APV – Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e. V.

# APV NEWS

03 • 2015

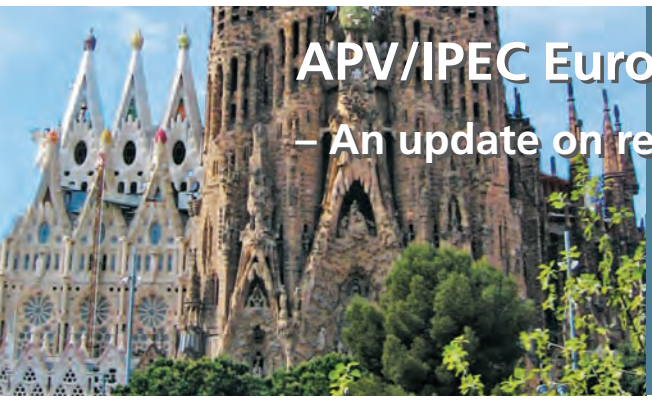
## Nachrichten und Mitteilungen

MAKING SCIENCE WORK

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

ipec EUROPE

APV MAKING SCIENCE WORK



# APV/IPEC Europe Excipient Conference 2015

## – An update on regulatory and application developments

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23 to 24 September 2015 · Barcelona, Spain

Course No. 3144

*including 3 parallel workshop sessions*

- *Change Management of Excipients according to IPEC Significant Change Guide*
- *Risk Assessment for Excipient GMP*
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**www.apv-mainz.de**

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# 8. Offizielle GAMP® 5 Konferenz

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- Industrie 4.0
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# Lokale Gruppen

## Montag, 15. Juni 2015

**Lokale APV-Gruppe Westfalen** ab 19:30 Uhr in Hövels-Hausbrauerei in Dortmund (Hoher Wall 5, 44137 Dortmund). Anmeldung erforderlich bis zum 10. Juni 2015 bei Dr. Kathrin Bartscher.

## Donnerstag, 16. Juli 2015

**Lokale APV-Gruppe Oberbayern** ab 19:30 Uhr in der Essence-Lounge, Gottfried-Keller-Str. 35, 81245 München, Telefon 089 80040025. Anmeldung erforderlich bis zum 10. Juli 2015 bei Dr. (USA) Julia Schulze-Nahrup.

## Mittwoch, 22. Juli 2015

**Lokale APV-Gruppe Rhein-Main** ab 19:30 Uhr. Ort wird noch bekanntgegeben.
Weitere Informationen erhalten Sie bei Cathrin Pauly.

## Mittwoch, 26. August 2015

**Lokale APV-Gruppe Nord** ab 18:30 Uhr im Hofbräuhaus (Esplanade 6, 20354 Hamburg)
Anmeldung erforderlich bis zum 20. August 2015 bei Birgit Mootz.

## Donnerstag, 03. September 2015

**Lokale APV-Gruppe Berlin** um 19:00 Uhr. Ort wird noch bekanntgegeben.
Anmeldung erforderlich bis zum 28. August 2015 bei Dr. Andreas Sachse.

# What's hot in European Journal of Pharmaceutics and Biopharmaceutics?

Stefanie Funke, Ludwig-Maximilians-Universität, D-München

C.G. Madsen et al./European Journal of Pharmaceutics and Biopharmaceutics 92 (2015) 1–7

## Simple measurements for prediction of drug release from polymer matrices – Solubility parameters and intrinsic viscosity

Claus G. Madsen, Anders Skov, Stefania Baldursdottir, Thomas Rades, Lene Jorgensen, Natalie J. Medlicott

