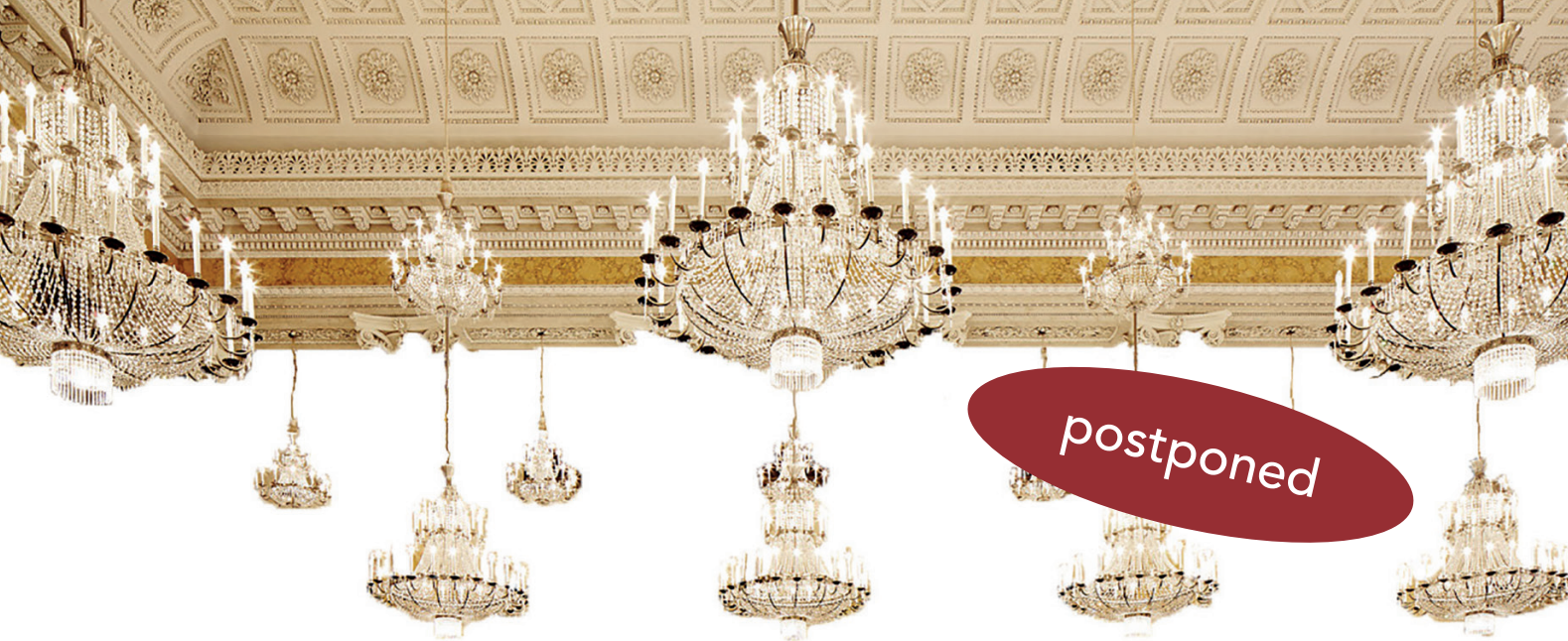
MAKING SCIENCE WORK

# Nachrichten und Mitteilungen

03 · 2020

# APV NEWS

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




# 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

## Vienna, Austria

8 - 11 February 2021

PBP WORLD MEETING

in combination with

ResearchPharm®
International Exhibition for R&D


www.worldmeeting.org

# Lokale Gruppen

Donnerstag, 23. Juli 2020

## Lokale APV-Gruppe Rhein-Neckar um 18:30 Uhr. Der Veranstaltungsort wird noch bekanntgegeben.

Weitere Informationen und Angaben zu dem Veranstaltungsort sowie den nächsten Terminen erhalten Sie bei Dr. Viktoria Riedel (viktoria.riedel@schwabe.de).

