APV – Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e. V.

APV NEWS

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Nachrichten und Mitteilungen

MAKING SCIENCE WORK

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

Ocular delivery

This June over 40 scientists from university, industry and regulatory authority met in Berlin for the APV high toned conference on Ocular Drug Delivery – State-of-the-Art and New Concepts. The conference was held in the Wyndham Mitte Hotel located in the former East Berlin. Topics of the 15 talks ranged from novel innovative drug delivery technologies for small and large molecules to regulatory aspects and packaging materials.

After a friendly welcome by the two chairmen Professor emeritus Dr. Robert Gurny (University of Geneva) and Dr. Rainer Alex (F. Hoffmann – La Roche AG) day 1 started with an overview on ocular diseases and their treatment by Prof. Dr. Behar-Cohen (Jules Gonin Eye Hospital/ Department of Ophthalmology of University of Lausanne). In the presentation common diseases such as age related macular degeneration (AMD), diabetic retinopathies, glaucoma and dry eye were discussed, but also the current epidemic rise of myopia in Asia as well as in Europe. Following Prof. Dr. Arto Urtti (University of Helsinki) presented about ocular anatomy, physiology and pharmacokinetics and Dr. Pascal Furrer (University of Geneva) gave a summary about ocular dosage forms and delivery options. The rest of the day was focused on gene delivery including a case study (Dr. Jean-Philippe Combal, GenSight) followed by a guided bus city tour around Berlin and a dinner at the hotel restaurant. This gave the opportunity to come together and network with the other participants in a nice atmosphere.

On Day 2 a large variety of topics in the field of ocular dosage forms were presented by various people from academia and industry including small start-ups as well as big pharma. Pascal Furrer gave an overview about formulation development as well as regulatory requirements. Dr. Ann Daughtery from Genentech presented the strategies for sustained delivery of biologics to the back of the eye and the industrial approach to overcome this challenge. This topic was further analyzed by Dr. Signe Erickson who presented ForSight's innovative refillable port drug delivery system. After the lunch break, Dr. Laurence Feraille (IRIS Pharma) and Dr. Margaret E. Collins (Charles River Labs) presented approaches for pre-clinical in vivo (animal) testing for ocular formulations to the front and back of the eye including challenges associated with different species. Then Dr. Schubert presented Maropack's Blow-Fill-Seal technique as a potential packaging method for eye drops and Loïc Martin from Pylote introduced the PYCLEAR™ Mineral microspheres technology which enables preservative free dosage forms. The last talk was held by Dr. Frédéric Lallemand from Santen SAS. He gave a closer look into the bench to bedside development of Ikervis®, a cationic emulsion formulation of cyclosporine for the treatment of severe keratitis in patients with dry eye disease. The conference was concluded by the two chairmen, who expressed their gratitude to all participants for the great atmosphere during the two days of the conference.

The APV conference on ocular drug delivery covered a broad field of different topics, which offered insight into current state of the art research and development of ophthalmic drug products. Further the event gave all participants the opportunity to meet other scientists working in a similar field, which led to interesting and informative discussions as well as scientific exchange after the talks and during the coffee breaks. Many thanks to APV for the opportunity to participate in the well-organized and highly scientific conference as well as the good time in Germany's capital Berlin.

Lokale Gruppen

Mittwoch, 14. September 2016

Lokale APV-Gruppe Berlin um 19:00 Uhr. Ort wird noch bekanntgegeben.

Anmeldung erforderlich bis zum 05. September 2016 bei Dr. Andreas Sachse (andreas.sachse@cpl-sachse.de).

Mittwoch, 12. Oktober 2016

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

Weitere Informationen erhalten Sie bei Cathrin Pauly (pauly@aspiras.de).

Lokale APV-Gruppe Oberbayern

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

Lokale APV-Gruppe Basel ab 19:30 Uhr im Restaurant Gifthüttli (http://www.gifthuettli.ch/).

Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Dr. Julia Matilainen (julia.matilainen@roche.com).

