15th Annual Meeting

PSSRC Virtual 2021

Day 3: 13th October

Analytics, Processing II and Amorphous & Stability II

15th Annual Meeting PSSRC Virtual 2021

Timetable

Time				Schedule					
UK/PT	CEST	FIN	NZ						
08:00	09:00	10:00	19:00	**Welcome and Introduction**					
Session Details				**Parallel Session A: Analytics I** Chair: Blaž Grilc			**Parallel Session B: Processing II** Chair: Bram Bekaert		
				Presenter	**Organisation**	**Presentation**	**Presenter**	**Organisation**	**Presentation**
08:10	09:10	10:10	19:10	Karlis Berzins	University of Otago	A new frontier for non-destructive spatial analysis of pharmaceutical solid dosage forms: micro-spatially/spatially offset low-frequency Raman spectroscopy(micro-SOLFRS/SOLFRS)	Vincent Kimmel	Technische Universität Dortmund	Global 1D model for twin-screw-extruders in pharmaceutical applications
08:25	09:25	10:25	19:25	Amelie Mattusch	Technische Universität Dortmund	Investigation of Flow-Induced Effects on the Dissolution of APIs	Snezana Radivojev	RCPE	The influence of mucus on the permeability of inhalable APIs
08:40	09:40	10:40	19:40	Johanna Kölbel	University of Cambridge	Toward in-situ Observation of the Structure of Crystallising Magnesium Sulfate Solutions	Manuel Zettl	RCPE	Design and Characterisation of a Novel Continuous Vacuum Drying Technology
08:55	09:55	10:55	19:55	René Brands	Technische Universität Dortmund	Application of UV-Vis spectroscopy as an in-line monitoring tool for tableting	Jack Creswick	University of Strathclyde	Analysis of Novel Spherical Agglomerates: Compaction Behaviour and Impact on Tablet Properties
09:10	10:10	11:10	20:10	Keir Murphy	University of Strathclyde	Terahertz Analysis of Glass Simulation Samples	Jayant Iyer	RCPE	Milling-induced amorphisation in Mifepristone and the implications on oxidative stability
09:25	10:25	11:25	20:25	**Break**					
Session Details				**Parallel Session C: Analytics II** Chair: Keir Murphy			**Parallel Session D: Amorphous & Stability II** Chair: Johanna Kobel		
				Presenter	**Organisation**	**Presentation**	**Presenter**	**Organisation**	**Presentation**
09:35	10:35	11:35	20:35	Blaž Grilc	University of Ljubljana	Development of a buccal films with the assistance of image analytics	Keyoomars Khorami	The University of Copenhagen	Co-amorphous drug-phospholipid systems – bridging the gap between amorphous solid dispersions and lipid based drug
09:50	10:50	11:50	20:50	Peter Remoto	University of Otago	Isothermal dehydration of nitrofurantoin monohydrate II: A low frequency Raman spectroscopy study	Eline Boel	KU Leaven	Solvent influence on manufacturability, phase behavior and morphology of amorphous solid dispersions prepared via bead coating
10:05	11:05	12:05	21:05	Pedro Martin Salvador	Ghent University	Model based scale up of a spray drying process for a protein based product	Qi Li	University of Cambridge	The metastable for of theophylline observed during phase transitions ***pre-recorded***
10:20	11:20	12:20	21:20	Selma Celikovic	RCPE	Observer Design for Granule Moisture in the ConsiGma™-25 Fluid Bed Dryer	Črt Dragar	University of Ljubljana	Multi-Core Magnetic Nanocarriers for Drug Delivery
10:35	11:35	12:35	21:35	Runqiao Dong	University of Cambridge	Visualising Features of Liquid Transport through Coated Tablets Using Terahertz Pulsed Imaging	Please see parallel session C.		
10:50	11:50	12:50	21:50	**Closing Remarks**					

Session A: Analytics I

A new frontier for non-destructive spatial analysis of pharmaceutical solid dosage forms: micro-spatially/spatially offset low-frequency Raman spectroscopy (micro-SOLFRS/SOLFRS)

K. Bērziņš[1], S. J. Fraser-Miller[1], K. C. Gordon[1]

[1]Department of Chemistry, University of Otago, Dunedin 9016, New Zealand

PURPOSE

A non-intrusive multi-dimensional analysis method can be useful in many pharmaceutical applications, especially for the analysis of solid dosage forms, where spatial information using conventional analytical methods can typically only be obtained after destructive manipulations with samples prior to or during the measurements. This study demonstrated a new combination method of low-frequency and spatially offset Raman spectroscopy (SORS) method called spatially offset low-frequency Raman spectroscopy (SOLFRS) via the analysis of a number of model systems that showcase its capabilities for probing the layer (for example, coating) content/thickness characteristics as well as monitoring solid-state form transformations spatially.

METHODS

Celecoxib, lactose monohydrate (α-LM) and its stable anhydrous form (α-L_S) as well as polyvinylpyrrolidone (PVP) were used as model compounds, and were incorporated in a variety of different multi-layer/multi-component tablets. Raman measurements were conducted using an in-house built system, and using both traditional SORS (SOLFRS) and micro-SORS (micro-SOLFRS) experimental arrangements. The associated data analysis was facilitated by the application of a variety of different chemometric techniques.

RESULTS

In all the explored scenarios, micro-SOLFRS/SOLFRS proved superior to the more commonly used mid-frequency (fingerprint) Raman region that is used in SORS, yielding better Raman signals from the subsurface. This aspect, for example, not only enabled a more accurate determination of surface layer (i.e., coating) thickness characteristics, but also allowed to probe much deeper subsurface areas.

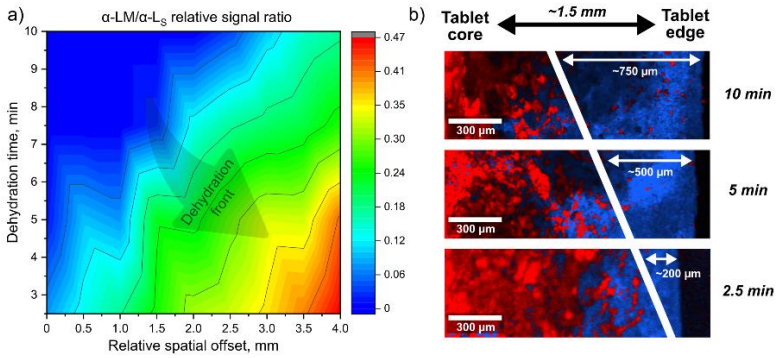


Figure 1 (a) α-LM / α-L_S relative signal ratio projection from SOLFRS data collected at different time-points after isothermal dehydration of α-LM tablets at 160 ˚C; (b) TrueComponent® (MCR-like) analysis of Raman microscopy data of the selected areas within the cross-sections of the same tablets (red color denotes α-LM, whereas blue color - α-L_S).

CONCLUSION

This exemplary study showcases the potential advantages of the newly developed Raman subtechnique, which, as evident by different explored tangible scenarios, can not only be applicable in pharmaceutical analysis, but also other research fields.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contribution of New Zealand eScience Infrastructure (NeSI) high-performance computing facilities and the support from the Dodd-Walls Centre for Photonic and Quantum Technologies.

Investigation of flow-induced effects on the dissolution of APIs

A. Mattusch, G. Schaldach, J. Bartsch, M. Thommes

Department of Biochemical and Chemical Engineering, Laboratory of Solids Process Engineering, TU Dortmund University, Dortmund, Germany

PURPOSE

In numerous cases, the improvement of the dissolution rate is in focus of drug formulation development. A standard approach in this case is particle size reduction, which is less effective for surface reaction limited drugs than for diffusion controlled APIs. Accordingly, consideration of drug-solvent interactions is necessary for understanding the dissolution behavior.[1] In this context, the investigation of flow-induced effects can contribute to the description of a comprehensive drug dissolution model, as the diffusion of hydrated molecules into the bulk medium can be improved by increasing the flow velocity[2].

METHODS

In a constructed rectangular flow channel, a sample of pure API was overflowed with water under laminar flow conditions. Particle image velocimetry (PIV) was used to investigate the flow profile in the sample region. The measurement of dissolved API was performed from a buffer reservoir continuously by UV/Vis spectroscopy, while dissolution experiments were conducted at different flow rates, adjusted via a pulsationfree gear pump.

