APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER **ISSUE 1/2019 - APRIL**

TABLE OF CONTENTS

DRUG DELIVERY EVENTS

BACK TO TABLE OF CONTENTS

+ **Biopharmaceutics meets Formulation Development – Setting justified Drug Delivery Targets**
April 11-12 2019 | Frankfurt am Main, Germany | KN 6768 — Details

Respiratory Drug Delivery Europe (RDD Europe 2019)
May, 07-10, 2019 | Lisbon, Portugal — Details

+ **APV Expert Workshop: Quality by Design based formulation strategies in continuous processing**
June 05-06, 2019 | Leicester, United Kingdom | KN 6771 — Details

+ **3D Printing in Pharma – 4 years after the first FDA approval: where are we now?**
May 23-24 2019 | Antwerp, Belgium | KN 6781 — Details

3rd Edition of Global conference on Pharmaceutics and Drug Delivery Systems (PDDS 2019)
June 24-26, 2019 | Paris, France — Details

46th Annual Meeting & Exposition of the Controlled Release Society
July 21–24, 2019 | Valencia, Spain — Details

Skin and Formulation, 5th Symposium & 17th Skin Forum
September 23-24, 2019 | Reims, France — Details

+ **12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology**
March 23-26, 2020 | Vienna, Austria — Details

Suggest a meeting to be announced!

Tribute to the late Dr. Michael Horstmann

Sadly, Dr. Michael Horstmann, one of the long-standing members of the Drug Delivery Focus Group, passed away on 12 January 2019. The Focus Group members who knew him personally including myself have fond memories of working together with him on organizing seminars and workshops and on preparing articles for the Newsletter.

In tribute to him we reproduce in English an obituary that first appeared in German in the APV magazine 01/2019.

Louise Rosenmayr-Templeton

THE APV GRIEVES FOR DR. MICHAEL HORSTMANN

A tribute written on behalf of the APV Executive Board, the Drug Delivery Focus Group and the APV Headquarters by Jörg Breitkreutz, Johannes Bartholomäus, Georg Böck and Martin Bornhöft.

On 12 January 2019 Michael Horstmann died in Neuwied, Germany aged 63 years. It is with great sadness and dismay that members of the APV Executive Board, the Drug Delivery Focus Group and the APV headquarters in Mainz learnt of his death.

Michael Horstmann studied pharmacy at the Philipps-University, Marburg and gained his PhD in pharmacology at the Wilhelms University, Münster. In 1985 he began his industrial career at Beiersdorf AG in Hamburg as a laboratory manager in the then new area of transdermal delivery. In 1987 he built further on his experience in transdermal delivery and accepted a management position in research and development at Lohmann Therapy Systems (LTS), the largest European transdermal patch manufacturer. During his time at LTS he also dedicated himself to the development of oral films, at that time a new dosage form. In 2010 he left LTS having reached the position of Head of R&D and patents. His next role was as Chief Technology Officer for Tesa SE where he employed his many years of experience in transdermal and oral film development and production to support Tesa's new Pharma business. Finally, he was Head of Technology Excellence at Acino AG before founding his own consultancy firm, transdermalpharma, in 2014.

A distinguishing feature of Michael was that no matter where he was, and what he was doing, his interests stretched far beyond that of "pure work" alone. This became apparent early with his involvement in the school magazine "Holtzwurm" while he was at the Helmholtz-Gymnasium, Essen. In 1985 he became a member of the APV and became active in our not-for-profit organization. For 10 years he was a member of the Drug Delivery Focus Group and contributed significantly to the work of the group through organization of scientific seminars and training courses and the preparation of informative, well-written articles for the Newsletter. Of particular note is that through his work and close co-operation with the Skin Forum, the Skin Forum has held its annual meeting together with the APV for several years now. His last contribution to the Society was the organization and co-moderation of the first APV winter conference on oral dispersible dosage forms in Innsbruck. Sadly, shortly afterwards his illness, which he bore with dignity and patience, prevented his further active involvement in the APV.

Michael Horstmann made long-lasting contributions to the APV and for this reason was honoured with its silver honorary pin in 2015. He was a highly respected expert and member of our Society and was blessed with extensive knowledge, high commitment and open-mindedness. His early death leaves behind a gap that cannot be filled, and is of great sadness to all those who knew him. Our special condolences go to his family. The APV will always hold his memory in high esteem.

INBRIJA™ (levodopa inhalation powder)

In December 2018 the FDA approved Inbrija™ (levodopa inhalation powder) from Acorda Therapeutics Inc. (NY, USA) for the intermittent treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa [1, 2]. Around 1 million patients in the USA and 1.2 million in Europe suffer from Parkinson's which is a progressive, neurological condition characterized by motor symptoms such as tremor, rigidity and slowness of movement but which can occur in conjunction with other non-motor symptoms e.g. mild memory loss [3, 4]. The main treatment option in the US is levodopa in association with carbidopa, the latter inhibiting the breakdown of levodopa in the peripheral circulation and, thus, enabling its delivery to the brain. However, in the course of long-term therapy, patients on levodopa typically begin to suffer from OFF periods during which their symptoms worsen despite being much improved at others. Up to 40% of US Parkinson's patients report having such OFF periods. The OFF periods are associated with low levels of dopamine and can be experienced on waking, prior to the next dose, following a delay or reduced absorption of oral levodopa therapy due to delayed or erratic gastric emptying, or due to competition for absorption of levodopa with amino acids in foods. They can also occur suddenly and without warning. Inbrija™ enables the dopamine levels to be rapidly boosted as the levodopa is delivered rapidly into the bloodstream from the lungs.

