MAKING SCIENCE WORK

Nachrichten und Mitteilungen

International Association for Pharmaceutical Technology
Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V.
Gemeinnütziger wissenschaftlicher Verein

03 · 2018

APV NEWS

Formulating better medicines for children

Meeting the needs of the children

10th conference of the European Paediatric Formulation Initiative

11 - 13 September 2018 · Course No. 6729

preconference workshops • table top exhibition
poster sessions • soapbox sessions • sponsoring opportunities

submission deadline 20 May 2018

EuPFi

APV MAKING SCIENCE WORK

A conference organised by the International Association for Pharmaceutical Technology in partnership with the European Paediatric Formulation Initiative

APV/IPEC Europe Excipient Conference 2018

18 - 19 September 2018
Cologne · Germany

– An update on regulatory developments and their application –

OBJECTIVES

- Implementation of GMP in an excipient manufacturing site
- Qualification and auditing of suppliers
- Analytical data and certificates of analysis for excipients
- The European Pharmacopoeia's General Methods Modernisation Programme
- USP – Strategies and Opportunities for Excipient Standard Setting
- Particulate matter in pharmaceutical starting materials and drug products
- Regulatory and technical challenges for excipients in parenteral formulations
- Formulation topics

The entire program is available on **www.apv-mainz.de**

Kölner Lichter - KölnTourismus GmbH, photograph by Dieter Jacobi

WORKSHOPS:
Achieving compliance for Excipients using IPEC Guidelines

How to implement appropriate GMPs in an excipients manufacturing site
– "What brings you from ISO 9001 to Excipient GMP"

Using IPEC Guidelines to streamline the audit process and simplify supplier oversight
– "Audit Preparation & Supplier Performance Evaluation: a win-win partnership"

Analytical data and COAs of suppliers
– "How to enable pharma industry to outsource excipient testing to suppliers"

the future of excipients is in our hands

IPEC EUROPE APV

Detailierte Informationen zu unserem Kursprogramm finden Sie unter:

www.apv-mainz.de

Lokale Gruppen

Mittwoch, 30. Mai 2018
Lokale APV-Gruppe Rhein-Main ab 19:30 Uhr. Der Veranstaltungsort wird noch bekanntgegeben.
Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Cathrin Pauly (pauly@aspiras.de)

Mittwoch, 06. Juni 2018
Lokale APV-Gruppe Köln/Bonn/Aachen ab 18:30 Uhr im Brauhaus Sünner im Wallfisch in Köln (Salzgasse 13, 50667 Köln).
Anmeldung erforderlich bis zum 30. Mai 2018 bei Dr. Heiko Spilgies (heiko@spilgies.de).

Dienstag, 11. September 2018
Lokale APV-Gruppe Berlin um 19:00 Uhr in den Firmenräumen der PDA Europe gGmbH (Am Borsigturm 60, 13507 Berlin).
Anmeldung erforderlich bis zum 04. September 2018 bei Dr. Andreas Sachse (andreas.sachse@cpl-sachse.de).

Lokale APV-Gruppe Basel
Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Dr. Lars Restetzki (lars.restetzki@roche.com).

Lokale APV-Gruppe Westfalen
Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Dr. Johanna Mosig (johanna.mosig@bayer.com).

Lokale APV-Gruppe Mecklenburg-Vorpommern
Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Katharina Tietz (katharina.tietz@uni-greifswald.de).

Lokale APV-Gruppe Oberbayern
Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Dr. (USA) Julia Schulze-Nahrup (jsn@pharmoveo.de).

What´s hot in European Journal of Pharmaceutics and Biopharmaceutics?

Christoph Marschall, Ludwig-Maximilians-Universität, D-München

Katharina Tietz et al./European Journal of Pharmaceutics and Biopharmaceutics 123 (2018) 71–83
Bioequivalence of locally acting lozenges: Evaluation of critical in vivo parameters and first steps towards a bio-predictive in vitro test method
Katharina Tietz, Sina I. Gutknecht, Sandra Klein

Locally-acting lozenges are among the most common types of solid dosage forms applied in the oral cavity. Since no guidance on the in vitro demonstration of local bioequivalence is available, we wanted to develop a new bio-predictive test method for dissolution of lozenges based on a set of physiological parameters relevant to lozenge dissolution in the oral cavity. An in vivo sucking study determining the impact of different lozenge (candy) bases and flavours on sucking times, saliva osmolality and salivary flow rates was performed in 6 volunteers. In vivo sucking times were compared with in vitro dissolution times observed in experiments with official dissolution methods. In vitro dissolution times of all formulations were significantly longer than average in vivo sucking times (20–30 vs. <5 min) indicating that official test methods are not applicable for predicting in vivo dissolution of lozenges. Therefore, we developed and evaluated a novel test apparatus enabling the simulation of forces applied by tongue and hard palate during sucking. Results obtained in a first set of in vitro experiments came very close to those obtained in vivo. This novel in vitro approach is thus very promising in terms of predicting the bioequivalence of locally-acting lozenges.