RESULTS

For the investigation of the flow velocity impact on the dissolution the use of the constructed flow channel was beneficial, since the velocity profile of the overflow stream is constant. In general, differences in the dissolution behavior related to the applied flow rate were identified. The experiments confirmed that a greater mass flux can be achieved with a higher flow velocity if the substance is classified as diffusion controlled.[2] This flow-induced effect can be attributed to the reduction of the hydrodynamic boundary layer: Due to the decreased diffusion length, the process of dissolution increasingly depends on the surface reaction, which means a liberation of the API from the solid in a near-surface layer (see Figure).

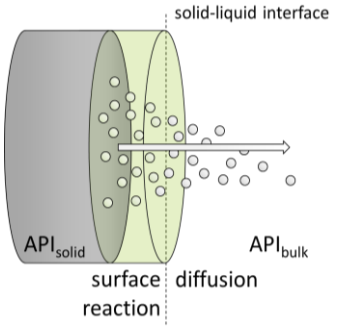


Figure. Schematic of API dissolution as model of surface reaction and diffusion-convection.

CONCLUSION

With the developed method for the measurement of the dissolution behavior it is possible to investigate differences of API dissolution depending on the flow velocity. These tests can be performed under laminar flow conditions and with a flow profile that is constant across the width of the sample. The relation to the layer thickness seems to be suitable to correlate flow-induced differences with substance-specific parameters, e.g. the mass flux of pure surface reaction.

CHALLENGES

A direct measurement of the layer thickness at different flow velocities as well as a correlation of the investigated dissolution behavior to substance parameters seems to be beneficial for modeling the dissolution behavior. In addition, two different layers could be distinguished: A flow-induced boundary layer and a boundary layer which is due to the pure kinetics of dissolution. The correlation between both, hydrodynamic and concentration boundary layer, is not yet known. Therefore it is desirable to consider the layer thickness in a differentiated manner when investigating flow-induced effects of the dissolution of APIs.

REFERENCES

1. Paus R, Ji Y, Braak F, Sadowski G, Dissolution of Crystalline Pharmaceuticals: Experimental Investigation and Thermodynamic Modeling. *Industrial & Engineering Chemistry Research*. 2015;54(2):731-742. doi:10.1021/ie503939w.
2. Sleziona D, Mattusch A, Schaldach G, Ely DR, Sadowski G, Thommes M, Determination of Inherent Dissolution Performance of Drug Substances. *Pharmaceutics*. 2021;13(2):146. doi:0.3390/pharmaceutics13020146.

Toward in-situ Observation of the structure of crystallising magnesium sulfate solutions

J. Kölbel[1], Q. Li[1], T. Threlfall[2], J. A. Zeitler[1]

[1]Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK
[2]University of Southampton, Southampton, UK

PURPOSE

Terahertz time-domain spectroscopy (THz-TDS) is used to study the crystallisation process of $MgSO_4 \bullet 7H_2O$ and investigate the behaviour of both the crystals and the solvent. It provides information about changes in the system even before crystals are detected.

METHODS

THz-TDS is a very useful tool to study hydrates and crystallisation [1]. By utilising a custom-built cell, terahertz transmission spectra are acquired during the crystallisation while the progress is monitored with an attached optical imaging probe. The temperature is precisely controlled with a circulating water bath.

RESULTS

The crystallisation process of $MgSO_4 \bullet 7H_2O$ in a crystallisation cell with a thickness of 100µm is investigated at temperatures between 6 and 20°C and at different concentrations, and the results of a number of measurements were reproducible. Temperature-independent changes in the spectra are observed before a spectral feature at 1.6 THz emerges. Careful spectral investigation allows to extract information about the amorphous phase before and during the crystallisation.

CONCLUSION

Terahertz time-domain spectroscopy combined with optical analysis is used to study the crystallisation of $MgSO_4 \bullet 7H_2O$ of different concentrations and temperatures. The emergence and change of a spectral feature at 1.6 THz clearly reflect the progress of the crystallisation. The setup can be applied to investigate a system between 4 and 90 °C without modification, while circulating another liquid cooled with dry ice will further expand the temperature range.

CHALLENGES

Crystallisation is an erratic process. It is challenging to control experimental conditions as much as possible, and for example eliminate seeds and ensure a stable temperature. In the current setup, crystallisation usually starts at interface boundaries such as the inlet of the crystallisation cell. Exact experimental conditions cannot easily be reproduced and many repeats are necessary. The investigation of processes just prior to crystal growth is also possible and this is the focus of on-going work. A stagnant system was studied as a start, and the use of an additional syringe pump will facilitate solution flow through the cell during measurements.

ACKNOWLEDGEMENTS

JK would like to thank the EPSRC Cambridge Centre for Doctoral Training in Sensor Technologies and Applications (EP/L015889/1) and AstraZeneca for funding. QL would like to thank the Chinese Scholarship Council for funding.

REFERENCES

1. Soltani A Gebauer D, Duschek L, et al. Crystallisation caught in the act with terahertz spectroscopy: non-classical pathway for l-(+)-tartaric acid, *Chem. Eur. J.*, 23 (2017): 14128-14132. doi:10.1002/chem.201702218.

Application of UV-Vis spectroscopy as an in-line monitoring tool for tableting

R. Brands[1], M. Zimmermann[1], J. Bartsch[1], M. Thommes[1]

[1]Laboratory of Solids Process Engineering, Technical University Dortmund, Dortmund, Germany

PURPOSE

For a fully continuous pharmaceutical process line the material traceability is a pre-requisite, while the feasibility of real time release is a substantial benefit. Crucial in this context are the residence time distribution RTD and the drug content or content uniformity. The application of UV-Vis spectroscopy as process analytical technology is a promising alternative for the in-line determination [1,2] of these parameters during tableting.

METHODS

Tableting experiments were conducted on a rotary tablet press (102i, FETTE Compacting, Schwarzenbek, Germany) and for process monitoring an UV-Vis spectroscope (Inspectro X, ColVisTec, Berlin, Germany) was used. Theophylline served as tracer for the residence time tests and as model drug substance during the blending test for content uniformity determination.

RESULTS

In-line RTD determination was reproducible for all investigated process parameter sets. Figure 1 (left) highlights exemplary the determined cumulative residence time distribution F for one process parameter set and repetition. The same set-up was successfully used to monitor the drug content during the blending tests, which was validated via sampling and an off-line reference method. This is also illustrated for one run at constant process parameters in Figure 1 (right).

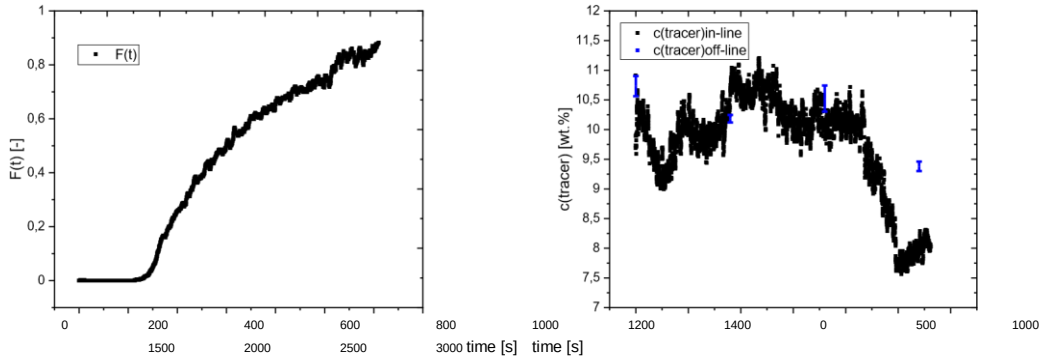


Figure 1. (left) Cumulative residence time distribution F(t) for the tracer and (right) tracer concentration determination in-line and off-line (av, n=10) during blending test; both at a throughput of 25,000 tablets per hour and a Fill-O-Matic speed of 90 rpm

CONCLUSION

In this first study, in-line UV-VIS spectroscopy was proven as a sufficient tool for RTD determination and content uniformity monitoring during tabletting. Therefore this technology is a potential enabler in terms of material traceability and product real-time release for a fully continuous pharmaceutical process line.

CHALLENGES

In future studies, this approach is expanded. Of particular interest are RTD influencing variables, a measurement set-up optimization as well as adaption of this approach to monitor direct feeding.