In Inbrija™ the levodopa is formulated with 1,2 dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and sodium chloride as a spray-dried powder. Each capsule contains 42 mg active ingredient with two capsules per dose being administered up 5 times daily using the Inbrija™ inhaler. The inhaler is based on the ARCUS™ technology which Acorda acquired when it bought Civitas Therapeutics in 2014. The breath-actuated inhaler delivers more drug into the lungs than standardized inhalers by changing the shape and size of the powder particles. The inhaler has been shown under standardized *in vitro* testing conditions to deliver an emitted dose of 36.1 mg of levodopa with no significant difference being observed when the flow rate and volume was varied from 20 liters per minute/1L up to 90 liters per minute/2L [1, 3].

FDA approval was based on the results of a Phase 3, 12-week, randomized, placebo controlled, double blind study involving patients with mild to moderate Parkinson's suffering from OFF episodes. The trial showed that levodopa delivered using the Inbrija™ delivery system had an onset of action as early as 10 minutes. In addition, patients receiving Inbrija™ had a statistically significant improvement in motor function at 12 weeks compared with placebo as measured by a reduction in Unified Parkinson's Disease Rating Scale (UPDRS) Part III score at 30 minutes post-dose (-9.83 points and -5.91 points respectively; p=0.009). Inbrija™ was also investigated in a Phase 3 long-term, active-controlled, randomized, open-label study in 398 patients assessing safety and tolerability over one year. This study confirmed the safety of the treatment with the average reduction in FEV1 (forced expiratory volume in 1 second) from baseline being the same (-0.1 L) for the active and observational groups. Patients with chronic lung conditions were excluded from this trial [1, 3].

The most common side-effects associated with Inbrija™ treatment in clinical trials were cough, nausea, upper respiratory tract infection, and discoloured sputum. Its use in patients with chronic lung conditions such as asthma and COPD is not recommended due to the increased risk of bronchospasm.

Inbrija was launched in the US at the end of February [5]. A regulatory submission for the product was also submitted to the European Medicines Agency (EMA) in March 2018 with a decision on its approval anticipated before the end of 2019.

DEXTENZA® Opthalmic Insert

The FDA approved Dextenza™ (dexamethasone opthalmic insert) 0.4 mg from Ocular Therapeutix (MA, USA) for the treatment of pain following ophthalmic surgery at the very end of November 2018 [6, 7, 8]. Dextenza™ is a corticosteroid loaded intracanalicular insert manufactured from polyethylene glycol conjugated to fluorescein. It is based on the hydrogel platform developed by Dr. Amar Sawhney [9].

Each 3 mm, cylindrical insert contains 0.4 mg dexamethasone, 4-arm polyethylene glycol (PEG) N-hydroxysuccinimidyl glutarate (20K), trilysine acetate, N-hydroxysuccinimide-fluorescein, dibasic sodium phosphate, monobasic sodium phosphate and water for injection. The presence of the fluorescein is to enable visualization of the insert. The product does not contain preservatives.

Dextenza™ is inserted in the lower lacrimal punctum in the eye lid, and into the canaliculus. After insertion the insert hydrates to deliver the anti-inflammatory for up to 30 days. The Dextenza™ insert resorbs and clears through the nasolacrimal duct. It therefore does not have to be removed after the end of treatment but can be displaced by saline irrigation or manual manipulation if required. Its use is contraindicated if eye infections are present.

The product is designed to overcome the issues associated with the administration of dexamethasone eyedrops after ophthalmic surgery such as frequent and complicated dosing regimens, difficulties with administration (often the patients are elderly and suffer from other health problems), poor administration technique and low patient compliance. Administration of the insert is conducted by the physician immediately after surgery. It swells on contact with fluid to fit snugly into the canaliculus to deliver the drug in a sustained manner over the post-operative period.

Approval was based on the results of two randomized, multicenter, double-blind, parallel group, vehicle-controlled studies in patients who had undergone cataract surgery. In both studies a significantly higher number of those receiving Dextenza™, reported no post-operative pain up to 8 days after surgery (Study 1- 80 % and Study 2 - 77%) compared with those receiving the vehicle (Study 1 - 43% and Study 2 - 59%). The most common reported side-effects in the

two Phase 3 and one Phase 2 clinical studies involving Dextenza™ were anterior chamber inflammation including iritis and iridocyclitis, an increase in intraocular pressure and a reduction in visual acuity.

FDA approval is third time lucky for Ocular Therapeutix as the company has previously received two complete response letters from the agency due to manufacturing and QC testing deficiencies [10].

References and Further Information

[1] Entry for Inbrija™ on Drugs@FDA

[2] Acorda Therapeutics Announces FDA Approval of INBRIJA™ (levodopa inhalation powder). http://ir.acorda.com/investors/investor-news/investor-news-details/2018/Acorda-Therapeutics-Announces-FDA-Approval-of-INBRIJA-levodopa-inhalation-powder/default.aspx.

[3] Acorda Therapeutics website. http://www.acorda.com/products/products/inbrija.

[4] Parkinson's UK website. https://www.parkinsons.org.uk/.

[5] Acorda Therapeutics Announces Commercial Launch of INBRIJA™ (levodopa inhalation powder). http://ir.acorda.com/investors/investor-news/investor-news-details/2019/Acorda-Therapeutics-Announces-Commercial-Launch-of-INBRIJA-levodopa-inhalation-powder/default.aspx.

