



APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

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DRUG DELIVERY EVENTS

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Provided by Christoph Blümer

◇ [Current Trends in Pediatric Drug Delivery \(APV course 6268\)](#)

November 24th - 25th 2009, Berlin, Germany

The course will give an overview of current trends in pediatric drug delivery: Neglecting pediatric populations as done in the past, which led to considerable stagnancy in the development of age-specific dosage forms, dosing and dispensing devices, is today no longer accepted by the regulatory authorities in the US and in Europe. For a better understanding of the recent trends in this course experts with different backgrounds and perspectives on pediatric drug development will present and discuss the current challenges and opportunities in this field with a focus on the following topics:

- Specific pediatric patient population requirements (Clinic, Market) [Details](#)
- Current regulatory requirements in the EU and the US, e.g. experiences from Pediatric Investigational Plans (PIPs)
- Age specific drug delivery aspects (Neonates, infants, older children)
- Drug delivery options for different routes of application (Oral, parenteral, pulmonary, transdermal etc.)
- Preparation of extemporaneous formulations
- Taste masking aspects
- Pediatric dosing devices

[Drug Delivery to the Lungs - DDL20](#)

Dec. 9th - 11th 2009, Edinburgh, Scotland, UK [Details](#)

[10th US-Japan Symposium on Drug Delivery Systems](#)

Dec. 16th - 20th 2009, Lahaina, Maui, Hawaii [Details](#)

[14th Annual Drug Delivery Partnerships](#)

Jan 25th - 27th, Orlando, Florida, US [Details](#)

◇ [Patent Workshop for Scientists & Managers in Drug Product Development \(APV course 6287\)](#)

Feb 25th - 26th 2010, Berlin, Germany

This course is designed to convey a solid understanding of patents and their role in the pharmaceutical industry, and to provide the attendee with the professional skills required to collaborate successfully with patent experts. Especially recommended for scientists and managers who are involved in evaluating inventions, preparing patent applications, supporting freedom-to-operate analyses, or who are members of due diligence teams. [Details](#)

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

Onsolis™ (fentanyl buccal soluble film) (Biodelivery Sciences International)

Onsolis™ is a soluble film designed to deliver the opioid analgesic, fentanyl, when applied to the buccal mucosa of the cheek pouch. It was approved by the FDA in July 2009 for the management of breakthrough pain in adult cancer patients already receiving and tolerant to opioid therapy. It is available in a variety of strengths (200, 400, 600, 800 and 1200 mcg) to allow dose titration. The initial starting dose is 200 mcg with one dose permitted per breakthrough episode with a maximum of 4 doses per day. It is not equivalent on a mcg per mcg basis with any other fentanyl product.

Onsolis™ uses Biodelivery Science International's BioErodible MucoAdhesive (BEMA™) delivery technology, which consists of a pink layer of soluble polymeric films bonded onto a white inactive one. The pink part of the bilayer is bioadhesive and contains the active as the citrate salt. It is this side of the film that is placed in contact with the buccal mucosa by the patient. The white layer is thought to isolate the bioadhesive one from the saliva and, hence, reduce drug loss through swallowing. The amount of fentanyl delivered transmucosally is proportional to the film surface area. The polymers contained in the formulation are carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and polycarbophil. The film has been shown to dissolve in 15 to 30 minutes after application, during which time it should not be manipulated with the tongue or finger(s) and eating should be avoided.

The absorption pharmacokinetics of fentanyl from Onsolis™ is a combination of an initial rapid absorption from the buccal mucosa and a more sustained one from swallowed drug reaching the bloodstream via the GI tract. The absolute bioavailability of fentanyl from Onsolis™ was found to be 71%, with approximately 51% being due to absorption across the buccal mucosa. Of that swallowed about 20 % escapes hepatic and intestinal first-pass elimination and becomes systemically available. An Onsolis™ film, if chewed and swallowed, is therefore likely to result in lower peak concentrations and bioavailability. During clinical development the relative bioavailability of Onsolis™ 800 mcg was compared in a study involving 12 adult volunteers with the transmucosal fentanyl citrate formulation, Actiq® 800mcg (a lozenge-type solid drug matrix on a stick). In this study the bilayer film was shown to result in a faster rate and extent of absorption achieving a 62% larger C_{max} and a 40% greater systemic exposure (AUC_{inf}) compared with Actiq®.