REFERENCES

1. Wesholowski J, Berghaus A, Thommes M. Inline Determination of Residence Time Distribution in Hot-Melt-Extrusion. Pharmaceutics. 2018;10(2):49. doi:10.3390/pharmaceutics10020049.
2. Wesholowski J, Prill S, Berghaus A, et al. Inline UV/Vis spectroscopy as PAT tool for hot-melt extrusion. Drug Delivery and Translational Research. 2018;8:1595–1603. doi:10.1007/s13346-017-0465-5.

Terahertz analysis of glass simulation samples

Keir Murphy[1,2], Mira Naftaly[4], Alison Nordon[3], Daniel Markl[1,2]

[1]EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation, Glasgow, Scotland
[2] Strathclyde Institute for Pharmacy and Biomedical Science, University of Strathclyde, Glasgow, United Kingdom
[3] Strathclyde Institute of Pure and Applied Chemistry, University of Strathclyde, Glasgow, Scotland [2]National Physical Laboratory, London, United Kingdom

PURPOSE

This project aims to model the effects of powder, granules, and compacts on terahertz (THz) spectroscopic. This greater understanding will enable the development of novel PAT applications for THz spectroscopy in drug product manufacturing. The project will utilise simulation samples consisting of a matrix material (PTFE/UHMWPE) and glass beads. These glass beads vary in particle size and concentration added to the simulation samples, highlighting the effect of such properties and scattering[1] on THz spectra.

METHODS

Simulation samples were created that consist of a matrix material and glass beads (10% w/w) (Soda-lime/borosilicate glass) compacted into a pellet utilising a compaction simulator at various compaction pressures (HB50, Huxley Bertram, Cambridge). The samples were then analysed utilising terahertz time-domain spectroscopy (THz-TDS) (Teraview LX, Cambridge) and subsequently modelled. The refractive index (RI) obtained from the THz analysis was plotted against compaction pressure to determine the pressure required to minimise sample porosity.

RESULTS

The first step in validating the sample preparation method was to determine the optimal compaction pressure for creating the pellets to attain as close to zero porosity as possible[2]. To this end, glass bead samples (10% w/w) pellets were produced using various compaction pressures and matrix materials. The RI (at 1 THz) of these samples was plotted against the compaction pressure to determine the optimal pressure to minimise porosity.

CONCLUSION

This pressure study highlighted that 392 MPa was required for PTFE samples to minimise porosity for both pure and 10% w/w glass bead samples (soda-lime glass beads). For PE pellets, the RI does not increase with compaction pressure; instead, the RI (at 1 THz) remains constant. This suggests that the optimal pressure is significantly lower as the RI has already reached its maximum with this material, and therefore UHMWPE is not suitable for use as the matrix material due to its significant porosity.

CHALLENGES

While PTFE powder is suitable due to its low porosity when compacted at the appropriate pressure, the refractive index shows anomalous behaviour upon the addition of glass beads. The refractive index of all glass bead samples shows a sharp rise to 1 THz, followed by a rapid drop. Due to this behaviour, the refractive index of the samples is not stable over the dynamic range causing significant issues in the data analysis and, by extension, the modelling of the results.

Currently, there are two theories as to how this occurs; firstly, this could be attributed to the quantity of material a particular photon in the beam path encounters. For example, one photon may encounter one glass bead. Another could encounter multiple, leading to a difference in delay; once the waveforms are convoluted together, this delay could cause the drop off observed. The second more straightforward explanation is that the type of glass causes this anomalous behaviour as soda-lime glass is a very absorbent material in the THz domain and shows a similar refractive index profile to that of the PTFE glass bead samples.

ACKNOWLEDGEMENTS

The author would like to thank EPSRC, National Physical Laboratory and the Future Continuous Manufacturing and Advanced Crystallisation Research Hub.

REFERENCES

1. Franz, M., Fischer, B. M., & Walther, M., The Christiansen effect in terahertz time-domain spectra of coarse-grained powders. *Applied Physics Letters*, *92*(2), 2–4. https://doi.org/10.1063/1.2831910
2. Markl, D., Strobel, A., Schlossnikl, R., Bøtker, J., Bawuah, P., Ridgway, C., Rantanen, J., Rades, T., Gane, P., Peiponen, K. E., & Zeitler, J. A., Characterisation of pore structures of pharmaceutical tablets: A review. In International Journal of Pharmaceutics (Vol. 538, Issues 1–2, pp. 188–214). Elsevier B.V. https://doi.org/10.1016/j.ijpharm.2018.01.017

Parallel Session B: Processing II

Global 1D model for twin-screw-extruders in pharmaceutical applications

V. Kimmel[1], J. Winck[1], M. Thommes[1]

[1]Laboratory of solids process engineering, Technische Universität Dortmund, Dortmund, Germany

PURPOSE

Twin-screw extrusion processes are well established in the food and plastic industries. In pharmaceutical research, twin-screw extruders are used to improve the oral bioavailability of new developed active pharmaceutical ingredients (APIs) by dispersing them into polymeric carriers. One major challenge is the prediction of optimal process conditions in the development of new material formulations. Therefore, the knowledge of the temperature profile, the mixing properties and the shear stress along the extruder is necessary. In this context, numerical simulations, which contains physical models, are a promising tool to complement extensive series of experiments and thus reduce time and costs. Due to the history of twin- screw extrusion, the existing models do apply well to food and plastic processing but not to pharmaceutical applications, where various sub-processes like grinding, mixing, melting and dissolution occur. One exampleis the phase interaction between the polymer and the API during the production of amorphous solid dispersions (ASDs). However, the dissolution of the API into the polymer, based on molecular effects such asdiffusion, is not well understood. The aim of this study is the modelling of pharmaceutical sub-processes and the implementation in a predictive software tool.

METHODS

In this study, a 1D simulation was implemented in the programming language Python in order to calculate various process parameters and product properties along the extruder in axial direction. Therefore, the extruder was divided into smaller sections in axial direction and ordinary differential equations were solved numerically for each one. The physical models are based on the similarity theory by Pawlowski[1] and the extension to twin-screw extruders by Kohlgrüber[2]. For these models, dimensionless screw parameters (A and B parameters) are used, which characterize the extruder regarding to the throughput, the pressure build-up and the power input. Since these dimensionless screw parameters are essential for the 1D simulation and unknown for the most screw elements, an experimental setup was built in order to be able to determine them and finally validate the entire simulation. The experimental setup was a self-constructedvertical twin-screw extruder, which is geometrically similar to the commercial Leistritz ZSE 27 extruder.

RESULTS

The first results of the 1D simulation, calculating fundamental process conditions such as pressure, power and degree of filling, are consistent with data from the literature of Eitzlmayr[3]. The experimental validation of the 1D simulation of this study is not completed up to now. After the validation, this simulation will be the base for the implementation of models to describe several pharmaceutical sub-processes. In conclusion,the understanding and prediction of pharmaceutical extrusion processes offers great potential to improve twin-screw extrusion for pharmaceutical applications. Furthermore, costs and effort can be saved in the development of new formulations.

REFERENCES

1. Pawlowski J, Die Ähnlichkeitstheorie in der physikalisch-technischen Forschung. *Springer Verlag*. Heidelberg. 1971;ISBN: 9783642650963.
2. Kohlgrüber K, Der gleichläufige Doppelschneckenextruder: Grundlagen, Technologie, Anwendungen. *Hanser Verlag*. München.2016; doi:10.3139/9783446435971
3. Eitzlmayr A, et al. Experimental characterization and modeling of twin-screw extruder elements for pharmaceutical hot melt extrusion. *American Institute of Chemical Engineers Journal.* 2013; 59(11):4440 – 4450. doi:https://doi.org/10.1002/aic.14184.

The influence of mucus on the permeability of inhalable APIs

S. Radivojev[1,2], L. Kargl[1], C. Meindl[2], J. T. Pinto[1], A. Paudel[1,3], E. Fröhlich[1,2]

[1]Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria
[2]Center for Medical Research, Medical University of Graz, Stiftingtalstrasse 24, 8010 Graz, Austria
[3]Institute of Process and Particle Engineering, Graz University of Technology, Inffeldgasse 13, 8010 Graz, Austria

PURPOSE

Many possibilities have been recognized in the use of inhalation as a route for the delivery of drugs. Nevertheless, the *in-vitro* methods that are commonly used for other delivery routes are still in development. In the absence of standards for inhaled drugs, the most commonly used cells to assess permeation in inhalation are Calu-3. Even though a certain amount of mucus is produced, this might not be enough to define the impact that the secretion might have on the drug dissolution and absorption[1]. Thus, our work focused on the investigation of the mucus barrier impact on the apparent permeability of inhaled drugs.