[6] Entry for Dextenza® on Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

[7] Ocular Therapeutix™ Announces FDA Approval of DEXTENZA® for the Treatment of Ocular Pain Following Ophthalmic Surgery. http://investors.ocutx.com/phoenix.zhtml?c=253650&p=irol-newsArticle&ID=2378993.

[8] Ocular Therapeutics website https://www.ocutx.com.

[9] Sawhney AS, Jarrett P, Bassett M, Blizzard C, inventors; Incept, LLC, assignee. Drug delivery through hydrogel plugs. US patent 8,409,606 B2. April 2, 2013.

[10] Palmer E. Unable to head off the FDA, Ocular Therapeutix gets second CRL for eye drug. Fierce Pharma. https://www.fiercepharma.com/regulatory/unable-to-head-off-fda-ocular-therapeutix-gets-second-crl-for-eye-drug.

DRUG DELIVERY PEOPLE

BACK TO TABLE OF CONTENTS

Provided by Dr. Lea Ann Dailey

We would like to introduce **GUY VAN DEN MOOTER** as our featured Drug Delivery Scientist for this newsletter issue. Prof. Van den Mooter studied pharmacy and industrial pharmacy at the University of Leuven (KU Leuven) and received his PhD from the same university in 1994. Following this, he worked as scientist in the department of pharmaceutical development at Janssen Pharmaceutica (Belgium) until 1996. From 1997 until 1999 he was a post-doctoral researcher in the laboratory for Pharmacotechnology and Biopharmacy (KU Leuven) until he accepted an appointment as assistant professor at KU Leuven in 1999. In 2009, he was appointed full professor at the same institute.

Prof. Van den Mooter teaches courses on physical pharmacy, pharmaceutical technology and preformulation in undergraduate and graduate level programmes.

His research interests focus on the physical chemistry of enabling formulation strategies like amorphous solid dispersions, nanoparticles, and mesoporous silica, and thermal analytical techniques which support his research. He has published more than 260 peer reviewed papers in the field, with more than 9500 citations, in addition to being a member of the Belgian Pharmacopeia commission. Furthermore, he is on the editorial board of Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmacology, European Journal of Pharmaceutical Sciences and International Journal of Pharmaceutics. In 2007, he founded FORMAC Pharmaceuticals N.V., a drug delivery company focused on the formulation of poorly soluble active pharmaceuticals, using a unique formulation platform based on mesoporous silica materials to overcome solubility-limited bioavailability.

DRUG DELIVERY COMPANIES

BACK TO TABLE OF CONTENTS

Provided by Dr. Dieter Becker

HOVIONE (Loures, Portugal)

Founded:	1959
Location:	Loures, Portugal
Ownership:	Privately owned (Ivan and Diane Villax)

Employees:	1,600
Key technology:	- CMO for API, particle engineering, drug products, analytics - Own API production for sale (69 commercial APIs and 51 under development) - **Special technologies**: Pharmaceutical spray drying & spray congealing in small and large scale. inhaled powders, hot melt extrusion
Products:	Examples of products for sale: betamethasone and devrivatives, doxycycline etc In the last 5 years more than 70 NCEs have been developed or supported. Production sites: Loures, Portugal; Cork, Ireland; Macau, China, New Jersey, USA all approved by FDA, EMA, Japan and many other health authorities.
Development status:	Hovione has had products on the market since 1960 (API) and pharmaceutical spray drying since about 2002
Partnerships:	Flexible collaboration such as licensing, investment and co-development business models.
Website:	https://www.hovione.com
Contact:	Hovione FarmaCiencia SA Sete Casas, 2674 – 506 Loures, Portugal Tel: +351 21 982 9000 Email: contact@hovione.com

FEATURED ARTICLE

BACK TO TABLE OF CONTENTS

MESOPOROUS SILICA: FROM EXCIPIENT TO DRUG DELIVERY SYSTEM

By Manoj Koranne (W.R. Grace, Columbia, USA), Fred Monsuur, Joachim Quadflieg (both W.R. Grace, Worms, Germany)

Solid dispersions have become an accepted method to improve the amorphous stability and increase the solubility of drug substances. Mesoporous silicas are an attractive option to create amorphous solid dispersions and a significant amount of research is on-going on its efficacy and safety as a functional excipient for enhanced drug delivery. As a part of this ongoing research, specific silica properties suitable for improving drug delivery as well as special techniques to use silica for solubility enhancement have been developed. This article is a basic overview of the background, theory, materials, and methods used by a growing number of researchers. It is focused on microparticulate mesoporous silicas for drug delivery, particularly silica-based solid dispersions for oral dosage forms. The overview provides a brief history and description of the materials, identifies its applications, discusses a theoretical basis and mechanisms for amorphisation and drug release from mesoporous silicas.

1. Introduction

An estimated 40% of the approved drugs and nearly 90% of developmental pipeline drugs consist of poorly soluble molecules. [1] In addition, several marketed drugs also suffer from poor solubility, low permeability, resulting in rapid elimination from the body.

Using compendial excipients to improve solubility of poorly soluble drugs and hence its bioavailability is an attractive option because it requires no additional regulatory approval. For example, polymeric compounds once used only as tablet coatings have emerged as significant solubility enhancers. For example, hydroxypropyl methyl cellulose (HPMC), polyvinyl pyrrolidone (PVP) are now used as solubility enhancers forming solid amorphous dispersions. [2,3] However, stability of these solid amorphous dispersions continues to be a challenge, particularly in humid environments.

