Monday, June 20th 2016

3:00 - 5:00 PM	Walking Tour, Sponsored by Huxley Bertram
5:00 - 7:00	Welcome Reception, Sponsored by Huxley Bertram

Tuesday, June 21st 2016

8:15-9:00 AM	Registration & Breakfast
9:00-9:10	Welcome: Kevin Bittorf CSF President
9:10-10:00	Keynote: James Elliott, University of Cambridge: Computational Prediction of Powder Tablettability: from Molecular to Continuum Scales
10:00-10:50	Keynote: John Strong, Abbvie: Prediction of Drucker-Prager-cap model parameters for mixtures from single component data
10:50-11:15	Break
11:15-12:05 PM	Keynote: Antonios Zavaliangos, Drexel: On the Use of the Compaction Simulator for Understanding Sticking Propensity
12:05-1:15	Lunch
1:15-1:55	Alberto Cuitino, Rutgers: Toward Predicting Tensile Strength of Pharma Tablets by Ultrasound Measurement in Continuous Manufacturing
1:55-2:35	Thomas Baxter, Jenike: When powders flow like water: two-phase flow modeling of a press feed system
2:35-3:15	Peter Wildfong, Duquesne: Investigation of the Compaction-Induced Structural Changes to Theophylline Using PXRD and Total Scattering Analysis
3:15-3:40	Break
3:40-4:20	Serena Schiano (Winner of last year's poster presentation), University of Surrey: The Effect of Roll Compaction On Flowability and Tableting Behavior of Granules
4:20-5:00	William Ketterhagen, Pfizer: Prediction of Lubrication-Based Tensile Strength Reduction via DEM and Compartment Model Approach
5:00	Concluding remarks
5:00-6:45	Poster Presentation and Cocktail Hour, Sponsored by Takeda
7:00-9:00	Awards Dinner: Kinsale, Sponsored by Vertex

Wednesday, June 22nd 2016

8:30-9:00 AM	Registration & Breakfast
9:00-9:10	Welcome to Day 2
9:10-10:00	Keynote: Pingjun Tan, Vertex Pharmaceuticals: Understanding of tooling effects on powder mechanical behavior during the uniaxial compression process
10:00-10:20	Break
10:20-11:45	User Presentations 1) Sean Garner, AbbVie 2) Debbie Hooper, Greenwich/Pfizer 3) Vivienne Gray, BMS 4) Marco Bellini, Berlin Free University 5) Jovana Radojevic, Drexel 6) Balazs Demuth, Budapest/Janssen
11:45-1:00 PM	Lunch
1:00-1:40	Gerard Klinzing, Merck: Optimizing the Design of Tablets from Mechanical Properties to Shape
1:40-2:20	Jeff Katz, Amgen: Full Out-of-Die Compressibility And Compactibility Profiles From 2 Tablets
2:20-3:00	Vincent Mazel, Bordeaux: Evolution of the Die-Wall Pressure During The Compression of Biconvex Tablets: Experimental Results and Comparison
3:00-3:20	Break
3:20-4:00	Jeff Hemenway, Gilead: Application Of Compaction Simulation As A Response Factor In Formulation And Process Development Does: A Case Study For A High Drug Loading Roller Compacted Product
4:00-4:40	Balázs Démuth, Budapest Univ. of Technology & Economics: Downstream process of an electrospun solid dispersion
4:40-5:00	Concluding Remarks

JUNE 21ST
9:10-10:00

Computational Prediction of Powder Tablettability: From Molecular to Continuum Scales

James Elliott, University of Cambridge

The relationship between the bulk flow and compaction behaviour of powders and the size, shape and physical properties of their constituent particles is complex and poorly understood from a fundamental point of view. In particular, for pharmaceutical drug products, it is desirable to know whether a particular compound or formulation will be straightforward to manufacture into a tablet at a very early stage in development, before significant quantities of material are available for experimental analysis. In this talk, I will survey a range of modelling techniques, from the molecular through to the continuum scale, which can be used to predict powder properties, and how these can be integrated into a multiscale modelling framework that can be validated against experiment. Discrete (or distinct) element modelling techniques provide a particle-level description of the powder, but rely on accurate parameterisation of contact models which is increasingly obtained from atomistic or first-principles modelling techniques. Continuum modelling techniques, such as the finite element method, can be used to analyse much larger amounts of powder through the use of constitutive relations parameterised from experiment or particle-based models. These recent advances in numerical models have enabled the optimization of process and materials design in pharmaceutical powder systems.

