



# APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER | ISSUE 1/2009

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## DRUG DELIVERY EVENTS

Provided by Christoph Blümer

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**CRS: German Chapter Annual Meeting / Young Scientist Meeting in Pharmaceutics**  
Halle/Saale (D), March 19<sup>th</sup> - 20<sup>th</sup> 2009

[Details](#)

**CRS Satellite: Oral Multi-particulate Drug Delivery Systems - Challenges and Opportunities**  
Vienna (A), March 24<sup>th</sup> - 25<sup>th</sup> 2009

[Details](#)

**The Third Annual Drug Delivery Summit**  
San Francisco (CA), May 14<sup>th</sup> - 15<sup>th</sup> 2009

[Details](#)

**[Suggest a meeting to be announced!](#)**

## REVIEW OF DRUG DELIVERY EVENTS

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### APV COURSE SUMMARY - "POORLY WATER SOLUBLE DRUGS: SUCCESSFUL FORMULATION APPROACHES"

November, 04<sup>th</sup> - 05<sup>th</sup> 2008, Basle

*By Carsten Timpe, Ph.D., Novartis Pharma AG, Pharmaceutical Analytical Development (PHAD PDU ORA 1), CH-Basle*

#### 1. Current Trends in Drug Delivery for Poorly Soluble Drugs

A broad overview about current trends in drug delivery for poorly soluble drugs was given by more than 10 expert speakers at the APV course No. 6206 in Basel (Switzerland) from November 4 - 5 2008. The course was organized by the APV Drug Delivery Focus Group and chaired by Dieter Becker, Ph.D. (who developed the course concept) and supported by Carsten Timpe, Ph.D. (both Novartis Pharma). More than 50 international participants from the pharmaceutical industry and universities participated in the course at the Mercure Hotel in Basel.



Dieter Becker started with an introductory presentation about the drug delivery market for poorly soluble drugs which require significantly larger investments in development costs. Circa 30 % of all novel drug candidates are poorly water soluble. Major marketed drug products like Neoral® and Prograf® have become blockbusters but would have never attained their high market share without efficient enabling drug delivery technologies.



## 2. Physical and Chemical Properties of Poorly Soluble Drugs

### *Taking a closer look at solubility issues*

In the morning session on November 4 [Bernd Riebesehl, Ph.D. from Speedel](#) (Switzerland) gave an introduction to the root causes indicators for solubility and permeability limited absorption. Modern solubility profiling equipment that analyzes and visualizes the dataset is recommended. Deviations from solubility/pH profiles of ionizable drugs could be driven by micellar aggregation. Gels and liquid crystal formation could be responsible for blocking tablet disintegration, thus, reducing drug absorption. Possible platforms for improving solubility are prodrugs, cyclodextrin inclusion complexes, SMEDDS solutions, solid dispersions, nanoparticles, suitable salts and polymorphs or co-crystals. Among those the ones which allow for high drug loadability and sufficient stability are preferred.



### *Choosing the optimal solid state form*

The next presentation about the relationship between the solid state form of a drug and corresponding solubility properties was given by [Rolf Hilfiker, Ph.D. from Solvias AG](#) (Switzerland). Polymorphism of drugs can affect the whole life cycle during drug development: a stable polymorph needs to be identified, the existence of solvates is important for formulation development, polymorph forms could be patented and finally different polymorphs could differ regarding bioavailability. The speaker explained the background of the Norvir case: After the production of about 240 batches a new polymorph with worse solubility and bioavailability showed up without an early warning signal. As a consequence large investments in money (1 billion USD) and personnel resources were required to develop a new formulation.



Apart from salts, co-crystals could generally be considered during drug development if an API cannot be crystallized, has insufficient solubility, undesirable properties or simply for IP reasons. Stabilizing amorphous states by adding polymers can be monitored by DSC (Glass transition temperature T<sub>g</sub>). Polymorphs can be characterized by thermal (DSC, TG-FTIR, TG-MS, hot stage microscopy) and spectroscopic methods (XRPD, NIR, Raman, terahertz spectroscopy, ss-NMR). Determination of polymorphic purity is important in case of metastable solids selected for development and if prior art exists (e.g. IP infringements).

## 3. Simulation tools

### *Simulation for poorly absorbed drugs*

[Stefan Willmann, Ph.D. \(Bayer Technology Services\)](#) gave an introduction into the in-silico tool PK-Sim<sup>®</sup> which is based on the ACAT model (Advanced Compartmental & Transit Model). During his presentation he pointed out that such tools can facilitate the prediction of the rate and extent of absorption from in vitro data. With the help of the parameter sensitivity analysis it is possible to estimate the influence of formulation factors (e.g. drug substance particle size distribution) on pharmacokinetics. In addition these tools allow for a better planning of clinical studies, e.g. BE studies (e.g. probability to meet BE criteria by adjusting blood sampling protocols). Overall these tools represent a supportive element in the formulation development process. New elements like fluid balances in the GI tract (secretion/resorption), variations in GI tract passages, excipients roles and gastric and metabolic transporter distribution patterns in the gut (pediatric populations!) will be integrated into the next version of the software.