The quest for better and new substances for solubility enhancement has also spurred innovation among other types of excipients, including silicon dioxide. Using Mesoporous Silicas (MPS) for solubility enhancement has gained the attention of formulators due to its tunable porosity, high surface area, inertness, and good biocompatibility. The porous structure of silica can decrease the melting point and crystallinity of entrapped drug. MPS has good flow properties and additional steps such as milling or sizing prior to tableting and capsule filling can often be simplified. This results in high recovery rates and minimizes the chances of the processed drug converting to its crystalline state. [4]

Tailoring porosity, activating the surface, and essentially "engineering" various properties of the silica particle, have made mesoporous silica a unique and versatile material highly interesting to formulators as a platform for drug delivery. Silica can be synthesized by various routes. Depending on the type of synthesis, its pores are formed differently. The method of synthesis also dictates the concentration of surface hydroxyl groups on the silica. Taken together, these properties deliver the specific shape, size, pore uniformity and, ultimately, silica's potential as an effective drug delivery platform.

2. MPS Materials

According to International Union of Pure and Applied Chemistry of Porous Media, porous materials are classified according to their pore diameter as presented in table 1 below. [5]

Types of pore	Mean pore diameter, nm
Micropore	Less than 2
Mesopore	Between 2 and 50
Macropore	Greater than 50

Table 1: Classification of porous media.

The pores can be of different shapes such as spherical or cylindrical with varying arrangements. Some structures may have large pores (more than 50nm) in one dimension, but the width of the same pore may be in the mesopore range and hence material can be considered as Mesoporous.

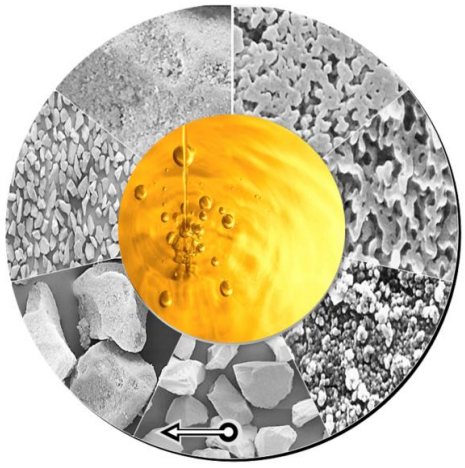

Figure 1: SEM pictures of Mesoporous Silica with magnification level increasing clockwise (data courtesy of Grace).

3. History from Excipient to Drug Delivery

For decades, silica has been used primarily as a glidant and a general processing aid. As a glidant, it reduces the interparticulate friction of bulk powders, allowing the particles to flow more efficiently. This function is important because it improves the content uniformity of tablets and capsules and the speed at which these can be produced. When used as a general processing aid, silica can be used for carrying liquids and reducing tribo-electrostatic charges. It also serves as an anti-tacking agent reducing drying times in pharmaceutical coatings, among other functions. In these applications, silica usage is typically between 0.5 and 2 percent.

For moisture sensitive API's or ingredients, mesoporous silica can also improve physical and chemical stability during processing and in the final dosage forms. This protection can extend the shelf-life of a drug product and/or sustain its therapeutic effect.

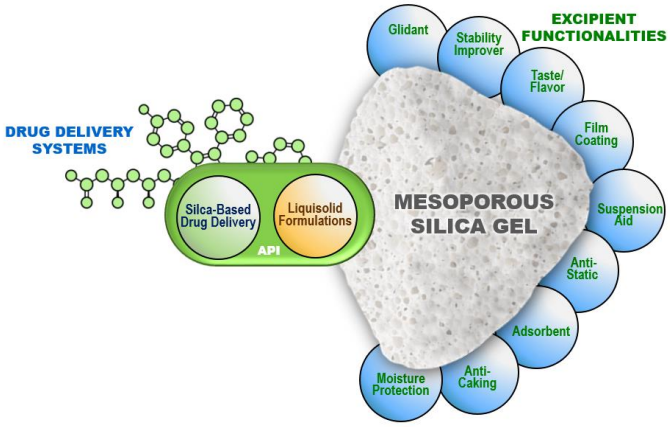

Figure 2: Silica Functionalities as they relate to Excipient Applications and Interactions with Active Pharmaceutical Ingredients.

First use of MPS to increase the dissolution profile of the drug was reported in 1972 by Monkhouse and Lach [6] using SYLOID® synthetic amorphous silica gel and was further elaborated by Yang, Glemza and Jarowski. [7] This mechanism is based on the stabilization of drug molecules in an amorphous state in the pores of the silica. Since amorphous drugs solubilize more easily compared to their crystalline form, the bioavailabilty of drug molecules is enhanced. However, the crystal form of the drug molecule is more stable due to its lower energy and drugs tended to recrystallize in the pores of silica over a period. This in-stability of the amorphous form (physical and chemical stability) has remained a major concern in developing drug delivery systems. [8,9]

In the mid-2000's Johan Martens initiated a collaboration with Guy Van den Mooter at the University of Leuven to address the "instability" issue in silica-based solid amorphous dispersions. [10] Their collaboration led to formation of Formac Pharmaceuticals, where in they developed a pharmacompliant "ordered mesoporous silicas" (OMS) for solubility enhancement. These silicas are amorphous in nature, but have a long-range order, with very uniform pore sizes and pore size distributions. Formac Pharmaceuticals formed a collaboration with W.R. Grace and Co, to scale-up the synthesis process and market the products for drug delivery. The collaboration efforts led to optimization of pore sizes that would increase the stability of the drug molecules, when loaded in the pores of the silica. In 2011 Formac Pharmaceuticals and Grace successfully demonstrated first human trial of silica-based drug delivery.