Purpose:
This study describes how protein release from polymer matrices correlate with simple measurements on the intrinsic viscosity of the polymer solutions used for casting the matrices and calculations of the solubility parameters of polymers and solvents used.
Method:
Matrices of poly(DL-lactide-co-glycolide) (PLGA) were cast with bovine serum albumin (BSA) as a model drug using different solvents (acetone, dichloromethane, ethanol and water). The amount of released protein from the different matrices was correlated with the Hildebrand and Hansen solubility parameters of the solvents, and the intrinsic viscosity of the polymer solutions. Matrix microstructure was investigated by transmission and scanning electron microscopy (TEM and SEM). Polycaprolactone (PCL) matrices were used in a similar way to support the results for PLGA matrices.
Results:
The maximum amount of BSA released and the release profile from PLGA matrices varied depending on the solvent used for casting. The maximum amount of released BSA decreased with higher intrinsic viscosity, and increased with solubility parameter difference between the solvent and polymer used. The solvent used also had an effect on the matrix microstructure as determined by TEM and SEM. Similar results were obtained for the PCL polymer systems.
Conclusions:
The smaller the difference in the solubility parameter between the polymer and the solvent used for casting a polymer matrix, the lower will be the maximum protein release. This is because of the presence of smaller pore sizes in the cast matrix if a solvent with a solubility parameter close to the one of the polymer is used. Likewise, the intrinsic viscosity of the polymer solution increases as solubility parameter differences decrease, thus, simple measurements of intrinsic viscosity and solubility parameter difference, allow the prediction of protein release profiles.

S. Horiuchi, G. Winter/European Journal of Pharmaceutics and Biopharmaceutics 92 (2015) 8–14

## CMC determination of nonionic surfactants in protein formulations using ultrasonic resonance technology

Shohei Horiuchi, Gerhard Winter

Biological products often contain surfactants as stabilizers in their formulations to avoid surface adsorption, interfacial denaturation and aggregation of the protein drug and thereby improve the overall pharmaceutical quality of the product. On the other hand, when the surfactant concentration exceeds the critical micelle concentration (CMC) in a protein formulation, protein-loaded micelles could be formed which could potentially be the cause of immunogenicity. Therefore, the actual CMC and the presence of micelles generally need to be confirmed for each protein formulation because the CMC is affected by the presence of protein and other formulation factors. In this study, the ultrasonic resonance technology (URT) was applied to determine CMC of surfactants in pharmaceutical protein solutions in comparison with surface tensiometry (TE) and dynamic light scattering (DLS). According to our results, the ultrasonic resonance technology can easily and precisely provide CMCs of surfactants in protein formulations while it is not working for protein-free formulations. This indicates that the signal we measure with ultrasonic velocity comes from complex micelles composed of surfactant and protein molecules. DLS did not provide reliable data for protein/surfactant systems. Interestingly, a protein formulation with arginine and polysorbate 20 behaved differently when studied with TE and URT allowing us to see that arginine is bound to protein and that the complex interacts with the surfactant.

T. Müller et al./European Journal of Pharmaceutics and Biopharmaceutics 92 (2015) 130–138

## Influence of small amorphous amounts in hydrophilic and hydrophobic APIs on storage stability of dry powder inhalation products

Thorsten Müller, Regina Krehl, Jörg Schiewe, Claudius Weiler, Hartwig Steckel

The effects of different manufacturing methods to induce formation of amorphous content, changes of physico-chemical characteristics of powder blends and changes of aerodynamic properties over storage time (6 months) analyzed with the Next Generation Impactor (NGI) are investigated. Earlier studies have shown that standard pharmaceutical