Biodelivery Science International believes that the product has the potential to capture a significant share of the US market for the licensed indication in adult cancer patients (currently worth \$700 million) and estimates that the annual peak sales for Onsolis™ will reach over \$200 million for America alone. The company has sold the commercialization rights for North America and Europe to MEDA AB.

Further Information: <http://www.biodeliverysciences.com> and <http://www.onsolis.com>

Lamictal® XR Extended-Release Tablets and Lamictal® Orally Disintegrating Tablets (GlaxoSmithKline)

The extended release formulation of the antiepileptic drug, lamotrigine, was approved in July 2009 by the FDA for the adjunctive therapy of partial onset seizures, with or without secondary generalization, in patients not younger than 13 years. The tablets are available in four strengths (25mg, 50 mg, 100 mg and 200 mg) and are administered once daily instead of twice for the immediate release formula. The extended release tablets are also supplied in patient titration kits, in order to facilitate the gradual increase in dosage required with this drug to reduce the potential for the development of life-threatening rash.

The extended release formula is based on GSK's DiffCORE™ technology. This consists of a modified release eroding core, coated with an enteric coat that has two apertures drilled through it on either side of the tablet face. The combination of apertures and core allow drug release to start in the stomach and continue at a sustained rate over a period of approximately 12-15 hours. This release profile enables the serum levels of lamotrigine to increase gradually, and takes advantage of the fact that regional permeability studies have shown that this drug is readily absorbed anywhere between the stomach and the ascending colon. Inactive ingredients include hypromellose and methacrylic acid copolymer dispersion.

The extended release tablets are not the only novel lamotrigine dosage form that has reached the market this year. In May 2009 the FDA approved an orally disintegrating tablet of this drug. This formula was developed in collaboration with Eurand. It uses two of this drug delivery company's technologies, AdvaTab® (orally disintegrating tablet technology) and Microcaps® (taste-masking coatings) to provide Lamictal in a pleasant-tasting tablet that disintegrates on the tongue and that may be taken with or without liquid. The orally disintegrating tablets, like the immediate release ones, are approved for a wider range of indications than Lamictal® XR including monotherapy of partial seizures and bipolar disorder. Lamotrigine had net US sales of 765 million pounds sterling in 2006 but has recently suffered from generic competition. GSK hopes to increase sales of the branded drug through the introduction of these two new dosage forms.

Further Information:

<http://www.lamictalxr.com/>, <http://www.lamictal.com/>, <http://www.eurand.com/> and <http://www.gsk.com>

CAPSULATION PHARMA AG (Berlin, Germany)

Capsulation Pharma develops drug delivery system based on polyelectrolytes, to produce sustained release injectable formulations, oral formulations with improved bioavailability or coatings for drug eluting devices. The company is a spin-off from the Max-Planck Society. In 2008, Capsulation acquired Nanodel (profiled in APV Drug Delivery Newsletter 1, 2007).

Fact sheet:

Founded:	2001
Location:	Berlin, Germany
Ownership:	Private company
Employees:	Approximately 20
Key technology:	<p>The company is built on the use of polyelectrolytes for oral and injectable drug delivery systems. Capsulation uses only polyelectrolytes that are well established and accepted for pharmaceutical use, such as collagen, chitosan, and protamine. These compounds are used predominately in two different systems:</p> <ul style="list-style-type: none"> - Layer-by-layer assembly to obtain microspheres for parenteral controlled release. Nanoparticles are assembled layer-by-layer in a stepwise approach, allowing incorporation of active ingredient. - Microparticles formed by complexation of cationic and anionic polyelectrolytes and encapsulation of the active ingredients; microparticles can be formed in a size range from 50 nm – 15 um. <p>Use of the technology platforms with both small molecule drugs as well as biologicals has been proven.</p>
Products:	Several products in pre-clinical development
Development status:	Lead product in pre-clinical development currently.
Partnerships:	Partnership with Bayer Schering, partnership with NascaCell on delivery of aptamers, other commercial partnerships undisclosed
Website:	http://www.capsulation.com/
Contact:	<p>Capsulation AG Alexander Herrmann, Chief Financial Officer Volmerstr. 7b D-12489 Berlin Germany info@capsulation.com</p>

Biodegradable

A material is biodegradable if it is chemically degraded into smaller molecules within a biological environment or in the presence of a biological material. [Write a comment on this definition](#)

According to this definition, virtually all biological and most synthetic materials are biodegradable as their degradation in a biological environment is only a matter of time. In fact, biodegradation is used for very different degrees of degradability in the various technical fields. In drug delivery, biodegradable polymers have become particularly important as drug carriers, especially for parenterally administered controlled release formulations. Biodegradability should not be confused with solubility: A polymeric carrier may dissolve in a physiological fluid without any chemical degradation.

