GAZETTE

New technologies:

Making better tablets

(see page 24)

Gamlen Tableting Ltd.

APGI thesis award 2016/2017

Dr Stephan STREMERSCH

(see page 21)

11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmeceutical Technology

19-22 March 2018

Granada, Spain

Deadline for abstract submission: 15 November 2017

(see page 4)

SANOFI

2017

N°32

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CONTENT

APGI Thesis Award 2017

SANOFI

The "APGI YOUNG INVESTIGATOR AWARD" (sponsored by Sanofi and delivered jointly by SANOFI and APGI) recognizes the most outstanding doctoral thesis in the field of Pharmaceutical Technology each year.

If you defended your PhD thesis between 15 November 2016 and 14 November 2017, you can candidate for the 2016 "APGI YOUNG INVESTIGATOR AWARD".

Editorial

Dear Colleagues

The **deadline for abstract submission for the 11th World Meeting** on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology is approaching: the **15th November 2017**. The conference will be held in Granada, Spain, on 19 -22 March 2018. It will be the largest congress in our field in Europe next year: Close to 1000 abstracts and more than 1300 participants are expected.

We jointly organize this international conference together with our German friends (the APV - Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik), our Italian friends (the ADRITELF - Associazione Docenti e Ricercatori Italiani di Tecnologie e Legislazione Farmaceutiche), our Spanish friends (the SEFIG - Sociedad Española de Farmacia Industrial y Galénica) and many other societies in our field.

I personally believe that this international collaboration is of crucial importance, because it allows the organization of a scientific conference in our domain, which has the critical mass to attract scientists from academia, industry and regulatory organizations to come together and exchange. It is a place to personally meet colleagues from all over the world and to initiate fruitful collaborations.

For this reason we intentionally continue the “physical” poster presentations, allowing young as well as more experienced scientists to present their latest research findings at poster boards. This is an ideal opportunity for the participants to ask questions, and for the presenters to give more comprehensive background information. And maybe most importantly: These face-to-face discussions allow getting to know each other and to initiate new collaborations, or to find help when facing critical challenges. Walking through the poster board rows can give interesting ideas and allows getting an update on most recent developments. We do not intend to replace these “physical” poster presentations by other means in the future, they are and will remain an integral part of our World Meetings on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology.

I would like to sincerely thank the APV, ADRITELF, SEFIG and all other societies, who help organizing this meeting, for all their efforts and energy. It requires prioritizing international (and not national) interests, which is not straightforward. But I am convinced that this collaboration is highly fruitful and very important.

Prof. Juergen Siepmann

11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

19-22 March 2018, *Granada, Spain*

In continuation of the very successful scientific meetings in Budapest, Paris, Berlin, Florence, Geneva, Barcelona, Malta, Istanbul, Lisbon and Glasgow, the *11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology* will be held in Granada in 2018.

This conference is jointly organized by the APGI, APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik) and ADRITELF (Associazione Docenti e Ricercatori Italiani di Tecnologie e Legislazione Farmaceutiche) and many other European societies.

It has gained an ever increasing impact in our field: With close to 1000 submitted abstracts and more than 1300 participants it has become the **largest meeting in our domain in Europe**, attracting scientists from all over the world. It is organized every two years: in March or April of all even years.

Importantly, the **entire spectrum of topics in Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology will be covered**, including for instance the engineering aspects during the manufacturing process, the portfolio of commercially available excipients enabling formulation of a large variety of medicinal products, the underlying physico-chemical principles, cutting-edge characterization techniques as well as potential pitfalls and hurdles to be overcome during product development, manufacturing and characterization.
The conference will be held on 3.5 days: From Monday (noon) until Thursday (evening).

From Tuesday to Thursday, 4 parallel sessions with oral presentations will be held:

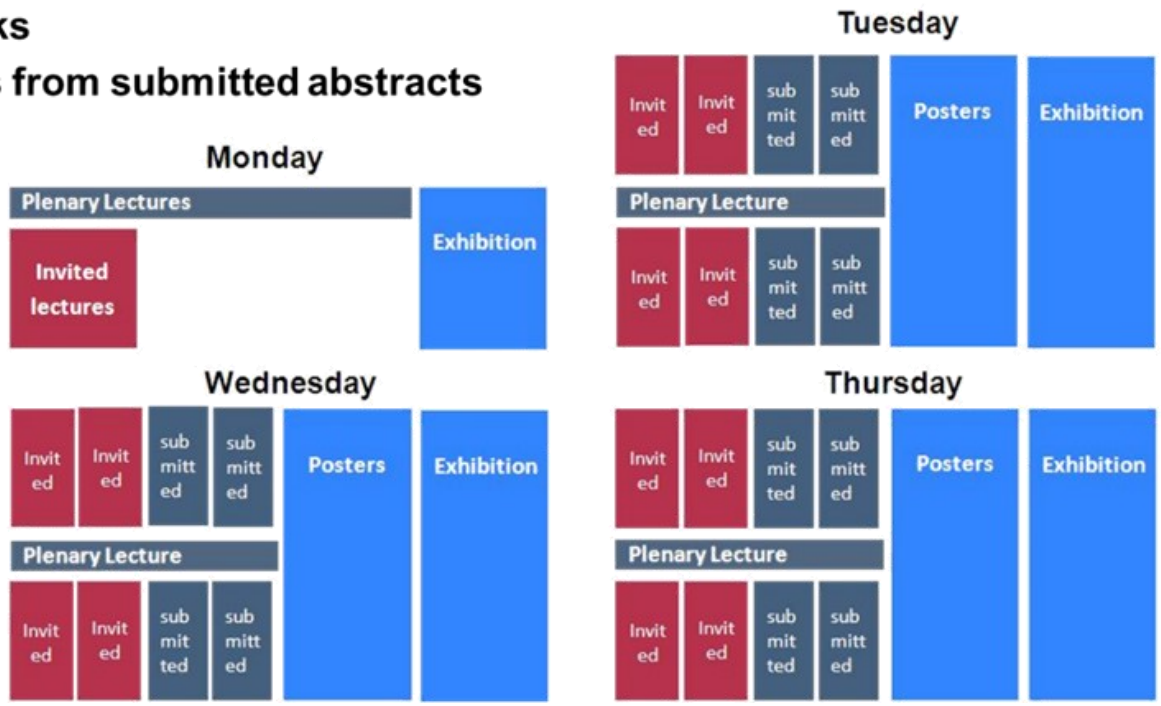
2 Sessions on industry-related topics, presented by distinguished invited speakers, giving overviews on the current state of the art in the respective fields,

2 Sessions with short talks selected from submitted abstracts, presenting the latest research findings in the broad field of Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology.

