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SUMMARY OF FALL 2006 EFFUSIVITY PUBLICATIONS AT ISPE AND AAPS

The following combines the abstracts from eight effusivity posters into one single reference file for easier access and sharing. The key application phrase is underlined in each title. Each of the posters is available on request from the authors or info@mathisinstruments.com

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1. "The Use of Thermal Effusivity to Measure Manufacturing End-point for Sensitive Controlled Release Matrix **Wet Granulations**", Neil Stinson, Shire Pharmaceutical

2. "Simultaneous Measurement of Chemical and Physical Characteristics for In-line Blend Uniformity utilizing Effusivity (Mathis ESP™) and **Near-IR** (Zeiss Corona). Understanding, mapping, and utilizing design space to increase product knowledge and decrease development requirements", Neil Stinson, Shire Pharmaceutical

3. "Evaluation of In-line Wireless Thermal Effusivity Data and **HPLC Assay** Values in Predicting Different States of Uniformity in Ibuprofen Blends", S, Hall[1], S. Closs[1], M. Turnbull[1] M. Emanuel[2], N. Mathis[2], [1] Patheon Inc, [2] Mathis Instruments Ltd.

4. "Evaluation of In-line **Repeatability and Reproducibility** in a Dynamic Blend Process using Wireless Thermal Effusivity". S, Hall[1], S. Closs[1], M. Turnbull[1] M. Emanuel[2], N. Mathis[2], [1] Patheon Inc, [2] Mathis Instruments Ltd.

5. "**Production-scale** Real-time Blending and Lubrication Profiling using Thermal Effusivity", Patrick Okoye[1], Jamie Mckee[2], Lisa Lippai[1], Joe Manias[2], David Mayers[2], Nancy Mathis[1]. 1. Mathis Instruments Ltd, Fredericton, NB, Canada; 2. Purdue Pharma, Pickering, ON, Canada

6. "Physico-chemical Behaviors of Pseudopolymorphs of **Magnesium Stearate** in Directly Compressible Formulations under Real-time Monitoring Using Thermal Effusivity", Patrick Okoye[1], Samantha Compton[2], Michael Kelly[2], Doug Kirsch[3], Michael Emanuel[1], Dale Natoli[3], and Stephen H. Wu[2], 1. Mathis Instruments Ltd, Fredericton, NB, E3C 2N5, Canada; 2. Tyco Healthcare/Mallinckrodt Pharmaceuticals, St Louis, MO 63147, 3. Natoli Engineering Company, Inc, St. Charles, MO 63304

7. "A Comparison of Shear Cell and Effusivity Methods to Determine **Flow** Properties of Common Excipients and Blends", Bryan J. Ennis[1], Michael Emanuel[2],[1]E&G Associates, Inc., Nashville, TN 37215 USA; [2]Mathis Instruments Ltd., Fredericton, NB Canada

8. "Evaluation of a Simple On-line **Sampler** Modification for FBD Profiling and Endpoint Utilizing Effusivity", Timothy J. Smith[1], Michael Emanuel[2], Patrick Okoye[2], [1]Vector Corporation, Marion, IA, USA, [2]Mathis Instruments Ltd., Fredericton, NB, Canada.

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FOR IMMEDIATE RELEASE

Five Effusivity Studies Submitted to ISPE for Publication

July 26, 2006 Fredericton, NB – Mathis Instruments Ltd. announced today that five publications detailing significant advancements in effusivity applications for pharmaceutical processing have been submitted to the International Society for Pharmaceutical Engineering. The research supporting these publications has been performed by three pharmaceutical companies.

Patheon's work on blending has resulted in two topics. The first is a fundamental study of effusivity's capabilities and is entitled "Evaluation of In-line Repeatability and Reproducibility in a Dynamic Blend Process using Wireless Thermal Effusivity". The primary objective was to use a Measurement System Analysis (MSA) technique to evaluate the repeatability and reproducibility achieved in a dynamic blend process using an in-line wireless Mathis ESP™. This work repeats an earlier study at Patheon that used Mathis's non-wireless version of the instrument.

Patheon's second study correlates the real time effusivity readings of the wireless Mathis ESP to conventional HPLC test methods and establishes the practicality of the Mathis system for monitoring blend uniformity and segregation potential. The paper shows the connection between physical blend uniformity measured by effusivity and chemical blend uniformity measured by HPLC and is entitled "Evaluation of In-line Wireless Thermal Effusivity Data and HPLC Assay Values in Predicting Different States of Uniformity in Ibuprofen Blends".