METHODS

The mucus was scraped from the porcine trachea and washed with PBS, until visible free of the blood and subsequently lyophilized. Prior to use, mucus was rehydrated with distilled water (1:1) and warmed to 37°C. 48 µL of mucus were applied on the cell grown inserts and centrifuged at 400 rpm. This was enough to cover the whole insert. Fluorescein experiments as well as microscopic analysis were done to investigate potential negative impact of the centrifugation on the cells. Permeability of four inhalable drugs, with distinct characteristics was studied, with and without mucus presence. The selected drugs were salbutamol sulphate (SS), tiotropium bromide (TioBr), formoterol fumarate (FF) and budesonide (BUD).

RESULTS

Fluorescein experiments as well as microscopic studies showed that the force of centrifugation did not disrupt the intercellular junctions between the cells thus they were suitable for our experiments. The permeability of hydrophobic BUD was lowered, approximately by half due to the presence of mucus. This might be due to hydrophobic interactions occurring between the mucus and BUD. The observed impact was seen for both air-liquid (ALI) and liquid-liquid (LC) interface. On the other hand, positively charged TioBr and FF permeated more in the ALI interface, compared to LC. Seeing that LC cultivated cells have more tight junctions, this could result in a tighter membrane, hindering the permeation[2]. In ALI, the observed behaviour could have been due to the accumulation of molecules within the mucus, forming a higher concentration gradient that increased the permeation rate. Finally, SS showed similar permeation with and without mucus for LC setup, while for ALI a notable decrease was seen. Possibly, negatively charged mucin parts slowed the permeation of SS.

CONCLUSION

Our study showed how mucus can distinctly impact the permeability of inhaled drugs and potentially influence drug bioavailability. To further support these observations, more molecules should be screened.

CHALLENGES

Preparation and handling of mucus *in-vitro* as well as its application onto the cell inserts were main challenges of this work. Our initial setup is still being adapted and further studies are being done.

REFERENCES

1. Cingolani E. et al, *Eur. J. of Pharm. and Biopharm.* 141 (2019) 210-220
2. Khanvilkar K. et al, *Adv. Drug Deliv. Rev.* 48 (2001) 173-193

Design and characterisation of a novel continuous vacuum drying technology

M. Zettl[1], I. Aigner[2], P. van der Wel[3], H. Schroettner[4], , M. Krumme[2], J.G. Khinast[1,5]

[1] Research Center Pharmaceutical Engineering (RCPE) GmbH, 8010 Graz, Austria
[2] Novartis Pharma AG, Novartis Campus, 4056 Basel, Switzerland
[3] Hosokawa Micron B.V., Gildenstraat 26, 7005 BL Doetinchem, Netherlands
[4] Graz University of Technology, Institute for Electron Microscopy and Nanoanalysis, 8010 Graz, Austria
[5] Graz University of Technology, Institute for Process and Particle Engineering, 8010 Graz, Austria

PURPOSE

In the ongoing transition towards continuous manufacturing methods within the pharmaceutical industry, several process steps have not yet been sufficiently developed. Drying, being the last step in the manufacturing of active pharmaceutical ingredients (APIs) is one of them. As the materials within the process are subject to mass and heat transfer simultaneously, and often show poor process behaviour, they are usually prone to unwanted effects such as agglomeration and attrition. Therefore, the need for a new continuous technology, minimising the effect of drying on the particle morphology is evident. [1]

METHODS

This presentation will focus on a newly developed continuous drying technology, in which the unique design allows a balancing of forced feed, powder bed movement as well as residence time. The influence of different process parameters (mass flow, air flow, rotational speed, temperature, inlet moisture, vacuum level) is investigated as well as their influence on the final particle properties (morphology via scanning electron microscopy (SEM) and particle size distribution (PSD)). An estimate for the residence time distribution (RTD) is evaluated, too. As the main test substance, Ibuprofen with varying inlet moisture levels (10 to 50 wt. %) was used.

RESULTS

The results show that this technology can be used for drying cohesive powders (<100 µm) in the range of 0.5 to 2.0 kg/h, on dry basis, with negligible effect on the particle shape and size. Additionally, for some configurations it was possible to continuously dry from a still pump-able state (50 wt. % inlet moisture) to below 1 wt. % residual moisture in the product, closing the gap to upstream continuous filtration methods. In this range, the PSD was maintained and the residual moistures of the product for some process configurations could be reduced to below 1 wt. %.

CONCLUSION

In summary, the presented continuous technology introduces a robust drying process, suitable to dry temperature-sensitive cohesive particles at low mass flows under vacuum, closing the gap for the last step in continuous API production.

CHALLENGES

The main challenge when drying poorly flowable, cohesive particles is an unpredictable hold-up and thus RTD behaviour. Therefore special care had to be taken for the design of the conveying principle within the newly developed dryer.

ACKNOWLEDGEMENTS

This work has been funded within the Austrian COMET Program under the auspices of the Austrian Federal Ministry of Transport, Innovation and Technology (BMVIT), the Austrian Federal Ministry of Economy, Family and Youth (BMWFJ) and by the State of Styria (Styrian Funding Agency SFG). COMET is managed by the Austrian Research Promotion Agency FFG. We acknowledge the support of Alina Fürntratt, Michael Piller and Patrick Vorraber (all RCPE).

REFERENCES

Add references as appropriate. Please use the style as shown in the following two examples.

1. Zettl M, Aigner I, Mannschott T, et al., Characterization of a Novel Drying Technology for Continuous Processing of Cohesive Materials: An Ibuprofen Case Study. *Organic Process Research and Development*. 2021;25(4):769-780. doi:10.1021/acs.oprd.0c00413.

Analysis of novel spherical agglomerates: compaction behaviour and impact on tablet properties

J. Creswick, V. Raval, A. Florence, D. Markl

Strathclyde Institute of Pharmacy and Biomedical Sciences, EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation, University of Strathclyde, Glasgow, Scotland

PURPOSE

The purpose of this study is primarily to link material properties with tablet performance by measuring particle, powder bulk, and tablet properties. A bespoke compaction simulator is used to compact tablets containing either novel spherical agglomerates, or the non agglomerated form of the active pharmaceutical ingredient (API). The compaction simulator allows for precise control of the tablets produced; this compaction data and breaking force measurements were collected to assess the effects of agglomeration on tablet mechanical performance.

METHODS

Continuous made spherically agglomerated (AGC), batch made spherically agglomerated (AGB), and non-agglomerated (PC) benzoic acid (BA) make up the APIs used. Magnesium Stearate (MgSt) acts as lubricant, while microcrystalline cellulose (MCC) was chosen as it deforms mostly plastically. Tablets of equal weight are compacted at a range of thicknesses and pressures (2.11-2.85 mm and 50-400 MPa, respectively). Differences in compactability, compressibility, and tabletability are analysed. Compaction load and punch position readings are captured *in-situ*, while tablet mechanical performance is assessed via breaking force measurements.

RESULTS

Position control mode used to produce 540 tablets (270 AGC, 270 PC) across 10 groups. AGC results indicate good weight uniformity. Ejection shear stress slightly higher for PC at lower compaction pressure. Ejection shear stress increases with increasing compression pressure. Larger immediate axial recovery evident in AGC batch which yields an increase in porosity recovery. PC demonstrated higher degrees of compactibility, compressibility, and tabletability. AGC results indicate more predictable compaction behaviour – PC demonstrates significant changes in tensile strength and solid fraction.

CONCLUSION

Initially, it appears that PC demonstrates superior compaction behaviour. However, results are inconsistent and AGC may actually allow greater control of compaction behaviour and therefore be favourable. Further testing required.

CHALLENGES

The PC batch of tablets compact to a smaller diameter than the die. Why? How is one able to accurately quantify the degree of agglomerate/particle fragmentation? Why, at pressures beyond agglomerate fragmentation, do agglomerated tablets (AGC) still demonstrate greater porosity recovery vs. the non-agglomerated group?

ACKNOWLEDGEMENTS

EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation.