The figure below shows the general structure of the conference.

International Conferences and Workshops

4 parallel oral sessions
9 plenary lectures
36 invited talks
72 short talks from submitted abstracts



In Grenada, the following **hot topics** will be particularly addressed by invited talks from world-wide leading scientists in the respective fields:

- Advanced Characterization Techniques
- Biopharmaceutics
- Continuous Manufacturing
- Data Integrity
- Dermal and Transdermal Drug Delivery
- Drug-device Combinations/Combination Products
- Nanotechnology/Nanomaterials
- New Challenges in Oral Drug Delivery
- New Manufacturing Technologies
- New Materials
- Peptide and Protein Formulations
- Personalized Medicines/Pediatric/Geriatrics

In addition, the following **plenary lectures** will be highlighting hot key trends in our field:

- Oral delivery of peptides for gastrointestinal targets

Jean-Christophe Leroux, Swiss Federal Institute of Technology, Switzerland

- In vivo drug release from oral solid dosage forms

Abdul Basit, University College London, United Kingdom

- Transmucosal drug delivery (nasal, oral, ocular)

Maria José Alonso, University of Santiago de Compostela, Spain

Also**, invited lectures** giving overviews on the current state in the art in various fields will be given by:

- Ajit Narang, Genentech, United States
- Alvaro Goyanes, University College London, United Kingdom
- Andreas Dietzel, University of Technology Braunschweig, Germany

- Anette Larsson, Chalmers University of Technology, Sweden
- Begona Delgado Charro , University of Bath, United Kingdom
- Bill Williams, University of Texas, United States
- Carmen Alvarez Lorenzo, University de Santiago de Compostela, Spain
- Clive Wilson, University of Strathclyde, United Kingdom
- Elias Fattal, University of Paris XI, France
- Fabio Beltram, Scuola Normale Superiore, Italy
- Flora Felsolvalyi, Roche, Switzerland
- Francesco Puoci, University de Calabria, Italy
- Jan Hendrik Schattka, Evonik, Germany
- Jean Doucet, CEA and Novitom, France
- Jennifer Dressman, University of Frankfurt, Germany
- Jens Frahm, Max Planck Institute for Biophysical Chemistry, Germany
- José Louis Jorcano, University Carlos III of Madrid, Spain
- Klaus Wening, Gruenenthal, Germany
- Paolo Mangiagalli, Sanofi, France
- Raymond Schiffelers, University of Utrecht, Netherlands
- Stéphane Beilles, Sanofi, France
- Thomas de Beer, University of Ghent, Belgium
- Véronique Préat , University of Louvain, Belgium
- Wolfgang Friess, University of Munich, Germany.

Furthermore, during the entire conference, the accompanying **exhibition ResearchPharm** provides a cross-disciplinary platform for pharmaceutical scientists working in all fields of drug development in industry, academia and regulatory bodies. This exhibition is continuously growing and offers the possibility to present and learn about the most recent trends and products in the area of pharmaceutical ingredients, developing and processing equipment, analytical technologies, medicinal products, medical devices and contract manufacturing.

An important key feature of this conference is that **young and experienced scientists from academia and industry will also present their latest research achievements in the form of physical posters**: This allows for fruitful exchanges between the participants of the conference and the authors. These face-to-face meetings in front of poster boards are very efficient and informative. They allow asking questions and giving more comprehensive background information, and maybe most importantly: They offer the ideal opportunity to create new personal contacts (or to strengthen existing contacts) between scientists working in different areas and providing various types of backgrounds. Such personal exchanges can be crucially important to initiate new collaborations and to find help when facing all types of challenges.

Please note that the **deadline for abstract submission is 15 November 2017!**
For more information, please visit the meeting's website at: www.worldmeeting.org

The organizing committee cordially invites you to join the 11th World Meeting and would be glad to welcome you in Granada!

11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

19-22 March 2018, *Granada, Spain*

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2nd European Conference on Pharmaceutics: Novel Dosage Forms, Innovative Technologies

3-4 April 2017, Krakow, Poland

After the great success of the 1st European Conference on Pharmaceutics in Reims (France), the second Conference was reorganized this year by the APGI, ADRITELF and APV in Krakow (Poland) from 3 to 4 April. The conference was attended by 500 participants from 44 countries (engineers, scientists, managers, students, and exhibitors). The conference was jointly organized by APV (German "International Association for Pharmaceutical Technology"), A.D.R.I.T.E.L.F. (Italian "Associazione Docenti Ricercatori Italiani di Tecnologie e Legislazione Farmaceutiche") and APGI (French "International Society of Drug Delivery Sciences and Technology). The welcome reception started on the evening with a 30 min performance of the SLOWIANKI Ensemble at the Sala Audytoryjna. After the performance, there have been beverages and snacks at the exhibition area allowed doing networking with participants from all over the world and also got in contact with old and new friends. It has to be pointed out that the goal of the APGI, ADRITELF and APV was to create a new series of international scientific meetings, the: European Conferences on Pharmaceutics which was held in Reims, France, 2015 and this year in Krakow. During the opening ceremony Prof. Joerg Breitkreutz (President of APV), Prof. Anna Maria Fadda (President of A.D.R.I.T.E.L.F) and Prof. Juergen Siepmann (President of APGI) welcomed the participants amongst others.

The two days meeting gave world-wide leading experts in the field to share their professional experiences through plenary lectures and invited talks on hot topics. In Krakow, this includes: Dr. Marco Gentile, Dompe, Italy - Plenary Lecture "From bench to bedside – from technologies to clinical success", Dr. Karym El Sayed, Bayer, Germany - Plenary Lecture "Smart Devices from an industrial perspective". Prof. Maria Nowakowska from Jagiellonian University in Poland gave a very interesting talk in the "Smart Drugs and Smart Devices" session entitled "Macromolecular candidates for novel drugs and delivery systems" followed by Prof. Dan Peer from Tel Aviv University who talked about "Novel Strategies for targeted drug delivery".

Furthermore, Dr. Marc Rohrschneider from Boehringer Ingelheim in Germany presented the combination products for inhalation vs. injection.