At the same time, Grace conducted research on using non-ordered compendial silicas to identify optimal pore sizes for stabilizing amorphous drug molecules in the pores of the silica. Commercial activities started between 2013-2015 when Grace launched the first compendial mesoporous silica excipients for Drug Delivery (SYLOID® XDP Silica, SilSol™ Silica). At the same time Grace also optimized the pore size and its distribution for liqui-solid strategies. Below is a detailed description of the two drug delivery systems, namely liquisolid system and solvent impregnation system.

4. Mesoporous Silica Loading and Delivery of Poorly Soluble Drugs

4.1 Liquisolid systems

Lipid based drug delivery systems like simple oils, self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) are often used for delivery of poorly soluble drugs. These systems offer improved biocompatibility in contrast to standard excipients which may create compatibility issues.

Lipid based formulations can also be used to protect moisture sensitive molecules, peptide, proteins from hydrolysis and to improve enzymatic stability. [11] However, most of the lipids are liquids or semisolids and are difficult to formulate in solid dosage forms.

One way to address this issue is to convert these liquid and semisolid lipids into free-flowing powders and thus design robust solid dosage forms. To achieve this, absorption on solid carriers is an advantageous technique, as the carriers display high surface area and high pore volume, high absorption capacity, ease of processing, and ability to generate lipid loaded free flowing powders which can be converted into solid dosage forms like tablets and capsules. [12]

In order to carry the lipid various inorganic materials like Mesoporous Silica Gel (MSG), Granulated Fumed Silica (GFS) and Magnesium Aluminum Silicates (MAS) can be used. However, incomplete desorption of the lipid remains an important challenge in the commercialization of this technology. [13] Grace has developed an optimized silica-based absorbent which has high absorption capacity AND can maintain good flow properties even after absorption of oils/lipids AND is able to provide complete desorption of oils from the pores of the silica. In addition, Grace has developed processing techniques and formulations to convert the oil loaded silicas into solid dosage forms.

Grace's mesoporous silica called SYLOID® XDP silica also has added features like, high bulk density to allow ease of processing and the ability to deliver maximum amounts of liquid in a given volume such as a capsule. This combination of density and absorptive capacity is called volumetric absorptive capacity. [14] The drug molecule release profiles with Grace's mesoporous silica are better compared to other carriers due to the optimized pore size and pore volume, and higher number of silanol groups on the silica surface.

4.2 Solvent impregnation versus solvent free systems

As described above, Grace has conducted research and developed techniques for enhancing the solubility and hence the bioavailability of poorly soluble drugs using compendial silicas. Based on this research, solvent impregnation techniques have been developed. Such a technique entails the following:

1. Dissolving a poorly soluble drug in an organic solvent. Solvents such as ethanol, isopropanol, or acetone are usually suitable.
2. Impregnating and drying the drug loaded solvent in the pores of the silica. This step can be achieved via several commercially available unit operations. A rapid mixer granulator, a spray dryer, or a fluid bed dryer can be used for this operation. This leads to a dry powder of the drug loaded in the pores of silica.
3. Converting the silica loaded with drug substance into a solid oral dosage form such as a tablet or a capsule.

In order to ensure that the drug substance is loaded effectively in the pores of the silica and to effectively suppress recrystallization, the silica must be processed under tightly controlled conditions.

After an API is loaded into the porous network of amorphous silica particles, the formation of crystalline material is prevented by the confined space of the pores which are slightly larger than the API, thereby reducing molecular mobility. The high internal surface area and hydrophilicity of MPS positively effects the wetting properties which results in fast release profiles.

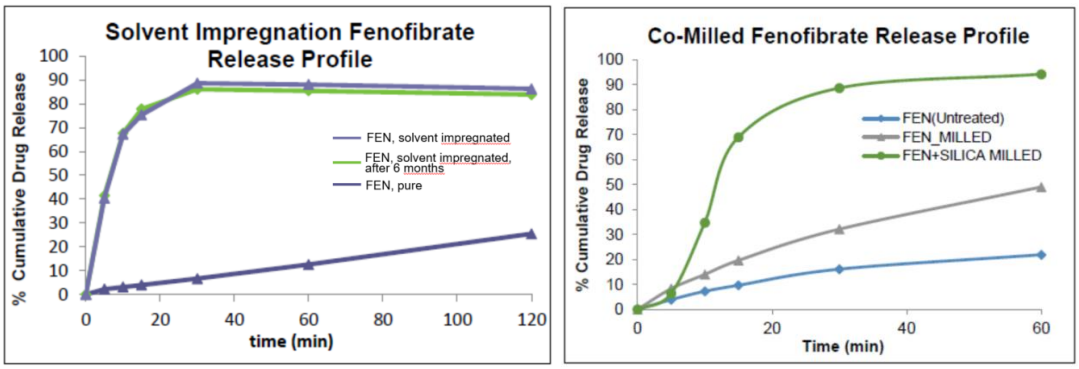

Fig. 3 Cumulative Drug Release of Solvent Impregnated Fenofibrate (left) and Co-milled Fenofibrate (right).

The focus of majority of work on silica-based drug delivery is using organic solvents. However, for effective use in pediatric formulations a "solvent-free" strategy is necessary. More recent work is focused on solvent-free strategies for amorphization. One such technique involves highly intense "dry milling" of the poorly soluble drug and silica. It is speculated that the high internal surface area of mesoporous silica is densely covered with silanol groups and provides the conditions for hydrogen bonding with a drug and resulting in amorphization upon intense milling. [15]

To ensure silica-based solid dispersions are stable, API loading should be limited to about 30 to 50 percent depending on the loading strategy (liquisolid, solvent based impregnation, melting or co-micronisation).