Dienstag, 08. September 2020

## Lokale APV-Gruppe Berlin um 19:00 Uhr. Der Veranstaltungsort wird noch bekanntgegeben.

Weitere Informationen und Angaben zu dem Veranstaltungsort sowie den nächsten Terminen erhalten Sie bei Dr. Andreas Sachse (andreas.sachse@cpl-sachse.de).

Mittwoch, 30. September 2020

## Lokale APV-Gruppe Rhein-Main ab 19:30 Uhr. Der Veranstaltungsort wird noch bekanntgegeben.

Weitere Informationen und Angaben zu dem Veranstaltungsort sowie den nächsten Terminen erhalten Sie bei Cathrin Pauly (pauly@aspiras.de).

## Lokale APV-Gruppe Basel

Weitere Informationen und Angaben zu den nächten Terminen erhalten Sie bei Dr. Lars Restetzki (lars.restetzki@roche.com).

## Lokale APV-Gruppe Westfalen

Weitere Informationen und Angaben zu den nächten Terminen erhalten Sie bei Dr. Johanna Anlahr (johanna.anlahr@bayer.com).

## Lokale APV-Gruppe Nordrhein

Weitere Informationen und Angaben zu den nächten Terminen erhalten Sie bei Klaus Wening (klaus.wening@grunenthal.com).

## Lokale APV-Gruppe Mecklenburg-Vorpommern

Weitere Informationen und Angaben zu den nächten 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?

Eduard Trenkenschuh, Ludwig-Maximilians-Universität, D-München

E. Jacqueroux et al./ European Journal of Pharmaceutics and Biopharmaceutics 148 (2020) 27-37

**Value of quantifying ABC transporters by mass spectrometry and impact on in vitro-to-in vivo prediction of transporter-mediated drug-drug interactions of rivaroxaban**

E. Jacqueroux, S. Hodin, S. Saib, Z. He, V. Bin, O. Delézay, X. Delavenne, X. Delavenne

ABC transporters, such as P-gp and BCRP, are involved in rivaroxaban pharmacokinetics and can lead to drug-drug interactions (DDIs). Investigations of the victim role for rivaroxaban and transporter-mediated DDI are commonly performed using in vitro models. However, interpretation of rivaroxaban efflux transport and DDI studies in cell models may be influenced by P-gp and BCRP transporter abundance. This study aimed to develop an LC-MS/MS quantification method for assessing the relationship between transporter expression and functionality in Caco-2ATCC, Caco-2ECACC, MDCK-MDR1, MDCK-BCRP cell models. First, the relative and absolute quantities of the transporters were determined by LC-MS/MS. P-gp and BCRP expression was then confirmed by western blotting and immunofluorescence staining. Finally, P-gp and BCRP functional activities and half-inhibitory concentrations (IC50s) of two specific inhibitors (verapamil and ko143) were determined by bidirectional transport experiments. P-gp and BCRP protein expression was detected at the cell membrane and was greater in the respective transfected models. Efflux ratios were correlated with P-gp and BCRP quantities. The lowest IC50s were obtained in the MDCK-MDR1 and MDCK-BCRP models for verapamil and ko143, respectively. In conclusion, this study demonstrated that LC-MS/MS can accurately quantify P-gp and BCRP efflux transporters and thereby improve the interpretation of transport data and in vitro-in vivo correlations.