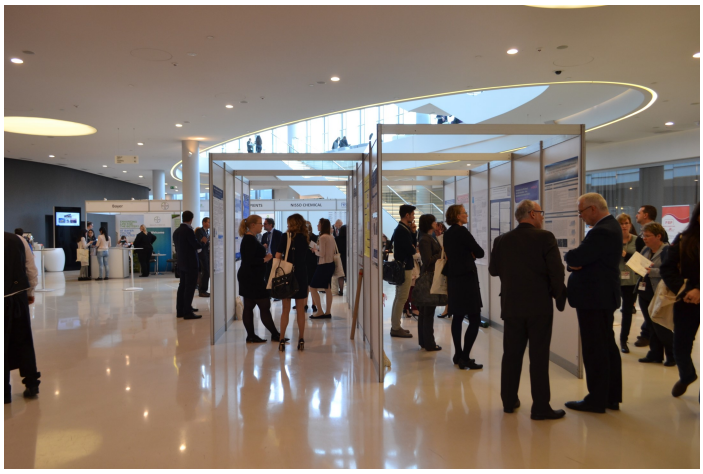
At the same time, short talks on "Preformulation and dermal/transdermal" have been presenting in the parallel session, including: Joana Pinto from Austria "A time-dependent study on the impact of engineering on the physicochemical characteristics of inhalable particles", Dr. Paulo Oliveira from France "Solid state transformations of dexamethasone induced by milling", Raphael Wiedey from Germany "How do process parameters influence the density distribution in ribbons from roll compaction?", Claire-Hélène Brachais from France " Influence of plasticizers on different properties of films obtained from film- forming solutions". Moreover, Dr. Dominique Lunter from Germany illustrated a very important imaging analysis for skin penetration "Skin penetration analysis by confocal Raman microspectroscopy-potentials and pitfalls", and last but not least for this morning session, Dr. Helen Quinn from North Ireland reported a very interesting talk on "An in vivo study investigating the translational potential of microneedles for use in the older population".

International Conferences and Workshops

It has to be pointed out that short talks were selected from submitted abstracts or invited talks.

After lunch break which was included in the registration fees, short talks as well as invited speakers started in the two parallel sessions. Invited talks presented very interesting topics on “Novel strategies to overcome physiological barriers”, including: Dr. Laurent Hortala from Sanofi in France “Oral delivery of macromolecules”, Prof. Claus-Michael Lehr from Helmholtz Center in Saarbruecken in Germany “Drug delivery to lung”, and Prof. Christel Mueller-Goymann from University of Braunschweig in Germany “Drug delivery to the skin and skin appendages”. In the parallel session, short talks was dedicated to Oral delivery, this includes: Glenn Verstraete from Belgium “A comparative study between melt granulation/ compression, hot melt extrusion and injection molding for the manufacturing of oral sustained release polyurethane matrices”, Dr. Michael Repka from USA “Simulating zero order drug release via pharmaceutical hot melt extrusion and 3D printing technology”, Dr. Andreas Zimmer from Austria “Improving drug release and stability of solid lipid forms”, Alessia Lazzari from Germany “Xanthan gum as rate-controlling polymer for alcohol resistant theophylline matrix tablets”, Denise Steiner from Germany “Individualized medications with poorly water-soluble APIs-Instant ODFs”, and Isabell Speer from Germany “Novel dissolution method for oral film preparations with modified drug release”.

Next day, the conference started on the morning session with very interesting invited talks on “Enabling Technologies for Poorly Bioavailable Drugs”, this includes: “New clothes for the emperor: Novel approaches to amorphous and lipid base drug delivery” given by Prof. Thomas Rades from University of Copenhagen in Denmark, “Industrial case studies on poorly bioavailable drugs” presented by Dr. Geert Verreck from J&J in Belgium, and “Nanofiber technologies for poorly soluble drugs” reported by Prof. Duncan Craig from UCL London in United Kingdom. Furthermore, very interesting short talks have been presenting in the parallel session, including: Drug nanosuspensions in solid oral dosage forms, lipophilic encapsulation in PLGA-PEG nanoparticles, the use of chitosan nanospheres containing cyclodextrins, polyamide-paclitaxel nanoparticles for colon cancer targeting, nanostructured lipid carriers for ophthalmic administration and si-RNA-complexed liposomes for cervical cancer treatment. In this morning session, awards were also announced, this includes: APGI Young Investigator Award, JDDST Best Paper Award and Honoring Professor A.T. Florence. After the lunch break included in the registration fees, invited talks continued with “Novel Delivery Strategies for Non-Lipinski Molecules”, this includes: “Overcoming biological barriers in cancer through tailored nanoparticles” given by Prof. Fabiana Quaglia from University of Naples in Italy, “Peptide delivery: where do we stand and what are the next steps” illustrated by Dr. Christophe Chassaing from Ipsen in France, and “Supramolecular harnessed architectures for active drug delivery” reported by Prof. Paolo Calicetti from Padua in Italy.



International Conferences and Workshops

At the same time in the parallel session, short talks from the "selected submitted abstracts" have been reporting on "Manufacturing & Engineering and Advanced Drug Delivery", this includes: Hot melt extrusion, In-line Raman spectroscopy, 3D Bio-printer, The importance of the co-processing in the manufacturing procedure and method design to a linear level IVIV correlation. Furthermore, poster presentations exhibiting during the whole conference gave the opportunity to get an update on the most recent research in Pharmaceutics and to personally exchange deeply with the authors. Also, an industrial exhibition accompanied the Conference and allowed the participants learning about the latest trends and newest products in the area of pharmaceutical ingredients, developing & processing equipment, analytical technologies, medicinal products & devices and many other fields. Thus, the conference was a perfect occasion for young as well as for established scientists from academia and industry from all over the world to present their work and discuss with old and new colleagues deeply about challenges of innovative drug delivery systems.

All coffee and lunch breaks as well as the welcome reception was included in the registration fees and was held in the industrial exhibition and poster presentation area in order to facilitate discussions between participants, exhibitors and presenters.

Last, but definitely not least we would like to thank Industrial sponsors for their great support, their continuous and fruitful collaborations. This conference would not be possible without the support of the sponsors.

We are looking forward to seeing you at the 3rd European Conference on Pharmaceutics in Bologna in 2019!

2nd European Conference on Pharmaceutics: Novel Dosage Forms, Innovative Technologies

3-4 April 2017, Krakow, Poland

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3nd European Conference on Pharmaceutics

1 – 2 April 2019, Bologna (Italy)

Venue
Bologna Congressi
Piazza della Costituzione 4/a
40128 Bologna (Italy)
www.bolognacongressi.it

Following the great success of the 1st European Conference on Pharmaceutics: Drug Delivery, (Reims, France, 2015) and the 2nd European Conference on Pharmaceutics: Drug Delivery, (Krakow, Poland, 2017), it is now our great pleasure to announce the third congress of this new series of international meetings, which will be held in Bologna, Italy, on 1 to 2 April 2019.

The European Conferences on Pharmaceutics are held every two years (in March/April of the uneven years). They are jointly organized by the A.D.R.I.T.E.L.F. ("Associazione Docenti Ricercatori Italiani di Tecnologie e Legislazione Farmaceutiche"), APGI ("International Society of Drug Delivery Sciences and Technology") and APV ("International Association for Pharmaceutical Technology").
The Conference will be a great opportunity for young as well as for established scientists from academia and industry worldwide to present their work and discuss challenges and hurdles during the development of innovative drug delivery systems.