Pieter-Jan Van Bockstal et al./European Journal of Pharmaceutics and Biopharmaceutics 123 (2018) 108–116
Global Sensitivity Analysis as Good Modelling Practices tool for the identification of the most influential process parameters of the primary drying step during freeze-drying
Pieter-Jan Van Bockstal, Séverine Thérèse F.C. Mortier, Jos Corver, Ingmar Nopens, Krist V. Gernaey, Thomas De Beer

Pharmaceutical batch freeze-drying is commonly used to improve the stability of biological therapeutics. The primary drying step is regulated by the dynamic settings of the adaptable process variables, shelf temperature Ts and chamber pressure Pc. Mechanistic modelling of the primary drying step leads to the optimal dynamic combination of these adaptable process variables in function of time. According to Good Modelling Practices, a Global Sensitivity Analysis (GSA) is essential for appropriate model building. In this study, both a regression-based and variance-based GSA were conducted on a validated mechanistic primary drying model to estimate the impact of several model input parameters on two output variables, the product temperature at the sublimation front Ti and the sublimation rate m_{sub}. T_s was identified as most influential parameter on both T_i and m_{sub}, followed by Pc and the dried product mass transfer resistance α_{Rp} for T_i and m_{sub}, respectively. The GSA findings were experimentally validated for sub via a Design of Experiments (DoE) approach. The results indicated that GSA is a very useful tool for the evaluation of the impact of different process variables on the model outcome, leading to essential process knowledge, without the need for time-consuming experiments (e.g., DoE).

J. Eriksson et al./European Journal of Pharmaceutics and Biopharmaceutics 124 (2018) 1–12
Pulmonary absorption – estimation of effective pulmonary permeability and tissue retention of ten drugs using an ex vivo rat model and computational analysis
Johanna Eriksson, Erik Sjögren, Helena Thörn, Katarina Rubin, PerBäckman, Hans Lennernäs

Permeation of inhaled drugs across the pulmonary epithelium can regulate the rate and extent of local drug absorption and hence the pulmonary tissue concentration. Therefore, understanding pulmonary epithelial transport could be important for successful design of novel inhaled medicines. To enhance understanding of pulmonary epithelial transport, drug transport data were generated for a set of inhaled compounds (n = 10) in the single-pass, isolated perfused rat lung model. A compartmental in silico model was used to estimate pulmonary permeability and tissue retention. The theoretical model was also used to re-analyze previously obtained historical drug transport data from the isolated perfused lung (n = 10) with re-circulating buffer. This was performed to evaluate the re-circulating model for assessing tissue retention measurements and to increase the number of data points. The tissue retention was an important parameter to estimate to be able to describe the drug transport profiles accurately of most of the investigated compounds. A relationship between the pulmonary permeability and the intrinsic (carrier-mediated transport inhibited) permeability of Caco-2 cell monolayers (n = 1–6) was also established. This correlation ($R2 = 0.76$, $p < .0001$) suggests that intrinsic Caco-2 permeability measurements could offer early predictions of the passive transcellular permeability of lung epithelium to candidate drugs. Although, for some compounds a deviation from the correlation suggests that other transport mechanisms may coexist. The compartmental in silico model was successful in describing the pulmonary drug transport profiles of the investigated compounds and has potential for further development to investigate the effects of

formulations with different features on the pulmonary overall absorption rate.

E. S. Bochmann et al./European Journal of Pharmaceutics and Biopharmaceutics 124 (2018) 34–42
Numerical simulation of hot-melt extrusion processes for amorphous solid dispersions using model-based melt viscosity
Esther S. Bochmann, Kristina E. Steffens, Andreas Gryczke, Karl G. Wagner

Simulation of HME processes is a valuable tool for increased process understanding and ease of scale-up. However, the experimental determination of all required input parameters is tedious, namely the melt rheology of the amorphous solid dispersion (ASD) in question. Hence, a procedure to simplify the application of hot-melt extrusion (HME) simulation for forming amorphous solid dispersions (ASD) is presented. The commercial 1D simulation software Ludovic® was used to conduct (i) simulations using a full experimental data set of all input variables including melt rheology and (ii) simulations using model-based melt viscosity data based on the ASDs glass transition and the physical properties of polymeric matrix only. Both types of HME computation were further compared to experimental HME results. Variation in physical properties (e.g. heat capacity, density) and several process characteristics of HME (residence time distribution, energy consumption) among the simulations and experiments were evaluated. The model-based melt viscosity was calculated by using the glass transition temperature (T_g) of the investigated blend and the melt viscosity of the polymeric matrix by means of a T_g-viscosity correlation. The results of measured melt viscosity and model-based melt viscosity were similar with only few exceptions, leading to similar HME simulation outcomes. At the end, the experimental effort prior to HME simulation could be minimized and the procedure enables a good starting point for rational development of ASDs by means of HME. As model excipients, Vinylpyrrolidone-vinyl acetate copolymer (COP) in combination with various APIs (carbamazepine, dipyridamole, indomethacin, and ibuprofen) or polyethylene glycol (PEG 1500) as plasticizer were used to form the ASDs.