Shire Pharmaceuticals is also reporting correlative work, but with in-line near infrared as the correlated technique rather than off-line HPLC. The paper is entitled "Simultaneous Measurement of Chemical and Physical Characteristics for In-line Blend Uniformity Utilizing Effusivity (Mathis ESP™) and Near-IR (Zeiss Corona)." "The main goal of this work was to increase product knowledge and decrease development requirements through improved understanding and mapping, and utilizing design space", says Neil Stinson, Shire Pharmaceutical Inc.

At Purdue Pharma, real-time profiles of production-scale batches were generated during routine manufacturing of various pharmaceutical products. The blending and lubrication processes were profiled and compared to the compression and product release data. The results helped Purdue Pharma to understand the possible causative factors of process deviations during routine manufacture. Their paper is entitled "Production-scale Real-time Blending and Lubrication Profiling using Thermal Effusivity".

The last work moves away from blending and into wet granulation. Neil Stinson at Shire has a second paper entitled "The Use of Thermal Effusivity to Measure Manufacturing End-point for Sensitive Controlled Release Matrix Wet Granulations". "The work at Shire represents the first in-line use of effusivity for wet granulation in a high shear mixer. "Mathis has worked with Vector to create process profiles in fluidized granulation, but Neil's work represents an important new application for effusivity", commented Ralph Beier, Director of Sales and Marketing at Mathis Instruments.

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The Use of Thermal Effusivity to Measure Manufacturing End-point for Sensitive Controlled Release Matrix Wet Granulations

Neil Stinson, Shire Pharmaceutical

Background:

- Typical wet granulations are stopped based on time of wet massing, power consumption, change in power consumption (delta), or product temperature. In early stage scale-up, it was determined that the standard end-point determinants would not work to produce consistent granules batch-to-batch for this process. This matrix granulation had two significant challenges when looking at achieving consistent end-point control. The first is that the granulation is over 95% API. The second is the use of a high viscosity and medium viscosity binder, one being added through the liquid phase solution delivery and the other added through the dry blend. Since granulation is a physical process, Shire decided to look for a means to measure the physical characteristics of granule. Thermal Effusivity was selected with the target of finding a method for achieving a consistent and reproducible physical granule that met its desired chemical interaction. Utilizing Thermal Effusivity measures and is influenced by the critical physical attributes of the granulation. Examples of influences on thermal effusivity: Material Composition, Particle size, Density, Moisture Content, and Mass.

Abstract:

- Preliminary studies using at-line effusivity measurement have demonstrated that effusivity can predict the power consumption plateau and over-granulation points minutes in advance of power consumption. Studies utilizing in-line effusivity have been conducted to investigate the use of thermal conductivity as an end-point determinant for wet matrix granulations. The in-line measurements were taken through a modified side discharge valve. The ability to place the sensor in the sidewall is optimal for measurement because it ensures the effusivity sensor is seeing constant force and product contact. Eliminating the variable of force is important for measuring effusivity, since it measures physical properties of the product. The in-line effusivity values measured by the Mathis ESP™ have been compared to main impeller power consumption data (torque).

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Simultaneous Measurement of Chemical and Physical Characteristics for In-line Blend Uniformity utilizing Effusivity (Mathis ESP™) and Near-IR (Zeiss Corona). Understanding, mapping, and utilizing design space to increase product knowledge and decrease development requirements.

Neil Stinson, Shire Pharmaceutical

Abstract

- International Conference on Harmonization (ICH) Draft Guidance- (ICHQ8) challenges the industry to understand their products “Design Space” through sound science. Developing a diversified Process Analytical Technology (PAT) Toolbox will be key to understanding and implementing quality by design. This study challenged the use of two PAT technologies running simultaneously to understand when a blend is truly uniform. The study is utilizing both thermal effusivity and Near-IR to measure and compare physical uniformity to chemical uniformity respectively. The study uses two formulations ranging from less than 1% drug load up to 40% drug load to minimize statistical error. The study was not intended to identify either as better tool, but rather to show how the tools can be used together to develop a better understanding of the entire window of uniformity. The study looked for periods throughout processing where standard interval methods (thief sampling), effusivity, and NIR agree or disagree on the degree of uniformity in the blend. The intent is to demonstrate that both tools provide different, but valuable information about the quality of the blend.