Plenary lectures as well as invited talks on hot topics will be given by world-wide leading experts in the field. The current state of the art will be presented through overviews in the respective domains and outlooks on future perspectives.
Importantly, best submitted abstracts will be selected for short talks which will be presented in parallel to the invited talks session.
Furthermore, poster presentations will give the opportunity to get an update on the most recent research in Pharmaceutics and to personally exchange with the authors.

During the Conference an industrial exhibition will be present allowing learning about latest pharmaceutical technologies, newest prod-ucts in the area of pharmaceutical ingredients, developing & processing equipment, analytical technologies, medici-nal products & devices.
All coffee and lunch breaks as well as the welcome reception will be included in the registration fees and be held in the industrial exhibition and poster presentation area in order to facilitate discussions between participants, exhibi-tors and presenters. Information regarding **Sponsoring** and **Exhibition** is already available on the conference website:
http://www.europeanmeeting.org/home/exhibition-sponsoring/

International Conferences and Workshops

Bologna is a town with a millennial cultural tradition and world-wide recognized characteristics of hospitality and openness to ideas and people. Bologna is considered, among the major Italian cities, to be the one with the best quality of life, due to the perfect blend of tradition, history, art and innovation. The University of Bologna (Alma Mater Studiorum) is the oldest universities of the Western World and one of the largest in Italy. One should not forget the superb Bolognese gastronomic tradition. Tortellini, tagliatelle, lasagne and mortadella are just a few of the culinary delights that have made the city world famous for its gastronomic tradition and have earned it the epithet “Bologna the Fat”.

It is our great pleasure to welcome you in Bologna 2019!

Moreover, Bologna is a crucial node of the Italian **transport network**, allowing people to reach Bologna very easily and cheaply. The Bologna “Guglielmo Marconi” **International airport** offers direct flights to major national and international

Workshop on Oral Controlled Release

6 July 2017, Lille, France

With 130 participants (mainly from the industry) from 17 countries all over the world (e.g. Japan, Israel, Dubai, North and South America) the “Oral Controlled Release Workshop” was a great success.

For the first time, the APGI organized a workshop specifically dedicated to oral controlled release dosage forms.

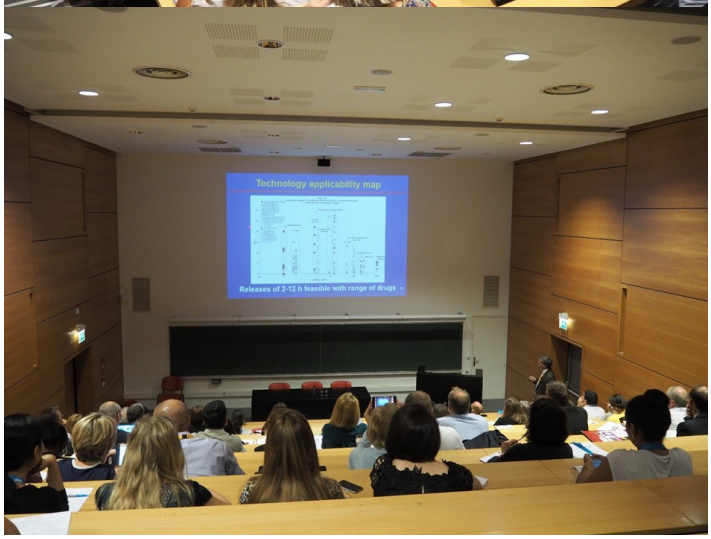
During the one day event, oral presentations from academia and industry as well as practical demonstrations (in small groups) were held. In addition, an industrial exhibition provided an update on the current state of the art in the field of oral controlled release. An overview on the available excipients, preparation techniques and apparatuses, characterization methods and future strategies were given by world-wide leading experts in this domain. For instance, Prof Jennifer Dressman from the University of Frankfurt presented applications of biorelevant media in drug development. Dr. Klaus Wening from Gruenenthal gave a very interesting talk on abuse deterrent formulations and Thorsten Cech from BASF on formulation strategies to avoid alcohol-induced dose dumping. Prof. Juergen Siepmann gave an overview on drug release mechanisms and mathematical modeling for solid oral controlled release dosage forms. Oral controlled release formulation strategies for high dose drugs and water-insoluble drugs were presented by Prof. Roland Bodmeier from the Freie Universitaet Berlin. Prof. T. Rades from the University of Copenhagen presented recent advances in the characterization techniques of solid dosage forms and Prof. Thomas De Beer from the University of Ghent gave a talk on PAT for process monitoring and control of continuous tablet manufacturing processes. Dr. Jonathan Goole from the Free University of Brussels presented oral modified-release drug delivery systems based on multilayered microparticles in a liquid dosage form. Furthermore, Dr. Miriam Robota from Evonik and Dr. Paul Smith from Colorcon were reporting on customized profiles using polymers and the development of controlled release matrices.

The entire spectrum, ranging from engineering aspects during the manufacturing process, the portfolio of commercially available excipients allowing to formulate a large variety of drugs, the underlying mass transport mechanisms and physical principles, characterization methods for the key properties of the devices as well as potential pitfalls and hurdles to be overcome during product development were addressed.

Industrial exhibition

Workshop on Oral Controlled Release

6 July 2017, Lille, France



Oral presentations from academia and industry
(Prof. T. Rades and Prof. R. Bodmeier)

Practical demonstrations

Workshop on Oral Controlled Release

6 July 2017, Lille, France

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APGI YOUNG INVESTIGATOR AWARD

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If you defended your PhD thesis between 15 November 2016 and 14 November 2017, you can candidate for the 2016 "APGI YOUNG INVESTIGATOR AWARD".

Please send a pdf file of your thesis (in French or English) and a short curriculum vitae, by 24 November 2017, to APGI (apgi.asso@u-psud.fr) and Géraldine Piel (geraldine.piel@ulg.ac.be). The file can be sent by We Transfer (a compressed version would be appreciated).