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Anna-Maria Pötzl · APV e.V.

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Hersteller/Typ	Listenpreis	mtl. Rate
Audi A6 Limousine 55 TFSI quattro S tronic 250kW/340PS inkl. Audi connect, MMI-Navigation, 2 Zonen-Klimaautomatik, PDC v+h, LED-Scheinwerfer, 18" LM-Felgen etc.	50.950,00 €	549,00 €
BMW 218i Active Tourer 80kW/109PS inkl. Klimaautomatik, PDC hinten, Automatische Heckklappenbetätigung, Armauflage vorn, Tempomat, 16" LM-Felgen V-Speiche 471 etc.	25.000,00 €	275,00 €
BMW X1 sDrive18i 103kW/140PS inkl. PDC hinten, Klimaautomatik, Ablagenpaket, Tempomat mit Bremsfunktion, Automatische Heckklappenbetätigung, 17" LM-Felgen etc.	28.403,00 €	279,00 €
BMW X3 xDrive20i 135kW/184PS Automatic inkl. Navigation, Klimaautomatik, PDC, Innen- und Außenspiegelpaket, Sitzheizung vorne, Lordosenstütze vorne, 18" LM-Räder etc.	41.008,00 €	385,00 €
BMW X4 xDrive30i 185kW/252PS Automatic inkl. Klimaautomatik, Navigationssystem, M-Sportfahrwerk, Sitzheizung Fahrer/Beifahrer, Ablagenpaket, 18" LM-Räder etc.	49.832,00 €	479,00 €
Ford Focus Cool & Connect Turnier 1,0l EcoBoost 74kW/100PS inkl. Navi SYNC3, Klimaanlage, Parkpilotsystem vorn + hinten, Tempomat, Sportsitze vorn, 16" LM-Räder etc.	19.832,00 €	165,00 €
Ford C-MAX Cool & Connect 1,0l EcoBoost 74kW/100PS inkl. Navigationssystem inkl. Ford SYNC 3, Nebelscheinwerfer, Klimaanlage, Park-Pilot-System hinten etc.	19.580,00 €	189,00 €
Mercedes A 200 Limousine 120kW/163PS inkl. Metallic, Navi Premium Paket, Klimaautomatik, Park-Assistent PARKTRONIC Rückfahrkamera, LED, Sitzheizung vorne, 17" LM-Räder etc.	32.090,00 €	349,00 €
Mercedes C 200 T-Modell 135kW/184PS inkl. Metallic, 9G-TRONIC, Klimaautom., LED-Scheinwerfer, High-End Infotainment-Paket, Sitzheizung vorn, Park- u. Fahrassistenz-Paket etc.	43.445,00 €	519,00 €
Mini One D Countryman 85kW/116PS inkl. Grey-Metallic, Klimaautomatik, Radio MINI Visual Boost, Lichtpaket, Nebelscheinwerfer, Sitzheizung Fahrer/Beifahrer, LM-Räder etc.	25.555,00 €	199,00 €
Volvo V40 T2 Momentum 90kW/122PS inkl. Navigation, Infotainmentsystem Sensus Connect mit HIGH PERFORMANCE Sound, Klimaautomatik, LED Scheinwerfer, LM-Räder etc.	23.992,00 €	179,00 €
Volvo XC60 D4 Momentum 140kW/190PS inkl. 12,3" Display, Sensus-Navi, LED Scheinwerfer, Klimaautomatik, Tempomat, Spurhalteassistent, 18" LM-Räder, etc.	38.571,00 €	299,00 €
VW UP GTI 1,0l TSI 85kW/115PS 6-Gang inkl. Klimaanlage, Radio Composition Sound Plus, Sitzheizung, Sportfahrwerk, Sportlenkrad in Leder, 17" LM-Räder "Brands Hatch" etc.	14.265,00 €	159,00 €
VW Touareg 3,0l V6 TDI SCR 210kW/286PS inkl. 8-Gang-Automatik, Navi, Klimaautomatik, LED-Scheinwerfer, Einparkhilfe, Spurhalteassistent, Tempomat, Winterpaket, etc.	51.979,00 €	489,00 €