Domenico Colucci et al./ European Journal of Pharmaceutics and Biopharmaceutics 148 (2020) 148-159

**A new mathematical model for monitoring the temporal evolution of the ice crystal size distribution during freezing in pharmaceutical solutions**

Domenico Colucci, Davide Fissore, Antonello A. Barresi, Richard D. Braatz

The freezing step plays a key role in the overall economy of the vacuum freeze-drying of pharmaceuticals, since the nucleation and crystal growth kinetics determine the number and size distribution of the crystals formed. In this work, a new mathematical model of the freezing step of a (bio)pharmaceutical solution is developed and validated. Both nucleation and crystal growth kinetics are modeled and included in a one-dimensional population balance (1D-PBM) that describes, given the product temperature measurement, the evolution of the pore size distribution during freezing. The developed model is coupled with the real-time measurements obtained from an infrared video camera. The ending time of the primary drying stage, and the maximum temperature inside the material, simulated through a simplified model of the process and the pore distribution forecast, resulted in good agreement with experimental values. The resulting Process Analytical Technology (PAT) has the potential to boost the development and optimization of a freeze-drying cycle and the implementation of a physically grounded Quality-by-Design approach in the manufacturing of pharmaceuticals. A more general mathematical model, including the aforementioned population balance, of a vial filled with a solution of sucrose was also developed and used to further validate the approach.

Andreas Tostorff et al./ European Journal of Pharmaceutics and Biopharmaceutics 149 (2020) 105-112

**Study of the interaction between a novel, protein-stabilizing dipeptide and Interferon-alpha-2a by construction of a Markov state model from molecular dynamics simulations**

Andreas Tosstorff, Günther H.J. Peters, Gerhard Winter

We recently reported the discovery of a novel protein stabilizing dipeptide, glycyl-D-asparagine, through a structure-based approach. As the starting hypothesis leading to the discovery, we postulated a stabilizing effect achieved by binding of the dipeptide to an aggregation prone region on the protein's surface. Here we present a detailed study of the interaction mechanism between the dipeptide and Interferon-alpha-2A (IFN) through the construction of a Markov state model from molecular dynamics trajectories. We identify multiple binding sites and compare these to aggregation prone regions. Additionally, we calculate the lifetime of the protein-excipient complex. If the excipient remained bound to IFN after administration, it could alter the protein's therapeutic efficacy. We establish that the lifetime of the complex between IFN and glycyl-D-asparagine is extremely short. Under these circumstances, stabilization by stoichiometric binding is consequently no impediment for a safe use of an excipient.

Katja Pajula et al./ European Journal of Pharmaceutics and Biopharmaceutics 150 (2020) 43-49

**Detection of amorphous-amorphous phase separation in small molecular co-amorphous mixtures with SEM-EDS**

Katja Pajula, Juha Hyyryläinen, Arto Koistinen, Jari T.T. Leskinen, Ossi Korhonen

Amorphicity is one possible way to increase the solubility of poorly water soluble drugs. However, amorphous solids are thermodynamically unstable and tend to recrystallize

with material-specific kinetics. Crystallization is not the prime phenomenon in the whole process, although it is the easiest to measure. The primary phenomenon prior to the crystallization of glass is phase separation, the detection of which is very rarely reported among small molecular compounds. In the present study, a scanning electron microscope with energy dispersive X-ray spectrometer (SEM-EDS) was used to detect very early stage amorphous-amorphous phase separation in co-amorphous drug mixtures. Miscibility was calculated for five studied mixtures based on the Flory-Huggins method and four immiscible pairs and one partial miscible pair were selected for the laboratory experiments. Co-amorphous samples (n = 3) were prepared by melt-quench method and stored at the elevated temperature to induce the separation of amorphous phases. Each sample was stored at the same relative percentage temperature between glass transition temperature Tg and melting temperature Tm. Immediately after the sample preparation, the full amorphousness was verified with polarizing light microscopy. Before SEM-EDS analysis, the samples were fractured into two pieces and measurements were done from cross-section (from the bulk sample). All five pairs phase separated during two days of storage at the elevated temperature. The study proved that SEM-EDS was able to detect a very small phase separated regions in the amorphous sample, as amorphous-amorphous phase separation was detected in four out of five pairs. However, the surface roughness could affect the analysis and give a false indication of phase separation. SEM-EDS also supported calculation results, since every studied pair showed phase separation during study, as was predicted on the grounds of Flory-Huggins miscibility calculation.