German: [Bioabbaubar](#)

Biocompatible

A material is biocompatible if it does not adversely affect a biological environment.

[Write a comment on this definition](#)

Biocompatibility can also have quite different shades of meaning in different technical fields. In drug delivery, it means that a material is well tolerated by the organism or tissue to which it is administered. This tolerability does not require biodegradability. For example, all implants must be relatively biocompatible, but depending on their design and functionality they may not dissolve or degrade.

German: [Biokompatibel](#)

[Suggest a term to be defined](#)

[Suggest a definition](#)

DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

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MARTYN DAVIES is Professor of Biomedical Surface Chemistry at the School of Pharmacy, University of Nottingham, UK. He is a qualified pharmacist and graduated with First Class Honours from the Chelsea School of Pharmacy (now Kings College, London). He gained his PhD from the same institution under the supervision of Mike Newton. After a year at the Manchester School of Pharmacy covering John Fell's sabbatical leave in 1984, he was appointed to a lectureship at Nottingham in 1985. He was promoted to Reader in 1991 and then to a personal Chair in 1996. During this period, he was also Head of the Life, Health & Agricultural Sciences Division, Graduate School (1995-97). From 2000 to 2003 Martyn Davies was Head of the School of Pharmacy at Nottingham.



His current research interests focus on the study of the surface properties of biomolecular assemblies, advanced delivery systems and new generation biomaterials. They include surface nanoengineering, the self-assembly of surfaces and the characterisation of drug delivery systems. His work involves the application of a range of advanced surface analytical techniques such as AFM, SIMS, XPS and SPR to define the surface properties, functionality and performance of biomolecular, pharmaceutical and biomaterial systems.

Prof. Davies is also the co-founder and (until Jan 2008) Head of the Laboratory of Biophysics and Surface Analysis (LBSA), a Research Division of the School of Pharmacy. The LBSA has an international leading reputation and track record in scanning probe microscopy and surface chemical analysis of pharmaceuticals, polymers and biomaterials. The LBSA remains the only grouping to receive the GlaxoSmithKline International Achievement Award (2003), given for "internationally recognized work on drug delivery and new techniques for surface and interface analysis". He has also been involved with the formation of a number of University spin-out companies. In particular, he is co-founder and Chairman of a successful spin-out from the LBSA, Molecular Profiles Ltd, which was awarded the Queens Award for Enterprise in the category of Innovation in 2007.

In the course of his academic career, Professor Davies has published over 350 scientific papers and supervised more than 60 PhD students and 30 postdoctoral fellows. His scientific work has led to a number of prizes including the Controlled Release Society's Young Investigator Award (1997) and the Distinguished Service Award of the CRS (2008). He was the Scientific Secretary of the CRS (2001-7), and a participant in the European Science Foundation Forward Look on Nanomedicine. He has recently been re-elected to the UK's Engineering and Physical Sciences Research Council Peer Review College. He has organised numerous international scientific conferences and is on the editorial boards of four scientific journals (Journal of Controlled Release, Advanced Drug Delivery Reviews, Journal of Pharmaceutical Sciences, European Journal of Pharmaceutical Sciences). He is a Fellow of the Royal Society of Chemistry, American Institute of Biological Engineering and Royal Pharmaceutical Society of Great Britain.

FEATURED ARTICLE

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AN UPDATE ON TECHNOLOGIES FOR INHALED NANOMEDICINES

By Lea Ann Dailey, PhD

Pharmaceutical Science Division, King's College London, 150 Stamford Street, London SE1 9NH, UK