## 4. Formulation strategies and enabling technology approaches

### *Integrated early formulation strategy*

[Gerrit Hauck, Ph.D. \(Sanofi-Aventis\)](#) presented the Sanofi-Aventis integrated early formulation strategy: Development timelines are shortened by moving from a sequential to a parallel processing. Efficient formulations reduce the number of iterative cycles e.g. by assessing physico-chemical properties of compounds prior to start of formulation development, using prediction software tools and trying to standardize the development e.g. considering a limited number of formulation technologies, e.g. applying NanoCrystal dispersions. Delivery challenges are overcome by standard (oral solutions, suspensions, i.v. solutions etc.) and enabling approaches I - III: The enabling approach I is driven by solubility issues, preferred technologies i.e. nanodispersions, lipid-based delivery systems, enabling approach II is driven by permeability or metabolic issues: alternative application routes (i.e. i.v., subcutaneous) need to



be taken into consideration due to insufficient oral exposure. In case of the enabling approach III the compound has permeability or metabolic issues and alternative application routes need to be developed due to high medical needs (e.g. intra-articular application).

#### *Oral nano-sized self-emulsifying drug delivery systems*

Prof. Anette Müllertz from the Danish University of Pharmaceutical Sciences gave an overview about rational development of oral nano-sized self-emulsifying (SNEDDS) drug delivery systems: Lipid based formulations are one of many approaches to increase bioavailability of poorly soluble drugs which have sufficient solubility in lipid excipients. Nowadays these systems are classified in four types I – IV according to C. Pouton. Self-emulsifying drug delivery systems are isotropic mixtures and can comprise of a lipid phase, hydrophobic surfactants (HLB < 12), hydrophilic surfactants (HLB > 12) and hydrophilic cosolvents (e.g. ethanol) plus the aqueous phase. In water they form oil-in-water emulsions/microemulsions. Microemulsions can contain nanoparticles < 100 nm and can enhance the bioavailability of poorly soluble drugs (i. e. Neoral® formulation for Cyclosporin). Important is beside sufficient drug loadability the retention of the drug in micelles in contact with physiological media (avoiding precipitation). Prof. Müllertz presented a Probucol case study performed in a mini-pig model with a comparison of a SNEDDS-type formulation with particle sizes in the range of 45 nm versus a SMEDDS-type system with large particles of 4.6 µm – astonishingly there was no significant effect of the emulsion particle size and basically no food effect observed. For a rational development of a lipid formulation the in-vitro lipolysis model (hydrolysis of triglycerides to fatty acids and monoglycerides) should be applied in addition to conventional dissolution testing to better characterize the precipitation potential of such formulations. For the Probucol study some kind of IVIVR could be shown with the lipolysis model with similar Probucol in-vitro releases for SNEDDS and SEDDS formulations.



#### *Nano-particulate systems*

At the end of the first day Prof. Heike Bunjes from the Technical University of Braunschweig (Germany) gave an overview about nanoparticulate systems (nanoemulsions, drug nanosuspensions): Poorly water soluble drugs can be solubilized in nano-carriers allowing the applicability in aqueous media, improving dissolution and bioavailability. Colloidal lipid emulsions (parenteral fat emulsions), S(M)EDDS systems, liposomes (i.v. drug delivery), (mixed) micelles, polymer nanoparticles (e.g. novel i.v. delivery system for Paclitaxel, tradename Abraxane®) and drug nanoparticles (prepared by nanomilling or high pressure homogenization) for peroral drug delivery and nanoemulsions (drug + oily carrier + stabilizers) were covered in the presentation. Formulation challenges (i.e. limited drug solubility in the oily phase, interaction of drug with emulsifier layer, drug precipitation in the aqueous phase) and solutions (e.g. supersaturated/supercooled systems) were discussed. Drug nanosuspensions have been successfully marketed (e.g. Rapamune® tablets). The challenges are typically the stabilization of such suspensions (steric stabilization with polymers, electrostatic stabilization with surfactants) to avoid Ostwald ripening/particle growth and further processing (drying by spray drying for instance). In special cases liquid dosage forms may be advantageous (pediatric applications). As a conclusion Prof. Bunjes underlined that there is no universal, "one fits all" nanoparticulate drug delivery system.



#### *Social event*

The participants of the course enjoyed the evening cruise on the river Rhine and had lots of opportunities for making network contacts during the dinner – a typical Swiss supper was served by the boat staff.



Prof. Guy van den Mooter, University of Leuven (Belgium) opened the lecture on the 2<sup>nd</sup> day: The rationale for using solid dispersions for poorly soluble drugs is to overcome high lattice energies of poorly soluble drugs by embedding the drug in an inert carrier or matrix. While in solid solutions the particle size reduction of the dispersed drug at molecular level is strictly only possible in crystalline carriers (substitutional, interstitial solid solution), most of the pharmaceutical carriers are amorphous (e.g. pharmaceutical polymers) – therefore these systems should be better called “glass solutions”. Glass solutions are thermodynamically metastable system with the risk of phase separation and drug recrystallization, hence physical instability. Preparation of solid dispersions can be based on solvent (i.e. spray drying) or heat methods (i.e. hot melt extrusion, melt granulation). The different technologies were explained more in detail. As an interesting example to lower processing temperatures for thermolabile drugs, Prof. van den Mooter presented a hot melt extrusion process of ethylcellulose combined with super- or subcritical CO<sub>2</sub>: carbon dioxide acts here as a plasticizer and temperatures could be lowered between ca. 30-50°C. An overview about different carrier types and analytical characterization techniques (DSC: Analysis of T<sub>g</sub> following the Gordon-Taylor equation, NIR) was given and the speaker closed his presentation with a comparison of pros and cons of solid dispersions – among the different benefits the carriers (mainly surface active agents) can maintain supersaturation in the GI tract while a better understanding of the physical structure of a solid dispersion and the prediction of the shelf-life are the real challenges for these systems.