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Evaluation of In-line Wireless Thermal Effusivity Data and HPLC Assay Values in Predicting Different States of Uniformity in Ibuprofen Blends

S, Hall[1], S. Closs[1], M. Turnbull[1] M. Emanuel[2], N. Mathis[2],
[1] Patheon Inc, [2] Mathis Instruments Ltd.

PURPOSE

The primary objective of this study was to correlate the effusivity readings of the Mathis ESP-04 Wireless System to conventional HPLC test methods and establish the practicality of the Mathis system in monitoring blend uniformity and segregation potential.

METHOD

Three blends containing 10 % API (Ibuprofen) of fine, normal and coarse particle size were final blended along with 15% Starch 1500 (Colorcon), 37.5% Lactose Monohydrate Fast Flo (Foremost Farms), and 37.5% Avicel PH102 (FMC) using a 16 qt. V-blender filled at 80% capacity with a rotation speed of 12 rpm. In-line wireless thermal effusivity sensors readings were taken at pre-determined equal intervals during mixing using a Mathis ESP-04 instrument in order to create effusivity blend profiles to monitor uniformity. HPLC samples were extracted at some of these same intervals in order to construct HPLC blend profiles and compared to profiles created during in-line effusivity monitoring. Thermal effusivity readings were correlated to HPLC blend homogeneity samples obtained from conventional sample thieves. The resulting data was analyzed in order to evaluate the effectiveness of thermal effusivity in detecting uniformity of blend as well as identifying periods of non-homogeneity.

RESULTS

The blend data generated established a correlation between the in-line wireless effusivity profiles and uniformity results using conventional HPLC methods. Data from the three blends demonstrated the ability of the thermal effusivity system in identifying the different blend dynamics caused by a shift in API particle size. Thermal effusivity profiles were able to identify both periods of blend uniformity and non-homogeneity that were confirmed by HPLC samples taken using sampling thief. Further, the results indicate that the effusivity profiles can be used to create real time blend models able to predict optimal blend condition and blend segregation potential.

CONCLUSION

In a development environment, extensive process knowledge generated allows a robust production protocol to be developed. This resulting blend process signature is completely transferable and responds to variations in incoming particle size and blend conditions. Scale up challenges are overcome by allowing material to be blended until uniform rather than to a non-scaleable marker of uniformity such as time.

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Evaluation of In-line Repeatability and Reproducibility in a Dynamic Blend Process using Wireless Thermal Effusivity

S, Hall[1], S. Closs[1], M. Turnbull[1] M. Emanuel[2], N. Mathis[2],
[1] Patheon Inc, [2] Mathis Instruments Ltd.

PURPOSE

The primary objective of this study was to use a Measurement System Analysis (MSA) technique to evaluate the repeatability and reproducibility achieved in a dynamic blend process using an in-line Mathis ESP-04 Wireless System.

METHOD

Five common excipients used in the pharmaceutical industry that represent a broad range of effusivity values were involved in single component "mixing" using a 16 qt V-Blender (O'Hara Technologies). The excipients used were Sodium Bicarbonate (Church and Dwight), Sucrose Fine (Redpath), Dicalcium Phosphate (Rhodia), Lactose Fast Flo (Foremost Farms), and Avicel PH102 (FMC). The 16 qt V-Blender was retrofitted with four in-line thermal effusivity sensors. Each excipient was mixed in the 16 qt. V-blender until 20 thermal effusivity data points were collected for each sensor (total data points collected per excipient: 80). All data collected was evaluated using MSA ANOVA analysis methods where each component data set was evaluated for repeatability and reproducibility as a means of understanding total observed variation in the sensor signal during testing.

RESULTS

Analysis of MSA ANOVA data was able to determine that approximately 99% of the observed variation was due to true product variation between the materials tested. The less than 1% signal attributed to "noise" within the measurement system could be partitioned into repeatability and reproducibility variation. Of this, a third of the variation was as a result of repeatability (variation within a single sensor) while two thirds was a result of reproducibility (variation between all sensors).

CONCLUSION

The data generated in the MSA study confirmed the ability of the in-line wireless thermal effusivity sensors to distinguish between common pharmaceutical excipients in a real time dynamic blending environment. In a PAT method development exercise, quantifying measurement error allowed the setting of meaningful specifications for blend endpoint detection involving a multi-sensor system. Knowing the source of variation directs efforts to reduce error and further improve sensitivity. The information provided by the MSA study facilitated the improvement of sensor positioning resulting in an overall improvement in measurement precision.