1. Why are Nanomedicines Interesting as Pulmonary Drug Delivery Formulations?

From iPods to drug delivery formulations, it seems that everything must be 'nano' these days. Is it just a passing trend? The successful development story of nanomedicines such as Abraxane[®] (a parenteral paclitaxel delivery system composed of drug-encapsulated albumin nanoparticles; Abraxis BioScience Ltd.) suggests otherwise. Abraxane[®] is the perfect example of how nanoparticulate drug delivery formulations can be far superior to more traditional formulation strategies. This albumin-based nanoparticle formulation was developed because previous paclitaxel formulations used Cremophor EL[®], a polyethoxylated castor oil, and ethanol to produce an injectable emulsion of the drug. The high toxicity of Cremophor EL[®] limited the applicable dose a patient could receive at one treatment. The makers of Abraxane[®] exploited the natural affinity of paclitaxel to the human serum protein, albumin, which allowed the incorporation of the drug within the nanoparticles and eliminated the need for toxic excipients. This in turn made it possible to administer

higher, more effective doses of the chemotherapeutic in one injection. Additionally, the albumin nanoparticles are small enough (~130 nm) to enter into tumour tissue through the leaky, fenestrated tumour vasculature, whilst remaining too large to enter healthy tissue with an intact endothelial barrier. This effectively leads to passive tumour targeting with an accompanying reduction in adverse side effects at a higher chemotherapeutic dose [1]. Such advantages may be exploited not only for oral and parenteral administration routes, but alternative routes as well. Specifically, the field of pulmonary drug delivery has been intensely interested in utilising the potential advantages of nanomedicines to improve both the safety and efficacy of inhaled medicines. But why are nanomedicines interesting as pulmonary drug delivery formulations?

We have known for a long time that pulmonary drug delivery offers many potential advantages over other delivery routes, such as oral or parenteral delivery. The lungs have a high solute permeability, a large surface area for absorption, and limited proteolytic activity. Via non-invasive inhalation, drugs can be delivered locally to the lung for the treatment of respiratory diseases, such as asthma or cystic fibrosis, or alternatively, systemic drug delivery can be achieved by targeting delivery to the alveolar region. Whether local or systemic, this targeted delivery can potentially result in a reduction of the overall dose and the amount of side effects that result from high levels of systemic drug exposure. For systemically active compounds, pulmonary drug delivery is also especially suited to achieve a rapid onset of action, to avoid first-pass metabolism or to deliver biotherapeutics (i.e. peptides and proteins) that cannot be delivered orally owing to enzymatic degradation and poor intestinal membrane permeability. Yet, many of the advantages of pulmonary drug delivery, such as rapid onset of action, can also be considered a serious drawback in some cases. In fact, the short lung residence time of most inhaled compounds is one of the most common problems of inhalation therapies, especially those designed for local delivery. Strategies to control or prolong lung residence time for inhaled drugs are therefore very useful. The idea to develop colloidal drug carriers with controlled release properties found its origins in this very real clinical problem.

In addition to controlling lung residence time, nanoparticle systems are finding increased use in the formulation of poorly soluble drugs. The larger specific surface area of nanosystems enhances dissolution profiles of poorly soluble compounds and can thus enhance the bioavailability of these drugs. There has been increased interest in such formulation enhancements for the more common poorly soluble compounds for inhalation, such as inhaled corticosteroids. Nanoparticulate formulations of drugs are also very versatile when it comes to choosing an inhaler device. They can be delivered either as aqueous suspensions using nebulisers of all types and can also be suitably formulated as suspensions in common propellants, such as HFA134a, for administration using pressurized metered dose inhaler systems. Most nanoparticle formulations are, however, further processed into dry powders for inhalation using various dry powder inhaler devices.

The following sections describe a selection of technological advances in nanoparticle systems for pulmonary drug delivery reported within the past two years, with a particular focus on the manufacturing technologies and formulation aspects.

2. Recently Published Reports on Formulation Strategies for Inhalable Nanomedicines

Nano-Salbutamol: A Human Deposition Study

Very intriguing data was published in February 2009 on the results of a human deposition study comparing the aerosol performance of a nano-sized salbutamol sulfate formulation (~60 nm) compared with a standard micronized form of the drug [2]. The nano-salbutamol formulation was prepared by a liquid anti-solvent precipitation technique followed by spray-drying with no further excipients used in the formulation. Both the resulting nano-salbutamol and standard micronized salbutamol particles were then radiolabelled with Tc-99m and blended with inhalation grade lactose. Both formulations were administered to healthy volunteers (n=10) using a Rotahaler[®] device and lung deposition was evaluated by gamma-scintigraphy. As shown in Table 1, delivery of the nano-salbutamol formulation was considerably enhanced compared to the micronised salbutamol with an even deposition throughout the lung and a significantly higher deposition rate.

Table 1 – A comparison of inhaled nano- and micro-salbutamol deposition data in healthy volunteers [2].