### *Cyclodextrines*

Marcus Brewster, Ph.D. (Johnson & Johnson) gave a presentation about the oral and parenteral use of cyclodextrins in formulation development. Cyclodextrins form non-covalent, dynamic complexes with appropriately sized lipophiles. By complex formation undesirable “guest” attributes are temporarily camouflaged. On the other hand dilution and other interactions give rise to rapid decomplexation. Cyclodextrins can be used for a variety of applications, e.g. enhanced solubility/bioavailability, but also to reduce odors or tastes or enhance drug stability. Dr. Brewster presented a table with more than 20 approved products approved in different countries. In many of them β-Cyclodextrin is used which is orally safe but is parenterally associated with nephrotoxicity related to in-situ precipitation in the kidney. Multiple cyclodextrin derivatives have been developed during the last decades: Improved 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin have made it to the market. They are amorphous isomeric mixtures, highly water soluble, have minimal detergent-like effects and retain the complexation potential of the β-Cyclodextrin. Both are safe and depict useful functional excipients with applications to oral, parenteral and other administration routes. Both cyclodextrins will most likely play a greater role in drug development of poorly soluble drugs.



## 5. Bioavailability testing

### *Testing the bioavailability of poorly water soluble drugs in animals and humans*

Prof. Werner Weitschies from the Ernst-Moritz-Arndt University of Greifswald (Germany) spoke about the difficulties in using animal PK data for human prediction: While rats and dogs are the animal species mostly used for preclinical studies, the GI tract of the pigs correlates better with the human gastrointestinal system. Authors have tried to correlate human absorption with rat and dog absorption of 64 respectively 43 drugs: A better correlation was found for rats than for the dogs. Prof. Weitschies emphasized that water and solid contents applied to different animal species (rats, mice, dogs) can differ significantly (i.e. few µl in mouse versus 50 – 250 ml in dogs, humans). Species-specific differences in solubilization power for poorly soluble drugs were discussed (i.e. much higher solubilization of dipyridamole in fasted canine intestinal fluids). Differences in physical stress in the GI tract in the small intestine of dogs and humans were rather marginal and results nicely comparable. An IVIVC case study of a level C correlation tested in dogs and humans was presented – a good correlation was found. Despite these positive results the presenter emphasized that the predictive value of animals models for human PK remains in dispute.



## 6. Extended Release Formulations

### *Development strategies for extended release formulations*

Dr. Robert Becker from Biogen Idec (Ismaning, Germany) presented modified release principles for poorly soluble drugs: coated systems, matrix systems (inert matrix, erodible and swellable systems), osmosis and ion exchanges based delivery approaches. An example for an osmotic controlled system is Concerta<sup>®</sup>, a trilayer capsule-shaped tablet for methylphenidate with a rate controlling membrane, a push compartment that pushes the drug through a laser-drilled orifice. Absorption site mapping e.g. with a non-invasive Enterion<sup>®</sup> capsule could be a prerequisite for the rational development of an extended release formulation. Solubilization strategies for a poorly soluble drug could be pH modification, solid

dispersions/solutions, nanodispersions and ion exchange resins. Dr. Becker presented pH-mediated release from pellets for a weak base and a resinate concept case study for a poorly soluble drug with Amberlite<sup>®</sup>, an insoluble, strongly acidic, sodium form cation exchange resin which is not absorbed and excreted as potassium salt. Significant improvement of the bioavailability (75 fold to control), dose linearity and no dose dumping was observed. For drugs that show incomplete drug absorption in the GI tract (narrow absorption window) gastroretentive dosage forms could be an option (low/high density forms, bioadhesive approaches, swelling systems) preventing emptying through the pyloric sphincter. As a conclusion PK PD correlation is mandatory for an appropriate extended release formulation strategy whereas the solubilization strategy triggers the modified release strategy.



## 7. Partnering with drug delivery companies

The last presentation was given by Nicole Balten, Ph.D. (Novartis, Switzerland) about aspects of partnering with drug delivery companies. A phase specific model of collaborations at Novartis covers all kinds of interactions with drug delivery companies from non confidential information exchange to feasibility studies, full development and commercial supply activities. In a due diligence assessment the likelihood of success, timelines for development, costs and benchmarks will be evaluated. On the IP side it is i.e. important to check how good the patent protection of the focused technology is, if there is an added value of using the technology, the risks for using it (patent infringements) and of course the price for using the technology (payment for license). A sound project management (e.g. agreement on project plan, major deliverables, decision point, communication etc.) is needed to overcome challenges like different time zones, alliances with more than 2 partners, different company and country specific cultures.