9:10-10:00

Prediction Of Drucker-Prager-Cap Model Parameters For Mixtures From Single Component Data

John Strong, Abbvie

In the evolution of drug product development, formulation design has progressed from more of a paint-by-numbers approach to a materials science exercise that considers the properties that individual components add to the blend. The ability to predict at an early stage the manufacturability (e.g., tabletability) and performance of a given blend greatly facilitates the robust and efficient development of formulation drug products. In pursuit of this goal, pharmaceutical scientists have attempted, and to some extent achieved, blend models which utilize individual component data to predict blend behavior. These blend models have spanned a range of complexity from simple lever rules to physicochemical mechanistic approaches. An example of a semi-empirical phenomenological model that has shown some utility is a tablet tensile strength prediction based on individual component tensile strengths. Another popular modeling approach is Finite Element Analysis using the Drucker-Prager/Cap (DPC) model to predict tablet properties such as density distribution. In this work, we hypothesized that the extraction of the DPC model parameters for binary mixtures could be characterized from the individual components of the mixture. This study explored the use of a simple geometric mixing rule approach to predict the DPC model parameters for binary mixtures from the single components. The validity of the geometric mixing rule approach was verified by comparing the loading-unloading behavior for the compaction of cylindrical flat-faced tablets at various weight-to-weight concentrations from both experimental and finite element simulation results. Further verification of the approach was achieved by comparing density distributions results from micro-computed tomography (μCT) and the FEM. The results show that the proposed mixture rule approach can be used to adequately predict the stress and density distributions of binary mixtures based upon the properties of the single component powders.

11:15-12:05

On the Use of the Compaction Simulator for Understanding Sticking Propensity

Antonios Zavaliangos, Drexel

The issue of sticking is often manifested in production after a significant number of tablets is compacted. In this presentation we will first explored various techniques available in literature that claim to evaluate the propensity of formulations for sticking. Emphasis will be given to the techniques that can be realized on the compaction simulator (not an actually production press). Some new approaches to this problem will also be presented and evaluated.

June 21st
1:15-1:55

Toward predicting tensile strength of pharmaceutical tablets by ultrasound measurement in continuous manufacturing

Alberto Cuitino, Rutgers

Ultrasound testing has been recently introduced as a non-destructive method to measure tablet strength. This requires the measurement of the time of flight of an acoustic wave pulse traveling through the specimen from the transmitting transducer to the receiving one. Young's modulus can be extracted by measuring the speed of sound of the transmitted ultrasound signal for a known sample size. We can then relate the Young's modulus with the mechanical strength of the compacted granular solids, which is usually tested by destructive methods such as diametrical compression test. These destructive tests not only damage the structure of a tablet and cause loss of product, but also provide limited information about the mechanical state of a tablet and cannot be included in an on-line process.

In this study, cylindrical tablets were prepared in two ways: batch and continuous. The formulation was kept constant (90% lactose monohydrate, 9% acetaminophen, and 1% magnesium stearate), while the compaction force and level of shear strain varied. Young's modulus and tensile strength were measured using ultrasound testing and hardness tester, respectively. It was observed that, as the blend was exposed to an increasing level of shear strain, the speed of sound values decreased and the tablets became both softer and mechanically weaker. We also noticed that in order to predict the hardness of a tablet, we need to take two properties into account: Young's modulus and relative density of that tablet. Ultrasound testing was found to be very sensitive in differentiating tablets with similar formulation but produced under different processing conditions, thus, providing a fast, and non-destructive method to be placed on/at-line after tablet production for hardness prediction.