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Production-scale Real-time Blending and Lubrication Profiling using Thermal Effusivity

Patrick Okoye[1], Jamie Mckee[2], Lisa Lippai[1], Joe Manias[2], David Mayers[2], Nancy Mathis[1]. 1. Mathis Instruments Ltd, Fredericton, NB, Canada; 2. Purdue Pharma, Pickering, ON, Canada

PURPOSE

Real-time profiles of production-scale batches were generated during routine manufacturing of various pharmaceutical products. The blending and lubrication processes were profiled and compared to the compression and product release data. The results helped to understand the possible causative factors of process deviations during routine manufacture.

METHODS

Production-sized V-blenders were retrofitted with four on-line effusivity sensors (ESP^{TM}) to monitor the blending process. Different commercial products, comprising of multiple excipients and active ingredients, were profiled during blending and lubrication according to their batch records. Subsequently, an instrumented press was used for the compression. The tablet physical attributes such as hardness, tablet weight, thickness, friability, and compression forces were measured or monitored under pre-set criteria. The blend and finished product samples were analyzed in accordance to established product release guidelines.

RESULTS

The results were compiled over 4 months and show that effusivity has a predictive capability to recognize deviations in raw materials or uncontrolled environmental conditions that influence upstream product attributes. Effusivity served as a screening tool to alert operators during blending that a variation had occurred and that the batch being processed was behaving differently than previous batches. For the batches where the compression and/or product quality results confirmed the effusivity prediction and were also not within normal operating conditions, additional analysis was performed on the excipients to attempt to determine route cause...

CONCLUSIONS

The effusivity technology was successfully utilized in a production environment to profile product during blending and lubrication. The real-time results predicted the blend uniformity with good correlation to chemical assay results. Additionally, the lubrication profile showed good correlation to the desired tablet physical attributes and final product release criteria. The results can be used as feed-backward process alerts to understand the genesis of process deviations. The results can be used as feed-forward process guides to facilitate tablet press set-up in the future so that the process adapts to the material variation.

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Physico-chemical Behaviors of Pseudopolymorphs of Magnesium Stearate in Directly Compressible Formulations under Real-time Monitoring Using Thermal Effusivity

Patrick Okoye[1], Samantha Compton[2], Michael Kelly[2], Doug Kirsch[3], Michael Emanuel[1], Dale Natoli[3], and Stephen H. Wu[2]
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PURPOSE
The influence of magnesium stearate (MgSt) on blends and finished solid dosage products has presented significant challenge to drug manufacturing resulting from poor production efficiency to variability in drug disintegration and dissolution. This study looked at the physicochemical behaviors of pseudopolymorphs of magnesium stearate (as lubricant) in directly compressible formulations using microcrystalline cellulose and dibasic calcium phosphate as diluents. Acetaminophen (APAP) was used as the active drug. Effusivity sensors were also evaluated as an on-line, real-time PAT tool for monitoring of blending and lubrication process. The sensitivity of the blends to different pseudopolymorphs of the lubricant was studied as a function of the relative amount of excipients to the levels of lubricant and lubrication time.

METHODS
A fractional factorial design of experiment with acetaminophen, MgSt pseudopolymorphs, diluents, lubrication time, and % MgSt as factors, was used. The blending was carried out in a one cubic-foot V-Blender retrofitted with four on-line effusivity sensors. Compression was conducted using a ten-station instrumented press. The tablet physical attributes such as hardness, tablet weight, thickness, friability, ejection force, knock-off, pre-compression, and compression forces were measured or monitored. The blend assay and content uniformity were analyzed using high performance liquid chromatography at ultra-violet wavelength of maximum absorbance at about 244 nm. Additional physicochemical and thermal analyses were conducted using Laser diffraction, Differential Scanning Calorimetry, and Scanning Electron Microscope.

RESULTS The results indicated that the online effusivity sensors could predict the blend uniformity range and optimal lubrication. Additionally, the results also indicated that the difference in lubrication profiles between the batches was not only attributable to differences in the percent of MgSt used, but also, suggested some correlations to the pseudopolymorphs of MgSt employed. Finally, the tablet physical attributes showed correlation to the pseudopolymorphs of MgSt used.