## DRUG DELIVERY PRODUCTS

Provided by Dr. Louise Rosenmayr-Templeton

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### MEPACT<sup>®</sup> (IDM Pharma S.A.)

In December 2008 the EMEA recommended that MEPACT<sup>®</sup>, a liposomal powder for suspension for infusion, be granted a marketing authorisation for the treatment of high-grade, resectable, non-metastatic osteosarcoma in children and young people. The product is used in combination with other chemotherapeutic agents following surgical resection. In a Phase 3 trial involving patients aged between 2-30 years at the time of initial diagnosis, addition of MEPACT<sup>®</sup> to the chemotherapeutic regimen was shown to improve overall survival compared with chemotherapy alone.

The product contains 4 mg of mifamurtide (also known as L-MTP-PE), a conjugate of muramyl tripeptide linked to dipalmitoyl phosphatidyl ethanolamine. It is therefore a derivative of muramyl dipeptide, the smallest repeating immunostimulatory unit of the *mycobacterium sp.* cell wall used in complete Freund's adjuvant.

Free muramyl tripeptide has been shown to activate macrophages and monocytes in *in vitro* and *in vivo* models and it is this ability that is thought to be responsible for the formulation's anti-tumour activity. The phosphatidyl-ethanolamine component of mifamurtide enables its spontaneous insertion into the bilayer of the multilamellar liposomes formed, when this conjugate is mixed with other lipids during product manufacture.

The benefits of delivering muramyl tripeptide in this way are three-fold. Firstly, the size and composition of the liposomes formed result in passive targeting to tissues, such as the liver, lung and spleen that are rich in macrophages. These same formulation characteristics also promote the phagocytosis of the mifamurtide-loaded carriers by the target cells. Secondly, the intracellular release of the active moiety from the degrading liposomes is slow, resulting in sustained cell activation which is particularly pronounced in the case of monocytes. Thirdly, as mifamurtide is a chemical conjugate and the liposomes in which it is incorporated are rapidly phagocytosed, the amount of free muramyl tripeptide in the circulation is minimised, hence, reducing toxicity.

MEPACT<sup>®</sup> has orphan drug status in the EU and the US. It has yet to be approved by the FDA but, if successful, it will be marketed in the US under the trade name Junovan<sup>®</sup>.

### KEPPRA<sup>®</sup> XR (UCB Pharma)

2008 saw the approval of a number of controlled release formulations of well-known drugs including a once-daily formulation of Keppra<sup>®</sup>, UCB's blockbuster treatment for epilepsy. Keppra<sup>®</sup> XR was approved by the FDA in September 2008 as an adjunct therapy for the treatment of partial onset seizures in patients of 16 years and over. The white film-coated tablets contain 500 mg of the active, levetiracetam, in a sustained release matrix and enable a reduction in dosing frequency from twice to once daily. The new formulation is not expected to have a major impact on the side-effect profile of levetiracetam, which includes drowsiness, dizziness and, in some patients, behavioral disorders such as anxiety and irritability. However, in a controlled clinical trial, the pattern of adverse reactions observed for the sustained release formulation differed somewhat from that seen in studies involving the immediate release product. This was attributed to the smaller number of patients involving in testing Keppra<sup>®</sup> XR and not to the change in formulation itself.

UCB hopes the introduction of the new formulation will strength its portfolio, give patients greater choice and ward off generic competition as levetiracetam comes off patent. Sales of Keppra<sup>®</sup> in 2007 stood at over 1,026 million €.

**LIFECYCLE PHARMA A/S** (Hørsholm, Denmark)

Lifecycle Pharma develops improved oral dosage forms based on their proprietary Meltdose® technology. The company has one product on the market and several in clinical development.

**Fact sheet:**

Founded:	2002, spin-off from Lundbeck A/S
Location:	Hørsholm, Denmark
Ownership:	Public company, listed on Copenhagen stock exchange
Employees:	113
Key technology:	<p><b>Meltdose Technology</b></p> <p>Meltdose technology is a formulation technology aimed at improving absorption and bioavailability of poorly soluble compounds. The technology is based on the preparation of tablets from solid solutions in a melted carrier, using no water or organic solvents. The active ingredient is dissolved in a melted vehicle, which is subsequently sprayed on to a particulate carrier material (e.g. lactose) using fluid bed equipment. Subsequently, the vehicle solidifies and the active ingredient is captured as a solid dispersion either as a solid solution or in a nano-crystalline state. The technology allows for significant control over the size of the particles formed and manufacturing is performed in a one step process.</p>
Products:	<p><u>LCP-FenoChol</u>: FDA approved product for the treatment of dyslipidemia as an adjunct to diet in adult patients.</p> <p><u>LCP-Tacro</u>: once-a-day formulation of tacrolimus to prevent rejection in kidney and liver transplants. Phase III studies on-going in stable kidney transplant recipients and Phase II studies on-going for autoimmune hepatitis.</p> <p><u>LCP-Atorfen</u>: fixed dose combination therapy for treatment of dyslipidemia. Phase II completed</p> <p><u>LCP-Feno</u>: a generic fenofibrate. Completed pilot studies for dyslipidemia</p>
Development status:	<p>First product based on the Meltdose technology was approved for sale in the US in February 2008 (LCP-FenoChol)</p> <p>Phase III clinical studies on-going for once-a-day tacrolimus</p> <p>Two compounds ready to enter pivotal trials</p>
Partnerships:	<p>Sciele Pharma</p> <p>Sandoz</p>
Website:	<a href="http://www.lcpharma.com">http://www.lcpharma.com</a>
Contact:	<p>Jim New (CEO)</p> <p>Kogle Allé 4</p> <p>Hørsholm, Denmark</p> <p>Phone: +45 70 33 33 00</p> <p>Fax: +45 36 13 03 19</p> <p>e-mail: <a href="mailto:info@lcpharma.com">info@lcpharma.com</a></p>