	Nano-salbutamol	Micronised salbutamol
	% of nominal dose	
Remaining in capsule	2.1 ± 1.4	2.3 ± 1.2
Remaining in inhaler	8.6 ± 2.1	10.0 ± 3.2
Emitted dose	89.1 ± 2.8	87.7 ± 5.6
Oropharynx	25.3 ± 4.5*	58.4 ± 6.1
Central lung	20.0 ± 2.7*	10.9 ± 1.8
Intermediate lung	21.3 ± 3.1*	8.7 ± 1.6
Peripheral lung	22.6 ± 2.4*	8.9 ± 1.5
Whole lung	64.1 ± 3.7**	28.3 ± 5.2
Exhalation filter	0.1 ± 0.1	0.0 ± 0.0

* $p < 0.05$, ** $p < 0.001$

The authors postulated that the enhanced lung deposition of the nano-salbutamol formulation may have been a result of the spherical nature and smoother surface of the spray-dried nanoparticles resulting in fewer cohesive interactions with the lactose carrier and a greater percentage of detachment during inhalation. Further, it was postulated that the lighter nanoparticles are more likely to disengage from the lactose surface as a result of centrifugal forces during lactose particle spin movements induced by the inspiratory airflow. Another very interesting feature of the nano-salbutamol formulation was the prolonged residence time of the drug compared to the standard micronised formulation. This was attributed to a deeper and more even deposition of the nanoparticles, which was thought to slow the overall rate of particle clearance from the airways. Although further data is necessary to establish the full clinical benefits of nano-sized drug particles in inhalation therapies, the results from this study suggest that current paradigms regarding the optimal particle size of inhaled drugs may need to be re-evaluated.

Nano-Aerosol Generation via Evaporation-Condensation

A multidisciplinary group of researchers from Novosibirsk, Russia, recently described their design of a device for the generation of nano-sized aerosols composed of poorly soluble drugs, using indomethacin as a model compound [3] using vaporisation and subsequent drug condensation as the mechanism of particle generation. Briefly, the drug substance is superheated at the end of a tube flushed with argon gas to generate a saturated drug vapor. As the vapor travels along the tube, the temperature drops creating a supersaturated vapor, which results in vapor nucleation and nanoparticle formation. The nano-aerosol is then diluted to the desired concentration for administration (in the case of this study to a nose-only murine exposure chamber). By adjusting parameters such as airflow and temperature, narrow particle size populations could be generated ranging from 3 – 200 nm. An aerosol spectrometer coupled to the aerosol generator made it possible for the investigators to determine real time particle sizes and lung deposition. They found that the lung deposition efficiency increased significantly as particle diameters decreased below 100 nm. Murine inhalation of the amorphous indomethacin nano-aerosol also offered significant systemic protection against an inflammatory stimulus (i.e. histamine injection into the paw) at doses that were magnitudes of order lower than the orally effective dose, thus, providing a proof-of-concept for nano-aerosols generated by the evaporation-condensation technique.

Although the aerosol generator device described in the above study was designed for research purposes only, it is worth mentioning that a small, portable vaporisation-condensation aerosol device (the Staccato[®] system) has already been developed by Alexza Pharmaceuticals (Palo Alto, CA, USA) for aerosol administration of systemically acting drugs. Alexza is hoping to file for FDA approval of their first Staccato[®] product, inhaled loxapine for the acute treatment of agitation in patients suffering from schizophrenia or bipolar disorder, in the first quarter of 2010. Further compounds currently in Phase I/II clinical trials include Staccato[®] perchlorperazine, alprazolam, fentanyl and zaleplon. Although using the same principle of aerosol generation via evaporation-condensation, the Staccato[®] system does not generate nano-aerosols, but rather particles with aerodynamic diameters between 1-5 μm [4]. However, if further evidence accumulates showing an enhanced therapeutic profile for nano-aerosols compared to microparticulate aerosols (especially for poorly soluble drugs), it may be feasible to adapt the Staccato[®] system to generate smaller particle sizes. One major drawback of the evaporation-condensation method of aerosol generation is that it is only applicable to thermally stable drug compounds. On the other hand, this delivery system requires no further excipients in the formulation, which circumvents many major concerns about formulation safety.