CONCLUSIONS
The effusivity sensors predicted the blend uniformity with good correlation to chemical assay results. Additionally, the lubrication profile showed good sensitivity to the

pseudopolymoph or MgSt type used as lubricant. These behaviors were supported by finished product results, as well as, physicochemical and thermal analysis.

A Comparison of Shear Cell and Effusivity Methods to Determine Flow Properties of Common Excipients and Blends

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PURPOSE

Powder flow affects solids dosage operations through material handling problems, segregation, tablet/capsule uniformity, and fill control. Shear cells determine simple flow indices from which you can estimate the likelihood of powder arching or ratholing, mass discharge rates, blend segregation, stress transmission in tabletting, or plug strength in encapsulation. In contrast, effusivity measurements are a function of the heat transfer characteristics of powders, and are easily applied to process measurements of blend uniformity and segregation, as well as powder flow rate. This work explores flowability relationships between effusivity and shear cell measurements for a range of pharmaceutical excipients, as well as some model blends.

METHODS

Flow functions, bulk density, and friction angles were determined from an iShear™ rotary shear cell. The flow function is a measure of powder strength versus compaction stress history. Excipients included pure grades of avicel, dicalcium phosphate, lactose monohydrate, fast flow lactose, non-pareils (sugar beads), as well as blends with varying levels of cabosil and magnesium stearate. Minimum openings to prevent arching, as well as expected mass discharge rates were determined from this data. Effusivity measurements have been made for the excipient samples under a variety of test methods used to control the evolution of bulk density in the sample. Namely, an effusivity profile is determined as a function of time, with controlled vibration or impact energy between steps.

RESULTS

Shear properties are a strong function bulk density. Different excipients differ in terms of flowability, largely due to how the bulk density is affected by evolution of stress. For example, if a given lot of material compacts more than another, its flow properties will degrade. A clear relationship is illustrated between large rises in powder strength (or flow function) and changes in bulk density with shear, as well as both theoretical and experimental mass discharge rates. Furthermore, as heat transfer is strongly affected by the number of point contacts in a bulk powder, normalized effusivity profiles correlated with bulk density behavior as measured by shear cell. Effusivity values were observed to rise with vibration time, leveling off at a steady state value, which is a function of applied sample pressure. Effusivity can also decrease with a drop in applied pressure. Excipients with large permanent changes in effusivity correlated with poor flow behavior, as established by shear cell.

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CONCLUSIONS

Mass discharge rates and minimum opening sizes to prevent powder arching correlated with the powders flow function, as determined by shear cell. In addition, effusivity may be a rapid tool to assess the important evolution of bulk density, which has a controlling influence on overall powder flowabiliy.

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Evaluation of a Simple On-line Sampler Modification for FBD Profiling and Endpoint Utilizing Effusivity

Timothy J. Smith[1], Michael Emanuel[2], Patrick Okoye[2], [1]Vector Corporation, Marion, IA, USA, [2]Mathis Instruments Ltd., Fredericton, NB, Canada

PURPOSE

To improve monitoring processes in a fluid bed. Currently, process parameters monitored in a fluid bed, such as outlet temperature and humidity, are normally inadequate for determination of process end-point. Moisture analyzers are used to measure LOD, however the analysis is lengthy and can only be made off-line. The purpose of this study was to evaluate the capability of effusivity to monitor and profile a typical granulation and drying process in a fluid bed, and to develop criteria for end-point determination, thus creating an efficient PAT tool.

METHOD

It is known that effusivity measurements are sensitive to physical properties of powders, including moisture content, density and particle size. The powder in a fluid bed is fluidized and continuously in motion. This prevents any effusivity measurement directly in the chamber, since the effusivity sensor needs to be in firm and reproducible contact with the powder being measured.
A sampler has been designed to extract material from the fluid bed, bring it in contact with the sensor and then discharged it back into the fluid bed, all done while sealed from the external environment. This sampler enabled effusivity measurements on-line and real time.

RESULTS

A correlation between on-line effusivity measurements and LOD has been observed. A typical granulation and drying process has been profiled, and end-point criteria has been developed. Reproducibility of the end-point criteria has been established. On-line endpoints were verified to be between the specified ranges for LOD and particle size.

CONCLUSIONS

This study has shown that the effusivity sensor can efficiently monitor on-line typical fluid bed processes, and in most cases replace the off-line, LOD measurements. It can therefore be used as a PAT tool to control the process.