**MUCOADHESION**

*A state in which two surfaces, at least one of which is of a mucous membrane, are held together for an extended period of time by interfacial forces. [Write a comment on this definition](#)*

Accordingly, mucoadhesion is a subcategory of bioadhesion. An example of mucoadhesion in pharmaceutical science is the adhesion of a buccal patch on the mucosa of the oral cavity. Certain polymers such as polyacrylic acid, chitosan and sodium carboxymethylcellulose may be used in gels, films, and other formulations to impart mucoadhesive properties.

German: [Mucoadhäsion](#)

French: [Provide a translation](#)

Spanish: [Provide a translation](#)

## BIOADHESION

***A state in which two surfaces, at least one of which is of a biological material, are held together for an extended period of time by interfacial forces. [Write a comment on this definition](#)***

The definition closely follows that recently proposed by John Smart (The basics and underlying mechanisms of mucoadhesion. *Advanced Drug Delivery Reviews* 57, 2005, 1556–1568). An example of bioadhesion is the attachment of a transdermal patch to the skin of a patient, wherein the skin is the biological surface. In contrast, biological interactions on a molecular level, such as the binding of a neurotransmitter to a receptor, are not usually understood as bioadhesion because it does not involve surfaces (according to material science). Interestingly, in other technical fields, bioadhesion is also used for the adhesion between two non-biological surfaces where it is affected by a glue, or adhesive, of (semi-) natural origin.

German: [Bioadhäsion](#)

French: [Provide a translation](#)

Spanish: [Provide a translation](#)

[Suggest a term to be defined](#)

[Suggest a definition](#)

## DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

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**JEAN-CHRISTOPHE LEROUX** was born in Montreal (Canada) in 1969. He received his B.Pharm. from the University of Montreal, followed by a Ph.D. in Pharmaceutical Sciences (1995) from the University of Geneva (Switzerland). From 1996 to 1997 he completed postdoctoral training at the University of California, San Francisco and then joined the University of Montreal as an assistant professor. He was promoted to the ranks of associate professor in 2002 and full professor in 2007. In 2001, he was awarded the Canada Research Chair in Drug Delivery. Prof. Leroux joined the Institute of Pharmaceutical Sciences at ETHZ as full professor in September 2008.



His research interests include the design of novel biopolymers, stimuli-responsive drug delivery systems (liposomes, micelles and gels) and the targeting of anticancer drugs. Recently he has been involved in the development of new polymer therapeutics for Celiac disease. He is the author or co-author of more than 100 refereed articles, 14 book chapters and 14 patents/patent applications. He is the associate editor of the *EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS* and serves on the editorial board of 5 journals including the *JOURNAL OF CONTROLLED RELEASE* and the *JOURNAL OF PHARMACEUTICAL SCIENCES*. He has received several prestigious distinctions and fellowships including the *CRS-Capsugel* (1997 and 2003), *AFPC-Astra Zeneca* (2003) and *CRS young investigator* awards (2004) and the *Steacie Fellowships* (2008) for innovative research in pharmaceutical technology.

## FEATURED ARTICLE

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### IN VIVO IN VITRO CORRELATION (IVIVC) OF INHALATION DOSAGE FORMS

*By Herbert Wachtel, Drug Delivery Department, Pharmaceutical Physics, Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Str. 173, D-55218 Ingelheim am Rhein, Germany*

#### 1. Introduction

In vivo in vitro correlations (IVIVCs) are implicitly assumed in many fields of pharmaceutical development. In case of their (individual) successful validation IVIVCs may guide and speed up development, and they may provide the rationale for the design space in which production can be optimized.

Focusing on inhalation dosage forms, inhalers are the interface between the patient and the formulation including the active pharmaceutical ingredient (API). Due to the large variability within the patient population, fine tuning of the dosage form is difficult in the clinical environment. A viable approach tries to determine correctly the typical patient properties and preferences (in vivo), in order to build a reproducible model for bench top testing (in vitro). By definition, such a model represents one example of IVIVC if in vivo drug deposition in the body – or more preferably a therapeutic effect – can be predicted. Using these models, more realistic checks of device performance may be obtained than those achievable by compendial testing. Nevertheless compendial in vitro models [1], [2] have their place in quality control and release testing. To date international harmonization and standardization of compendial methods have the unmatched advantage. However, the first steps towards standardized realistic mouth- and throat models have been initiated [3], [4]. These innovations and the current discussion of the scientific rationale – if any – for in vitro dissolution tests for inhalation dosage forms [5] motivate this article.