## Impressum:

**Redaktion**
Prof. Jörg Breitkreutz (Präsident der APV)
Dr. Martin Bornhöft (Leiter der Geschäftsstelle der APV)

**Vorstand der APV**
Prof. Dr. Johannes Bartholomäus · Dr. Kathrin Bartscher · Dr. Karoline Bechthold-Peters · Prof. Dr. Jörg Breitkreutz · Prof. Dr. Heribert Häusler · Prof. Dr. Sandra Klein · Dr. Hans Lindner · Dr. Martin Lück

**Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e. V. (APV)**
Kurfürstenstr. 59 · 55118 Mainz · Germany
Telefon +49 6131 9769-0
Telefax +49 6131 9769-69
email apv@apv-mainz.de
web www.apv-mainz.de

**Verlag**
ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH
Baendelstockweg 20 · 88326 Aulendorf · Germany
Telefon +49 7525 940-0
Telefax +49 7525 940-180
email info@ecv.de
web www.ecv.de





**Druck**
Holzmann Druck GmbH & Co. KG
Gewerbestr. 2 · 86825 Bad Wörishofen · Germany

**Satz**
Anna-Maria Pötzl · APV e.V.

Leasing auch für andere Investitionsgüter

## Leasing und Finanzierung von Investitionsgütern zu günstigen Konditionen:

- ✓ schont das Eigenkapital
- ✓ schafft Liquidität
- ✓ ist bilanzneutral
- ✓ erhöht die Eigenkapitalquote
- ✓ verbessert das Rating
- ✓ ermöglicht den Einsatz neuester Technologie
- ✓ auch „sale and lease back“ möglich

## Sehr interessant auch für Nutzer von Maschinen für die Pharmaindustrie:

- ✓ niedrige Leasingraten statt hoher Kaufpreise
- ✓ Erweiterung der Dienstleistungspalette vom Verkäufer zum Full-Service-Anbieter
- ✓ erhöhte Kompetenz als „all in one“-Anbieter
- ✓ kein Bonitäts-/Ausfallrisiko für Hersteller/Händler
- ✓ Finanzierung von Neu- und Gebrauchtmaschinen
- ✓ Abdeckung der kompletten Produktpalette

Unser Kooperationspartner bietet Leasing von Neu- und Gebrauchtfahrzeugen zu Sonderkonditionen an. Alle Marken und Modelle sind lieferbar. Die nachfolgende Tabelle gibt nur wenige aktuelle Beispiele möglicher Modelle und Marken wieder.
NEU: Vorführwagen (VfW) aus dem Leasing-Pool und Dienst-/Werkswagen (DW) zu attraktiven Konditionen erhältlich.

Alle Preise in Euro zuzüglich gesetzlicher Mehrwertsteuer. Beschaffung durch die Leasing-Gesellschaft. 36 Monate Laufzeit, ohne Anzahlung, Laufleistung 15.000 km pro Jahr, gewerbliches Leasing, Angebote freibleibend. Der Nachlass auf den Listenpreis ist in die ermäßigte Rate einkalkuliert.

Anfragen bitte an apv@apv-mainz.de, das Leasing-Unternehmen wird sich dann mit Ihnen in Verbindung setzen.