1:55-2:35

When powders flow like water: two-phase flow modeling of a press feed system

Thomas Baxter, Jenike

Production rate limitations can develop when feeding fine powders to a press, granulator or mill. These powder feed rate limitations arise when the powder interacts with entrained air, resulting in adverse "two-phase" (powder-air) flow effects. Two-phase flow problems can result in out-of-specification tablets, requiring operating at below target production rates. A critical step in developing a robust process, including conducting Quality by Design (QbD) studies, is modeling two-phase flow behavior in the press feed system.

Two-phase flow risks can be accounted for during process design by:

- Measuring key flow properties to use as inputs in the two-phase flow model;
- Computational modeling the two-phase flow effects based upon first principle models;
- Evaluating potential corrective actions through two-phase modeling.

The two-phase modeling software uses key powder flow properties, including:

- Permeability
- Compressibility
- Specific gravity of a particle
- Wall friction angles (phi-prime, f')
- Effective angle of internal friction (delta, d) measured via a cohesive strength test.

The two-phase model as includes the press feed system geometry and process parameters as inputs. The model outputs include parameters that dictate two-phase flow behavior, such as vertical solids stress, interstitial gas pressure, bulk density and normalized gas pressure gradient. These modeling outputs are used to predict whether flow problems will occur and analyze potential corrective actions, including modifying the geometry of the press feed system, increasing the permeability of the powder and adding venting.

June 21st
4:20-5:00

Prediction of Lubrication-Based Tensile Strength Reduction via DEM and Compartment Model Approaches

William Ketterhagen, Pfizer

Lubricants such as magnesium stearate are typically added to the powder blend or granulation in the manufacture of pharmaceutical tablets and capsules in order to reduce the friction between the powder and the tablet press or encapsulator components. The presence of the lubricant is generally necessary to improve manufacturability of the dosage form, but if the lubricated blend is exposed to excessive shear strain during processing prior to tableting or encapsulation, the lubricant can become too highly dispersed, resulting in adverse effects on quality attributes of the final dosage form. These effects can include an increase in wetting contact angle, a slowdown in disintegration and dissolution, and a reduction in tensile strength.

In this work, two different modeling approaches are described to quantitatively predict the extent of lubrication in a powder feed system and the resulting impact on quality attributes of interest. In the first approach, a framework using the discrete element method (DEM) is described where a companion study in a lab-scale, high-shear mixer is used to map the extent of lubrication predicted in the DEM model to an experimentally relevant tensile strength prediction. In a second modeling approach, a compartment modeling approach is developed to model the powder flow pattern and predict the lubrication-based tensile strength reduction. Parameter estimation is conducted through the use of a separate experiment utilizing an input step change in powder feed from undyed to dyed material. The tensile strength predictions from each of these modeling approaches are compared to experimental tensile strength data determined by compaction simulation of stratified samples from batch manufacture.

June 22nd
9:10-10:00

Understanding of tooling effects on powder mechanical behavior during the uniaxial compression process

Pingjun Tan, Vertex Pharmaceuticals

1:00-1:40

Optimizing the Design of Tablets from Mechanical Properties to Shape

Gerard Klinzing, Merck

Tablet dosage forms comprise a significant portion of global pharmaceutical sales. Despite this prevalence, elegance defects still arise throughout production. Therefore, new tablet formulations must be optimized to minimize the incidence of tablet defects which negatively impact productivity and could result in patient complaints. Defects or failure modes such as chipping, abrasion, and sticking are all related to a tablet’s microstructure which is innately a function of the material properties of the drug product composition. Consequently, the microstructure of a tablet is a key physical attribute which must be better understood in order to reduce defects associated with downstream processes such as film coating and packaging. Calibrated computational models provide a method to understand how density gradients vary within tablets. Tablet images of different shapes, sizes, and those incorporating embossing can be modeled computationally thus minimizing the time needed for optimal tool selection. These computational models may be used to predict specific microstructural features which will help optimize the shape and size of marketed products.