#### 2. Expectations concerning IVIVC of inhaled dosage forms

Classical IVIVC links dissolution data to bioavailability or even to the prediction of the therapeutic action. In the field of aerosol medicine, evidence has shown that correct deposition is the most important performance indicator. Only hypo-

thetically, the next step to investigate may be the dissolution test of inhaled formulations because at present there seems to be no compelling evidence that such dissolution testing might be crucial for the currently approved inhalation products [5]. However, the final goal of investigating IVIVCs may be a statement of bioequivalence of inhalation products which is an opportunity for generic drugs. In general, two applications of inhaled dosage forms may be envisaged:

#### Topical treatment

Local diseases of the lung are treated and, while the transition of API into the pulmonary blood circulation may be helpful, the transition into the systemic body circulation is not required and sometimes might even give rise to adverse effects.

#### Systemic treatment

If systemic diseases are treated via the inhalative route, the largest reachable surface with the thinnest air blood barrier is targeted. Therefore the aerosol should enter deep into the lung periphery and deposit in the alveoli. Good permeation properties (and/or solubility) may help to achieve sufficient concentrations of API in the systemic circulation.

In summary the prerequisite for any therapeutic action is the presence of the API in the lung. The prediction of local drug deposition is difficult - because of the individual geometry of the airways (some ways may be blocked), - because of the air flow rates and - because of the residence times of the aerosol inside the lung before exhalation. In comparison with e.g., oral dosage forms, the inhalative route offers many more degrees of freedom how and where in the respiratory tract the API might deposit.

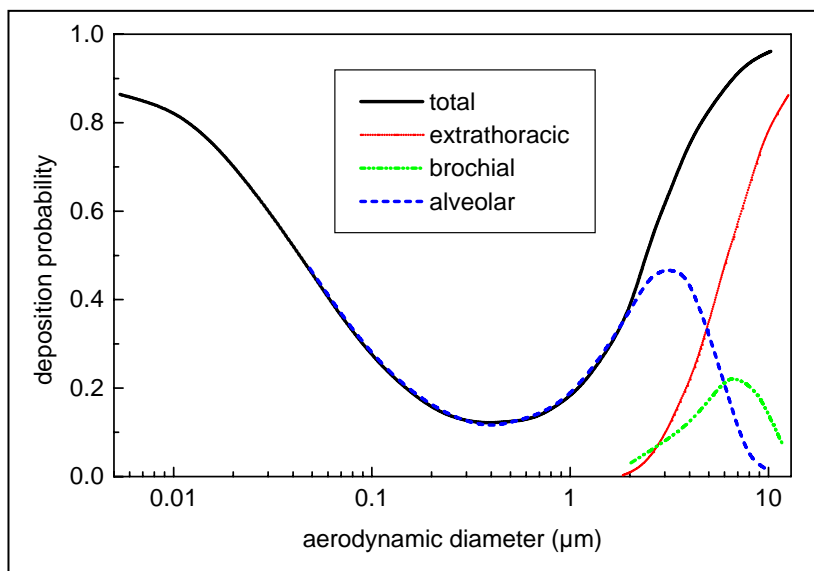


Fig. 1: Deposition as function of the aerodynamic diameter at a mean flow rate of 0.75 L/s and a breathing cycle period of 4 s for oral breathing after Heyder et al. [8]. Alveolar deposition is maximized between 1-5 µm.

Aerosol physics describes three major mechanisms of deposition of particles in the lung: i) impaction, ii) sedimentation, iii) diffusion. In all three cases the aerodynamic diameter (or the particle mass) and the breathing pattern (air flow rate, breath holding time (or resulting residence time)) are the decisive parameters. It is expected that these parameters and basic geometrical data be included in any IVIVC of inhalative dosage forms. The foundations of targeting defined regions in the respiratory tract are summarized in general reports [6], [1], [7]. The key learning is the size dependence of particle deposition in the average lung (of healthy volunteers) on the aerodynamic particle diameter, as shown in Fig. 1 according to the pioneering work by Heyder et al. [8]. This dependence is the scientific justification for the aerodynamic assessment of the particle size of inhalation dosage forms. Due to the relatively fast uptake of the currently marketed APIs by the lung, the steps after the initial deposition have received less attention in IVIVCs of inhalation dosage forms so far. Animal models provide the only way to assess the sometimes complex fate of inhaled particles after deposition, in spite of clearance mechanisms being species dependent [9].

### 3. Inhalers and their compendial testing

Examples of wide-spread inhaler types are listed in Table 1. Depending on the dose strength, on physico-chemical properties as well as on compatibility of the active agent, the doctor's choice of inhaler classes is more or less limited. Further restrictions arise from licensing and/or patent issues.

The performance and the reliability of inhalation dosage forms depend on their correct use. While on the average the handling of the inhalers is continuously simplified, it remains for the patient to inhale correctly. This requires repeated and inhaler-dependent training. However, in many health systems it is not clear, who should provide this training and, as a result, many patients do not use their inhalation dosage form correctly [10].

Table 1: Typical classes of inhalers. Only trends can be given, the large number of different devices and formulations require discussion on a case by case basis.