Controlled Aggregation or Flocculation of Nanoparticles

The group of Cory Berkland at the University of Kansas, School of Engineering has developed a strategy of controlled nanoparticle aggregation or flocculation to produce dry powders of inhalable nanoparticle clusters. They have used their manufacturing platform to create formulations for a wide variety of compounds both for local and systemic applications. These include budesonide, nifedipine, insulin and a combination chemotherapeutic system containing paclitaxel and cisplatin. The primary strategy is to produce nanoparticle suspensions of the neat drug via a solvent/anti-solvent precipitation technique. The drug was dissolved in either acetone or ethanol and injected into an aqueous solution whilst being subject to sonication. Surfactant excipients such as stearic acid, cetyl alcohol, PVA, PVP or lecithin were used to stabilise the drug nanoparticles in suspension. Afterwards, nanoparticles were flocculated under controlled conditions via the addition of either sodium chloride or L-leucine as a flocculating agent. The resulting agglomerates were then freeze-dried to remove all residual solvents and characterised for their aerodynamic properties. A similar strategy was also used to create agglomerated polymeric nanoparticle protein carrier systems. In this case, biodegradable cationic poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles were produced by a emulsion-solvent evaporation method and coated with the cationic lipid DOTAP (1,2-dioleoyl-3-trimethylammonium-propane). The cationic nanoparticles were then flocculated under controlled conditions by addition of negatively charged protein (ovalbumin was used as a model) and in the presence of PBS. The protein-loaded agglomerates were then lyophilized and characterised for their aerodynamic properties.

Table 2 contains an overview of the properties from the 'best' systems published by the group.

Table 2. Properties of selected pulmonary drug delivery systems composed of flocculated or agglomerated nanoparticles [data from ref. 5-9].

	Budesonide	Nifedipine	Paclitaxel/Cisplatin	Insulin	OVA/PLGA
Nanoparticle stabilising Excipients	Lecithin	Stearic acid	PVP K90/lecithin	None	DOTAP
Flocculating agent (*or anti-solvent)	L-leucine	Sodium chloride	L-leucine	Ethanol*	Ovalbumin/PBS
Nanoparticle size (nm)	160.9 ± 15.6	470 ± 40	299 ± 10	293 ± 42	271.5 ± 9.1
Agglomerate size (µm)	3.1 ± 0.6	11 ± 6	5.9 ± 3.0	3.4 ± 1.4	~5
Process yield (%)	95.5 ± 4.9	91 ± 4	89 ± 2	NA	NA
MMAD** (µm)	1.3 ± 0.2	1.4 ± 0.1	1.8 ± 0.04	2.3 ± 1.9	2.6 ± 1.6
Fine particle fraction <3.3 µm (% at 30 L/min air flow)	84.3 ± 3.9	94 ± 4	71 ± 1	NA	NA

** Mass Median Aerodynamic Diameter

The advantages of the flocculated/agglomerated nanoparticle systems described above are their excellent aerodynamic properties and high drug contents combined with the need for relatively low amounts of non-toxic excipients. In the case of the budesonide particles, the flocculated nanoclusters dissolved significantly faster than micronized budesonide. This system may therefore represent another model for the formulation of poorly soluble inhalable drugs. It will be interesting to follow the further evaluation of these systems, especially with regard to their *in vivo* performance and shelf-lives.

A Summary of Individual Study Reports on Nanoparticles for Pulmonary Drug Delivery

In addition to the platform technologies described above, a number of individual studies were reported over the past two years that describe inhalable nanoparticle systems from the initial development stages through to *in vivo* pharmacokinetic and proof of principle studies in animal models. Table 3 contains an overview of reports describing new systems and their *in vitro* characterisation, while Table 4 contains brief summaries of nanoparticle systems tested in *in vivo* models.

Table 3. An overview of early development nanoparticle drug carrier systems for inhalation