## Kfz-Leasing

⚠ Alle Fahrzeuge mit der Abgasnorm Euro 6d-Temp

| Hersteller/Typ | Listenpreis | mtl. Rate |
|---|---|---|
| Audi A1 Sportback S line 35 TFSI S tronic 110kW/150PS "LW" inkl. Navigation plus, Audi connect, PDC v+h/Kamera, Tempomat, Sportsitze, Sitzheizung vorn, Klimaaaut., 17" LMR etc. | 30.180,00 € | 299,00 € |
| Audi Q2 Sportback S line sport 35 TFSI S tronic 110kW/150PS "LW" inkl. Navi plus, Technology selection, S line Sportpaket, Panorama-Glasdach, PDC v+h/Kamera, 19" LMR +WKR etc. | 41.630,00 € | 399,00 € |
| Audi A5 Cabrio sport 40 TFSI S tronic 140kW/190PS "LW" inkl. Leder Millano, Navi plus, S line selection, Technology selection, Assistenzpaket Stadt, Matrix LED, 19" LMR etc. | 53.214,00 € | 499,00 € |
| Audi A8 50TDI Q OLED EZ 02-2019 210kW/285PS Automatik "LW" inkl. Standheizung, Matrix LED, Leder Valcona, Assistenzsysteme, Luftfederung, Massagesitze, Leder Valcona etc. | 107.563,00 € | 639,00 € |
| BMW X1 sDrive18i "Advantage" 103kW/140PS inkl. Business Paket, Navi, Klimaautomatik, PDC hinten/Kamera, Tempomat, SHZ Fahrer/Beifahrer, autom. Heckklappenbetätigung etc. | 31.050,00 € | 299,00 € |
| BMW 330e Touring "Advantage" 215kW/292PS Systemleistung inkl. Automatic, Business Paket Professional, Klimaautomatik, PDC, Sitzheizung Fahrer/Beifahrer, Tempomat, 17" LMR etc. | 46.723,00 € | 409,00 € |
| BMW 520d Limousine "Sport Line" 140kW/190PS inkl. Business Paket, Live Cockpit Connected Drive, Klimaaautom., Driving Assist., Parking Assist., 19" LMR W-Speiche 663 Bicolor etc. | 51.445,00 € | 479,00 € |
| Mercedes E 350d Coupé Automatik 210kW/286PS "VfW" inkl. AMG Exterieur/Interieur, Business Paket, Drive Pilot, Distronic Plus, PDC/Kamera, DYNAMIC Select, 20" AMG LMR etc. | 61.130,00 € | 549,00 € |
| Mercedes GLC 400d 4MATIC Coupé 9G-TRONIC 243kW/330PS inkl. Business-Paket, AMG- Line, Schiebedach, Standheizung, Exclusive Interieur, Advanced Soundsystem, 20" AMG LMR etc. | 65.795,00 € | 739,00 € |
| MINI Cooper Cabrio "Pepper" 100kW/136PS inkl. Klimaautomatik, Connected Media, Driving Assistant, PDC hinten, Tempomat, Sitzheizung vorn, Business Paket, 16" LMR etc. | 25.496,00 € | 259,00 € |
| Skoda Karoq "Drive 125" 1,5 TSI 110kW/150PS inkl. Business Amundsen Navi, DAB+, Smartlink, Metallic, Lenkrad beheizb., Klimaautomatik, PDC v+h/Kamera, Tempomat, 17" LMR etc. | 27.815,00 € | 199,00 € |
| Skoda Karoq "Sportline" 2,0 TSI 4x4 140kW/190PS DSG "LW" inkl. Businesspaket Columbus, Abstandsassistent ACC, PDC v+h/Kamera, Standheizung, AHK schwenkbar, 19" LMR etc. | 39.231,00 € | 259,00 € |
| VW T-Roc Cabriolet "Style" 1.0l TSI OPF 85kW/115PS 6-Gang inkl. Navi, 2-Zonen-Klimaautomatik, Parklenkassistent, Winterpaket, Windschott, 17" LMR "Mayfield" mit GJR etc. | 26.601,00 € | 279,00 € |
| VW Tiguan "Highline" 1.5l TSI ACT OPF 110kW/150PS DSG inkl. 3-Zonen Klimaautomatik, Einparkhilfe v+h, Sitzheizung vorn, LED Scheinwerfer, Spurhalteassist., 18" LMR "Dublin" etc. | 32.071,00 € | 199,00 € |