Milling-induced amorphisation in Mifepristone and the implications on oxidative stability

J. Iyer[1], M. Brunsteiner[1], I. Saraf[1], A. Paudel[1,2]
[1]Research Center Pharmaceutical Engineering GmbH (RCPE), 8010 Graz, Austria
[2]Institute of Process and Particle Engineering, Graz University of Technology, 8010 Graz, Austria

PURPOSE

Energy intensive mechanical processes applied during drug substance or product manufacturing, like milling, sieving, compaction, or transport etc. can result in a partial and unintended amorphization of crystalline materials. This could have repercussions leading to physical and chemical instabilities, such as phase transitions and induction of various solid state reactions.[1,2,3] While phase transitions are relatively better understood, solid state chemical reactions like auto-oxidation are still not well investigated, especially in the case partially disordered solids .[3] Here, we present results, investigating to the chemical reactivity (auto-oxidation) of Mifepristone (MFP) in the solid state. The overall aim is to provide a rational basis for predictive stability models that explain propensity of oxidation due to milling induced amorphisation.

METHODS

Crystalline MFP was ball milled for durations ranging from 5 min to 180 min. The time required for complete amorphisation was identified using mDSC, PXRD and Raman spectroscopy. The un-milled (crystalline) MFP, partially crystalline MFP and completely amorphous MFP were subjected to elevated oxygen pressure at different temperatures in RapidOxy® and the extent of degradation of the exposed samples was quantified using UPLC method. Additionally, replicate samples were placed in the oven at same temperatures and different RHs, but at ambient oxygen conditions and analysed using UPLC.

RESULTS

Under elevated oxygen and much lower humidity attained in RapidOxy®, the propensity of degradation in milled samples increased depending on the presence of amorphous content. Interestingly, Raman analysis did not show any evidence of re-crystallisation. However, samples placed in the oven under the same temperature/elevated humidity conditions showed a higher propensity of compounds to re-crystallise and there was negligible degradation in these samples.

CONCLUSION

Amorphous and partially crystalline MFP underwent prominent oxidative degradation under with no detectable crystallization at low RH and higher oxygen concentration. In contrast, at ambient oxygen concentration and elevated RH, crystallization of MFP was prevailing over auto-oxidation. Through ongoing investigation, we aim to thoroughly deonvolute the propensity of an amorphous API towards oxidation versus crystallization.

CHALLENGES

Methods to measure the crystalline content did not show a good agreement among DSC *vs* PXRD/Raman.

ACKNOWLEDGEMENTS

Sincere thanks to RCPE for the research facilities, and industrial partners (Az, J&J, Pfizer and UCB Pharma, Felmi ZFE).

REFERENCES

1. Adrjanowicz K et. al. Effect of Cryogrinding on the Chemical Stability of Sparingly Water-Soluble Drug Furosemide, *Pharmaceutical Research.* 2011;28:3220-3236. doi: 10.1007/s11095-011-0496-4.
2. Ivana S et. al. Identification of Degradation Products of Praziquantel during Mechano-chemical Activation, *Journal of Pharmaceutical and Biomedical Analysis*. 2011;158:291-295. doi: 10.1016/j.jpba.2018.07.002.
3. Dattatray M. et. al. Solid-state reactivity of Mechano-activated Simvastatin: Atypical relation to Powder Crystallinity, *Journal of Pharmaceutical Sciences.* 2019;108(10):3272-3280. doi: 10.1016/j.xphs.2019.05.032.

Parallel Session C: Analytics II

Development of a buccal films with the assistance of image analytics

B. Grilc, O. Planinšek[1]

[1]The Chair of Pharmaceutical Technology, University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

PURPOSE

Formulation of buccal films in early stages of development could be very challenging in terms of obtaining a coherent film. In this study we demonstrate the use of computer vision aided by neural network as a helping tool for formulation development.

METHODS

Series of mucoadhesive buccal films based on Na-alginate, containing valsartan (API) were prepared at various compositions. Contents of main polymer, API, plasticisers, co-solvent and water were varied. Films were developed on glass plate by solvent casting method. Each batch was cut in rectangular shaped films of size 20x30 mm and packed in Al pouches. Films thickness, uniformity of mass and content were evaluated. Appearance of films was studied with stereoscopic microscope and polarized light microscope. Images of bulk film before and after cutting were taken under controlled conditions. All obtained images were embedded with a neural network Inception v3 and further classified with the use of data science methods such as distancing and hierarchical clustering. Film dissolution properties were also evaluated by the use of three methods including the modified USP IV apparatus as presented in the study of Speer et al.[1]

RESULTS

The optimisation step of buccal film development revealed the key factors affecting the quality of the valsartan loaded films. With the aid of neural network the evaluation of visual results was simplified and it enabled the objective decision making in the further steps of development. Films with higher API content variability were clustered in common class as a result of image analytics. Clustering of the images taken by polarized light microscope proposed the crystalline or amorphous state of the API in the films. Furthermore the formulations were categorised according to quality of the film edge. Dissolution testing revelled significant differences in the drug release rate of formulations. Two main release rate classes were identified within the formulation results.

CONCLUSION

The use of computer aided formulation development is slowly emerging in the field of pharmaceutical development. In this study was shown that image analytics can serve as a tool that can help guiding the development of the formulation in the first stage of development when the quality can be judged by the appearance of the films.

CHALLENGES

Image analytics alone was shown as a promising tool for guiding the film formulation development, however connecting the images to the film quantitative composition and comparing all data together is still a challenge.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the Chair of Pharmaceutical Technology for support of presented study.

REFERENCES

1. Speer I, Preis M, and Breitkreutz J, Dissolution Testing of Oral Film Preparations: Experimental Comparison of Compendial and Non-Compendial Methods. *International Journal of Pharmaceutics* 2019; 561: 124–34. doi:https://doi.org/10.1016/j.ijpharm.2019.02.042.

Isothermal dehydration of nitrofurantoin monohydrate II: A low frequency Raman spectroscopy study

P. Remoto[1], K. Bērziņš[1], S. J. Fraser-Miller[1], J. Rantanen[2], T. Rades[2], T. Korter[3], K. C. Gordon[1]
[1]Department of Chemistry, University of Otago, Dunedin 9016, New Zealand.
[2]Department of Pharmacy, University of Copenhagen, Copenhagen 1165, Denmark
[3]Department of Chemistry, Syracuse University, New York 13244, United States

PURPOSE

Raman spectroscopy offers a rapid, non-destructive, and relatively inexpensive method for measuring complex mixtures and systems, with the potential for identifcation, quantification, classification and process monitoring of pharmaceutical systems. The low-frequency Raman region (< 300 cm^{-1}) is of particular value to solid state analysis because it probes phonon/intermolecular modes which are extremely sensitive to changes in the solid sate of a compound or system.

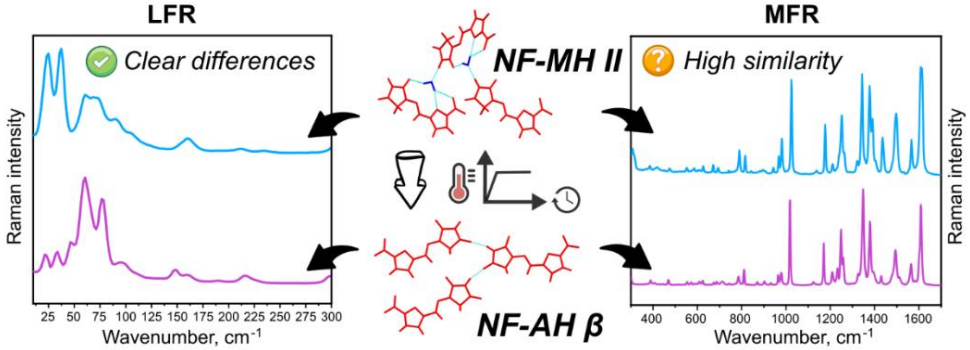
Previous reports have stated that the popular antibacterial medication, nitrofurantoin, exists in multiple solid-state forms, with at least two hydrates (I and II) and two anhydrous forms (α and β). In this work, we monitor the isothermal dehydration kinetics of nitrofurantoin monohydrate II using Raman spectroscopy contrasting the mid- (300 – 1800 cm^{-1}, intramolecular vibrations) and low-frequency (15 – 300 cm^{-1}, intermolecular vibrations) Raman regions.

METHODS

The isothermal dehydration experiments were carried out on powder nitrofurantoin monohydrate II. Raman spectra were collected using an in-house built system using a set of volume Bragg gratings to filter out the dominant Rayleigh scattering. The sample temperature was controlled using a variable temperature stage and controller. A timeseries of spectra were collected with a measurement window for each spectrum of 0.34 s. The resulting spectra were evaluated using multiple curve resolution.