APGI thesis award 2016/2017

Dr Stephan STREMERSCH

Laboratory for General Biochemistry and Physical Pharmacy,

Faculty of Pharmaceutical Sciences, Ghent University

Promoters: Prof. S. De Smedt, Prof. K. Raemdonck,

Prof. K. Braeckmans

has been awarded for his Ph.D. thesis entitled:

"Exploring extracellular vesicles for siRNA delivery and Raman-based diagnostics"

Abstract

Extracellular vesicles (EVs) are membranous structures that are released by cells in the surrounding biofluid. EVs consist of a lipid and protein shell that encapsulates an aqueous core containing, among others, proteins and nucleic acids. It is believed that the molecular composition of EVs is in part actively regulated by the producing cell and, once released, it has been demonstrated that EVs are able to interact with other cells. As they are composed of numerous, potentially bioactive molecules, this interaction can induce phenotypic alternations in the recipient cell. In this respect, EVs are increasingly considered as important mediators of intercellular communication, enabling the functional transfer of (macro)molecules from one cell to another. Their inherent physiological effects can be exploited in a therapeutic context for which numerous examples are provided and discussed in chapter 1 (e.g. cell free vaccination, MSC surrogate therapy, etc.). Interestingly, it is believed that part of the induced alterations are due to the EV's ability to fuse with the cell and/or endosomal membrane, thus allowing subsequent delivery of their nucleic acid cargo (e.g. miRNAs and mRNAs) to the receptive cell's cytoplasm. This is a very interesting feature that attracted the attention of the drug delivery community, given that efficient cytoplasmic delivery of macromolecular biotherapeutics (including nucleic acids and proteins) is currently one of the major hurdles hampering clinical translation of biologics with an intracellular target.

In this thesis the ability of EVs to functionally deliver small interfering RNA (siRNA) was explored. Despite some interesting earlier reports in the literature on the value of EVs as bio-inspired drug carriers, many fundamental biological questions, pertaining to the EV biodistribution, cell uptake specificity and cargo release, remain largely unanswered to date. Additionally, technical hurdles such as inadequate purification strategies and the lack of an efficient loading strategy for macromolecular therapeutics should be overcome to reliably assess the true advantage EVs might have over current state-of-the-art delivery strategies (e.g. liposomes and viral vectors).

A first step in pursuit of harnessing EVs for siRNA delivery is the development of a method to obtain purified vesicles. It is important to realize that EVs represent only a fraction of the cell's secretome. Different methods to isolate and purify EVs out of conditioned cell medium and biological fluids have been suggested. These approaches rely on the EV's typical size, density, solubility, surface components or a combination of the above. Currently, no consensus on a gold standard protocol exists, which hampers unambiguous comparison of different studies and increases the risk of misconceptions due to residual impurities when using insufficiently stringent purification protocols. In chapter 3 a number of commonly used techniques to purify EVs from endogenous (e.g.protein complexes) and exogenous (e.g. fluorescent dyes) components were compared. Protocols based on a density gradient and size-exclusion chromatography outperformed differential centrifugation- and precipitation-based approaches. In combination with a better understanding of the influence of the respective isolation procedures on the EV functionality, these observations can contribute to the implementation of a more standardized purification protocol.

A second technical hurdle that was addressed in this thesis, is the loading of isolated EVs with exogenous siRNA. One of the strategies suggested in the literature is the electroporation of EVs in the presence of the siRNA of interest. Despite the fact that this technique has already been adopted by different groups, the underlying biophysical loading mechanism was never thoroughly investigated.

In chapter 2 an in-depth study on this process revealed that electric pulses in electroporation buffers result in extensive precipitation of siRNA into salt aggregates. This phenomenon was a consequence of metal ions, released from the cuvette electrodes, forming insoluble aggregates with the hydroxide ions present in pH neutral buffers.

APGI thesis award 2016/2017

During this aggregate formation process, siRNAs (and EVs) are co-precipitated. As a result, the encapsulation efficiency for siRNA is easily overestimated when commonly used electroporation conditions and quantification techniques are employed. When preventing aggregation, e.g. by using chelating acidic buffers or polymer-based cuvettes, the measured encapsulation of siRNA into EVs decreased to negligible amounts.

The shortcomings of electroporation and the current lack of alternatives to load hydrophilic macromolecules into EVs prompted us to explore new approaches. In chapter 4 we developed a generally applicable method to attach siRNA to the surface of isolated EVs by means of a cholesterol anchor. Moreover, given the complexity and heterogeneity of EV isolates and the previously described loading artifacts with electroporation, here we used a combination of three complementary assays to confirm and quantify siRNA loading (i.e. a gel retention assay, an antibody capture assay and a density gradient co-localization assay). As this approach was also able to load pre- formed liposomes with siRNA with comparable efficiency, a direct comparison between EVs and synthetic liposomes with regard to siRNA delivery could be made. To this end, we selected negatively charged, fusogenic liposomes with a size distribution comparable to EVs. Unfortunately, under the tested in vitro conditions, EVs underperformed compared to the liposomes for their ability to functionally deliver the siRNA therapeutic, which could be attributed to the lack of an intrinsic mechanism to induce endosomal escape prior to trafficking to lysosomes for degradation. Likewise, the endogenously present miRNAs were not functionally delivered to recipient cells. These observations question the efficiency and universal applicability of EVs as a gene therapy nanocarrier.

Besides therapeutic applications, EVs have also been the subject of investigation in a diagnostic context. The EV architecture and part of the molecular composition are common among EVs isolated from different cells. However, some EV-associated components are unique for the producing cell type and even cellular status. Moreover, upon in vivo release, part of the EVs end up in neighboring biological fluids making them available for liquid biopsies. In this respect, EVs can be considered as easy accessible windows on otherwise difficult to reach (diseased) cells. These features make them ideal biomarker candidates for early disease detection and treatment monitoring.

Yet, as contextualized in chapter 1, to optimally exploit EVs in a diagnostic setting, there is a need for new characterization techniques which can attain high sensitivity on a single vesicle level. In an attempt to address this need, in chapter 5 a nanotechnological platform relying on enhanced Raman spectroscopy for individual EV characterization, was developed. The signal enhancement was evoked by decorating the surface of each individual vesicle with a gold nanoparticle-based plasmonic substrate, which allowed to obtain a Raman spectrum with acceptable acquisition speed. Subsequently, the acquired spectra could be subjected to downstream analysis using dedicated multivariate statistical models allowing to discriminate between EVs derived from red blood cells and EVs derived from melanoma cells. Furthermore, due to the single vesicle approach, this technique was able to quantify the relative abundance of each EV type in a mixture.

Conclusions

In conclusion, in a first part of this dissertation the potential of EVs as a drug delivery carrier for siRNA was assessed. We could obtain pure EVs by means of a density gradient purification protocol and load them by exploiting the hydrophobic interaction between the EV membrane and a cholesterol tag covalently attached to one of the siRNA strands. However, under the experimental conditions EVs were unable to bypass the endolysosomal degradation pathway and hence were unable to functionally deliver siRNA upon cellular internalization. To a certain extent, our observations temper the high expectations linked to exploiting EVs as a drug delivery carrier and call for a more in-depth biological understanding of the EV's cellular delivery mechanism and related cell type specificity. Nonetheless, other therapeutic applications of EVs, as discussed in chapter 6, are very promising and are already developed up to market level (e.g. EV- based immunotherapy). In the second part of this dissertation, we developed a new nanotechnological platform that allows the fast characterization of individual EVs via surface enhanced Raman spectroscopy. As EVs are very promising biomarkers, the high sensitivity inherent to the developed technology makes this an attractive platform to explore further in a diagnostic setting.