Current work examines how different materials affect density distributions in tablets of different shapes. Materials are classified into different groups by their mechanical behavior and new materials are developed computationally without the need for additional model calibration. In addition, an optimization software was utilized to determine robust tablet shapes and embossing features. Future works will provide guidance on how tablet shape and density affect the resulting mechanical properties of the tablet such as strength and damage.

June 22nd
1:40-2:20

Full Out-of-Die Compressibility and Compactibility Profiles from 2 Tablets

Jeff Katz, Amgen

Compressibility and compactibility profiles are frequently used to provide insight into the fundamental mechanical behavior of powders during compaction. From a data collection prospective, generating an out-of-die compressibility profile and the corresponding compactiblity profile requires compacting separate tablets at every pressure of interest. These methods are time consuming and also require a considerable amount of raw material for testing. In this work, a method is presented that can be used to generate full out-of-die compressibility and compactiblity profiles using the data from only 2 tablets.

Three commonly used pharmaceutical excipients were evaluated due to differences in their predominant deformation behavior. Data were collected using a Huxley-Bertram compaction simulator (Model #HB1088). Each material was compacted at speeds ranging from 4-400 mm/s using constant loading/unloading rates, and using compression profiles simulating a Hata 38 Station press at speeds ranging from 25 – 75 RPM. One tablet was compacted at the maximum pressure of interest and a second tablet at a relatively low pressure. The in-die data collected during compaction with the maximum pressure of interest and the solid fraction change after ejection for both tablets were used to generate a profile equivalent to a complete out-of-die compressibility profile. After measuring the tensile strengths of each tablet, a compactiblity profile was produced by fitting the out-of-die porosity and tensile strength data to the Ryshkewitch-Duckworth equation. This method generated accurate out-of-die compressibility & compactiblity profiles for the materials studied. Not only is this technique computationally simple, but in cases where only small amounts of raw material are available, this method allows a detailed understanding of a material's mechanical behavior to be assessed.

2:20-3:00

Evolution of the die-wall pressure during the compression of biconvex tablets: experimental results and comparison to FEM simulation

Vincent Mazel, Bordeaux

Capping is a classical manufacturing problem for tablets, which is known to affect more biconvex tablets than flat-faced ones. One reason could be the development of a higher residual die-wall pressure during unloading. Unfortunately, contradictory results were published on the subject. In this work, the evolution of the die-wall pressure during the compaction of biconvex tablets was studied experimentally and using FEM modelling. It was compared with the case of flat-faced tablets.

Experimental and numerical results showed that, during the compression of biconvex tablet, a lower maximum die-wall pressure and a higher residual die-wall pressure were obtained compared to the case of flat-faced tablet. Moreover, both approaches showed, for biconvex tablets, a temporary increase of the die-wall pressure at the end of the unloading phase. FEM demonstrated that this phenomenon was due to a gradual loss of contact between the punch and the tablet from the side to the center. This complex unloading behavior causes the temporary increase of the die-wall pressure and the development of a shear stress between the convex part and the land of the tablet. This could explain the capping tendency of biconvex tablets.

JUNE 22ND
3:20-4:00

Application of Compaction Simulation as a Response Factor in Formulation and Process Development DoEs: A Case Study for a High Drug Loading Roller Compacted Product