RESULTS

The low-frequency regions (LFR) show very distinct changes in the dehydration of nitrofurantoin monohydrate II to nitrofurantoin anhydrous β in comparison to the mid-frequency Raman region.



The onset of dehydration at 110°C was detected on different timescales between the low- and mid-frequency Raman regions, in which the latter observed the dehydration onset ~ 100 s earlier.

CONCLUSION

This study demonstrates the solid-state form sensitivity advantages of the low-frequency Raman region for monitoring dehydration. The fast, sensitive, and non-destructive nature of this technique can be applied to in-situ measurements of pharmaceuticals and to a broader scope of research.

ACKNOWLEDGEMENTS

Acknowledgements to New Zealand eScience Infrastructure (NeSI) for the computational resources and the Dodd-Walls Centre for Photonic and Quantum Technologies for support.

Model based scale up of a spray drying process for a protein based product

P. Martin-Salvador[1,2], T. De Beer [2], A. Kumar [1]

[1]Pharmaceutical Engineering Research Group (PharmaEng), Department Pharmaceutical Analysis, Ghent University, Belgium
[2]Laboratory of Pharmaceutical Process Analytical Technology (LPPAT), Department Pharmaceutical Analysis, Ghent University, Belgium

PURPOSE

The design of large production scale spray drying processes is usually the labor-intensive experimental based result of scale up from lab or pilot scale tests. Although several pharmaceutical commercial products produced via spray drying are on the market (such as the inhaled insulin Exubera® before it was withdrawn), the drying of protein based products is challenging due to the potential loss of their physicochemical properties by spray drying related stresses.
Physical modelling can be applied to understand and predict the drying kinetics of the sprayed starting solution (droplets) and resulting particles under varying operating conditions. This knowledge framework can also be used as an efficient scale up tool hence reducing experimental campaigns.
Therefore, this project aims at developing modelling tools with special attention to predicting the history that every droplet and particle experiences during the drying process. This will allow spray drying process development with control of the drying stresses on the sensitive protein based products.

METHODS

For this study, the model of Parti and Paláncz, 1974 [1] is used. This is a 1-dimensional model in which the rate of drying is defined by the mass transfer from the droplet surface to the bulk of the drying air. Heat transfer is defined similarly. A critical moisture content splits the drying behaviour into 2 phases, above which droplets shrink and their loss of volume is defined by the moisture loss. The droplet becomes a particle below critical moisture content. Hence, its diameter remains constant and moisture loss creates pores. At this stage, the drying rate is hindered by a linear function that becomes zero at the equilibrium moisture content.

RESULTS

The model is first calibrated using proprietary data from a protein based product. It is then used to define the acceptable dimensions of a large scale spray dryer by matching the predicted droplet temperature profile inside the drying chamber of a lab scale spray dryer, known to result in a product with high protein activity. A sensitivity analysis was performed to confirm that reasonable changes in input parameters have contained effects on the temperature profile; namely we investigated the inlet flows and temperatures, mean droplet size, heat loss coefficient, and drying chamber diameter.

CONCLUSION

The model allowed predicting the potential large scale spray dryer dimensions leading to similar drying conditions as using the small scale spray dryer in which the protein based product is successfully dried.

CHALLENGES

This modelling approach is not without assumptions (e.g. both drying air and droplets follow a perfect plug flow through the chamber). Limitations of this type of model are discussed extensively, for example, in [2]. In the future, we plan to extend the model with a population balance, which will increase the ability of the model to make more accurate predictions.

REFERENCES

1. M. Parti, B. Paláncz, Mathematical model for spray drying, *Chemical Engineering Science*, 1974, 29(2):355-362, doi:10.1016/0009-2509(74)80044-8.
2. A. Razmi, H. Jubaer, M. Krempski-Smejda, M. Jaskulski, J. Xiao, X. Dong Chen & M. Wai Woo (2021) Recent initiatives in effective modeling of spray drying, *Drying Technology*, DOI: 10.1080/07373937.2021.1902344

Observer design for granule moisture in the consigma™-25 fluid bed dryer

Selma Celikovic[1,2], Jakob Rehrl[1], Stephan Sacher[1], Martin Horn[2], Johannes Khinast[1,3]

[1] Research Center Pharmaceutical Engineering GmbH (RCPE), 8010 Graz, Austria
[2] Institute of Automation and Control, Graz University of Technology, 8010 Graz, Austria
[3] Institute of Process and Particle Engineering, Graz University of Technology, 8010 Graz, Austria

PURPOSE

Continuous pharmaceutical manufacturing offers several advantages, such as increased production speed and efficiency. ConsiGma™-25 is a continuous production line integrating a twin-screw granulator, fluid bed dryer (FBD), and tablet press. The granule moisture after the FBD is considered to be an intermediate critical quality attribute. In the common operation mode, the FBD is operated with constant drying parameters. In order to optimize the performance of this unit, and to make it robust against potential process disturbances, an adequate control concept needs to be developed. Such a sophisticated feedback control concept would keep the granule moisture close to the reference value by adjusting the FBD parameters, such as drying time or temperature. However, in order to develop a control concept, a real-time granule moisture measurement is required. The FBD consists of six dryer cells and a real-time measurement of this quantity is expensive and potentially not feasible in all of the cells. Therefore, a first step toward the controller development is to design an observer to predict the granule moisture from the acquired process parameters in real-time.

METHODS

In order to design an observer to predict granule moisture, a model of a dryer cell is required. This model needs to be kept as simple as possible to allow its real-time execution in parallel with the process. Differential equations based on the physical laws suggested in [1] are further developed and simplified, leading to a dynamic model of the FBD. The drying parameters provided via sensors are considered as model inputs. The measured granule temperature is considered as a model output. The proposed state observer provides an estimate of the granule moisture based on the process model and the available real-time measurements.

RESULTS

A trivial observer, i.e., a copy of the FBD model is implemented in the simulation. A pilot plant test run is executed. During this run, one dryer cell is equipped with a near infrared (NIR) spectrometer, measuring the granule moisture in this cell for comparison purposes. A good agreement between the measured and predicted granule moisture is achieved.

CONCLUSION

The predictive quality of the FBD model is confirmed by the results of the trivial observer. Both, the granule moisture and the granule temperature are estimated reasonably well. However, the observer performance is expected to be further improved by including the measured granule temperature as a correction term.

CHALLENGES

The FBD model based on the physical laws is strongly non-linear. In contrast to the trivial observer, the development of more sophisticated observer concepts is not straight forward, and further model simplifications need to be done.

ACKNOWLEDGEMENTS:

This work was funded through the Austrian COMET–Competence Centres for Excellent Technologies programme. The COMET programme is operated by the Austrian Research Promotion Agency (FFG) on behalf of the Federal Ministry for Transport, Innovation and Technology (BMVIT) and the Federal Ministry for Digital and Economic Affairs (BMDW). Our projects are also funded by Land Steiermark and the Styrian Business Development Agency (SFG). This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 870062.

REFERENCES

1. Rehrl J., Sacher S., Horn M., Khinast J., End-Point Prediction of Granule Moisture in a ConsiGma™-25 Segmented Fluid Bed Dryer. *Pharmaceutics*. 2020*; 12(5), 452*. doi:10.3390/pharmaceutics12050452.

Visualising features of liquid transport through coated tablets using terahertz pulsed imaging

R. Dong[1], J.A. Zeitler[1]

[1]Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, CB3 0AS, UK

PURPOSE

The effectiveness of coating is evaluated via in vitro dissolution testing where profiles of percentage drug release over time is recorded. However, there is a lot more going on even before the first drug molecule in the core dissolves and gets diffused out of the tablet. It is of great research interest to see also how liquid propagates through the coating layer and crosses the coating-core interface, how the gelling of the coating layer develops and affects the subsequent flow in tablet core.

Different techniques have been used in this pursuit, including MRI methods, thermo gravimetric analysis, UV imaging, to name a few. Terahertz time-domain spectroscopy (THz-TDS) and terahertz pulsed imaging (TPI) stand out as safe, non-destructive and fast measuring techniques. There has been a commercial TPI system on the market that can perform analysis and direct measurement on tablet coating thickness[1]. In recent years, TPI has also been demonstrated to be able to visualize the liquid transport process for uncoated tablets at sub-second time resolution[2]. This study takes a step forward and employed TPI to investigate the liquid transport behaviour of, for the first time, coated tablets in real time measurements, aiming to provide extra insights into the role of coating on the tablet performance.