Early Stage Nanocarrier Characterisation Studies	
1	<p>Li X, <i>et al.</i> (2009) Preparation of honokiol-loaded chitosan microparticles via spray-drying method intended for pulmonary delivery. <i>Drug Deliv</i> 16(3):160-6</p> <p><i>Formulation description:</i> Spray-dried composite particles containing mannitol, chitosan and honkiol (drug) Nanoparticles</p> <p><i>Study objectives:</i> Characterisation of powder flow and aerosol properties; <i>in vitro</i> drug release profiles</p> <p><i>Major findings:</i> Mannitol content significantly influenced drug release rate</p>
2	<p>Klinger C, <i>et al.</i> (2009) Insulin micro- and nanoparticles for pulmonary delivery. <i>Int J Pharm</i> 377(1-2):173-9</p> <p><i>Formulation description:</i> Spray-dried microparticles containing nano-precipitated insulin</p> <p><i>Study objectives:</i> Characterisation of spray-drying conditions, powder and aerosol properties</p> <p><i>Major findings:</i> Delivery of nano-precipitated spray-dried insulin from a capsule based inhaler showed a higher fine particle fraction than the Exubera® system</p>
3	<p>Beck-Boichsitter M, <i>et al.</i> (2009) Pulmonary drug delivery with aerosolizable nanoparticles in an <i>ex vivo</i> lung model. <i>Int J Pharm</i> 367(1-2):169-78</p> <p><i>Formulation description:</i> Nebulised aqueous suspension of carboxyfluorescein (model hydrophilic drug) encapsulated in polymeric nanoparticles composed of short PLGA chains grafted onto an amine-substituted poly(vinyl alcohol) backbone</p> <p><i>Study objectives:</i> Characterisation of particle physicochemical properties; rate of compound permeation into perfusate after nebulisation into an isolated perfused lung</p> <p><i>Major findings:</i> Greater lung retention for nanoparticle system compared to free compound</p>
4	<p>Nguyen J, <i>et al.</i> (2008) Fast degrading polyesters as siRNA nano-carriers for pulmonary gene therapy. <i>J Control Rel</i> 132(3):243-51</p> <p><i>Formulation description:</i> siRNA encapsulated in polymeric nanoparticles composed of short PLGA chains grafted onto an amine-substituted poly(vinyl alcohol) backbone</p> <p><i>Study objectives:</i> Characterisation of particle physicochemical properties; <i>in vitro</i> gene knockdown</p> <p><i>Major findings:</i> Nanoparticles were stable after nebulisation, showed rapid break-down and siRNA release, and achieved 80-90% knockdown in H1299 luc cells with only 5 pmol anti-luc siRNA</p>

- 5 Grenha A, *et al.* (2008) **Microspheres containing lipid/chitosan nanoparticle complexes for pulmonary delivery of therapeutic proteins.** *Eur J Pharm Biopharm* 69(1):83-93
Formulation description: Spray-dried microparticles containing insulin-loaded chitosan / tripolyphosphate / phospholipid nanoparticles and Mannitol
Study objectives: Characterisation of particle physicochemical properties; powder flow and aerodynamic properties
Major findings: Nanoparticle-containing powders have good aerodynamic properties for high lung deposition and phospholipid content can influence the rate of protein release from the nanoparticles

Table 4. An overview of nanoparticle drug carrier performance after aerosol delivery *in vivo*