SANOFI

Journée d'information APGI-SETARAM

30 Mai 2017, *Lyon, France*

Le 30 mai 2017, la société SETARAM a reçu dans ses locaux de Caluire, près de Lyon, les participants au séminaire APGI-SETARAM sur le thème : « formulations pharmaceutiques : caractérisation, stabilité par analyse thermique et calorimétrie ». Cet événement donnait suite à un premier séminaire qui avait eu lieu en octobre 2009, plus axé sur les applications de la microcalorimétrie à la caractérisation des principes actifs et formulations pharmaceutiques.
La journée a débuté par une présentation de l'Association de Pharmacie Galénique Industrielle, représentée par Mr Régis Cazes, directeur marketing stratégique de la société MENDELPHARM, suivie d'une introduction de la société SETARAM par Rémi André, directeur de la technologie et de l'innovation. Ce dernier a ensuite détaillé les différentes techniques d'analyse thermique et de calorimétrie, et quelques utilisations classiques dans le domaine de la caractérisation des formules pharmaceutiques et de leurs constituants. Cette première présentation avait pour but de mettre tous les participants à niveau sur les technologies disponibles afin d'entrer ensuite dans des considérations plus scientifiques.
Bertrand Roduit, directeur R&D de la société AKTS, spécialisée dans le traitement de données thermocinétiques et leur exploitation à des fins de simulation de comportement ou de stabilité, a ensuite présenté des méthodes cinétiques avancées pour déterminer la durabilité de produits pharmaceutiques. Ces méthodes se basent sur des essais de stabilité dans des conditions accélérées et standardisées, par calorimétrie à balayage de température ou isotherme, mais également sur la base d'autres techniques d'analyse. Une démonstration dynamique des logiciels qui permettent le traitement des données et la simulation a été réalisée par Mr Roduit.
Didier Clénet, chercheur spécialiste en formulation et stabilité chez Sanofi-Pasteur a ensuite donné une présentation très complémentaire de la précédente sur des applications des méthodes de cinétiques avancées pour la prédiction de stabilité des composés biothérapeutiques et des vaccins, en support au développement de la formulation. Les exemples concernaient la stabilité de protéines, d'antigènes, d'anticorps monoclonaux, la stabilité à l'oxydation d'huiles utilisées comme émulsifiants dans certains vaccins et la présentation concluait sur l'intérêt de ces méthodes pour donner des consignes de stockage en température des produits.
Les interventions suivantes se sont plutôt intéressées aux formes solides, avec une première présentation de Vincent Faivre, maître de conférences à l'institut Gallien Paris-Sud, sur des applications d'un couplage original entre la diffraction des rayons X et la calorimétrie, connu également sous le nom de microcalix. Ces applications concernaient notamment la caractérisation de mélanges complexes et l'influence du polymorphisme sur les procédés de mise en forme. Les exemples traitaient entre autres de l'étude du polymorphisme de mélanges de lipides, du behenate de glycérol utilisé comme excipient pharmaceutique, et de l'étude de la cristallisation lors de procédés de prilling qui permettent la formation de microsphères et qui sont notamment utilisables pour la mise en forme de principes actifs à libération prolongée.
Rémi André a ensuite repris la parole pour introduire la méthode d'étude de la compatibilité entre les principes actifs et les excipients par microcalorimétrie en mode isotherme par palier (step-isothermal). Il a illustré son propos avec quelques exemples montrant l'intérêt de cette méthode par rapport à d'autres utilisant la DSC de façon classique, et donnant des pistes d'interprétation des courbes obtenues. Julien COLLARD, chargé de laboratoire préformulation chez Beaufour Ipsen Industrie a ensuite complété ce sujet en montrant un cas pratique d'utilisation de la méthode microcalorimétrique par palier pour la sélection de formulations pharmaceutiques par l'étude de la compatibilité binaire principe actif-excipient. La bonne concordance des résultats entre cette méthode et une méthode employant l'HPLC a été soulignée, pour des mélanges binaires variés principe actif vs. agent de charge, lubrifiant, liant ou agent de pelliculage.
La journée s'est terminée par des ateliers pratiques qui ont permis des échanges détaillés et fructueux entre les participants et les spécialistes du laboratoire d'application de SETARAM, dont Christine Mayoux est la responsable. Ces ateliers concernaient principalement la détermination de pureté de principes actifs par la méthode dite de Van't Hoff en utilisant un appareil de type DSC131evo et les aspects pratiques de la mise en œuvre de la méthode de compatibilité principe actif-excipient à l'aide du microcalorimètre µSC.

« *Je remercie l'APGI et Setaram pour l'organisation de ce séminaire. Cette journée était très intéressante, de par la qualité des présentations des différents intervenants. Mais, aussi grâce à l'équilibre entre "théorie" et "pratique" proposé. Elle m'a notamment permis de mieux cerner les besoins expérimentaux du domaine pharmaceutique.* », Mickaël Simond, Société CALNESIS.

Making better tablets

Dr Michael Gamlen
Gamlen Tableting Ltd
http://gamlentableting.com

Why tablets?

Tablets remain the most used pharmaceutical dosage form by both number and volume. This is the case for a variety of reasons. The per unit manufacturing cost of tablets is lower than any other widely available dosage form, and what human activity is not driven by cost these days? As important, they are an extremely flexible dosage which can be developed with a very wide range of final properties. The final tablet has to fulfil a number of characteristics including the ability to deliver the correct amount of drug substance into the patient's system at the required rate, as well as possess physicochemical characteristics that make it easy to handle, administer and store. In addition, it has to meet the particular requirements of particular type. For example, dispersible products must be of a suitable size, hardness, texture and stability, as well as taste and smell.

In general compression mixture to be compacted needs to meet three key requirements:

- Adequate flow
- Adequate compressibility
- Adequate lubrication

Using modern tablet presses, flow is not usually a problem and the critical quality attributes of the compression mixture which cause most problems are those relate to the compression and lubrication properties of the compression mixture. However, these attributes are rarely, if ever, measured as part of the manufacturing process because it has not been possible to assess them.

New Technology

This problem has been addressed by the development of the Gamlen range of instruments. These are designed to measure the key critical quality attributes of materials (drug substances, excipients and compression mixes) using a small, simple to use Powder Compaction Analyser – see Figure 1.