Lokale APV-Gruppe Westfalen ab 19:30 Uhr in Hövels Hausbrauerei (Hoher Wall 5-7, 44137 Dortmund, Tel.: 0231/914547-0, www.hoevels-hausbrauerei.de).

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

Lokale APV-Gruppe Köln/Bonn/Aachen ab 19:00 Uhr in Peters Brauhaus (Mühlengasse 1, 50667 Köln, www.peters-brauhaus.de) statt.

Weitere Informationen und Angaben zu den nächsten Terminen erhalten Sie bei Dr. Heiko Spilgies (heiko@spilgies.de).

Liebe APV-Mitglieder,

nach der erfolgreichen Gründung mehrerer lokaler Gruppen würden wir das Konzept der lokalen APV-Gruppen gerne auch in weiteren Regionen etablieren. Bitte sprechen Sie uns an, wenn Sie Interesse an einer Teilnahme an einer lokalen Gruppe in Ihrer Region haben oder als Ansprechpartner, unterstützt durch die APV-Geschäftsstelle, für eine neue lokale Gruppe zur Verfügung stehen würden.

Wir freuen uns auf Ihre Rückmeldung!

Ansprechpartner: Dr. Martin Bornhöft, Email: mb@apv-mainz.de, Tel: + 49 6131 9769-30

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

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

S. Mangal et al./European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 110–116

Applying surface energy derived cohesive–adhesive balance model in predicting the mixing, flow and compaction behaviour of interactive mixtures

Sharad Mangal, Felix Meiser, Geoffrey Tan, Thomas Gengenbach, David A.V. Morton, Ian Larson

Objective
In this study, we investigated the applicability of cohesive–adhesive balance (CAB) model to predict the interactive mixing behaviour of small excipient particles. Further, we also investigated the application of this CAB model to predict the flow and compactibility of resultant blends.
Methods
Excipients created by co-spraying polyvinylpyrrolidone (PVP, a model pharmaceutical binder) with various l-leucine concentrations were used for this study. Paracetamol was used as model active pharmaceutical ingredient (API). The surface energy was used to derive the work of cohesion (W_{co}) and work of adhesion (W_{ad}) to predict the interactive mixing behaviour of the excipients with paracetamol. The blends were visualised under a scanning electron microscopy microscope to assess the interactive mixing behaviour. In addition, the flow performance and tabletting behaviour of various blends were characterised.
Results
The surface-energy derived work of adhesion (W_{ad}) between excipient and paracetamol particles increased, while the corresponding work of cohesion (W_{co}) between excipient particles decreased, with increasing l-leucine concentrations. In blends for which the work of cohesion was higher than the work of adhesion ($W_{co} > W_{ad}$), small excipient particles were apparent as agglomerates. For excipients with 5% and higher l-leucine concentrations, the work of adhesion between excipient and paracetamol particles was higher than or equivalent to the work of cohesion between excipient particles ($W_{ad} > W_{co}$) and agglomerates were less apparent. This is an indicator of formation of homogeneous interactive mixtures. At 5% (w/w) excipient proportions, blends for which $W_{ad} > W_{co}$ demonstrated higher compactibility than other blends. Furthermore, at 10% (w/w) and higher excipient proportions, these blends also demonstrated better flow performance than other blends.
Conclusion
In conclusion, this is the first study to demonstrate that surface-energy derived CAB data effectively predict the interactive mixing behaviour of small excipient particles. Furthermore, at certain proportions of small excipient particles the CAB model also predicts the flow and compaction behaviour of the API/excipient blends.

S. Funke et al./European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 200–215

Optimization of the bake-on siliconization of cartridges. Part I: Optimization of the spray-on parameters

Stefanie Funke, Julia Matilainen, Heiko Nalenz, Karoline Bechtold-Peters, Hanns-Christian Mahler, Wolfgang Friess

Biopharmaceutical products are increasingly commercialized as drug/device combinations to enable self-administration. Siliconization of the inner syringe/cartridge glass barrel for adequate functionality is either performed at the supplier or drug product manufacturing site. Yet, siliconization processes are often insufficiently investigated. In this study, an optimized bake-on siliconization process for cartridges using a pilot-scale siliconization unit was developed. The following process parameters were investigated: spray quantity, nozzle position, spray pressure, time for pump dosing and the silicone emulsion concentration.