Inhaler	Operation principle	Inhaler complexity	Formulation type	Formulation complexity	Comment
<b>nebulizer</b>					
Formulation dependent sub-types	Two-phase nozzle, piezo-electric, etc.	High fine particle fraction difficult to achieve	Solution	Acceptable	Many breathing cycles = time consuming
			suspension		
			emulsion	Unknown	
<b>Double jet impinger</b>	Mechanically driven piston with special nozzle	Relatively high (nozzle, mechanics)	Solution	Acceptable	Soft mist inhaler reduces throat depos. at low air flow rate
<b>p-MDI</b>		Acceptable, breath actuation is mechanically demanding		Reformulation for HFAs	economical
Formulation dependent sub-types	Propellant driven (HFAs)		Solution	More complex than for CFCs	
			suspension		
			emulsion	Unknown	
<b>DPI</b>					
premetered		Increasing with # of doses in multi-dose dev.	<b>premetered</b>		
	Passive, driven by breath	acceptable	Ordered mixtures, force control agents	Powder know- how required	Simple coordination
	Active, energy source required	increased	Maybe more tolerant with respect to powder properties	Powder properties may be out ruled by device	
reservoir		Depending on flow ability and homog. density of powder	<b>reservoir</b>		
	Passive, driven by breath	Metering and humidity protection are issues	Good flow ability required	Powder and particle engineering recommended	Simple coordination
	Active, energy source required	3rd generation, still under development		Hope for simple formulations	

Apart from a large number of pharmaceutical quality tests, inhalation dosage forms are subjected to tests of the uniformity of delivered dose and to the aerodynamic assessment of fine particles. During these tests a defined air flow is generated and passed through the inhaler under test. The total amount of API collected under defined conditions in the given set-up is called the delivered dose. Unless otherwise specified, the delivered dose is often used as label claim. Sometimes the metered dose of p-MDIs or multidose DPIs is given on the label. The particle size distribution of the API within the aerosol is characterized by the apparatuses briefly listed in Table 2. As a rule of thumb, two measurements per day are performed by a highly specialized analyst using one of the set-ups described in Table 2.

Table 2: Apparatuses used for the aerodynamic assessment of fine particles used in aerosol medicine. The European and the US Pharmacopoeia are well harmonized.

Name in Ph. Eur. 1/2008	A	removed	C	D	-	E	
Specification	Inhalation tester made of glass	Metal impinger (cancelled)	Multi stage liquid impinger	Andersen cascade-impactor	Marple-Miller-cascade-impactor	Next Generation Pharmaceutical impactor	
air flow rate (l/min)	p-MDI	60 ± 5	60 ± 5	30 ± 5%	28,3 ± 5%	-	30 ± 5%
	DPI	60 ± 5	60 ± 5	Q ± 5%	Q ± 5%	Q ± 5%	Q ± 5%
	nebulizer	60 ± 5	60 ± 5	-	-	-	(15 ± 5%)
number of stages incl. filter	2	2	5	9	6	8	
	(no filter)			+ Presep. (DPI)		+ Presep. (DPI)	
sample inlet ("throat")	modified	rectangular	USP	USP	USP	USP	
	round-bottomed flask	elbow	inlet	inlet	inlet	inlet	
Name in USP_31	p-MDI	-	-	apparatus 1	-	apparatus 6	
	DPI	-	-	apparatus 4	apparatus 3	apparatus 5	

p-MDI = pressurized Metered Dose Inhaler; DPI = Dry Powder Inhaler

Q = Volume flow rate @ pressure drop of 4 kPa; USP inlet = sample inlet according to USP

#### 4. Upcoming trends in inhaler testing

In the past, a coarse separation into large particles, which were thought to be lost, and the fine particle dose (aerodynamic diameter e.g. below 5  $\mu\text{m}$ , penetrating into the lung) was sufficient for size characterization. Now the particle size distribution becomes more defined by grouping several stages of cascade impactors and providing e.g. 3 group values which all have their proper tolerance bands. Even more strict approaches aim at comparing the complete size distributions of inhalation products. However, this high effort in vitro does not take into account the large variability from patient to patient. In view of IVIVC, a more realistic throat is desirable because the inhaler design can modify the air flow in the mouth-throat region by use of an anatomically shaped mouthpiece and by a suitable aerodynamic design of the aerosol duct inside the inhaler. Examples of throat models have been proposed by Finlay (see Fig. 2b, idealized geometry [3]) and Olsson (not shown, realistic oropharyngeal geometries [4]), for example.