4.3 Release mechanism

Once the silica-loaded drug formulation enters the gastrointestinal tract, capillary action drives water into the pores of the silica. Subsequently, the strong affinity of silica's surface to water ("like for like") provides the mechanism for drug release. This strong absorptive action displaces the amorphous API from the MPS.

In this way, highly bioavailable, amorphous forms of APIs are readily delivered into the gastrointestinal tract to provide the intended therapeutic effect.

The immediate release of drug from mesoporous silica can result in precipitation. Therefore, research towards the use of precipitation inhibitors has been and remains an important topic. [16]

Over the last years it has been shown that existing dissolution methods might not be sufficient to provide biorelevant in-vitro-in-vivo-correlation (IVIVC). In consequence, developing better predictive tools for formulation performance evaluation is and should be an ongoing exercise. [17]

5. Conclusion and Future

Decades of research, advanced engineering and deep understanding of physiochemical processes have identified new ways to stabilize drug molecules and increase solubility. Coupled with the increasing number of promising drug candidates that cannot be formulated due to poor crystalline solubility, this has created the need for new tools to enhance bioavailability. Solid dispersions and hot melt extrusion have matured over the last decade to be used effectively by the industry. However, newer, simpler ways are being developed. Silica provides a well-known, compendial material. Using the extraordinary combination of controlled pore structures, surface area with its hydrophilic silanol groups and particle sizes, new techniques are maturing to enlarge the toolbox for formulators. Additional work with silica continues to characterize the operating envelope for process equipment such as fluid bed dryers and spray dryers, extrusion, and twin-screw granulation. Research is ongoing towards the understanding and predicting when liquisolids and solvent-free silica-based techniques can be used effectively.

Literature/References:

[1] Kalepu and Nikkanti, Insoluble drug delivery strategies: Review of recent advances and business prospects, Acta Pharmaceutica Sinica B 5 (2015) 442

[2] A.T.M. Serajuddin, Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs, J. Pharm. Sci. 88 (10) (1999) 1058– 1065

[3] W.L. Chiou, Pharmaceutical applications of solid dispersion system, J. Pharm. Sci. 60 (9) (1971) 1281– 1302.

[4] Hirofumi Takeuchi, Shinsuke Nagira, Hiromitsu Yamamoto, Yoshiaki Kawashima Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method. Powder Technology 141 (2004) 187–195

[5] Sing KSW, Everett DH, Haul RAW, Moscou L, Pierotti RA, Rouquerol J, Siemieniewska T. Reporting physisorption data for gas/solid systems with special reference to the determination of surface area and porosity. Pure Appl Chem (1985) 57(4):603–619

[6] Monkhouse D. C., Lach J. L., Use of adsorbents in enhancement of drug dissolution J. Pharm. Sci., 61 (1972), 1435-1441

[7] K. Y. Yang, R. Glemza, C. I. Jarowski Effects of Amorphous Silicon Dioxides on Drug Dissolution. Journal of Pharmaceutical Sciences (1979) Vol. 68. No. 5

[8] Datta S., Grant D. J. W., Nat. Rev. Drug Discov., 3 (2004), 42—57

[9] Andronis V., Yoshioka M., Zografi G., J. Pharm. Sci., 86 (1997), 346-351.

[10] M. Van Speybroeck, V. Barillaro, T.D. Thi, R. Mellaerts, J. Martens, J. van Humbeeck, J. Vermant, P. Annaert, G. Van den Mooter, P. Augustijns, JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 98, NO. 8, August 2009,

[11] Date A.A., Desai N., Dixit R., Nagarsenker M. Selfnanoemulsifying Drug Delivery Systems: Formulation Insights, Applications and Advances. Nanomedicine (2010) 5:1595–1616.

[12] Hentzschel C.M., Sakmann A., Leopold C.S. Suitability of various excipients as carrier and coating materials for liquisolid compacts. Drug Dev. Ind. Pharm. (2011) 37:1200–1207.

[13] Van Speybroeck M., Williams H.D., Nguyen T.H., Anby M.U., Porter C.J., Augustijns P. Incomplete desorption of liquid excipients reduces the in vitro and in vivo performance of self-emulsifying drug delivery systems

[14] Y. Choudhari, F. Monsuur, et al. Amorphous Solid Dispersions, Theory and Practise Chapter 23 (2014) Mesoporous silica drug delivery systems.

[15] F. Monsuur, Y Choudhari, U Reddy, et al. Solvent free amorphisation for paediatrics using mesoporous silica, Int J of Pharmaceutics (2016) Vol. 551, 1135-1136

[16] Sen Xu, Wei-Guo Dai, Drug precipitation inhibitors in supersaturable formulations, Int J of Pharmaceutics 453 (2013), 36-43

[17] Philippe Berben, Joachim Brouwers, Patrick Augustijns, The artificial membrane insert system as predictive tool for formulation performance evaluation, International Journal of Pharmaceutics 537 (2018) 22–29

DRUG DELIVERY LITERATURE

BACK TO TABLE OF CONTENTS

Provided by Dr. Carsten Timpe

Structural modifications of DS for solubility enhancement (Amorphous Drug Delivery Systems, Cocrystals, Polymorphism etc.)

Cyclodextrin complexes: Perspective from drug delivery and formulation, Jacob S, Nair AB. Cyclodextrin complexes: Perspective from drug delivery and formulation. Drug Dev Res. 2018 Aug;79(5):201-217.