A spray quantity of 4 mg emulsion showed best, immediate atomization into a fine spray. 16 and 29 mg of emulsion, hence 4–7-times the spray volume, first generated an emulsion jet before atomization was achieved. Poor atomization of higher quantities correlated with an increased spray loss and inhomogeneous silicone distribution, e.g., due to runlets forming build-ups at the cartridge lower edge and depositing on the star wheel. A prolonged time for pump dosing of 175 ms led to a more intensive, long-lasting spray compared to 60 ms as anticipated from a higher air-to-liquid ratio. A higher spray pressure of 2.5 bar did not improve atomization but led to an increased spray loss. At a 20 mm nozzle-to-flange distance the spray cone exactly reached the cartridge flange, which was optimal for thicker silicone layers at the flange to ease piston break-loose. Initially, 10 µg silicone was sufficient for adequate extrusion in filled cartridges. However, both maximum break-loose and gliding forces in filled cartridges gradually increased from 5–8 N to 21–22 N upon 80 weeks storage at room temperature. The increase for a 30 µg silicone level from 3–6 N to 10–12 N was moderate. Overall, the study provides a comprehensive insight into critical process parameters during the initial spray-on process and the impact of these parameters on the characteristics of the silicone layer, also in context of long-term product storage. The presented experimental toolbox may be utilized for development or evaluation of siliconization processes.

E. J. T. Weele et al./European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 226–234

Development, preclinical safety, formulation, and stability of clinical grade bevacizumab-800CW, a new near infrared fluorescent imaging agent for first in human use

Eva J. ter Weele, Anton G.T. Terwisscha van Scheltinga, Matthijs D. Linssen, Wouter B. Nagengast, Ingo Lindner, Annelies Jorritsma-Smit, Elisabeth G.E. de Vries, Jos G.W. Kosterink, Marjolijn N. Lub-de Hooge

There is a dire need for better visualization of cancer and analysis of specific targets in vivo. Molecular imaging with fluorescence is gaining more and more attention, as it allows detection of these targets and has advantages over radioactivity, such as no radiation dose, and lower costs. A key challenge in optical imaging however, is translation of the newly developed tracers from pre-clinical phase to clinical application. We describe the development and safety testing of clinical grade bevacizumab-800CW, an antibody-based targeted agent for non-invasive imaging of vascular endothelial growth factor A (VEGF-A). Development included implementing the manufacturing process and analytical methods according to current Good Manufacturing Practice (cGMP), formulation studies, extended characterization and stability testing. For safety pharmacology an extended single dose toxicity study in mice was performed.
Bevacizumab-800CW was formulated in isotonic phosphate buffered sodium chloride solution at pH 7. The production was robust and showed a reproducible labeling efficiency, and no impurities. The binding affinity to VEGF-A remained intact. The optimized product meets all release specifications, is stable up to at least 3 months and its characteristics did not significantly differ from the unlabeled bevacizumab. Toxicity testing in mice showed no remarkable findings.
In conclusion, sterile bevacizumab-800CW (6 mg = 6 ml) can be produced in stock according to current Good Manufacturing Practice. It is ready for first-in-human use.