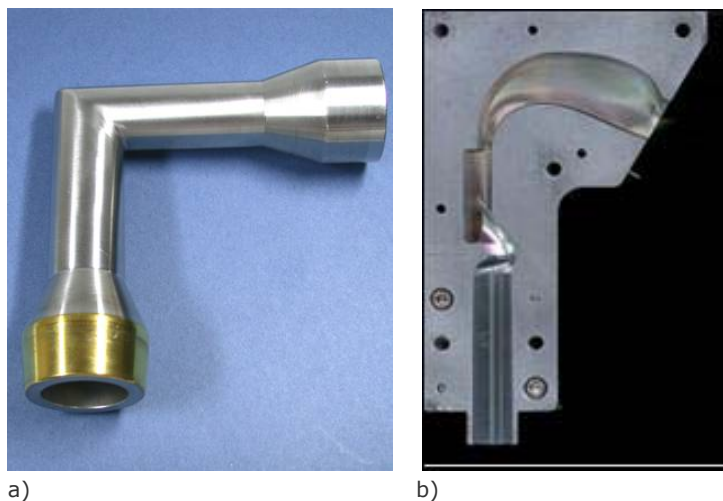


Fig. 2: a) USP induction port b) view into Finlay's idealized human throat (one half removed)

Using realistic flow profiles mimicking the inhalation of patients (see Fig. 3), the operation of inhalers can be monitored under conditions which are close to the situation „in vivo“ but provide the advantage of excellent repeatability for checking the reproducibility of drug delivery by the inhaler under test. In favourable cases, instead of analyzing many stages of a cascade impactor, the collection of API having passed the throat model in a single filter assembly is predictive for the amount of API entering the lungs [4].

Simulations in silico have either been based on bolus inhalation data, radio label studies, or calculations of particle deposition from first principles, e.g. the geometry of human airways is digitized and modelled from lips to alveoli. Applying deposition mechanisms (impaction, sedimentation, diffusion, etc.) during the flight of imaginary particles along the computer model, predictions on the deposition in the lung are possible. For example, MediBreathe Drug Inhalation Modelling [11] claim, that they can compute the complete delivery process from the inhaler to the lung tissue, where systemic uptake takes place and is simulated.

#### 5. Impact of inhaler design

When discussing IVIVC it must be remembered that many clinical tests are performed with well-trained patients who know how to handle their inhaler and that the in vitro tests are carried out by experts, a fact which largely excludes handling problems. The clinical programme therefore is supplemented by handling studies. These studies become extremely important for the young and the old patients. Results of handling studies directly influence the design of the inhaler and ensure that the inhalers (and therefore the inhalation dosage form under test) can be successfully used by the largest possible patient population. The inhaler design will be discussed from different perspectives:

##### *Impact on the correct use and the adherence to protocol / prescriptions*

Requirements for the ideal inhaler have been postulated for example by Ganderton [11]. The intention is that the inhalers be easy and self-explanatory to use. In reality, the large number of different inhalers makes the selection of the right device difficult. Moreover, once the patient has learned the correct use of „his“ inhaler, on the personal level it is difficult to change the inhaler type or even to substitute the same type by one of another manufacturer because of differences in outer appearance, feel and grip, handling and possibly smell/taste.

##### *Impact on the formulation and on the overall performance of the drug product*

The aerosol generation principle dictates some functional elements and their shape as well as the suitable formulation. To a certain degree, the challenges of the development can be shifted from the inhaler construction to the formulation

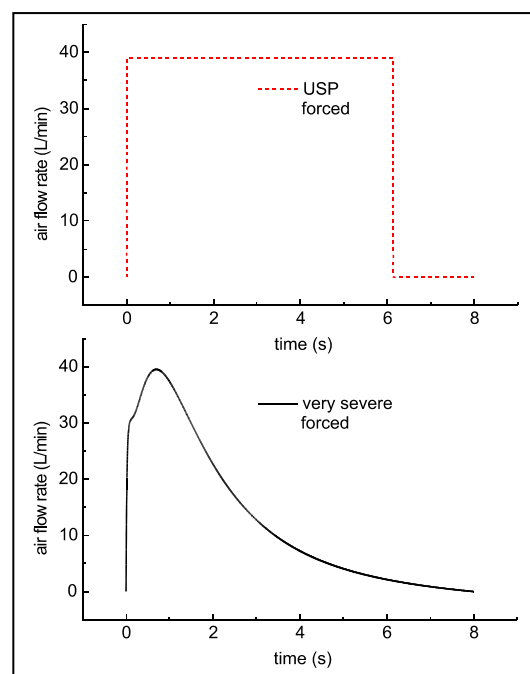


Fig. 3: Top: breathing pattern according to USP (Example HandiHaler 39 L/min @ 4 kPa) and corresponding average breath of severe COPD Patient fit to a model function (bottom).

design and vice versa. In order to identify the best solution, a decision matrix is helpful. In some cases, the same API is available in different formulations and inhalers, respectively. When comparing the therapeutic effect and the required dose, a simple statement can be given: higher efficiency is reached, the lower the dose and the larger the therapeutic effect. For example, von Berg et al. have shown in children that Berodual administered via Respimat (a new double jet impinger which creates a soft mist) results in a larger increase of FEV<sub>1</sub> (forced expiratory volume in 1 second) than an approximately doubled dose administered via p-MDI coupled to a spacer [12].

## 6. Conclusion

Inhalation dosage forms require high investments in development as inhaler, formulation, and patients all may contribute to variability in the physical delivery of drug to the target, e.g. nose, lung or regions thereof. This results in expensive clinical trials. IVIVCs and practical models based on them help to speed up the optimization work in the lab for inhaled dosage forms but it will be very difficult to derive statements of bioequivalence.

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## DRUG DELIVERY LITERATURE

Provided by Dr. Karsten Cremer

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### 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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