operations lead to structural disorders which may influence drug delivery and product stability. In this investigation, fully amorphous drug samples produced by spray-drying (SD) and ball-milling (BM) as well as semi-crystalline samples (produced by blending and micronization) are studied and compared to fully crystalline starting material. The amorphous content of these hydrophilic and hydrophobic active pharmaceutical ingredients (APIs) was determined using a validated one-step DVS-method. For the conducted blending and micronization tests, amorphous amounts up to a maximum of 5.1% for salbutamol sulfate (SBS) and 17.0% for ciclesonide (CS) were measured. In order to investigate the impact of small amorphous amounts, inhalable homogenous powder mixtures with very high and low amorphous content and a defined particle size were prepared with a Turbula blender for each API. These blends were stored (6 months, 45% RH, room temperature) to evaluate the influence of amorphous amounts on storage stability. The fine particle fraction (FPF: % of emitteddose < 5 µm) was determined with the NGI at defined time points. The amorphous amounts showed a major effect on dispersion behavior, the mixtures of the two APIs showed differences at the beginning of the study and significant differences in storage stability. The FPF values for SBS decreased during storage (FPF: from 35% to <27%) for the blend with high amorphous amounts, in contrast the initially re-crystallized sample achieved a comparable constant level of about 25%. For the hydrophobic CS a constantly increasing FPF (from 6% to >15%) over storage time for both types of blends was determined. Therefore, prolonged stability of amorphous parts and an incalculable behavior for CS blends are supposed, in contrast, SBS showed a controllable FPF after conditioning.

A. Bitterlich et al./European Journal of Pharmaceutics and Biopharmaceutics 92 (2015) 171–179

## Process parameter dependent growth phenomena of naproxen nanosuspension manufactured by wet media milling

A. Bitterlich, C. Laabs, I. Krautstrunk, M. Dengler, M. Juhnke, A. Grandeury, H. Bunjes, A. Kwade

The production of nanosuspensions has proved to be an effective method for overcoming bioavailability challenges of poorly water soluble drugs. Wet milling in stirred media mills and planetary ball mills has become an established top-down-method for producing such drug nanosuspensions. The quality of the resulting nanosuspension is determined by the stability against agglomeration on the one hand, and the process parameters of the mill on the other hand. In order to understand the occurring dependencies, a detailed screening study, not only on adequate stabilizers, but also on their optimum concentration was carried out for the active pharmaceutical ingredient (API) naproxen in a planetary ball mill. The type and concentration of the stabilizer had a pronounced influence on the minimum particle size obtained. With the best formulation the influence of the relevant process parameters on product quality was investigated to determine the grinding limit of naproxen. Besides the well known phenomenon of particle agglomeration, actual naproxen crystal growth and morphology alterations occurred during the process which has not been observed before. It was shown that, by adjusting the process parameters, those effects could be reduced or eliminated. Thus, besides real grinding and agglomeration a process parameter dependent ripening of the naproxen particles was identified to be a concurrent effect during the naproxen fine grinding process.


## Impressum:

**Redaktion**

Prof. Dr. Jörg Breitkreutz (Präsident)
Dr. Martin Bornhöft (Leiter Geschäftsstelle)

**Vorstand der APV**

Dr. Rainer Alex · Dr. Hermann Allgaier · Dr. Kathrin Bartscher · Prof. Dr. Jörg Breitkreutz · Prof. Dr. Heribert Häusler · Prof. Dr. Sandra Klein · Dr. Alexandra Steckel · Dr. Andreas Rummelt

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# APV NEWS – Leasing-Highlights zu Sonderkonditionen

## Kfz-Leasing: Vorteile für APV-Mitglieder

Die APV hat für ihre Mitglieder einen Rahmenvertrag mit einem bekannten Leasing-Unternehmen geschlossen. Als Kooperationspartner der APV bietet das Unternehmen Leasing von Neu- und Gebrauchtfahrzeugen zu Sonderkonditionen. 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, 15.000 km pro Jahr, 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.

## JETZT NEU: Leasing auch für andere Investitionsgüter

Leasing und Finanzierung zu günstigen Konditionen sind auch für Investitionsgüter wie Walzenpressen, Verpackungsmaschinen, Laboreinrichtungen etc. über die APV möglich. Sprechen Sie uns an.