Jeff Hemenway, Gilead

Presented here is an overview of the practical application of compaction simulation to assess fundamental mechanical properties and evaluate high speed press replication performance for final powder blends from designed experiments and other key development batches. This example is presented as a case study for a relatively high drug loading BCS class 2 compound in a tablet formulation that is manufactured using a roller compaction process. Compaction simulation was used to study the mechanical properties of the DoE final powder blends at commercially relevant speeds. Tabletability, compactability and compressibility profiles were generated using 10 mm flat-faced tooling and a single edge sign wave profile at a maximum punch velocity of approximately 680 mm/s and 10 ms dwell time. Results were analyzed using the Design Expert, version 9 (Stat-Ease Inc., Minneapolis, MN, USA). A stepwise regression by backward elimination was used to identify significant responses with $\geq 95\%$ confidence (i.e., $p \leq 0.05$). Compression replication was used to evaluate high-speed compression performance. Punch profiles were derived for a model commercial scale press and product specific tooling using Press Profiler software version 4.0.9 (Phoenix Calibration & Services Ltd, West Midlands, UK). Compression profiles were generated using product specific tableting parameters at simulated press speeds of 75 rpm with maximum punch velocities of approximately 800 mm/s and 6 ms dwell times.

A formulation optimization study was conducted as a five factor, fractional factorial 25-1 design of experiments using a fixed roller compaction process. The design factors studies were drug loading, API powder properties (e.g. mean particle size), lubrication level, excipient A level, and excipient B grade. A predictive model was identified for the effect of formulation design factors on tabletability. The statistical analysis showed main effects for lubrication level, excipient A level and API particle size and an interaction between drug loading and excipient B grade. Additional lubrication sensitivity studies were conducted to further assess the compression risk associated with a wider range of lubrication levels and final blending times for the optimized formulation. High speed compression replication was used to evaluate the final blends from the lubrication sensitivity batches. Higher lubrication levels and longer blend times result in decreased force/hardness profiles and capping on hardness testing (w/o precompression). The addition of between 10 and 25% precompression resolved issue with capping on hardness testing and resulted in acceptable compression profiles on the simulated press at speeds up to 75 RPM (>2500 tpm) for all lubrication levels at the longest blend times. The results predict coverage of a suitable range for the commercial scale final blending process.

The roller compaction process was developed using a four-factor central composite design to study the factors of roller compaction force, roll gap, roll speed, and screen size on process and product performance. Statistical analysis of the mechanical properties of the final blends resulted in relatively weak models, likely due to the presence of complex interactions, but the overall effects of the design factors on tabletability were clearly seen. High speed replication studies for the center point and extreme over/under compacted final blends demonstrated acceptable compression performance for the process parameter ranges studied. Approximately 10% precompression was required for all strengths to eliminate tablet capping and lamination at higher compression forces for undergranulated and center point processing conditions. The results from these studies along with other key response factors resulted in the identification of a suitable design space for the roller compaction process.

JUNE 22ND
4:00-4:40

Investigation of the peculiar features of the downstream process of an electrospun solid dispersion

Balázs Démuth, Budapest Univ. of Technology & Economics

Purpose

The purpose of the present work was to assess the particular properties of the downstream processing of the electrospun, itraconazole-PVPVA64 solid dispersion. As the main part of the work, a design of experiments was planned in order to systematically study the compression behavior of electrospun material (EM) while it was intended to produce fast disintegrating tablets, to optimize the formulation and the tableting process.

Methods

Tablets were compressed on a Huxley Bertram compaction simulator (Cambridge, UK). A 32 design of experiments was carried out (dependent variables: tensile strength, disintegration time). Results were evaluated with Statistica software (Tulsa, USA).

Results

The residual solvent content of solid dispersion prepared by high speed electrospinning could be pressed under the limitations before further application (300 ppm for dichloromethane and 700 ppm for ethanol) by simple drying on a tray.

Tableting blends: based on particle size measurements (sieve method and laser diffraction method) the EM is prone to aggregate though these aggregates were disrupted during mixing with excipients. Based on scanning electron microscope images MCC particles were covered by the EM due to their structured surface. This was confirmed later by Raman mapping of the subsequent tablets.

Design of experiments: tensile strength was almost only dependent on compression force; hence a linear model would be adequate. For disintegration time, fillers ratio was also significant along with interactions (quadratic effects). A saddle point was found at 76.25% fillers ratio. Tensile strength and disintegration times were in the pharmaceutically useful range. At low fillers ratio disintegration time increased very quickly due to the formation of a gelling polymer network. According to Raman maps in a tablet where fillers:EM ratio was 1:1, EM occupied a lot of space in the tablet, and in addition, high concentration of it was detected on MCC particles.