METHODS

The tablet core is made of pure MCC (Avicel® PH-102), which was prepared at a range of porosities by die compaction. Opadry®II clear, a PVA-based immediate release coating blend, was used as coating material. All tablets were coated on only one side in a vacuum compression moulding system (MeltPrep GmbH). The coating thickness was analysed using an automated TPI system (Imaga 2000, TeraView) and then each individual tablet was placed in a customized flow cell, where the coated surface of tablet is exposed to a steady flow of water from below. Above the flow cell, a commercial time-domain terahertz system (TeraPulse 4000, TeraView Ltd) with a reflection probe was used to acquire the terahertz time-domain waveforms while water penetrated the tablet.

RESULTS

Distinctive stages of liquid transport are consistently observed across all coated samples from terahertz waveforms: a) Water propagating through the coating layer, b) Water being stopped by the core-coating interface while the interface being dissolved over time, c) Water breaching the interface and continue to penetrate into the tablet core. These stages can then be quantified and compared with each other for relative contribution in delaying the drug dissolution.

The liquid penetration rates through coating were found to be related to the surface peak intensity of coating from TPI scan as well as coating uniformity, while the 'breaching' time of interface is found to be positively correlated to the ratio of reflectivity between the outside and inside of the coating interfaces, and the water penetration rate through the core, though much slowed still strongly correlated to the core porosity. The kinetics of each stage of flow can in turn be signalled by other parameters.

CHALLENGES

The technique used to apply coating in this study is chosen out of convenience to demonstrate the feasibility of the methodology and is not a close resemblance of film-coating that is commonly used in the industry. The features resolved thus may be dependent on how the coating is applied. The quality of the melted coating was also found to be highly correlated to the core porosity. Would this also be the case for other more common coating techniques including film-coating?

REFERENCES

1. Shen, Y.C. Terahertz pulsed spectroscopy and imaging for pharmaceutical applications: A review. *International Journal of Pharmaceutics* 2011, *417*, 48-60. doi: 10.1016/j.ijpharm.2011.01.012.
2. Markl, D., Wang, P., Ridgway, C., Karttunen, A.P., Bawuah, P., Ketolainen, J., Gane, P., Peiponen, K.E., Zeitler, J.A. Resolving the Rapid Water Absorption of Mesoporous Functionalised Calcium Carbonate Powder Compacts by Terahertz Pulsed Imaging. *Chemical Engineering Research and Design* 2017, pp. 1-10. doi: 10.1016/j.cherd.2017.12.048.

Parallel Session D: Amorphous & Stability II

Co-amorphous drug-phospholipid systems – bridging the gap between amorphous solid dispersions and lipid based drug delivery

Keyoomars Khorami[1], Anette Müllertz[1] and Thomas Rades[1,2]
[1] Department of Pharmacy, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark
[2] Faculty of Science and Engineering, Åbo Akademi University, FI-20521 Turku, Finland

PURPOSE

The purpose of the study is to investigate the potential use of lecithin as co-former to develop co-amorphous solid dispersions for a range of poorly water-soluble drugs. We envisage co-amorphous drug-phospholipid systems as a mixture of amorphous solid dispersions and lipid based drug delivery systems. As such, it is hypothesized that they form an excellent basis both for poorly water-soluble lipophilic compounds ("grease ball" molecules) and poorly water soluble compounds with high melting points ("brick dust" molecules), and thus may be broadly applicable.

METHODS

Initially, equimolar drug – phospholipid mixtures were prepared with different preparative techniques, including quench cooling (QC), solvent evaporation (SE) and vibrational ball milling (BM). The solid-state form of the resulting systems was analyzed by differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD). Furthermore, co-amorphous drug-phospholipid mixtures at molar ratios of 20:1, 10:1, 5:1, 3:1 2:1, 1.5:1 1:1 1:1.5, 1:2, 1:3, 1:5 and 1:10 were prepared by SE and spray drying (SD). The solid-state form and physical stability of the systems were analyzed by DSC, hot stage microscopy and XRPD during storage at room temperature, both at 50-75% RH and at dry conditions.

RESULTS

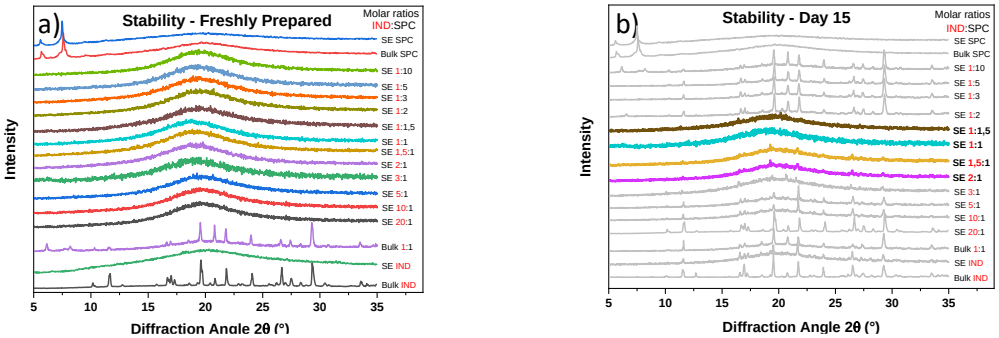


Figure 1: Diffractograms of (a) freshly prepared IND-SPC systems (b) IND-SPC systems at day 15.

IND and CCX – phospholipid systems resulted in amorphous solid dispersions using all three preparation techniques. SE data was in agreement with Gautschi *et al.* 2015 [1].

- CNZ and FBT – phospholipid systems were not able to support the formation of amorphous mixtures using any of the three preparation methods at equimolar ratio.
- IND: Soy phosphatidyl choline (SPC) at molar ratios of 1:1 and 1,5:1 prepared with SE and SD were the most physically stable systems (stability study is ongoing).

CONCLUSION

Solvent-free preparation methods such as BM, cryo-BM and QC are feasible methods to form co-amorphous drug-phospholipid complexes (for some drugs at equimolar ratio). The amorphous systems prepared by SE and SD showed higher physical stability than the pure amorphous drug close to and at the equimolar ratio of IND:SPC.

CHALLENGES

Degradation of drug-phospholipid systems prepared by BM. Quantification of the degradation by HPLC-CAD.

ACKNOWLEDGEMENTS

We would like to thank Phospholipid Research Center (Heidelberg, Germany) for the financial support and Lipoid GmbH (Ludwigshafen, Germany) for providing samples of phospholipids.

REFERENCES

1. Gautschi N, Van Hoogevest P, Kuentz M. Amorphous drug dispersions with mono- and diacyl lecithin: On molecular categorization of their feasibility and UV dissolution imaging. International journal of pharmaceutics. 2015;491(1-2):218-30.

Solvent influence on manufacturability, phase behavior and morphology of amorphous solid dispersions prepared via bead coating

E. Boel[1], F. Giacomini[1], G. Van den Mooter[1]

[1]Department of Pharmaceutical and Pharmacological Sciences, Drug Delivery and Disposition, KU Leuven, Leuven, Belgium

PURPOSE

Bead coating or fluid-bed coating serves as an auspicious solvent-based amorphous solid dispersion (ASD) manufacturing technique in respect of minimization of potential physical stability issues.[1] However, the impact of solvent selection on the bead coating process and its resulting pellet formulation is, to the best of our knowledge, never investigated before. This study therefore aims to investigate the influence of the solvent on the bead coating process itself (*i.e.* manufacturability) and on solid-state characteristics of the resulting ASDs coated onto beads. For this purpose, the drug-polymer system felodipine (FEL)-poly(vinylpyrrolidone-co-vinyl acetate) (PVP-VA) was coated onto microcrystalline cellulose (MCC) beads from acetonitrile (ACN), methanol (MeOH), ethanol (EtOH), acetone (Ac), 2-propanol (PrOH), dichloromethane (DCM) and ethyl acetate (EthAc).

METHODS

The crystallization tendency of FEL in each of the selected solvents was evaluated with spray drying and subsequent modulated differential scanning calorimetry (mDSC) analysis. Equilibrium solubility of FEL was determined in the different solvents and quantification of concentrations was done by High Performance Liquid Chromatography (HPLC). Film casting was performed as screening test to gain initial insight into drug-polymer miscibility of FEL-PVP-VA systems casted from various solvents and ASDs were manufactured with bead coating. Their phase behavior was evaluated by means of mDSC, X-ray powder diffraction (XRPD) and thermogravimetric analysis (TGA). Scanning electron microscopy (SEM) was applied to visualize possible surface crystallization and to evaluate coating thickness and morphology.