| Hersteller/Typ | Listenpreis | mtl. Rate |
|---|---|---|
| Audi A3 Sportback Attraction 1.2 TFSI 81kW/110PS inkl. Klimaanlage, Navigationspaket, Einparkhilfe hinten, Sitzheizung, Anschlussgarantie etc. | 19.622,00 € | 235,00 € |
| Audi A6 Limousine 2.0 TDI ultra 110kW/150PS inkl. Navi, Klimaautomatik, LM-Felgen, Einparkhilfe plus, Sitzheizung vorn, Anschlussgarantie etc. | 33.631,00 € | 399,00 € |
| BMW 116i 3-Türer 80kW/109PS inkl. Navigationssystem, Klimaanlage, PDC, Sitzheizung vorn, Armauflage vorn verschiebbar, Lordosenstütze etc. | 21.387,00 € | 239,00 € |
| BMW 218i Active Tourer 100kW/136PS inkl. Navigationssystem, Klimaautomatik, PDC, Tempomat, LM-Felgen, Multifunktion für Lenkrad etc. | 24.958,00 € | 259,00 € |
| BMW X3 sDrive18d 110kW/150PS inkl. Navigationssystem, PDC, 17" LM-Räder, Klimaautomatik, Tempomat, Xenon-Licht, HiFi-Lautsprechersystem etc. | 36.118,00 € | 439,00 € |
| Jaguar XF Sportbrake 2.2 L Diesel 147kW/200PS inkl. Automatik, Navi, Leder, PDC/Rückfahrkamera, beheizbare Frontscheibe, Spiegel-Paket etc. | 47.345,00 € | 399,00 € |
| Jaguar F-Type Coupé „Vfw" 250kW/340PS inkl. Technology-Pack, Sicht-Paket, Memory-Paket, Sport-Abgasanlage m. Klappensteuerung, 19"-Felgen etc. | 67.441,00 € | 599,00 € |
| Mazda 3 5-Türer Center-Line1.8l MZR 88kW/120PS inkl. Metallic, Klimaautomatik, Navi, LM-Felgen, Xenon, Spurwechselassistent, PDC, Sitzheizung etc. | 19.471,00 € | 199,00 € |
| Mazda 6 Kombi Exclusive-Line D-150 FWD 110kW/150PS Diesel inkl. Metallic, Navi, Voll-LED mit AFLS, Klimaautomatik, Tempomat, PDC, LM-Felgen etc. | 28.857,00 € | 279,00 € |
| MINI One First 5-Türer 55kW/75PS inkl. Klimaanlage, Lichtpaket, Ablagenpaket, Bordcomputer, Fussmatten in Velours etc. | 15.252,00 € | 179,00 € |
| Porsche Boxster 195kW/265PS inkl. PCM Navigation, Alcantara, Multifunktionslenkrad, 2-Zonen-Klimaautomatik, Tempostat, Sitzheizung, LM-Räder etc. | 48.316,00 € | 679,00 € |
| Skoda Fabia III Combi 1.2 TSI Edition 66kW/90PS inkl. Metallic, Climatronic, Sitzheizung, Dachreling, variabler Ladeboden 17" LM-Felgen etc. | 15.899,00 € | 169,00 € |
| Skoda Superb Combi 2,0l TDI Best of 103kW/140PS inkl. Metallic, Navigation, Climatronic, Bi-Xenon, Lendenwirbelstütze, Tempomat, PDC etc. | 28.416,00 € | 279,00 € |
| Toyota Avensis Touring Sports Business Edition 2,0l D-4D 105kW/143PS inkl. Metallic, Navi/DAB+, Voll-LED, 17" LM-Felgen, PDC/Rückfahrkamera etc. | 28.496,00 € | 319,00 € |
| VW Sharan Comfortline 2,0l TDI BMT 103kW/140PS inkl. 7-Sitzer, Metallic, Navi, „Easy-Open"-Paket, LM-Räder, ParkPilot, Rückfahrkamera etc. | 38.176,00 € | 399,00 € |
| VW Touareg BMT 3,0l V6 150kW/204PS inkl. „Chrome & Style", Klimaautomatik, Bi-Xenon, Parkdistanzkontrolle, 17" LM-Räder, Tempomat etc. | 47.147,00 € | 439,00 € |

Vfw = Vorführwagen zu Sonderkonditionen, DW = Dienst-/Werkswagen (genannter Listenpreis=Kaufpreis)