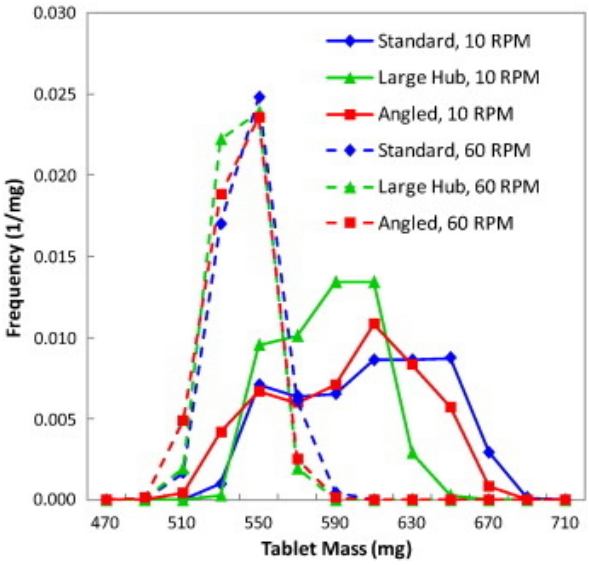

Fig. 13: Frequency distribution of tablet mass for a given paddle wheel shape and rotation speed [30]

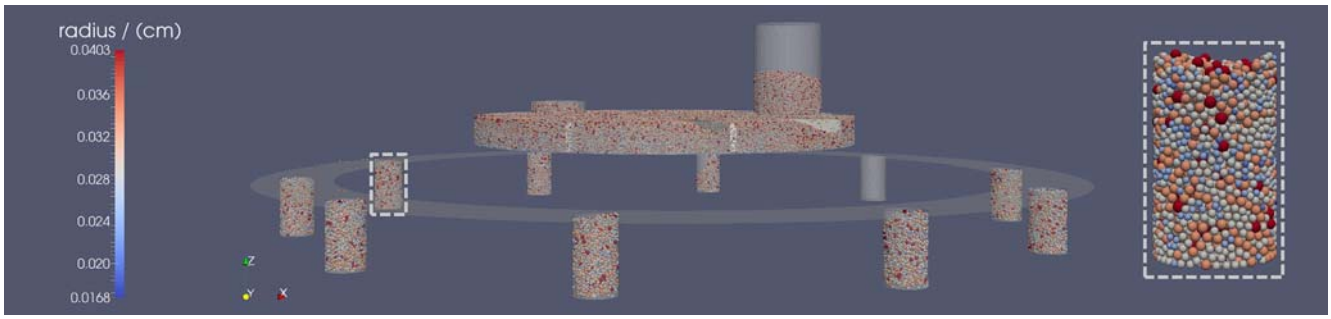

Fig. 14: Simulation of die filling with a model formulation of microcrystalline cellulose and a poly-disperse particle size distribution (API is assumed to have a radius of 167.5 µm) [31]

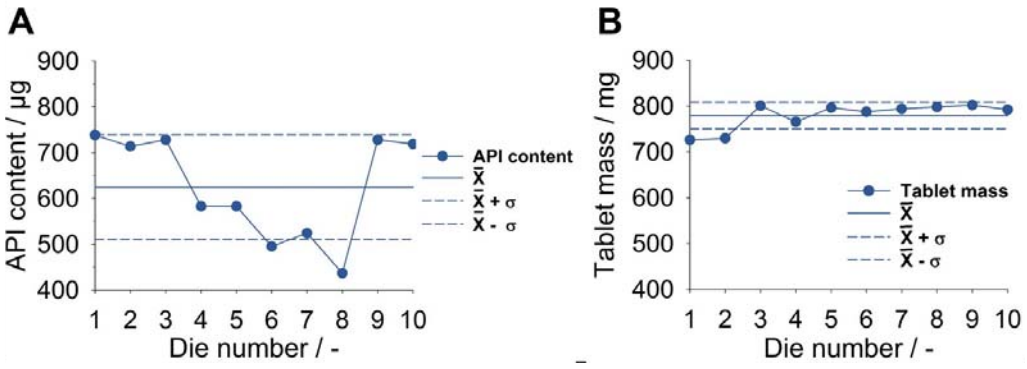

Fig. 15: Content uniformity (A) and weight variation (B) of the model formulation [31]

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

Our mission includes in particular the following tasks:

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

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