D. Preisig et al./European Journal of Pharmaceutics and Biopharmaceutics 105 (2016) 156–165

Mucoadhesive microparticles for local treatment of gastrointestinal diseases

Daniel Preisig, Roger Roth, Sandy Tognola, Felipe J.O. Varum, Roberto Bravo, Yalcin Cetinkaya, Jörg Huwyler, Maxim Puchkov

Mucoadhesive microparticles formulated in a capsule and delivered to the gastrointestinal tract might be useful for local drug delivery. However, swelling and agglomeration of hydrophilic polymers in the gastrointestinal milieu can have a negative influence on particle retention of mucoadhesive microparticles. In this work, we investigated the impact of dry-coating with nano-sized hydrophilic fumed silica on dispersibility and particle retention of mucoadhesive microparticles. As a model for local treatment of gastrointestinal diseases, antibiotic therapy of Clostridium difficile infections with metronidazole was selected. For particle preparation, we used a two-step fluidized-bed method based on drug loading of porous microcarriers and subsequent outer coating with the mucoadhesive polymer chitosan. The prepared microparticles were analysed for drug content, and further characterized by thermal analysis, X-ray diffraction, and scanning electron microscopy. The optimal molecular weight and content of chitosan were selected by measuring particle retention on porcine colonic mucosa under dynamic flow conditions. Mucoadhesive microparticles coated with 5% (weight of chitosan coating/total weight of particles) of low molecular weight chitosan showed good in vitro particle retention, and were used for the investigation of dispersibility enhancement. By increasing the amount of silica, the dissolution rate measured in the USP IV apparatus was increased, which was an indirect indication for improved dispersibility due to increased surface area. Importantly, mucoadhesion was not impaired up to a silica concentration of 5% (w/w). In summary, mucoadhesive microparticles with sustained-release characteristics over several hours were manufactured at pilot scale, and dry-coating with silica nanoparticles has shown to improve the dispersibility, which is essential for better particle distribution along the intestinal mucosa in humans. Therefore, this advanced drug delivery concept bears great potential, in particular for local treatment of gastrointestinal diseases.

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JETZT NEU: Leasing auch für andere Investitionsgüter

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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. Sonderkonditionen für Fahrzeuge der Marke Toyota auch für Privatkunden!

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

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Hersteller/Typ	Listenpreis	mtl. Rate
Audi A6 Limousine 2.0 TDI ultra 110kW/150PS inkl. S line Selection, Business-Paket, Navi, 19"LM-Felgen, PDC, Sitzheizung, LED-Scheinwerfer/Heckleuchten etc.	39.286,00 €	399,00 €
BMW 518d Touring 110kW/150PS inkl. Navigationssystem, HiFi-Lautsprechersystem, PDC, Dachreling, Klimaautomatik, Lordosenstütze vorne, Sitzheizung vorne etc.	39.118,00 €	299,00 €
Jaguar XF 20d Automatic 132kW/180PS inkl. Navi, Metallic, Klimaautomatik, 18"LM-Felgen, PDC mit Kamera, Tempomat, Panorama-Schiebedach, Assistenzpaket etc.	51.482,00 €	439,00 €
Lexus CT-200h Hybrid 73kW/100PS inkl. Automatik, Metallic, Navi, Klimaautomatik, Premium-Audiosystem, PDC, LM-Räder, Alu-Sportpedalerie, Regensensor etc.	24.681,00 €	319,00 €
SEAT Ateca Style 1.4 EcoTSI 110kW/150PS inkl. AHK, Navi, Design-Exterior-Paket, Klimaautomatik, PDC, Sitzheizung vorne, 17"LM-Felgen, Privacy-Verglasung etc.	23.210,00 €	219,00 €
Skoda Superb III Combi 1.4 TSI Ambition 92kW/125PS inkl. Navi, DAB+, Verkehrs- und Müdigkeitserkennung, Klimaautomatik, LM-Felgen, PDC, Tempomat etc.	25.277,00 €	249,00 €
Toyota Aygo 5-Türer x-play 51kW/70PS inkl. Klimaanlage, Audiosystem, Bluetooth-Freisprecheinrichtung, LED-Tagfahrlicht, Lederlenkrad, Technik-Service etc.	10.374,00 €	119,00 €
Volvo XC60 D3 Summum 110kW/150PS inkl. Klimaautomatik, Lederpolster, Sitzheizung vorne, Fahrersitz mit Memory, Frontscheibenheizung, PDC, 18" LM-Felgen etc.	34.941,00 €	259,00 €

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