RESULTS

Differences in crystallization behavior were found for FEL spray dried from different solvents, and the glass forming ability (GFA) classification even depends on the solvent used. With film casting, the highest possible FEL weight fractions that still result in a one phase amorphous system, hence drug-polymer miscibility, differed for the various solvents. In contrast, with bead coating, the highest possible drug loadings were found to be equal for all solvents used.

CONCLUSION

A drug loading screening approach with bead coating revealed analogous ability to manufacture high drug-loaded ASDs from the different organic solvents. The results show no correlation with crystallization tendency or with equilibrium solubility of the drug in the different solvents, nor with the solvent-dependent drug-polymer miscibility obtained from film casting experiments. Distinct coating morphologies were however observed for PVP-VA and FEL-PVP-VA ASDs deposited onto beads from the various solvents.

CHALLENGES

The investigation on why distinct coating morphologies are obtained for PVP-VA and FEL-PVP-VA ASDs coated onto MCC beads from the various solvents.

ACKNOWLEDGEMENTS

The authors would like to thank Fonds Wetenschappelijk Onderzoek (FWO) for financial support.

REFERENCES

1. Mugheirbi NA, O'Connell P, Serrano DR, Healy AM, Taylor LS, Tajber L. A comparative study on the performance of inert and functionalized spheres coated with solid dispersions made of two structurally related antifungal drugs. *Molecular Pharmaceutics*. 2017;14:3718-3728. doi 10.1021/acs.molpharmaceut.7b00482.

The metastable form of theophylline observed during phase transitions

Qi Li[1], Eduardo. M. Paiva[2], Adam J. Zaczek[1], J. Axel Zeitler[1]

[1]Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK.
[2]Institute of Chemistry, State University of Campinas, Campinas, Brazil.

PURPOSE

The transition between theophylline form II (FII) and the monohydrate form (FM) depends on the ambient temperature and relative humidity (RH). Studies show that there is a metastable form III (FIII) during the dehydration of FM to FII (FM→FIII→FII).[1] Due to the very unstable nature of FIII, its structure has not previously been reported. This project utilised experimental methods combined with density functional theory (DFT) simulations to characterise the structural changes before, during, and after the dehydration.

METHODS

FII was purchased from Sigma-Aldrich and was used as received. FM was synthesised from FII according to the method described in the work of Pinon et al.[2] Powder x-ray diffraction (PXRD), mid-infrared absorption with attenuated total reflectance, Scanning Electron Microscopy, and Raman spectroscopy were applied to characterise the structural changes before and after the dehydration of FM. Terahertz spectroscopy was applied to track the dehydration process of FM under N_2 purging, and terahertz transmission spectra were also acquired for FII, FM, and FIII. All calculations were performed using the CRYSTAl17 software package with the PBE-D3 density functional and the 6,311G(d,p) basis set. Two possible FIII structures were proposed: Both excluded water from FIII, while one lattice was fixed (A) and the other was fully relaxed (B).

RESULTS

Results from experimental methods clearly proved the change of structure after dehydration, including the loss of transparency of the single crystals, the noticed differences of the PXRD patterns, Raman, and terahertz spectra. The first terahertz spectrum showed pronounced spectral features at 1.7 THz and 2.9 THz, while the intensities both decreased drastically with time. The computational results predicted that the two features are water vibrations along the a and c-axis, which correspond well with the dehydration process. The final spectrum reflected the very disordered structure of FIII with no clear features in the frequency range of interest, while simulated spectrum of FIII-B also only had very weak modes below 3 THz. The sample transformed to FII after being kept at around 20°C and 40 %RH for two days.

CONCLUSION

The combination of experimental and computational methods closely investigated the metastable state of theophylline during the dehydration of FM and its transition to FII. All methods detect the form and also agree on the fact that it is very disordered and very unstable. The simulations successfully predict the vibrations that are important for the dehydration, and also provide a possible structure of FIII.

CHALLENGES

The results showed FIII is a very disordered and unstable structure, while the predicted structure was calculated under the restrictions of symmetry group and also the absolute zero assumption. Maybe ab initio molecular dynamics is a better tool for describing molecular motions of the dehydration process?

ACKNOWLEDGEMENTS

QL would like to thank the Chinese Scholarship Council (CSC) for funding her Ph.D. studies.

REFERENCES

1. Phadnis N., Suryanarayanan R., Polymorphism in Anhydrous Theophylline – Implications on the Dissolution Rate of Theophylline Tablets. *Journal of Pharmaceutical Sciences*. 1997;86(11):1256-1263. doi: 10.1021/js9701418.
2. Pinon A. C., Rossini A.J., Widdifield C.M., Gajan D., Emsley L., Polymorphism of Theophylline Characterized by DNP Enhanced Solida-State NMR. *Molecular Pharmaceutics*. 2015;12(11):4146-4153. doi: 10.1021/acs.molpharmaceut.5b00610.

Multi-Core Magnetic Nanocarriers for Drug Delivery

Č. Dragar[1], T. Potrč[1], S. Nemec[1,2], R. Roškar[1], S. Pajk[1], S. Kralj[2], P. Kocbek[1,*]

[1] Faculty of Pharmacy, University of Ljubljana, 1000 Ljubljana, Slovenia;
[2] Department for Materials Synthesis, Jožef Stefan Institute, 1000 Ljubljana, Slovenia;
[*] Correspondence: petra.kocbek@ffa.uni-lj.si

PURPOSE

Among several types of nanostructures, iron-oxide-based magnetic nanocarriers (MNCs) have shown great potential for their use as targeted drug delivery systems[1]. However, the applicability of individual magnetic nanocrystals is limited due to ineffective spatial guidance, poor colloidal stability, low drug loading, and inadequate drug release[1,2]. Thus the main purpose of our study was to developed and characterize MNCs formulation with multiple γ-Fe_2O_3 nanocrystals in the core, which is expected to exert improved properties with respect to the individual magnetic nanocrystals.

METHODS

The innovative formulation of MNCs was prepared with a novel one-pot preparation method, based on hot homogenization of a hydrophobic phase with a nonpolar surfactant into an aqueous phase, using ultrasonication. The solvent-free hydrophobic phase (tetradecan-1-ol, γ-Fe_2O_3 nanocrystals, model drug, and surfactant) was dispersed into a warm aqueous surfactant solution, to form an emulsion with small droplets. Then, a pre-cooled aqueous phase was added, resulting in the formation of solid MNCs, which were characterized regarding their hydrodynamic size (PCS), zeta potential (LDA), morphology (TEM), magnetic susceptibility (VSM), composition (TGA), drug loading, and drug release.

RESULTS

The prepared MNCs consisted of ~20 % (w/w) γ-Fe_2O_3 nanocrystals in the core. They were spherical with mean hydrodynamic sizes <160 nm, drug loading up to 7.65 % (w/w), and showed good colloidal stability. The selection of surfactant was shown to be crucial, since the use of less hydrophobic surfactant in the hydrophobic phase enabled prolonged drug release, while the use of more hydrophobic surfactant prevented the drug release. Moreover, the surfactant selection influenced also MNC morphology and surface charge, while MNC size, iron oxide content, and drug loading were not affected[2].

CONCLUSION

The innovative formulation of multi-core MNCs for drug delivery with good colloidal stability and magnetic susceptibility was successfully prepared by a novel one-pot preparation method. The selection of the surfactant was shown to have an important influence on the key characteristics of MNCs, including drug release, thus further development is needed to achieve controlled drug release from such MNCs.

CHALLENGES

The drug loading and tailored drug release from multi-core MNCs remain challenging, thus our current research is focused on mesoporous silica shell-coated MNCs to improve drug loading and achieve the controlled drug release.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the Slovenian Research Agency for research core funding No. P1-0189 and No. P2-0089, and for the funding of projects No. J1-7302 and No. J3-7494.

REFERENCES

1. Kralj et al. Design and fabrication of magnetically responsive nanocarriers for drug delivery. *Current Medicinal Chemistry*. 2017; 24 (5): 454-469.
2. Dragar et al. Bioevaluation methods for iron-oxide-based magnetic nanoparticles. *Materials.* 2019; 12 (3): 1-14.