Figure 1. Gamlen D series

The D series instrument shown compacts tablets one at a time to a load set by the user. The force required to detach the tablet from the punch tip is measured, and then the force required to eject the tablet from the die – see schematic in Figure 2.

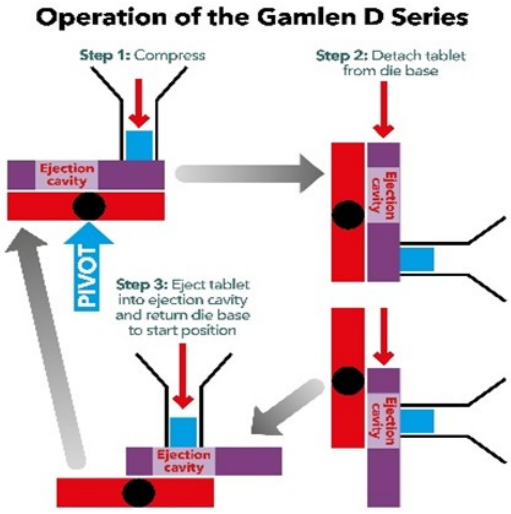

Figure 2. Gamlen D series Operation

Punch force and position are *measured throughout the process. The tablets are then fractured by the user under tensile testing conditions.*

When the data are analysed using the Gamlen Dashboard analysis system, a complete evaluation of the compressibility and lubrication properties of the material are automatically generated. The data are displayed in a format which makes it easy to see where the tablet lies on the Quality scale, and which aspects of the product properties present a risk. During product development, the data are used to assist the formulator in the improvement of the formula and the manufacturing process. During routine manufacture the data are used to check the properties of the current batch against the same tests performed on previous batches to check whether any changes in compression or lubrication properties are present.

Characterising tablets

An important set of compaction property measurements has recently been set out USP Monograph <1062.. These key relations are defined there as "compressibility", "compactibility", and "tabletability". These relationships are calculated from three key measurements – of tablet **compaction pressure**, tablet **tensile fracture stress** (TTFS), and tablet **density**. It should be noted that compressibility and compactibility have been previously defined in other compaction contexts (such as powder metallurgy). Compressibility (solid fraction vs compaction pressure), compactibility (solid fraction vs tensile strength) and tabletability (compaction pressure vs tensile strength), taken together, give a very complete picture of the compaction properties of materials. Their relationship is seen in the Compaction Triangle –Figure 3.

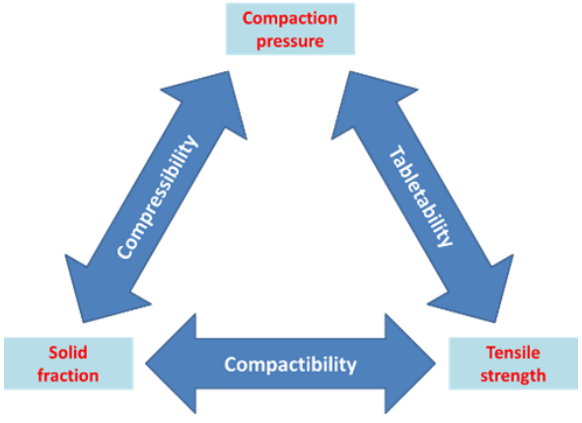

***Figure 3.* Compaction Triangle**

The complete range of measurements reported by the Gamlen Dashboard are:

1. Compaction pressure (derived from punch load and punch size)
2. 2.Detachment stress profile and peak detachment stress (derived from take-off force and punch size
3. Ejection stress profile and peak ejection stress
4. At-pressure and ejection tablet density
5. Tabletability profile
6. Compactibility profile
7. Compressibility profile

With the input of the major pharma groups including GSK, Pfizer, Sawai Pharmaceuticals and others, and using data from the literature, we have developed preferred working limits and ranges for all of these parameters and can readily explain how they can be used to assess tablet quality. The target value for tabletability (compaction pressure vs tablet tensile fracture stress) is a strength of 2 MPa at a pressure of 200 MPa. This has been accepted by most of the pharma majors as a desirable value, with a lower fracture stress limit of around 1 MPa at the same pressure. The relative density of the product is targeted at 90% or less, although actual values up to 95% are not uncommon. The risk of high density formulations is over-compaction and capping. Compactability is assessed from the visually from the compactibility plot by determining whether the product is still able to undergo additional compaction even at the highest loads tested. If not, then production problems should be expected unless the product is improved.

Measurements relating to lubrication are derived from the detachment and ejection measurements. Ejection stress should not exceed 5 MPa, although for some products even this value is too high; individual products with ejection stresses of less than 1 MPa have been found to cause problems. There is no agreed standard for detachment (take-off) stress but we recommend a similar limit as for ejection. For both measurements (ejection and detachment stress) the principle risk is of picking and sticking, although in some cases poor lubrication can also result in capping.

Evaluating excipients

An important property of an excipient, particularly if it is intended to be used as a direct compression agent, is its ability to incorporate drug substances without showing adverse effects on tablet properties. If an excipient was only able to accept a small proportion of drug substance, clearly its value as a direct compression agent would be limited. This requirement was first evaluated in the 1970s (Refs). In this study, we evaluated addition of a poorly compressible drug substance – ascorbic acid (AA) – on the tableting properties of a proprietary direct compression agent PROSOLV EASYtab. A series of blends which included increasing amounts of AA were prepared, and compressed at a range of compaction pressures. The results are reported below.

Tabletability

The widely accepted target for tabletability is a fracture stress of at least 2 MPa at a compaction pressure of 200 MPa. TTFS of 1 MPa at a pressure of 200 MPa is the minimum which is likely to be acceptable for large scale manufacturing; lower values result in tablet handling problems and risk of capping from over-compression. This limit is based on very extensive studies, and has been independently accepted by most major pharma companies.

The data on EASYtab are shown in Figure 4.