Stability constant, factors affecting complexation, techniques to enhance complexation efficiency, the preparation methods for molecular inclusion complexes and release of guest molecules are discussed in brief. In addition, different CD derivatives and their pharmacokinetics are elaborated. Further, the significance of CD complex in aqueous solubility, dissolution and bioavailability, stability, and taste masking is explained. The recent advancement of CDs in developing various drug delivery systems is highlighted.

Peptide, Protein-based Drug Delivery

Alginate matrices for protein delivery - a short review : Wawrzyńska E, Kubies D. Alginate matrices for protein delivery - a short review. Physiol Res. 2018 Oct 30;67(Supplementum 2):S319-S334.

The primary objective of this article is to review the literature related to recent advances in the application of alginate matrices in protein delivery in regenerative medicine. A special emphasis is put on the relevance of delivery of growth factors and chemokines.

Dermal and Transdermal Drug Delivery

Recent advances in ultrasound-based transdermal drug delivery. Seah BC, Teo BM., Int J Nanomedicine. 2018 Nov 20;13:7749-7763.

This review outlines the background information pertaining to sonophoresis and then discusses the individual sections of sonophoretic research. These areas include the sonophoretic application of various drugs, dual-frequency sonophoresis, synergistic combinations of transdermal drug delivery techniques, and the use of nanosized carriers in ultrasound-based transdermal delivery. The various challenges associated with sonophoretic drug delivery and trends of future research are also highlighted.

Gene Drug Delivery, Gene Therapy, siRNAs

Delivery of viral vectors for gene therapy in intimal hyperplasia and restenosis in atherosclerotic swine, Hall S, Agrawal DK. Delivery of viral vectors for gene therapy in intimal hyperplasia and restenosis in atherosclerotic swine. Drug Deliv Transl Res. 2018 Aug;8(4):918-927.

In this review, the most recent advances were examined and critically reviewed in viral vector gene therapy obtained from studies using porcine model of atherosclerosis.

Nanosystem-based Drug Delivery

Polymer nanoparticles for the intravenous delivery of anticancer drugs: the checkpoints on the road from the synthesis to clinical translation. Ferrari R, Sponchioni M, Morbidelli M, Moscatelli D. Nanoscale. 2018 Dec 13;10(48):22701-22719.

In this review article some of the key aspects concerning the development of a polymer-based nanoparticle formulation for intravenous drug delivery are discussed. Since numerous preparations fail before and during clinical trials, the aim of the articles is to emphasize the main issues that a nanocarrier has to face once injected into the body. These include biocompatibility and toxicity, drug loading and release, nanoparticle storage and stability, biodistribution, selectivity towards the target organs or tissues, internalization in cells and biodegradability.

Polymeric nanogels as drug delivery systems, Kousalová J, Etrych T. Polymeric nanogels as drug delivery systems. Physiol Res. 2018 Oct 30;67(Supplementum 2):S305-S317.

The present review focuses on the description of the design, synthesis and physico-chemical and biological evaluation of polymer nanogels. Nanogels are robust swollen cross-linked polymer nanoparticles that can be used as highly efficient and biodegradable carriers for the transport of drugs in controlled drug delivery. In this article, various types of nanogels are described and methods for their preparation discussed. The possibility of using synthesized nanosystems for targeting are reviewed to show the potential of tailored structures to reach either solid tumor tissue or direct tumor cells. Finally, the methods for encapsulation or attachment of biologically active molecules, e.g. drugs, proteins, are described and compared.

Recent Patents on Polymeric Electrospun Nanofibers and Their Applications in Drug Delivery, Patel G, Yadav BKN. Recent Patents on Polymeric Electrospun Nanofibers and Their Applications in Drug Delivery. Recent Pat Nanotechnol. 2018;12(3):174-179.

In this paper, a detailed information is reported about researches and developments related to electrospun polymer nanofibers including its fabrication process, structure, properties, characterization, applications, and patent. Amongst all the patents available, 18 most relevant granted patents and 14 filed patents was summarized in the review article.

Role of dendrimers in advanced drug delivery and biomedical applications: a review, Akbarzadeh A, Khalilov R, Mostafavi E, Annabi N, Abasi E, Kafshdooz T, Herizchi R, Kavetskyy T, Saghfi S, Nasibova A, Davaran S. ,Exp Oncol. 2018 Oct;40(3):178-183.

This article reviews role of dendrimers in advanced drug delivery and biomedical applications.

Ocular Drug Delivery

Ocular Pharmacokinetics of a Topical Ophthalmic Nanomicellar Solution of Cyclosporine (Cequa®) for Dry Eye Disease. Mandal A, Gote V, Pal D, Ogundele A, Mitra AK. Pharm Res. 2019 Jan 7;36(2):36.

This review presents a comprehensive insight on formulation development, preclinical and clinical pharmacokinetic results of Cequa®. Additionally, the translational development of Cequa® from the laboratory benchtop to patient bedside has been discussed.

L. Chitosan-Based In Situ Gels for Ocular Delivery of Therapeutics: A State-of-the-Art Review, Malik A, Gupta M, Gupta V, Gogoi H, Bhatnagar R. Novel application of trimethyl chitosan as an adjuvant in vaccine delivery. Int J Nanomedicine. 2018 Nov 23;13:7959-7970.

This review describes in situ gelling systems resulting from the association of chitosan with various stimuli-responsive polymers with emphasis on the mechanism of gel formation and application in ophthalmology. It also comprises the main techniques for evaluation of chitosan in situ gels, along with requirements of safety and ocular tolerability.