In Vivo Nanocarrier Characterisation Studies	
1	<p>Bivas-Benita, <i>et al.</i> (2009) Pulmonary delivery of DNA encoding <i>Mycobacterium tuberculosis</i> latency antigen Rv1733c associated to PLGA-PEI nanoparticles enhances T cell responses in a DNA prime/protein boost vaccination regimen in mice. <i>Vaccine</i> 27(30):4010-7</p> <p><i>Formulation description:</i> Preformation of PLGA-PEI nanoparticles using solvent displacement (stabilizers: Tween 80® and Poloxamer 188) followed by adsorption of the antigen to the particle surface</p> <p><i>Study objectives:</i> Characterisation of physicochemical properties; <i>in vitro</i> and <i>in vivo</i> activity in the mouse</p> <p><i>Major findings:</i> Vaccine-loaded nanoparticles stimulated dendritic cell maturation and cytokine release <i>in vitro</i>. The aerosolized system was more effective than intramuscular injection of the vaccine with regards to T cell proliferation and IFN gamma production.</p>
2	<p>Tseng CL, <i>et al.</i> (2009) The use of biotinylated-EGF-modified gelatin nanoparticle carriers to enhance cisplatin accumulation in cancerous lungs via inhalation. <i>Biomaterials</i> 30(20):3476-85</p> <p><i>Formulation description:</i> Preformation of gelatin nanoparticles using a two-step desolvation procedure followed by cross-linking with glutaraldehyde. Cisplatin was loaded into the particles via a ligand exchange reaction of the Pt(II) from the chloride to the free carboxyl groups of gelatin. Surface modification using biotinylated EGF was the final step.</p> <p><i>Study objectives:</i> Characterisation of physicochemical properties, <i>in vitro</i> anticancer activity; <i>in vivo</i> drug pharmacokinetics in the mouse</p> <p><i>Major findings:</i> Nanoparticles with the targeting moiety were more potent than the free compound or encapsulated compound <i>in vitro</i>; Nebulisation of an aqueous nanoparticle suspension to the lungs of a mouse tumour model showed a significantly increased lung concentration and decreased serum concentration over 48 h of targeted nanoparticles compared to free and encapsulated compound.</p>
3	<p>Tomoda K, <i>et al.</i> (2009) Preparation and properties of inhalable nanocomposite particles for the treatment of lung cancer. <i>Colloids Surf B Biointerfaces</i> 71(2):177-82</p> <p><i>Formulation description:</i> Encapsulation of TAS-103 in PLGA nanoparticles using an emulsification-precipitation method with PVA as a stabiliser. Subsequent spray-drying with trehalose to form microparticles</p> <p><i>Study objectives:</i> Characterisation of aerodynamic properties and drug release rate; <i>in vitro</i> anti-cancer activity; <i>in vivo</i> pharmacokinetics in the rat</p> <p><i>Major findings:</i> Encapsulated TAS-103 was slightly more potent <i>in vitro</i> than the free compound; Administration of the encapsulated TAS-103 powder showed a significantly higher lung concentration in the first hour post-administration compared to the free compound, but no significant differences in concentration in the subsequent 7 h of the experiment. TAS-103 was eliminated from the lungs within 8 h.</p>
4	<p>Ohashi K, <i>et al.</i> (2009) One-step preparation of rifampicin/poly(lactic acid-co-glycolic acid) nanoparticle containing microspheres using a four-fluid nozzle spray drier for inhalation therapy of tuberculosis. <i>J Control Rel</i> 135(1):19-24</p> <p><i>Formulation description:</i> Rifampicin and PLGA were spray-dried from a methanol solution simultaneously with a mannitol solution from a four-nozzle spray-drier to produce drug/polymer nanoparticles (~213 nm) dispersed in mannitol microspheres</p> <p><i>Study objectives:</i> Characterisation of aerodynamic properties; <i>in vitro</i> and <i>in vivo</i> macrophage uptake studies; <i>in vivo</i> lung distribution studies in the rat</p> <p><i>Major findings:</i> Compared to traditionally prepared PLGA microspheres, the nanoparticles were taken up to a significantly lesser extent than microspheres both <i>in vitro</i> and <i>in vivo</i> (administered via endotracheal insufflation); Distribution of the nanocomposite formulation was more even in the lung compared to the traditional microspheres with a higher deposition in the periphery and a slower clearance rate of the nanoparticle formulation</p>

- 5 Yang W, *et al.* (2008) **High bioavailability from nebulized itraconazole nanoparticle dispersions with biocompatible stabilizers.** *Int J Pharm* 36(1-2):177-88
Formulation description: Ultra-rapid freezing (URF) of itraconazole with mannitol and lecithin
Study objectives: Characterisation of particle physicochemical properties; *in vivo* pharmacokinetics in the mouse
Major findings: Amorphous URF produced itraconazole nanoparticles of < 230 nm that showed significantly decreased dissolution times compared to 2 µm sized particles (enough to potentially merit a reclassification in the BCS system for the nanosized formulation). After nebulisation of an aqueous suspension to mice, the C_{max} was greater and t_{max} was lower compared to a reference itraconazole formulation prepared by spray-freezing into liquid
- 6 Sinswat P, *et al.* (2008) **Nebulization of nanoparticulate amorphous or crystalline tacrolimus – single dose pharmacokinetics study in mice.** *Eur J Pharm Biopharm* 69(3):1057-66
Formulation description: Ultra-rapid freezing (URF) of tacrolimus alone (crystalline) or with lactose (amorphous)
Study objectives: Characterisation of particle physicochemical; *in vivo* pharmacokinetics in the mouse
Major findings: Amorphous URF produced tacrolimus nanoparticles of < 230 nm that showed significantly decreased dissolution times compared to crystalline URF tacrolimus. After nebulisation of an aqueous suspension to mice, the amorphous formulation showed a greater C_{max} and lower t_{max} compared to the crystalline formulation

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DRUG DELIVERY LITERATURE

Provided by Dr. Karsten Cremer

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RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

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Gajbhiye V, Palanirajan VK, Tekade RK, Jain NK. *J Pharm Pharmacol.* 2009 Aug;61(8):989-1003.

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The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceuticals.

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OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

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

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

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