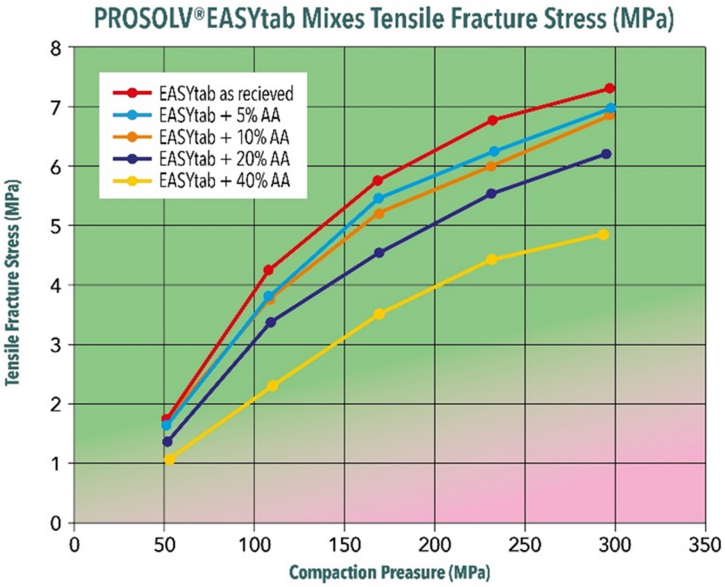

Figure 4. Tabletability profile

EASYtab has a very high tabletability, which is hardly affected by the addition of the active substance ascorbic acid, and is well away from the high risk pink zone. This shows that the material has high tolerance for even quite large amounts of incompressible material.

Compactability

The lower the porosity of tablet, the more likely you are to have problems manufacturing. In the Compactibility plot shown in Figure 5, the density of the tablet progressively increases, which is probably associated with reduced tablet porosity. (As the composition of the mixture is changing, the absolute density of the material will also change but the density was not measured in this study).

It is possible that the As Received material and the 40% AA formulations are reaching their compressibility limits at the highest pressure applied (300 MPa). The maximum density for these samples was at an applied pressure of 240 MPa with a reduction in density at 300 MPa. This observation would trigger further investigation to see if the formulation was actually reaching its compression limit.

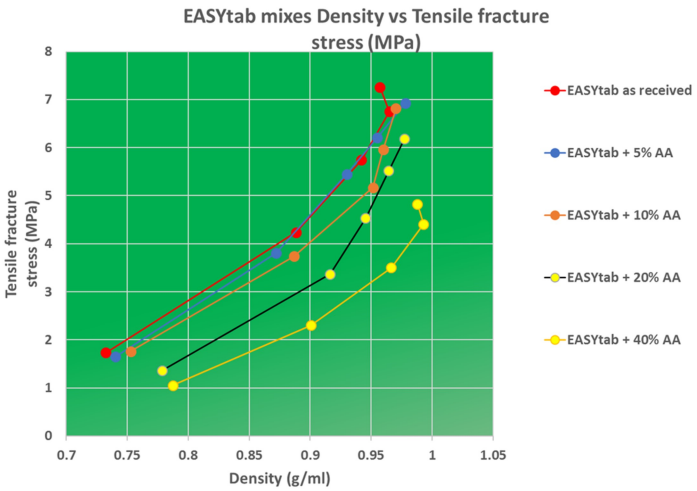

Figure 5. Compactibility plot

Ejection stress

Ejection is currently the primary measurement used to assess lubrication properties. Based on extensive experience, products with ejection stresses in excess of 5 MPa generate compaction problems including picking, sticking and capping.

The ejection stress of all the EASYtab formulations was well outside the problem zone shown in pink -see Figure 6. However, the adverse impact of the drug substance could be clearly seen. The ejection stress increases steadily with increasing AA content. Any concentration of AA about the values tested in this study would probably cause problems.

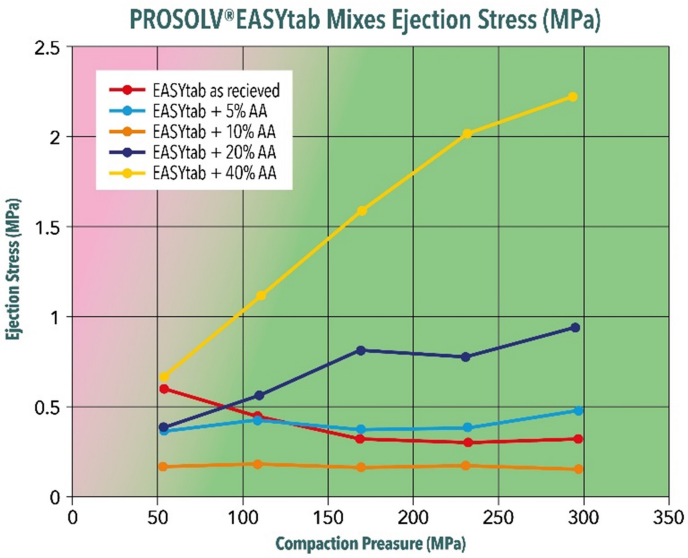

Figure 6. ***Ejection Stress***

Detachment stress

Detachment stress, or punch take-off force, is a less studied source of tableting problems. However clear links have been established between detachment stress and picking problems. For most materials the detachment and ejection stress values are similar; some materials have a much larger detachment than ejection stress, others have a much lower detachment than ejection stress. In the case of EASYtab, the detachment and ejection forces were similar – see Figure 7. Increasing amounts of "drug" substance caused increased detachment force, and maximum concentration used is approaching the limit of acceptability.

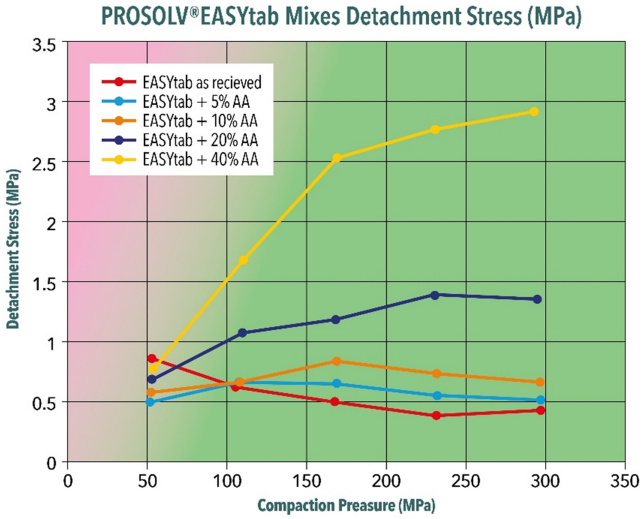

Figure 7. ***Detachment stress***

Summary and conclusions

This small study was completed in a few hours and required only a few grams of material. It clearly shows the impact of changes in formulation composition on the compressibility and lubrication properties of the model system. The data clearly show the impact of addition the model drug substance to the excipient with changes in tabletability, compactibility and lubrication behaviour. More information is available on our website www.gamlentableting.com. The system is being adopted by companies all over the world to help our customers make better tablets.

Agenda

APGI events

11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmeceutical Technology

19 - 22 March 2018

Granada, Spain

ADRITELF
Associazione Docenti Ricercatori Italiani di Tecnologie e Legislazione Farmaceutiche

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MAKING SCIENCE WORK

3nd European Conference on Pharmaceutics

1 – 2 April 2019, Bologna (Italy)

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