Dissolution behavior: it was found that magnesium stearate increases the wetting time of EM which can recrystallize during the dissolution test due to the elevated temperature and high humidity. Therefore the lubricant was changed to sodium stearyl fumarate with which total dissolution was achievable.

High speed tableting: preliminary experiments were carried out for high speed tableting of the EM on the compaction simulator which showed that this process seems feasible. The flowability and the tablet weight deviation remained the only questions. Therefore tablets were compressed on an 8-station rotary tablet press. Deviation was kept at low values, while tablet properties were satisfying, even at high speed.

Conclusions

During the formulation of an electrospun material important ascertainments were made. Design of experiments seemed an effective method to survey the tableting of an electrospun solid dispersion. With this and the optimization of the tableting an industrially acceptable formulation and process were realizable.

CSF 2016 POSTERS

Poster #	Title	Author	Affiliation
1	Strain rate profiles and powder compaction testing	Martin Bennett	Huxley Bertram
2	Pharmaceutical tabletting and QbD	Martin Bennett	Huxley Bertram
3	Determination of mechanical properties for mechanistic modeling of pharmaceutical powder compaction	Serena Schiano	University of Surrey
4	Interfacial strength of Bilayer pharmaceutical formulations	Jianyi Zhang	University of Surrey
5	A Materials Science Approach to Bilayer Tablet Compaction	Brian Breza	Bristol Myers Squibb
6	Correlation Among Crystal Structure, Mechanical Behavior, and Tabletability of the Model Materilas	Rahul Haware	Campbell University College of Pharmacy and Health Sciences
7	The diametral compression test for pharmaceutical tablets: reevaluation using the flattened disc geometry, finite element method modelling and digital image correlation.	V.Mazel	Univ. Bordeaux
8	Milling induced amorphisation of lactose studied by AFM and SEM	Maria Badal Tejedor	SP Technical Research Institute of Sweden
9	Evaluation of bilayer tablets interfacial adhesion via shear stress test	M.Bellini	College of Pharmacy, Freie Universitat Berlin
10	Loss of compactability in roller compaction – influencing parameters and analytical characterization	João Henriques	Hovione
11	Evaporation of binary mixtures and shell formation in spray dried droplets	P.C.Valente	Hovione
12	Multivariate Analysis of Powder Characteristics: A Step Towards a Predictive Tabletability Platform	J.Dhont	Ghent University
13	Investigating Segregation using in-line near-IR spectroscopy in 3D Printed Funnel Geometries	Cosima Hirschberg	University of Copenhagen
14	Toward predicting tensile strength and characterizing the acoustic properties of pharmaceutical tablets on continuous manufacturing platforms	Sonia Razavi	Rutgers
15	Assessing punch coatings by measuring adhesion risk to solve sticking issues	M.Winkett	Merlin Powder Characterization
16	Integrated flowsheet modeling and experimental validation in dry granulation : Effects of parameters changes on the compact characteristics	Seo-Young Park	University of Massachusetts, Lowell
17	Flowsheet Modeling of a Continuous Direct Compression Process at Production Scale	Shaun C Galbraith	University of Massachusetts, Lowell & Merck
18	Studying the feeding system impact on tablet properties using Styl'One	Susana Nieto-Bobadillaa	Medelpharm
19	Which test to characterize the interfacial strength of bilayer tablets?	Tchoreloff Pierre	Univ. Bordeaux
20	The impact of hot-melt extrusion on the compaction properties of amorphous polymers used in solid dispersions	Wouter Grymonpré	Ghent University
21	Atomic force microscopy (AFM) based approach to study the adhesive forces between tableting punches and model formulation ingredients	Andrew Parker	Juniper Pharma Services
22	Quality by Design of Continuous Hot Melt Extrusion: Functional characterisation of Dapsone solid dispersions	Elaine Stone	Merlin Powder Characterization