Perspectives on Physicochemical and In Vitro Profiling of Ophthalmic Ointments., Bao Q, Burgess DJ. Perspectives on Physicochemical and In Vitro Profiling of Ophthalmic Ointments. Pharm Res. 2018 Oct 15;35(12):234.

This review summarizes the physicochemical and in vitro profiling methods that have been previously reported for ophthalmic ointments. Specifically, insight is provided into physicochemical characterization (rheological parameters, drug content and content uniformity, and particle size of the API in the finished ointments) as well as important considerations (membranes, release media, method comparison, release kinetics and discriminatory ability) in in vitro release testing (IVRT) method development for ophthalmic ointments. Graphical Abstract Summary of the physicochemcial profiling and in vitro drug release testing (IVRT) for ophthalmic ointments.

Oral Drug Delivery

Nanodelivery systems and stabilized solid-drug nanoparticles for orally administered medicine: current landscape: Kermanizadeh A, Powell LG, Stone V, Møller P. Nanodelivery systems and stabilized solid-drug nanoparticles for orally administered medicine: current landscape. Int J Nanomedicine. 2018 Nov 16;13:7575-7605.

The review evaluates the progress of the utilization of nanodelivery-system carriers or stabilized solid-drug nanoparticles following oral administration, with particular attention on toxicological data. Mechanisms of cytotoxicity are discussed and the problem of extrapolating knowledge to human scenarios highlighted. Additionally, issues associated with administration of drugs via the oral route are underlined, while strategies utilized to overcome these are highlighted. This review aims to offer a balanced overview of strategies currently being used in the application of nanosize constructs for oral medical applications.

Advances with extended and controlled release formulations of antiepileptics in the elderly, Banach M, Miziak B, Borowicz-Reutt KK, Czuczwar SJ. Expert Opin. Pharmacother. 2019 Feb;20(3):333-341.

The authors of this paper have identified clinical studies of ER AED formulations used in elderly populations through literature searches looking, both, at their use in epileptic and non-epileptic indications. Additionally, immediate release (IR) and ER formulations of AEDs were compared whenever possible.

Pulmonary drug delivery

New developments in optimizing bronchodilator treatment of COPD: a focus on glycopyrrolate/formoterol combination formulated by co-suspension delivery technology, D'Urzo AD, Cazzola M, Hanania NA, Buhl R, Maleki-Yazdi MR. Int J Chron Obstruct Pulmon Dis. 2018.

*T*his paper r*eviews the impact of dual-bronchodilator treatment on COPD therapy and discusses recent clinical studies that are helping to develop a more comprehensive understanding of how* long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), *LAMA/LABA FDCs can improve patient outcomes*.

High dose dry powder inhalers to overcome the challenges of tuberculosis treatment, Momin MAM, Tucker IG, Das SC. High dose dry powder inhalers to overcome the challenges of tuberculosis treatment. Int J Pharm. 2018 Oct 25;550(1-2):398-417.

This review focuses on the development of high dose dry powder formulations for TB treatment with background information on the challenges of the current treatment of TB and the potential for pulmonary delivery. Particle engineering techniques with a particular focus on spray drying and a summary of the developed dry powder formulations using different techniques is also discussed.

Dry powder inhalers: An overview of the in vitro dissolution methodologies and their correlation with the biopharmaceutical aspects of the drug products, Velaga SP, Djuris J, Cvijic S, Rozou S, Russo P, Colombo G, Rossi A. Dry powder inhalers: An overview of the in vitro dissolution methodologies and their correlation with the biopharmaceutical aspects of the drug products. Eur J Pharm Sci. 2018 Feb 15;113:18-28.

This review provides an overview of the in vitro dissolution methodologies for dry inhalation products, with particular emphasis on dry powder inhalers, where the dissolution behavior of the respirable particles can have a role on duration and absorption of the drug.

ABOUT THE FOCUS GROUP

BACK TO TABLE OF CONTENTS

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 pharmaceutics.

Read more. ***Contact us.***

COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

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:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

MEMBERS OF THE APV DRUG DELIVERY FOCUS GROUP

Georg Böck, PhD
Focus Group Chairman
Boehringer Ingelheim Pharma, Biberach (D)

Johannes Bartholomäus, PhD
APV Liaison Officer
Pharmakreativ Consulting, Aachen (D)

Martin Bornhöft, PhD
APV Office, Mainz (D)

Rainer Alex, PhD
F. Hoffmann-La Roche, Basel (CH)

Carsten Timpe, PhD
F. Hoffmann-La Roche, Basel (CH)

Louise Rosenmayr-Templeton, PhD
Tower Pharma Consulting, Berndorf (A)

Bernd Riebesehl, PhD
Novartis Pharma, Basel (CH)

Lea Ann Dailey, PhD
Martin Luther University, Halle (D)

Bianca Brögmann, PhD
Evonik, Darmstadt (D)

Simon Geißler, PhD
Merck Serono, Darmstadt, (D)

Karsten Cremer, PhD
Pharma Patents, Basel (CH)

Florian Unger, PhD
Bayer, Wuppertal (D)

Peter van Hoogevest, PhD
Lipoid, Ludwigshafen (D)

Simone Wengner, PhD
Catalent, Eberbach (D)
(formerly R.P. Scherer)

Uwe Hanenberg, PhD
Catalent, Schorndorf (D)

Contact us!

EDITORIAL GROUP OF THE NEWSLETTER

Editor: Dr. Louise Rosenmayr-Templeton, Tower Pharma Consulting, Berndorf (A)
Layout: Christoph Blümer, Corden Pharma, Plankstadt (D)